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Kofi Asante-Duah

Public Health Risk Assessment for Human Exposure to Chemicals

Second Edition

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To: Dad—George Kwabena Duah
To: Mom—Alice Adwoa Twumwaa
To: Kojo Asante-Duah (a.k.a., K.J.)
To: Kwabena Asante Duah (a.k.a., Daddy-K./Kobby)
To: Adwoa Twumwaa Asante-Duah (a.k.a., Obaa-Sima A.T./Naana)
To: My Extraordinary Families (of Abaam, Kade, and Nkwantanan)
—and all the Off-springs & Off-shoots

&

To the Everlasting and Ever-Loving Memories of:
Daddy, George Kwabena Duah (a.k.a., GKD/Agya Duah)
Grandma, Nana Martha Adwoa Oforiwaa & Grandpa
Grandma, Nana Abena Nketia Owusua & Grandpa
Atta Kakra (a.k.a., Emmanuel Asare Duah)
Atta Panin (a.k.a., Ebenezer Asare Duah)
Osagyefo Dr. Kwame Nkrumah @GH

Preface

Risk to human health as a consequence of toxic materials found in modern societies is a matter of grave concern to the world community. What is more, risks to humans that arise from chemical exposures from a multiplicity of sources are a complex issue with worldwide implications. The effective management of human exposure to a variety of chemicals present in various sectors of society has therefore become a very important public health policy issue that will remain a growing social challenge for years to come. In fact, with a reasonable control and containment of most infectious conditions of the past millennium having been realized in most developed countries, and with the accompanying increase in life expectancies, much more attention seems to have shifted to degenerative health problems typically attributable to environmental or 'social' chemicals so very often encountered in modern societies. Many of the degenerative health conditions have indeed been linked to thousands of chemicals regularly encountered in human living and occupational/work environments. It is important, therefore, that human health risk assessments are carried out on a consistent basis—in order to be able to determine the potential impacts of the target chemicals on public health. Overall, risk assessment promises a systematic way for developing appropriate strategies to aid public health risk policy decisions in the arena of human exposures to chemicals.

Risk assessment generally serves as a tool that can be used to organize, structure, and compile scientific information to help identify existing hazardous situations or problems, anticipate potential problems, establish priorities, and provide a basis for regulatory controls and/or corrective actions. A key underlying principle of public health risk assessment is that some risks are somehow tolerable—a reasonable and even sensible view, considering the fact that nothing is wholly safe per se. In fact, whereas human exposures to large amounts of a toxic substance may be of major concern, exposures of rather limited extent may be trivial and hence should not necessarily be a cause for alarm. In order to be able to make a credible decision on the cut-off between what really constitutes a 'dangerous dose' and a 'safe dose', systematic scientific tools—such as those afforded by risk assessment—may be utilized. In this regard, therefore, risk assessment seems to represent an important

foundation in the development of effectual public health risk management strategies and policies.

This book provides a concise, yet comprehensive overview of the many facets/aspects of human health risk assessments in relation to chemical exposure problems. It presents some very important tools and methodologies that can be used to address chemical exposure and public health risk management problems in a consistent, efficient, and cost-effective manner. On the whole, the book represents a collection and synthesis of the principal elements of the risk assessment process that may be used to more effectively address issues pertaining to human exposures to chemicals found in modern societies. This also includes an elaboration of pertinent risk assessment concepts and techniques/methodologies for performing human health risk assessments. A number of illustrative example problems are interspersed throughout the book, in order to help present the book in an easy-to-follow, pragmatic manner.

Meanwhile, it is noteworthy that even though the main focus of this title is on risk assessment of the potential human health effects associated with chemical exposures, the same principles may be extrapolated to deal with other forms of human exposure problems (such as exposures to radionuclides and pathogens). Thus, the chemical risk assessment framework may be adapted and applied to human exposures to other agents—albeit many unique issues may have to be addressed for exposures to the new hazard/agent under consideration. In fact, the subject matter of this book can generally be used to aid in the resolution of a variety of environmental contamination and public health risk management problems.

On the whole, this book should serve as a useful reference for many professionals encountering risk assessment in relation to environmental contamination and public health risk management programs; it offers an understanding of the scientific basis of risk assessment and its applications to public health policy decisions. The specific intended audience includes public and occupational health practitioners and other public health and environmental health professionals, public policy analysts, environmental consulting professionals, consumer product manufacturers, environmental attorneys, environmental and health regulatory agencies, environmental and public health NGOs, and a miscellany of health, environmental, and consumer advocacy interest groups. The book is also expected to serve as a useful *educational/training resource for both students and professionals in the health-related and environmental fields*—particularly those who have to deal with human exposures to chemicals, public health risk assessment issues, and/or environmental health management problems. Written for both the novice and the experienced, the subject matter of this book is an attempt at offering a simplified and systematic presentation of public health risk assessment methods and application tools—all these facilitated by a design/layout that will carefully navigate the user through the major processes involved.

Finally, a key objective in preparing this revised edition to the book has been to, insofar as practicable, incorporate new key developments and/or updates in the field since the previous version was last published. Another notable feature of the revised edition is the sectional re-organization that has been carried out for some

topics—all meant to help with the overall flow of the presentations, but especially to facilitate a more holistic learning process/experience afforded by this book. All in all, the book is organized into five parts—consisting of 15 chapters and a set of 5 appendices, together with a bibliographical listing. It is the hope of the author that the five-part presentation offered by this title will provide adequate guidance and direction for the successful completion of public health risk assessment programs that are to be designed for any type of chemical exposure problem, and at any geographical location. The structured presentation should also help with any efforts to develop effectual classroom curricula for teaching purposes. Ultimately, the systematic protocols presented in this volume should indeed aid many a public health and related environmental professional to formulate and manage chemical exposure and associated problems more efficiently.

Washington, DC
8 August 2016

Kofi Asante-Duah

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Finally, it should be acknowledged that this book benefited greatly from review comments of several anonymous individuals, as well as from discussions with a number of professional colleagues. Any shortcomings that remain are, however, the sole responsibility of the author.

Contents

Part I
Problem Diagnosis: A General Overview of the Origins and Nature of Chemical Exposure Problems

This part of the book encompasses the following three specific chapters:

- Chapter 1, *Introduction*, presents a general background discussion on the wide-ranging sources/origins of environmental contamination and chemical exposure problems often encountered in practice, as well as elaborate on the likely implications/consequences of such types of problem situations. This chapter also provides a broad overview on the general types of issues that may have to be addressed in order to establish an effective risk management and/or corrective action program for chemical exposure problems.
- Chapter 2, *Anatomical and Physiological Perspectives on Human Exposure to Chemicals*, looks at the major human contact sites, target organs, and exposure scenarios that can be expected to become key players in the assessment of human exposure to, and response from, chemical hazards—all the while recognizing that several characteristics of the target chemicals of concern/interest, as well as the human contact sites, will typically provide an indication of the critical attributes of a given exposure.
- Chapter 3, *Archetypical Chemical Exposure Problems*, apprises the typically significant exposure scenarios that can be expected to become key players in the assessment of human exposure to, and response from, chemical hazards; it goes on to provide a general framework that may be used to guide the formulation of realistic exposure scenarios, as necessary to generate credible risk assessments.

Chapter 1
Introduction

In the landmark book—*Silent Spring*—from the early 1960s, Rachel Carson wrote: "For the first time in the history of the world, every human being is now subjected to contact with dangerous chemicals, from the moment of conception until death" (Carson 1962, 1994). What is more, this statement of some more than five decades ago is not about to change, given our dependency—maybe even obsession—with a so-called 'modern way of life'. Indeed, in everyday living, peoples around the world—directly or indirectly—are exposed to myriad sources and cocktails of chemical hazards. Ultimately, these endemic chemical exposure problems may pose significant risks to global populations because of the potential health effects; for instance, pesticides are believed to have accounted for some of the most advanced and persistent cases of variant human chemical sensitivity that became known to some clinicians and physicians in the fairly recent past (Ashford and Miller 1998; Randolph 1962, 1987). Risks to human health as a result of exposure to toxic materials present or introduced into our living and work environments are, therefore, a matter of grave concern to modern societies. To borrow again from Rachel Carson's *Silent Spring*, 'if we are going to live so intimately with these chemicals—eating and drinking them, taking them into the very marrow of our bones'—then at the very least, we should be able to determine the risks that we are exposed to, as well as know how to manage such risks, in order to ensure a worthwhile quality to our lives (Carson 1962, 1994).

In fact, it has become overwhelmingly apparent that many of the degenerative health conditions seen in modern societies may be linked to the innumerable chemicals regularly encountered in human living and occupational/work environments. What is more, with a reasonable control and containment of most infectious conditions and diseases of the past millennium having been realized in most developed countries, and with the consequential increase in life expectancies, much more attention seem to have shifted to degenerative health problems typically attributable to environmental or 'social' chemicals so very often encountered in modern societies. It is important, therefore, that human health risk assessments are undertaken on a consistent basis—in order to reasonably ascertain the potential

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impacts of the target chemicals of concern on public health. Overall, risk assessment promises a systematic way for developing appropriate strategies to aid public health risk policy decisions in the arena of human exposures to chemicals.

This book focuses on the holistic application of effectual risk assessment concepts and principles to support responsible and credible public health risk management programs as relates to chemical exposure problems. On the whole, it offers a good understanding of the scientific basis of the risk assessment paradigm and attributes, as well as its applications to public health policy decisions for chemical exposure situations.

1.1 Chemical Origins: Coming to Terms with the Several Chemicals in Modern Society

As a quintessential part of the story often told about chemicals prevalent in modern societies, synthetic pesticides became the symbols of progress during the postwar years and provided an unprecedented level of control over one type of environmental risks—more specifically, pest-related risks. As a notable example, the discovery of the insecticidal properties of dichlorodiphenyl trichloroethane [DDT] in 1939 by the Swiss scientist and Nobel Prize recipient, Paul Müller, began the modern chemical industrial revolution—and which then became a turning point in the shaping of both public health and agricultural history. In fact, as an important specific example, when the World Health Organization (WHO) was established in 1945, it relied primarily on DDT to control mosquito-borne diseases, especially malaria; the results of the WHO efforts were considered extraordinary for much of that period of time. However, as subsequently became quite apparent, these benefits were not realized without some significant (even if intangible) costs; among other things, growing mosquito-resistance to DDT necessitated the use of higher application rates, as well as the development and use of other related chlorinated compounds with similar attributes/concerns. Ultimately, DDT and its analogs became associated with significant environmental impacts globally—most notably, the apparent decline of certain avian species due to the chemical effects on egg shell integrity, etc. Indeed, to affirm how serious a problem the likely impacts generally had been, it is noteworthy that even in the far removed Arctic regions, it has been established that contamination of the arctic aquatic food-chain by organochlorine compounds and other anthropogenic chemicals has occurred (see, *e.g.*, Barrie et al. 1992; Dewailly et al. 1993; Lockhart et al. 1992; Muir et al. 1992; Thomas et al. 1992).

Now, making what seems like quantum leaps into the future with respect to the significant advances in the germane scientific fields associated with the chemical exposure problems of yesterdays does not appear to have insulated most biological organisms from the potential chemical impact or vulnerability problems seen today. In fact, in contemporary societies, it appears that there is no escape from potential

chemical exposure problems in any part of the world—especially with regards to those resulting from possible environmental contamination, and also from the usage of a wide variety of consumer products. After all, chemicals seem to have become an integral part of the global economy—providing key building blocks for the many products that seem to have proven beneficial to much of society. Still, depending on their use (or misuse), chemicals may have significantly harmful impacts on human health and the environment; for instance, evidence seems to be mounting about the believe that some chemicals found in everyday consumer products (*e.g.*, some plastic bottles and containers; liners of metal food cans; detergents; flame retardants; foods; toys; cosmetics; pesticides; etc.) may disrupt the endocrine system and affect the development of children and sensitive ecological species.

Broadly speaking, the key environmental chemicals of greatest concern are believed to be anthropogenic organic compounds. These typically include pesticides—*e.g.*, lindane, chlordane, endrin, dieldrin, toxaphene, and dichlorodiphenyl trichloroethane [DDT]; industrial compounds—*e.g.*, solvents such as trichloroethylene (or, trichloroethene) [TCE] and fuel products derived from petroleum hydrocarbons; and byproducts of various industrial processes—*e.g.*, hexachlorobenzene [HCB], polychlorinated biphenyls [PCBs], polychlorinated dibenzodioxins (or, polychlorodibenzo-*p*-dioxins) [PCDDs], and polychlorinated dibenzofurans (or, polychlorodibenzofurans) [PCDFs] (see, *e.g.*, Dewailly et al. 1993, 1996; Walker 2008). Many industries also produce huge quantities of highly toxic waste byproducts that include cyanide ions, acids, bases, heavy metals, oils, dyes, and organic solvents (Table 1.1). Further yet, other rather unsuspecting sources of environmental contaminants are beginning to add to the multitude of chemical exposure problems that contemporary societies face. For instance, low levels of reproductive hormones, birth control pills, steroids, antibiotics, analgesics, antidepressants, antineoplastics, parasiticides, and numerous other prescription and nonprescription drugs (in relation to both human medicinal and veterinary products), as well as some of their metabolites, have been detected in various water bodies around the world in recent times. In fact, a number of scientists and regulatory agencies around the world have come to recognize/acknowledge pharmaceuticals to be an emerging environmental problem of significant concern—culminating in the development of regulatory frameworks to address this issue; within such framework, it has been determined that approximately 10% of pharmaceutical products currently in use may potentially pose significant environmental risks (Küster and Adler 2014). At any rate, pharmaceuticals have probably entered, and been present in our environments since their use began (*i.e.*, for well over a century now)—albeit it has only recently been recognized as a significant environmental issue. What is more, given the rather continual and diffuse nature of pharmaceutical releases into the environment (usually through various point and nonpoint sources, and typically via municipal/domestic waste streams and/or sewage systems), trace levels of pharmaceuticals in the environment are not unexpected in most locales. Along with the pharmaceuticals, products used in everyday life (such as food additives, cosmetics, fragrances, plasticizers, cleaners, detergents, disinfectants, insect repellants, pesticides, fire retardants, etc.) are also turning up in

Table 1.1 Examples of typical potentially hazardous waste-streams from selected industrial sectors.

Sector/source	Typical hazardous waste-stream
Agricultural and food production	Acids and alkalis; fertilizers (e.g., nitrates); herbicides (e.g., dioxins); insecticides; unused pesticides (e.g., aldicarb, aldrin, DDT, dieldrin, parathion, toxaphene)
Airports	Hydraulic fluids; oils
Auto/vehicle servicing	Acids and alkalis; heavy metals; lead-acid batteries (e.g., cadmium, lead, nickel); solvents; waste oils
Chemical/pharmaceuticals	Acids and alkalis; biocide wastes; cyanide wastes; heavy metals (e.g., arsenic, mercury); infectious and laboratory wastes; organic residues; PCBs; solvents
Domestic	Acids and alkalis; dry-cell batteries (e.g., cadmium, mercury, zinc); heavy metals; insecticides; solvents (e.g., ethanol, kerosene)
Dry-cleaning/laundries	Detergents (e.g., boron, phosphates); dry-cleaning filtration residues; halogenated solvents
Educational/research institutions	Acids and alkalis; ignitable wastes; reactives (e.g., chromic acid, cyanides; hypochlorites, organic peroxides; perchlorates, sulfides); solvents
Electrical transformers	PCBs
Equipment repair	Acids and alkalis; ignitable wastes; solvents
Leather tanning	Inorganic chemicals (e.g., chromium, lead); solvents
Machinery manufacturing	Acids and alkalis; cyanide wastes; heavy metals (e.g., cadmium, lead); oils; solvents
Medical/health services	Laboratory wastes; pathogenic/infectious wastes; radionuclides; solvents
Metal treating/manufacture	Acids and alkalis; cyanide wastes; heavy metals (e.g., antimony, arsenic, cadmium, cobalt); ignitable wastes; reactives; solvents (e.g., toluene, xylenes)
Military training grounds	Heavy metals
Mineral processing/extraction	High-volume/low-hazard wastes (e.g., mine tailings); red muds
Motor freight/railroad terminals	Acids and alkalis; heavy metals; ignitable wastes (e.g., acetone; benzene; methanol); lead-acid batteries; solvents
Paint manufacture	Heavy metals (e.g., antimony, cadmium, chromium); PCBs; solvents; toxic pigments (e.g., chromium oxide)
Paper manufacture/printing	Acids and alkalis; dyes; heavy metals (e.g., chromium, lead); inks; paints and resins; solvents
Petrochemical industry/gasoline stations	Benzo-a-pyrene (BaP); hydrocarbons; oily wastes; lead; phenols; spent catalysts
Photofinishing/photographic industry	Acids; silver; solvents
Plastic materials and synthetics	Heavy metals (e.g., antimony, cadmium, copper, mercury); organic solvents
Shipyards and repair shops	Heavy metals (e.g., arsenic, mercury, tin); solvents

(continued)

Table 1.1 (continued)

Sector/source	Typical hazardous waste-stream
Textile processing	Dyestuff heavy metals and compounds (e.g., antimony, arsenic, cadmium, chromium, mercury, lead, nickel); halogenated solvents; mineral acids; PCBs
Timber/wood preserving industry	Heavy metals (e.g., arsenic); non-halogenated solvents; oily wastes; preserving agents (e.g., creosote, chromated copper arsenate, pentachlorophenol)

a number of aquatic environments (Erickson 2002; NRC 1999). Indeed, it is probably reasonable to assume that pollutants from pharmaceuticals and other everyday products have been in the human environments for as long as they have been in use—albeit it is only recently that proper analytical methods have been developed to detect them at the low levels typically found in the environment. Regardless, there currently are a number of uncertainties associated with the determination of risks associated with pharmaceuticals released into various environments—especially because of the inadequacy (or even lack) of knowledge concerning their fate in waste streams, and the variant environments in which they are typically found; their uptake, metabolism and excretion (*viz*., pharmacokinetics) upon entry into ecosystems; and their target affinity and functional effects (*viz*., pharmacodynamics) in non-target species or organisms (Arnold et al. 2014). Still, if pharmaceuticals in the environment are investigated and evaluated in a reasonably holistic fashion, then there is a better chance of properly accounting for their potential effects—even if not in a fully quantitative manner.

1.1.1 The Wide-Ranging Scope of Chemical Hazard Problems: A General Overview

A general review of various chemical materials and their usage in social contexts reveals that hazards from several of the commonly encountered 'social chemicals' could be problematic with respect to their potential human health impacts; this is illuminated by a limited number of the select examples enumerated below.

- *Arsenic* [*As*]. A poison famous from murder mysteries, arsenic [As] has been used in insecticides (among other uses, such as in alloying agents and wood preservatives)—and these have resulted in extensive environmental contamination problems. Also, there have been a number of medicinal, agricultural, and industrial uses for arsenic compounds; for example, arsenic has been used extensively in medicine (*viz*., Fowler's Solution) for the treatment of leukemia, psoriasis, and asthma, as well as in the formulation of anti-parasitic drugs. It is also noteworthy that arsenic is a naturally-occurring element distributed throughout the environment. Arsenic is indeed a ubiquitous element on earth

with metalloid properties and an overall complex chemistry. As a consequence, arsenic is introduced into waters through the dissolution of natural minerals and ores—and thus concentrations in groundwater in some areas are elevated as a result of releases from local rocks. Still, industrial effluents also contribute arsenic to waters in some areas. Accordingly, drinking water tends to pose the greatest threat to public health from arsenic exposures—with severe health effects having been observed in populations drinking arsenic-rich water over extended periods of time. Exposure at work, as well as mining and industrial emissions may also be significant in some locations. Meanwhile, it worth mentioning here that inorganic arsenic can occur in the environment in several forms; in natural waters—and thus in drinking-water—it is mostly found as trivalent arsenite, As(III) or pentavalent arsenate, As(V). Also notable is the fact that organic arsenic species—which is more common in seafood—are far less harmful to human health, and are also readily eliminated by the body.

Overall, human exposure to arsenic can result in serious health effects; for instance, large doses can cause gastrointestinal disorders—and even small quantities may be carcinogenic. Following long-term exposure, the first changes are usually observed in the skin—namely, pigmentation changes, and then thickening (hyperkeratosis). Cancer tends to be a late phenomenon, and usually estimated to take more than ten years to develop. Also, some studies have reported hypertensive and cardiovascular diseases, diabetes, and reproductive effects. On the other hand, absorption of arsenic through the skin is believed to be minimal—and thus hand-washing, bathing, laundry, etc. with water containing arsenic do not appear to pose significant human health risk. In any case, the relationship between arsenic exposure and other health effects is not quite as clear-cut; for instance, according to a 1999 study by the US National Academy of Sciences (NAS), long-term exposure to arsenic in drinking water causes cancer of the skin, lungs, urinary bladder, and may cause kidney and liver cancer. The NAS study also found that arsenic harms the central and peripheral nervous systems, as well as heart and blood vessels, and causes serious skin problems; it also may cause birth defects and reproductive problems. In particular, other fairly recent studies appear to strengthen the evidence of a link between bladder and lung cancer and exposure to arsenic in drinking water. Indeed, even very low concentrations of arsenic in drinking water are believed to be associated with a higher incidence of cancer. Additionally, some research by the US EPA's Office of Research and Development has shown that arsenic can induce an interaction of arsenic compounds with DNA, causing genetic alterations. The study found that methylated trivalent arsenic derivatives (which can be produced by the body in an attempt to detoxify arsenic) produce reactive compounds that cause DNA to break.

- *Asbestos.* A known human carcinogen, asbestos found a wide range of uses in various consumer products for a considerable period of time. Indeed, processed asbestos had typically been fabricated into a wide variety of materials used in consumer products (such as cigarette filters, wine filters, hair dryers, brake linings, vinyl floor tiles, and cement pipes), and also in a variety of construction

materials (*e.g.*, asbestos-cement pipes, floorings, friction products, roofing, sheeting, coating and papers, packing and gaskets, thermal insulation, electric insulation, etc.). Notwithstanding the apparent useful commercial attributes, asbestos emerged as one of the most complex, alarming, costly, and tragic environmental health problems (Brooks et al. 1995). Among other things, its association with lung cancer has been proven—and notably with synergistic effect observed in relation to cigarette smoke exposures.

It is noteworthy that, there are two general sub-divisions of asbestos: the serpentine group—containing only chrysotile (which consists of bundles of curly fibrils); and the amphibole group—containing several minerals (which tend to be more straight and rigid). Anyhow, because asbestos is neither water-soluble nor volatile, the form of concern with respect to human exposure relates to the microscopic fibers (usually reported as, or measured in the environment in units of fibers per m^3 or fibers per cc). In the end, for asbestos fibers to cause any disease in a potentially exposed population, they must gain access to the potential receptor's body. Since they do not pass through the intact skin, their main entry routes are by inhalation or ingestion of contaminated air or water (Brooks et al. 1995)—with the inhalation pathway apparently being the most critical in typical exposure scenarios. In fact, for asbestos exposures, inhalation is expected to be the only significant exposure pathway worth expending resources to appraise. Consequently, potential human exposure and intake is derived based on estimates of the asbestos concentration in air, the rate of contact with the contaminated air, and the duration of exposure. Subsequently, the intake can be integrated with the toxicity index for asbestos to determine the potential risks associated with any exposures; this then forms a basis for developing appropriate public health risk management actions.

- *Bisphenol-A* (*BPA*). A rather familiar example of a chemical finding widespread use in varieties of consumer products, BPA is a human-made chemical used in linings of metal food cans/containers to prevent the degradation of the metal, as well as in some plastic food packaging and other plastic products (particularly in hard polycarbonate plastics). The critical concern with such applications, though, relates to the fact that the chemical constituent is believed to act as a weak estrogen in the body—purported to impact biological systems even in very low doses. Indeed, BPA is generally shown to be a weak endocrine disruptor that mimics the effects of natural estrogen in the body, which at high doses can lead to adverse developmental and reproductive effects in humans; even so, there seems to be significant controversy surrounding the evaluation of this chemical's effects at low doses—i.e., those levels similar to or lower than typical human exposures in practice.

  Overall, it is notable that BPA has been studied extensively for several decades now; indeed, evaluating potential risks associated with food packaging materials in particular has been a scientific challenge for centuries—perhaps going back to the beginning of modern civilization. Even so, there still does not appear to be clear consensus on its standing with respect to public health implications associated with its use in consumer products.

- *Lead* [*Pb*]. Inorganic lead is one of the topmost anthropogenic pollutants—and is now deemed one of the most ubiquitous toxic substances (Chakraborty et al. 2012; Snape and Townsend 2008; Lobinski and Marczenko 1996); it has been used since antiquity, but its use seems to have increased exponentially during the twentieth century (Levallois et al. 1991; Harrison and Laxen 1981). Most commonly, lead has been used in water supply systems, gasolines, automobile batteries, and paints for a long time in modern human history; this, in turn, has resulted in extensive releases into the environment. The typical sources of environmental lead contamination include industry (such as metal smelters and lead-recycling facilities), paints, and exhaust from motor vehicles that used leaded gasoline. Domestic water supply systems have also been a major source of human exposure to lead. As a result of past and current industrial uses, lead has in fact become a common environmental pollutant globally, and is often more problematic in economically disadvantaged and minority-populated areas or regions globally.

  Overall, various uses of lead—such as in storage batteries and as organic anti-knocking additives (tetraalkyllead) to petrol/fuels, cables, solders, steel products, ammunition, shielding systems from radiation and X-rays, circuit boards in computers and electronics equipment, superconductor and optical technology, insecticides, pigments, paints, ceramics, enamels, glass, plastics and rubber products, coal-fired power plants/stations, wastes from runoff and incineration, as well as other industrial effluents—have contributed significantly for the widespread distribution of lead in the environment (Ritson et al. 1999; Hansmann and Koppel 2000). Meanwhile, it is noteworthy that, although legislations have been implemented in various jurisdictions to enforce the use of alternative petroleum additives and recover lead from used batteries in contemporary times, the uses of lead seem to somehow continue unabated in other areas of application—including, for instance, from some planes flying on leaded aviation fuels, smelting plants, industrial boilers, battery makers, coal-burning power plants, and road surfaces. Further elaboration on this subject matter is presented below in Sect. 1.1.2.

  Known, among others things, to be neurotoxic as well as a cause of anaemia, lead has indeed come to be recognized as a primary public health hazard globally (see, *e.g.*, Needleman and Gatsonis 1990; Pirkle et al. 1985; Schwartz 1994). In part, this is due to the fact that Pb can harm a wide variety of organ systems—including the nervous, cardiovascular, kidney, immune, hematological, reproductive, and developmental systems; indeed, exposure to Pb is also likely to result in cancer effects. Meanwhile, it is noteworthy that lead's biggest risks seem to be towards young children—and particularly to their developing nervous systems; in fact, there seem to be significant evidence of cognitive effects even in populations with relatively low mean blood-Pb levels (of between 2 and 8 μg/dL—thus suggesting there may not quite be any known threshold below which scientists could be confident that there will not be any harmful cognitive effects from Pb exposures.

Nutritionally or physiologically lead is not an essential nutrient for either humans or other organisms; on the contrary, it is toxic, bioaccumulative and persistent. In general, lead toxicity derives from the fact that it is absorbed through respiratory or digestive routes, and then preferentially binds to RBCs for distribution to the body tissues. Common observable human health effects include nausea and irritability at low levels, and brain damage at large doses. Of special significance is the storage of lead in the human bone, where its half-life may be in excess of twenty years. Also, the threat of lead poisoning in children and pregnant women is of particular public health concern; ultimately, lead poisoning can cause a number of adverse human health effects—but this is particularly detrimental to the neurological development of children. Further discussion of the effects of lead is provided below in Sect. 1.1.2.

- *Mercury* [*Hg*]. A nervous system toxin, mercury [Hg], is a significant environmental pollutant in several geographical regions/areas (although far less common than the more ubiquitous lead)—especially because of its use in: measuring instruments (*e.g.*, thermometers and manometers); medicines (as antiseptics); dental practice; lamps; and fungicides. Remarkably, Hg can exist in different forms which control its availability, complex distribution, and toxicity; it can be present in both organic and inorganic forms in the environment.

  The typical major sources of Hg to the human environment generally consist of the release of elemental Hg from manometers used to measure the flow of natural gas through pipelines and distribution systems, electrochemical industries, and certain fungicides (Henke et al. 1993; Stepan et al. 1995). Potential sources of airborne Hg releases include combustion of fossil fuels, chlor-alkali plants, waste incineration, mining and smelting of Hg ores, and industrial processes involving the use of Hg (ATSDR 1999a, b; Porcella 1994). Inorganic Hg may [also] be present in soil due to atmospheric deposition of Hg released from both natural and anthropogenic sources as elemental or inorganic Hg vapor, or as inorganic Hg adsorbed to particulate matter. Mercury is indeed a widely distributed hazardous pollutant and has received enormous attention globally because of its persistence in environments, high toxicity to organisms, reactivity and tendency to form more toxic organic mercury compounds, as well as biomagnifications capability along the food web (Jiang et al. 2006; Craig 1986; Beckvar et al. 1996). Typically, Hg released into the environment will persist for a long time—and during which intervening periods the Hg can change between the organic and inorganic forms. Of special interest, one form of organic Hg—namely, methylmercury—can produce a buildup in certain fish; thus, even very low levels of Hg in the ocean and lakes can contaminate the target fish to the point of being a significant environmental and public health concern.

  Overall, the form of Hg and the manner of human exposure determine the nature and/or type of the consequential health effects. Long-term exposure to either organic or inorganic Hg can permanently damage the brain, kidneys, and developing fetuses. Commonly observable human health effects from exposure to large doses of organic Hg compounds include brain damage, often fatal.

- *Organochlorine Compounds/Persistent Organic Pollutants* [*POPs*]. Most organochlorine compounds—including the chlorinated aromatic hydrocarbons, such as PCBs (that have been widely used in electrical transformers) and DDT (that has been widely used as a powerful pesticide/insecticide)—have proven to be notoriously persistent in the environment. PCBs and DDT are indeed persistent lipophilic chlorinated organic compounds that have been used rather extensively globally—as noted in the additional discussions offered below. Meanwhile, it is also noteworthy here that, in various organisms, DDT is slowly transformed to the even more stable and persistent DDE (dichlorodiphenyl dichloroethylene). In view of the intransigent characteristics, these types of chemicals generally qualify for classification as part of the group often referred to as *persistent organic pollutants* [POPs].

  PCBs are the family of chemicals formed by attaching one or more chlorine atoms to a pair of connected benzene rings; depending on the number and position of chlorine atoms attached to the biphenyl ring structure 209 different PCB congeners can be formed—with the chemical and toxicological properties of the PCBs varying from one congener to the next. Traditionally, PCBs found use in heat exchange and dielectric fluid; as stabilizers in paints, polymers, and adhesives; and as lubricants in various industrial processes. More specifically, in the past, PCBs had been used in the manufacture of electrical transformers and capacitors due to the fact that they generally exhibit low flammability, high heat capacity, and low electrical conductivity—and are indeed virtually free of fire and explosion hazards. PCBs also found several 'open-ended applications' (referred to as such, due to the relative ease with which the PCB may enter the environment during use, in comparison to a 'closed system' for transformer/capacitor use) in products such as plasticizers, surface coatings, ink and dye carriers, adhesives, pesticide extenders, carbonless copy paper, dyes, etc. For instance, they gained widespread use in plasticizers because PCBs are permanently thermoplastic, chemically stable, non-oxidizing, non-corrosive, fire resistant, and are excellent solvents. Also, PCBs have been used in laminating adhesive formulations involving polyurethanes and polycarbonates to prepare safety and acoustical glasses; the PCBs have been used in adhesive formulas to improve toughness and resistance to oxidative and thermal degradation when laminating ceramics and metals. Furthermore, PCBs have been used in paints and varnishes to impart weatherability, luster, and adhesion. Broadly speaking, PCBs have also been used in 'nominally closed systems' (due to the relative ease with which the PCB may enter the environment during use, when compared to a 'closed system' such as for transformer/capacitor use) as hydraulic fluids, heat transfer fluids, and lubricants.

  Meanwhile, it is noteworthy that the primary non-occupational source of PCB exposure is food—especially fish from contaminated waters; indeed, ATSDR has noted that the primary route of exposure to PCBs in the general population appears to involve the consumption of contaminated foods, particularly meat, fish and poultry. Thus, recreational and subsistence fishers who eat large amounts of locally caught fish might be at increased risk for exposure to

PCBs. Small amounts of PCBs can also be found in almost all outdoor and indoor air, soil, sediments, surface water, and animals—albeit people are exposed to PCBs primarily from contaminated foods and breathing contaminated air. In the final analysis, the high lipophilicity and the resistance to biodegradation of most organochlorine compounds allow the bioaccumulation of these chemicals in fatty tissues of organisms and their biomagnification through food chains (Dewailly et al. 1996). Anyhow, as a consequence of humans being located at the top of most food chains, therefore, relatively high levels of these compounds have been found in human adipose tissues, blood lipids, and breast milk fat.

DDT, which belongs to the chlorinated insecticide family, was used extensively from the early 1940s to about the early 1970s for agricultural and public health purposes. It is noteworthy that, although its use has long been banned or curtailed in most industrialized nations, leftover DDT products are suspected to have had continued applications to a degree of concern in some parts of the world even long after the ban, especially in the developing nations.

Overall, POPs have become environmental disaster stories, especially in view of their potential to cause severe health effects. For instance, some PCB congeners and DDT isomers possess an endocrine-disrupting capacity, and are believed to contribute to breast cancer risk and various reproductive and developmental disorders (Colborn et al. 1993; Davis et al. 1993; Dewailly et al. 1994a, b, 1996; Falck et al. 1992; Wolff et al. 1993). Indeed, there are several adverse health effects associated with both PCBs and DDT—as, for example, tests on animals show that PCBs can harm reproduction and growth, as well as can cause skin lesions and tumors. Furthermore, when PCB fluid is partially burned (as may happen in the event of a transformer fire), PCDDs and PCDFs are produced as byproducts—and these byproducts are indeed even much more toxic than the PCBs themselves. For instance, dioxin is associated with a number of health risks, and has been shown to cause cancer of the liver, mouth, adrenal gland, and lungs in laboratory animals; furthermore, tests on rats have shown that furans can cause anemia and other blood problems.

By and large, most of the POPs often encountered tend to persist in the environment, as the 'group name' suggests—generally concentrating upward in the food-chain; for instance, most PCB congeners have half-lives ranging from months to several years. Indeed, persistent chemicals have continued to present ongoing challenges to global environmental communities. Consequently, in May 2004, the 'Stockholm Convention' was put in place—in an attempt to stem the tide, so to speak; this international treaty codified a worldwide effort to eliminate POPs—focusing first on twelve of the most prominent chemicals (including DDT, dioxins, PCBs, and certain pesticides). What is more, there is the growing realization that at least certain POPs constitute a global problem that need to be addressed on a global scale. In fact, by virtue of their physiochemical properties, many of the POPs are subject to global environmental transport and distribution—with some passing through food chains (that ultimately may accumulate in some species that serve as food sources for

humans). Consequently, the persistence trait can lead not only to enduring local contamination problems, but also to 'cross-boundary' distribution of such POPs. For such reasons, therefore, efforts to control the most persistent and especially more easily 'spreadable' chemicals need to be based on international cooperation. The Stockholm Convention and a number of additional treaties, as well as related programs from international organizations such as the United Nations Environmental Programme (UNEP) , attempt to appropriately tackle these issues.

As a final point, it is noteworthy that the global environmental transport of persistent chemicals makes identification of individual sources of any given exposure a daunting task. Indeed, it is often the case that persistent chemicals will have numerous, widespread sources. In addition, atmospheric transport tends to be significantly important for those situations tied into combustion sources—especially because this means the persistent chemicals can be transported greater distances. Consequently, at any given location, the persistent chemicals of interest are likely derived from many sources—some near, some far, and many in between. Indeed, given this complexity, successfully sorting out the different sources of persistent chemicals at a given location is extremely difficult. On the whole, given the numerous widely dispersed sources and the complexities added by long distance ambient transport and subsequent deposition, it is often difficult to identify specific sources of persistent chemicals in the environment. Also worth mentioning here is the fact that, because persistent chemicals have such long biological half-lives, the body burden typically builds up gradually, and incremental inputs from specific sources are not always discernible.

- *Phthalates*. These represent a class of human-made industrial chemicals often employed to increase the flexibility, transparency, durability, and longevity of plastics; they are generally used in soft, flexible plastics, polyvinyl chloride (PVC) products, and in a variety of personal care products (*e.g.*, shampoos, lotions, etc.).

  As a notable feature, since phthalates are not chemically bound to their substrates, they are easily released into the environment, potentially resulting in widespread human exposures; indeed, a number of studies have shown that most people have metabolites of phthalates in the urine—among other things. Ostensibly, phthalate metabolites are consistently detected in urine of pregnant women worldwide—i.e., despite the fact that they are metabolized and excreted quickly, perhaps because of their high volume use in a variety of products (Ferguson et al. 2014a, b). This is of significant concern because, among other things, recent studies seem to suggest that pregnant women exposed to phthalates found in plastics and personal care products is associated with increased levels of biomarkers of oxidative stress (which damages the body's proteins, lipids, and DNA). Also, it is noteworthy that there have been concerns of the anti-androgenic effects from phthalate exposures; in fact, these chemicals are anti-androgenic and can adversely impact androgen-sensitive tissues during specific windows of mammalian development.

On the whole, infants and children are particularly susceptible to phthalate exposures through personal care products and mouthing of toys, etc.; what is more, they exhibit a greater adverse effect upon exposure because of their increased dosage per unit body surface area, metabolic capabilities, and developing endocrine and reproductive systems (Sathyanarayana et al. 2008). For such reasons, the European Union has restricted the use of some phthalates in children's toys since the late 1990s [*viz*., 1999]—and the United States took some legislative measure, by enacting restrictive laws in 2008, to curb the use of various phthalates in all children's toys and some childcare products; other global institutions and agencies have also considered some form of protective measures in this regard.

The above enumeration—illuminating the 'two-edged sword' nature of a variety of 'social chemicals'—could be continued for several different families of both naturally occurring and synthetic groups of chemicals or their derivatives. Indeed, continuing research keep revealing new outcomes and concerns for a wide range of chemicals encountered on a regular basis in modern societies; for instance, both phthalates and bisphenol-A are believed to be endocrine disruptors (*i.e*., chemicals that may interfere with the production/activity of hormones leading to adverse health effects). On the whole, all of the above types of situations represent very important public health risk management problems that call for proper resolutions on what toxic insults are tolerable, and also on what levels of exposure may indeed pose significant danger—*i.e*., 'which/what dose makes the poison?' At any rate, it seems indisputable that human exposure to chemicals and the likely consequential health problems are generally a logical derivative of human activities and/or lifestyles. Even so, much of modern society is probably not about to abandon the hazard-causing activities and materials—albeit most chemical products are often used in a more regulated manner in this day and age.

1.1.2 The Wide-Ranging Scope of Chemical Hazard Problems: Lead Exposures as an Example

Lead is a naturally occurring element that humans have used for a variety of purposes since about the beginning of modern civilization—and various human activities have resulted in the extensive spread of lead throughout the environment. Consequently, lead can now be found in the human physiological system of just about every individual—to the extent that several people have lead levels that are within an order of magnitude of levels associated with adverse health effects (Budd et al. 1998; Flegal and Smith 1992, 1995). Indeed, lead exposure is an international/global issue—since no contemporary society seems to be completely immune to the presence of lead in their environments. Also, both children and adults are susceptible to health effects from lead exposure—albeit the typical exposure pathways and effects are usually somewhat different for the different age groups.

Lead exposure in the general population (including children) occurs primarily through ingestion, although inhalation also contributes to lead body burden and may actually be the major contributor for workers in lead-related occupations. On the whole, most human exposure to lead occurs through ingestion or inhalation—and the general public is less likely to encounter lead that readily enters the human body through the skin (i.e., via dermal exposure). That said, it is also noteworthy almost all inhaled lead is absorbed into the body, whereas between 20% and 70% of ingested lead is absorbed—with children generally absorbing a higher percentage than adults (ATSDR 1999a, b). Anyhow, once absorbed into the body, lead may be stored for long periods in mineralizing tissue (*viz*., teeth and bones)—and then released again into the bloodstream, especially in times of calcium stress (e.g., during pregnancy, lactation, osteoporosis), or calcium deficiency; this would constitute an 'endogenous' exposure. Even more worrisome, lead poses a substantial threat to pregnant women and their developing fetuses—because blood lead readily crosses the placenta, putting the developing fetus at risk (especially with respect to the neurologic development of the fetus, since there is no blood-brain barrier at this stage). In general, the mother's blood Pb level serves as an important indicator of risk to the fetus.

To demonstrate the wide-ranging nature of the major historical 'exogenous' sources and associated pathways of lead exposure, a summary discussion (excerpted mostly from the US Agency for Toxic Substances and Diseases Registry literature) is offered below—with further details provided elsewhere (e.g., ATSDR 1999a, b). Overall, occupational lead exposures may occur in the following workers: lead mining, refining, smelting, and manufacturing industry employees; plumbers and pipe fitters; auto mechanics/repairers; glass manufacturers; shipbuilders; printers; plastic manufacturers; law-enforcement officers and military personnel; steel welders or cutters; construction workers; rubber product manufacturers; fuel station attendants; battery manufacturers and recyclers; bridge reconstruction workers; firing range instructors. Environmental lead exposures to the general population (including both children and adults) may occur via lead-containing paint (especially from past uses); leaded gasoline (that used to be a common choice in the past); soil/dust near lead industries, roadways, lead-painted homes; plumbing leachate (from pipes or solder); and ceramic ware. Hobbies and related activities are additional sources of lead exposure—and this may include glazed-pottery making; target shooting at firing ranges; lead soldering (e.g., electronics); painting; preparing lead shot or fishing sinkers; stained-glass making; car or boat repair; and home remodeling. Other potential sources of lead exposure may occur from use of certain folk remedies; cosmetics; and tobacco smoking. Further elaboration on some of the major sources is provided below.

- *Lead-Based Paints*. Lead-based paint (LBP) is a primary source of environmental exposure to lead in several places. For example, according to the US Centers for Disease Control and Prevention (CDC), between 83% and 86% of all homes built before 1978 in the United States have LBP in them—and the older the house, the more likely it is to contain LBP and to have a higher concentration of

lead in the paint. It is not surprising, therefore, that in 1993 the America Academy of Pediatrics identified LBP as the major source of lead exposure for children.

In general, as LBP deteriorates, peels off, chips away, is removed (e.g., during renovation activities), or pulverizes because of friction (e.g., in window sills), house dust and surrounding soil may become contaminated with lead (ATSDR 1999a, b). Subsequently, the lead released into the human environment can then enter the human body through normal hand-to-mouth activities and inhalation. Children are particularly at increased risk from the ingestion of paint chips—and children with pica behavior are at an even greater risk.

- *Automobile Emissions*. Prior to lead being phased out and then banned (in most places around the world) as a gasoline additive, automobile emissions were a major source of exposure to lead. Much of the lead released into the air (especially from automobiles in the past) and in recent times from industrial discharges is deposited onto the land or surface water. Anyhow, although some industries continue to discharge lead into the air, lead inhalation is no longer the major exposure pathway of significant concern for most developed economies; however, the same cannot be said about most of the developing economies—where lead inhalation exposures remain a significant public health concern. Also, it is suspected that leaded fuels may still be in use in some other countries—with the resulting emissions posing a major public health threat.

  In general, much of the lead discharged into the air is ultimately brought back to the ground surface or surface waters through wet or dry deposition (ATSDR 1999a, b). Past and present atmospheric emissions have, therefore, contributed to the extensive amounts of lead in soils globally—and areas of high traffic flow or near industrial release sources are likely to have greater concentrations of lead in soils and dust than the more remote areas.
- *Occupational Worker Exposures*. Workers (and indirectly, their families) in up to a hundred or more types of industries may experience occupational exposures to lead. In particular, workers in the lead mining, smelting, refining, and manufacturing industries typically experience the highest and most prolonged occupational exposures to lead. Others at increased risk from lead exposures include workers in brass/bronze foundries, rubber products and plastics industries, soldering, steel welding/cutting operations, battery manufacturing plants, and other manufacturing industries (ATSDR 1999a, b). Increased risk for occupational lead exposures also occur among construction workers, bridge maintenance and repair workers, municipal waste incinerator workers, pottery/ceramics industry employees, radiator/auto repair mechanics, and people working with lead solder. Furthermore, many so-called ‘cottage industries’ are actually located in the home or in residential areas—in which case both the workers and families in the homes (or even the neighborhoods) are potentially at risk from direct exposures.

  Overall, the major exposure pathways for industrial workers are inhalation and ingestion of lead-laden dust and fumes. Meanwhile, it should be mentioned here that occupational exposures can also produce secondary exposures in a

worker's family if, for instance, a worker brings home lead-contaminated dust on the skin, clothes, or shoes. Of course, workers can prevent such secondary exposures by showering and/or changing clothing before returning to their homes.

- *Consumer Products*. Drinking water, food, and alcohol can become significant sources of environmental exposure to lead. For instance, lead may occur in drinking water through leaching from lead-containing pipes, faucets, and solder found in plumbing of older buildings; leaching rates accelerate when water is acidic or hot, or when it has been standing in the pipes for extended periods (e.g., overnight). Indeed, faucet fixtures have been shown by a number of researchers to be a significant source of lead exposure (see, e.g., Samuels and Meranger 1984; Schock and Neff 1988; Gardels and Sorg 1989; Lee et al. 1989; Maas and Patch 1990; Patch et al. 1998). For instance, in their study conducted for some US residential water supply systems, it is notable that Patch et al. (1998) determined that: lead concentrations caused by faucets are significantly greater than lead concentrations that occur in the plumbing line just behind the faucets; bathroom faucets leach more lead than kitchen faucets; lead concentrations increase with standing times (for the water); newer faucets leach more lead than older faucets; and faucets manufactured primarily with sand-casting methods yield significantly higher lead concentrations than those manufactured with other methods.

  Lead may also contaminate food during production, processing, and packaging. Production sources may include soil lead uptake by root vegetables or atmospheric lead deposition onto leafy vegetables; processing and packaging sources of lead in consumer diets may include lead-soldered food cans, and some plastic food wrappers printed with lead-containing pigments. Other sources of food contamination include certain ceramic tableware, lead-glazed pottery, leaded-crystal glassware, certain so-called 'natural' calcium supplements, and bright red and yellow paints on bread bags. Yet additional sources of lead exposure have included wine and homemade alcohol that is distilled and/or stored in leaded containers (ATSDR 1999a, b).

  Even more, people using paints, pigments, facial cosmetics, or hair coloring with lead or lead acetate also increase their risk from lead exposures. For instance, certain lead-containing cosmetics (e.g., 'surma' and 'kohl') have been quite popular in some Asian countries. Also, certain folk remedies may result in significant lead exposures—as, for instance, the ingestion of certain home remedy medicines may expose people to lead or lead compounds. General examples of these types of consumer products include certain Mexican folk remedies; lead-containing remedies used by some Asian communities; and certain Middle Eastern remedies and cosmetics. Lastly, smoking cigarettes or even the breathing of second-hand smoke may potentially increase a person's exposure to lead—because tobacco smoke typically contains small amounts of lead (ATSDR 1999a, b).
- *Recreational and Related Activities*. Certain hobbies, home activities, and car repairs (e.g., radiator repair) can contribute to a person's lead exposures. Some

of the more common hobbies include glazed-pottery making; artistic painting; stained-glass making; glass or metal soldering; target shooting; electronics soldering; construction of bullets, slugs, or fishing sinkers; and house renovation involving scraping, remodeling, or otherwise disturbing lead-based paint (ATSDR 1999a, b).

- *Proximity to Active Release Sources*. People living near hazardous waste sites, lead smelters/refineries, battery recycling/crushing centers, or other industrial lead sources may be more easily exposed to lead and other lead-containing chemicals. For instance, industrial and mining activities may result in the release of lead and lead compounds into the air and soil; the releases will invariably be within the exposure setting of the neighboring communities. Local community residents may then be exposed to emissions from these sources through ingestion and/or inhalation of lead-contaminated dust or soils. The typical sources may range in size from large mines and hazardous waste sites to small garages working with old car batteries. Indeed, even abandoned industrial lead sites (such as old mines or lead smelters) may continue to pose significant potential public health hazards.

Anyhow, once it enters the human body, the absorption and biologic fate of lead depends on a variety of factors. An especially important determinant is the physiologic characteristics of the exposed person—including nutritional status, health, and age. Children and pregnant women, for example, can absorb up to 70% of ingested lead, whereas an average general adult typically absorbs up to 20%; most inhaled lead in the lower respiratory tract is absorbed (ATSDR 1999a, b). The chemical form of lead, or lead compounds, entering the body is also an important factor; for instance, organic lead compounds (far rarer since the discontinuation of most leaded gasoline additives) are metabolized in the liver, whereas inorganic lead (the most common form of lead) does not undergo such transformation.

In the end, most of the lead that is absorbed into the body is excreted either by the kidney (in urine) or through biliary clearance (ultimately, in the feces). The percentage of lead excreted and the timing of excretion depend on a number of factors—with a number of studies indicating that adults excrete the majority of an absorbed fraction of lead. Ultimately, adults may retain only 1% of absorbed lead, but children tend to retain much more than adults; in infants from birth to 2 years, approximately one-third of the total amount of lead tends to be retained (ATSDR 1999a, b). Once in the bloodstream, the absorbed lead that has not excreted is exchanged/distributed primarily among three compartments—namely, blood; soft tissue (liver, kidneys, lungs, brain, spleen, muscles, and heart); and mineralizing tissues (bones and teeth), which typically contain the vast majority of the lead body burden. Indeed, the bones and teeth of adults contain more than 95% of the total lead in the body (ATSDR 1999a, b). In times of stress, the body can mobilize stored lead, thereby increasing the level of lead in the blood. Although the blood generally carries only a small fraction of the total lead body burden, it serves as the initial receptacle of absorbed lead and distributes lead throughout the body, making it available to other tissues (or for excretion). In general, the body tends to accumulate

lead over a lifetime and normally releases it very slowly; thus, both past and current elevated exposures to lead increase a person's risks for lead effects. In any event, to facilitate public health risk management decisions on lead exposure problems, blood lead level measurements become important because it is about the most widely used measure of lead exposure.

1.2 Public Health and Socio-Economic Implications of Chemical Exposure Problems

It is apparent that the mere presence of a chemical exposure source within a community or a human population habitat zone can invariably lead to potential receptor exposures—possibly resulting in both short- and long-term effects on a diversity of populations within the 'zone of influence.' By and large, any consequential chemical intake can cause severe health impairments or even death, if taken in sufficiently large amounts. Also, there are those chemicals of primary concern that can cause adverse impacts even from limited exposures. Still, human populations are continuously in contact with varying amounts of chemicals present in air, water, soil, food, and other consumer products—among several other possible sources. Such human exposures to chemical constituents can indeed produce several adverse health effects in the target receptors, as well as potentially impart significant socioeconomic woes to affected communities. For instance, historical records (see, *e.g.*, Table 1.2) have clearly demonstrated the dangers that may result from the presence of chemical exposure situations within or near residential communities and human work environments or habitats (Alloway and Ayres 1993; Ashford and Miller 1998; BMA 1991; Brooks et al. 1995; Canter et al. 1988; Gibbs 1982; Grisham 1986; Hathaway et al. 1991; Kletz 1994; Levine 1982; Long and Schweitzer 1982; Meyer et al. 1995; Petts et al. 1997; Rousselle et al. 2014; Williams et al. 2008). In fact, these types of cases/situations vis-à-vis the growing global awareness to the potential harms from exposures to the numerous and cocktails of chemicals within modern human environments in part prompted the 'World Summit on Sustainable Development' (held in Johannesburg in 2002) into making a global political commitment to effect sound chemicals management by 2020—albeit this seemingly noble effort may elude some economically-struggling countries or regions of the world. In any event, further international efforts aimed at realizing this goal of 'sound chemicals management' subsequently resulted in the adoption of the 'Strategic Approach to International Chemicals Management' platform by the United Nations Environment Programme's Governing Council in February 2006, at Dubai. In the end, all attempts to 'strike a balance' for such efforts may have to employ various risk assessment tools directed at providing a high level of protection to human health and the environment.

Table 1.2 Selected typical examples of potential human exposures to hazardous chemicals/materials

Chemical hazard location	Source/nature of problem	Contaminants of concern	Nature of exposure settings and scenarios, and observed effects
Love Canal, Niagara Falls, New York, USA	Section of an abandoned excavation for a canal was used as industrial waste landfill	Various carcinogenic and volatile organic chemicals—including hydrocarbon residues from pesticide manufacture	Section of an abandoned excavation for a canal that lies within suburban residential setting had been used as industrial waste landfill. Problem first uncovered in 1976
			Industrial waste dumping occurred from the 1940s through the 1950s; this subsequently caused entire blocks of houses to be rendered uninhabitable
			Potential human exposure routes included direct contact and also various water pathways
	Site received over 20,000 tonnes of chemical wastes containing more than 80 different chemicals		Several apparent health impairments—including birth defects and chromosomal abnormalities—observed in residents living in vicinity of the contaminated site
Chemical Control, Elizabeth, New Jersey, USA	Fire damage to drums of chemicals—resulting in leakage and chemical releases	Various hazardous wastes from local industries	The Chemical Control site was adjacent to an urban receptor community; site located at the confluence of two rivers
			Leaked chemicals from fire-damaged drums contaminated water (used for fire-fighting)—that subsequently entered adjacent rivers
			Plume of smoke from fire deposited ash on homes, cars, and playgrounds
			Potential exposures mostly via inhalation of

(continued)

Table 1.2 (continued)

Chemical hazard location	Source/nature of problem	Contaminants of concern	Nature of exposure settings and scenarios, and observed effects
			airborne contaminants in the plume of smoke from the fire that blew over surrounding communities
Bloomington, Indiana, USA	Industrial wastes entering municipal sewage system	PCBs	PCB-contaminated sewage sludge used as fertilizer—resulting in crop uptakes
	Sewage material was used for garden manure/fertilizer		Also discharges and runoff into rivers resulted in potential fish contamination
			Direct human contacts and also exposures via the food chain (as a result of human ingestion of contaminated food)
Times Beach, Missouri, USA	Dioxins (tetrachlorinated dibenzo(*p*)dioxin, TCDD) in waste oils sprayed on public access areas for dust control	Dioxins (TCDD)	Waste oils contaminated with dioxins (TCDD) were sprayed in several public areas (residential, recreational, and work areas) for dust control of dirt roads, etc. in the late 1960s and early 1970s
			Problem was deemed to present extreme danger in 1982—i.e., from direct contacts, inhalation, and probable ingestion of contaminated dust and soils
Triana, Alabama, USA	Industrial wastes dumped in local stream by a pesticide plant	DDT and other compounds	High DDT metabolite residues detected in fish consumed by community residents
			Potential for human exposure via food chain—i.e., resulting from consumption of fish

(continued)

Table 1.2 (continued)

Chemical hazard location	Source/nature of problem	Contaminants of concern	Nature of exposure settings and scenarios, and observed effects
Woburn, Massachusetts, USA	Abandoned waste lagoon with several dumps	Arsenic compounds, various heavy metals, and organic compounds	Problem came to light in 1979 when construction workers discovered more than 180 large barrels of waste materials in an abandoned lot alongside a local river
			Potential for leachate to contaminate groundwater resources, and also for surface runoff to carry contamination to surface water bodies
			High levels of carcinogens found in several local wells—which were then ordered closed
			Potential human receptors and ecosystem exposure via direct contacts and water pathways indicated
			Inordinately high degree of childhood leukemia observed. This apparent excess of childhood leukemia was linked to contaminated well water in the area. In general, leukemia and kidney cancers in the area were found to be higher than normal
Santa Clarita, California, USA	Runoff from an electronics manufacturing industry resulted in contamination of drinking water	Trichloroethylene (TCE) and various other volatile organic compounds (VOCs)	TCE and other VOCs contaminated drinking water in this community (due to runoff from industrial facility)
			Excess of adverse reproductive outcomes, and excess of major cardiac anomalies among infants suspected

(continued)

Table 1.2 (continued)

Chemical hazard location	Source/nature of problem	Contaminants of concern	Nature of exposure settings and scenarios, and observed effects
Three Mile Island, Pennsylvania, USA	Overheating of nuclear power station in March 1979	Radioactive materials	Small amount of radioactive materials escaped into atmosphere
			Emission of radioactive gases—and potential for radioactivity exposures
			Unlikely that anyone was harmed by radioactivity from incident. Apparently, the discharge of radioactive materials was too small to cause any measurable harm
European Union Member States, EU	Furniture treated with dimethylfumarate (DMFu)—together with possible (persisting) cross-contamination from the primary sources	Dimethylfumarate (DMFu)	Furniture identified as possible cause/source of numerous cases of dermatitis [induced by dimethylfumarate (DMFu)] in several European Union Member States. Apparently, DMFu had been used to prevent mold development in various items—including furniture; these DMFu-contaminated items in dwellings ostensibly posed substantial threats to the health of the occupants
	Numerous patients in Europe were reported to suffer from DMFu-induced dermatitis		Thousands of patients were diagnosed with severe dermatitis, with a few cases even requiring hospitalization; studies concluded that the likely cause of this furniture dermatitis epidemic was contact allergy due to DMFu
	Dermatological symptoms attributed to contact with DMFu-treated consumer products—mostly shoes and sofas/furniture		DMFu had typically been used as a biocide for preventing mold

(continued)

Table 1.2 (continued)

Chemical hazard location	Source/nature of problem	Contaminants of concern	Nature of exposure settings and scenarios, and observed effects
			development that can deteriorate furniture or shoes during storage or transport—thus serving as an anti-mold agent for various polyurethane, polyvinyl chloride, leather and similar products
Flixborough, England, UK	Explosion in nylon manufacturing factory in June 1974	Mostly hydrocarbons	Hydrocarbons processed in reaction vessels/reactors (consisting of oxidation units, etc.). Destruction of plant in explosion, causing death of 28 men on site and extensive damage and injuries in surrounding villages
			Explosive situation—i.e., vapor cloud explosion
Chernobyl, Ukraine (then part of the former USSR)	Overheating of a water-cooled nuclear reactor in April 1986	Radioactive materials	Nuclear reactor blew out and burned, spewing radioactive debris over much of Europe
			General concern relates to exposure to radioactivity
			About 30 people reported killed immediately, or died within a few months that may be linked to the accident. It has further been estimated that several thousands more may/could die from cancer during the next 40 years or so as a result of incident

(continued)

Table 1.2 (continued)

Chemical hazard location	Source/nature of problem	Contaminants of concern	Nature of exposure settings and scenarios, and observed effects
Seveso (near Milan), Italy	Discharge containing dioxin contaminated a neighboring village over a period of approximately 20 min in July 1976	Dioxin and caustic soda	Large areas of land contaminated—with part of it being declared uninhabitable
			Mostly dermal contact exposures (resulting from vapor-phase/gas-phase deposition on the skin)—especially from smoke particles containing dioxin falling onto skins, etc. About 250 people developed the skin disease, chloracne, and about 450 were burned by caustic soda
Lekkerkirk (near Rotterdam), The Netherlands	Residential development built on land atop layer of household demolition waste and covered with relatively thin layer of sand. Housing project spanned 1972–1975	Various chemicals—comprised mainly of paint solvents and resins (containing toluene, lower boiling point solvents, antimony, cadmium, lead, mercury, and zinc)	Rising groundwater carried pollutants upward from underlying wastes into the foundations of houses. This caused deterioration of plastic drinking water pipes, contamination of the water, noxious odors inside the houses, and toxicity symptoms in garden crops
	Problem of severe soil contamination was discovered in 1978. Evacuation of residents commenced in the summer of 1980		Several houses had to be abandoned, while the waste materials were removed and transported by barges to Rotterdam for destruction by incineration. Polluted water was treated in a physico-chemical purification plant

(continued)

Table 1.2 (continued)

Chemical hazard location	Source/nature of problem	Contaminants of concern	Nature of exposure settings and scenarios, and observed effects
Union Carbide Plant, Bhopal, India	Leak of methyl isocyanate from storage tank in December 1984	Methyl isocyanate (MIC)	Leak of over 25 tonnes of MIC from storage tank occurred at Bhopal, India
			In general, exposure to high concentrations of MIC can cause blindness, damage to lungs, emphysema, and ultimately death
			MIC vapor discharged into the atmosphere—and then spread beyond plant boundary, killing well over 2000 people and injuring several tens of thousands more
Kamioka Zinc Mine, Japan	Contaminated surface waters	Cadmium	Water containing large amounts of cadmium discharged from the Kamioka Zinc Mine into river used for drinking water, and also for irrigating paddy rice
			Ingestion of contaminated water and consumption of rice contaminated by crop uptake of contaminated irrigation water
			Long-term exposures resulted in kidney problems for population
Minamata Bay and Agano River at Niigata, Japan	Effluents from wastewater treatment plants entering coastal waters near a plastics-manufacturing factory	Mercury—giving rise to the presence of the highly toxic methylmercury	Accumulation of methylmercury in fish and shellfish
			Human consumption of contaminated seafood—resulting in health impairments, particularly severe neurological symptoms

Overall, it is unarguable that modern societies are very much dependent on chemicals, and the chemicals industry is undeniably an important sector of the global economy and general lifestyles; in fact, from food production to numerous consumer care products (for health, personal care and household goods), most of the contemporary global populace are more likely than not to come into contact with chemicals on a daily/regular basis. On the other hand, there seem to be an ever-increasing number of health impacts known or suspected to be attributable to these same chemicals much of the world has become so dependent on. But ultimately, 'uncontrolled' human exposures to chemicals can result in a reduction of life-expectancy—and possibly a period of reduced quality of life (*e.g.*, as caused by anxiety from exposures, diseases, etc.). The presence of toxic chemicals can therefore create potentially hazardous situations and pose significant risks of concern to society at large. In general, however, potential health and socio-economic tribulations are averted by carefully implementing substantive corrective action and/or risk management programs appropriate for the specific chemical exposure problem on hand; indeed, a variety of methods for identifying and linking all the multiple chemical sources to the human receptor exposures (as discussed throughout this book) are often used to facilitate the development of a sound public health risk management program in this regard.

1.2.1 The General Nature of Human Health Effects From Chemical Exposures

Several health effects may arise if/when people are exposed to certain chemicals introduced into the human environments. In fact, depending on their use, most chemicals may have significantly harmful and wide-ranging impacts on human health and the environment; for instance, evidence seems to be mounting about the believe that some chemicals found in everyday consumer products (*e.g.*, some plastic bottles and containers; liners of metal food cans; detergents; flame retardants; food; toys; cosmetics; pesticides; etc.) may disrupt the endocrine system and affect the development of children and sensitive ecological species. [*Endocrine disruptors* are naturally-occurring compounds or human-made substances that may mimic or interfere with the function of hormones in the human body; they may turn on, shut off, or modify signals that hormones carry, which may then affect the normal functions of tissues and organs. (By the way, these chemicals have also been referred to as 'endocrine modulators'; 'environmental hormones'; and 'endocrine-active compounds'.) Endocrine disrupting chemicals may indeed interfere with the body's own hormone signals because of their structure and activity. Thus, when absorbed in the body, an endocrine disruptor can decrease or increase normal hormone levels; mimic the body's natural hormones; or alter the natural production of hormones. Many of these substances have been linked with developmental, reproductive, neural, immune, and other problems in wildlife and laboratory

animals; some research suggests that these substances are also adversely affecting human health in similar ways, resulting in reduced fertility and increased incidences or progression of some diseases. Meanwhile, it should be recognized here that the *endocrine system* is one of the body's main communication networks—generally responsible for controlling numerous body functions.] Among other concerns, therefore, endocrine disruption is a very important public health concern—recognizing that the endocrine system keeps our bodies in balance, maintaining homeostasis and guiding proper growth and development. In real life, people may generally be exposed to endocrine disruptors through the foods and beverages consumed, medicines taken, pesticide applications, and cosmetic usage; thus, exposures may be through the diet, skin, water, and air. What is more, it is noteworthy that some environmental endocrine disrupting chemicals (such as DDT, dioxins, and polychlorinated biphenyls [PCBs] used in electrical equipment) are highly persistent and slow to degrade in the environment—making such chemicals potentially hazardous over a rather extended period of time.

On the whole, the following represent the major broad categories of human health effects that could be anticipated from exposure to chemicals typically found in contemporary societies (Andelman and Underhill 1988; Asante-Duah 1998; Ashford and Miller 1998; Bertollini et al. 1996; Brooks et al. 1995; Grisham 1986; Hathaway et al. 1991; Lippmann 1992):

- Carcinogenicity (i.e., capable of causing cancer in humans and/or laboratory animals)
- Heritable genetic and chromosomal mutation (i.e., capable of causing mutations in genes and chromosomes that will be passed on to the next generation)
- Developmental toxicity and teratogenesis (i.e., capable of causing birth defects or miscarriages, or damage to developing foetus)
- Reproductive toxicity (i.e., capable of damaging the ability to reproduce)
- Neurotoxicity (i.e., capable of causing harm to the nervous system)
- Alterations of immunobiological homeostasis
- Congenital abnormalities.

Furthermore, most of the archetypical chemicals of concern will usually possess either of the following toxicity attributes:

- Acute toxicity (i.e., capable of causing adverse effects, and possibly death, from even short-term exposures)
- Chronic toxicity (i.e., capable of causing long-term damage, other than cancer).

In the final analysis, several different symptoms and human health effects may be produced from exposure to various potentially toxic chemicals commonly found in consumer products and/or encountered in the human environments. Table 1.3 lists some typical symptoms, health effects, and other biological responses that could be produced from a wide range of toxic chemicals commonly encountered in the human environment. Indeed, a number of 'social chemicals' are known or suspected to cause cancer; several others may not have carcinogenic properties—but are, nonetheless, of significant concern due to their systemic toxicity effects.

Table 1.3 Some typical health effects resulting from chemical exposures: a listing for selected toxic chemicals in the human environments.

Chemical	Typical health effects/symptoms and toxic manifestations/ responses
Arsenic and compounds	Acute hepatocellular injury, anemia, angiosarcoma, cirrhosis, developmental disabilities, embryotoxicity, heart disease, hyperpigmentation, peripheral neuropathies
Antimony	Heart disease
Asbestos	Asbestosis (scarring of lung tissue)/fibrosis (lung and respiratory tract)/lung cancer, mesothelioma, emphysema, irritations, pneumonia/pneumoconioses
Benzene	Aplastic anemia, CNS depression, embryotoxicity, leukemia and lymphoma, skin irritant
Beryllium	Granuloma (lungs and respiratory tract)
Cadmium	Developmental disabilities, kidney damage, neoplasia (lung and respiratory tract), neonatal death/fetal death, pulmonary edema
Carbon tetrachloride	Narcosis, hepatitis, renal damage, liver tumors
Chromium and compounds	Asthma, cholestasis (of liver), neoplasia (lung and respiratory tract), skin irritant
Copper	Gastrointestinal irritant, liver damage
Cyanide	Asthma, asphyxiation, hypersensitivity, pneumonitis, skin irritant
Dichlorodiphenyl trichloroethane (DDT)	Ataxic gait, convulsions, human infertility/reproductive effects, kidney damage, neurotoxicity, peripheral neuropathies, tremors
Dieldrin	Convulsions, kidney damage, tremors
Dimethylfumarate (DMFu)	Dermatological symptoms/effects (contact dermatitis)—*viz*., skin irritation and skin sensitization, cutaneous allergic reactions; possible respiratory allergic symptoms or diseases
Dioxins and furans (PCDDs/PCDFs)	Hepatitis, neoplasia, spontaneous abortion/fetal death; bioaccumulative
Formaldehyde	Allergic reactions; gastrointestinal upsets; tissue irritation
Lead and compounds	Anemia, bone marrow suppression, CNS symptoms, convulsions, embryotoxicity, neoplasia, neuropathies, kidney damage, seizures; biomagnifies in food chain
Lindane	Convulsions, coma and death, disorientation, headache, nausea and vomiting, neurotoxicity, paresthesias
Lithium	Gastroenteritis, hyperpyrexia, nephrogenic diabetes, Parkinson's disease
Manganese	Bronchitis, cirrhosis (liver), influenza (metal-fume fever), pneumonia, neurotoxicity
Mercury and compounds	Ataxic gait, contact allergen, CNS symptoms; developmental disabilities, neurasthenia, kidney and liver damage, Minamata disease; biomagnification of methyl mercury
Methylene chloride	Anesthesia, respiratory distress, death
Naphthalene	Anemia
Nickel and compounds	Asthma, CNS effects, gastrointestinal effects, headache, neoplasia (lung and respiratory tract)
Nitrate	Methemoglobinemia (in infants)

(continued)

Table 1.3 (continued)

Chemical	Typical health effects/symptoms and toxic manifestations/ responses
Organo-chlorine pesticides	Hepatic necrosis, hypertrophy of endoplasmic reticulum, mild fatty metamorphosis
Pentachlorophenol (PCP)	Malignant hyperthermia
Phenol	Asthma, skin irritant
Polychlorinated biphenyls (PCBs)	Embryotoxicity/infertility/fetal death, dermatoses/chloracne, hepatic necrosis, hepatitis, immune suppression, endocrine effects, neurologic effects, cardiovascular effects, musculoskeletal issues, gastrointestinal systems effects
Silver	Blindness, skin lesions, pneumonoconiosis
Toluene	Acute renal failure, ataxic gait, neurotoxicity/CNS depression, memory impairment
Trichloroethylene (TCE)	CNS depression, deafness, liver damage, paralysis, respiratory and cardiac arrest, visual effects
Vinyl chloride	Leukemia and lymphoma, neoplasia, spontaneous abortion/fetal death, tumors, death
Xylene	CNS depression, memory impairment
Zinc	Corneal ulceration, esophagus damage, pulmonary edema

Source: Compiled from various sources—including, Blumenthal (1985), Chouaniere et al. (2002), Grisham (1986), Hughes (1996), Lave and Upton (1987), Rousselle et al. (2014), Rowland and Cooper (1983), Williams et al. (2008); and personal communication with Dr. Kwabena Duah, Australia (2002)

1.3 Strategically Managing the Chemical Exposure Problem: The Need for Public Health Risk Assessment

Risk assessment is a tool used to organize, structure, and compile scientific information in order to help identify existing hazardous situations or problems, anticipate potential problems, establish priorities, and provide a basis for policy decisions about regulatory controls and/or corrective actions. A key underlying principle of public health risk assessment is that some risks are tolerable—a reasonable and even sensible view, considering the fact that nothing is wholly safe *per se*. In fact, whereas human exposures to large amounts of a toxic substance may be of major concern, exposures of rather limited extent may be trivial and therefore should not necessarily be a cause for alarm. In order to be able to make a credible decision on the cut-off between what really constitutes a 'dangerous dose' and a 'safe dose', systematic scientific tools—such as those afforded by risk assessment—may be utilized. In this regard, therefore, risk assessment seems to represent an important foundation in the development of effectual public health risk management strategies and policies for populations subjected to toxic chemical insults and assaults.

The principal objectives of a public health risk management program usually will consist of the following typical tasks:

- Determine if a hazardous substance exists and/or may be contacted by humans
- Estimate the potential threat to public health, as posed by the chemical substances of concern
- Determine if immediate response action is required to abate potential problems
- Identify possible remedy or corrective action strategy(s) for the situation
- Provide for public health informational needs of the population-at-risk, in the potentially affected community.

Overall, risk assessment provides one of the best mechanisms for completing the tasks involved here. Indeed, a systematic and accurate assessment of risks associated with a given chemical exposure problem is crucial to the development and implementation of a cost-effective corrective action plan. Consequently, risk assessment should generally be considered as an integral part of most public health risk management programs that are directed at controlling the potential effects of chemical exposure problems. The application of risk assessment can indeed provide for prudent and technically feasible and scientifically justifiable decisions about corrective actions that will help protect public health in a most cost-effective manner.

In practice, several groups of peoples around the world are exposed to a barrage of chemical constituents on a daily basis—typically through their use of a variety of consumer products, and via exposure to ambient environmental contaminants. Because of the several health and socioeconomic implications normally associated with most chemical exposure problems, it is important to generally use systematic and technically sound methods of approach in the relevant scientific evaluations oftentimes needed to support crucial risk management decisions. Usually, risk assessments—which allow receptor exposures to be estimated by measurements and/or models—assist in the determination of potential health problems associated with the use of specific consumer products. The exposure assessment component of this process tends to be particularly complicated by the huge diversity in usage and composition of consumer products, and also by the variability of the types and sources of environmental contaminants in the human living and work environments (van Veen 1996; Vermeire et al. 1993). Additionally, it is noteworthy that, the huge diversity in consumer products usage and composition typically results in intermittent exposures to varying amounts and types of products that also contain varying concentrations of chemical compounds.

As part of the efforts aimed at designing an effectual risk assessment paradigm or framework in the application of the various risk assessment tools (meant to help resolve a given problem on hand), one should be cognizant of the fact that developments in other fields of study—such as data management systems—are likely to greatly benefit the public health analyst. In fact, an important aspect of public health risk management with growing interest relates to the coupling of environmental/public health data with Geographic Information System (GIS)—in order to allow for an effectual risk mapping of a study area with respect to the

location and proximity of risk to identified or selected populations. In a nutshell, the GIS can process geo-referenced data and provide answers to questions such as: the distribution of selected phenomena and their temporal changes; the impact of a specific event on populations; or the relationships and systematic patterns of chemical exposures vis-à-vis observed health trends in a region; etc. Indeed, it has been suggested that, as a planning and policy tool, the GIS technology could be used to 'regionalize' a risk analysis process. Once risks have been mapped using GIS, it may then be possible to match estimated risks to risk reduction strategies, and also to delineate spatially the regions where resources should be invested, as well as the appropriate public health risk management strategies to adopt for various geographical dichotomies. Meanwhile, it should also be recognized that, there are several direct and indirect legislative issues that affect public health risk assessment programs in different regions of the world. Differences in legislation amongst different nations (or even within a nation) tend to result in varying types of public health risk management strategies being adopted or implemented. Indeed, legislation remains the basis for the administrative and management processes in the implementation of most public health policy agendas. Despite the good intents of most regulatory controls, however, it should be acknowledged that, in some cases, the risk assessment seems to be carried out simply to comply with the prevailing legislation—and may not necessarily result in any significant hazard or risk reduction.

Finally, it seems appropriate to conclude here with what the two-time/two-subject Polish-French Nobel Prize winning Scientist/Professor, Marie Curie (also known as Maria Skłodowska-Curie), said once upon a time—*viz*.: "Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less". In this same light, developing credible tools with hallmarks of clarity and understandability—such as may be afforded by a well-designed risk assessment program—becomes important in facilitating effective risk prevention or minimization, risk management or control, and risk communication for the miscellany of chemical exposure problems that have become ubiquitous/prevalent, perhaps even inescapable, for much of contemporary societies. Indeed, done properly, risk perception may hopefully lean more towards pragmatic reality—and thus take away some of the unwarranted fears that at times force public health risk managers to 'misallocate' resources to deal with relatively low-risk issues, whiles potentially high-risk or significant risk problems sit unattended. Ultimately, understanding and/or knowing the true dimension of the prevailing risks would help us to mitigate or control any potential threats in a more prudent/meaningful way.

Chapter 2
Anatomical and Physiological Perspectives on Human Exposure to Chemicals

Human exposure to chemicals is virtually an inevitable part of life in this day and age. Such exposures may occur via different human contact sites and target organs, and also under a variety of exposure scenarios. The contact sites represent the physical areas of initial chemical contacting with the human body, and the target organs are the internal body organs that tend to transport, process, and/or store the absorbed chemicals; an exposure scenario is a description of the activity that brings a human receptor into contact with a chemical material, product, or medium. To evaluate potential receptor impacts upon chemical contacting, chemical exposure investigations—typically consisting of the planned and managed sequence of activities carried out to determine the nature and distribution of hazards associated with potential chemical exposure problems—can be systematically designed and effectively used to address human exposure and response to the chemical toxicants so-encountered.

This chapter looks at the major human contact sites, target organs, and exposure scenarios that can be expected to become key players in the assessment of human exposure to, and response from, chemical hazards. Several characteristics of the chemicals of concern as well as the human contact sites will typically provide an indication of the critical features of exposure; these will also provide information necessary to determine the chemical's distribution, uptake, residence time, magnification, and breakdown to new chemical compounds. In particular, the physical and chemical characteristics of the chemicals as well as the target organs involved can significantly affect the intake, distribution, half-life, metabolism, and excretion of such chemicals by potential receptors.

K. Asante-Duah, *Public Health Risk Assessment for Human Exposure to Chemicals*,
Environmental Pollution 27, DOI 10.1007/978-94-024-1039-6_2

2.1 An Overview of Human Contact Sites and Target Organs Most Susceptible to Chemical Exposures

The major routes of both intentional and accidental exposure of chemicals to humans (and indeed various other living organisms) tend to include the following (Brooks et al. 1995; Homburger et al. 1983; Hughes 1996):

- The skin—i.e., the percutaneous route;
- The lungs—i.e., the inhalation-respiration pulmonary route; and
- The mouth—i.e., the oral route

Minor routes of exposure may consist of rectal, vaginal, and parenteral (i.e., intravenous or intramuscular, a common means for the administration of drugs or toxic substances in test subjects) (Homburger et al. 1983). Indeed, the manner in which a chemical substance is taken up and/or enters the complex physiologic system of an organism is very much dependent on the physical and chemical properties of the contacted substance—and to some extent, the nature of the primary contact site as well. For instance, the pulmonary system is most likely to take in vapor-phase and very fine, respirable particulate matter; non-respirable particulates usually enter the body via the oral route; and absorption through the skin is possible for most physical forms, but especially from contacts with liquids and adhering solid materials.

In general, upon human exposure to chemical substances, the contacted material is often absorbed into the receptor bloodstream via three primary routes—i.e., inhalation, oral ingestion, and dermal/skin contact. The three corresponding primary physiological routes of absorption associated with the human body are comprised of the respiratory system; the digestive system; and the percutaneous (i.e., through the skin). Thus, an awareness of these anatomical and physiological characteristics associated with each route of absorption is important as a first step in understanding how toxicants enter (and perhaps even how they behave in) the human body.

2.1.1 Fundamentals of Human Physiology

Several organ systems exist in the human body; the most important physiological elements/organs crucial to the study of human exposure to chemicals are annotated below—and discussed in greater details elsewhere (e.g., Berlow et al. 1982; Berne and Levy 1993; Brum et al. 1994; Davey and Halliday 1994; Dienhart 1973; Frohse et al. 1961; Guyton 1968, 1971, 1982, 1986; Hughes 1996; Roberts 2014; Scanlon and Sanders 1995; Willis 1996).

- *The Skin*. The skin is a highly organized, heterogeneous, and multi-layered organ of the human body. It serves as a protective layer that impedes the entry of

harmful agents and chemicals into the human body. Indeed, the skin is more than just an inert barrier, since it supports a multitude of life functions; overall, this should be viewed as a dynamic, living tissue whose permeability characteristics are susceptible to change.

The skin, which is in fact the largest organ in the body, consists of two primary layers: the nonvascular *epidermis* layer, and the highly vascularized *dermis* layer—but is also separated from deeper body tissues by a *subcutaneous* layer, called the *hypodermis* (Fig. 2.1). By far, the greatest area of the skin is composed of the epidermal cell layer, and most toxicants absorbed through the skin do so through epidermal cells—albeit, despite their much smaller total areas, cells in the follicular walls and in sebaceous glands are much more permeable than epidermal cells. Anyhow, the outermost layer of the epidermis—called the *stratum corneum*—is thought to provide the major barrier to the absorption into the circulation system for most substances deposited on the skin surface; below this layer lays the viable epidermis containing enzymes that metabolize certain penetrating substances—albeit enzymes may also be active in the stratum corneum.

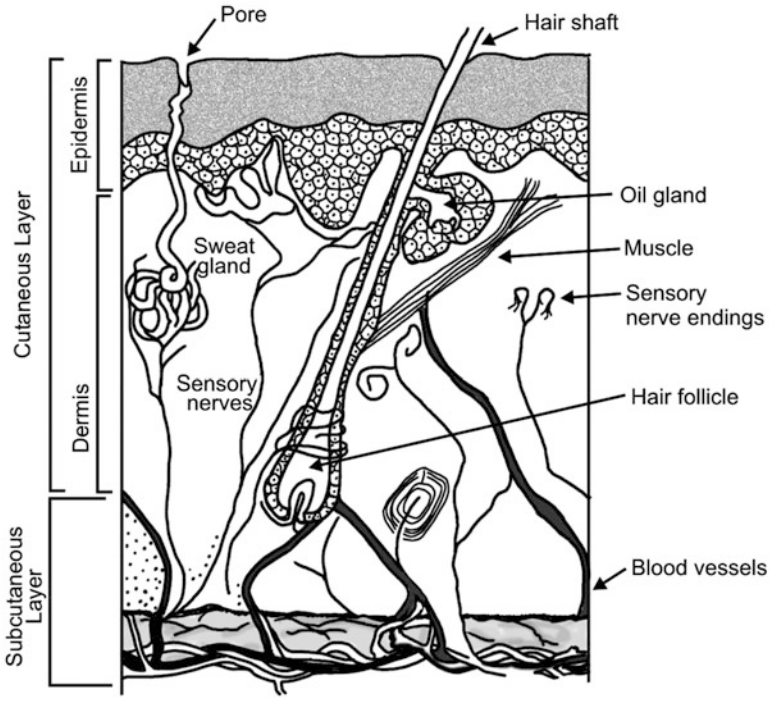

Fig. 2.1 Illustrative sketch of the general structure of the human skin (as a dermal contact exposure route for chemical materials)

The *vascular system*, representing the bloodstream, is of concern for the distribution of absorbed chemical substances; this extends through the dermis and subcutaneous layers, but not the epidermis. Consequently, the skin functions as a barrier to the entry of many toxic substances into the human body. In fact, when toxicants become localized in the epidermis, local toxicity (rather than systemic toxicity) is the likely result; this is because the epidermis is avascular (i.e., having no blood vessels)—and without a transport mechanism, toxicants cannot be distributed to other areas of the body where systemic toxicity may result (Hughes 1996).

On the whole, it is apparent that several routes of absorption are possible through the skin—the most common being the cutaneous adsorption of a toxicant, followed by passive diffusion through the epidermis into the dermis where the toxicant might enter a blood vessel. Indeed, passage into the dermis is enhanced if the toxicant enters a sweat gland or hair follicle; since these structures originate in the dermis and penetrate through the epidermis, this route effectively bypasses the protective barrier provided by the epidermis (Hughes 1996). Meanwhile, it is noteworthy that the permeability coefficient (K_p) is a key parameter in estimating dermal absorption—albeit the extent of absorption of a compound in humans is often dependent on the anatomical site to which the compound is applied. The permeability of the skin to a toxic substance is indeed a function of both the substance and the skin. At any rate, for all practical purposes, it is also worth mentioning that the K_p values can only be calculated from steady-state absorption rates that usually occur only after prolonged exposure (minutes to hours) to an infinite dose. Calculation of exposure to aqueous solutions of chemicals during swimming and bathing are instances where permeability constants can be used to approximate percutaneous absorption (USEPA 1992a, b, c, d, e).

- *The Respiratory System*. The human respiratory system is comprised of a series of organs and body parts—most importantly: the mouth, the nose, the trachea, and the lungs (Fig. 2.2). In general, the lungs represent the site of respiration in the human body; here, inhaled air enters the lungs, where it encounters a huge area of tissue that allows the exchange of gas in the lungs with gas in the blood. If the lung tissue is damaged, the alveoli walls may be destroyed (causing emphysema) or scar tissue may form in the bronchioles (causing chronic bronchitis). [The alveoli are the small air sacs in the lungs through which oxygen passes from the lungs into the bloodstream—partly absorbed into red blood cells, and then carried to the rest of the body; carbon dioxide passes from the bloodstream into the lungs—to be exhaled.]

  Damage to the lungs may be caused by various factors—including recurrent infections, severe asthma, smoking, and air pollution problems. Indeed, certain air pollutants have a direct effect on the ability of the human body to transport oxygen; for example, lead poisoning interferes with the body's ability to manufacture hemoglobin (which carries oxygen in the red blood cells)—and this can produce severe chronic anemia. It is noteworthy that, the 'suspended particles' in air pollution (i.e., soot, dust, and smoke) tend to present a unique sort of

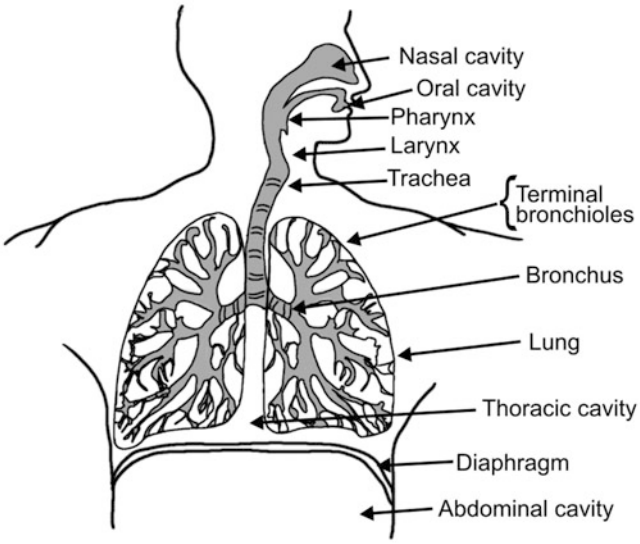

Fig. 2.2 Illustrative sketch of the general structure of the human respiratory system (as an inhalation exposure route for chemical materials)

problem; such particles tend to collect on the walls of the bronchial tubes and interfere with the ability of the lungs to get rid of irritants—due to interference with gas exchanges. Also, other particles—for example, asbestos and some other industrial fibers and particulates—have the ability to cause cancer. Anyhow, in general, only particulate matter of size $\leq$10 μm (referred to as PM10 or PM-10) can usually be transported through the upper respiratory system into the lungs—and this includes fine particulate matter known as PM2.5, as well as the ultrafine particles ($PM_{0.1}$); PM10 is indeed among the most harmful of all air pollutants—representing a major component of air pollution that threatens both human health and the environment. [PM_{10} is particulate matter with an aerodynamic diameter of up to 10 μm (i.e., 10 micrometers or less in diameter)—and this consists of the fine and coarse particle fractions combined; $PM_{2.5}$ is particulate matter with an aerodynamic diameter of up to 2.5 μm (i.e., 2.5 μm or less in diameter)—and this is referred to as the fine particle fraction (which per definition includes the ultrafine particles); and $PM_{0.1}$ is particulate matter with an aerodynamic diameter of up to 0.1 μm, referred to as the ultrafine particle fraction. The PM_{10} fraction comprises both coarse particles ($PM_{10–2.5}$) and fine particles ($PM_{2.5}$), while fine particles ($PM_{2.5}$) include the ultrafine particles ($PM_{0.1}$). Hence, because PM_{10} encompasses $PM_{2.5}$ which in turn includes $PM_{0.1}$, these three fractions should never be added together per se.] In the final analysis, when inhaled, these particles evade the respiratory system's natural defenses and lodge deep in the lungs.

Overall, each region of the respiratory system contributes a unique functional component that prohibits or limits the ability of toxicants to enter the body. Even

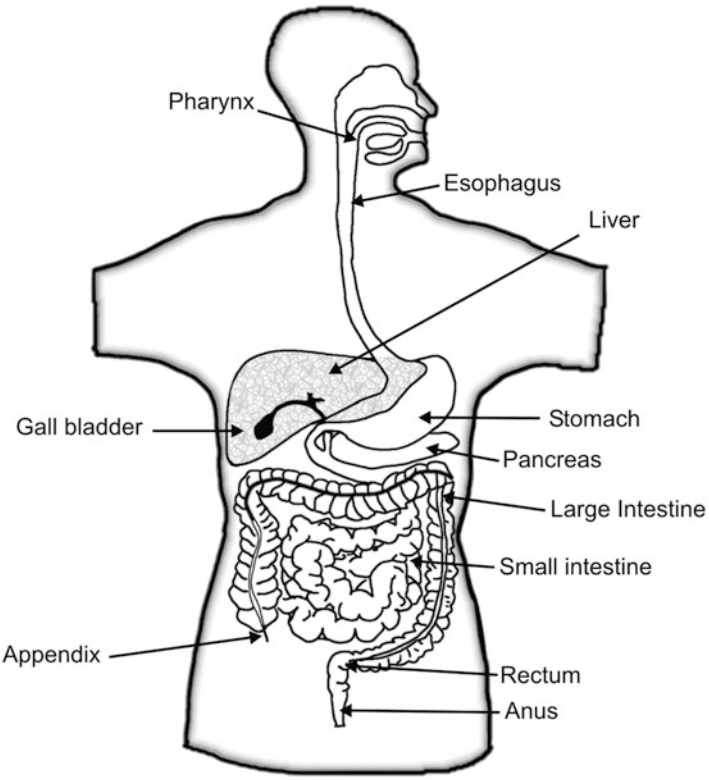

Fig. 2.3 Illustrative sketch of the general structure of the human digestive system (as an ingestion exposure route for chemical materials)

so, the respiratory system, by its close anatomical and physiological association with the cardiovascular system, also constitutes one of the prime sites for absorption and distribution of toxicants (Hughes 1996). The pulmonary system is indeed the site of entry for numerous toxicants in the human living and work environments.

- *The Digestive System.* The broad features of the human gastrointestinal tract—including the mouth, pharynx, esophagus, stomach, small intestines, large intestine, rectum, and the anus—are shown in Fig. 2.3. In general, the mouth receives and chews food; the esophagus carries the food to the stomach; the stomach liquefies the food and begins digestion; the small intestine does the major job of breaking down the food molecules into smaller units—which can then be absorbed into the bloodstream; and the large intestine removes water and forms the feces from waste food matter. The *small intestine* is indeed the most important organ for absorbing food (and of course toxic chemicals as well, if present) along the gastrointestinal tract. Although absorption into the bloodstream can occur in the stomach (which is the muscular sac that stores food and other materials taken through the mouth), this entry route is generally considered

minor relative to that which occurs in the small intestine. For materials that remain undigested and/or unabsorbed in the body, the *large intestine* serves as the final major organ of the gastrointestinal tract whose function is to store and concentrate feces to be excreted later.

- *The Circulatory System*. The distribution and removal of chemicals after they are absorbed or after entering the human body is a very important aspect of toxicological studies. The distribution of chemical toxins occurs through the circulatory or vascular system (whereas removal may occur through the kidneys). The human circulatory system, therefore, represents a very important route of distribution that comes into play following the exposure of an organism to 'external' chemicals.
- *The Liver*. The liver may be considered as a filter for the blood, as well as a control system for regulating the levels of chemicals (including certain important nutrients); it is also a place where toxic substances can be transformed via detoxification reactions. The liver, therefore, represents an organ system most important in facilitating chemical transformations in the human body.
- *The Kidneys*. When blood passes through the kidneys, substances not needed by the body (including toxic substances and their metabolites) are generally separated and excreted in the urine. The kidneys, therefore, serves as an important organ that broadly facilitates excretions from the body. Indeed, the kidneys contribute a large share of the work required to eliminate toxic substances from the human body.

Overall, chemical contacting or exposure may necessarily occur via the first three of the above-listed physiological elements (*viz*., the skin structure, the respiratory system, and the digestive system), whereas the transport and fate of the chemicals in the human body (i.e., pertaining to the distribution and removal of any chemicals entering the human body) will generally be dictated or influenced by the latter three (*viz*., the circulatory system, the liver, and the kidneys). These organ systems do indeed represent primary routes of chemical absorption by the human body.

2.1.2 Target Organ Toxicity

Target organ toxicity is defined as the adverse effects or disease states manifested in specific organs in the human body. The key toxicity endpoints and corresponding major disease states arising from, or attributable to, toxicity imposed on human body organs include the following (Brooks et al. 1995; Davey and Halliday 1994; Hughes 1996; Klaassen et al. 1996):

- *Dermatotoxicity* [*e.g., Dermal Sensitization, Dermal Irritation, Skin Corrosivity, Phototoxic Reaction, etc*.]—i.e., adverse effects produced by toxicants in the skin; this occurs when, in general, dermatotoxins are present at skin contact sites.

Skin toxicity reactions are diverse and may involve any one or several combinations of the skin components; for instance, the situation may consist of phototoxic reactions—a condition of dermal irritations induced by a chemical agent in the presence of ultraviolet light, etc.

- *Developmental Toxicity*—i.e., adverse toxin-induced effect during pregnancy, or as a result of parental exposure to toxicants; this occurs when a toxic insult or assault on an individual/organism results in an adverse effect during pregnancy, or as a result of parental exposure during the gestation period. This is generally manifested at any point in the life span of the affected organism or person. [See also, 'Reproductive Toxicity' discussed below.]
- *Hematotoxicity*—i.e., blood cell toxicity; this occurs when too many or too few of the different blood cell components (i.e., erythrocytes, leukocytes, and thrombocytes) are present in an individual/organism, or when structural anomalies occurring in blood components interfere with normal functioning. Hematotoxins alter the general characteristics of blood cells to produce symptoms.
- *Hepatotoxicity* [or *Hepatic Toxicity*]—i.e., toxic effects in the liver; this occurs when liver toxicants (typically characterized as being cytotoxic or cholestatic) enter the liver. Cytotoxic mechanisms affect hepatocytes, and are responsible for different types of liver injury; and cholestatic mechanisms affect the flow of bile.
- *Immunotoxicity*—i.e., any adverse or dysfunctional effect on the structure or functioning of the immune system (or indeed on other closely related systems), typically the result of exposure to immunotoxic chemicals; this usually occurs when there is an immune system dysfunction resulting from exposure to potential immunotoxicants. Immunotoxic chemicals (or immunotoxicants) can indeed result in adverse effects on the normal functioning of the immune system; usually, functional immunosuppression is the main concern. It is noteworthy that concern over the potential toxic effects of chemicals on the immune system arises from the critical role of the immune system in maintaining overall health. Indeed, it is well recognized that suppressed immunological function can result in increased incidence and severity of infectious or systemic diseases as well as some types of cancer. Conversely, inappropriate enhancement of immune function or the generation of misdirected immune responses can precipitate or exacerbate development of allergic and autoimmune diseases. Thus, both suppression and enhancement of immune function may be viewed as illuminating the potential immunotoxic effects of chemicals.
- *Nephrotoxicity*—i.e., toxic effects in the kidney; this occurs when nephrotoxins are present. The pathologies associated with renal- or nephro-toxicity are dependent on the anatomical region of the nephron affected by the toxicant.
- *Neurotoxicity* [*viz.*, *Central or Peripheral Neurotoxicity*]—i.e., toxic effects to the nervous systems; this occurs when toxicants interrupt the normal mechanisms of neuronal communication. Neurotoxins are known to alter neurons in the nervous system; they interfere with the communication ability of neurons, impeding receptor or motor neuron signaling and central nervous system (CNS) functioning.

- *Pulmonotoxicity* [or *Respiratory Tract Toxicity*]—i.e., disease states in the respiratory system resulting from inhalation of toxicants; this occurs when pulmonotoxins enter the respiratory system. Ultimately, consequential effects are considered crucial if/when toxic responses results in a decreased ability for the lung to exchange oxygen and carbon dioxide across the lung membrane walls.
- *Reproductive Toxicity*—i.e., adverse effects of chemical substances on the sexual function and fertility in adult males and females, as well as associated developmental toxicity in the offspring of the target organisms or persons; this occurs when there is a toxic effect or outcome from a substance on the reproductive ability of an organism or individual , and indeed in relation to the development of its offspring as well. In general, effects on reproduction or development can be a reflection of toxicity to endocrine regulation or direct toxicity to the reproductive tissues; for males, this most often reflects altered libido or changes in sperm quality (*viz*., count, motility, or morphology)—and for females, this affects libido or fertility and initial development of the ova. [See also, 'Developmental Toxicity' discussed above.]

Indeed, toxicity is unique for each organ, since each organ is an assemblage of tissues, and each tissue is a unique assemblage of cells. Consequently, under the influence of a chemical toxicant, each organ will manifest different disease states (from toxicity) that depend on the structural and functional characteristics of the cells present (Brooks et al. 1995; Davey and Halliday 1994; Hughes 1996).

In general, human exposure to chemical constituents present in consumer products and/or in the environment can produce several adverse effects and/or specific diseases. For example, human exposures to certain chemicals may result in such diseases as allergic reaction, anemia, anxiety, asthma, blindness, bronchitis, various cancers, contact dermatitis, convulsions, embryotoxicity, emphysema, pneumonoconiosis, heart disease, hepatitis, obstructive lung disease, memory impairment, nephritis, and neuropathy. In effect, human exposures to chemicals can cause various severe health impairment or even death if intake occurs in sufficiently large amounts. Also, there are those chemicals of primary concern that can cause adverse impacts, even from limited exposures.

2.2 The General Nature of Chemical Hazards and Human Response from Exposure to Chemical Substances

There generally are varying degrees of hazards associated with different chemical exposure problem situations. Such variances may be the result of both chemical-specific and receptor-specific factors and/or conditions. Thus, chemical exposure problems may pose different levels of risk, depending on the type of chemicals and extent of contacting by the receptor; the degree of hazard posed by the contacted substance will generally be dependent on several factors, including the following:

- Physical form and chemical composition;
- Quantities contacted;
- Reactivity;
- Toxicity effects; and
- Local conditions and environmental setting (e.g., temperature, humidity, and light)

Also, it is worth mentioning here that the biological effects of two or more toxic substances can be different in nature and degree, in comparison to those of the individual substances acting alone (Williams and Burson 1985). Chemical interactions between substances may indeed affect the individual chemical toxicities—'positively' or 'negatively'—in that, both/all substances may act upon the same physiologic function, or all substances may compete for binding to the same physiologic receptor. In situations where both/all substances act upon the same physiologic function, their total effects may be simply *additive* (i.e., the simple arithmetic sum of the individual effects), or they may be *synergistic* (i.e., the situation when the total effect is greater than the simple arithmetic sum of the effects of each separately). Under some circumstances, the outcome is a *potentiation* effect—which occurs when an 'inactive' or 'neutral' substance enhances the action of an 'active' one; and in yet other situations, it may be one of *antagonism*—in which case an 'active' substance decreases the effect of another 'active' one.

In the end, it is very important to comprehensively/adequately characterize the nature and behavior of all chemicals of potential concern—with careful consideration given to the above-stated and related factors. Thenceforth, depending on the numbers and types of chemicals involved, as well as the various receptor-specific factors, significantly different human response could result from any given chemical hazard and/or exposure situation.

2.2.1 Classification of Chemical Toxicity

Human response to chemical exposures is as much dependent on the toxicity of the contacted substance as it is on the degree of exposure—among other factors. Chemical toxicity may be characterized using variant nomenclatures—but generally done in relation to the duration and location of exposure to an organism, and/or in accordance with the timing between exposure to the toxicant and the first appearance of symptoms associated with toxicity. The categories commonly encountered in public health risk assessments are identified and contrasted below (Brooks et al. 1995; Davey and Halliday 1994; Hughes 1996).

- *Acute vs. Chronic toxicity*. *Acute toxicity* involves the sudden onset of symptoms that last for a short period of time (usually less than 24 h), whereas *chronic toxicity* results in symptoms that are of long, continuous duration. In general, the cellular damage that produces the symptoms associated with acute toxicity is usually reversible, whereas there tends to be a permanent outcome from chronic

toxicity due to the irreversible cellular changes that would have occurred in the organism. In fact, if cellular destruction and related loss of function are severe, then death of the organism may result.

It is noteworthy that, the terms 'acute' and 'chronic' as applied to toxicity may also be used to describe the duration of exposure—namely, 'acute exposure' and 'chronic exposure'. Indeed, it has become recognized that acute and chronic exposure to a number of toxicants will usually parallel acute and chronic toxicity—albeit, in some cases, acute exposure can lead to chronic toxicity (Hughes 1996).

- *Local vs. Systemic toxicity*. *Local toxicity* occurs when the symptoms resulting from exposure to a toxicant are restricted or limited to the site of initial exposure, whereas *systemic toxicity* occurs when the adverse effects occur at sites far removed from the initial site of exposure. The latter effects are those elicited after absorption and distribution of the toxicant from its entry point to a distant site. Indeed, toxicants are often absorbed at one site, and then are subsequently distributed to distant regions of the receptor through transport within the organism via the blood or lymphatic circulatory systems. In general, it tends to be easier to attribute a toxic response in the case of local toxicity (because the response occurs at the site of first contact between the biological system and the toxicant), in comparison to systemic toxicity.
- *Immediate vs. Delayed toxicity*. *Immediate toxicity* arises when symptoms occur rapidly (usually within seconds to minutes) following the exposure of an organism to a toxicant, whereas *delayed toxicity* generally results long after exposure—and therefore sometimes adds to the difficulty in establishing a cause-and-effect relationship in this latter case. Indeed, the relationship between causative agents or toxicants and the pathologic symptoms or toxicity is relatively more easily established in the case of 'immediate toxicity'. [By the way, it is notable that these effects have also been referred to as acute and chronic, respectively.]

Overall, a good understanding of the time-dependent behavior of a toxicant as related to its absorption, distribution, storage, biotransformation, and elimination is necessary to explain how such toxicants are capable of producing 'acute' or 'chronic' toxicity, 'local' or 'systemic' toxicity, and 'immediate' or 'delayed' toxicity (Hughes 1996). Consequently, *toxicokinetics* (which is the study of the processes of absorption, distribution, storage, biotransformation, and elimination in relation to toxicants as they interact with living organisms) becomes a very important area of examination during the appraisal of human exposures to chemicals. Also, *toxicodynamics* (which examines the mechanisms by which toxicants produce unique cellular effects within an organism) is another important area of study in this respect; it consists of the study of the interaction of chemical substances with target sites, and the subsequent reactions leading to adverse effects. In the end, whether reversible or irreversible cellular injury occurs upon exposure of an organism to a given toxicant will depend on the duration of exposure as well as the specific toxicokinetic properties of the toxicant (Hughes 1996).

2.2.2 *Factors Influencing Chemical Toxicity to Humans and Human Response to Chemical Toxicants*

The severity of adverse effects resulting from exposures to any given chemical substance depends on several factors—particularly those annotated in Box 2.1. Moreover, the potential for adverse health effects on populations contacting hazardous chemicals can involve any organ system(s). The target and/or affected organ (s) will also depend on several factors—especially the specific chemicals contacted; the extent of exposure (i.e., dose or intake); the characteristics of the exposed individual (e.g., age, gender, body weight, nutritional status, psychological status, genetic make-up, immunological status, susceptibility to toxins, hypersensitivities); the metabolism of the chemicals involved; time of the day during exposure and weather conditions (e.g., temperature, humidity, barometric pressure, season); and the presence or absence of confounding variables such as other diseases (Brooks et al. 1995; Derelanko and Hollinger 1995; Grisham 1986; Hughes 1996). In any event, within the human body, a chemical may be metabolized, or it may be stored in body fat (as typical of some fat-soluble substances such as DDT that accumulate in the body and become more concentrated as they pass along the food-chain)—or indeed excreted unchanged. Metabolism will probably make some chemicals more water-soluble, and thus more easily excreted—albeit, sometimes, metabolism increases toxicity (WHO 1990).

Box 2.1 Factors Potentially Influencing Human Response to Toxic Chemicals

- Nature of toxic chemical (i.e., the types, behavior and effects of the chemical substance and its metabolites)
  - Physical/chemical properties of the agent
  - Chemical potency
  - Mechanism of action
  - Interactions between chemicals in a mixture
  - Absorption efficiency (i.e., how easily the chemical is absorbed)
- Exposure characteristics
  - Dose (because large dose may mean more immediate effects)
  - Route of exposure
  - Levels and duration of exposure
  - Timing and frequency of exposure
  - Storage efficiency (i.e., accumulation and persistence of chemical in the body)
  - Time of day during exposure (as hormones and enzyme levels are known to fluctuate during the course of a day—i.e., circadian rhythms)

(continued)

Box 2.1 (continued)

- Environmental factors relating to weather conditions (since temperature, humidity, barometric pressure, season, etc., potentially affect absorption rates)

- Individual susceptibility
  - Age (since the elderly and children are more susceptible to toxins, and therefore may show different responses to a toxicant)
  - Gender (since each sex has hormonally controlled hypersensitivities—and thus females and males may exhibit different responses to a toxicant)
  - Body weight (which is inversely proportional to toxic responses/effects)
  - Nutritional status (because, in particular, a lack of essential vitamins and minerals can result in impaired cellular function and render cells more vulnerable to toxicants and vice versa—e.g., levels of nutrients like iron, calcium, and magnesium can protect against cadmium absorption and retention in the human body)
  - Hormonal status (e.g., associated with menopause and pregnancy in women)
  - Psychological status (because stress increases vulnerability)
  - Genetics (because different metabolic rates, related to genetic background, affects receptor responses)
  - Immunological status and presence of other diseases (because health status influences general metabolism and may also affect an organism's interaction with toxicants)
  - Anatomical variability (i.e., variations in anatomical parameters between genders, and between healthy people *vs.* those with pre-existing 'obstructive' disease conditions)

- Hazard controls
  - Source reduction
  - Administrative/institutional and engineering controls
  - Personal protective equipment/clothing
  - Safe work practices

- Medical intervention
  - Screening
  - Treatment

2.2.2.1 Distribution and Storage of Toxicants in the Human Body

Distribution of toxicants (following exposure and absorption) occurs when a toxicant is absorbed, and then subsequently enters the lymph or blood supply for transport to other regions of the human body; the lymphatic system is indeed a part of the circulatory system and drains excess fluid from the tissues (Davey and Halliday 1994; Hughes 1996). By and large, several factors affect the distribution of toxicants to tissues in the human body—most importantly the following:

- Physical and chemical properties/characteristics of the toxicant
- Concentration gradient (between the amount of the toxicant in the blood as compared to the tissue)
- Volume of blood flowing through a specific tissue or organ in the human body
- Affinity of toxicants for specific tissues (i.e., tissue specificity or preference of the toxicant)
- Presence of special structural barriers to slow down toxicant entrance.

Ultimately, storage results when toxicants accumulate in specific tissues of the human body, or become bound to circulating plasma proteins (Hughes 1996). The common storage sites/locations for toxicants in the human body tissues include circulating plasma proteins, bones, liver, kidneys, and fat. Further elaboration of the major factors that affect the distribution and storage of toxicants within human body tissues can be found elsewhere in the literature (e.g., Davey and Halliday 1994; Hughes 1996).

2.2.2.2 Toxicokinetics/Pharmacokinetics vs. Toxicodynamics/Pharmacodynamics

Fundamentally, *toxicokinetics* is comprised of a process that entails the uptake of potentially toxic substances by the body, the biotransformation they undergo, the distribution of the substances and their metabolites in the tissues, and the elimination of the target substance of interest and its metabolites from the body (*viz.*, absorption-distribution-metabolism-excretion); both the amounts and the concentrations of the substances of interest and their metabolites are studied in these situations. [By the way, it is noteworthy here that the term 'toxicokinetics' has essentially the same meaning as '*pharmacokinetics*'—but the latter term is usually restricted to the study of pharmaceutical substances.]

Broadly speaking, *pharmacodynamics*/*toxicodynamics* consist of the interaction of potentially toxic substances with target sites, and the subsequent reactions leading on to adverse effects (e.g., biochemical and tissue effects); it refers to the relationship between chemical concentration at the site of action and the resulting effect, including the time course and intensity of general and adverse effects—also recognizing that the effect of a chemical present at the site of action is determined by that chemical's binding with a receptor.

In practice, it is apparent that the mechanisms involved in both the toxicokinetic and toxicodynamic behaviors of a given chemical of interest would generally exert significant influence on the likely human health impacts.

2.3 The Pharmacokinetics and Pharmacodynamics of Chemicals in Human Exposure Environments

Pharmacokinetics (PK) [or toxicokinetics (TK)] consists of the absorption, distribution, metabolism, and excretion (ADME) of chemicals in a biological system or entity. In general, the science of pharmacokinetics describes the time course disposition of a xenobiotic, its biotransformed products, and its interactive products within the body. This includes a description of the compound's absorption across the portals of entry, transport and distribution throughout the body, biotransformation by metabolic processes, interactions with biomolecules, and eventual elimination from the body (Saleh et al. 1994). The processes involved are typically evaluated through PK modeling efforts.

PK modeling offers a mathematical approximation of the PK processes used to predict internal concentrations of chemicals and their metabolites—i.e., following an external dosing or exposure of a target receptor to the chemicals of interest/concern. Invariably, PK models serve as tools that can be used to improve the accuracy of extrapolations across species, routes of exposure, durations of exposure, and concentrations; mechanistic data are typically necessary for the proper application of pharmacokinetic modeling, particularly in the selection of the appropriate dose metric—and can indeed support inferences regarding the nature of cross-species pharmacodynamics (*viz*., how a chemical substance may affect the body).

Pharmacodynamics (or toxicodynamics)—sometimes described as what a chemical substance does to the body—involves receptor binding (including receptor sensitivity), post-receptor effects, and chemical interactions. On the whole, pharmacodynamics refer to the relationship between a chemical substance concentration at the site of action and the resulting effect, including the time course and intensity of general and adverse effects.

It is noteworthy that, in essence, pharmacokinetics represents the science of how the body affects or handles a chemical substance, and pharmacodynamics is the study of how a specific chemical substance affects the body. Indeed, all chemical substances have specific mechanisms of action and various adverse effects that are caused by pharmacological interactions in the body. Pharmacodynamics (*i.e*, how a chemical substance may affect the body), together with pharmacokinetics (i.e., what the body does to a chemical substance), ultimately helps explain the relationship between the dose and response for a given chemical exposure situation—i.e., a chemical substance's effects on an organism. Overall, the pharmacologic response depends on the chemical substance binding to its target, and the concentration of the chemical substance at the receptor site influences the substance's ultimate effect.

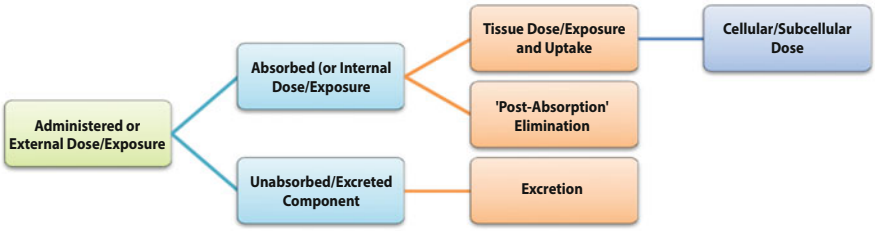

Fig. 2.4 Basics of toxicokinetics: mass balance concepts in chemical exposure situations

In practice, based on the fundamental concept of mass balance, it becomes apparent that affected organisms or receptors would generally exhibit the following basic traits/attributes in relation to an 'administered dose' following exposure to any given chemical (Fig. 2.4):

(i) Absorbed (or Internal) dose—generally comprising of the parts retained (i.e., metabolized and/or sequestered), as well as the portions subsequently eliminated (via urine, feces, breath, sweat, skin/hair, etc.); and
(ii) Unabsorbed (i.e., Excreted) component.

At the end of the day, the goal of most toxicokinetic or pharmacokinetic studies is to track the internal dose or target tissue dose of a chemical and/or its metabolites over time, following the exposure of a given receptor to the chemical substances of interest.

2.3.1 Elements of Toxicokinetics/Pharmacokinetics

Toxicokinetics is traditionally divided into four types of processes, namely (NRC 1987; Davey and Halliday 1994; Hughes 1996; Andersen 2003; Reddy et al. 2005; Lipscomb and Ohanian 2007; WHO 2010a, b):

1. Absorption (or uptake)—for which the rate and extent can be quite important; this can be used to estimate bioavailability.
2. Distribution (i.e., movement of the chemical in the body of an organism)—used to estimate tissue dose, and to identify sites of potential accumulation.
3. Metabolism (or biotransformation)—providing a measure of enzyme activity level, as well as a measure of relative enzyme affinity.
4. Elimination (of substance of interest and metabolites from the body)—represented by the clearance level, as well as the chemical half-life ($T_{1/2}$).

Absorption describes the process of a chemical crossing a surface barrier (tissue epithelium) and entering the blood of an organism. The rate of absorption is often reflected in the time to reach peak blood concentration, and the degree of absorption can be reflected in the per cent bioavailability—which, in some cases, can be estimated from chemical or physical properties.

Distribution relates to the movement of the chemical in the body of an organism. Chemicals generally partition between air and blood, and between blood and solid

tissues; the relative affinity of a chemical for blood versus air or tissue is described by partition coefficients—which are characteristically used in dosimetry and kinetic modeling. Typically, comprehensive toxicokinetic studies will provide data on doses in blood compartments, different tissues, and excreta over time. Among other things, distribution that occurs across the placenta (thus leading to fetal exposure, and via lactation to offspring) also represent additional example of typical concerns in relation to toxicant distribution.

Metabolism consists of the process by which enzyme systems change the chemical form of a toxicant (or even an endogenous molecule); in fact, for many chemicals, competing metabolic pathways may exist. Thus, whereas for some toxicants the effect of metabolism is often to increase the propensity for a material to be excreted (i.e., in some cases metabolism detoxifies a chemical), in other cases the metabolite is reactive and becomes the toxic form of significant concern.

Elimination of a substance and/or their metabolites from the body may occur via numerous routes, once absorbed—including via: urine (primarily for small or hydrophilic chemicals); feces (primarily for large molecules); breath (primarily for highly volatile chemicals); sweat (a relatively minor pathway for primarily small or hydrophilic chemicals); and skin/hair (a relatively minor pathway that is most important for metals and other chemicals that bind to proteins).

2.3.2 Physiologically-Based Pharmacokinetic (PBPK) Modeling

The handling of a chemical by the human body can be rather complex—as several processes (such as absorption, distribution, metabolism and elimination/excretion) work to alter chemical concentrations in tissues and fluids. On the other hand, simplifications of body processes are necessary to facilitate reliable prediction of a chemical's behavior in the body; one way to achieve such simplification modes is to apply mathematical principles to the various processes—which generally require that a model of the body be selected to start off the process. A basic type of model used in pharmacokinetics is the 'compartmental model'. Compartmental models are categorized by the number of compartments needed to describe a chemical's behavior upon entry into the human body; these may be one-compartment, two-compartment, or multi-compartment models. It is noteworthy that the compartments mentioned here do not necessarily represent a specific tissue or fluid—but rather may represent a group of similar tissues or fluids; to construct a compartmental model as a representation of the body, simplifications of body structures are made—as for instance, organs and tissues in which chemical distribution is similar are grouped into one compartment. Ultimately, these models can be used to predict the time course of chemical concentrations in the human body. It is also worth mentioning here that compartmental models are generally considered as 'deterministic'—because the observed chemical concentrations determine the type of compartmental model required to describe the pharmacokinetics of the chemical of interest. At any rate, it is generally best to use the simplest model that

accurately predicts changes in a chemical's concentrations over time—albeit more complex models are often required or needed to predict tissue chemical concentrations for a variety of reasons.

PBPK models [also referred to by 'Physiologically-based toxicokinetic' (PBTK) models] offer quantitative descriptions of the absorption, distribution, metabolism and excretion (ADME) of chemicals in biota or organisms based on interrelationships among key physiological, biochemical and physicochemical determinants of these processes; indeed, PBPK models facilitate more scientifically sound extrapolations across studies, species, routes and dose levels—and they are also fundamental to the development of biologically-based dose–response models used to address uncertainty and variability related to toxicodynamics and toxicokinetics (NRC 1987; Andersen 2003; Reddy et al. 2005; Lipscomb and Ohanian 2007; WHO 2010a, b). Overall, PBPK models would generally help in increasing precision of risk estimates, as well as an understanding of associated uncertainty and variability. This is achieved by reducing reliance on animal testing—and further realized via the establishment of biologically meaningful quantitative frameworks in which *in vitro* data can be more effectively utilized. [By the way, it is noteworthy here that, the terms 'pharmacokinetic' and 'toxicokinetic' can be considered to have the same meaning—and by extension, a 'physiologically-based pharmacokinetic (PBPK) model' is equivalent to a 'physiologically-based toxicokinetic (PBTK) model'.]

PBPK modeling broadly entails estimating internal dose measures for extrapolation across species, groups, doses, time, and age—by considering the target receptor's physiology (e.g., weight of organs and tissues; blood flows; etc.) and the physical-chemical, as well as biochemical constants of the assaulting compound of interest. In fact, with more emphasis being placed on internal (tissue) dose for quantitating exposure between species, PBPK modeling is finding ever-increasing use in the risk assessment process (Derelanko and Hollinger 1995). In general, physiologic models enable a public health risk analyst to quantitatively account for differences in pharmacokinetics that occur between different species, dose levels, and exposure regimens/scenarios. For example, PBPK models have been extensively used to predict the allowable exposure levels in human health risk assessment—usually via the utilization of animal studies through route-to-route, high-to-low dose, and laboratory animal-to-human extrapolations. Indeed, PBPK models can be rather powerful tools for interspecies extrapolations—i.e., provided the biological processes are well understood, and if the pertinent parameter values can be accurately measured. It is noteworthy however, that no one PBPK model can be used to represent the kinetics of all chemicals.

In general, the scope for the use of a PBPK model in a particular risk assessment essentially determines the intended model capability and the extent of model evaluation; ultimately, the purpose and capability of PBPK models should be characterized in terms of the species, life stage, exposure routes/windows and dose metrics that are central to their application in risk assessment (Clark et al. 2004; WHO 2010a, b). Further discussion on various key aspects of the nature of PBPK models and PBPK modeling mechanics is provided below; more elaborate

discussions on good PBPK modeling principles and practices can be found elsewhere in the literature (e.g., Andersen et al. 1995a; Kohn 1995; Clark et al. 2004; Gentry et al. 2004; Barton et al. 2007; Chiu et al. 2007; Clewell and Clewell 2008; Loizou et al. 2008; WHO 2010a, b).

2.3.3 Characterization of Physiologically-Based Pharmacokinetic (PBPK) Models

PBPK models are quantitative descriptions of the absorption, distribution, metabolism and excretion (ADME) of chemicals in biota based on interrelationships among key physiological, biochemical and physicochemical determinants of these processes; they are part of the broader continuum of increasingly data-informed approaches—ranging from the commonly adopted 'default-mode' evaluation modalities/strategies based on external dose, to more refined and biologically realistic dose-response models (WHO 2010a, b). Indeed, the processes and frameworks are also fundamental to the development of biologically-based dose-response models that can be used to address uncertainty and variability related to 'toxicokinetics' (TK) and 'toxicodynamics' (TD).

Among other things, PBPK models generally utilize physiologic and thermodynamic parameters in the evaluation processes involved; for instance, organ volumes, blood flows, and metabolic rate constants are typically determined—and these then become part of the model. Additional parameters, such as partition coefficients, are considered as belonging to the thermodynamic realm—but may also be chemical-specific. In practice, appropriate thermodynamic and biochemical parameters must be determined for each chemical of potential concern/interest.

2.3.3.1 PBPK Model Structure and Mechanics/Descriptors

Invariably, the structure of a PBPK model should be characterized in the form of boxes and arrows—with the organs and organ systems represented by the boxes, and the specific physiological or clearance processes identified by the arrows (Ramsey and Andersen 1984; Brightman et al. 2006; Krishnan and Andersen 2007; WHO 2010a, b). It is quite important that the model structure concocts the right balance of relevant attributes—such that it appropriately simulates dose metrics of relevance to the risk assessment task on hand; in the end, any model complexity and capability should be consistent with the intended purpose and underlying data—also recognizing that model complexity and the number of compartments may not necessarily be equated with accuracy and usefulness of the model description (WHO 2010a, b).

Broadly speaking, PBPK models are based on the following general assumptions regarding ADME (Rideout 1991; WHO 2010a, b):

- Mixing of the chemical in the effluent blood from the tissues is instantaneous and complete;
- Blood flow is unidirectional, constant, and non-pulsatile; and
- Presence of chemicals in the blood does not alter the blood flow rate.

Thus, any deviations from such general assumptions of PBPK models should be properly documented, and justification should also be provided.

Next, the equations employed in a PBPK model should certainly be consistent with the knowledge on the mechanisms of ADME for the particular chemical—and the type of rate equation for ADME should be consistent with biochemical evidence and first principles (Gerlowski and Jain 1983; Krishnan and Andersen 2007; WHO 2010a, b). Relevant methods for the estimation and analysis of chemical-specific parameters as well as biological input data for PBPK models are detailed elsewhere in the literature (see, e.g., Adolph 1949; Dedrick et al. 1973; Dedrick and Bischoff 1980; Beliveau et al. 2005; Krishnan and Andersen 2007; Rodgers and Rowland 2007; Schmitt 2008; ICRP 1975; Arms and Travis 1988; Davies and Morris 1993; Brown et al. 1997; Lipscomb et al. 1998; Barter et al. 2007; Lipscomb and Poet 2008; Price et al. 2003; Gentry et al. 2004; Thompson et al. 2009; Krishnan and Andersen 2007; WHO 2005b; Lipscomb and Ohanian 2007; WHO 2010a, b). At any rate, it is worth recalling here that PBPK models often contain differential equations (i.e., equations calculating the differential in a dependent variable, such as concentration, with respect to the independent variable, such as time) as well as 'nominal' descriptions (e.g., 'saturable metabolism'). In a typical PBPK model, each tissue group may be described mathematically by a series of differential equations that express the rate of change of a chemical of concern in each compartment. The rate of exchange between compartments is based on species-specific physiological parameters. Also, the number of compartments and their interrelationships will vary depending on the nature of the chemical being modeled.

At the end of the day, the accuracy of mathematical and computational implementations of PBPK models should be verified in an explicit and systematic manner. Indeed, regardless of how well the simulations of a PBPK model matches a data set, its structure should not violate what is known about the physiology of the modeled organism. If the model cannot reproduce PK profiles with any realistic parameter values or it can do so only by using values that are inconsistent with the current state of knowledge, then one can reasonably conclude that the model structure or the parameters are inadequate. Accordingly, the model assumptions, processes, parameters and structure should have a reasonable biological basis and be consistent with the available data on the PK and PD of the chemical being modeled (Chiu et al. 2007; Gentry et al. 2004; Marcus and Elias 1998; WHO 2008; Veerkamp and Wolff 1996; Rescigno and Beck 1987; WHO 2010a, b). For all intent and purpose, a pragmatic approach might be to focus on clearly characterizing mathematical descriptions that are either different from existing/published PBPK models, or that cannot be readily and unequivocally derived from corresponding flow diagrams (WHO 2010a, b).

2.3.3.2 Documenting PBPK Modeling Outcomes/Results

The documentation of a PBPK model intended for use in risk assessment requires the inclusion of sufficient information about the model and its parameters—at least so that an experienced modeler can accurately reproduce and evaluate its performance. Indeed, in order to facilitate transparency, reproducibility and credibility, the developer should systematically document the characteristics of a PBPK model such that clear understanding of the input-output relationships, etc. is unquestionable and discernible—albeit the general extent of documentation might depend upon the end use. Overall, PBPK model documentation should address the following broad topics (WHO 2010a, b):

- Scope and purpose of the model;
- Model structure and biological characterization;
- Mathematical description of ADME;
- Computer implementation and verification;
- Parameter estimation and analysis;
- Model validation and evaluation;
- Evaluation/justification of dose metrics; and
- 'Specialized' analysis, if any and/or applicable.

Finally, it is worth the mention here that, the continuous involvement of a risk assessor right from the problem formulation stage could indeed be important in helping the expert modeler consider and address critical issues of relevance to developing PBPK models applicable to the specific risk assessment problem on hand.

2.3.4 Application/Use of Mechanistic Data and Physiologically-Based Pharmacokinetic (PBPK) Models in Risk Assessments

Physiologically-based pharmacokinetic (PBPK) [or physiologically-based toxicokinetic (PBTK)] models have found rather important applications in risk assessment in recent times. WHO (2010a, b), among others, provide succinct general guiding principles for PBPK-based risk assessments—especially with regards to: choice of critical studies; selection of PBPK models; evaluation of dose metrics; and determination of human exposures. Overall, PBPK models provide a documentable and scientifically defensible means of bridging the gap between critical toxicity studies and human risk estimates—by facilitating interspecies, inter-individual, high dose-to-low dose, and route-to-route extrapolations. In particular, the domain of the application of PBPK models shifts the focus of exposure and risk determinations from one consisting of the administered/external dose to a measure of internal dose, the latter of which is more closely associated

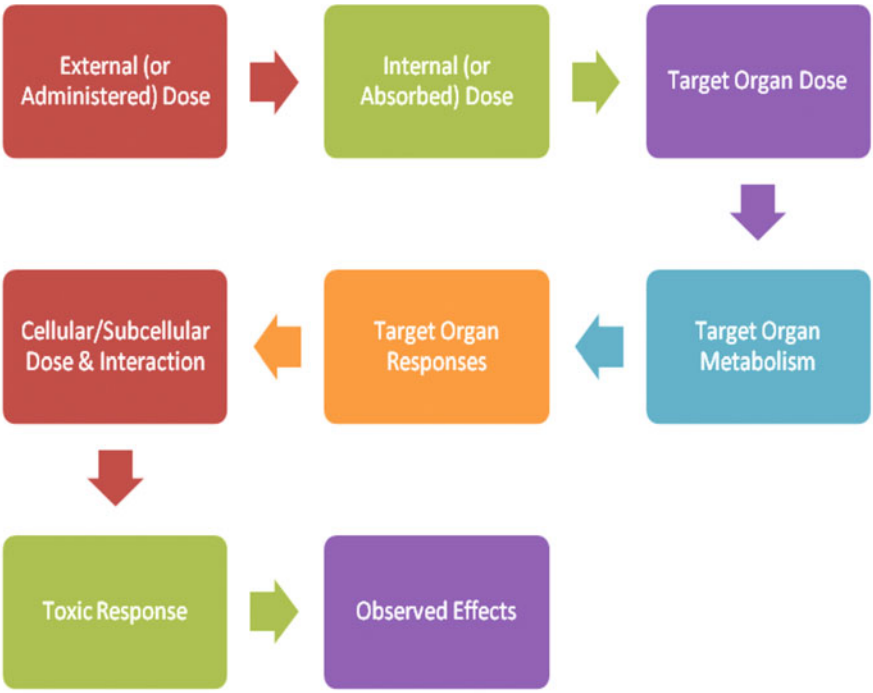

Fig. 2.5 Relationship between 'administered dose' and 'observed effects': Representation of the general pathways leading from 'external dose' to 'toxic response'/'observed effects' for a typical chemical exposure problem

with the toxic/tissue responses and related observable effects (Fig. 2.5). Even so, it must be acknowledged that the PBPK models will not quite remove all of the uncertainties associated with the risk assessment process—since, for instance, these models would not specifically address TD uncertainty in most cases (WHO 2010a, b).

In the final analysis, the level of confidence in a PBPK model intended for use in risk assessment depends critically on its ability to provide reliable predictions of dose metrics. It is therefore important to carefully evaluate whether the model is reliable enough with respect to its predictions of the dose metric for the risk assessment (Iman and Helton 1988; Farrar et al. 1989; Krewski et al. 1995; Campolongo and Saltelli 1997; Nestorov 2001; Gueorguieva et al. 2006b; Chiu et al. 2007; Loizou et al. 2008; WHO 2010a, b). Ideally, a PBPK model should be compared with data that are reasonably informative regarding the parameters to which the dose metric predictions are sensitive—and which presupposes the use of sensitivity and uncertainty analyses to identify the parameters of concern (i.e., those that are least certain, but have the most influence on the dose metric) (WHO 2010a, b). In closing, it is noteworthy that comparison of simulations with available PK data is not the only basis for developing confidence in a PBPK model for

application in risk assessment; equally important are aspects relating to the biological basis and reliability of dose metric predictions supported by variability, uncertainty and sensitivity analyses (WHO 2010a, b).

2.3.5 *Post-PBPK Modeling and Dosimetry Adjustments: The Pragmatic Role of Tissue/Target Organ Dosimetry in Risk Assessments*

The application of PBPK modeling for dose-response analysis generally offers a more accurate extrapolation to human exposure conditions by providing an evaluation based on target tissue or cellular/subcellular dose (WHO 2010a, b). Indeed, internal (tissue) doses of chemicals have been increasingly interpreted with PBPK models as a means to address the difference between species, routes and dose-dependent kinetics beyond the scope of an external dose (Clewell and Andersen 1985, 1987; Clewell et al. 2002; Clark et al. 2004; Chiu et al. 2007; Loizou et al. 2008; Thompson et al. 2009). The PBPK models have also been used to extrapolate within life stages (Clewell et al. 2004; Yoon and Barton 2008; Verner et al. 2009), as well as to address variability among individuals in a population (Bois 2001; Hack et al. 2006; Barton et al. 2007). It is remarkable that a major advantage of PBPK models over empirical compartmental descriptions is the apparent greater extrapolation power the former seems to offer. PBPK models are essentially intended to estimate target tissue dose in species even under exposure conditions for which few or no data exist. Thus, this approach provides a risk assessor with an opportunity to conduct interspecies, intra-species, high dose-to-low dose, and route-to-route extrapolations for chemicals present individually or as mixtures—all the while utilizing the most appropriate level of confidence, even where data may be rather limited. In fact, an even greater degree of refinement may be further achieved post-PBPK modeling—such as via target organ dosimetry adjustments.

Broadly speaking, *dosimetry* may be viewed as comprising of techniques that facilitate the accurate measurement or calculation of the absorbed dose arising from specific environmental exposures—or indeed the overall assessment/determination of the absorbed dose received by the human body, following a chemical exposure situation. More specifically, dosimetry as envisaged here, consists of the calculation of the absorbed dose in tissue as a result of an organism's exposure to a chemical of interest or concern. Thus, to ensure an even more refined dose-response outcome from the computational intricacies of PBPK modeling efforts, dosimetry adjustments may be layered into the overall assessment process utilized in these types of scenarios.

As discussed in some of the preceding sections, pharmacokinetic [PK] (or toxicokinetic, TK) studies determine the fate of a chemical in the body based on the rate of absorption into the body, distribution and storage in tissues, metabolism, and excretion. These PK processes are incorporated into a

mathematical model structure on the basis of the interplay among critical physiological characteristics (e.g., body weight or blood flows), physicochemical attributes (e.g., tissue and blood partitioning) and biochemical properties (e.g., liver metabolic or urinary excretion rates) of a chemical. Anyhow, it is notable that such models are not intended to precisely characterize the PK processes per se—but rather represent a reasonable interpretation of the available data by addressing the relationships between an external dose and internal tissue or cellular dose (WHO 2010a, b). Ultimately, refinements in risk assessment can be based upon additional scientific data that can be used as a basis to estimate internal exposure dose or concentration; target organ dosimetry adjustments represent such a refinement approach.

In practice, subsequent to case-specific problem identification and project scoping, human health risk assessments are typically conducted on the basis of the stipulated problem formulation, hazard identification, dose-response assessment, exposure assessment and risk characterization (NRC 1983; WHO 1999, 2005a, 2008, WHO 2010a, b). The dose-response assessment frequently involves the identification of a 'point-of-departure' (POD) for deriving the 'acceptable external exposure concentration' or 'tolerable daily dose' for humans, including sensitive individuals; credible appraisal mechanisms are therefore crucial to such efforts—and WHO (2010a, b), among others, provides a succinct elaboration on the relationship between external dose and toxic response for an increasingly 'data-informed' dose-response analysis.

Chapter 3
Archetypical Chemical Exposure Problems

Human exposure to chemicals may occur via different human contact sites and target organs (such as discussed in Chap. 2), and also under a variety of exposure scenarios; broadly speaking, an exposure scenario is a description of the activity that brings a human receptor into contact with a chemical material, product, or medium. Chemical exposure investigations (typically consisting of the planned and managed sequence of activities carried out to determine the nature and distribution of hazards associated with potential chemical exposure problems) can be properly designed to help define realistic exposure scenarios—and then subsequently used to address human exposure and likely response to chemical toxicants.

Indeed, it has become apparent that human exposures to chemicals found in human environments and/or in various consumer products may occur via multiple routes, as well as from multiple sources. Accordingly, it is important in a comprehensive assessment of potential human exposure problems or situations, to carefully evaluate all possible combinations of pathways and sources—and then to further aggregate these exposures over time (and perhaps spatially as well, to the extent considered appropriate for a given receptor). Ultimately, the development of a spatiotemporal, multi-source, multi-chemical, and multi-route framework that holistically addresses a potential receptor's vulnerability seems imperative, if a reliable risk determination outcome is to be achieved. This chapter apprises the typically significant exposure scenarios that can be expected to become key players in the assessment of human exposure to, and response from, chemical hazards; it goes on to provide a general framework that may be used to guide the formulation of realistic exposure scenarios, as necessary to generate credible risk assessments.

K. Asante-Duah, *Public Health Risk Assessment for Human Exposure to Chemicals*,
Environmental Pollution 27, DOI 10.1007/978-94-024-1039-6_3

3.1 Formulation of Archetypical Chemical Exposure Problems

Human populations may become exposed to a variety of chemicals via several different exposure routes—represented primarily by the inhalation, ingestion/oral, and dermal exposure routes (Fig. 3.1). Congruently, human chemical uptake occurs mainly through the skin (from dermal contacts), via the inhalation passage (from vapors/gases and particulate matter), and/or by ingestion (through oral consumptions). Under such circumstances, a wide variety of *potential* exposure patterns can be anticipated from any form of human exposures to chemicals. As an illustrative example, a select list of typical or commonly encountered exposure scenarios in relation to environmental contamination problems might include the following (Asante-Duah 1998; HRI 1995):

- Inhalation Exposures
  - Indoor air—resulting from potential receptor exposure to contaminants (including both volatile constituents and fugitive dust) found in indoor ambient air.
  - Indoor air—resulting from potential receptor exposure to volatile chemicals in domestic water that may volatilize inside a house (e.g., during hot water showering), and then contaminate indoor air.
  - Outdoor air—resulting from potential receptor exposure to contaminants (including both volatile constituents and fugitive dust) found in outdoor ambient air.

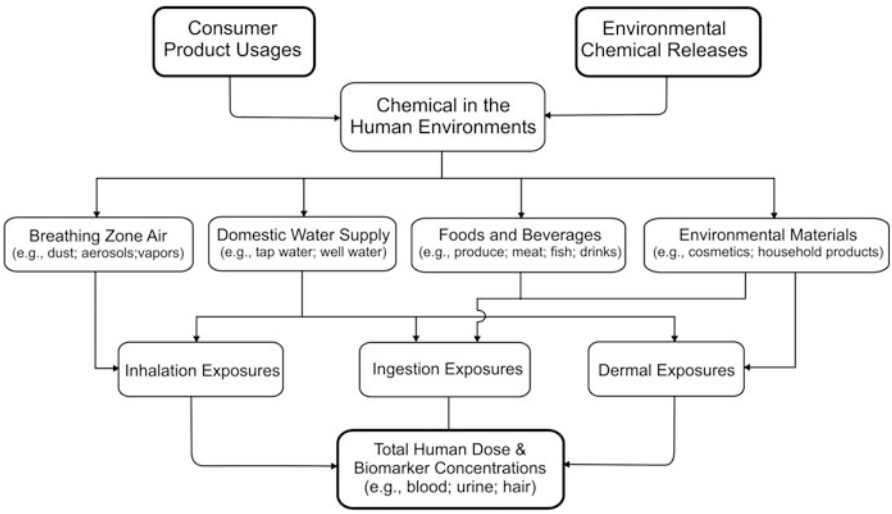

Fig. 3.1 Major types of human exposures to chemicals: a simplified 'total' human exposure conceptual model

  - Outdoor air—resulting from potential receptor exposure to volatile chemicals in irrigation water, or other surface water bodies, that may volatilize and contaminate outdoor air.

- Ingestion Exposures
  - Drinking water—resulting from potential receptor oral exposure to contaminants found in domestic water used for drinking or cooking purposes.
  - Swimming—resulting from potential receptor exposure (via incidental ingestion) to contaminants in surface water bodies.
  - Incidental soil ingestion—resulting from potential receptor exposure to contaminants found in dust and soils.
  - Crop consumption—resulting from potential receptor exposures to contaminated foods (such as vegetables and fruits produced in household gardens that utilized contaminated soils, groundwater, or irrigation water during the cultivation process).
  - Dairy and meat consumption—resulting from potential receptor exposure to contaminated foods (such as locally grown livestock that may have become contaminated through the use of contaminated domestic water supplies, or from feeding on contaminated crops, and/or from contaminated air and soils).
  - Seafood consumption—resulting from potential receptor exposure to contaminated foods (such as fish and shellfish harvested from contaminated waters or that have been exposed to contaminated sediments, and that consequently have bioaccumulated toxic levels of chemicals in their edible portions).

- Dermal Exposures
  - Showering—resulting from potential receptor exposure (via skin absorption) to contaminants in domestic water supply.
  - Swimming—resulting from potential receptor exposure (via skin absorption) to contaminants in surface water bodies.
  - Direct soils contact—resulting from potential receptor exposure to contaminants present in outdoor soils.

These types of exposure scenarios will typically be evaluated as part of an exposure assessment component of a public health risk management program. It should be emphasized, however, that this listing is by no means complete, since new exposure scenarios are always possible for case-specific situations; still, this demonstrates the multiplicity and inter-connectivity nature of the numerous pathways via which populations may become exposed to chemical constituents. Indeed, whereas the above-listed exposure scenarios may not all be relevant for every chemical exposure problem encountered in practice, a number of other exposure scenarios not listed or even alluded to here may have to be evaluated for the particular local conditions of interest—all the while recognizing that comprehensive human exposure assessments must include both direct and indirect exposure from ingredients found in various environmental compartments (such as in ambient

air, water, soil, the food-chain, consumer products, etc.). In any event, once the complete set of potential exposure scenarios has been fully determined for a given situation, the range of critical exposure pathways can then be identified to support subsequent evaluations.

In the end, careful consideration of the types and extent of potential human exposures, combined with hazard assessment and exposure-response information, is necessary to enable the completion of a credible human health risk assessment. For instance, the hazard assessment for a consumer product or component thereof relates to the potential human health effects, and the exposure-response assessments involve an examination of the relationship between the degree of exposure to a product or component and the magnitude of any specific adverse effect(s). Additionally, the exposure assessment (which is very critical to determining potential risks) requires realistic data to determine the extent of possible skin, inhalation, and ingestion exposures to products and components (Corn 1993). Subsequent efforts are then directed at reaching the mandated goal of a given case-specific risk determination—recognizing that the goal of a human health risk assessment under any given set of circumstances would typically be to describe, with as little uncertainty as possible, the anticipated/projected risk (or indeed an otherwise lack of risk) to the populations potentially at risk (e.g., a given consumer or population group); this is done in relation to their exposure to potentially hazardous/toxic chemicals that may be contained in a variety of consumer/household products and/or found within their inhabited/occupied environments. Ultimately, the resulting information generated can then be used to support the design of cost-effective public health risk management programs.

3.1.1 The Case for Human Exposures to Airborne Chemical Toxicants

Airborne pollutants can generally be transported over long distances—and this could result in the deposition of pollutants very far removed from the primary source of origination (i.e., far away from where they were first produced or used). For example, high levels of pesticides (such as DDT, chlordane, and toxaphene) have been found to be present in beluga whales from the Arctic—i.e., in locations where such chemicals were not known to have been used (see, *e.g.*, Barrie et al. 1992; Dewailly et al. 1993; Lockhart et al. 1992; Muir et al. 1992; Thomas et al. 1992). In fact, airborne chemical toxicants can very well impact population groups that are geographically widely dispersed. Of particular interest are air emissions from chemical release sources (such as industrial facilities) that often represent a major source of human exposure to toxic or hazardous substances; indeed, the emissions of critical concern often relate to volatile organic chemicals (VOCs), semi-volatile organic chemicals (SVOCs), particulate matter, and other chemicals associated with wind-borne particulates such as metals, PCBs, dioxins, etc. As a

consequence, air pollution presents one of the greatest risk challenges to human health globally—especially recognizing the characteristically long list of health problems potentially caused or aggravated by air pollution, including various forms of respiratory ailments, cancers, and eye conditions/irritations (Holmes et al. 1993).

Airborne chemical toxicants can indeed impact human population via numerous trajectories. For instance, among several other possibilities and issues, volatile chemicals may be released into the gaseous phase from such sources as landfills, surface impoundments, contaminated surface waters, open/ruptured chemical tanks or containers, etc. Also, there is the potential for subsurface gas movements into underground structures such as pipes and basements, and eventually into indoor air. Additionally, toxic chemicals adsorbed to soils may be transported to the ambient air as particulate matter or fugitive dust. Moreover, several consumer products and materials in the human living and work environments will tend to release potentially hazardous chemicals into the human breathing zone/space.

Overall, chemical release sources can pose significant risks to public health as a result of possible airborne release of particulate matter laden with toxic chemicals, and/or volatile emissions. In fact, even very low-level air emissions could pose significant threats to exposed individuals, especially if toxic or carcinogenic contaminants are involved. Consequently, there is increased concern and attention to the proper assessment of public health risks associated with chemical releases into air. Of particular concern, it has become recognized that certain air pollutants have a direct effect on the ability of the human body to transport oxygen (Berlow et al. 1982). For example, lead poisoning interferes with the body's ability to manufacture hemoglobin (which carries oxygen in the red blood cells)—and this can produce severe chronic anemia; carbon monoxide replaces oxygen on hemoglobin molecules—and thus reduces the efficiency with which the blood transfers oxygen to the cells. Also, some toxic gases (such as the oxides of sulfur and nitrogen, and also ozone) that are often found in the smog of cities as a result of industrial pollution can present major health hazards; for example, nitrogen and sulfur oxides typically will form very strong acids when they dissolve in the water present in membrane linings—and these gases can cause damage to the bronchial tubes and alveoli.

Finally, it is noteworthy that, to enable credible risk estimation in relation to human exposure to airborne chemical toxicants, there usually should be a reliable appraisal of the airborne concentrations of the target chemicals. The chemical concentration in air—oftentimes represented by the 'ground-level concentration' (GLC)—is a function of the source emission rate and the dilution factor at the points of interest (usually the potential receptor location and/or 'breathing zone').

3.1.1.1 Indoor Air Quality Problems: General Sources of Indoor Volatile [Organic] Chemicals

There are a number of different kinds of indoor environments—with the most prominent consisting of offices or commercial buildings, homes, and schools—

each with unique characteristics and associated problems. Generally speaking, indoor exposure sources may exist due to indoor activities (such as via showering activities, or the use of certain consumer products) and/or as a result of particular building characteristics (including those that culminate in releases from building structural components). Indoor exposures also can occur when substances are transported from outdoor sources into a building [as for example, when contaminated soil is tracked into buildings, or gases volatilize from underlying contaminated soil or groundwater—usually referred to as 'vapor intrusion' (discussed further below)].

Regardless of the sources, indoor air contaminants can impose significant risks onto occupants of the invaded structure. For instance, among other potential indoor air quality issues, certain volatile organic compounds (VOCs), such as formaldehyde and toluene, can have concentrations tens of times higher indoors than they are outdoors due to off-gassing from synthetic building materials, furnishing, etc. Additional significant contributors to such indoor emissions may include chemically-formulated personal care products, insecticides, household cleaners, etc. Ultimately, poor indoor air quality can elicit a variety of health symptoms ranging from respiratory ailments such as asthmatic wheezing and chronic lung disease to non-specific symptoms such as headache, fatigue, and general discomfort. In reality, individual sensitivities can vary considerably, and multiple pollutants and/or building factors may additionally contribute to protracted and 'erratic' symptoms—potentially making it difficult for investigators to pinpoint specific causative agents.

It is notable that indoor sources of VOCs have indeed become ubiquitous—resulting in detectable levels of contaminants in indoor air at numerous locations, often at concentrations above 'regulatory levels' of concern. Thus, being able to distinguish between vapor intrusion and other indoor sources of VOCs is quite important in any likely risk management and abatement efforts designed to protect potential receptors from possible exposures to such contamination. At any rate, it is also noteworthy here that various other mechanisms can actually add and/or exacerbate indoor air quality problems as a whole; thus, it is imperative to consistently make the best effort to understand all potential sources, and to ultimately carry out reasonably holistic evaluations—i.e., one that, among other things, judiciously/effectually utilize proper sampling equipment and analytical protocols for such problem situations.

3.1.1.2 Chemical Vapor Intrusion into Buildings

Vapor intrusion (VI) of chemicals generally refers to the migration of volatile chemicals from the subsurface into an overlying building; more specifically, it is defined as the vapor-phase migration of (usually toxic) VOCs from a subsurface environment (e.g., contaminated soil and/or groundwater) into overlying or nearby structures/buildings (e.g., through floor slabs and foundation joints or cracks, gaps around utility lines, etc.), subsequently accumulating (to potentially 'unacceptable'

or 'unsafe' levels) and potentially persisting in the indoor air—ultimately with consequential impacts on the indoor air quality, and thus potentially posing risks to building occupants. Generally speaking, VOCs are characterized by relatively high vapor pressures that permit these compounds to vaporize and enter the atmosphere under normal conditions; because of these characteristics, the VI phenomenon is particularly unique or prevalent to this class of organic chemicals. Still, it is also notable that although VOCs typically present the most common concerns in regards to vapor intrusion issues, there are a number of other contaminant families that may similarly engender vapor intrusion problems—including other 'vapor-forming' chemicals such as some SVOCs, elemental mercury, and radionuclides.

By and large, volatile chemicals in buried wastes or other subterranean contaminated soils/groundwater can emit vapors that may in turn migrate through subsurface soils (and/or via sub-slabs, crawlspaces, etc.) into the indoor air spaces of overlying buildings. When this happens, the chemical concentrations in the released soil gas typically would decrease (or attenuate) as the vapors migrate through materials from the contamination sources into the overlying structures. This attenuation is usually the result of processes that control vapor transport in the soil materials (e.g., diffusion, advection, sorption, and potentially biotransformation), as well as processes that control the transport and dilution of vapors as they enter the building and mix with indoor air (e.g., pressure differential and building ventilation rates). Indeed, several other physicochemical and ambient environmental factors may generally affect the ultimate fate and behaviors of the chemicals of interest in any given VI problem situations.

As an archetypical illustrative example of a VI problem scenario, consider a situation whereby chlorinated solvents or petroleum products are accidentally released at an industrial or commercial facility—which then migrates downward and reaches groundwater where it can slowly dissolve and form contaminant plumes. Subsequently, the volatile compounds can volatilize and travel upwards as soil vapors to reach the ground surface; in situations where buildings or other occupied structures sit atop such ground surface, contaminant vapors can seep through foundation cracks/joints and contaminate indoor air—presenting potentially serious public health concerns. Indeed, in view of the fact that many of the typical volatile compounds [such as benzene, tetrachloroethylene/perchloroethylene (PCE) , and trichloroethylene (TCE)], are considered carcinogenic, there is always the concern that even relatively low levels of such chemicals inhaled by building occupants can pose unacceptable long-term health risks. On the other hand, evaluation of the VI pathway tends to be complicated by 'background' volatile compound contributions (e.g., due to potential confounding effects of household VOC sources from consumer products, etc.), as well as considerable spatial and temporal variability in soil vapor and indoor air concentrations. Undeniably, vapor migration from subsurface environments into indoor air is often affected by many variables—not the least of which include building characteristics, anthropogenic conditions, and meteorological influences or seasonal changes; subsequent attenuation due to diffusion, advection, sorption, and potential degradation processes may also occur during movements from the contaminant source

into the receptor exposure zones. Consequently, it makes more sense to employ 'multiple lines of evidence' to support and adequately/holistically evaluate the vapor intrusion pathway and associated potential risks to public health.

Finally, it is worth mentioning that VI is considered an 'emerging' and growing public health problem/concern that requires deliberate planning efforts—and even more importantly, careful assessment and management strategies to avert potential 'hidden' but serious public health hazard situations. This might mean implementing aggressive VI pathway assessment at potentially contaminated sites or impacted structures—and then ensuring the implementation of appropriate vapor mitigation measures, as necessary.

3.1.2 Water Pollution Problems and Human Exposures to Chemicals in Water as an Example

Historically, surface waters were among the first environmental media to receive widespread attention with regards to environmental/chemical pollution problems. This attention was due in part to the high visibility and extensive public usage of surface waters, as well as for their historical use as 'waste receptors' (Hemond and Fechner 1994). Anyhow, surface water contamination may also result from contaminated runoff and overland flow of chemicals (from leaks, spills, etc.), as well as from chemicals adsorbed onto mobile sediments. In addition, it has to be recognized that groundwater resources are just about as vulnerable to environmental/chemical contamination; typically, groundwater contamination may result from the leaching of toxic chemicals from contaminated soils, or the downward migration of chemicals from lagoons and ponds, etc. Further yet are the likely complexities associated with possible groundwater–surface water interactions—since this would usually affect the mixing and transfer of contaminants from one source to the other in a rather complex manner. Ultimately, there is a crucial water quality problem that engenders important exposure scenarios worth devoting significant resources to help resolve.

Next, another major but often seemingly 'hidden' concern with regards to water quality management programs that should not be overlooked relates to the issue of eutrophication—i.e., the nutrient enrichment of the water and the bottom of surface water bodies. Indeed, human-made eutrophication has been considered one of the most serious global water quality problems for surface water bodies during the past few decades. Meanwhile, it is worth mentioning here that increasing discharges of domestic and industrial wastewater, the intensive use of crop fertilizers, the rise in airborne pollution, and the natural mineralization of streamflows can be seen as some of the primary causes of this undesirable phenomenon. Typical symptoms of eutrophication include, among other things, sudden algal blooms, water coloration, floating water-plants and debris, excretion of toxic substances that causes taste and odor problems in drinking water production/supply systems, and sometimes fish

kills. These symptoms can result in limitations of water use for domestic, agricultural, industrial, or recreational purposes. In addition, the nitrates coming from fertilizer applications tend to eventually become drinking water hazards, especially because the nitrate ion (NO_3^-) is reduced to the nitrite ion (NO_2^-) in the human body following the consumption of the nitrate-containing water—and the nitrite destroys the ability of hemoglobin to transport oxygen to the cells; in fact, high nitrate concentrations in drinking water are particularly dangerous to small infants.

In the end, the appraisal of human exposure to chemicals in contaminated water problems should address all intake sources—including that resulting from water ingestion, as well as from dermal contacting and inhalation of the volatile constituents in water. Finally, it is also worth mentioning the fact that groundwater is extensively used by public water supply systems in several places around the world; thus, it is always important to give very close attention to groundwater pollution problems in chemical exposure evaluation programs.

3.1.3 Contaminated Soil Problems and Human Exposures to Chemicals on Land

Contaminated soils may arise in a number of ways—many of which are the result of manufacturing and other industrial activities or operations. In fact, much of the soil contamination problems encountered in a number of places globally are the result of waste generation associated with various forms of industrial activities. In particular, the chemicals and allied products manufacturers are generally seen as the major sources of industrial hazardous waste generation that culminates in contaminated soil problems. These industries generate several waste types, such as organic waste sludge and still bottoms (containing chlorinated solvents, metals, oils, etc.); oil and grease (contaminated with polychlorinated biphenyls [PCBs], polyaromatic hydrocarbons [PAHs], metals, etc.); heavy metal solutions (of arsenic, cadmium, chromium, lead, mercury, etc.); pesticide and herbicide wastes; anion complexes (containing cadmium, copper, nickel, zinc, etc.); paint and organic residuals; and several other chemicals and byproducts that have the potential to contaminate lands. Ultimately, such industrial and related activities lead to the births of contaminated lands that are generally seen as complex problems with worldwide implications.

In addition to the above situations involving direct releases at a given locale, several different physical and chemical processes can also affect contaminant migration from contaminated soils; thus, contaminated soils can potentially impact several other environmental matrices. For instance, atmospheric contamination may result from emissions of contaminated fugitive dusts and volatilization of chemicals present in soils; surface water contamination may result from contaminated runoff and overland flow of chemicals (from leaks, spills, etc.), and chemicals adsorbed to mobile sediments; groundwater contamination may result from the

leaching of toxic chemicals from contaminated soils, or the downward migration of chemicals from lagoons and ponds; etc. Consequently, human exposures to chemicals at contaminated lands may occur in a variety/multiplicity of ways—including via the following more common example pathways:

- Direct inhalation of airborne vapors, and also respirable particulates.
- Deposition of airborne contaminants onto soils, leading to human exposure via dermal absorption or ingestion.
- Ingestion of food products that have been contaminated as a result of deposition onto crops or pasture lands, and subsequent introduction into the human food chain.
- Ingestion of contaminated dairy and meat products from animals consuming contaminated crops or waters.
- Deposition of airborne contaminants onto waterways, uptake through aquatic organisms, and eventual human consumption of impacted aquatic foods.
- Leaching and runoff of soil contamination into water resources, and consequential human exposures to contaminated waters in a water supply system.

Contaminated lands, therefore, will usually represent a potentially long-term source for human exposure to a variety of chemical toxicants; thus, risk to public health arising especially from soils at contaminated lands is a matter of grave concern.

3.1.4 Human Exposures to Chemicals in Foods and Household/Consumer Products

Food products represent a major source of human exposure to chemicals, even if in incrementally minute amounts. For example, a number of investigations have shown that much of the seafood originating from most locations globally contains detectable levels of environmental pollutants (such as Pb, Cr, PCBs, dioxins and pesticides). Also, chemicals such as tartrazine, a previously revered food preservative that was widely used in some countries, has now been determined to cause allergies in significant numbers of human populations; consequently, there is a clear move away from the use of such chemicals—as, for example, is demonstrated by the fact that 'chips' and indeed many other food items sold in South Africa had at some point in time proudly displayed on the packaging that the products are 'tartrazine-free', etc. (Personal Communication with Dr. Kwabena Duah). At any rate, because of the potential human exposure to the variety of toxic/hazardous chemicals, it is very important to understand the potential human health risks associated with these exposures and the likely public health implications of such chemicals being present in the food sources or other consumer products.

In general, human dietary exposure to chemicals in food (and indeed similar consumable or even household products) depends both on [food] consumption

patterns and the residue levels of a particular chemical on/in the food or consumer product—generally expressed by the following conceptual relationship (Driver et al. 1996; Kolluru et al. 1996):

$$\text{Dietary Exposure} = f(\text{Consumption}, \text{Chemical concentration}) \tag{3.1}$$

Typically, as an example, multiplying the average consumption of a particular food product by the average chemical concentration on/in that food provides the average ingestion rate of that chemical from the food product. In reality, however, estimation of dietary exposure to chemicals—such as pesticides or food additives—becomes a more complex endeavor, especially because of the following likely factors (Driver et al. 1996; Kolluru et al. 1996):

- Occurrence of a particular chemical in more than one food item.
- Variation in chemical concentrations in food products and other consumer items.
- Person-to-person variations in the consumption of various food products.
- Variation in dietary profiles across age, gender, ethnic groups, and geographic regions.
- Fraction of consumable food product actually containing the chemical of concern (e.g., treated with a given pesticide).
- Possible reductions or changes in chemical concentrations or composition due to transformation during transport, storage, and food preparation.

In the end, the inherent variability and uncertainty in food consumption and chemical concentration data tend to produce a high degree of variability in the concomitant dietary exposure and risk for a given chemical. For instance, the dietary habits of a home gardener may result in an increase or decrease in exposure—possibly attributable to their unique consumption rates, as well as the contaminated fractions involved.

In general, individual consumers may indeed ingest significantly different quantities of produce and, depending on their fruit/vegetable preferences, may also be using more of specific crops that are efficient accumulators of contaminants/chemicals (or otherwise). Consequently, both food consumption and chemical concentrations data are best represented or characterized by dynamic distributions that reflect a wide range of values, rather than by a single value. Under such circumstances, the distribution of dietary exposures and risks may be determined by using both the distribution of food consumption levels and the distribution of chemical concentrations in food (see, e.g., Brown et al. 1988; Driver et al. 1996; National Research Council [NRC] 1993a, b, c; Rodricks and Taylor 1983; USEPA 1986a, b, c, d, e, f).

3.2 Quantification Process for the General Types of Human Exposures to Chemical Toxicants

The likely types and significant categories of human exposures to a variety of chemical materials that could affect public health risk management decisions are generally very much dependent on the specific routes of receptor exposures; the fundamental quantification elements that may be utilized for the key distinctive routes of general interest are annotated below (Al-Saleh and Coate 1995; Corn 1993; OECD 1993).

- *Skin Exposures*. The major types of dermal exposures that could affect public health risk management decisions consist of dermal contacts with chemicals present in consumer products or in the environment, and also dermal absorption from contaminated waters. Dermal exposures that results from the normal usage of consumer products may be expressed by the following form of generic relationship:

$$\text{Dermal Exposure} = \frac{\{[\text{CONC}] \times [\text{PERM}] \times [\text{AREA}] \times [\text{EXPOSE}]\}}{[\text{BW}]} \tag{3.2}$$

  where: CONC is the concentration of material (in the medium of concern); PERM is the skin permeability constant; AREA is the area of exposed skin (in contact with the medium); EXPOSE is the exposure duration (i.e., duration of contact); BW is the average body weight.

  In general, fat-soluble chemical substances, and to some extent, the water-soluble chemicals can be absorbed through even intact skins—also recognizing that, by and large, skin characteristics such as sores and abrasions may facilitate or enhance skin/dermal uptakes. Environmental factors such as temperature and humidity may also influence skin absorption of various chemicals. Furthermore, the physical state (i.e., solid *vs*. liquid *vs*. gas), acidity (i.e., pH), as well as the concentration of the active ingredient of the contacted substance will generally affect the skin absorption rates/amounts.
- *Oral Exposures*. Ingestion takes place when chemical-containing food materials, medicines, etc. are consumed via the mouth or swallowed. The major types of chemical ingestion exposures that could affect public health risk management decisions consist of the oral intake of contaminated materials (e.g., soils intake by children exercising pica behavior), food products (e.g., plant products, fish, animal products, and mother's milk), and waters. Ingestion exposures that results from the normal usage of consumer products may be expressed by the following form of generic relationship:

$$\text{Oral Exposure} = \frac{\{[\text{CONC}] \times [\text{CONSUME}] \times [\text{ABSORB}] \times [\text{EXPOSE}]\}}{[\text{BW}]} \tag{3.3}$$

where: CONC is the concentration of material (i.e., the concentration of the contaminant in the material ingested—e.g., soil, water, or food products such as crops, and dairy/beef); CONSUME is the consumption amount/rate of material; ABSORB is the per cent (%) absorption (i.e., the gastrointestinal absorption of the chemical in solid or fluid matrix); EXPOSE is the exposure duration; BW is the average body weight.

The total dose received by the potential receptors from chemical ingestions will, in general, be dependent on the absorption of the chemical across the gastro-intestinal (GI) lining. The scientific literature provides some estimates of such absorption factors for various chemical substances. For chemicals without published absorption values and for which absorption factors are not implicitly accounted for in toxicological parameters, absorption may conservatively be assumed to be 100%.

- *Inhalation Exposures to Volatiles*. Exposures to volatile chemical materials that results from the normal usage of consumer products may be expressed by the following form of generic relationship:

$$\text{Inhalation Exposure to Volatiles} = \frac{\{[\text{VAPOR}] \times [\text{INHALE}] \times [\text{RETAIN}] \times [\text{EXPOSE}]\}}{[\text{BW}]} \tag{3.4}$$

where: VAPOR is the vapor phase concentration of material (i.e., the concentration of chemical in the inhaled air); INHALE is the inhalation rate (of the exposed individual); RETAIN is the lung retention rate (i.e., the amount retained in the lungs); EXPOSE is the exposure duration (i.e., the length of exposure of the exposed individual); BW is the average body weight (of the exposed individual).

It is noteworthy that, as an example, showering—which represents one of the most common and universal human activities—generally encompasses a system that promotes release of VOCs from water (due to high turbulence, high surface area, and small droplets of water involved). In fact, some studies have shown that risks from inhalation while showering can be comparable to—if not greater than—risks from drinking contaminated water (Jo et al. 1990a, b; Kuo et al. 1998; McKone 1987; Richardson et al. 2002; Wilkes et al. 1996). Thus, this exposure scenario represents a particularly important one to evaluate in a public health risk assessment, as appropriate. In this case, the concentration of any contaminants in the shower air is assumed to be in equilibrium with the concentration in the water. In another example that takes into consideration the fact that the degree of dilution in the indoor air of a building is generally far less than situations outdoors, contaminant vapors entering/infiltrating into a building structure may represent a significantly higher risk to occupants of such buildings. In fact, the migration of subsurface contaminant vapors into buildings can become a very important source of human exposure via the inhalation route. As appropriate, therefore, a determination of the relative significance of vapor

transport and inhalation as a critical exposure scenario should be given serious consideration during the processes involved in the characterization of chemical exposure problems, and in establishing environmental quality criteria and/or public health goals. Risk assessment methods can generally be used to make these types of determination—i.e., as to whether or not vapor transport and inhalation represent a significant exposure scenario worth focusing on in a given study. For example, a risk characterization scenario involving exposure of populations to vapor emissions from cracked concrete foundations/floors can be determined on such basis, in order for responsible risk management and/or mitigative measures to be adopted.

- *Inhalation Exposures to Particulate Matter*. Exposures to inhalable chemical particulates that results from the normal usage of consumer products may be expressed by the following form of generic relationship:

$$\text{Inhalation Exposure to Particulates} = \frac{\{[\text{PARTICLE}] \times [\text{RESPIRABLE}] \times [\text{INHALE}] \times [\text{ABSORB}] \times [\text{EXPOSE}]\}}{[\text{BW}]} \tag{3.5}$$

where: PARTICLE is the total aerosol or particulate concentration of material; RESPIRABLE is the % of respirable material; INHALE is the inhalation rate; ABSORB is the % absorbed; EXPOSE is the exposure duration; BW is the average body weight. It is noteworthy that, in general, only particulate matter of size $\leq$10 μm (referred to as PM-10 or PM10) can usually be transported through the upper respiratory system into the lungs.

In addition to the above major exposure situations, it must be acknowledged that accidental exposures may also occur via the same routes (i.e., from dermal contact, oral ingestion, and/or inhalation). Furthermore, chemical vapors or aerosols may be absorbed through the lungs.

Indeed, the analysis of potential human receptor exposures to chemicals found in our everyday lives and in the human living and work environments often involves several complex issues. In all cases, however, the exposures are generally evaluated via the calculation of the average daily dose (ADD) and/or the lifetime average daily dose (LADD). Typically, the carcinogenic effects (and sometimes the chronic non-carcinogenic effects) associated with a chemical exposure problem involve estimating the LADD; for non-carcinogenic effects, the ADD is commonly used. The ADD differs from the LADD, in that the former is not averaged over a lifetime; rather, it is the average of the daily dose pertaining to the actual number of days of exposure. Additionally, the maximum daily dose (MDD) will typically be used in estimating acute or subchronic exposures. Details of the requisite algorithms for estimating potential human exposures and intakes under variant scenarios are elaborated in Chap. 9.

Part II
A Public Health Risk Assessment Taxonomy: Nomenclatural Components, Concepts, Principles, and Evaluation Strategies

This part of the book is comprised of the following three specific chapters:

- Chapter 4, *Principles and Concepts in Risk Assessment*, discusses key fundamental principles and concepts that will be expected to facilitate the application and interpretation of risk assessment information—and thus make it more suitable in public health risk management decisions.
- Chapter 5, *Attributes of a Public Health Risk Assessment*, discusses key attributes that will facilitate the application and interpretation of risk assessment information—and thus make it more useful in public health risk management decisions, recognizing that a good understanding of several important attributes of the risk assessment mechanisms would generally help both the risk assessor/analyst and the risk manager in practice.
- Chapter 6, *General Basic Planning Considerations for a Chemical Exposure Characterization Activity*, catalogs and elaborates the pertinent planning considerations, foundational building blocks/elements, and general requirements that would likely assure a reasonably cost-effective implementation of a chemical exposure investigation and characterization activity—particularly in relation to environmental contamination issues/problems; this includes a general discussion of the key elements for effectual problem conceptualization/formulation, chemical fate and behavior appraisement concepts, as well as the steps typically taken to develop comprehensive work-plans in data collection activities that are often necessary to support the characterization and management of environmental contamination and related potential chemical exposure problems.

Chapter 4
Principles and Concepts in Risk Assessment

In its application to chemical exposure problems, the risk assessment process is used to compile and organize the scientific information that is necessary to support environmental and public health risk management decisions. The approach is used to help identify potential problems, establish priorities, and provide a basis for regulatory actions. Indeed, it is apparent that the advancement of risk analysis in regulatory decision-making—among several others—has helped promote rational policy deliberations over the past several decades. Yet, as real-world practice indicates, risk analyses have often been as much the source of controversy in regulatory considerations as the facilitator of consensus (ACS and RFF 1998). Anyhow, risk assessment can appropriately be regarded as a valuable tool for public health and environmental decision-making—albeit there tends to be disagreement among experts and policy makers about the extent to which its findings should influence decisions about risk. To help produce reasonable/pragmatic and balanced policies in its application, it is essential to explicitly recognize the character, strengths, and limitations of the analytical methods that are involved in the use of risk analyses techniques in the decision-making process.

Overall, risk assessment methods commonly encountered in the literature of environmental and public health management, and/or relevant to the management of chemical exposure problems characteristically require a clear understanding of several fundamental issues/tenets and related attributes. This chapter discusses key fundamental principles and concepts that will be expected to facilitate the application and interpretation of risk assessment information—and thus make it more suitable in public health risk management decisions.

K. Asante-Duah, *Public Health Risk Assessment for Human Exposure to Chemicals*,
Environmental Pollution 27, DOI 10.1007/978-94-024-1039-6_4

4.1 Fundamental Principles of Chemical Hazard, Exposure, and Risk Assessments

Hazard is that object with the potential for creating undesirable adverse consequences; *exposure* is the situation of vulnerability to hazards; and *risk* is considered to be the probability or likelihood of an adverse effect due to some hazardous situation. Indeed, the distinction between hazard and risk is quite an important consideration in the overall appraisal of risk possibilities and/or scenarios; broadly speaking, it is the likelihood to harm as a result of exposure to a hazard that distinguishes risk from hazard. Accordingly, a substance is considered a hazard if it is capable of causing an adverse effect under any particular set of circumstance (s)—whereas risk generally reflects the probability that an adverse effect will occur under actual or realistic circumstances, also taking into account the potency of the specific substance and the level of exposure to that substance. For example, a toxic chemical that is hazardous to human health does not constitute a risk unless human receptors/populations are exposed to such a substance—as conceptually illustrated by the Venn diagram representation shown in Fig. 4.1. Thus, from the point of view of human exposure to chemicals, risk can be defined as the probability that public health could be affected to various degrees (including an individual or group suffering injury, disease, or even death) under specific set of circumstances.

The integrated and holistic assessment of hazards, exposures and risks are indeed a very important contributor to any decision that is aimed at adequately managing any given hazardous situation. To this end, potential risks are estimated by considering the following key elements:

- Probability or likelihood of occurrence of harm;
- Intrinsic harmful features or properties of specified hazards;

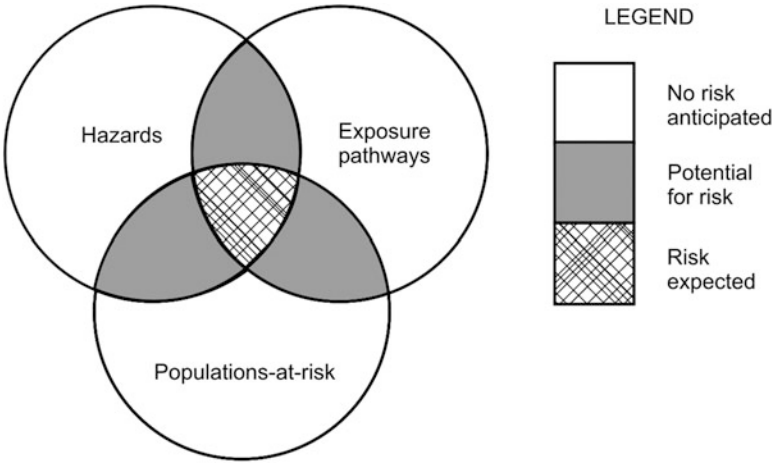

Fig. 4.1 When do hazards actually represent risks?

- Population-at-risk (PAR);
- Exposure scenarios; and
- Extent of expected harm and potential effects.

On the whole, a complete assessment of potential hazards posed by a substance or an object typically involves, among several other things, a critical evaluation of available scientific and technical information on the substance or object of concern, as well as the possible modes of exposure. In particular, it becomes increasingly apparent that potential receptors will have to be exposed to the hazards of concern before any risk could be said to exist. Overall, the availability of an adequate and complete information set is an important prerequisite for producing sound hazard, exposure, and risk assessments.

4.1.1 The Nature of Chemical Hazard, Exposure, and Risk

Hazard is broadly defined as the potential for a substance or situation to cause harm, or to create adverse impacts on populations and/or property. It represents the undetermined loss potential, and may comprise of a condition, a situation, or a scenario with the potential for creating undesirable consequences. The degree of chemical hazard will usually be determined from the type of exposure scenario and the potential effects or responses resulting from any exposures. Next, whereas there may be no universally accepted single definition of risk, this generally may be considered as the probability or likelihood of an adverse effect, or an assessed threat to persons due to some hazardous situation; it is a measure of the probability and severity of adverse consequences from an exposure of potential receptors to hazards—and may simply be represented by the measure of the frequency of an event.

Procedures for analyzing hazards and risks may typically be comprised of several steps (Fig. 4.2), consisting of the following general elements:

- Hazard Identification and Accounting
  - Identify hazards (including nature/identity of hazard, location, etc.)
  - Identify initiating events (i.e., causes)
  - Identify resolutions for hazard
  - Define exposure setting
- Vulnerability Analysis
  - Identify vulnerable zones or locales
  - Identify concentration/impact profiles (or levels/degrees of hazards) for affected zones
  - Determine populations potentially at risk (such as human populations, and critical facilities)
  - Define exposure scenarios

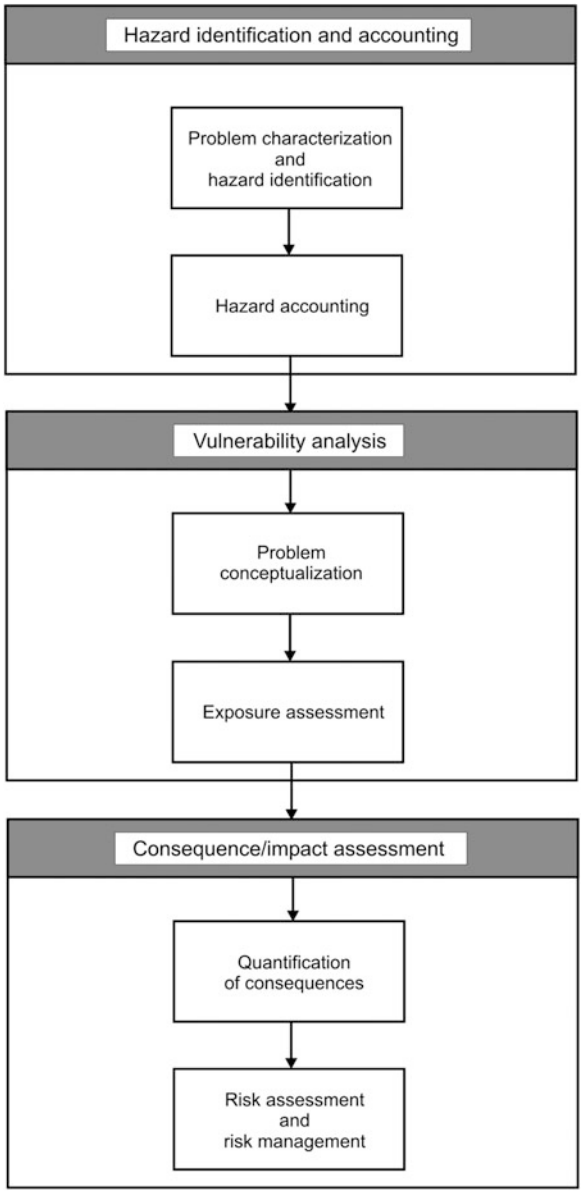

Fig. 4.2 Basic steps in the analyses of hazards and risks

- Consequences/Impacts Assessment
  - Determine risk categories for all identifiable hazards
  - Determine probability of adverse outcome (from exposures to hazards)
  - Estimate consequences (including severity, uncertainties, etc.).

Some or all of these elements may have to be analyzed in a comprehensive manner, depending on the nature and level of detail of the hazard and/or risk analysis that is being performed. Anyhow, the analyses typically fall into two broad categories—namely: endangerment assessment (which may be considered as contaminant-based, such as human health and environmental risk assessment associated with chemical exposures); and safety assessment (which is system failure-based, such as probabilistic risk assessment of hazardous facilities or installations). At the end of the day, the final step will be comprised of developing risk management and/or risk prevention strategies for the problem situation.

4.1.1.1 Hazard Vs. Risk: Portraying the Nomenclatural Differences

Invariably, hazard characterization will often form an important foundational basis for most environmental and public health risk management programs; the general purpose of such hazard characterization is to make a qualitative judgment of the effect(s) caused by an agent or stressor under consideration, and its relevance to a target population of interest. Clearly, in translating hazard characterization into corresponding risk value or indicator, the processes involved need to consider, among other things, the severity of critical effects and the specific affected population groups, etc.; for instance, in determining 'safe exposure limits' associated with human exposure to nitrate, it is important to recognize the fact that infants are very sensitive to nitrate exposures (related to methemoglobinemia)—whereas this critical effect would not be relevant to the development of an occupational exposure limit. Consequently, it is important to carefully consider the scenarios of interest (with respect to population, duration, exposure routes, etc.) in such characterization efforts, in order to arrive at realistic and pragmatic risk conclusions—and subsequently an effectual risk management plan of action.

It is noteworthy that, irrespective of the type of analytical protocols adopted for any given evaluation scenarios, a clear distinction between the terms 'hazard' and 'risk' can become a major issue to contend with in various important risk communication and/or risk management efforts. This may be especially true in any attempts to relay risk appraisal outcomes to a potentially impacted community that may, rightly or wrongly, perceive likely threat levels as being 'unacceptable'. Thus, it becomes even more important to come up with proper clarification nomenclatures that explicitly recognize the fact (as well as properly convey the message) that 'hazard' is generally defined as the potential to harm a target population, whereas 'risk' would typically encompass the probability of exposure along with the extent of damage. After all, hazard is associated only with the *intrinsic ability* of an agent, stressor, or situation to cause adverse effects to a target population or receptor—and this ability may never even materialize if the targets are adequately protected and/or are immune from exposure; in contrast, risk typically would take the probability and the scale of damage into account—based on the fact or assumption that a harmful event will inevitably occur. Hence, the 'decisive factor' under such circumstances is the appropriate weighting of the possible scale of damage

with the probability of exposure and the related harm—culminating in risk being generally deemed as the probability of occurrence of a harmful event (Scheer et al. 2014). In a way, defining risk therefore becomes a process of combining what might be viewed as 'possibilistic' measures with probability concepts (and perhaps with other qualitative indicators as well) in order to arrive at credible risk measures.

4.1.2 Basis for Measuring Risks

Risk represents the assessed loss potential, often estimated by the mathematical expectation of the consequences of an adverse event occurring. It is generically defined by the product of the two components of the probability of occurrence (p) and the consequence or severity of occurrence (S), *viz.*:

$$\text{Risk} = p \times S \tag{4.1}$$

When interpreted as the probability of a harmful event to humans or to the environment that is caused by a chemical, physical, or biological agent, risk can also be described by the following conceptual relationship:

$$\text{Risk} = [f(\text{I}) \times f(\text{P})] - f(\text{D}) \tag{4.2}$$

where f(I) represents an 'intrinsic risk' factor that is a function of the characteristic nature of the agent or the dangerous properties of the hazard; f(P) is a 'presence' factor that is a function of the quantity of the substance or hazard released into the human environment, and of all the accumulation and removal methods related to the chemical and physical parameters of the product, as well as to the case-specific parameters typical of the particular environmental setting; and f(D) represents a 'defense' factor that is a function of what society can do in terms of both protection and prevention to minimize the harmful effects of the hazard. Meanwhile, it could perhaps be argued that the most important factor in this equation is f(D); this may include both the ordinary defense mechanisms for hazard abatement, as well as some legislative measures. In effect, the level of risk is very much dependent on the degree of hazard as well as on the amount of safeguards or preventative measures against adverse effects; consequently, risk can also be conveniently defined by the following simplistic conceptual relationships:

$$\text{Risk} = \frac{[\text{Hazard}]}{[\text{Preventative Measures}]} \tag{4.3}$$

or

$$\text{Risk} = f\{\text{Hazard}, \text{Exposure}, \text{Safeguards}\} \tag{4.4}$$

where 'Preventative Measures' or 'Safeguards' is considered to be a function of exposure—or rather inversely proportional to the degree of exposure; the 'Preventative Measures' or 'Safeguards' components represent the actions that are generally taken to minimize potential exposure of target populations to the specific hazards.

It is notable that, invariably, the estimation of risks involves an integration of information on the intensity, frequency, and duration of exposure for all identified exposure routes associated with the exposed or impacted group(s); for instance, an identifiable risk may represent the probability for a chemical to cause adverse impacts to potential receptors as a result of exposures over specified time periods. Anyhow, the risk measures commonly give an indication of the probability and severity of adverse effects (Fig. 4.3)—and this is generally established with varying degrees of confidence according to the importance of the decision involved.

In general, measures used in risk analysis take various forms, depending on the type of problem, degree of resolution appropriate for the situation on hand, and the analysts' preferences. Thus, the risk parameter may be expressed in quantitative terms—in which case it could take on values from zero (associated with certainty for no-adverse effects) to unity (associated with certainty for adverse effects to occur). In several other cases, risk is only described qualitatively—such as by use of descriptors like 'high', 'moderate', 'low', etc.; or indeed, the risk may be described in semi-quantitative/semi-qualitative terms. In any case, the risk qualification or quantification process will normally rely on the use of several measures, parameters and/or tools as reference yardsticks (Box 4.1)—with 'individual lifetime risk' (represented by the probability that the individual will be subjected to an adverse effect from exposure to identified hazards) being about the most commonly used measure of risk. At any rate, it is also worth mentioning here that the type or nature of 'consuming/target audience' must be given careful consideration in choosing the type of risk measure or index to adopt for a given program or situation.

Box 4.1 Typical/Common Measures, Parameters, and/or Tools That Form the Basis for Risk Qualification or Quantification

- Probability distributions (based on probabilistic analyses)
- Expected values (based on statistical analyses)
- Economic losses or damages
- Public health damage
- Risk profile diagrams (e.g., iso-risk contours plotted on area map, to produce an iso-risk contour map)
- Incidence rate (defined by the ratio of [number of new cases over a period of time]:[population at risk])

(continued)

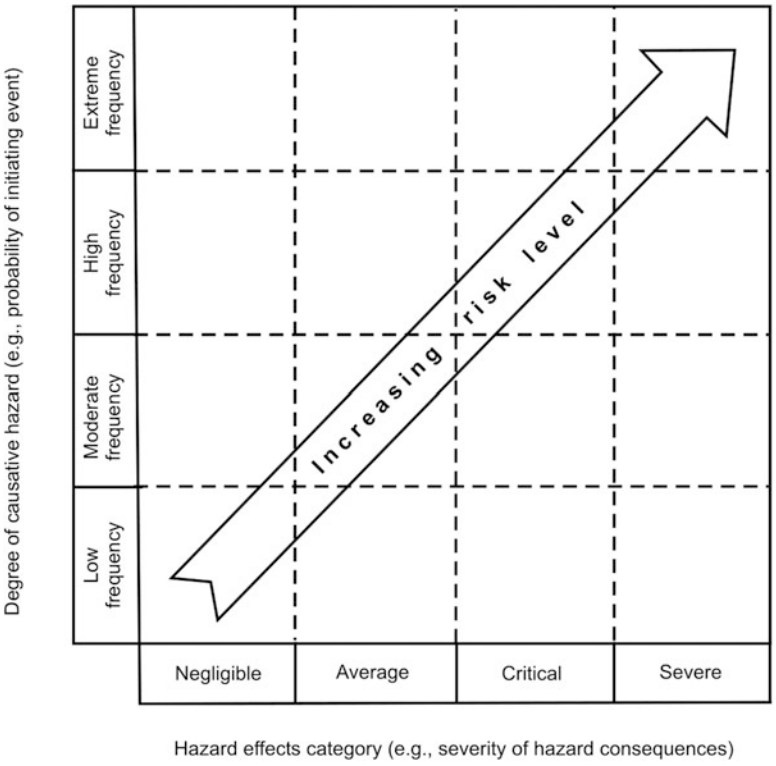

Fig. 4.3 General conceptual categories of risk measures

Box 4.1 (continued)

- Prevalence rate (defined by the ratio of [number of existing cases at a point in time]:[total population])
- Relative risk (i.e., risk ratio) (defined by a ratio such as [incidence rate in exposed group]:[incidence rate in non-exposed group])
- Attributable risk (i.e., risk difference) (defined by an arithmetic difference, such as [incidence among an exposed group]—[incidence among the non-exposed group])
- Margin of safety (defined by the ratio of [the highest dose level that does *not* produce an adverse effect]:[the anticipated human exposure])
- Individual lifetime risk (equal to the product of exposure level and severity, e.g., [dose × potency])
- Population or societal risk (defined by the product of the individual lifetime risk and the population exposed)

(continued)

Box 4.1 (continued)

- Frequency-consequence diagrams (also known as F-N curves for fatalities, to define societal risk)
- Quality of life adjustment (or quality adjusted life expectancy, QALE)
- Loss of life expectancy (given by the product of individual lifetime risk and the average remaining lifetime)

4.1.3 What Is Risk Assessment?

Several somewhat differing definitions of risk assessment have been published in the literature by various authors to describe a variety of risk assessment methods and/or protocols (see, e.g., Asante-Duah 1998; Cohrssen and Covello 1989; Conway 1982; Cothern 1993; Covello et al. 1986; Covello and Mumpower 1985; Crandall and Lave 1981; Davies 1996; Glickman and Gough 1990; Gratt 1996; Hallenbeck and Cunningham 1988; Kates 1978; Kolluru et al. 1996; LaGoy 1994; Lave 1982; Neely 1994; Norrman 2001; NRC 1982, 1983, 1994a, b; Richardson 1990, 1992; Rowe 1977; Scheer et al. 2014; Turnberg 1996; USEPA 1984; Whyte and Burton 1980). In a generic sense, risk assessment may be considered to be a systematic process for arriving at estimates of all the significant risk factors or parameters associated with an entire range of 'failure modes' and/or exposure scenarios in connection with some hazard situation(s). It entails the evaluation of all pertinent scientific information to enable a description of the likelihood, nature, and extent of harm to human health as a result of exposure to chemicals (and really other potential stressors) present in the human environments.

Risk assessment is indeed a scientific process that can be used to identify and characterize chemical exposure-related human health problems. In its application to the management of chemical exposure problems, the process encompasses an evaluation of all the significant risk factors associated with all feasible and identifiable exposure scenarios that are the result of specific chemicals being introduced into the human environments. It may, for instance, involve the characterization of potential adverse consequences or impacts to a target (human) population or groups that are potentially at risk due to exposure to chemicals found in consumer products and/or in the environment.

Overall, the public health risk assessment process seeks to estimate the likelihood of occurrence of adverse effects resulting from exposures of human receptors to chemical, physical, and/or biological agents present in the human living and work environments. The process entails a mechanism that utilizes the best available scientific knowledge to establish case-specific responses that will ensure justifiable and defensible decisions—as necessary for the management of hazardous situations in a cost-efficient manner. The process is also concerned with the assessment of the

importance of all identified risk factors to the various stakeholders whose interests are embedded in a candidate problem situation (Petak and Atkisson 1982).

4.1.4 The Nature of Risk Assessments

Traditionally, risk assessment methods have been viewed as belonging to one of several general major categories—typically under the broad umbrellas of: hazard assessment, exposure assessment, consequence assessment, and risk estimation (Covello and Merkhofer 1993; Norrman 2001). The *hazard assessment* may consist of monitoring (e.g., source monitoring and laboratory analyses), performance testing (e.g., hazard analysis and accident simulations), statistical analyses (e.g., statistical sampling and hypotheses testing), and modeling methods (e.g., biological models and logic tree analyses). The *exposure assessment* may be comprised of monitoring (e.g., personal exposures monitoring, media contamination monitoring, biologic monitoring), testing (e.g., laboratory tests and field experimentation), dose estimation (e.g., as based on exposure time, material disposition in tissue, and bioaccumulation potentials), chemical fate and behavior modeling (e.g., food-chain and multimedia modeling), exposure route modeling (e.g., inhalation, ingestion, and dermal contact), and populations-at-risk modeling (e.g., general population *vs.* sensitive groups). The *consequence assessment* may include health surveillance, hazard screening, animal tests, human tests, epidemiologic studies, animal-to-human extrapolation modeling, dose-response modeling, pharmacokinetic modeling, ecosystem monitoring, and ecological effects modeling. The *risk estimation* will usually take such forms as relative risk modeling, risk indexing (e.g., individual risk *vs.* societal risk), nominal *vs.* worst-case outcome evaluation, sensitivity analyses, and uncertainty analyses. Detailed listings of key elements of the principal risk assessment methods are provided elsewhere in the literature (e.g., Covello and Merkhofer 1993; Norrman 2001). Meanwhile, it is notable that most of the techniques available for performing risk assessments are structured around decision analysis procedures—since such approach tends to better facilitate comprehensible solutions for even complicated problems. Invariably, the risk assessment process can be used to provide a 'baseline' estimate of existing risks that can be attributed to a given agent or hazard, as well as to determine the potential reduction in exposure and risk under various mitigation scenarios.

Risk assessment is indeed a powerful tool for developing insights into the relative importance of the various types of exposure scenarios associated with potentially hazardous situations. But as Moeller (1997) points out, it has to be recognized that a given risk assessment provides only a snapshot in time of the estimated risk of a given toxic agent at a particular phase of our understanding of the issues and problems. To be truly instructive and constructive, therefore, risk assessment should preferably be conducted on an iterative basis—being continually updated as new knowledge and information become available.

As a final point here, it is noteworthy that, in general, some risk assessments may be classified as *retrospective*—i.e., focusing on injury after the fact (e.g., nature and level of risks at a given contaminated site), or it may be considered as *predictive*—such as in evaluating possible future harm to human health or the environment (e.g., risks anticipated if a newly developed food additive is approved for use in consumer food products, etc.). Anyhow, in relation to the investigation of chemical exposure problems, it is apparent that the focus of most public health risk assessments tends to be on a determination of potential or anticipated risks to the populations potentially at risk.

4.1.5 Recognition of Uncertainty as an Integral Component of Risk Assessments

A major difficulty in decision-making resides in the uncertainties of system characteristics for the situation at hand. *Uncertainty* is the lack of confidence in the estimate of a variable's magnitude or probability of occurrence. Invariably, scientific judgment becomes an important factor in problem-solving under uncertainty, and decision analysis provides a means of representing the uncertainties in a manner that allows informed discussion. The presence of uncertainty means, in general, that the best outcome obtainable from an evaluation and/or analysis cannot necessarily be guaranteed. Nonetheless, as has been pointed out by Bean (1988), decisions ought to be made even in an uncertain setting—otherwise several aspects of environmental (and related public health) management actions could become completely paralyzed. Indeed, there are inevitable uncertainties associated with just about all risk estimates, but these uncertainties do not invalidate the use of the risk estimates in the decision-making process. However, it is important to identify and define the confidence levels associated with the particular evaluation—also recognizing that, depending on the specific level of detail of a risk assessment, the type of uncertainty that dominates at each stage of the analysis can be quite different.

Uncertainty analysis can indeed be performed qualitatively or quantitatively—with sensitivity analysis often being a useful adjunct to the uncertainty analysis. *Sensitivity analysis* entails the determination of how rapidly the output of a given analysis changes with respect to variations in the input data; thus, in addition to presenting the best estimate, the evaluation will also provide a range of likely estimates in the form of a sensitivity analysis. In fact, it is generally recommended that a sensitivity analysis becomes an integral part of a detailed risk evaluation process. Through such analyses, uncertainties can be assessed properly, and their effects on given decisions accounted for in a systematic way. In this manner, the risk associated with given decision alternatives may be properly delineated, and then appropriate corrective measures can be taken accordingly.

In view of the fact that risk assessment may constitute a very crucial part of the overarching environmental and public health management decision-making

process, it is essential that all the apparent sources of uncertainty be well documented. Indeed, the need to be explicit about uncertainty issues in risk analysis has long been recognized—and this remains a recurrent theme for policy analysts and risk management practitioners. In general, the uncertainty can be characterized via sensitivity analysis and/or probability analysis techniques—with the technique of choice usually being dependent on the available input data statistics. Broadly speaking, sensitivity analyses require data on the range of values for each exposure factor in the scenario—and probabilistic analyses require data on the range and probability function (or distribution) of each exposure factor within the scenario. Further discussion of this topic appears later on in Chap. 12 of this title.

4.1.6 *Risk Assessment* Versus *Risk Management: The Dichotomy Between Risk Assessment and Risk Management*

Risk assessment has been defined as the 'characterization of the potential adverse health effects of human exposures to environmental hazards' (NRC 1983). In a typical risk assessment, the extent to which a group of people has been or may be exposed to a certain chemical is determined; the extent of exposure is then considered in relation to the kind and degree of hazard posed by the chemical—thereby allowing an estimate to be made of the present or potential risk to the target population. Depending on the problem situation, different degrees of detail may be required for the process; in any event, the continuum of acute to chronic hazards and exposures would typically be fully investigated in a comprehensive assessment, so that the complete spectrum of risks can be defined for subsequent risk management decisions.

The risk management process—that utilizes prior-generated risk assessment information—involves making a decision on how to protect public health. Examples of risk management actions include: deciding on how much of a given chemical of concern/interest an operating industry or company may discharge into a river; deciding on which substances may be stored at a hazardous waste disposal facility; deciding on the extent to which a hazardous waste site must be cleaned up; setting permit levels for chemical discharge, storage, or transport; establishing levels for air pollutant emissions; and determining the allowable levels of contamination in drinking water or food products. In a way, this generically portrays how risk management is distinct from risk assessment—but nevertheless maintains a fundamental relationship.

At the end of the day, risk assessment is generally conducted to facilitate risk management decisions. Whereas risk assessment focuses on evaluating the likelihood of adverse effects, risk management involves the selection of a course of action in response to an identified risk—with the latter often based on many other factors (e.g., social, legal, political, or economic) over and above the risk

assessment results. Essentially, risk assessment provides *information* on the likely health risk, and risk management is the *action* taken based on that information (in combination with other 'external' but potentially influential factors).

4.2 Fundamental Concepts in Risk Assessment Practice

The general types of risk assessment often encountered in practice may range from an evaluation of the potential effects of toxic chemical releases known to be occurring, up through to evaluations of the potential effects of releases due to events whose probability of occurrence is uncertain (Moeller 1997). Regardless, in order to adequately evaluate the risks associated with a given hazard situation, several concepts are usually employed in the processes involved. Some of the fundamental concepts and definitions that will generally facilitate a better understanding of the risk assessment process and application principles, and that may also affect risk management decisions, are introduced below in this section.

4.2.1 Qualitative Versus *Quantitative Risk Assessment*

In public health risk assessments, quantitative tools are often used to better define exposures, effects, and risks in the broad context of risk analysis. Such tools will usually employ the plausible ranges associated with default exposure scenarios, toxicological parameters, and indeed other assumptions and policy positions. Although the utility of numerical risk estimates in risk analysis has to be appreciated, these estimates should be considered in the context of the variables and assumptions involved in their derivation—and indeed in the broader context of likely biomedical opinion, host factors, and actual exposure conditions. Consequently, directly or indirectly, qualitative descriptors also become part of a quantitative risk assessment process. For instance, in evaluating the assumptions and variables relating to both toxicity and exposure conditions for a chemical exposure problem, the risk outcome may be provided in qualitative terms—albeit the risk levels are expressed in quantitative terms.

In general, the attributable risk for any given problem situation can be expressed in qualitative, semi-quantitative, or quantitative terms. For instance, in conveying qualitative conclusions regarding chemical hazards, narrative statements incorporating 'weight-of-evidence' or 'strength-of-evidence' conclusions may be used—i.e., in lieu of alpha-numeric designations alone being used. In other situations, pure numeric parameters are used—and yet in other circumstances, a combination of both numeric parameters and qualitative descriptors are used in the risk presentations/discussions.

4.2.1.1 Risk Categorization

Oftentimes in risk studies, it becomes necessary to put the degree of hazards or risks into different categories for risk management purposes. A typical risk categorization scheme for potential chemical exposure problems may involve a grouping of the 'candidate' problems on the basis of the potential risks attributable to various plausible conditions—such as high-, intermediate- and low-risk problems, as conceptually depicted by Fig. 4.4. Under such classification scheme, a case-specific problem may be designated as 'high-risk' when exposure represents real or imminent threat to human health; in general, the high-risk problems will prompt the most concern—requiring immediate and urgent attention or corrective measures to reduce the threat. Indeed, to ensure the development of adequate and effectual public health risk management or corrective action strategies, potential chemical exposure problems may need to be prudently categorized in a similar or other appropriate manner during the risk analysis. In the end, such a classification would likely facilitate the development and implementation of a more efficient public health risk management or corrective action program.

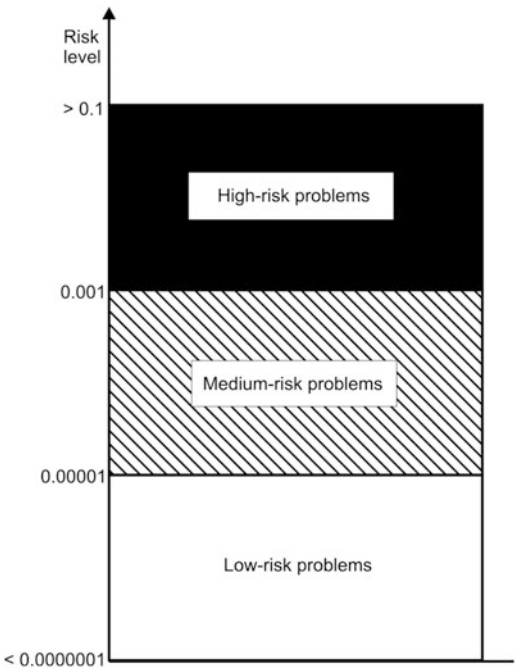

Fig. 4.4 A conceptual representation of typical risk categories for chemical exposure problems

4.2.2 Conservatisms in Risk Assessments

Many of the parameters and assumptions used in hazard, exposure, and risk evaluation studies tend to have high degrees of uncertainties associated with them—thereby potentially clouding the degree of confidence assigned to any estimated measures of safety. Conversely, 'erring on the side of safety' tends to be the universal 'mantra' of most safety designers and analysts. To facilitate a prospective safe design and analysis, it is common practice to model risks such that risk levels determined for management decisions are preferably over-estimated. Such 'conservative' estimates (also, often cited as 'worst-case', or 'plausible upper bound' estimates) used in risk assessment are based on the supposition that pessimism in risk assessment (with resultant high estimates of risks) is more protective of public health and/or the environment.

Indeed, in performing risk assessments, scenarios have often been developed that will reflect the worst possible exposure pattern; this notion of *'worst-case scenario'* in the risk assessment generally refers to the event or series of events resulting in the greatest exposure or potential exposure. Also, quantitative cancer risk assessments are typically expressed as plausible upper bounds rather than a tendering of estimates of central tendency; but then, when several plausible upper bounds are added together, then the question arises as to whether the overall result is still plausible (Bogen 1994; Burmaster and Harris 1993; Cogliano 1997). At any rate, although it is believed that the overall risk depends on the independence, additivity, synergistic/antagonistic interactions among the carcinogens, and the number of risk estimates (as well as on the shapes of the underlying risk distributions), sums of upper bounds still provide useful information about the overall risk. On the other hand, gross exaggeration of actual risks could lead to poor decisions being made with respect to the oftentimes very limited resources available for general risk mitigation purposes. Thus, after establishing a worst-case scenario, it is often desirable to also develop and analyze more realistic or 'nominal' scenarios, so that the level of risk posed by a hazardous situation can be better bounded—via the selection of a 'best' or 'most likely' sets of assumptions for the risk assessment. But in deciding on what realistic assumptions are to be used in a risk assessment, it is imperative that the analyst chooses parameters that will, at the very worst, result in erring on the side of safety. Anyhow, it is notable that a number of investigators (see, e.g., Anderson and Yuhas 1996; Burmaster and von Stackelberg 1991; Cullen 1994; Maxim, *in* Paustenbach 1988) have been offering a variety of techniques that could help make risk assessments more realistic—i.e., rather than the dependence on wholesale compounded conservative assumptions.

By and large, there generally is the need to systematically undertake sensitivity analyses, among other things; this may indeed include the use of multiple assumption sets that reflect a wider spectrum of exposure scenarios. This is important because controls based on the so-called upper-bound estimate or worst-case scenario may address risks that are almost nonexistent and impractical. In fact, risk assessment using extremely conservative biases do not necessarily provide risk

managers with the quality information needed to formulate efficient and cost-effective management strategies. Also, using plausible upper-bound risk estimates or worst-case scenarios may lead to spending scarce and limited resources to regulate or control insignificant risks—whiles at the same time more serious risks are probably being ignored. Thus, 'blind' conservatism in individual assessments may not be optimal or even truly conservative in a broad sense if some problematic sources of risk are not addressed, simply because other less serious ones are receiving undue attention. For such reasons, the overall recommendation is to strive for accuracy rather than conservatism.

4.2.3 *Individual* Versus *Group Risks*

In the application of risk assessment to environmental and public health risk management programs, it often becomes important to distinguish between 'individual' and 'societal' risks—in order that the most appropriate metric/measure can be used in the analysis of case-specific problems. *Individual risks* are considered to be the frequency at which a given individual could potentially sustain a given level of adverse consequence from the realization or occurrence of specified hazards. *Societal risk*, on the other hand, relates to the frequency and the number of individuals sustaining some given level of adverse consequence in a given population due to the occurrence of specified hazards; the population risk provides an estimate of the extent of harm to the population or population segment under review.

Broadly speaking, four types of risks may be differentiated for most situations—namely:

- Risks to individuals
- Risks to the general population
- Risks to highly exposed subgroups of a population
- Risks to highly sensitive subgroups of a population

The latter three categories may then be considered as belonging to the 'societal' or 'group' risk category—representing population risks associated with more than one person or the individual. Individual risk estimates represent the risk borne by individual persons within a population—and are more appropriate in cases where individuals face relatively high risks. However, when individual risks are not inequitably high, then it becomes important during resources allocation, to deliberate on possible society-wide risks that might be relatively higher. Indeed, risk assessments almost always deal with more than a single individual. However, individual risks are also frequently calculated for some or all of the persons in the population being studied, and these are then put into the context of where they fall in the distribution of risks for the entire population.

Finally, it is noteworthy that, at an individual level, the choice of whether or not to accept a risk is primarily a personal decision. However, on a societal level

(wherein values tend to be in conflict, and decisions often produce prospective 'winners' and 'losers') the decision to accept or reject a risk tolerance level is much more difficult (Cohrssen and Covello 1989). In fact, no numerical level of risk will likely receive universal acceptance; on the other hand, the idea of perchance eliminating all risks is virtually an impossible task—especially for our modern societies in which people have become so accustomed to numerous 'hazard-generating' luxuries of life. Congruently, for many activities and technologies of today, some level of risk would normally have to be tolerated in order for one to benefit from the activity or technology. Consequently, levels of risk that may be considered tolerable or relatively 'safe enough' should generally be identified/defined—at least on the societal level—to facilitate rational risk management and related decision-making tasks. Under such circumstances, it must be acknowledged that individuals at the high end of a risk distribution/spectrum are often of special interest to risk managers—especially when considering various actions to mitigate the risk; these individuals often are either more susceptible to the identified adverse health effect than others in the population, or are more highly exposed individuals, or both.

4.2.4 Consideration of Risk Perception Issues

The general perception of risks tends to vary amongst individuals and/or groups, and may even change with time. Risk perception may therefore be considered as having both spatial and temporal dimensions. In general, the public often views risk differently vis-à-vis the typical risk estimates developed by technical experts. Indeed, this notion ties in very well with the concept that public perception of risk is a function of hazard and the so-called 'outrage' factors; the 'outrage' component describes a range of (more or less abstract) factors, other than the actual likelihood of a hazard, that contribute to an enhanced or variant perception of the estimated risk (Sandman 1993; Slovic 1993, 1997). Conceivably, these 'outrage' factors explain why multiple hazards of similar magnitude can at times be perceived as having vastly differently levels of concomitant risk. In any event, whereas public outrage is not tangible, it is still real—and must therefore be addressed to ensure program success.

In general, risks that are involuntary (e.g., environmental risks) or 'novel' seem to arouse more concern from target/affected populations than those that are voluntary (e.g., associated with use of certain cosmetics and other consumer products) or 'routine'; thus, the latter tends to be more acceptable to the affected individuals (van Leeuwen and Hermens 1995). Similarly, 'natural' toxins and contaminants in foods may be considered reasonably acceptable (even though they may cause illness), whereas food additives (used in foodstuffs to assist in preservation) may not be as much acceptable to some people (Richardson 1986). Also, perceptions about risk tend to be influenced by: the sources of information; styles of presentation; personal background and educational levels; cultural contexts; and the dimensions of a particular risk problem. For instance, there seem to be reasonable

documentation and recognition regarding cultural explanations for some risk management controversies that have occurred in fairly recent times (see, e.g., Earle and Cvetkovich 1997)—i.e., in regards to the ways people differ in their thinking about risk (or risk acceptability for that matter). In fact, several value judgments become an important component of the consequential decision-making process—with the value judgments involving very complex social processes.

A fairly well established hierarchy of risk 'tolerability' has indeed emerged in recent times that involve several issues/factors—including those enumerated in Box 4.2 (Cassidy 1996; Cohrssen and Covello 1989; Lowrance 1976). Anyhow, in the final analysis, issues relating to risk perception become a very important consideration in environmental and public health risk management decisions—especially because, in some situations, the perception of a group of people may alter the priorities assigned to the reduction of competing risks. In fact, the differences between risk perception and risk estimation could have crucial consequences on the assessment, management, and communication of risks. This is because the particular risks estimated in a given risk assessment may not necessarily be consistent with the perceptions or concerns of those individuals most directly affected.

Heuristic Reasoning Structure vs. 'Formalized' Risk Assessment

Cognitive heuristics tend to dictate or form the basis of risk perception often observed in the general (lay) population—i.e., rather than systematic or structured reasoning that tend to form the basis of formulating a 'formal' risk assessment carried out by most scientific experts. Even so, these apparently different arms or paths to risk management decisions are not necessarily incompatible or inconsistent. Indeed, it has been suggested (*e.g.*, MacGillivray 2014) that significant aspects of risk assessment can initially be represented as heuristics (i.e., despite their generally rough and rather contingent nature)—but then only to be subsequently supplanted by using the insights from this to work toward a useful analytical framework for characterizing the process in a more formal manner. In actual fact, the heuristic elements of carrying out a risk assessment could (and probably should) be viewed or understood as a way of structuring, authenticating and/or formalizing the overall risk assessment process, as a true scientific practice (MacGillivray 2014). After all, among several other things, 'weight-of-evidence' (WoE) heuristics/approaches have become increasingly prominent in a variety of environmental decision-making scenarios—with these generally following the logic that there are often multiple lines of evidence that bear on a particular causal inference, and which therefore need to be weighted and aggregated prior to making a final decision; such process may in principle be guided by some formal algorithm or set of rules—albeit in practice, it typically takes the form of factors-based judgments (MacGillivray 2014). Ultimately, the integrated approach of using heuristics concepts together with 'formalized' structures could benefit the overall risk assessment process by adding additional layer/degree of consistency, transparency, and even some level of predictability in both the processes involved as well as the final outcomes.

Box 4.2 Key Factors Affecting the 'Tolerability' of Risk by Individuals and Society

- Voluntariness (i.e., Voluntary *vs.* Involuntary exposures)
- Response time (i.e., Delayed *vs.* Immediate effects)
- Source (i.e., Natural *vs.* Human-made risks)
- Controllability (i.e., Controllable *vs.* Uncontrollable)
- Perception of personal control
- Familiarity with the type of hazard (i.e., Old/Known *vs.* New/Unknown hazards or risks)
- Perceptions about potential benefits (i.e., Exposure is an essential *vs.* Exposure is a luxury)
- Nature of hazard and/or consequences (i.e., Ordinary *vs.* Catastrophic)
- Perception of the extent and type of risk
- Perceptions about comparative risks for other activities
- Reversibility of effects (i.e., Reversible *vs.* Irreversible)
- Perceptions about available choices (i.e., No alternatives available *vs.* Availability of alternatives)
- Perceptions about equitability/fairness of risk distribution
- Continuity of exposure (i.e., Occasional *vs.* Continuous)
- Visual indicators of risk factors or levels (i.e., Tangible *vs.* Intangible risks)

4.2.5 *Deterministic* Versus *Probabilistic Risk Assessments*

Deterministic risk assessment methods generally involve exclusive use of key data sets that lead to specific 'singular' and/or 'monotonic' outcomes—often considered the 'traditionalist' approach. *Probabilistic* [or, *Stochastic*] methods of approach typically entail the application of statistical tools that incorporate elements of random behavior in key data sets—often viewed as the more 'contemporaneous' approach.

In the application of risk assessment to environmental and public health risk management programs, it has become come practice to utilize either or both of deterministic and probabilistic methods of approach—in efforts to facilitate the most effectual decision-making processes, and that would adequately support public health risk management needs. In practice, the deterministic approach to risk assessments can be said to be the classical or traditional tool preceding the development of stochastic or probabilistic methodologies. On the other hand, because deterministic models generally do not explicitly consider uncertainty in key variables and/or model parameters, such models provide a rather limited picture to support effectual risk management programs. Even so, deterministic

models can be relied upon to a great extent for certain preliminary studies—i.e., usually prior to a more detailed stochastic optimization or simulation study. Indeed, stochastic methods typically come into use when the deterministic approach is found to be somehow deficient. Regardless, stochastic processes may be conveniently evaluated in such a manner, and conclusions associated with them drawn and treated, as if the process was somehow deterministic.

Meanwhile, it is noteworthy that, despite its usefulness, stochastic data do not improve the original poor records per se—but merely improve the quality of designs made with whatever records are available (Fiering and Jackson 1971); also, the processes involved will generally provide an idea of the confidence that can be placed on the adopted design value (McMahon and Mein 1986). Thus, notwithstanding any shortcomings, it is still an undisputable fact that the stochastic methods of approach tend to offer a more complete use of the information content of the usually limited data series; the result is the increase in the variations and spectrum of the possible solutions and methods for the design of complex safety and risk management systems. All the same, it must be acknowledged that some of the theoretical-based methods found in the literature cannot at times be used by themselves in practice, especially in the case of limited and/or 'unreliable' data series; under such circumstances, analysts may do well to choose a deterministic method of approach.

Finally, it is worth mentioning here that during the past several decades, there have been several important developments in analytical and statistical methods used in various risk assessment programs, as well as in the design of a variety of safety-related systems—albeit some of the basic classical or 'traditionalist' elements/methods for such efforts are still often utilized by contemporary practitioners. In general, the application of the new or 'non-traditional' scientific methods or tools is particularly justified when it provides answers to questions that cannot quite be resolved by traditional methods in an effectual manner. Notwithstanding, it must be cautioned that stochastic methods are by no means a panacea for executing risk assessment programs per se. In fact, many shortcomings (such as lack of knowledge concerning the underlying stochastic processes) might tend to cause decisions to be less optimal than had the phenomena been treated as deterministic. Each decision that has a stochastic input, however, must be realized as such and the proper methodology employed; the use of stochastic methods in risk assessments is, after all, an attempt to widen and extend our knowledge on key parameters and improve our decision-making ability. In a number of situations, this is accomplished by generating longer hypothetical sequences of events based on the statistical and probability characteristics of the past or existing records; the generated sequences of data are then used to identify the components that contribute to error and uncertainty in the specific program under review.

4.3 Risk Acceptability and Risk Tolerance Principles: *de Minimis* Versus *de Manifestis* Risk Criteria

An important concept in risk management is that there are levels of risk that are so great that they must not be allowed to occur at all cost, and yet there are other risk levels that are so low that they are not worth bothering with even at insignificant costs—known, respectively, as *de manifestis* and *de minimis* levels (Kocher and Hoffman 1991; Suter 1993; Travis et al. 1987; Whipple 1987). Risk levels between these bounds are typically balanced against costs, technical feasibility of mitigation actions, and other socioeconomic, political and legal considerations—in order to determine their acceptability or tolerability. In any event, with maintenance of public health and safety being a crucial goal for public health risk management decisions, it should be recognized upfront in any risk analysis that reasons such as budgetary constraints alone may not be used as justification for establishing an acceptable risk level that is on the higher side of a risk spectrum.

On the whole, the concept of *de manifestis* risk is usually not seen as being controversial—because, after all, some hazard effects are clearly unacceptable. However, the *de minimis* risk concept tends to be controversial—in view of the implicit idea that some exposures to, and effects of, pollutants or hazards are acceptable (Suter 1993). With that noted, it is still desirable to use these types of criteria to eliminate obviously trivial risks from further risk management actions—considering the fact that society cannot completely eliminate or prevent all human and environmental health effects associated with chemical exposure problems. Indeed, virtually all social systems have target risk levels—whether explicitly indicated or not—that represent tolerable limits to danger that the society is (or must be) prepared to accept in consequence of potential benefits that could accrue from a given activity. This tolerable limit is often designated as the *de minimis* or *'acceptable'* risk level. Thus, in the general process of establishing 'acceptable' risk levels, it is possible to use *de minimis* levels below which one need not be concerned (Rowe 1983); it is notable that current regulatory requirements are particularly important considerations in establishing such acceptable risk levels.

At the end of the day, it is apparent that the concept of 'acceptable risk level' relates to a very important issue in risk assessment—albeit the desirable or tolerable level of risk is not always attainable. Anyhow, it is noteworthy that risk acceptability (i.e., the level of risk that society can allow for a specified hazard situation) usually will have a spatial and temporal variability to it.

4.3.1 The de Minimis *or 'Acceptable' Risk*

Risk is *de minimis* if the incremental risk produced by an activity is sufficiently small, such that there is no incentive to modify the activity (Cohrssen and Covello 1989; Covello et al. 1986; Fischhoff et al. 1981; Whipple 1987). These represent

risk levels judged to be too insignificant to be of any social concern or to justify use of risk management resources to control them, compared with other beneficial uses for the often limited resources available in practice. In simple terms, the *de minimis* principle assumes that extremely low risks are trivial and need not be controlled. A *de minimis* risk level would therefore represent a cutoff, below which a regulatory agency could simply ignore related alleged problems or hazards.

The concept of *de minimis* or *acceptable* risk is essentially a threshold concept, in that it postulates a threshold of concern below which there would be indifference to changes in the level of risk. Meanwhile, it is notable that considerable controversy exists with regards to the concept of 'acceptable' risk in the risk/decision analysis literature; this is because, in practice, acceptable risk is the risk associated with the most acceptable decision—rather than being acceptable in an absolute sense. It has indeed been pointed out by some experts that acceptable risk is often decided in the political arena, and that 'acceptable' risk really means 'politically acceptable' risk (Massmann and Freeze 1987). On the whole, the selection of a *de minimis* risk level is contingent upon the nature of the risks, the stakeholders involved, and a host of other contextual variables (such as other risks being compared against). This means that *de minimis* levels will be fuzzy (in that they can never be precisely specified), and relative (in that they will depend on the special circumstances). Also, establishing a *de minimis* risk level is often extremely difficult because people perceive risks differently. More so, the cumulative burden of risks could make a currently insignificant risk become significant in the future. Consequently, stricter *de minimis* standards will usually become necessary in dealing with newly introduced risks that affect the same population groups.

There are several general approaches to deriving the *de minimis* risk levels—but the method of choice should be wholly justifiable based on the expected socioeconomic, environmental, and public health impacts. A common approach in placing risks in perspective is to list many risks (which are considered similar in nature), along with some quantitative measures of the degree of risk. Anyhow, typically, risks below the level of one-in-a-million (i.e., 10^{-6}) chance of premature death will often be considered insignificant or *de minimis* by regulatory agencies in most nations, since this compares favorably with risk levels from several 'normal' human activities—e.g., 10^{-3} for smoking a pack of cigarette/day, or rock climbing, etc.; 10^{-4} for heavy drinking, home accidents, driving motor vehicles, farming, etc.; 10^{-5} for truck driving, home fires, skiing, living downstream of a dam, use of contraceptive pills, etc.; 10^{-6} for diagnostic X-rays, fishing, etc.; and 10^{-7} for drinking about 10 L of diet soda containing saccharin, etc. (Paustenbach 1988; Rowe 1977, 1983; Whipple 1987). In considering a *de minimis* risk level, however, the possibility of multiple *de minimis* exposures with consequential large aggregate risk should not be overlooked. In fact, Whipple (*in* Paustenbach 1988) suggests the use of a *de minimis* probability idea that will help develop a generally workable *de minimis* policy.

In summary, *de minimis* is a lower bound on the range of acceptable risk for a given activity. When properly utilized, a *de minimis* risk concept can help prioritize risk management decisions in a socially responsible and beneficial way. It may also

be used to define the threshold for regulatory involvement. Indeed, it is only after deciding on an acceptable risk level that an environmental or public health risk management program can be addressed in a most cost-effective manner. Ultimately, in order to make a determination of the best environmental or public health risk management strategy to adopt for a given problem situation, a pragmatic and realistic acceptable risk level ought to have been specified *a priori*.

4.3.2 *The 'Safety Paradigm' in Public Health Risk Assessment: 'The Dose Makes the Poison'—So, What Dose Is Safe Enough?*

Current level of knowledge shows that many metals may be considered essential to normal cellular activity and evolutionary development. However, in excess, these same elements may cause toxic responses—as, for example, are noted below for the select list of essential and medically important metals (Berlow et al. 1982; Hughes 1996).

- Aluminum [Al]—finds medical uses in antacids, and also in dialysis fluids. However, it has an associated toxic effect of dialysis dementia with excesses.
- Cobalt [Co]—found in vitamin B12 as an essential metal, but can cause polycythemia and cardiomyopathy in excesses. Like iron (Fe^{2+}) in hemoglobin, Co^{2+} serves to hold the large vitamin molecule together, and to make it function properly.
- Copper [Cu]—facilitates the synthesis of hemoglobin, but may cause microcytic anemia when present in excessive amounts. Indeed, Cu is required for a variety of roles in the human body, several of which are connected to the use of iron. Although the total amount of Cu in the body is rather small, its deficiency may result in weak blood vessels and bones, as well as possible nerve damage.
- Gold [Au]—finds medical uses in pharmaceuticals (rheumatoid arthritis), but excesses could result in nephropathies.
- Iron [Fe]—important to the formation of RBCs (*viz*., erythropoiesis), but may cause liver or cardiovascular damage in excesses. In the human body, the iron-containing molecule (called hemoglobin) carries oxygen from the lungs to the rest of the human body. Indeed, small amounts of Fe are found in molecules that use oxygen in every tissue cell. It is noteworthy that, although the actual need for iron is very low (approximately 1–1.5 mg/day for a normal person), about ten times as much must be taken in human foods, mostly because only a small fraction of the iron passing through the human body is absorbed.
- Lithium [Li]—finds medical uses in pharmaceuticals (depression), but excesses may result in nephropathies and cardiopathies.
- Manganese [Mn]—is an enzyme potentiator, but may cause CNS (central nervous system) disorders and manganese pneumonitis in excesses. Indeed, Mn has many essential functions in every cell. However, Mn is also highly

neurotoxic and the effects are largely irreversible; consequently, the recommended exposure limits have been lowered drastically in a number of countries in recent years. It is noteworthy that, with its increased industrial use and emissions into the general environment, the harmful effects of Mn cannot be overlooked—and close monitoring seems prudent.
- Molybdenum [Mo]—is an enzyme cofactor, but may cause anemia and diarrhea in excesses. Indeed, Mo is part of several important enzymes.
- Selenium [Se]—is an enzyme cofactor, but subject to cause neuropathies, dermatopathies, decreased fertility, and teratogenesis in excesses.
- Zinc [Zn]—is essential (as Zn^{2+}) for the normal growth of genital organs, wound healing, and general growth of all tissues. It is also associated with the hormone insulin, which is used to treat diabetes. Even so, excess of this essential nutrient is not recommended. It is noteworthy that oysters are believed to be an unusually rich source of Zn.

In fact, it is notable that even some of the more 'suspicious' chemicals (e.g., arsenic and chromium) are believed to be essential nutrients in rather small amounts—albeit are extremely toxic in slightly elevated/larger amounts. Thus, even the essential elements can be toxic at concentrations that are too high, and yet a deficiency of these same metals can also be harmful to the health of most living organisms—including humans. For such reasons, it is quite important to make a very clear distinction between the therapeutic and toxic properties of chemicals—recognizing that these properties are sometimes, but not always, indistinguishable except by dose.

In closing, it is remarkable that the sixteenth century Swiss philosopher and physician-alchemist, Paracelsus, indicated once upon a time that: 'all things are poison and nothing is without poison, only the dose permits something not to be poisonous'—i.e., only the dose of a substance usually determines its toxicity. Indeed, this notion makes it even more difficult to ascertain the levels that constitute hazardous human exposure to chemicals. But careful application of risk assessment and risk management principles and tools should generally help remove some of the fuzziness in defining the cut-off line between what may be considered a 'safe level' and what apparently is a 'dangerous level' for most chemicals.

4.4 Risk Assessment Implementation Strategy

A number of techniques are available for conducting risk assessments. Invariably, the preferred methods of approach generally consist of the several basic procedural elements/components that are further outlined in Chap. 7 of this book. In any event, the key issues requiring significant attention in the processes involved will typically involve finding answers to the following questions:

- What chemicals pose the greatest risk?
- What are the concentrations of the chemicals of concern in the exposure media of interest?
- Which exposure routes are the most important?
- Which population groups, if any, face significant risk as a result of the possible exposures?
- What are the potential adverse effects of concern, given the exposure scenario (s) of interest?
- What is the range of risks to the affected populations?
- What are the public health implications for any identifiable corrective action and/or risk management alternatives?

As a general guiding principle, risk assessments should be carried out in an iterative fashion, and in a manner that can be appropriately adjusted to incorporate new scientific information and regulatory changes—but with the ultimate goal being to minimize public health and socioeconomic consequences associated with a potentially hazardous situation. Typically, an iterative approach would start with relatively inexpensive screening techniques—and then for hazards suspected of exceeding the *de minimis* risk, further evaluation is conducted by moving on to more complex and resource-intensive levels of data-gathering, model construction, and model application (NRC 1994a, b).

In effect, risk assessments will normally be conducted in an iterative manner that grows in depth with increasing problem complexity. Consider, as an example, a site-specific risk assessment that is used to evaluate/address potential health impacts associated with chemical releases from industrial facilities or hazardous waste sites. A tiered approach is generally recommended in the conduct of such site-specific risk assessments. Usually, this will involve two broad levels of detail—i.e., a 'screening' (or 'Tier 1') and a 'comprehensive' (or 'Tier 2') evaluation. In the screening evaluation, relatively simple models, conservative assumptions, and default generic parameters are typically used to determine an upper-bound risk estimate associated with a chemical release from the case facility. No detailed/comprehensive evaluation is warranted if the initial estimate is below a pre-established reference or target level (i.e., the *de minimis* risk). On the other hand, if the screening risk estimate is above the 'acceptable' or *de minimis* risk level, then the more comprehensive/detailed evaluation (that utilizes more sophisticated and realistic data evaluation techniques than were employed in the 'Tier 1' screening) should be carried out. This more comprehensive next step will confirm the existence (or otherwise) of significant risks—which then forms the basis for developing any risk management action plans. The rationale for such a tiered approach is to optimize the use of resources—in that it makes efficient use of time and resources, by applying more advanced and time-consuming techniques to chemicals of potential concern and scenarios only where necessary. In other words, the comprehensive/detailed risk assessment is performed only when truly warranted. Irrespective of the level of detail, however, a well-defined protocol should always be used to assess the potential risks. Ultimately, a decision on the

level of detail (e.g., qualitative, quantitative, or combinations thereof) at which an analysis is carried out will usually be based on the complexity of the situation, as well as the uncertainties associated with the anticipated or predicted risk.

As a final note here, it is worth mentioning that human exposures to radiological contaminants may be evaluated in a manner similar to the chemical exposure problems alluded to—albeit certain unique issues may have to be taken into consideration for the radiological exposures. Meanwhile, it is notable that, for the most part, the archetypical radiological exposures may occur through medical and dental X-rays; naturally-occurring radioactive materials in soils and groundwater; ambient air; and indeed various food sources, as well as several other consumer product sources.

Chapter 5
Attributes of a Public Health Risk Assessment

It has long been recognized that, nothing is wholly safe or dangerous *per se,* but that the object involved, and the manner and conditions of use determine the degree of hazard or safety. Consequently, it may rightly be concluded that there is no escape from all risk, no matter how remote, but that there only are choices among risks (Daniels 1978). In that spirit, risk assessment is usually designed to offer an opportunity to help understand a system better—usually by adding an orderliness and completeness to a problem evaluation. It must be acknowledged, however, that risk assessment has usefulness only if it is properly applied. Also, the risk analyst must be cognizant of the fact that hazard perception and risk thresholds—all of which can have significant impact on the ultimate risk decision—tend to be quite distinct in different regions or locations. Indeed, a good understanding of several important attributes of the risk assessment mechanisms would generally help both the risk assessor and the risk manager in practice. This chapter discusses key attributes that will facilitate the application and interpretation of risk assessment information—and thus make it more useful in public health risk management decisions.

5.1 General Attributes of Risk Assessment

The conventional paradigm for risk assessment tends to lean towards its *predictive* nature—which generally deals with localized outcomes of a particular action that could result in adverse effects. However, there also has been increasing emphasis on assessments of the effects of environmental and public health hazards associated with 'in-place' or existing chemical exposure problems; this assessment of past pollutions and exposures, with possible on-going consequences, generally falls under the umbrella of what has been referred to as *retrospective* risk assessment (Suter 1993). The impetus for a retrospective risk assessment may be a source, observed effects, or evidence of exposure. Source-driven retrospective assessments

K. Asante-Duah, *Public Health Risk Assessment for Human Exposure to Chemicals*,
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typically arise from observed pollution or exposures that requires elucidation of possible effects (e.g., hazardous waste sites, spills/accidental releases, consumer product usage, etc.); effects-driven retrospective assessments usually ensue from the observation of perceptible effects in the field that requires explanation (e.g., localized public health indicators, fish or bird kills, declining populations of a species, etc.); and exposure-driven retrospective assessments are normally prompted by evidence of exposure without prior evidence of a source or effects (e.g., the case of a scare over mercury found in the edible portions of dietary fish). In all cases, however, the principal objective of the risk assessment is to provide a basis for actions that will minimize the impairment of the environment and/or of public health, welfare and safety.

In general, risk assessment—which seems to be one of the fastest evolving tools for developing appropriate strategies in relation to environmental and public health management decisions—seeks to answer three basic questions:

- What could potentially go wrong?
- What are the chances for this to happen?
- What are the anticipated consequences, if this should indeed happen?

A complete analysis of risks associated with a given situation or activity will likely generate answers to these questions. Indeed, tasks performed during a risk assessment will generally help answer the infamous questions of: 'how safe is safe enough?' and/or 'how clean is clean enough?' Subsequently, risk management becomes part of the overall evaluation process—in order to help address the archetypical follow-up question of: 'what can be done about the prevailing situation?' At this point in time, a decision would typically have to be made as to whether any existing risk is sufficiently high to represent a public health concern—and if so, to determine the nature of risk management actions. Appropriate mitigative activities can then be initiated by implementing the necessary corrective action and risk management decisions.

5.1.1 The Purpose

The overall goal in a risk assessment is to identify potential 'system failure modes' and exposure scenarios—and this is achieved via the fulfillment of several general objectives (Box 5.1). This process is intended to facilitate the design of methods that will help reduce the probability of 'failure', as well as minimize the attending public health, socioeconomic, and environmental consequences of any 'failure' and/or exposure events. Its overarching purpose is to provide, insofar as possible, complete information sets to risk managers—so that the best possible decision can be made concerning a potentially hazardous situation. Indeed, as Whyte and Burton (1980) succinctly indicate, a major objective of risk assessment is to help develop risk management decisions that are more systematic, more comprehensive, more accountable, and more self-aware of appropriate programs than has often been the

case in the past. The risk assessment process provides a framework for developing the risk information necessary to assist risk management decisions; information developed in the risk assessment will typically facilitate decisions about the allocation of resources for safety improvements and hazard/risk reduction. Also, the analysis will generally provide decision-makers with a more justifiable basis for determining risk acceptability, as well as aid in choosing between possible corrective measures developed for risk mitigation programs.

When all is said and done, the information generated in a risk assessment is often used to determine the need for, and the degree of mitigation required for chemical exposure problems. For instance, risk assessment techniques and principles are frequently utilized to facilitate the development of effectual site characterization and corrective action programs for contaminated lands scheduled for decommissioning and subsequent re-development for mixed uses (e.g., residential housing and commercial properties). In addition to providing information about the nature and magnitude of potential health and environmental risks associated with the contaminated land problem, the risk assessment also provides a basis for judging the need for any type of remedial action (Asante-Duah 1998). Furthermore, risk assessment can be used to compare the risk reductions afforded by different remedial or risk control strategies. Indeed, the use of risk assessment techniques in contaminated land cleanup plans in particular, and corrective action programs in general, are becoming increasingly important and popular in so many localities. This is because the risk assessment serves as a useful tool for evaluating the effectiveness of remedies at contaminated sites, and also for establishing cleanup objectives (including the determination of cleanup levels) that will produce efficient, feasible, and cost-effective remedial solutions. Typically, the general purpose for this type of problem situation is to gather sufficient information that will allow for an adequate and accurate characterization of the potential risks associated with the project site. In this case, the risk assessment process is used to determine whether the level of risk at a contaminated site warrants remediation, and then to further project the amount of risk reduction necessary to protect public health and the environment. On this basis, an appropriate corrective action plan can then be developed and implemented for the case site and/or the impacted area.

Box 5.1 An Annotation of Typical General Objectives of a Risk Assessment

- Determining if potentially hazardous situations exist—i.e., determine 'baseline' risks and the possible need for corrective action.
- Providing a consistent process for evaluating and documenting public and environmental health threats associated with a potential hazardous situation.
- Estimation of the potential threat to public health and/or the environment that is posed by a facility or hazardous situation—e.g., evaluation of health impacts of emission from industrial facilities and other sources; evaluation of health impacts of chemicals migrating from hazardous waste sites; etc.

(continued)

Box 5.1 (continued)

- Evaluation of potential risks of new facilities and development projects.
- Estimation of potential health risks associated with use of several chemicals and consumer products—to ensure the development and implementation of acceptable public health policies.
- Pre-marketing safety evaluation of new chemicals (such as pesticides, food additives, drugs, etc.) and other consumer products.
- Post-marketing safety evaluation of existing chemicals (such as pesticides, food additives, drugs, etc.) and other consumer products.
- Determination of the relative size of different problem situations—in order to facilitate priority setting, where necessary.
- Preliminary project scoping—in order to identify possible data gaps in an exposure and risk evaluation problem.
- Determining if there is a need for an immediate response action.
- Identifying possible corrective action strategies.
- Providing basis for comparing and choosing between several remedial action alternatives.
- Providing a basis for determining the levels of chemicals that can remain at a given locale, and still be adequately protective of public health and the environment.
- Providing for the risk management informational needs of property owners and general community.
- Evaluation of product liability and toxic tort claims.

5.1.2 The Attributes

The risk assessment process typically utilizes the best available scientific knowledge and data to establish case-specific responses in relation to hazard-receptor interactions. Depending on the scope of the analysis, the methods used in estimating risks may be either qualitative or quantitative—or indeed combinations thereof. Thus, the process may be one of data analysis or modeling, or a combination of the two. In fact, the type and degree of detail of any risk assessment depends on its intended use; its purpose will generally shape the data needs, the protocol, the rigor, and related efforts. In the end, the process of quantifying risks does, by its very nature, give a better understanding of the strengths and weaknesses of the potential hazards being examined. It also shows where a given effort can do the most good in modifying a system—in order to improve their safety and efficiency. Meanwhile, it is worth the mention here that the processes involved in any risk assessment usually require a multidisciplinary approach—often covering several areas of expertise in most situations.

The major attributes of risk assessment that are particularly relevant to environmental and public health risk management programs include the following:

- Identification and ranking of all existing and anticipated potential hazards
- Explicit consideration of all current and possible future exposure scenarios
- Qualification and/or quantification of risks associated with the full range of hazard situations, system responses, and exposure scenarios
- Identification of all significant contributors to the critical pathways, exposure scenarios, and/or total risks
- Determination of cost-effective risk reduction policies, via the evaluation of risk-based remedial action alternatives and/or the adoption of efficient risk management and risk prevention programs
- Identification and analysis of all significant sources of uncertainties.

As previously noted in Sect. 4.1.5 and elsewhere, there are inherent uncertainties associated with all risk assessments. This is due in part to the fact that the analyst's knowledge of the causative events and controlling factors usually is limited, and also because the results obtained oftentimes tend to be dependent on the methodology and assumptions used. Furthermore, risk assessment can impose potential delays in the implementation of appropriate corrective measures—albeit the overall gain in program efficiency, as well as other potential advantages, is likely to more than compensate for any delays. But as Moeller (1997) points out, unless care is exercised and all interacting factors considered, then the outcome could be a risk assessment directed at single issues, followed by ill-conceived management strategies—and this can create problems worse than those the management strategies were designed to correct in the first place. In fact, the single-issue approach can also create 'public myopia' by excluding the totality of [feasible] alternatives and consequences essential for a more informed public/stakeholder preferred choice; consequently, it is imperative to ensure a more comprehensive evaluation that contemplates multiple feasible alternative management strategies.

5.2 Diagnostic and Investigative Attributes of Risk Assessment

Risk assessment is often considered an integral part of the diagnostic assessment of chemical exposure problems. In its application to the investigation of chemical exposure problems, the risk assessment process encompasses an evaluation of all the significant risk factors associated with all feasible and identifiable exposure scenarios. It includes a characterization of potential adverse consequences or impacts to the populations potentially at risk from the chemical exposure. Procedures typically used in the risk assessment process will characteristically be comprised of the following key tasks:

- Identification of the sources of chemical exposures
- Determination of the chemical exposure routes
- Identification of populations potentially at risk
- Determination of the specific chemicals of potential concern
- Determination of frequency of potential receptor exposures to chemicals
- Evaluation of chemical exposure levels
- Determination of receptor response to chemical exposures
- Estimation of likely impacts or damage resulting from receptor exposures to the chemicals of potential concern.

At the end of the day, potential risks are estimated by considering the probability or likelihood of occurrence of harm; the intrinsic harmful features or properties of specified hazards; the populations potentially at risk; the exposure scenarios; and the extent of expected harm and potential effects.

In most applications, risk assessment is used to provide a baseline estimate of existing risks that are attributable to a specific agent or hazard; the baseline risk assessment consists of an evaluation of the potential threats to human health and the environment in the absence of any remedial or response action. Among several other things, the risk assessment process can also be used to determine the potential reduction in exposure and risk under various corrective action scenarios, as well as to support remedy selection in risk mitigation/abatement or control programs.

5.2.1 Baseline Risk Assessments

Baseline risk assessments involve an analysis of the potential adverse effects (current or future) caused by receptor exposures to hazardous substances in the absence of any actions to control or mitigate these exposures—i.e., under an assumption of 'no-action'. Thus, the baseline risk assessment provides an estimate of the potential risks to the populations-at-risk that follows from the receptor exposure to the hazards of concern, when no mitigative actions have been considered. Because this type of assessment identifies the primary threats associated with the situation, it also provides valuable input to the development and evaluation of alternative risk management and mitigative options. In fact, baseline risk assessments are usually conducted to evaluate the need for, and the extent of, corrective action in relation to a hazardous situation; that is, they provide the basis and rationale as to whether or not remedial action is necessary. Ultimately, the results of the baseline risk assessment are generally used for reach the following goals:

- Document the magnitude of risk at a given locale, as well as the primary causes of the risk.
- Help determine whether any response action is necessary for the problem situation.
- Prioritize the need for remedial action, where several problem situations are involved.
- Provide a basis for quantifying remedial action objectives.

- Develop and modify remedial action goals.
- Support and justify 'no further action' decisions, as appropriate—by documenting the likely inconsequentiality of the threats posed by the hazard source(s).

On the whole, baseline risk assessments are designed to be case-specific—and therefore may vary in both detail and the extent to which qualitative and quantitative analyses are used. Also, it is noteworthy that the level of effort required to conduct a baseline risk assessment depends largely on the complexity and particular circumstances associated with the hazard situation under consideration.

5.2.2 Comparative Risk Assessments

Comparative risk assessment (CRA) has become an important aspect of risk analysis. In essence, CRA is directed at developing risk rankings and priorities that would put various kinds of hazards on an ordered scale—as, for instance, from 'small' to 'large' (or indeed pegged to other similar scales); it is notable that the following two principal forms of CRA are commonly identifiable in the literature (ACS and RFF 1998; NRC 1989a, b):

- *Specific risk comparisons*—that involve evaluations of distinct risks on the basis of likelihood and severity of effects. This form of CRA is comprised of a side-by-side evaluation of the risk (on an absolute or relative basis) associated with exposures to a few substances, products, or activities. Such comparisons may involve similar risk agents (e.g., the comparative cancer risks of two chemically similar pesticides) or widely different agents (e.g., the cancer risk from a particular pesticide compared with the risk of death or injury from automobile travel). Specific risk comparisons can be particularly useful when one is considering the relative importance of risks within the context of similar products, activities, or risk management actions. A rather popular application has been in the area of risk communication—where such comparisons have been helpful in enhancing non-technical audiences' understanding of the significance of varying risk levels (as for example, weighing the expected risks of new products or technologies against those that are already accepted or tolerated). Paired comparisons of reasonably similar risks represent the most straightforward application of comparative risk analysis; such evaluations may be carried out simply based on the estimated risk levels and the extent of anticipated harm. For example, a pair of chemical pesticides might be compared with respect to their expected chronic health effects, adjusted for likelihood.
- *Programmatic comparative risk assessment*—which seeks to make macro-level (i.e., 'big-picture') comparisons among many and widely different types of hazards/risks. This is usually carried out in order to provide information for setting regulatory and budgetary priorities for hazard reduction. In this kind of comparison, risk rankings are based on the relative magnitude of risk (i.e., which

hazards pose the greatest threat), or on relative risk reduction opportunities (e.g., the amount of risk that can be avoided with available technologies and resources). In fact, by its nature, programmatic CRA spans many, dissimilar risks and provides an organized forum for value debates over what is likely to be important in gauging the seriousness of a hazard, and in establishing priorities. Arguably, the major strength of programmatic CRA is the opportunity it provides for discussion and debate among various important points of view—especially those from technical experts, policy makers, and the public.

Indeed, methods for appropriately carrying out these kinds of analyses seem controversial within some quarters, as is the concept of using relative risk comparisons to establish priorities for hazard reduction. The challenges are particularly difficult when comparisons across widely different risks are involved. Additionally, all risk comparisons become considerably more complex when the views of differing individuals are brought into focus—many of whom may disagree on matters pertaining to the relevant attributes for comparisons, the trade-off relationships to be assumed, and the way uncertainty should be included in the analysis. Furthermore, sizable uncertainties—such as relates to the nature of health effects, the level of exposures, or various other factors—can make it difficult to combine the various attributes of a hazard into a single risk measure and, thereby, blunt the precision of the comparison process (ACS and RFF 1998). In general, risk comparisons are especially useful in situations requiring the comparison of the risks of alternative options, and also for gauging the importance of different causes of the same hazard.

5.2.3 Public Health Risk Assessments

A public health assessment typically consists of a review of available information about hazardous substances in the human environments—followed by an evaluation of whether exposure to these substances might cause any harm to people. Meanwhile, it must be emphasized here that a public health assessment is *not* the same thing as a 'medical examination' or a 'community health study'—albeit it can sometimes lead to those latter types of evaluation, as well as to other public health risk management actions. In any event, all forms of public health assessment would generally consider the following key issues or concerns:

- Levels (or concentrations) of hazardous substances present.
- Likelihood that people might be exposed to chemicals present in a locale.
- Exposure pathways and routes (such as breathing air, drinking or contacting water, contacting or eating soil, or eating food) via which people might become exposed to the chemicals of concern.
- Nature of harm the substances might cause to people (i.e., the chemical toxicity).
- Potential health impacts on populations working and/or living near the chemical source(s).

- Other dangers that could potentially exacerbate the likely effects of the chemical exposure problems.

The following three primary sources of information may be used to make the above determinations:

- *Environmental data* – such as information about the chemical constituents and how people could come in contact with them;
- *Health data*—including available information on community-wide morbidity and mortality rates, or the local incidences of illness, disease, and death in comparison with national and/or other regional/provincial/state incident rates; and
- *Community concerns*—such as reports from the public about how a hazardous chemical exposure is affecting the community's health and/or quality of life.

Ultimately, the public health assessment may be used to identify health studies or other public health risk management actions (such as community environmental health education) that might be needed. To this end, the requisite types of support information may generally be gathered through well-designed exposure investigations; the information generated by this process provides a basis for actions by policy makers—usually consisting of actions taken to prevent or reduce population exposures to hazardous substances.

5.2.3.1 Conducting an Exposure Investigation

An exposure investigation is one approach commonly used to develop better characterization with respect to past, current, and possible future human exposures to hazardous substances in the human living and work environments—and indeed to more thoroughly evaluate existing and possible health effects related to those exposures. In such endeavors, information is typically gathered using three principal methods of approach during an exposure investigation, *viz*.:

- *Biomedical testing*—consisting, for example, of the gathering and evaluation of urine or blood samples; this can then serve as an important source of fundamental information during an exposure investigation. Biomedical samples can show current (and sometimes past) exposures to a chemical constituent.
- *Environmental testing*—typically associated with contaminated environmental media (such as adulterated food, soil, water, or air) can serve as an important source of information gathered and evaluated during an exposure investigation. Investigators may focus environmental testing on where people live and/or work, or indeed any place where they might come in contact with the substances under investigation.
- *Exposure-dose reconstruction analyses*—involving the use of environmental sampling information and computer models to estimate the constituent levels that people may have been exposed to in the past, or could become exposed to in

the future. These models can then be used to draw various conclusions about the receptor exposure durations and levels of exposures.

In the end, the types of information so-derived can be used to evaluate how a person's health might be affected. Typically, a team of scientists with various specialties in environmental sampling and computer analyses, geographic information systems, epidemiology, toxicology, and medicine is assembled to work on this kind of investigation. The team uses information from the exposure investigations and other scientific resources to make public health policy decisions, prepare reports, and recommend appropriate public health risk management actions.

5.2.4 Biomonitoring and the Utility of Exposure Biomarkers

It seems apparent that exposure assessment oftentimes becomes a rather weak link in the assessment of risks arising from chemical exposure problems; to compensate for some of the shortcomings, utilization of exposure biomarkers usually will provide some improved strength to this component of a risk assessment. Invariably, the types of endpoints associated with biomarkers tends to provide evidence that exposure has occurred—with consequential absorption by the body; these endpoints also provide the kind of data that might be compared to exposure measurements and analyzed through pharmacokinetic modeling, in order to estimate target tissue dose and risk (Saleh et al. 1994). Furthermore, biomarkers serve as a means of determining aggregate/cumulative risks—by providing a measure of integrated exposure (i.e., exposures occurring via all plausible/realistic routes into the human body or other organism). Exposure biomarker information does indeed seem to be quite important in the evaluation of the impacts resulting from human exposure to a variety of chemicals.

Broadly speaking, two basic types of biomarkers may generally be defined, namely (Saleh et al. 1994):

(1) Residue analysis (of parent compounds or metabolites) in easily sampled matrices; and
(2) Endpoints that represent interactions between xenobiotic and endogenous components (e.g., enzyme inhibition, protein adducts, receptor complexes, antibody-antigen complexes, and mutation).

Both of the above types of biomarkers are used in general biomonitoring studies, in order to facilitate the assessment of exposures more fully—with direct biomonitoring specifically consisting of the routine analysis of human tissues or excreta for direct or indirect evidence of chemical exposures. For instance, detection of certain compounds (such as pesticides) in the human body or an organism generally indicates that: an exposure has occurred; the chemical is bioavailable, having been absorbed; and a dose to critical body tissues may have been incurred (Saleh et al. 1994). It is noteworthy, however, that several variables do indeed affect

the overall biomarker assessment process. For example, target tissue dose depends upon the exposure rate as well as the kinetics of the chemical uptake, intake, internal distribution, and storage/elimination.

Overall, considering the large variation in susceptibility to toxicant insults of the general population, it is plausible that neither detection nor determination of concentration of a toxicant in tissues of individuals or the general population may satisfactorily provide a quantitative estimate of risk to human health per se (Saleh et al. 1994). In fact, the extent to which a human population is susceptible to a toxic stressor depends not only on the intensity and duration of exposure—but also on the rate of uptake, intake, metabolism, storage, excretion, abundance of target macromolecules at the cellular level, and potential for adaptation to the toxicant (Saleh et al. 1994; WHO 2010a, b). Notwithstanding any limitations, however, the biological monitoring of certain chemical residues and metabolites in the human body continues to become increasingly important in the surveillance of occupationally and environmentally exposed individuals. This is especially true because biomonitoring data can complement occupational and environmental monitoring data (e.g., personal exposure measurements, ambient and micro-environmental measurements, as well as human activity pattern information) in reducing the uncertainty inherent in exposure or risk assessments.

As a final point here, it is noteworthy that regulations controlling chemical use and exposures have traditionally focused on a determination of external exposure levels that protect against human health and ecological impacts. On the other hand, as biomonitoring information becomes more readily available/attainable/etc., there is some movement toward a use of 'internal biomarkers' as a preferred basis for regulation—albeit it probably would be unwise to base regulatory controls solely on the detection of low concentrations within human tissues.

5.2.4.1 Methods of Measurement

Environmental and biological monitoring are two key elements in the determination of human exposures to chemicals for risk assessment and risk management decisions. The common methods of the biomonitoring process often involve the chemical analyses of readily sampled matrices (such as urine and blood) for parent compounds and/or metabolites. Also, immuno-chemical methods continue to be developed for screening purposes—and perhaps even beyond screening investigations. Indeed, although a number of innovative biomarkers for human exposure to chemicals have been reported and/or recorded (such as relates to DNA alterations, protein adducts and changes to enzymatic and immunological systems), measurement of pollutants and their metabolites in blood and urine have continued to dominate human biomonitoring efforts (Saleh et al. 1994). Anyhow, to ensure an effective biomonitoring program, it is important to ascertain that, among other things, the most appropriate biological matrix is sampled, and that the most important analytes are properly investigated in the ensuing laboratory analyses using the most appropriate analytical methods.

Finally, it is notable that there have indeed been vastly improved technical abilities to detect and measure even exceedingly low chemical concentrations that may appear in human tissues, blood, and even breast milk in contemporary times. This has, therefore, enabled biomonitoring programs to be conducted on a broader scale—and in which human populations can be surveyed for rather low levels of chemical residues in their bodies. As a consequence, increase in blood levels of some environmentally persistent chemicals over time have been observed—sometimes causing widespread public concern, even when the levels observed are not thought to necessarily constitute significant health hazards.

5.2.5 *The Role of Epidemiology in Public/Human Health Risk Assessments*

Epidemiology is the study of the distribution of, and contributors to, disease in human populations—and this can indeed aid in quantifying public health risks to a target population. More specifically, epidemiology compares disease rates in an exposed population group to that in an unexposed group—as for example, an examination of asthma rates in children in a community living near an industrial facility with copious emissions *versus* a similar group who live in an area away and not impacted by such emission types, all the while accounting for potential confounding factors, etc. Broadly speaking, this represents a branch of public health studies that evaluates relationships between human exposures and adverse outcomes with specific populations or target groups. A typical epidemiological study may consist of the assessment and/or evaluation of potential or suspected causal associations between specific exposures of interest and identifiable adverse outcomes of concern.

There are several types of epidemiological study designs that can be utilized in public health risk assessment practice; however, the nature of archetypical initial question(s) generated during a problem formulation stage may tend to dictate the specific type of epidemiological study design likely adopted in a given situation. Three of the major study designs are:

(i) *Cohort Studies*—that follow exposed and non-exposed people over time to determine if disease rates differ in the two groups;
(ii) *Case-control Studies*—used to determine whether exposures in the past differ in diseased and non-diseased people; and
(iii) *Cross-sectional Studies*—for which exposures and disease status are determined simultaneously in a group of individuals (i.e., a 'picture-pair' at a precise moment in time).

Cohort studies are the most frequently used type in public health risk assessments—in part because they often have large sample sizes and extensive exposure information within the available databases or related resources.

One of the primary advantages of epidemiological studies is that, it measures exposures and diseases in affected humans—thus making it unnecessary to extrapolate the results from laboratory animal studies. On the other hand, it is often difficult to directly measure certain exposures in people. In addition, whereas one can generally expose animals or cells to very high doses of chemicals, it is certainly unethical (if not impossible, or simply unacceptable) to purposefully dose up humans with chemicals that could potentially cause significant harm to them. Furthermore, it is generally difficult to find enough proper study subjects (especially on a frequent enough basis) who would have received high enough dose levels that could be properly measured to provide the requisite information needed to make credible risk management decisions. Indeed, whereas animal studies offer a convenient way to assess the toxic effects of chemical exposures in a controlled environment, biological differences among species, as well as high doses used in animal studies, are important sources of uncertainty in extrapolating animal studies to humans for purposes of risk assessment. Using human data to assess human risk offers certain advantages over using animal studies, but there certainly is a trade-off. For instance, when rat subjects are exchanged for humans in an experimental study, greater insight is generally gained into the toxicological relevance of exposures; however, because similarly high doses of a chemical cannot necessarily be administered to humans, particularly for longer-term studies, exposure estimates in human studies may be highly uncertain. Additionally, human studies also must account for other environmental exposures, as well as the influence of dietary and lifestyle factors—perhaps among several other 'non-laboratory-standardized' factors. Ultimately, results from both epidemiological and laboratory-based studies usually will be needed to resolve the issue of whether or not a chemical can cause a disease, and if it can do so in humans.

Finally, it is noteworthy that whereas a single epidemiological study can rarely be used for a true causal assessment, the consistency of findings across several epidemiological studies can provide a powerful test of a causal hypothesis. Overall, an integrative use of epidemiology and epidemiological principles in the risk assessment process would tend to add holistic value/dimension to the entire process—especially if this would assist in identifying and evaluating hazards, as well as facilitate a more effectual risk management program that is designed to mitigate or remedy the likely hazardous problem situation encountered in practice. In any event, it is also notable that, despite its usefulness, epidemiological studies can be misleading—as for instance, by possibly suggesting an association between a chemical present in the human environment and an adverse effect or disease when the observed effect is indeed due to confounding factors or even poor study design.

5.3 Risk Assessment as an Holistic Tool for Environmental and Public Health Management

Risk assessment is a process used to determine the magnitude and probability of actual or potential harm that a hazardous situation poses to human health and the environment. As an holistic approach to environmental and public health management, risk assessment integrates all relevant environmental and health issues and concerns surrounding a specific problem situation, in order to arrive at risk management decisions that are acceptable to all stakeholders. Among other things, the overall process should generally incorporate information that helps to answer the following pertinent questions:

- Why is the project/study being undertaken?
- How will results and conclusions from the project/study be used?
- What specific processes and methodologies will be utilized?
- What are the uncertainties and limitations surrounding the study?
- What contingency plans exist for resolving newly identified issues?

Also, effective risk communication should be recognized as a very important element of the holistic approach to managing chemical exposure and related environmental hazard problems (Asante-Duah 1998). Thus, a system for the conveying of risk information derived from a risk assessment should be considered as a very essential integral part of the overall technique.

For the most part, risk assessment has been used in much of Europe for a relatively constrained set of purposes—chiefly to assess new and existing chemical substances (including pesticides), pharmaceutical products, cosmetics and food additives; still, there is significant move for its application in the occupational health and safety field, as well as usage in site remediation decisions in some countries (see, e.g., Cairney 1995; Ellis and Rees 1995; HSE 1989a, b; Smith 1996). By contrast, risk assessment principles and methodologies have found extensive and a wide variety of applications in the United States for several years. Among other things, it has typically been used in the USA to: evaluate many forms of new products (e.g., foods, drugs, cosmetics, pesticides, consumer products); set environmental standards (e.g., for air and water); predict the health threat from contaminants in air, water, and soils; determine when a material is hazardous (i.e., to identify hazardous wastes and toxic industrial chemicals); set occupational health and safety standards; and evaluate soil and groundwater remediation efforts (see, e.g., Asante-Duah 1998; ASTM 1995; McTernan and Kaplan 1990; Millner et al. 1992; NRC 1993a, b, c, 1995; Shere 1995; Sittig 1994; Smith 1996; Smith et al. 1996; Tsuji and Serl 1996). For now, risk assessment applications in most of the other parts of the world appear to remain a bit limited and sporadic. But this ‘status quo’ is expected to change before too long, as the world continues to search for cost-effective and credible environmental and public health management tools. In fact, in the wake of the June 1992 UN Conference on Environment and Development in Rio de Janeiro, the global/international community’s reliance on

risk assessment as an effectual environmental and/or public health management tool is likely to grow well into the future. A growing trend in its use is indeed expected, despite skepticism expressed by some who have considered the art and science of risk assessment more as a mythical subject rather than real (see, e.g., Shere 1995) —and also notwithstanding the fact that the process may indeed be fraught with several sources of uncertainty.

Finally, to effectively utilize it as a public health management tool, risk assessment should be recognized as a multidisciplinary process that draws on data, information, principles, and expertise from many scientific disciplines—including biology, chemistry, earth sciences, engineering, epidemiology, medicine and health sciences, physics, toxicology, and statistics, among others. Indeed, risk assessment may be viewed as bringing a wide range of subjects and disciplines—from 'archaeology to zoology'—together, to facilitate a more informed decision-making.

Chapter 6
General Basic Planning Considerations for a Chemical Exposure Characterization Activity

There are numerous planning engagements or actions that would typically be undertaken prior to carrying out most chemical exposure investigation and/or characterization activities. This chapter catalogs and elaborates the pertinent planning considerations, foundational building blocks/elements, and general requirements that would likely assure a reasonably cost-effective implementation of a chemical exposure investigation and characterization activity—particularly in relation to environmental contamination issues/problems; this includes a general discussion of the key elements for effectual problem conceptualization/formulation, chemical fate and behavior appraisement concepts, as well as the steps typically taken to develop comprehensive work-plans in data collection activities that are often necessary to support the characterization and management of environmental contamination and related potential chemical exposure problems.

6.1 Conceptualization of Chemical Exposure Problems

Conceptualization principles are an important starting point in formulating strategies to address most chemical exposure problems, regardless of the source of origination for the chemicals of interest and anticipated impacts. In general, a conceptual evaluation model is used to facilitate a more holistic assessment of the nature and extent of a chemical release and/or exposure problem. It also identifies all known and suspected or potential contamination sources; the types of contaminants and affected media; existing and potential exposure pathways; and the known or potential receptors that might be threatened. This information is frequently summarized in pictorial or graphical form, and generally backed up by problem-specific data. The development of an adequate conceptual model is indeed a very important aspect of the technical evaluation scheme necessary for the successful completion of most environmental and chemical exposure characterization programs. The framework integrates several types of information on the

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physical and environmental setting of the specific issue on hand—which then forms a basis for human health (and related) risk assessments. The conceptual model is also relevant to the development and evaluation of corrective action or remedy programs for a variety of chemical release and exposure problems.

Overall, a conceptual exposure model (CEM) provides a structured framework for characterizing possible threats posed by potential chemical release and/or exposure problems; these frameworks are usually developed in order to clearly and systematically identify and document likely contaminant sources, migration and exposure pathways, potential receptors, and how these individual elements are inter-connected. Ultimately, the CEM aids in the organization and analysis of basic information relevant to developing likely corrective action decisions about a problem situation. Thus, the development of a comprehensive CEM is often a recommended and vital part of corrective action assessments for chemical release and/or exposure problems. Meanwhile, it is worth the mention here that, as chemical exposure characterization activities move forward, the CEM may have to be revised as necessary—and then used to direct the next iteration of possible sampling activities necessary to complete the exposure characterization efforts. The 'finalized' CEM is then used to develop realistic exposure scenarios for the specific project on hand.

6.1.1 Elements of a Conceptual Exposure Model

Conceptual models generally establish a hypothesis about possible chemical or contaminant sources, chemical fate and behavior, and possible pathways of exposure to any populations potentially at risk (Fig. 6.1). The archetypical conceptual exposure model (CEM) will usually incorporate the following types of fundamental elements:

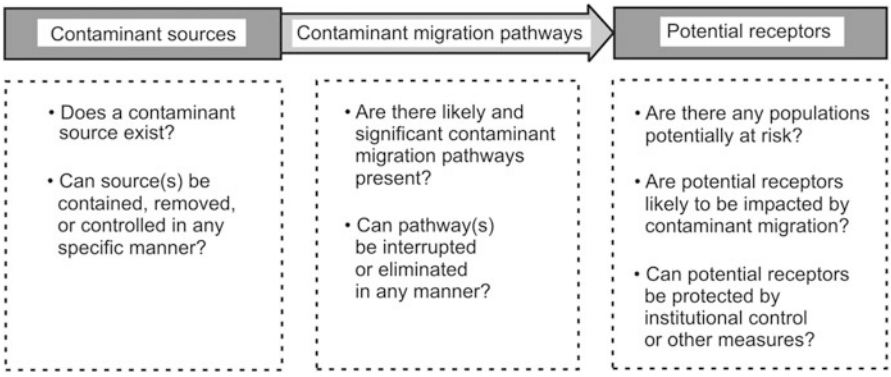

Fig. 6.1 General conceptual elements for a potential chemical exposure problem

- Identification of the contaminants of interest and determination of their physical/chemical properties
- Characterization of the source(s) of contamination and ambient conditions
- Delineation of potential migration pathways
- Identification and characterization of all populations and resources that are potentially at risk
- Determination of the nature of inter-connections between contaminant sources, contaminant migration pathways, and potential receptors.

Relationships among these elements provide a basis for testing a range of exposure hypotheses for a given chemical release and/or exposure problem.

For an archetypical environmental contamination and/or chemical exposure problem, evaluation of the CEM usually involves the following types of analyses:

- A *contaminant release analysis*—to determine contaminant release rates into specific environmental media over time. [This may include determining the spatial distribution of contaminants; appraising ambient conditions; determining the extent to which contaminant sources can be adequately identified and characterized; determining the likelihood of releases and/or exposures if the contaminants remain in-place; determining the extent to which natural and artificial barriers currently contain contaminants, and the adequacy of such barriers; identifying potential migration pathways; determining the extent to which the contaminants of interest have migrated or are expected to migrate from their source(s); and estimating the contaminant release rates into specific environmental media over time.]
- A *contaminant transport and fate analysis*—to provide guidance for evaluating the transport, transformation, and fate of contaminants in the environment following their release; to identify outside areas affected by contaminant migration; and to determine contaminant concentrations in these areas.
- An *exposed population analysis*—to determine the likelihood of human and ecological receptors coming into contact with the contaminants of concern.
- An *integrated exposure analysis*—to provide guidance for calculating and integrating exposures to all populations affected by the various exposure scenarios associated with the problem situation.

When all is said and done, the conceptual model helps to identify and document all known and suspected sources of contamination, types of contaminants and affected media, known and potential migration pathways, potential exposure pathways and routes, target receiving media, and known or potential human (and possibly ecological) receptors. Such information can be used to develop a conceptual understanding of the chemical release and/or exposure problem, so that potential risks to human health and the environment can be evaluated more completely. Eventually, the CEM will usually help identify data gaps, and further assist in developing strategies for data collection in support of public health risk management programs.

6.1.2 *Design of Conceptual Exposure Models and the Development of Exposure Scenarios*

Several considerations and evaluations are essential to the design of a realistic and truly representative CEM that will meet the overall goals of a risk assessment and environmental management program. Oftentimes, problem case history and preliminary assessment data become very useful sources of information for developing preliminary CEMs; subsequently, the CEM should be appropriately modified if the acquisition of additional data and new information necessitates a re-design. In fact, the CEM is typically prepared early on in the project, and then used to guide exposure investigations and pertinent decision-making; however, this CEM may have to be updated periodically whenever new information becomes available to elucidate a further understanding of the particular exposure problem. In the end, the complexity and degree of sophistication of a CEM usually is consistent with the complexity of the particular problem, and also the amount of data available.

6.1.2.1 Development of Exposure Scenarios: Integrating Contaminant Sources with Exposure Pathways and Receptors

An exposure scenario, which is a description of the activity that brings a population into contact with a chemical source or a contaminated environmental medium, usually is the next logical development or outcome that follows after the design of a CEM. Exposure scenarios are developed based on the movement of chemicals or contaminants of interest in various environmental compartments into the potential receptor zones (Fig. 6.2). In general, exposure scenarios are derived and modeled based on the movement of chemicals in various environmental compartments. The exposure scenario associated with a given chemical exposure problem may be well-defined if the exposure is known to have already occurred. In most cases associated with the investigation of potential chemical exposure problems, however, decisions typically have to be made about potential exposures that may not yet have occurred. Consequently, hypothetical exposure scenarios are generally developed for such applications.

Several tasks are usually undertaken to facilitate the development of complete and realistic exposure scenarios; the critical tasks include the following:

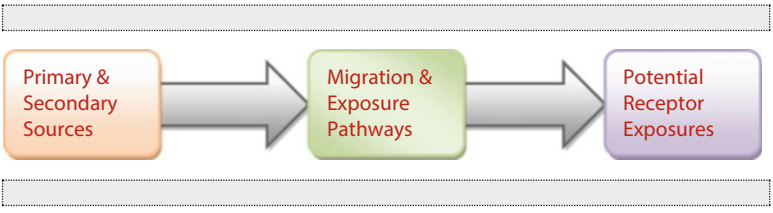

Fig. 6.2 Exposure scenario evaluation flow-diagram

- Determine the sources of chemical release or contamination
- Identify the specific constituents of concern
- Identify the affected environmental media
- Delineate contaminant migration pathways
- Identify potential receptors
- Determine potential exposure routes
- Construct a representative conceptual model for the specific problem situation
- Delineate likely and significant migration and exposure pathways.

Indeed, it is quite important to develop as realistic an exposure scenario as possible at all times; this can then be used to support an evaluation of the risks posed by the potential chemical exposure problem. Once the complete set of potential exposure scenarios have been fully determined, the range of critical exposure pathways can be identified. This information can then be used to design cost-effective sampling and investigation programs. The goal in this case will be to ensure a focused investigation, in order to be able to determine the specific potential exposure pathways of critical interest in a most cost-efficient manner. Ultimately, the exposure scenarios developed for a given chemical release and/or exposure problem can be used to support an evaluation of the risks posed by the subject case, as well as facilitate the implementation of appropriate decisions regarding the need for, and extent of, possible corrective actions to undertake.

Finally, it is noteworthy here that if numerous potential exposure scenarios exist, or if a complex exposure scenario has to be evaluated, it usually is helpful to use an 'event-tree' model (or similar framework/structure) to clarify potential outcomes and/or consequences. The event tree concept, as illustrated by Fig. 6.3, indeed offers an efficient way to develop exposure scenarios. By using such an approach, the

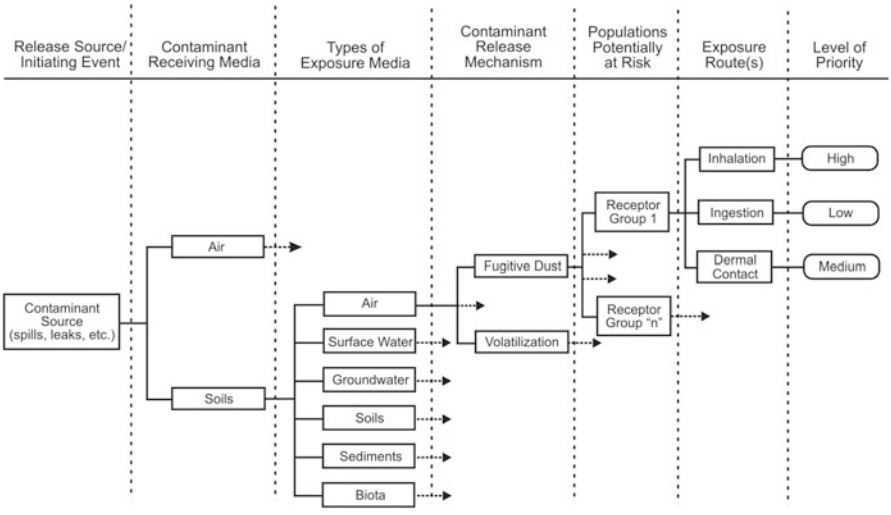

Fig. 6.3 Diagrammatic representation of example exposure scenarios using an 'event-tree'

various exposure contingencies can be identified and organized in a systematic manner. Once developed, priorities can be established to help focus the available effort on the aspects of greatest need. Invariably, a wide variety of *potential* exposure patterns may generally be anticipated from a given chemical exposure situation—culminating in a multiplicity of inter-connected pathways through which populations might become exposed to contamination. In the final analysis, the archetypal and commonly encountered exposure scenarios will usually be evaluated as part of the exposure characterization process for a given chemical exposure problem.

6.2 Fate and Behavior Appraisal for Chemicals of Potential Public Health Concern in Human Environments

A variety of chemicals originating from varying sources that are often encountered in human environments tend to be controlled by a complex set of processes—consisting of transport, transformation, degradation and decay, cross-media transfers, and/or biological uptake and bioaccumulation. Environmental fate and behavior analyses offer a way to assess the movement of chemicals between environmental compartments—further to the prediction of the long-term fate of such chemicals in the environment vis-à-vis potential human exposures. In fact, once a chemical is suspected or determined to present a potential health or environmental hazard, then the first concern relates to the likelihood for, and degree of, exposure.

This section identifies and discusses the relevant phenomena influencing the fate and behavior of chemicals encountered in human environments, together with the important factors affecting the processes involved. Indeed, a good understanding of the chemical fate and behavior is quite important—in order to be able to properly characterize the potential risks associated with chemicals encountered in human exposure environments, and to further develop appropriate risk management and/or remedial action plans for a chemical exposure problem. Thus, the processes and phenomena that affect the fate and behavior of chemicals encountered in human environments should be recognized as an important part of any chemical exposure characterization, risk determination, and/or risk management program.

6.2.1 Important Characteristics, Properties and Parameters Affecting the Destiny of Chemical Substances in Human Environments

As chemical substances are released into various environmental media, several factors contribute to their uptake, transformation, and migration/transport from one environmental matrix into another, or their phase change from one physical state into another. In general, examination of a chemical substance's physical and

chemical properties will often allow an estimation of its degree of environmental partitioning, migration and/or attenuation. Qualitative analysis of the fate of a chemical can also be made by analogy with other chemicals whose fate are well documented; that is, if the chemical under investigation is structurally similar to a previously well-studied one, some parallel can be drawn to the environmental fate of the analogue. In addition, several locale-specific characteristics—such as the amount of ambient moisture, humidity levels, temperatures and wind speed—may influence the environmental fate and behavior of chemicals. Other factors such as initial chemical concentration in the source or secondarily impacted media, as well as media pH may additionally affect the release of a chemical constituent from the environmental matrix in which it is found.

Overall, the physical and chemical characteristics of constituents present in human environments determine the fate and behavior properties of the chemical substances, and thus their degree of uptake, transformation, and/or migration through the environment. Some of the particularly important constituent properties affecting the fate and behavior of chemical substances in the human environment include the following (Grisham 1986):

- Solubility in water (which, for instance, relates to leaching, partitioning, and mobility in the environment).
- Partitioning coefficients (relating to cross-media transfers, bioaccumulation potential and sorption by organic matter).
- Hydrolysis (which relates to persistence in the environment or biota).
- Vapor pressure and Henry's Law constant (relating to atmospheric mobility and the rate of vaporization or volatilization).
- Photolysis (which relates to persistence as a function of exposure to light).
- Degradation/Half-life (relating to the degradation of contaminants and the resulting transformation products).
- Retardation factor (which relates to the sorptivity and mobility of the constituent within the solid-fluid media).

Further details and additional parameters of possible interest are presented in Appendix B of this book—with this topic receiving even more elaboration elsewhere in the literature (e.g., Devinny et al. 1990; Evans 1989; Hemond and Fechner 1994; Lindsay 1979; Lyman et al. 1990; Mahmood and Sims 1986; Mansour 1993; Neely 1980; Samiullah 1990; Swann and Eschenroeder 1983; Thibodeaux 1979, 1996; USEPA 1985a, 1989a, b, c, d, e, f; Yong et al. 1992).

6.2.2 Modeling Chemical Fate and Behavior in Human Environments

Environmental contamination can be transported far away from its primary source (s) of origination via a variety of natural and related processes—culminating in the

possible birth of secondary contaminant source and potential exposure problems. Conversely, some natural processes work to lessen or reduce contaminant concentrations in the environment through mechanisms of natural attenuation (such as dispersion/dilution, sorption and retardation, photolysis, and biodegradation). In the end, chemical contaminants entering the environment tend to be partitioned or distributed across various environmental compartments. Consequently, a good prediction of contaminant concentrations in the various environmental media is essential to adequately characterize environmental contamination and chemical exposure problems—the results of which can also be used to support risk assessment and/or risk management decisions. Typically, environmental fate and transport analysis and modeling is used to assess the movement of chemicals between environmental compartments. For instance, simple mathematical models can be used to guide the decisions involved in estimating and managing the potential spread of contaminant plumes; on the basis of the modeling results, and as appropriate or necessary, monitoring equipment or systems can then be located in areas expected to have elevated contaminant concentrations and/or in areas considered upgradient (or upwind), cross-gradient, and downgradient (or downwind) of a contaminant plume.

Mathematical algorithms are typically used to predict the potential for contaminants to migrate from one environmental media into another—or more importantly, from an environmental compartment into potential receptor locations or environmental compliance boundaries. For example, relevant exposure point concentrations associated with a contaminated land problem can be determined once the potentially affected populations are identified and the exposure scenarios are defined. Indeed, if the transport of compounds associated with this situation is considered to be under steady-state conditions, then monitoring data are generally adequate to determine potential exposure concentrations. On the other hand, if there are no data available, or if conditions are transient (such as pertains to a migrating plume in groundwater), then models are best used to predict exposure concentrations. Meanwhile, many factors—including the fate and transport properties of the chemicals of concern—must be carefully considered in the model selection process. [By the way, it is noteworthy that, for this type of problem (and in lieu of an established trend in historical data that indicates the contrary), a potentially contaminated land problem may be considered to be in steady-state with its surroundings.]

On the whole, mathematical models often serve as valuable tools for evaluating the behavior and fate of chemical constituents in various environmental media. The transport and fate of contaminants can be predicted through the use of various methods—ranging from simple mass-balance and analytical procedures to multidimensional numerical solution of coupled differential equations. Regardless, it is worth mentioning here that, due to the heterogeneity in environmental compartments and natural systems, models used for exposure assessments should be adequately tested, and insofar as possible, sensitivity runs should perhaps be carried out to help determine the most sensitive and/or critical parameters considered in the evaluation. Further discussions pertaining to the utility of wide-ranging

environmental models—including model selection criteria and limitations—can be found elsewhere in the literature of environmental and exposure modeling (e.g., CCME 1994; CDHS 1986; Clark 1996; Feenstra et al. 1991; Ghadiri and Rose 1992; Gordon 1985; Haith 1980; Honeycutt and Schabacker 1994; Johnson and Ettinger 1991; Jury et al. 1984; Mulkey 1984; NRC 1989a, b; Schnoor 1996; USEPA 1985b, 1987, 1988a, b; Williams et al. 1996). Finally, it must be emphasized here that, the effective use of models in contaminant fate and behavior assessment depends greatly on the selection of models most suitable for this purpose.

6.2.2.1 Model Selection

Numerous model classification systems with different complexities exist in practice—broadly categorized as analytical or numerical models, depending on the degree of mathematical sophistication involved in their formulation. Analytical models are models with simplifying underlying assumptions, often sufficient and appropriate for well-defined systems for which extensive data are available, and/or for which the limiting assumptions are valid. Whereas analytical models may suffice for some evaluation scenarios, numerical models (with more stringent underlying assumptions) may be required for more complex configurations and complicated systems. In any event, the choice of a model type that could be best used for specific applications is subject to numerous, sometimes convoluted, factors/constraints. Thus, simply choosing a more complicated model over a simple one will not necessarily ensure a better solution in all situations. In fact, since a model is a mathematical representation of a complex system, some degree of mathematical simplification usually must be made about the system being modeled. In these efforts, data limitations must be weighted appropriately, since it usually is not possible to obtain all of the input parameters due to the complexity (e.g., anisotropy and non-homogeneity) of natural systems.

Now, as a general word of caution, it is notable that the appropriateness of a particular model necessary to address environmental issues depends on the characteristics of the particular problem on hand; thus, the screening of models should be carefully tied to the project goals. Indeed, the wrong choice of models could result in the generation of false information—with consequential negative impacts on any decisions made thereof. On the other hand, the choice of appropriate fate and transport models that will give reasonable indications of the contaminant behavior will help produce a realistic conceptual representation of the problem—and this is important to the adequate characterization of any environmental contamination and chemical exposure problem, which in turn is a pre-requisite to developing reliable risk management policies and case-specific remedy strategies.

On the whole, the decisions about model selection can be a tricky one—often necessitating cautious warnings; this concern is best illustrated and summarized by the following interesting observation and note of comparison with 'social models' made by Kaplan (Kaplan 1964—as cited in Aris 1994), that: "Models are

undeniably beautiful, and a man may justly be proud to be seen in their company. But they may have their hidden vices. The question is, after all, not only whether they are good to look at, but whether we can live happily with them." This illustrative and somehow analogous view held by much of society about 'social models' does indeed compare very well with the underlying principles in the selection and use of environmental models—thus calling for the careful choice of such models to support chemical release and environmental management programs. Most importantly, it should be recognized that a given mathematical model that performs extremely well under one set of circumstances might not necessarily be appropriate for other similar or comparable situations for a variety of reasons.

In the end, the type of model selected to address any particular concern will be dependent on the overall goal of the assessment, the complexity of the problem, the type of contaminants of concern, the nature of the impacted and threatened media that are being considered in the investigation, and the type of corrective actions being considered. At any rate, it is noteworthy that in several environmental assessment situations, a 'ballpark' or 'order-of-magnitude' (i.e., a rough approximation) estimate of effectiveness for the contaminant behavior and fate is usually all that is required for most analyses—and in which case simple analytical models usually will suffice. General guidance for the effective selection of models in chemical release characterization and risk management decisions is provided in the literature elsewhere (e.g., CCME 1994; CDHS 1990; Clark 1996; Cowherd et al. 1985; DOE 1987; NRC 1989a, b; Schnoor 1996; USEPA 1985, 1987, 1988a, b; Walton 1984; Yong et al. 1992; Zirschy and Harris 1986).

6.2.3 Application of Mathematical Models

Models can be used to address a wide range of questions that may need to be answered in environmental contamination and chemical exposure problems, as well as their associated environmental management programs—such as in helping answer the following types of questions:

- What are the prevailing and future chemical release or contamination levels?
- Are modeling predictions of pollution or chemical release from a process or situation met in reality?
- How do pollutants or chemical releases behave in the environment?
- What is the response of the environment to receiving pollution or chemical releases?

One of the major benefits associated with the use of mathematical models in environmental and chemical release management programs relate to the fact that, environmental concentrations useful for exposure assessment and risk characterization can be estimated for several locations and time-periods of interest. Indeed, since field data frequently are limited and insufficient for accurately and completely characterizing environmental contamination and chemical exposure problems,

models can be particularly useful for studying spatial and temporal variability, together with potential uncertainties. In addition, sensitivity analyses can be performed—by varying specific parameters and then using models to explore the ramifications (as reflected by changes in the model outputs).

Models can indeed be used for several purposes in the study of environmental contamination and chemical exposure problems. More generally, mathematical models are often used to simulate the response of a simplified version of a complex system. As such, their results are imperfect. Nonetheless, when used in a technically responsible manner, they can provide a very useful basis for making technically sound decisions about an environmental contamination and/or chemical exposure problem. In fact, they are particularly useful where several alternative scenarios are to be compared. In such cases, all the alternatives are compared on a similar basis; thus, whereas the numerical results of any single alternative may not be exact, the comparative results indicating that one alternative is superior to others will usually be valid. Ultimately, the effective use of models in chemical release characterization and risk management programs depends greatly on the selection of models most suitable for its specified purpose.

Overall, the fate of chemical compounds released into the environment forms an important basis for evaluating the exposure of biological receptors to hazardous chemicals—because, once contaminants are released into the environment, the pollutants may be transported into various media and environmental matrices occupied by the receptors. For instance, releases from potential contamination sources can cause human exposures to contaminants in a variety of ways, such as the following:

- Direct inhalation of airborne vapors and also respirable particulates
- Deposition of airborne contaminants onto soils, leading to human exposure via dermal absorption or ingestion
- Ingestion of food products that have been contaminated as a result of deposition onto crops or pasture lands, and introduction into the human food chain
- Ingestion of contaminated dairy and meat products from animals consuming contaminated crops or waters
- Deposition of airborne contaminants on waterways, uptake through aquatic organisms, and eventual human consumption
- Leaching and runoff into water resources, and consequential human exposures to contaminated waters.

Mathematical models tend to play prominent roles in the evaluation of the above types of exposures. Multimedia transport models are generally employed in the prediction of the long-term fate of the chemicals in the environment. In fact, a variety of mathematical algorithms and models are commonly employed to support the determination of contaminant fate and transport in the environment—and which results are then used in estimating the consequential exposures and risks to potential receptors.

6.2.3.1 Scope of Application of Chemical Fate and Behavior Modeling for Exposure Analyses

Regardless of how much environmental and/or exposure monitoring data is available, it is almost always desirable to generate one or more of the following attributes (Schnoor 1996):

(i) An estimate of chemical concentrations under different sets of conditions;
(ii) Results for a future chemical loading scenario;
(iii) A predicted 'hindcast' or reconstructed history of chemical releases; and/or
(iv) Estimates at alternate [receptor or compliance] locations where field data do not exist.

Under such circumstances, environmental models usually come in quite handy. Characteristically, multimedia mathematical models are often used to predict the potential for contaminant migration from a chemical release source to potential receptors, using pathways analyses concepts.

The general types of modeling practices used in exposure assessments for archetypical environmental chemical release scenarios commonly consist of a use of atmospheric, surface water, groundwater, multimedia, and food-chain models. In their practical applications, several modeling scenarios will typically be simulated and evaluated using the appropriate models for a given environmental contamination or chemical release problem. For example, the study of a contaminated land problem may require the modeling of infiltration of rain water, erosion/surface runoff release of chemicals, emission of particulate matter and vapors, chemical fate and transport through the unsaturated zone, chemical transport through the aquifer system, and/or mixing of ground water with surface water—among other things (Fig. 6.4).

All in all, environmental models are typically designed to serve a variety of purposes—most importantly the following (Schnoor 1996):

- To gain better understanding of the fate and transport of chemicals existing in, or to be introduced into, the environment.
- To determine the temporal and spatial distributions of chemical exposure concentrations at potential receptor locations.
- To predict future consequences of exposure under various chemical loading or release conditions, exposure scenarios, and/or management action alternatives.
- To perform sensitivity analyses, by varying specific parameters, and then using models to explore the ramifications of such actions (as reflected by changes in the model outputs).

Ultimately, populations potentially at risk are designated, and then concentrations of the chemicals of concern are delineated or determined in each medium to which potential receptors may be exposed. Then, using the appropriate case-specific exposure parameter values, the intakes of the chemicals of concern can be estimated (see Chap. 9). Indeed, such evaluations could be about past or current

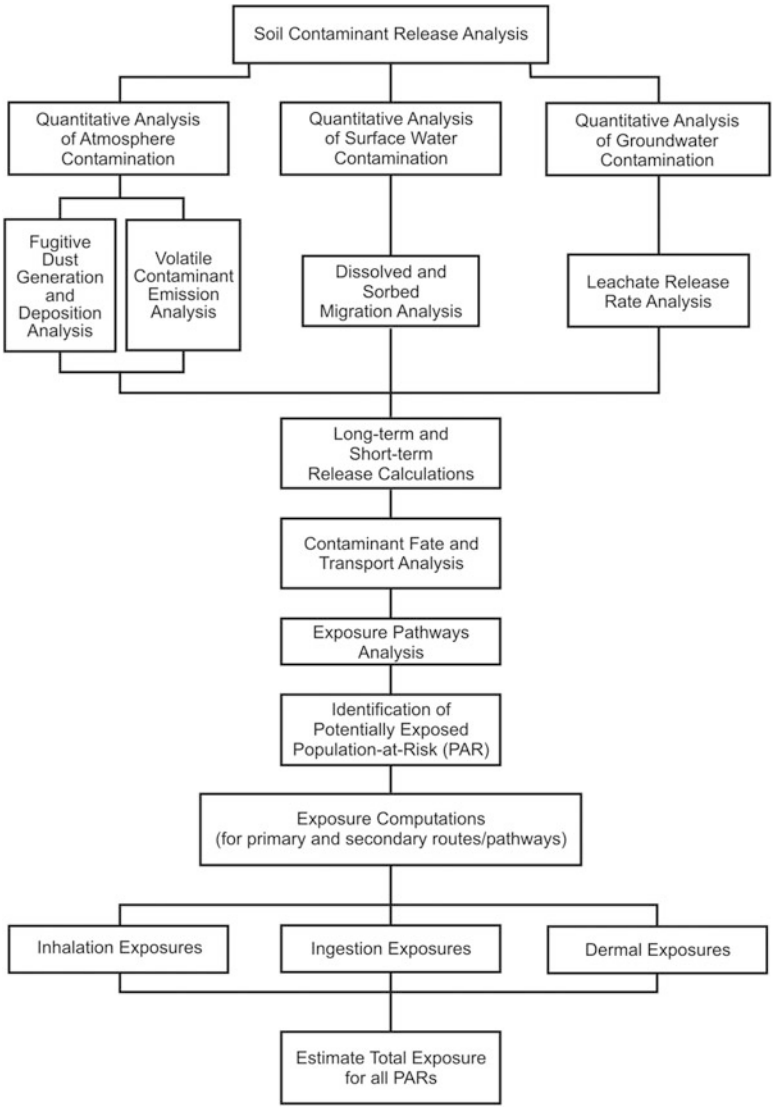

Fig. 6.4 An example conceptual representation of the relationship between multimedia contaminant transfers and multipathway exposure analyses

exposures, or exposures anticipated in the future; this therefore makes mathematical modeling even more valuable—especially in the simulation of events and conditions that may not yet have occurred.

6.2.3.2 Illustrative Example Application Scenarios for Simple Mathematical Models: The Case of Air Dispersion Modeling for Environmental Chemicals

Some simple example model formulations that may be employed in the estimation of the cross-media contaminant concentrations, and the requisite exposure point concentrations (that can be further used to facilitate responsible risk determinations) are presented below for the air migration pathway.

Atmospheric dispersion modeling has indeed become an integral part of the planning and decision-making process in the assessment of public health and environmental impacts from various chemical release problems. It is an approach that can be used to provide contaminant concentrations at potential receptor locations of interest based on emission rate and meteorological data. Naturally, the accuracy of the model predictions depends on the accuracy and representativeness of relevant input data. Broadly speaking, key model input data will include emissions and release parameters, meteorological data, and receptor locations. Typically, existing air monitoring data (if any) for the locale/area of interest can be utilized to facilitate the design of a receptor grid, as well as to select 'indicator chemicals' to be modeled. This can also provide insight into likely background concentrations. Indeed, in all situations, case-specific data should be used whenever possible—in order to increase the accuracy of the emission rate estimates.

Overall, a number of general assumptions are normally made in the assessment of contaminant releases into the atmosphere, including the following key ones:

- Air dispersion and particulate deposition modeling of emissions adequately represent the fate and transport of chemical emission to ground level.
- The composition of emission products found at ground level is identical to the composition found at source, but concentrations are different.
- The potential receptors are exposed to the maximum annual average ground-level concentrations from the emission sources for 24 h/day, throughout a 70-year lifetime—a rather conservative assumption.
- There are no losses of chemicals through transformation and other processes (such as biodegradation or photodegradation)—a rather conservative assumption.

In the end, the combined approach of environmental fate analysis and field monitoring should provide an efficient and cost-effective strategy for investigating the impacts of air pathways on potential receptors, given a variety of meteorological conditions.

Some select screening level air emission modeling procedures are discussed below for illustrative purposes only; these include the archetypical computational procedures for both volatile and non-volatile emissions—with the non-volatile compounds generally considered to be bound onto particulates by adsorption. [By the way, for the purposes of a screening evaluation, a volatile substance may be defined as any chemical with a vapor pressure greater than $[1 \times 10^{-3}]$ mmHg or

a Henry's Law constant greater than [1×10^{-5}] atm-m^3/mole (DTSC 1994). Thus, chemicals with Henry's Law constants less than or equal to these indicated values are generally considered as non-volatile compounds.] General and specific protocols for estimating releases or emission levels for contaminants from several sources are available elsewhere in the literature (e.g., CAPCOA 1990; CDHS 1986; Mackay and Leinonen 1975; Mackay and Yeun 1983; Thibodeaux and Hwang 1982; USEPA 1989a, b, 1989c, 1990a, b).

Screening Level Estimation of Airborne Dust/Particulate Concentrations: Particulate emissions from chemical release sources (e.g., potentially contaminated sites) can cause human exposures to chemical constituents in a variety of ways, including:

- Direct inhalation of respirable particulates
- Deposition on soils, leading to human exposure via dermal absorption or ingestion
- Ingestion of food products that have been contaminated as a result of deposition on crops or pasture lands and introduction into the human food chain
- Ingestion of contaminated dairy and meat products from animals eating contaminated crops
- Deposition on waterways, uptake through aquatic organisms, and eventual human consumption.

In the estimation of potential risks from particulate matter or fugitive dust inhalation, an estimate of respirable (oftentimes assumed to be <10 μm aerodynamic diameter, denoted by the symbol PM-10 or PM10) fraction and concentrations are required. The amount of non-respirable (>10 μm aerodynamic diameter) concentrations may also be needed to estimate deposition of wind-blown emissions which will eventually reach potential receptors via other routes such as ingestion and dermal exposures.

In general, air models for fugitive dust emission and dispersion can be used to estimate the applicable exposure point concentrations of respirable particulates from chemical release sources, such as contaminated lands. In such models, fugitive dust dispersion concentrations evaluated are typically represented by a three-dimensional Gaussian distribution of particulate emissions from the source (e.g., CAPCOA 1989; CDHS 1986; DOE 1987; USEPA 1989a, b, c, d, e, f; USEPA 1993). Oftentimes, a screening level assumption is made that, for non-VOCs, particulate contamination levels are directly proportional to the maximum soil concentrations.

Screening Level Estimation of Airborne Vapor Concentrations: The most important chemical parameters to consider in the evaluation of volatile air emissions are the vapor pressure and the Henry's Law Constant. Vapor pressure is a useful screening indicator of the potential for a chemical to volatilize from the media in which it currently exists. As a special example in relation to the utility of the Henry's Law Constant, it is notable that this is particularly important in estimating the tendency of a chemical to volatilize from a surface impoundment or water; it also indicates

the tendency of a chemical to, for example, partition between the soil and gas phase from soil water in the vadose zone or groundwater at a contaminated land. As an example in regards to the evaluation of a contaminated site problem, a vaporization model may be used to calculate flux from volatile compounds present in soils into the overlying air zone (DTSC 1994; USEPA 1990a, b, 1992a, b, c, d, e). Ultimately, the potential air contaminant concentration in the receptor's breathing zone that results from volatilization of chemicals through the soil surface is calculated over each discrete area of concern. A simple box model (e.g., Hwang and Falco 1986; USEPA 1990a, b, 1992a, b, c, d, e) can be used to provide an estimate of ambient air concentrations using a prior-calculated total emission rate; in this case, the length dimensions of the hypothetical box within which mixing will occur is usually based on the minimum dimensions of a residential lot in the applicable locality/region (Hadley and Sedman 1990).

6.3 The Chemical Exposure Characterization Process: General Framework for Project/Field Data Collection

As part of any potential chemical exposure characterization and/or corrective action assessment program designed to address potential chemical release and consequential exposure problems, a carefully executed investigative strategy or 'work-plan' may be developed to guide all relevant activities or decisions. Work-plans are generally required to specify the administrative and logistic requirements of potential chemical exposure investigation/characterization activities. A typical work-plan developed to facilitate the investigation of potential chemical release and related exposure problems will usually consist of the following key components:

- A sampling and analysis plan;
- A health and safety plan;
- An investigation-generated waste management plan;
- A project/program activity plan; and
- A quality assurance/quality control plan.

All the workplan elements, as represented by the summary listing in Box 6.1, should be adequately evaluated and appropriately documented. The major components and tasks required of most potential chemical exposure characterization and/or the corrective action evaluation workplans are elaborated further in the proceeding sections—with greater details offered elsewhere in the literature (e.g., Boulding 1994; CCME 1993; CDHS 1990; Keith 1988, 1991; USEPA 1985, 1987, 1988a, b, 1989a, b, c, d).

Box 6.1 General elements of a typical environmental or chemical exposure investigation/characterization work-plan

- Identification of general impacted subject(s), region or locale
- Number of individuals to be involved in each field sampling task and estimated duration of work
- Identification of sampling locations (preferably on a map to be provided in a detailed workplan)
- Number of samples to be obtained in the field (including blanks and duplicates), and the sampling location (illustrated on maps to be included in a detailed workplan)
- An elaboration of how investigation-generated wastes will be handled
- List of field and laboratory analyses to be performed
- A general discussion of data quality objectives (DQOs)
- Identification of possible interim remedies, as necessary, and/or risk management strategies
- A discussion of health and safety plans required for the investigation or corrective action activities, as well as that necessary to protect populations in the general vicinity of the impacted region or locale

6.3.1 The Sampling and Analysis Plan

Some form of a sampling and analysis plan (SAP) is an essential requirement of just about any environmental investigation/characterization program. SAPs generally are required to specify sample types, numbers, locations, and relevant procedures or strategies. In fact, the SAP typically will set the stage for developing cost-effective and effectual corrective action or remedy plans for potential environmental contamination and/or chemical exposure problems. Its purpose is to ensure that sampling and data collection activities will be comparable to, and compatible with previous (and possible future) data collection activities. Box 6.2 enumerates a checklist of the specific kinds of items that need to be ascertained in the development of a typical SAP (CCME 1993; Holmes et al. 1993; Keith 1988, 1991).

Box 6.2 Checklist for developing sampling and analysis protocols

- What observations at sampling locations are to be recorded?
- Has information concerning data quality objectives, analytical methods, analytical detection limits, etc., been included?
- Have instructions for modifying protocols in case of unanticipated problems been specified?
- Has a list of all likely sampling equipment and materials been prepared?

(continued)

Box 6.2 (continued)

- Are instructions for cleaning equipment before and after sampling available?
- Has instructions for each type of sample collection been prepared?
- Has instructions for completing sample labels been included?
- Has instructions for preserving each type of sample (such as preservatives to use, and also maximum holding times of samples) been included?
- Has instructions for packaging, transporting, and storing samples been included?
- Has instructions for chain-of-custody procedures been included?
- Has health and safety plans been developed?
- Is there a waste management plan to deal with wastes generated during the environmental impact investigation activities?

Overall, SAPs provide a mechanism for planning and approving field activities (USEPA 1988a, b, 1989b). Data necessary to meet the project objectives should be specified, including the selection of sampling methods and analytical protocols for the particular situation or project; this will also include an evaluation of multiple-option approaches that will ensure timely and cost-effective data collection and evaluation. The required level of detail and the scope of the planned investigation generally determine the 'data quality objectives' (DQOs)—with the DQOs setting the goals and requirements necessary for acquiring the appropriate data that satisfies the overarching needs of the project on hand. In any event, it is important that the sampling and analysis strategy is planned in such a manner as to minimize the costs associated with achieving the DQOs.

Typically, the SAP will comprise of two major components—namely (USEPA 1988a, b, 1989b):

1. A *quality assurance project plan* (QAPP)—that describes the policy, organization, functional activities, and quality assurance and quality control protocols necessary to achieve the DQOs dictated by the intended use of the data.
2. A *field sampling plan* (FSP)—that provides guidance for all fieldwork, by defining in detail the sampling and data-gathering methods to be used in a project. The FSP should be written so that even a field sampling team unfamiliar with the project is still able to gather the samples and any field information required for the project.

In general, the design of a sampling and analysis program and its associated quality assurance plan takes account of the variability in the entire measurement process along with the sources and magnitude of the variation in the results generated. It also provides a means of determining whether a sampling and analysis program meets the specified DQOs. Ultimately, effective protocols are required in

the sampling and laboratory procedures, in order to help minimize uncertainties in the environmental investigation process.

On the whole, the methods by which data of adequate quality and quantity are to be obtained to meet the overall project goals should be specified and fully documented in the SAP developed as part of a detailed environmental investigation work-plan. Among other things, an initial evaluation of a chemical release and consequential potential exposure problem should provide some insight into the types of contaminants, the populations potentially at risk, and possibly an approximation of the magnitude of the risk. These factors can then be combined to design a sampling plan, and to specify the size of sampling units to be addressed by each sample or set of samples. Also, it is notable that, in a number of situations, the laboratory designated to perform the sample analyses provides sample bottles, preservation materials, and explicit sample collection instructions; this is in part because of the complexity of typically having to gather so many different samples from various matrices that may also have to be analyzed using a wide range of analytical protocols.

In the end, the methods by which data of adequate quality and quantity are to be obtained to meet the overall project goals should be specified and fully documented in the SAP that is developed as part of a detailed environmental characterization work-plan. Meanwhile, it should also be recognized that the selection of analytical methods is an integral part of the processes involved in the development of sampling plans, since this can strongly affect the acceptability of a sampling protocol. Furthermore, the use of appropriate sample collection methods can be as important as the use of appropriate analytical methods for sample analyses—and vice versa.

6.3.1.1 Purpose of the Sampling and Analysis Program

Sampling and analysis of environmental pollutants is a very important part of the decision-making process involved in the management of potential chemical exposure and environmental contamination problems. Yet, sampling and analysis could become one of the most expensive and time-consuming aspects of an environmental management or potential chemical exposure characterization project. Even of greater concern is the fact that errors in sample collection, sample handling, or laboratory analysis can invalidate potential chemical exposure characterization projects or add to the overall project costs. As such, all environmental samples that are intended for use in potential chemical exposure characterization programs must be collected, handled, and analyzed properly, in accordance with all applicable/relevant methods and protocols.

The principal objective of a sampling and analysis program is to obtain a small and informative portion of the statistical population being investigated, so that chemical or contaminant levels can be established as part of a potential chemical exposure characterization and/or corrective action assessment program. Box 6.3 provides a convenient checklist of the issues that should be verified when planning

a sampling activity for a potential chemical exposure problem, in order that the project goals are attained.

Box 6.3 Sampling plan checklist

- What are the DQOs, and what corrective measures are planned if DQOs are not met (e.g., re-sampling or revision of DQOs)?
- Do program objectives need exploratory, monitoring, or both sampling types?
- Is specialized sampling equipment needed and/or available?
- Are field crew who are experienced in the required types of sampling available?
- Have all analytes and analytical methods been listed?
- Have required good laboratory practice and/or method QA/QC protocols been listed?
- What type of sampling approach will be used (i.e., random, systematic, judgmental, or combinations thereof)?
- What type of data analysis methods will be used (e.g., geostatistical, control charts, hypothesis testing, etc.)?
- Is the sampling approach compatible with data analysis methods?
- How many samples are needed?
- What types of QC samples are needed, and how many of each type of QC samples are needed (e.g., trip blanks, field blanks, equipment blanks, etc.)?

6.3.1.2 Elements of a Sampling and Analysis Plan: Sampling Requirements and Considerations

Environmental sampling activities associated with potential chemical exposure problems are generally carried out in order to help characterize the issue on hand via a risk determination process, and subsequently to facilitate any necessary corrective actions. Several project-specific requirements are important to achieving the requisite problem characterization goals. Indeed, several important issues come into play when one is making a decision on how to obtain reliable samples; these include considerations of the sampling objective and approach, sample collection methods, chain-of-custody documentation, sample preservation techniques, sample shipment methods, sample holding times, and analytical protocols. At any rate, all sampling plans should contain several fundamental elements—particularly as noted in Box 6.4. A detailed discussion of pertinent sampling considerations and strategies for various environmental matrices can be found elsewhere in the literature (e.g., CCME 1993; CDHS 1990; Holmes et al. 1993; Keith 1988, 1991; Lave and Upton 1987; USEPA 1988b, 1989b).

Box 6.4 Elements of a sampling plan

- Background information about impacted region or locale (that includes a description of the problem location and surrounding areas, and a discussion of known and suspected chemical release or contamination sources, probable migration pathways, and other general information about the physical and environmental setting)
- Sampling objectives (describing the intended uses of the data)
- Sampling location and frequency (that also identifies each sample matrix to be collected and the constituents to be analyzed)
- Sample designation (that establishes a sample numbering system for the specific project, and should include the sample number, the sampling round, the sample matrix, and the name of the site or case property)
- Sampling equipment and procedures (including equipment to be used and material composition of equipment, along with decontamination procedures)
- Sample handling and analysis (including identification of sample preservation methods, types of sampling jars, shipping requirements, and holding times)

Sampling and Analysis Design Considerations: A preliminary identification of the types of contaminants, the chemical release potentials, and also the potential exposure pathways should be made very early in a potential chemical exposure characterization effort; this is because these are crucial to decisions on the number, type, and location of samples to be collected. Indeed, knowledge of the type of contaminants will generally help focus more attention on the specific media most likely to have been impacted, or that remains vulnerable. Anyhow, regardless of the medium sampled, data variability problems may arise from temporal and spatial variations in field data. That is, sample composition may vary depending on the time of the year and weather conditions when the sample is collected. Ideally, samples from various media should be collected in a manner that accounts for temporal factors and weather conditions. If seasonal/temporal fluctuations cannot be characterized in the investigation, details of meteorological, seasonal, and climatic conditions during the sampling events must be well documented. For the most part, choosing an appropriate sampling interval that spans a sufficient length of time to allow one to obtain, for example, an independent groundwater sample will generally help reduce the effects of autocorrelation. Also, as appropriate, sampling both 'background' and 'compliance' locations at the same point-in-time should reduce temporal effects. Consequently, the ideal sampling scheme will typically incorporate a full annual sampling cycle. If this strategy cannot be accommodated in an investigation, then at least two sampling events should be considered—and these should probably take place during opposite seasonal extremes.

Similar decisions as above will typically have to be made regarding analytical protocols as well. For instance, due to the differences in the relative toxicity of the different species of some chemicals (as, e.g., chromium may exist as trivalent chromium [Cr+3], or as the more toxic hexavalent chromium [Cr+6]), chemical speciation to differentiate between the various forms of the chemicals of potential concern in relation to a chemical release and potential exposure situation may sometimes be required in the design of analytical protocols.

6.3.1.3 Sampling Protocols

Sampling protocols are written descriptions of the detailed procedures to be followed in collecting, packaging, labeling, preserving, transporting, storing, and documenting samples. In general, every sampling protocol must identify sampling locations—and this should include all of the equipment and information needed for sampling. Box 6.5 lists what might be considered the minimum documentation needed for most environmental sampling activities (CCME 1993; Keith 1988, 1991). In fact, the overall sampling protocol must identify sampling locations, as well as include all of the equipment and information needed for sampling, such as: the types, number, and sizes of containers; labels; field logs; types of sampling devices; numbers and types of blanks, sample splits, and spikes; the sample volume; any composite samples; specific preservation instructions for each sample type; chain of custody procedures; transportation plans; field preparations (such as filter or pH adjustments); field measurements (such as pH, dissolved oxygen, etc.); and the reporting requirements. The sampling protocol should also identify those physical, meteorological, and related variables to be recorded or measured at the time of sampling. In addition, information concerning the analytical methods to be used, minimum sample volumes, desired minimum levels of quantitation, and analytical bias and precision limits may help sampling personnel make better decisions when unforeseen circumstances require changes to the sampling protocol.

At the end of the day, the devices used to collect, store, preserve, and transport samples must *not* alter the sample in any manner. In this regard, it is noteworthy that special procedures may be needed to preserve samples during the period between collection and analysis. In any case, the more specific a sampling protocol is, the less chance there will be for errors or erroneous assumptions.

Box 6.5 Minimum requirements for documenting environmental sampling

- Sampling date
- Sampling time
- Sample identification number
- Sampler's name

(continued)

Box 6.5 (continued)

- Sampling location
- Sampling conditions or sample type
- Sampling equipment
- Preservation used
- Time of preservation
- Auxiliary data (i.e., relevant observations at sample location)

Sampling Strategies and Sample Handling Procedures: Broadly speaking, there are three basic sampling approaches—namely: random, systematic, and judgmental. There are also three primary combinations of each of these—i.e., stratified-(judgmental)-random, systematic-random, and systematic-judgmental (CCME 1993; Keith 1991). Additionally, there are further variations that can be found among the three primary approaches and the three combinations thereof. For example, the systematic grid may be square or triangular; samples may be taken at the nodes of the grid, at the center of the spaces defined by a grid, or randomly within the spaces defined by a grid. A combination of judgmental, systematic, or random sampling is often the most feasible approach to employ in the investigation of potential environmental contamination and chemical release problems. However, the sampling scheme should be flexible enough to allow relevant adjustments/modifications during field activities.

In general, several different methods are available for acquiring data to support chemical exposure characterization programs. The methodology used for sampling can indeed affect the accuracy of subsequent evaluations. It is therefore imperative to select the most appropriate methodology possible, in order to obtain the most reliable results attainable; Holmes et al. (1993), among others, enumerate several factors that should be considered when selecting a sampling method.

6.3.1.4 Laboratory Analytical Protocols

The selection of analytical methods is a key integral part of the processes involved in the development of sampling plans, since this can strongly affect the acceptability of a sampling protocol. For example, the sensitivity of an analytical method could directly influence the amount of a sample needed in order to be able to measure analytes at pre-specified minimum detection (or quantitation) limits. The analytical method may also affect the selection of storage containers and preservation techniques (Keith 1988; Holmes et al. 1993). Thus, the applicable analytical procedures, the details of which are outside the scope of this book, should be strictly adhered to.

Box 6.6 lists the minimum requirements for documenting laboratory work that may be performed to support chemical exposure characterization activities (CCME

1993; USEPA 1989a, b, c, d, e, f). In general, effective analytical programs and laboratory procedures are necessary to help minimize uncertainties in the investigation activities that are required to support potential chemical exposure characterization programs as well as possible remedy decisions. Guidelines for the selection of appropriate analytical methods are offered elsewhere in the literature (e.g., CCME 1993; Keith 1991; USEPA 1989a, b, c, d, e, f). Invariably, analytical protocol and constituent parameter selection are usually carried out in a way that balances costs of analysis with adequacy of coverage.

Box 6.6 Minimum requirements for documenting laboratory work

- Method of analysis
- Date of analysis
- Laboratory and/or facility carrying out analysis
- Analyst's name
- Calibration charts and other measurement charts (e.g., spectral)
- Method detection limits
- Confidence limits
- Records of calculations
- Actual analytical results

Selecting Laboratory Analysis Methods and Analytical Protocols—Laboratory and Analytical Program Requirements: The task of determining the essential analytical requirements involves specifying the most cost-effective analytical method that, together with the sampling methods, will meet the overall data quantity and quality objectives of an investigation activity. Oftentimes, the initial analyses of environmental samples may be performed with a variety of field methods used for screening purposes. The rationale for using initial field screening methods is to help decide if the level of pollution associated with a chemical release and potential chemical exposure situation is high enough to warrant more expensive (and more specific and accurate) laboratory analyses. Indeed, methods that screen for a wide range of compounds, even if determined as groups or homologues, are useful because they allow more samples to be measured faster and far less expensively than with conventional laboratory analyses. In the more detailed phase of the assessment, the sampling analysis is generally performed by laboratory programs that comprise routine and non-routine standardized analytical procedures and associated quality control requirements managed under a broad quality assurance program; these services are provided through routine analytical services and special analytical services.

In general, effective analytical programs and laboratory procedures are necessary to help minimize uncertainties in the investigation activities involving chemical release and potential chemical exposure situations. General guidelines for the selection of analytical methods and strategies are offered elsewhere in the literature (e.g., CCME 1993). Usually there are several methods available for most

environmental analytes of interest. Some analytes may have up to a dozen methods to select from; on the other hand, some analytes may have no proven methods available per se. In the latter case, it usually means that some of the specific isomers that were selected as representative compounds for environmental pollution have not been verified to perform acceptably with any of the commonly used methods.

6.3.2 The Health and Safety Plan

To minimize risks to chemical release investigation personnel (and possible nearby populations) as a result of potential exposure to environmental chemicals, health and safety issues must always be addressed as part of any field investigation activity plan. Proper planning and execution of safety protocols will help protect the chemical release investigation team from accidents and needless exposure to hazardous or potentially hazardous chemicals. In the processes involved, health and safety data are generally required to help establish the level of protection needed for a project investigation crew. Such data are also used to determine if there should be immediate concern for any population living in proximity of the problem location. Details of specific items of required health and safety issues and equipment are discussed elsewhere in the literature (e.g., Cheremisinoff and Graffia 1995; Martin et al. 1992; OBG 1988).

6.3.2.1 Purpose and Scope of a Health and Safety Plan

The purpose of a health and safety plan (HSP) is to identify, evaluate, and control health and safety hazards, and to provide for emergency response during environmental characterization and related fieldwork activities associated with a chemical release and/or exposure situation. The HSP specifies safety precautions needed to protect the populations potentially at risk during chemical release and potential chemical exposure characterization activities. Consequently, a project-specific HSP should be prepared and implemented prior to the commencement of any chemical release characterization or fieldwork activity associated with potential chemical exposure situations. All personnel associated with the project will generally have to comply with the applicable HSP. Also, the scope and coverage of the HSP may be modified or revised to incorporate any changes that may occur in the course of the investigation, or in the working conditions, following the development of the initial HSP.

Overall, the HSP should be developed to be in conformance with all the requirements for occupational safety and health, as well as applicable national, state/provincial/regional and local laws, rules, regulations, statutes, and orders, as necessary to protect all populations potentially at risk. Furthermore, all personnel involved with the environmental and/or chemical release characterization activities would have received adequate training, and there should be a contingency plan in

place that meets all safety requirements. For instance, in the United States, the HSP developed and implemented in the investigation of a potentially contaminated site should be in full compliance with all the requirements of the US Occupational Safety and Health Administration (OSHA) (i.e., OSHA: 29 CFR 1910.120); the requirements of US EPA (i.e., EPA: Orders 1420.2 and 1440.3); and indeed any other relevant state or local laws, rules, regulations, statutes, and orders necessary to protect the populations potentially at risk. Also, all personnel involved with on-site activities would have received a 40-hour OSHA Hazardous Waste Operations and Emergency Response Activities (HAZWOPER) training, including a commonly mandated 8-hour refresher course, where necessary.

As a final note, emergency phone numbers should be compiled and included in the HSP. Also, the directions to the nearest hospital or medical facility, including a map clearly showing the shortest route from the site to the hospital or medical facility should be kept with the HSP at the project location.

6.3.3 The Investigation-Generated/Derived Waste Management Plan

Investigation-derived wastes (IDWs) [also, Investigation-generated wastes (IGWs)] are those wastes generated during environmental and/or chemical release project characterization activities—particularly important in environmental contamination studies. Indeed, there are several ways by which IDWs may be produced.

The overarching objective of an IDW management plan is to specify procedures needed to address the handling of both hazardous and non-hazardous IDWs. The project-specific procedures should prevent contamination of clean areas, and should comply with existing regional and/or local regulations. Specifically, the IDW management plan should include the characterization of IDW; delineation of any areas of contamination; and the identification of waste disposal methods.

In general, the project manager should select investigation methods that minimize the generation of IDWs. After all, minimizing the amount of wastes generated during a chemical release characterization activity generally reduces the number of IDW/IGW handling problems and costs for disposal. Anyhow, insofar as possible, provisions should be made for the proper handling and disposal of IDWs/IGWs locally. In fact, most regulatory agencies do not recommend removal of IDWs from the place or region of origination, especially in situations where the wastes do not pose any immediate threat to human health or the environment; this is because removing wastes from such areas usually would not benefit human health and the environment, and could result in an inefficient spending of a significant portion of the total funds available for the case characterization and corrective action programs.

6.3.4 The Quality Assurance and Quality Control Plan

Quality assurance (QA) refers to a system for ensuring that all information, data, and resulting decisions compiled from an investigation (e.g., monitoring and sampling tasks) are technically sound, statistically valid, and properly documented. The QA program consists of a system of documented checks used to validate the reliability of a data set.

Quality control (QC) is the mechanism through which quality assurance achieves its goals. Quality-control programs define the frequency and methods of checks, audits, and reviews necessary to identify problems and corrective actions, thus verifying product quality. All QC measures should be performed for at least the most sensitive chemical constituents from each sampling event/date.

A detailed quality assurance/quality control (QA/QC) plan, describing specific requirements for QA and QC of both laboratory analysis and field sampling/analysis, should be part of the chemical release assessment and potential exposure characterization project work-plan. The plan requirements will typically relate to, but not limited to the following: the use of blanks, spikes, and duplicates; sample scheduling and sampling procedures; cleaning of sampling equipment; storage; transportation; data quality objectives (DQOs); chain-of-custody; reporting and documentation; audits; and methods of analysis. The practices to be followed by the project team and the oversight review—which will ensure that DQOs are met—must be clearly described in the QA/QC plan.

Several aspects of the chemical release assessment and potential exposure characterization program can, and should indeed be subjected to a quality assessment survey. In part, this is accomplished by submitting sample blanks (alongside the environmental samples) for analysis on a regular basis. The various blanks and checks that are recommended as part of the quality assurance plan include the following particularly important ones:

- *Trip Blank*—required to identify potential contamination of bottles and samples during travel and storage. To prepare the trip blank, the laboratory fills containers with contaminant-free water, and then delivers to the sampling crew; the field sampling crew subsequently ship and store these containers with the actual samples obtained from the project investigation activities. It is recommended to include one trip blank per shipment, especially where volatile chemicals are involved.
- *Field Blank*—required to identify potential contamination of samples during a sample collection activity. This is prepared in the same manner as the trip blank (i.e., the laboratory fills containers with contaminant-free water and deliver to the sampling crew); subsequently, however, the field sampling crew expose this water to air in the locale (just like the actual samples obtained from the project investigation activities). It is recommended to include one field blank per locale or sampling event/day.

- *Equipment Blank*—required in identifying possible contamination from sampling equipment. To obtain an equipment blank, sampling devices are flushed with contaminant-free water, which is then analyzed. Typically, equipment blanks become important only if a problem is suspected (such as using a bailer to sample from multiple groundwater wells).
- *Blind Replicates*—required to identify laboratory variability. To prepare the blind replicate, a field sample is typically split into three containers and labeled as different samples before shipment to the laboratory for analyses. It is recommended to include one blind replicate in each day's activities—or an average of one per 10 to 25 samples, where large numbers of samples are involved.
- *Spiked Samples*—required to help identify likely errors arising from sample storage and analysis activities. To obtain the spiked sample, known concentration(s) are added to the sample bottle and then analyzed. It is recommended to include one spiked sample per locale—or an average of one per 25 samples, where a large number of samples are involved.

Since data generated during a chemical release assessment and potential exposure characterization will provide a basis for risk management and possible remedial decisions, such data should give a valid representation of the true case-specific conditions. The development and implementation of a good QA/QC program during a sampling and analysis activity is indeed critical to obtaining reliable analytical results for the overall characterization program. The soundness of the QA/QC program has a particularly direct bearing on the integrity of the environmental sampling, and also the laboratory work. Thus, the general design process for an adequate QA/QC program, as discussed elsewhere in the literature (e.g., CCME 1994; USEPA 1987, 1988a, b), should be adhered to in the strictest manner practicable.

6.4 General Basic Requirements for Assessing Public Health Risks Arising from Exposure to Chemicals in the Human Environment

Chemical exposure characterizations typically will consist of the planned and managed sequence of activities carried out to determine the nature and distribution of hazards associated with the specific chemical exposure problem. The activities involved usually are comprised of several specific tasks—broadly listed to include the following:

- Problem definition/formulation (including identifying study objectives and data needs).
- Identification of the principal hazards.
- Design of sampling and analysis programs.

- Collection and analysis of appropriate samples.
- Recording or reporting of laboratory results for further evaluation.
- Logical analysis of sampling data and laboratory analytical results.
- Interpretation of study results (consisting of enumeration of the implications of, and decisions on corrective action or remedy).

In any event, to arrive at cost-effective public health risk management decisions, answers will typically have to be generated for several pertinent questions when one is confronted with a potential environmental contamination and/or chemical exposure problem (Box 6.7). In general, when it is suspected that a potential hazard exists at a particular locale, then it becomes necessary to further investigate the situation—and to fully characterize the prevailing or anticipated hazards. This activity may be accomplished by the use of a well-designed data collection in a chemical exposure or environmental investigation program. Ultimately, a thorough investigation—culminating in a risk assessment—that establishes the nature and extent of receptor exposures may become necessary, in order to arrive at appropriate and realistic corrective action and/or risk management decisions.

Box 6.7 Major issues important to making cost-effective public health risk management decisions for chemical exposure problems

- What is the nature of the chemical exposure(s)?
- What are the sources of, and the 'sinks' or receptors for, the chemicals of potential concern?
- What population groups are potentially at risk?
- What are the likely and significant exposure pathways and scenarios that connect chemical source(s) to potential receptors?
- What is the current extent of receptor exposures?
- What is the likelihood of health and environmental effects resulting from the chemical exposure?
- What interim measures, if any, are required as part of a risk management and/or risk prevention program?
- What corrective action(s) may be appropriate to remedy the prevailing situation?
- What level of residual chemical exposures will be tolerable or acceptable for the target receptors?

Finally, it is worth the mention here that, in order to get the most out of the environmental contamination and/or chemical exposure characterization, this activity must be conducted in a systematic manner. Indeed, systematic methods help focus the purpose, the required level of detail, and the several topics of interest—such as physical characteristics of the potential receptors; contacted chemicals; extent and severity of possible exposures; effects of chemicals on populations potentially at risk; probability of harm to human health; and possible residual

hazards following implementation of risk management and corrective action plans. Subsequently, the data derived from the environmental contamination and/or exposure investigation may be used to perform a risk assessment—which then becomes a key element in the public health risk management decision process.

Part III
A Risk Assessment Framework and Paradigm for Chemical Exposure Problems

This part of the book consists of the following six specific chapters:

- Chapter 7, *Principal Elements of a Public Health Risk Assessment for Chemical Exposure Problems*, discusses the principal elements and activities necessary for obtaining and integrating the pertinent information that will eventually allow effective public health risk management and corrective action decisions to be made about chemical exposure problems.
- Chapter 8, *Chemical Hazard Determination*, discusses the principal activities involved in the acquisition and manipulation of the pertinent chemical hazard information directed at answering the question of whether or not a chemical hazard exists to start with—i.e., to first of all determine whether or not a substance in question possesses potentially hazardous and/or toxic properties; ultimately, this would generally help in developing effective environmental and public health risk management decisions/programs about chemical exposure problems.
- Chapter 9, *Exposure Assessment: Analysis of Human Intake of Chemicals,* examines the principal exposure evaluation tasks that, upon careful implementation, should allow effective risk management decisions to be made about environmental contamination and/or chemical exposure problems.
- Chapter 10, *Determination of Chemical Toxicity*, discusses the major underlying concepts, principles, and procedures that are often employed in the evaluation of the hazard effects or toxicity of various chemical constituents found in consumer products and/or in the human environments.
- Chapter 11, *Chemical Risk Characterization*, elaborates the mechanics of the risk characterization process, together with example risk presentation modalities that would tend to, among several other things, facilitate effective risk management and/or risk communication efforts.
- Chapter 12, *Uncertainty and Variability Issues in Public Health Risk Evaluation*, discusses the key issues and evaluation modalities regarding uncertainty and variability matters that surround the overall risk assessment process.

Chapter 7
Principal Elements of a Public Health Risk Assessment for Chemical Exposure Problems

In planning for public health protection from the likely adverse effects caused by human exposure to chemicals, the first concern usually relates to whether or not the substance in question possesses potentially hazardous and/or toxic properties. As a corollary, once a 'social chemical' has been determined to present a potential health hazard, then the main concern becomes one of the likelihood for, and the degree of human exposure. In the final analysis, risk from human exposure to a chemical of concern is determined to be a function of dose or intake and potency of the substance, *viz*.:

$$Risk\ from\ chemical\ exposure = [Dose\ of\ chemical] \times [Chemical\ potency] \quad (7.1)$$

In effect, risk to an exposed population is understood by examining the exposure the population experiences relative to the hazard and the chemical potency information. Indeed, such formulations of the risk assessment paradigm are generally employed to help characterize health risks under existing exposure conditions, as well as to examine how risks might change if actions are taken to alter exposures, etc. (USEPA 2012). In general, both exposure and toxicity information are necessary to fully characterize the potential hazard of a chemical agent—or indeed any other hazardous agent for that matter. This chapter discusses the principal elements and activities necessary for obtaining and integrating the pertinent information that will eventually allow effective public health risk management decisions to be made about chemical exposure problems.

7.1 Characterization of Chemical Exposure Problems

Human exposure to a chemical agent is considered to be an episode comprised of the contacting at a boundary between a human body or organ and the chemical-containing medium, at a specific chemical concentration, for a specified time

K. Asante-Duah, *Public Health Risk Assessment for Human Exposure to Chemicals*,
Environmental Pollution 27, DOI 10.1007/978-94-024-1039-6_7

interval. Upon exposure, a receptor generally receives a dose of the chemical—and at relative measures/levels that may be quite different from the actual exposed amount; in fact, dose is different from (but occurs as a result of) an exposure (NRC 1991c)—with the dose defined as the amount of the chemical that is absorbed or deposited in the body of an exposed individual over a specified time. A clear understanding of such differences in the exposure parameters is indeed critical to the design of an adequate exposure characterization plan.

The characterization of chemical exposure problems is a process used to establish the presence or absence of chemical hazards, to delineate the nature and degree of the hazards, and to determine possible threats posed by the exposure or hazard situation to human health. The exposure routes (which may consist of inhalation, ingestion, and/or dermal contacts) and duration of exposure (that may be short-term [acute] or long-term [chronic]) will significantly influence the degree of impacts on the affected receptors. The nature and behavior of chemical substances also form a very important basis for evaluating the potential for human exposures to the possible toxic or hazardous constituents of the substance.

Now, whereas the need for and/or reliance on models and default assumptions is almost always inevitable in most chemical exposure characterization problems, the use of applicable empirical data in exposure assessments is strongly recommended whenever possible. In this regard, information obtained (through monitoring studies) from assessment of direct exposure (e.g., drinking contaminated water) and/or indirect exposure (e.g., accumulation of contaminants via the food chain) should preferably be used. Ideally, the assessment will include monitored levels of the chemical agent in the chemical-containing media, and in human tissues and fluids—in particular, estimates of the dose at a biologic target tissue(s) where an effect(s) may occur. Such information is necessary to accurately evaluate the potential health risk of exposed populations. Of course, in the absence of complete monitoring information, mathematical exposure assessment models may be employed. These models provide a methodology through which various factors, such as the temporal/spatial distribution of a chemical agent released from a particular source, can be combined to predict levels of human exposures. Even so, modeling may not necessarily be viewed as a fully satisfactory substitute for adequate data—but rather as a surrogate to be employed when confronted by compelling needs and inadequate data. In the end, uncertainty associated with these and indeed all other methods must be carefully documented and elucidated to the extent feasible.

7.1.1 Factors Affecting Exposure Characterization

Several chemical-specific, receptor-specific, and even environmental factors need to be recognized and/or evaluated as an important part of any public health risk management program that is designed to address problems that could arise from exposure of the public to various chemical substances. The general types of data

and information necessary for the investigation of potential chemical exposure problems relate to the following:

- Identities of the chemicals of concern;
- Concentrations contacted by potential receptors of interest;
- Receptor characteristics;
- Characteristics of the physical and environmental setting that can affect behavior and degree of exposure to the chemicals; and
- Receptor response upon contact with the target chemicals.

In addition, it is necessary to generate information on the chemical intake rates for the specific receptor(s), together with numerous other exposure parameters. Indeed, all parameters that could potentially impact the human health outcomes should be carefully evaluated; this includes the following especially important categories, as annotated/expounded below.

- *Exposure duration and frequency.* A single high-dose exposure to a hazardous agent may result in toxic effects quite different from those following repeated lower dose exposures. Thus, in evaluating chemical risks associated with a given problem situation, adequate consideration should be given to the duration—namely, acute (usually $\leq$14 days) *vs.* intermediate (usually 15–364 days) *vs.* chronic (usually $\geq$365 days); the intensity (i.e., dose rate *vs.* total dose); and the frequency (continuous or intermittent) of exposure. These exposure parameters have to be carefully evaluated, alongside any relevant pharmacokinetic parameters for the constituents of concern.
- *Exposure media and routes.* Exposure to hazardous substances is often a complex phenomenon—entailing exposures via multiple routes and/or media. Thus, all possible exposure media, pathways, and routes should be appropriately investigated and accounted for in the characterization of a chemical exposure situation.
- *Target receptor attributes.* Receptor behavior and activity patterns, such as the amount of time a receptor spends indoors compared with that spent outdoors, as well as its underlying variability in assessing potential human health effects should be carefully evaluated. Also, it should be recognized that factors such as nutritional status and lifestyle variables (e.g., tobacco smoking, alcohol consumption, and occupation) might all affect the health risks associated with the particular chemical exposure problem under consideration. Broadly stated, cultural issues/attributes of the target population should be carefully addressed; indeed, conducting a scientifically-supported exposure assessment for certain sub-populations would typically require development of appropriate ethnographic information—recognizing that certain culture-specific exposure assessments require unique approaches. As a matter of fact, because of unique cultural heritages, etc. of some groups within certain exposure evaluation zones, these receptors may experience exposures that may not be adequately characterized if an analyst simply resorts a use of the 'mainstream' methods of evaluation only. Under such circumstances of 'non-typical' exposure scenarios, it becomes

particularly important to obtain relevant, site-specific information—in order to be able to conduct an adequate and defensible exposure assessment.

- *Potential receptor exposures history*. Chemical exposure effects may occur in populations not only as a result of current exposure to agents but also from past exposures. Thus, past, current, and potential future exposure to hazardous substances should all be carefully evaluated as part of an overall long-term public health risk assessment program.

Indeed, the above listing is by no means complete for the universe of potential exposure possibilities—albeit represents the critical ones that must certainly be examined rather closely.

On the whole, most chemical exposure outcomes depend on the conditions of exposure such as the amount, frequency, duration, and route of exposure (i.e., ingestion, inhalation, and dermal contact). Also, for most environmental chemicals, available health effects information is generally limited to high exposures in studies of humans (e.g., occupational studies of workers) or laboratory animals; thus, evaluation of potential health effects associated with low levels of exposure generally encountered in the human living and work environments involves inferences based on the understanding of the mechanisms of chemical-induced toxicity. Furthermore, one should be cognizant of the fact that, in general, chemicals frequently affect more than one organ or system in the human body (e.g., liver, kidney, nervous system), and can also produce a variety of health endpoints (e.g., cancer, respiratory allergies, infertility). For all these reasons, among perhaps several others, uncertainty issues should be very carefully and comprehensively addressed in such evaluation efforts.

7.2 The Risk Assessment Process

Risk assessment is a scientific process that can be used to identify and characterize chemical exposure-related human health problems. Specific forms of risk assessment generally differ considerably in their levels of detail. Most risk assessments, however, share the same general logic—consisting of four basic elements, namely, hazard assessment, dose-response assessment, exposure assessment, and risk characterization (Fig. 7.1).

Hazard assessment describes, qualitatively, the likelihood that a chemical agent can produce adverse health effects under certain environmental exposure conditions. *Dose-response assessment* quantitatively estimates the relationship between the magnitude of exposure and the degree or probability for occurrence of a specific health effect. *Exposure assessment* determines the extent of human exposure. *Risk characterization* integrates the findings of the first three components to describe the nature and magnitude of health risk associated with environmental exposure to a chemical substance, or a mixture of substances. A discussion of these fundamental elements follows—with more detailed elaboration given in Chaps. 8–12 of this title,

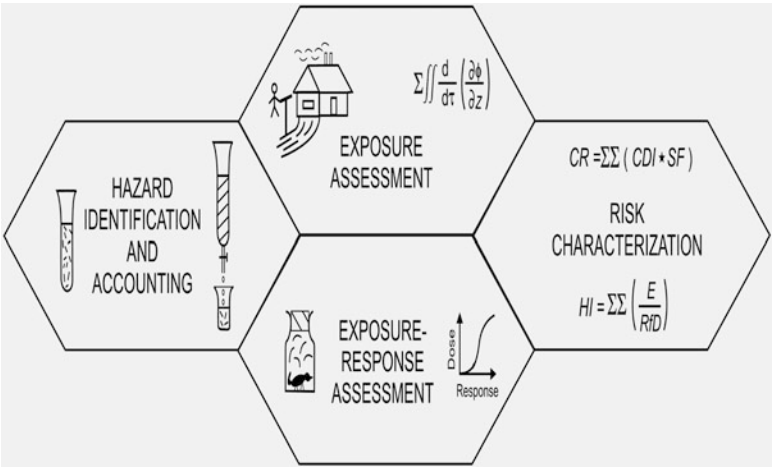

Fig. 7.1 Illustrative elements of a risk assessment process

and also elsewhere in the risk analysis literature (e.g., Asante-Duah 1998; Cohrssen and Covello 1989; Conway 1982; Cothern 1993; Gheorghe and Nicolet-Monnier 1995; Hallenbeck and Cunningham 1988; Huckle 1991; Kates 1978; Kolluru et al. 1996; LaGoy 1994; Lave 1982; McColl 1987; McTernan and Kaplan 1990; Neely 1994; NRC 1982, 1983, 1994a, b; Paustenbach 1988; Richardson 1990; Rowe 1977; Suter 1993; USEPA 1984b, 1989a, b, c, d, e, f; Whyte and Burton 1980).

7.2.1 Hazard Identification and Accounting

Hazard identification and accounting involves a qualitative assessment of the presence of, and the degree of hazard that an agent could have on potential receptors. The hazard identification consists of gathering and evaluating data on the types of health effects or diseases that may be produced by a chemical, and the exposure conditions under which public health damage, injury or disease will be produced. It may also involve characterization of the behavior of a chemical within the body and the interactions it undergoes with organs, cells, or even parts of cells. Data of the latter types may be of value in answering the ultimate question of whether the forms of toxic effects shown to be produced by a substance in one population group or in experimental settings are also likely to be produced in the general human population.

Hazard identification is not a risk assessment *per se*. This process involves simply determining whether it is scientifically correct to infer that toxic effects observed in one setting will occur in other settings—e.g., whether substances found to be carcinogenic or teratogenic in experimental animals are likely to have the

same results in humans. In the context of public health risk management for potential chemical exposure problems, this may consist of:

- Identification of chemical exposure sources;
- Compilation of the lists of all chemical stressors present at the locale and impacting target receptors;
- Identification and selection of the specific chemicals of potential concern (that should become the focus of the risk assessment), based on their specific hazardous properties (such as persistence, bioaccumulative properties, toxicity, and general fate and behavior properties); and
- Compilation of summary statistics for the key constituents selected for further investigation and evaluation.

Indeed, a major purpose of the hazard identification step of a public health risk assessment is to identify a subset of 'chemicals of potential concern' (CoPCs) from all constituents detected during an investigation. The CoPCs are a subset of the complete set of constituents detected during an investigation that are exclusively carried through the quantitative risk assessment process. On the whole, the selection of CoPCs identifies those chemicals observed that have the most potential to be a significant contributor to human health risks—recognizing that most risk assessments tend to be dominated by a few compounds of significant concern (and indeed a few routes of exposure as well); as a matter of fact, the inclusion of all detected compounds in the risk assessment often has minimal influence on the total risk—and thus generally considered an unnecessary burden. In any case, several factors are typically considered in identifying CoPCs for risk assessments—including toxicity and magnitude of detected concentrations, frequency of detection, and essential nutrient status. The so-identified CoPCs are then carried forward for quantitative evaluation in the subsequent (baseline) risk assessment. Overall, the CoPC screening process is intended to identify the following:

(i) Constituents that pose negligible risks—and therefore can be eliminated from further evaluation; and
(ii) Constituents that merit further evaluation, either quantitatively or qualitatively, based on their potential to adversely affect humans depending on specific types of exposures.

Finally, it is noteworthy that, in identifying the CoPCs, an attempt is generally made to select all chemicals that could possibly represent the major part (usually, $\geq$95%) of the risks associated with the relevant exposures.

7.2.2 Exposure-Response Evaluation

The *exposure-response evaluation* (or the *effects assessment*) consists of a process that establishes the relationship between dose or level of exposure to a substance and the incidence-cum-severity of an effect. It considers the types of adverse effects

associated with chemical exposures, the relationship between magnitude of exposure and adverse effects, and related uncertainties (such as the weight-of-evidence of a particular chemical's carcinogenicity in humans). In the context of chemical exposure problems, this evaluation will generally include a 'dose-response evaluation' and/or a 'toxicity assessment'. Dose-response relationships are typically used to quantitatively evaluate the toxicity information, and to characterize the relationship between dose of the contaminant administered or received and the incidence of adverse effects on an exposed population. From the quantitative dose-response relationship, appropriate toxicity values can be derived—and this is subsequently used to estimate the incidence of adverse effects occurring in populations at risk for different exposure levels. The toxicity assessment usually consists of compiling toxicological profiles for the chemicals of potential concern.

Dose-response assessment specifically involves describing the quantitative relationship between the amount of exposure to a substance and the extent of toxic injury or disease. Data are characteristically derived from animal studies or, less frequently, from studies in exposed human populations. There may be many different dose-response relationships for a substance if it produces different toxic effects under different conditions of exposure. Meanwhile, it is noteworthy that, even if the substance is known to be toxic, the risks of a substance cannot be ascertained with any degree of confidence unless dose-response relations are quantified.

7.2.3 Exposure Assessment and Analysis

An *exposure assessment* is conducted in order to estimate the magnitude of actual and/or potential receptor exposures to chemicals present in human environments. The process considers the frequency and duration of the exposures, the nature and size of the populations potentially at risk (i.e., the risk group), and the pathways and routes by which the risk group might be exposed. Indeed, several physical and chemical characteristics of the chemicals of concern will provide an indication of the critical exposure features. These characteristics can also provide information necessary for determining the chemical's distribution, intake, metabolism, residence time, excretion, magnification, and half-life or breakdown to new chemical compounds.

In general, exposure assessments involve describing the nature and size of the population exposed to a substance and the magnitude and duration of their exposure. The evaluation could concern past or current exposures, or exposures anticipated in the future. To complete a typical exposure analysis for a chemical exposure problem, populations potentially at risk are identified, and concentrations of the chemicals of concern are determined in each medium to which potential receptors may be exposed. Finally, using the appropriate case-specific exposure parameter values, the intakes of the chemicals of concern are estimated. The

exposure estimates can then be used to determine if any threats exist—based on the prevailing exposure conditions for the particular problem situation.

7.2.4 Risk Characterization and Consequence Determination

Risk characterization is the process of estimating the probable incidence of adverse impacts to potential receptors under a set of exposure conditions. Typically, the risk characterization summarizes and then integrates outputs of the exposure and toxicity assessments—in order to be able to qualitatively and/or quantitatively define risk levels. The process will usually include an elaboration of uncertainties associated with the risk estimates. Exposures resulting in the greatest risk can be identified in this process—and then mitigative measures can subsequently be selected to address the situation in order of priority, and according to the levels of imminent risks.

In general, risk characterizations involve the integration of the data and information derived/analyzed from the first three components of the risk assessment process (*viz.*, hazard identification, dose-response assessment, and exposure assessment)—in order to ascertain the likelihood that humans might experience any of the various forms of toxicity associated with a substance. [By the way, in cases where exposure data are not available, hypothetical risks can be characterized by the integration of hazard identification and dose-response evaluation data alone.] In the final analysis, a framework to define the significance of the risk is developed, and all of the assumptions, uncertainties, and scientific judgments from the three preceding steps are also presented. Meanwhile, to the extent feasible, the risk characterization should include the distribution of risk amongst the target populations. When all is said and done, an adequate characterization of risks from hazards associated with chemical exposure problems allows risk management and corrective action decisions to be better focused.

7.3 General Considerations in Public Health Risk Assessments

Human health risk assessment for chemical exposure problems may be defined as the characterization of the potential adverse health effects associated with human exposures to chemical hazards. In a typical human health risk assessment process, the extent to which potential receptors have been, or could be exposed to chemical hazards is determined. The extent of exposure is then considered in relation to the type and degree of hazard posed by the chemical(s)—thereby permitting an estimate to be made of the present or future health risks to the populations-at-risk.

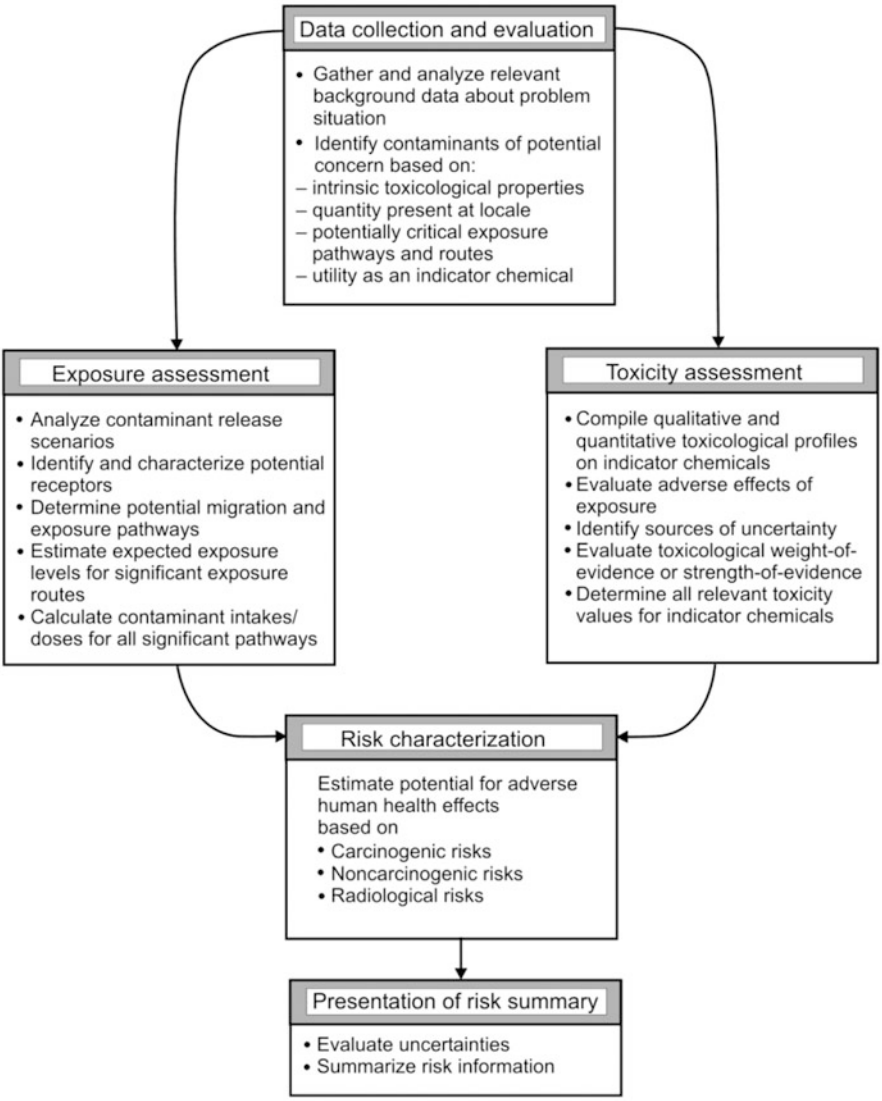

Fig. 7.2 A general protocol for the human health risk assessment process: fundamental procedural components of a risk assessment for a chemical exposure problem

Figure 7.2 shows the basic components and steps typically involved in a comprehensive human health risk assessment that is designed for use in environmental and public health risk management programs. Several key aspects of the human health risk assessment methodology are presented in the proceeding chapters of this volume—with additional details provided elsewhere in the literature (e.g., Hoddinott 1992; Huckle 1991; NRC 1983; Patton 1993; Paustenbach 1988; Ricci

1985; Ricci and Rowe 1985; USEPA 1984a, b, 1985, 1986a, b, c, d, 1987, 1989d, 1991a, b, c, d, 1992a, b, c, d, e; Van Leeuwen and Hermens 1995).

Invariably, the management of all chemical exposure problems starts with hazard identification and/or a data collection-cum-data evaluation phase. The data evaluation aspect of a human health risk assessment consists of an identification and analysis of the chemicals associated with a chemical exposure problem that should become the focus of the public health risk management program. In this process, an attempt is generally made to select all chemicals that could represent the major part of the risks associated with case-related exposures; typically, this will consist of all constituents contributing $\geq$95% of the overall risks. Chemicals are screened based on such parameters as toxicity, carcinogenicity, concentrations of the detected constituents, and the frequency of detection in the sampled matrix.

The exposure assessment phase of the human health risk assessment is used to estimate the rates at which chemicals are absorbed by potential receptors. Since most potential receptors tend to be exposed to chemicals from a variety of sources and/or in different environmental media, an evaluation of the relative contributions of each medium and/or source to total chemical intake could be critical in a multi-pathway exposure analysis. In fact, the accuracy with which such exposures are characterized could be a major determinant of the ultimate validity of the risk assessment.

The quantitative evaluation of toxicological effects consists of a compilation of toxicological profiles (including the intrinsic toxicological properties of the chemicals of concern, which may include their acute, subchronic, chronic, carcinogenic, and/or reproductive effects) and the determination of appropriate toxicity indices (see Chap. 10 and Appendix C).

Finally, the risk characterization consists of estimating the probable incidence of adverse impacts to potential receptors under various exposure conditions. It involves an integration of the toxicity and exposure assessments, resulting in a quantitative estimation of the actual and potential risks and/or hazards due to exposure to each key chemical constituent, and also the possible additive effects of exposure to mixtures of the chemicals of potential concern.

7.3.1 Determining Exposure-Related Health Effects

Exposure-related health effects of chemical substances introduced into the human living and work environments may be determined within the framework of a public health risk assessment process. In general, when evaluating the health impact of exposure to hazardous substances, the analyst should consider data from studies of human exposures as well as from the results of experimental animal studies. For health assessment purposes, the use of human data is preferred—because it eliminates (or at least reduces) uncertainties involved in extrapolating across species. However, human data are often unavailable, particularly for chronic, low-dose exposures. Furthermore, adequate human data are often not available to establish

a dose-response relationship. In the absence of adequate human data, therefore, the public health analyst must rely on the results of experimental animal studies. Also, in many chemical exposure situations, exposures must often be characterized as chronic and of low dose; meanwhile, it is apparent that health effects data and information for such exposures are often lacking. Again, in these types of situations, the health analyst may have to rely on studies that involve shorter exposures and/or higher dose levels. Ultimately, if such studies are used as the basis for a health assessment, the analyst should acknowledge the qualitative and quantitative uncertainties involved in those extrapolations. In the end, it is generally recommended that estimated chemical exposures be compared to studies or experiments involving comparable routes of exposure—*viz*., ingestion, inhalation, and dermal contact. However, in some instances, it may be necessary to utilize data from studies based on different exposure pathways or routes. Under such circumstances, extra caution should be used when eliciting/deriving conclusions from these 'surrogate' studies because of the uncertainties involved in route-to-route extrapolations—especially because of the likely concomitant differences in chemical absorption, distribution, metabolism, and excretion. In addition, a chemical might exert a toxic effect by one route of exposure, but not by another (e.g., chromium is reported to be carcinogenic by inhalation, but not by ingestion); such differences should be carefully evaluated.

Finally, it is noteworthy here that, to facilitate the development of responsible public health risk management programs, it is important for the public health analyst to use the best medical and toxicological information available to determine the health effects that may arise from exposure to the chemical constituents of concern. Such information can be derived from existing chemical-specific toxicological profiles or databases (*e.g*., 'Toxicological Profiles' from the ATSDR, and IRIS from the US EPA), standard toxicology textbooks, and scientific journals of environmental toxicology or environmental health. Analysts should also consult on-line databases for the most current toxicological and medical information. Furthermore, the analyst should clearly indicate in the health assessment reporting/documentation whether the case-specific health concerns of interest are for acute, intermediate, or chronic exposures.

7.3.2 Evaluating Factors That Influence Adverse Health Outcome

To ensure reliable public health policy decisions, the public health analyst should review the various factors that may enhance or mitigate health effects arising from exposure to chemicals present in the human living and work environments. Indeed, among other things, the analyst should also consider all other pertinent medical and toxicological information; the health implications for sensitive sub-populations; health implications of past and future exposures; and the effects of corrective/

control actions or interventions on human exposure. The particularly important issues are elaborated in the sections below.

7.3.2.1 Public Health Implications of Supplemental Medical and Toxicological Factors

As appropriate, several factors should normally be investigated and their health implications discussed in any given health assessment; typical factors that the public health analyst may generally consider in the evaluation of public health outcomes are annotated in Box 7.1. In general, in addition to the medical and toxicological factors identified here, the public health analyst should also consider population-specific factors that may enhance or mitigate health effects associated with exposure to the constituents of concern. Overall, the health effects identified by comparing dose estimates with toxicity values during a risk characterization should also be evaluated on the basis of other toxicological and medical factors that could potentially amplify or mitigate the effects of a chemical exposure.

Box 7.1 Typical medical and toxicological factors affecting public health outcomes

- Distribution of chemical within the body (i.e., the fate of the chemical after ingestion, inhalation, or dermal contact)
- Target organs (i.e., physiologic site of major toxicity)
- Toxicokinetics of substance (including possible transfer to cow's milk or nursing mother's milk)
- Enzyme induction (i.e., chemical induction of various enzyme systems may increase or decrease chemical toxicity)
- Cumulative effect of exposures to chemicals that bioaccumulate in the body (e.g., lead, cadmium, organochlorine pesticides)
- Chemical tolerance (i.e., decreased responsiveness to a toxic chemical effect resulting from previous exposure to that chemical or to a structurally related chemical)
- Immediate *versus* delayed effects (i.e., effects observed rapidly after a single exposure *versus* effects that occur after some lapse of time)
- Reversible *versus* irreversible effects (i.e., ability of affected organs to regenerate)
- Local *versus* systemic effects (i.e., whether the effect occurs at the site of first contact, or if the chemical must be absorbed and distributed before the effect is observed)
- Idiosyncratic reactions (i.e., genetically determined abnormal reactivity to a chemical that is qualitatively similar to reactions found in all persons—

(continued)

Box 7.1 (continued)

but may take the form of either extreme sensitivity to low doses or extreme insensitivity to high doses)
- Allergic reactions (i.e., adverse reaction to a chemical resulting from previous sensitization to that chemical or a structurally related one)
- Various other related disease effects (i.e., effect of chemical on previously diseased organ)

7.3.2.2 Health Implications for Sensitive Sub-populations

Characteristically, many sub-populations may be identifiable at a given study locale—and each sub-population may have special concerns that must be considered when ascertaining the public health implications of a chemical exposure problem. Perhaps the most crucial set of factors that an analyst must weigh are those that influence differential susceptibility to the effects of specific compounds. Indeed, age, gender, genetic background, nutritional status, health status, and general lifestyle may each influence the effects of chemical exposures; thus, the analyst should carefully consider the impact that each of these factors may have under a specific chemical exposure scenario for a given population. The key factors are elaborated below.

- *Age of Receptor*. Age-related susceptibility to the toxic effects of chemicals is probably more widespread than many public health analysts realize. Indeed, at some point in a human lifetime, every person is at an increased risk from chemical exposures because of age factors. At any rate, it is generally acknowledged that the very young are a particularly high-risk group that must be protected more stringently from the adverse effects of certain compounds. For example, the US EPA primary drinking water standard for nitrate had to be so-established to protect the most susceptible high-risk group—namely, infants in danger of developing methemoglobinemia. Similar age-related sensitivities have been reflected in 'allowable' levels set for lead in ambient air and in drinking water, as well as for mercury in aquatic systems. Then again, the very young are not always the age group necessarily linked with the most amplified risk situation. In fact, in some instances, adults are at greater risk of toxicity than infants or children; for example, past studies have shown that the young seem more resistant (than adults) to the adverse effects of renal toxicants such as fluoride and uranyl nitrate. Furthermore, fairly recent acknowledgment by many experts/investigators that elderly subpopulations may have significantly heightened susceptibility to chemical compounds because of lower functional capacities of various organ systems, reduced capacity to metabolize foreign compounds, and diminished detoxification mechanisms should be recognized.

- *Gender of Receptor*. Although gender-linked differences in toxic susceptibilities have not quite been extensively investigated, there is some scientific evidence to support the fact that certain adverse health effects may be mediated through hormonal influences and other factors that are dependent on the sex of the individual receptor. As an example, it is well documented that pregnant women are often at significantly greater risk from exposure to beryllium, cadmium, lead, manganese, and organophosphate insecticides than other members of the general population; this is because of the various physiologic modifications associated with the pregnancy. Also, a developing fetus is at greater risk from compounds that exert developmental effects.
- *Biochemical and/or Genetic Susceptibilities*. The presence of subpopulations with certain inherent biochemical and/or genetic susceptibilities should be given careful consideration when evaluating the potential health threats from a chemical exposure problem; this is because a number of studies indicate that genetic predisposition is an important determining factor in numerous disease states. Indeed, studies of some of these 'genetically-determined' diseases have shown an increased susceptibility to the toxic effects of certain chemicals. For example, certain percentages of some ethnic groups are known to suffer from inherited serum alpha-1-antitrypsin deficiency—which predisposes them to alveolar destruction and pulmonary emphysema. Persons with this deficiency are especially sensitive to the effects of certain pollutants. In general, this type of information can be used in conjunction with information on the ethnic makeup of populations in the study area, so as to better evaluate potential toxic effects associated with a chemical exposure problem. In addition, persons who have chronic diseases may also be at increased risk from exposure to certain chemicals; for example, individuals with cystic fibrosis are less tolerant of the respiratory and gastrointestinal challenges of some pollutants. Also, persons with hereditary blood disorders, such as sickle-cell anemia, have increased sensitivity to compounds such as benzene, cadmium, and lead—which are suspected 'anemia producers'. Thus, the importance of determining the presence and proximity of facilities such as hospitals or convalescent homes where sensitive subpopulations are likely to be found cannot be overemphasized. On the whole, when identifiable groups are known to be at risk from exposure to a chemical source, then it is quite important to determine the nature and magnitude of adverse health effects that could likely emerge (alongside any confounding factors), by undertaking extensive research of information contained in available medical and toxicological literature/databases, etc.
- *Socioeconomic Factors*. Socioeconomic status is not only an important indicator of human susceptibilities to specific pollutants, but such information may also help identify confounding nutritional deficiencies or behaviors that enhance a person's sensitivity to the toxic effects of chemical materials. For instance, studies have shown that dietary deficiencies of vitamins A, C, and E may increase susceptibility to the toxic effects of polychlorinated biphenyls (PCBs) and other chlorinated hydrocarbons, some pesticides, ozone, and various other substances. Other studies have also indicated that deficiencies in trace metals

such as iron, magnesium, and zinc exacerbate the toxic potential of fluorides, manganese, and cadmium. Meanwhile, it is notable that populations with sensitivities due to nutritional deficiencies have typically been associated with areas of low socioeconomic status and extreme poverty, or in areas with large numbers of indigents. Elderly populations have also been identified as a subgroup at risk of susceptibility because of nutritional deficits.

In general, demographic and land-use information can be used to help identify the relative socioeconomic status of exposed populations; this information may ultimately provide important clues for properly apprising the likely impacts of variant exposed population (sub)groups encountered during a health assessment activity. In fact, as part of the overall public health risk determination process, the public health analyst must carefully examine demographic information for particular groups on or near the study area or exposure source, and who might be especially sensitive to toxic effects. Any suspected high-risk groups should be explicitly identified in any ensuing health assessment report. For instance, locations of daycare centers, schools, playgrounds, recreational areas, hospitals and retirement or convalescent homes on or near a given site should be highlighted as important indications of the presence of sensitive subpopulations. Enumeration of ethnic groups within the population, as well as characterization of socioeconomic status may also indicate sensitive subpopulations near a study area or exposure source. It is noteworthy that, ultimately, information on the number and proximity of people in high-risk subpopulations is vital for developing an optimal public health risk management or mitigation plan.

Overall, subpopulations of special concern should be identified during a public health risk assessment process; those individuals or groups may be at increased risk because of greater sensitivity, compromised health status, concomitant occupational exposures, or indeed a variety of other reasons. Thus, if such individuals or groups really exist, then they should be explicitly identified in the health assessment—and then appropriate recommendations should be made specifically directed at their protection. Furthermore, other groups that are closely affiliated with a high-risk group—such as families of workers who may be (or have been) exposed through contact with work clothing or other secondary means—should perhaps be carefully evaluated as well.

7.3.2.3 Health Implications of Past and Future Exposures

A generally important aspect of the process of determining the public health implications of chemical exposures usually involves establishing a firm difference between that which constitutes ‘actual’ exposures (i.e., expected and/or completed exposures) *vs*. ‘potential’ exposures (i.e., possible but not necessarily complete exposures). When evaluating future ‘actual’ and ‘potential’ exposures, the analyst should also make a determination of the underlying causes for the anticipated exposures (e.g., from the continued use of specific consumer products, etc.)—so

that appropriate mitigative measures for such future exposures can be undertaken *a priori*. At any rate, in the attempt to ascertain the health implications of a chemical exposure problem, and in addressing a population-at-risk's health concerns, the public health analyst should endeavor to include past, current, and potential future exposures in the requisite documentation. Meanwhile, it has to be acknowledged here that, despite the fact that significant exposure may already have occurred, past exposures tend to be difficult to address—especially because they are difficult to quantify. To facilitate requisite efforts in the process of evaluating community health concerns about past hazard exposures, the analyst should review all available community-specific health outcome databases, such as morbidity data and disease registries—in order to determine a possible correlation between past and current health outcomes and past exposures. When past exposures have been documented, but health studies have not been performed, health effects studies or the review of community health records become very important.

7.3.2.4 Health Implications of Corrective Actions and Interventions

In determining the health implications of a chemical exposure situation, it is quite important that the analyst takes the effect(s) of remedial actions and other intervention programs into consideration. This is because previous, current, and/or planned remedial or risk management actions can significantly affect conclusions about exposure-related health concerns.

In general, when remedial response measures or other interventions have occurred previously, the analyst should consider the effect that those measures have had on the health of the target population. Similarly, if intervention is already occurring, the analyst should determine what likely effects this might have, moving forward. Furthermore, the health assessment should be responsive to community health concerns vis-à-vis the remedial actions. In addition, discussion offered in the health assessment with respect to the recognized exposure scenarios should clearly identify and differentiate between those exposure scenarios that still exist *vs.* the exposures that may have occurred in the past (but that have now been eliminated or significantly reduced by remedial action or other intervention programs).

7.4 Human Health Risk Assessment in Practice

Quantitative human health risk assessment often becomes an integral part of most environmental and public health risk management programs that are designed to address chemical exposure problems. In the processes involved, four key elements are important in arriving at appropriate risk management solutions—namely, the chemical hazard identification; the chemical toxicity assessment or exposure-response evaluation; the exposure assessment; and the risk characterization. Each

of these elements typically will, among other things, help answer the following fundamental questions:

- Chemical hazard identification step—'what chemicals are present in the human environments of interest?' and 'is the chemical agent likely to have an adverse effect on the potential human receptor?'
- Chemical toxicity assessment or exposure-response evaluation step—'what is the relationship between human exposure/dose to the chemical of potential concern and the response, incidence, injury, or disease as a result of the receptor exposure?' In other words, 'what harmful effects can be caused by the target chemicals, and at what concentration or dose?'
- Exposure assessment step—'what individuals, subpopulations, or population groups may be exposed to the chemical of potential concern?' and 'how much exposure is likely to result from various activities of the potential receptor—i.e., what types and levels of exposure are anticipated or observed under various scenarios?'
- Risk characterization step—'what is the estimated incidence of adverse effect to the exposed individuals or population groups—i.e., what risks are presented by the chemical hazard source?' and 'what is the degree of confidence associated with the estimated risks?'

Typically, the fundamental tasks involved in most human health risk assessments will consist of the key components shown in Box 7.2—revealing a methodical framework; a careful implementation of this framework should generally provide answers to the above questions. Illustrative examples of the practical application of the processes involved are provided in Chaps. 9, 11 and 13. Meanwhile, it cannot be stated enough that there are many uncertainties associated with public health risk assessments. These uncertainties are due in part to the complexity of the exposure-dose-effect relationship, and also the lack of, or incomplete knowledge/information about the physical, chemical, and biological processes within and between human exposure to chemical substances and health effects. On the whole, the major sources of uncertainty in public health risk assessments can be attributed to the following:

(i) Use of a wide range of data from many different disciplines (e.g., epidemiology, toxicology, biology, chemistry, statistics, etc.);
(ii) Use of many different predictive models and methods in lieu of actual measured data; and
(iii) Use of many scientific assumptions and science policy choices (i.e., scientific positions assumed in lieu of scientific data)—in order to bridge the information/knowledge gaps in the risk assessment process.

Ultimately, these diverse elements, along with varying interpretations of the scientific information, can produce divergent results in the risk assessment process—an outcome that often leads to some risk assessment controversies. Thus, it is very important to carefully and systematically identify all sources and types of uncertainty and variability—and then present them as an integral part of risk characterization process.

In closing, it is noteworthy that the scientific information about the hazards used in risk assessments is derived largely from observational epidemiology and experimental animal studies of specific substances or combinations of substances that are designed to identify their hazardous properties (namely, the types of harm they can induce in humans) and the conditions of exposure under which those harms are observed (namely, the dose and duration). Information from these studies will typically be used to develop the hazard identification and dose-response components of a risk assessment—all the while recognizing that the data used to develop these components usually arise from diverse sources and types of study designs that frequently lack strong consistency in methods; thus, reaching valid conclusions about them requires both careful scientific evaluations and experienced/informed judgments (OMB and OSTP 2007). Next, assessing exposure requires an evaluation of the nature of the population that is incurring exposures to the substances of interest and the conditions of exposure that it is experiencing (such as the dose and duration of exposure) (NRC 1991a, b, c). In the end, risk to the exposed population is understood by examining the exposure the population experiences relative to the hazard and dose–response information.

Box 7.2 Illustrative basic outline for a public health risk assessment report

Section Topic	Basic Subject Matter
General Overview	
	• Background information on the case problem or locale • The risk assessment process • Purpose and scope of the risk assessment • The risk assessment technique and method of approach • Legal and regulatory issues in the risk assessment • Limits of application for the risk assessment
Data Collection	
	• Chemical exposure sources of potential concern • General case-specific data collection considerations • Assessment of the data quality objectives • Identification of data gathering uncertainties
Data Evaluation	
	• General case-specific data evaluation considerations • Identification, quantification, and categorization of target chemicals • Statistical analyses of relevant chemical data • Screening and selection of the chemicals of potential concern • Identification of uncertainties associated with data evaluation

(continued)

Box 7.2 (continued)

Exposure Assessment	
	• Characterization of the exposure setting (to include the physical setting and populations potentially at risk) • Identification of the chemical-containing sources/media, exposure pathways, and potentially affected receptors • Determination of the important fate and behavior processes for the chemicals of potential concern • Determination of the likely and significant exposure routes • Development of representative conceptual model(s) for the problem situation • Development of realistic exposure scenarios (to include both current and potential future possibilities) • Estimation/modeling of exposure point concentrations for the chemicals of potential concern • Quantification of exposures (i.e., computation of potential receptor intakes/doses for the applicable exposure scenarios) • Identification of uncertainties associated with exposure parameters
Toxicity Assessment	
	• Compilation of the relevant toxicological profiles of the chemicals of potential concern • Determination of the appropriate and relevant toxicity index parameters • Identification of uncertainties relating to the toxicity information
Risk Characterization	
	• Estimation of the human carcinogenic risks from carcinogens • Estimation of the non-carcinogenic effects for systemic toxicants • Sensitivity analyses of relevant parameters • Identification and evaluation of uncertainties associated with the risk estimates
Risk Summary Discussion	
	• Summarization of risk information • Discussion of all identifiable sources of uncertainties

Chapter 8
Chemical Hazard Determination

The first issue in any attempt to conduct a public health risk assessment for chemical exposure problems relates to answering the seemingly straight-forward question: 'does a chemical hazard exist?' Thus, all environmental and public health risk management programs designed for chemical exposure situations usually will start with a hazard identification and accounting; this initial process sets out to determine whether or not the substance in question possesses potentially hazardous and/or toxic properties. This chapter discusses the principal activities involved in the acquisition and manipulation of the pertinent chemical hazard information directed at answering this question; ultimately, this would generally help in developing effective environmental and public health risk management decisions/programs about chemical exposure problems.

8.1 Chemical Hazard Identification: Sources of Chemical Hazards

The chemical hazard identification component of a public health risk assessment involves first establishing the presence of a chemical stressor that could potentially cause adverse human health effects. This process usually includes a review of the major sources of chemical hazards that could potentially contribute to a given chemical exposure and possible risk situation. Indeed, chemical hazards affecting public health risks typically originate from a variety of sources (Box 8.1)—albeit their relative contributions to actual human exposures are not always so obvious. Needless to say, there is a corresponding variability in the range and types of hazards and risks that may be anticipated from different chemical exposure problems.

Oftentimes, qualitative information on potential sources and likely consequences of the chemical hazards is all that is required during this early stage (i.e.,

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the hazard identification phase) of the risk assessment process. To add a greater level of sophistication to the hazard identification process, however, quantitative techniques may be incorporated into this process—to help determine, for instance, the likelihood of an actual exposure situation occurring. The quantitative methods may include a use of mathematical modeling and/or decision analyses techniques to determine chemical fate and behavior attributes following human exposure to a chemical vis-à-vis the likely receptor response upon exposure to the chemical of potential concern. For instance, physicochemical data can be used to predict a chemical's physical hazard, reactivity, and pharmacokinetics—including attributes such as absorption by different exposure routes, distribution inside the receptor, and likely metabolites associated with the subject chemical. Indeed, physicochemical and structural properties of a chemical of interest/concern are quite critical for chemical characterization processes—especially because they can help in the prediction of a chemical's potential to pose a physical hazard, its reactivity, and its pharmacokinetic characteristics (such as bioavailability and likely routes of exposure). Ultimately, this initial evaluation for a chemical exposure problem should provide great insight into the nature and types of chemicals, the populations potentially at risk, and possibly some qualitative ideas about the magnitude of the anticipated risk.

Box 8.1 Examples of major sources of chemical hazards potentially resulting in public health problems

- Consumer products (including foods, drinks, cosmetics, medicines, etc.)
- Urban air pollution (including automobile exhausts, factory chimney stacks, etc.)
- Contaminated drinking water
- Industrial manufacturing and processing facilities
- Commercial service facilities (such as fuel stations, auto repair shops, dry cleaners, etc.)
- Landfills, waste tailings and waste piles
- Contaminated lands
- Wastewater lagoons
- Septic systems
- Hazardous materials stockpiles
- Hazardous materials storage tanks and containers
- Pipelines for hazardous materials
- Spills from loading and unloading of hazardous materials
- Spillage from hazardous materials transport accidents
- Pesticide, herbicide, and fertilizer applications
- Contaminated urban runoff
- Mining and mine drainage
- Waste treatment system and incinerator emissions

8.2 Data Collection and Evaluation Considerations

The process involved in a public health risk assessment for chemical exposure problems will usually include a well-thought out plan for the collection and analysis of a variety of chemical hazard and receptor exposure data. Ideally, and to facilitate this process, project-specific 'work-plans' can be designed to specify the administrative and logistic requirements of the general activities to be undertaken – as discussed in Chap. 6, and excerpted below. A typical data collection work-plan that is used to guide the investigation of chemical exposure problems may include, at a minimum, a sampling and analysis plan together with a quality assurance/quality control plan. The general nature and structure for such types of work-plans, as well as further details on the appropriate technical standards for sample collection and sample handling procedures, can be found in the literature elsewhere (e.g., Asante-Duah 1998; ASTM 1997b; Boulding 1994; CCME 1993; CDHS 1990; Keith 1988, 1991; Lave and Upton 1987; Petts et al. 1997; USEPA 1989a, b).

In general, all sampling and analysis should be conducted in a manner that maintains sample integrity and encompasses adequate quality assurance and control. Also, specific samples collected should be representative of the target materials that are the source of, and/or 'sink' for, the chemical exposure problem. And, regardless of its intended use, it is noteworthy that samples collected for analysis at a remote location are generally kept on ice prior to and during transport/shipment to a certified laboratory for analysis; also, completed chain-of-custody records should accompany the samples to the laboratory.

Indeed, sampling and analysis can become a very important part of the decision-making process involved in the management of chemical exposure problems. Yet, sampling and analysis could also become one of the most expensive and time-consuming aspects of such public health risk management programs. Even of greater concern is the fact that errors in sample collection, sample handling, or laboratory analysis can invalidate the hazard accounting and exposure characterization efforts, and/or add to the overall project costs. All samples that are intended for use in human exposure and risk characterization programs must therefore be collected, handled, and analyzed properly—in accordance with all applicable/relevant methods and protocols. To ultimately produce data of sound integrity and reliability, it is important to give special attention to several issues pertaining to the sampling objective and approach; sample collection methods; chain-of-custody documentation; sample preservation techniques; sample shipment methods; and sample holding times. Chapter 6 contains a convenient checklist of the issues that should be verified when planning such type of sampling activity.

Overall, highly effective sampling and laboratory procedures are required during the chemical hazard determination process; this is to help minimize uncertainties associated with the data collection and evaluation aspects of the risk assessment. Ultimately, several chemical-specific parameters (such as chemical toxicity or potency, media concentration, ambient levels, frequency of detection, mobility, persistence, bioaccumulative/bioconcentration potential, synergistic or antagonistic

effects, potentiation or neutralizing effects, etc.) as well as various receptor information are further used to screen and help select the specific target chemicals that will become the focus of a detailed risk assessment.

8.2.1 Data Collection and Analysis Strategies

A variety of data collection and analysis protocols exist in the literature (e.g., Boulding 1994; Byrnes 1994; CCME 1993, 1994; Csuros 1994; Garrett 1988; Hadley and Sedman 1990; Keith 1992; Millette and Hays 1994; O'Shay and Hoddinott 1994; Schulin et al. 1993; Thompson 1992; USEPA 1982, 1985, 1992a, b, c, d, e; Wilson 1995) that may be adapted for the investigation of human exposure to chemical constituents found in consumer products and in the human environments. Regardless of the processes involved, however, it is important to recognize the fact that most chemical sampling and analysis procedures offer numerous opportunities for sample contamination and/or cross-contamination from a variety of sources (Keith 1988). To be able to address and account for possible errors arising from 'foreign' sources, quality control (QC) samples are typically included in the sampling and analytical schemes. The QC samples are analytical 'control' samples that are analyzed in the same manner as the 'field' samples—and these are subsequently used in the assessment of any cross-contamination that may have been introduced into a sample along its life cycle from the field (i.e., point of collection) to the laboratory (i.e., place of analysis).

Invariably, QC samples become an essential component of all carefully executed sampling and analysis programs. This is because, firm conclusions cannot be drawn from the investigation unless adequate controls have been included as part of the sampling and analytical protocols (Keith 1988). To prevent or minimize the inclusion of 'foreign' constituents in the characterization of chemical exposures and/or in a risk assessment, therefore, the concentrations of the chemicals detected in 'control' samples must be compared with concentrations of the same chemicals detected in the 'field' samples. In such an appraisal, the QC samples can indeed become a very important reference datum for the overall evaluation of the chemical sampling data.

In general, very well designed sampling and analytical protocols are necessary to facilitate credible data collection and analysis programs. Sampling protocols are written descriptions of the detailed procedures to be followed in collecting, packaging, labeling, preserving, transporting, storing, and tracking samples. The selection of appropriate analytical methods is also an integral part of the processes involved in the development of sampling plans—since this can strongly affect the acceptability of a sampling protocol. For example, the sensitivity of an analytical method could directly influence the amount of a sample needed in order to be able to measure analytes at pre-specified minimum detection (or quantitation) limits. The analytical method may also affect the selection of storage containers and preservation techniques (Keith 1988; Holmes et al. 1993). In any case, the devices

that are used to collect, store, preserve, and transport samples must *not* alter the sample in any manner. In this regard, it is noteworthy that special procedures may be needed to preserve samples during the period between collection and analysis.

Finally, the development and implementation of an overall good quality assurance/quality control (QA/QC) project plan for a sampling and analysis activity is critical to obtaining reliable analytical results. The soundness of the QA/QC program has a particularly direct bearing on the integrity of the sampling as well as the laboratory work. Thus, the general process for developing an adequate QA/QC program, as discussed in Chap. 6 of this book and elsewhere in the literature (e.g., CCME 1994; USEPA 1987, 1992a, b, c, d, e), should be followed religiously. Also, it must be recognized that, the more specific a sampling protocol is, the less chance there will be for errors or erroneous assumptions.

8.2.2 Reporting of 'Censored' Laboratory Data

Oftentimes, in a given set of laboratory samples, certain chemicals will be reliably quantified in some (but not all) of the samples that were collected for analysis. Data sets may therefore contain observations that are below the instrument or method detection limit, or indeed its corresponding quantitation limit; such data are often referred to as 'censored data' (or 'non-detects' [NDs]). In general, the NDs do not necessarily mean that a chemical is not present at any level (i.e., completely absent)—but simply that any amount of such chemical potentially present was probably below the level that could be detected or reliably quantified using a particular analytical method. In other words, this situation may reflect the fact that either the chemical is truly absent at this location or sampled matrix at the time the sample was collected—or that the chemical is indeed present, but only at a concentration below the quantitation limits of the analytical method that was employed in the sample analysis.

In fact, every laboratory analytical technique has detection and quantitation limits below which only 'less than' values may be reported; the reporting of such values provides a degree of quantification for the censored data. In such situations, a decision has to be made as to how to treat such NDs and associated 'proxy' concentrations. The appropriate procedure depends on the general pattern of detection for the chemical in the overall investigation activities (Asante-Duah 1998; HRI 1995). In any case, it is customary to assign non-zero values to all sampling data reported as NDs. This is important because, even at or near their detection limits, certain chemical constituents may be of considerable importance or concern in the characterization of a chemical exposure problem. However, uncertainty about the actual values below the detection or quantitation limit can also bias or preclude an effectual execution of subsequent statistical analyses. Indeed censored data do create significant uncertainties in the data analysis required of the chemical exposure characterization process; such data should therefore be handled in an appropriate manner—for instance, as elaborated in the example methods of approach provided below.

8.2.2.1 Derivation and Use of 'Proxy' Concentrations

'Proxy' concentrations are usually employed when a chemical is not detected in a specific sampled medium per se. A variety of approaches are offered in the literature for deriving and using proxy values in environmental data analyses, including the following relatively simpler ones (Asante-Duah 1998; HRI 1995; USEPA 1989a, 1992a, b, c, d, e):

- *Set the sample concentration to zero*. This assumes that if a chemical was not detected, then it is not present—i.e., the 'residual concentration' is zero. This involves or calls for very compelling assumptions, and it can rarely be justified that the chemical is not present in the sampled media. Thus, it represents a least conservative (i.e., least health-protective) option.
- *Drop the sample with the non-detect for the particular chemical from further analysis*. This will have the same effect on the data analysis as assigning a concentration that is the average of concentrations found in samples where the chemical was detected.
- *Set the proxy sample concentration to the sample quantitation limit (SQL)*. For NDs, setting the sample concentration to a proxy concentration equal to the SQL (which is a quantifiable number used in practice to define the analytical detection limit) makes the fewest assumptions and tends to be conservative, since the SQL represents an upper-bound on the concentration of a ND. This option does indeed offer the most conservative (i.e., most health-protective) approach to chemical hazard accounting and exposure estimation. The approach recognizes that the true distribution of concentrations represented by the NDs is unknown.
- *Set the proxy sample concentration to one-half the SQL*. For NDs, setting the sample concentration to a proxy concentration equal to one-half the SQL assumes that, regardless of the distribution of concentrations above the SQL, the distribution of concentrations below the SQL is symmetrical. [It is noteworthy that, when/if the subject data are highly skewed then a use of the SQL divided by the square-root-of-two (i.e., SQL/$\sqrt{2}$) is recommended, instead of one-half the SQL.]

In general, in a 'worst-case' approach, all NDs are assigned the value of the SQL – which is the lowest level at which a chemical may be accurately and reproducibly quantitated; this approach biases the mean upward. On the other hand, assigning a value of zero to all NDs biases the mean downward. The degree to which the results are biased will depend on the relative number of detects and non-detects in the data set, and also the difference between the reporting limit and the measured values above it. Oftentimes, the common practice seems to utilize the sample-specific quantitation limit for the chemical reported as ND. In fact, the goal in adopting such an approach is to avoid underestimating exposures to potentially sensitive or highly exposed groups such as infants and children, but at the same time attempt to

approximate actual 'residual levels' as closely as possible. Ultimately, recognizing that the assumptions in these methods of approach may, in some cases, either overestimate or underestimate exposures, the use of sensitivity analysis to determine the impact of using different assumptions (e.g., ND = 0 *vs.* ND = SQL/2 *vs.* ND = SQL/$\sqrt{2}$; etc.) is encouraged.

Other methods of approach to the derivation of proxy concentrations may involve the use of 'distributional' methods; unlike the simple substitution methods shown above, distributional methods make use of the data above the reporting limit in order to extrapolate below it (USEPA 1992a, b, c, d, e). Indeed, even more robust methods than this may be utilized in such applications for handling censored data sets. In any event, selecting the appropriate method to adopt for any given situation or problem scenario generally requires consideration of the degree of censoring, the goals of the assessment, and the degree of accuracy required.

Finally, it is noteworthy that, notwithstanding the options available from the above procedures of deriving and/or using 'proxy' concentrations, re-sampling and further laboratory analysis should always be viewed as the preferred approach to resolving uncertainties that surround ND results obtained from sampled media. Thence, if the initially reported data represent a problem in sample collection or analytical methods rather than a true failure to detect a chemical of potential concern, then the problem could be rectified (e.g., by the use of more sensitive analytical protocols) before critical decisions are made based on the earlier results.

8.3 Statistical Evaluation of Chemical Sampling/ Concentration Data

Once the decision is made to undertake a public health risk assessment, the available chemical exposure data has to be carefully examined/appraised—in order to, among other things, arrive at a list of chemicals of potential concern (CoPCs); the CoPCs represent the target chemicals of focus in the risk assessment process. In general, the target chemicals of significant interest or concern to chemical exposure problems may be selected for further detailed evaluation on the basis of several specific and miscellaneous important considerations—such as shown in Box 8.2. The use of such selection criteria should generally compel an analyst to continue with the exposure and risk characterization process only if the chemicals represent potential threats to public health. For such chemicals, general summary statistics would commonly be compiled; meanwhile, it is worth the mention here that, where applicable, data for samples and their duplicates are typically averaged before summary statistics are calculated—such that a sample and its duplicate are ultimately treated as one sample for the purpose of calculating summary statistics (including maximum detection and frequency of detection). Where constituents are not detected in both a sample and its duplicate, the resulting

values are the average of the sample-specific quantitation limits (SSQLs). Where both the sample and the duplicate contain detected constituents, the resulting values are the average of the detected results. Where a constituent in one of the pair is reported as not detected and the constituent is detected in the other, the detected concentration is conservatively used to represent the value of interest. On the whole, the following summary statistics are typically generated as part of the key statistical parameters of interest:

- *Frequency of detection*—reported as a ratio between the number of samples reported as detected for a specific constituent and the total number of samples analyzed.
- *Maximum detected concentration*—for each constituent/receptor/medium combination, after duplicates have been averaged.
- *Mean detected concentration*—typically the arithmetic mean concentration for each constituent/receptor/medium combination, after duplicates have been averaged, based on detected results only.
- *Minimum detected concentration*—for each constituent/area/medium combination, after duplicates have been averaged.

Next, the proper exposure point concentration (EPC) for the target populations potentially at risk from the CoPCs would be determined; an EPC is the concentration of the CoPC in the target material or product at the point of contact with the human receptor.

Box 8.2 Typical important considerations in the screening for chemicals of potential concern for public health risk assessments

- Status as a known human carcinogen *versus* probable or possible carcinogen
- Status as a known human developmental and reproductive toxin
- Degree of mobility, persistence, and bioaccumulation
- Nature of possible transformation products of the chemical
- Inherent toxicity/potency of chemical
- Concentration-toxicity score—reflecting concentration levels in combination with degree of toxicity (For exposure to multiple chemicals, the chemical score is represented by a risk factor, calculated as the product of the chemical concentration and toxicity value; the ratio of the risk factor for each chemical to the total risk factor approximates the relative risk for each chemical—giving a basis for inclusion or exclusion as a CoPC)
- Frequency of detection in target material or product (Chemicals that are infrequently detected may be artifacts in the data due to sampling, analytical, or other problems, and therefore may not be truly associated with the consumer product or target material under investigation)

(continued)

Box 8.2 (continued)

- Status and condition as an essential element—i.e., defined as essential human nutrient, and toxic only at elevated doses (For example, Ca or Na generally does not pose a significant risk to public health, but As or Cr may pose a significantly greater risk to human health)

The EPC determination process typically will consist of an appropriate statistical evaluation of the exposure sampling data—especially when large data sets are involved. Statistical procedures used for the evaluation of the chemical exposure data can indeed significantly affect the conclusions of a given exposure characterization and risk assessment program. Consequently, appropriate statistical methods (e.g., in relation to the choice of proper averaging techniques) should be utilized in the evaluation of chemical sampling data. Meanwhile, it is noteworthy that over the years, extensive technical literature has been put forward regarding the 'best' probability distribution to utilize in different scientific applications—and such resources should be consulted for appropriate guidance on the statistical tools of choice.

8.3.1 Parametric Versus *Nonparametric Statistics*

There are several statistical techniques available for analyzing data that are not necessarily dependent on the assumption that the data follow any particular statistical distribution. These distribution-free methods are referred to as *nonparametric* statistical tests—and they have fewer and less stringent assumptions. Conversely, several assumptions have to be met before one can use a *parametric* test. At any rate, whenever the set of requisite assumptions is met, it is always preferable to use a parametric test—because it tends to be more powerful than the nonparametric test. However, to reduce the number of underlying assumptions required (such as in a hypothesis testing about the presence of specific trends in a data set), nonparametric tests are typically employed.

Nonparametric techniques are generally selected when the sample sizes are small and the statistical assumptions of normality and homogeneity of variance are tenuous. Indeed, nonparametric tests are usually adopted for use in environmental impact assessments because the statistical characteristics of the often messy environmental data make it difficult, or even unwise, to use many of the available parametric methods. It is noteworthy, however, that the nonparametric tests tend to ignore the magnitude of the observations in favor of the relative values or ranks of the data. Consequently, as Hipel (1988) notes, a given nonparametric test with few underlying assumptions that is designed, for instance, to test for the presence of a trend may only provide a 'yes' or 'no' answer as to whether or not a trend may

indeed be present in the data. The output from the nonparametric test may not give an indication of the type or magnitude of the trend. To have a more powerful test about what might be occurring, many assumptions must be made—and as more assumptions are formulated, a nonparametric test begins to look more like a parametric test. It is also noteworthy that, the use of parametric statistics requires additional detailed evaluation steps—with the process of choosing an appropriate statistical distribution being an important initial step.

8.3.1.1 Choice of Statistical Distribution

Of the many statistical distributions available, the Gaussian (or normal) distribution has been widely utilized to describe environmental data; however, there is considerable support for the use of the lognormal distribution in describing such data. Consequently, chemical concentration data for environmental samples have been described by the lognormal distribution, rather than by a normal distribution (Gilbert 1987; Leidel and Busch 1985; Rappaport and Selvin 1987; Saltzman 1997). Basically, the use of lognormal statistics for the data set X1, X2, X3, Xn requires that the logarithmic transform of these data (i.e., *ln*[X1], *ln*[X2], *ln*[X3], *ln* [Xn]) can be expected to be normally distributed.

In general, the statistical parameters used to describe the different distributions can differ significantly; for instance, the central tendency for the normal distributions is measured by the arithmetic mean, whereas the central tendency for the lognormal distribution is defined by the geometric mean. In the end, the use of a normal distribution to describe environmental chemical concentration data, rather than lognormal statistics will often result in significant over-estimation, and may be overly conservative—albeit some investigators have argued otherwise (e.g., Parkhurst 1998). In fact, Parkhurst (1998) argues that geometric means are biased low and do not quite represent components of mass balances properly, *whereas* arithmetic means are unbiased, easier to calculate and understand, scientifically more meaningful for concentration data, and more protective of public health. Even so, this same investigator (Parkhurst 1998) still concedes to the non-universality of this school of thought—and these types of arguments and counter-arguments only go to reinforce the fact that no one particular parameter or distribution may be appropriate for every situation. Consequently, care must be exercised in the choice of statistical methods for the data manipulation exercises carried out during the hazard accounting process—and indeed in regards to other aspects of a risk assessment.

8.3.1.2 Goodness-of-Fit Testing

Recognizing that the statistical procedures used in the evaluation of chemical exposure data should generally reflect the character of the underlying distribution of the data set, it is preferable that the appropriateness of any distribution assumed

or used for a given data set be checked prior to its application. This verification check can be accomplished by using a variety of goodness-of-fit methods.

Goodness-of-fit tests are formal statistical tests of the hypothesis that a specific set of sampled observations is an independent sample from the assumed distribution. The more common general tests include the Chi-square test and the Kolmogorov-Smirnov test; common goodness-of-fit tests specific for normality and log-normality include the Shapiro-Wilks' test and D'Agostino's test (see, e.g., D'Agostino and Stephens 1986; Gilbert 1987; Miller and Freund 1985; Sachs 1984). At any rate, it is worth mentioning here that goodness-of-fit tests tend to have notoriously low power—and indeed are generally best for rejecting poor distribution fits, rather than for identifying good fits. In general, if the data cannot be fitted well enough to a theoretical distribution, then perhaps an empirical distribution function or other statistical methods of approach (such as bootstrapping techniques) should be considered.

Another way to determine the specific probability distribution that adequately models the underlying population of a data set is to test the probability of a sample being drawn from a population with a particular probability distribution; one such test is the W-test (Shapiro and Wilk 1965). The W-test is particularly important in assessing whether a sample is from a population with a normal probability distribution; the W-test can also be used to assess if a sample belongs to a population with a lognormal distribution (i.e., after the data has undergone a natural logarithm transformation). It is noteworthy that, the W-test (as developed by Shapiro and Wilk) is limited to a small sample data set size (of 3 to 50 samples). However, a modification of the W-test that allows for its use with larger data sets (up to about 5000 data points) is also available (e.g., in the formulation subsequently developed by Royston) (Royston 1995).

8.3.2 Statistical Evaluation of 'Non-detect' Values

During the analysis of environmental sampling data that contains some NDs, a fraction of the SQL is usually assumed (as a proxy or estimated concentration) for non-detectable levels—instead of assuming a value of zero, or neglecting such values. This procedure is typically used, provided there is at least one detected value from the analytical results, and/or if there is reason to believe that the chemical is possibly present in the sample at a concentration below the SQL. The approach conservatively assumes that some level of the chemical could be present (even though a ND has been recorded) and arbitrarily sets that level at the 'appropriate' percentage of the SQL.

In general, the favored approach in the calculation of the applicable statistical values during the evaluation of data containing NDs involves the use of a value of one-half of the SQL. This approach assumes that the samples are equally likely to have any value between the detection limit and zero, and can be described by a normal distribution. However, when the sample values above the ND level are

log-normally distributed, it generally may be assumed that the ND values are also log-normally distributed; the best estimate of the ND values for a log-normally distributed data set is the reported SQL divided by the square root of two (i.e., $\frac{SQL}{\sqrt{2}} = \frac{SQL}{1.414}$) (CDHS 1990; USEPA 1989a). Also, in some situations, the SQL value itself may be used if there is strong enough reason to believe that the chemical concentration is closer to this value, rather than to a fraction of the SQL. If it becomes apparent that serious biases could result from the use of any of the preceding methods of approach, more sophisticated analytical and evaluation methods may be warranted.

8.3.3 Selection of Statistical Averaging Techniques

Reasonable discretion should generally be exercised in the selection of an averaging technique during the statistical analysis of environmental sampling data—*viz.*, chemical concentration data in particular. This is because, among other things, the selection of specific methods of approach to determine the average of a set of environmental sampling data can have profound effects on the resulting concentration—especially for data sets coming from sampling results that are not normally distributed. For example, when dealing with log-normally distributed data, geometric means are often used as a measure of central tendency – in order to ensure that a few very high (or low) values on record do not exert excessive influence on the characterization of the distribution. However, if high concentrations do indeed represent 'hotspots' in a spatial or temporal distribution of the data set, then using the geometric mean could inappropriately discount the contribution of these high chemical concentrations present in the environmental samples. This is particularly significant if, for instance, the spatial pattern indicates that areas of high concentration for a chemical release are in close proximity to compliance boundaries or near exposure locations for sensitive populations (such as children and the elderly).

The geometric mean has indeed been extensively and consistently used as an averaging parameter in the past. Its principal advantage is in minimizing the effects of 'outlier' values (i.e., a few values that are much higher or lower than the general range of sample values). Its corresponding disadvantage is that, discounting these values may be inappropriate when they represent true variations in concentrations from one part of an impacted area or group to another (such as a 'hot-spot' *vs.* a 'cold-spot' *vs.* a 'normal-spot' region). As a measure of central tendency, the geometric mean is most appropriate if sample data are lognormally distributed, and without an obvious spatial pattern.

The arithmetic mean—commonly used when referring to an 'average'—is more sensitive to a small number of extreme values or a single 'outlier' compared to the geometric mean. Its corresponding advantage is that true high concentrations will not be inappropriately discounted. When faced with limited sampling data,

however, this may not provide a conservative enough estimate of environmental chemical impacts.

In fact, none of the above measures, in themselves, may be appropriate in the face of limited and variable sampling data. Contemporary applications tend to favor the use of an upper confidence limit (UCL) on the average concentration. Even so, if the computed UCL exceeds the maximum detected value amongst a data pool, then the latter is used as the source term or EPC. Finally, it has to be cautioned that in situations where there is a discernible spatial pattern to chemical concentration data, standard approaches to data aggregation and analysis may usually be inadequate, or even inappropriate.

8.3.3.1 Illustrative Example Computations Demonstrating the Potential Effects of Variant Statistical Averaging Techniques

To demonstrate the possible effects of the choice of statistical distributions and/or averaging techniques on the analysis of environmental data, consider a case involving the estimation of the mean, standard deviation, and confidence limits from monthly laboratory analysis data for groundwater concentrations obtained from a potential drinking water well. The goal here is to compare the selected statistical parameters based on the assumption that this data is normally distributed *versus* an alternative assumption that the data is lognormally distributed. To accomplish this task, the several statistical manipulations enumerated below are carried out on the 'raw' and log-transformed data for the concentrations of benzene in the groundwater samples shown in Table 8.1.

(1) *Statistical Manipulation of the 'Raw' Data*. Calculate the following statistical parameters for the 'raw' data: mean, standard deviation, and 95% confidence limits. [See standard statistics textbooks for details of applicable procedures involved.] The arithmetic mean, standard deviation, and 95% confidence limits (95% CL) for a set of n values are defined, respectively, as follows:

$$X_m = \frac{\sum_{i=1}^{n} X_i}{n} \tag{8.1}$$

$$SD_x = \sqrt{\frac{\sum_{i=1}^{n} (X_i - X_m)^2}{n-1}} \tag{8.2}$$

Table 8.1 Environmental sampling data used to illustrate the effects of statistical averaging techniques on exposure point concentration predictions

	Concentration of Benzene in Drinking Water (μg/L)	
Sampling Event	Original 'raw' data, X	Log-transformed data, $Y = ln(X)$
1	0.049	–3.016
2	0.056	−2.882
3	0.085	−2.465
4	1.200	0.182
5	0.810	−0.211
6	0.056	−2.882
7	0.049	−3.016
8	0.048	−3.037
9	0.062	−2.781
10	0.039	−3.244
11	0.045	−3.101
12	0.056	−2.882

$$CL_x = X_m \pm \frac{ts}{\sqrt{n}} \tag{8.3}$$

where: Xm = arithmetic mean of 'raw' data; SDx = standard deviation for 'raw' data; CLx = 95% confidence interval (95% CI) of 'raw' data; t is the value of the Student t-distribution [as expounded in standard statistical books] for the desired confidence level (e.g., 95% CL, which is equivalent to a level of significance of $\alpha = 5\%$) and degrees of freedom, (n–1); and s is an estimate of the standard deviation from the mean (Xm). Thus,

$Xm = 0.213$ μg/L

$SDx = 0.379$ μg/L

$CLx = 0.213 \pm 0.241$ (i . e., $-0.028 \leq CIx \leq 0.454$) and $UCLx = 0.454$ μg/L

where: $UCLx$ = 95% upper confidence level (95% UCL) of 'raw' data.

Note that, the computation of the 95% confidence limits for the untransformed data produces a confidence interval of 0.213 ± 0.109 $t = 0.213 \pm 0.241$ [where $t = 2.20$, obtained from the Student t-distribution for (n–1) = 12–1 = 11 degrees of freedom] – and which therefore indicates a non-zero probability for a negative concentration value; indeed, such value may very well be considered meaningless in practical terms—consequently revealing some of the shortcomings of this type of computational method of approach.

(2) *Statistical Manipulation of the Log-transformed Data*. Calculate the following statistical parameters for the log-transformed data: mean, standard deviation, and 95% confidence limits. [See standard statistics textbooks for details of applicable procedures involved]. The geometric mean, standard deviation, and 95 percent confidence limits (95% CL) for a set of n values are defined, respectively, as follows:

$$X_{gm} = anti\log\left\{\frac{\sum_{i=1}^{n} \ell n X_i}{n}\right\} \tag{8.4}$$

$$SD_x = \sqrt{\frac{\sum_{i=1}^{n}\left(X_i - X_{gm}\right)^2}{n-1}} \tag{8.5}$$

$$CL_x = X_{gm} \pm \frac{ts}{\sqrt{n}} \tag{8.6}$$

where: Xgm = geometric mean for the 'raw' data; SDx = standard deviation of 'raw' data (assuming lognormal distribution); CLx = 95% confidence interval (95% CI) for the 'raw' data (assuming lognormal distribution); t is the value of the Student t-distribution [as expounded in standard statistical books] for the desired confidence level and degrees of freedom, (n–1); and s is an estimate of the standard deviation of the mean (Xgm). Thus,

$Y_{a-mean} = -2.445$
$SDy = 1.154$
$CLy = -2.445 \pm 0.733$ (i . e., a confidence interval from -3.178 to -1.712)

where: Y_{a-mean} = arithmetic mean of log-transformed data; SDy = standard deviation of log-transformed data; and CLy = 95% confidence interval (95% CI) of log-transformed data. In this case, computation of the 95% confidence limits for the log-transformed data yields a confidence interval of -2.445 ± 0.333 $t = -2.445 \pm 0.733$ [where $t = 2.20$, obtained from the student t-distribution for (n-1) = 12–1 = 11 degrees of freedom].

Now, transforming the average of the logarithmic Y values back into arithmetic values yields a geometric mean value of $Xgm = e^{-2.445} = 0.087$. Furthermore, transforming the confidence limits of the log-transformed values back into the arithmetic realm yields a 95% confidence interval of 0.042 μg/L to 0.180 μg/L; recognize that these consist of positive concentration values only. Hence,

$Xgm = 0.087$ μg/L
$SDx = 3.171$ μg/L
$0.042 \leq CIx \leq 0.180$ μg/L
$UCLx = 0.180$ μg/L

where: $UCLx$ = 95% upper confidence level (95% UCL) for the 'raw' data (assuming lognormal distribution).

In consideration of the above, it is obvious that the arithmetic mean, $Xm = 0.213$ μg/L, is substantially larger than the geometric mean of $Xgm = 0.087$ μg/L. This may be attributed to the two relatively higher sample concentration values in the data set

(namely, sampling events #4 and #5 in Table 8.1)—which consequently tend to strongly bias the arithmetic mean; on the other hand, the logarithmic transform acts to suppress the extreme values. A similar observation can be made for the 95% upper confidence level (UCL) of the normally- and lognormally-distributed data sets. In any event, irrespective of the type of underlying distribution, the 95% UCL is generally a preferred statistical parameter to use in the evaluation of environmental data, rather than the statistical mean values.

The results from the above example analysis illustrate the potential effects that could result from the choice of one distribution type over another, and also the implications of selecting specific statistical parameters in the evaluation of environmental sampling data. In general, the use of arithmetic or geometric mean values for the estimation of average concentrations would tend to bias the EPC or other related estimates; the 95% UCL characteristically offers a better value to use—albeit may not necessarily be a panacea in all situations.

8.4 Estimating Chemical Exposure Point Concentrations from Limited Data

In the absence of adequate and/or appropriate field sampling data, a variety of mathematical algorithms and models are often employed to support the determination of chemical exposure concentrations in human exposure media or consumer products. Such forms of chemical exposure models are typically designed to serve a variety of purposes, but most importantly tend to offer the following key benefits (Asante-Duah 1998; Schnoor 1996):

- To gain better understanding of the fate and behavior of chemicals existing in, or to be introduced into, the human living and work environments.
- To determine the temporal and spatial distributions of chemical exposure concentrations at potential receptor contact sites and/or locations.
- To predict future consequences of exposure under various chemical contacting or loading conditions, exposure scenarios, or risk management action alternatives.
- To perform sensitivity analyses, by varying specific parameters, and then using models to explore the ramifications of such actions (as reflected by changes in the model outputs).

The results from the modeling are generally used to estimate the consequential exposures and risks to potential receptors associated with a given chemical exposure problem.

One of the major benefits associated with the use of mathematical models in public health risk management programs relate to the fact that, environmental concentrations useful for exposure assessment and risk characterization can be estimated for several locations and time-periods of interest. Indeed, since field

data are often limited and/or insufficient to facilitate an accurate and complete characterization of chemical exposure problems, models can be particularly useful for studying spatial and temporal variability, together with potential uncertainties. In addition, sensitivity analyses can be conducted by varying specific exposure parameters—and then using models to explore any ramifications reflected by changes in the model outputs.

In the end, the effective use of models in public health risk assessment and risk management programs depends greatly on the selection of the models most suitable for its stated purpose. The type of model selected will characteristically be dependent on the overall goal of the assessment, the complexity of the problem, the type of CoPCs, the nature of impacted and threatened media that are being evaluated in the specific investigation, and the type of corrective actions contemplated. A general guidance for the effective selection of models used in chemical exposure characterization and risk management decisions is provided in the literature elsewhere (e.g., Asante-Duah 1998; CCME 1994; CDHS 1990; Clark 1996; Cowherd et al. 1985; DOE 1987; NRC 1989a, b; Schnoor 1996; USEPA 1987, 1988a, b; Yong et al. 1992; Zirschy and Harris 1986)—with some excerpts presented in Chap. 6 of this title. It is noteworthy that, in several typical environmental assessment situations, a 'ballpark' or 'order-of-magnitude' (i.e., a rough approximation) estimate of the chemical behavior and fate is usually all that is required for most analyses—and in which case simple analytical models usually will suffice. Some relatively simple example models and equations that are often employed in the estimation of chemical concentrations in air, soil, water, and food products are provided below for illustrative purposes.

- *Screening Level Estimation of Chemical Volatilization into Shower Air*. A classic scenario that is often encountered in human health risk assessments relates to the volatilization of contaminants from contaminated water into shower air during a bathing/showering activity. A simple/common model that may be used to derive contaminant concentration in air from measured concentration in domestic water consists of a very simple box model of volatilization. In this case, the air concentration is derived from volatile emission rate by treating the shower as a fixed volume with perfect mixing and no outside air exchange, so that the air concentration increases linearly with time.

  On the whole, the following equation can be used to determine the average air concentration in the bathroom *during* a shower activity (generally for chemicals with a Henry's Law constant of $\geq 2 \times 10^{-7}$ atm-cu m/mol only) (HRI 1995):

$$Csha = \frac{[\mathrm{Cw} \times f \times \mathrm{Fw} \times \mathrm{t}]}{2 \times [\mathrm{V} \times 1000\ \mu\mathrm{g/mg}]} \tag{8.7}$$

  where *Csha* is the average air concentration in the bathroom during a shower activity; *Cw* is the concentration of contaminant in the tap water (μg/L); ƒ is the fraction of contaminant volatilized (unitless); *Fw* is the water flow rate in the shower (L/hour); *t* is the duration of shower activity (hours); and *V* is the

bathroom volume (m^3). Similarly, the following equation can be used to determine the average air concentration in the bathroom *after* a shower activity (generally for chemicals with a Henry's Law constant of $\geq 2 \times 10^{-7}$ atm-m^3/mol only) (HRI 1995):

$$Csha2 = \frac{[\mathrm{Cw} \times f \times \mathrm{Fw} \times \mathrm{t}]}{[\mathrm{V} \times 1000\ \mu\mathrm{g/mg}]} \tag{8.8}$$

It is noteworthy that, water temperature is a key variable that affects stripping efficiencies and the mass transfer coefficients for the various sources of chemical releases into the shower air.

In the above simplified representations, the models assume that: there is no air exchange in the shower—which assumption tends to overestimate contaminant concentration in bathroom air; there is perfect mixing within the bathroom (i.e., the contaminant concentration is equally dispersed throughout the volume of the bathroom)—which assumption tends to underestimate contaminant concentration in shower air; the emission rate from water is independent of instantaneous air concentration; and the contaminant concentration in the bathroom air is determined by the amount of contaminants emitted into the box (i.e., $[Cw \times \mathfrak{f} \times Fw \times t]$) divided by the volume of the bathroom (V) (HRI 1995).

- *Estimation of Household Air Contamination due to Volatilization from Domestic Water Supply*. Contaminated water present inside a home can result in the volatilization of chemicals into residential indoor air—e.g., via shower stalls, bathtubs, washing machines, and dishwashers. Under such scenarios, chemical concentrations in household indoor air due to contaminated domestic water may be estimated for volatile chemicals (generally for chemicals with a Henry's Law constant of $\geq 2 \times 10^{-7}$ atm-cu m/mol only), in accordance with the following relationship (HRI 1995):

$$Cha = \frac{[C_w \times \mathrm{WFH} \times f]}{[\mathrm{HV} \times \mathrm{ER} \times \mathrm{MC} \times 1000\ \mu\mathrm{g/mg}]} \tag{8.9}$$

where: *Cha* is the chemical concentration in air (mg/m^3); *Cw* is the concentration of contaminant in the tap water (μg/L); *WFH* is the water flow through the house (L/day); $\mathfrak{f}$ is the fraction of contaminant volatilized (unitless); *HV* is the house volume (m^3/house); *ER* is the air exchange rate (house/day); and *MC* is the mixing coefficient (unitless). It is noteworthy that, water temperature is a key variable that affects stripping efficiencies and the mass transfer coefficients for the various sources of chemical releases into the indoor air.

- *Contaminant Bioconcentration in Meat and Dairy Products*. In many cases, the tendency of certain chemicals to become concentrated in animal tissues relative to their concentrations in the ambient environment can be attributed to the fact that the chemicals are lipophilic (i.e., they are more soluble in fat than in water). Consequently, these chemicals tend to accumulate in the fatty portion of animal tissue. In general, the bioconcentration of chemicals in meat is dependent

primarily on the partitioning of chemical compounds into fat deposits (HRI 1995). Consequently,

$$Cx = BCF \times F \times Cw \tag{8.10}$$

where: Cx is the chemical concentration in animal tissue or dairy product; BCF is the chemical-specific bioconcentration factor for tissue fat—indicating the tendency of the chemical to accumulate in fat; F is the fat content of the tissue or dairy product; and Cw is the chemical concentration in water fed to the animal (HRI 1995; USEPA 1986a, b, c, d, e, f). Overall, the concentration of such bioaccumulative chemicals in animal tissue (or other animal products for that matter) may be seen as a reflection of the chemical's inherent bioconcentration capacity—as represented by the BCF.

- *Estimation of Contaminant Concentrations in Fish Tissues/Products*. Fish tissue contaminant concentrations may be predicted from water concentrations using chemical-specific BCFs, which predict the accumulation of contaminants in the lipids of the fish. In this case, the average chemical concentration in fish, based on the concentration in water and a BCF is estimated in accordance with the following relationship (HRI 1995):

$$Cf = Cw \times BCF \times 1000 \tag{8.11}$$

where Cf is the concentration in fish (μg/kg), Cw is the concentration in water (mg/L), and BCF is the bioconcentration factor. In situations where fish tissue concentrations are predicted from sediment concentrations, a two-step process is used; first, sediment concentration is used to calculate water concentrations, and then the water concentrations are used to predict fish tissue concentrations—with the former being carried out in accordance with the following equation:

$$Cw = \frac{\text{Csediment}}{[K_{\text{oc}} \times \text{OC} \times \text{DN}]} \tag{8.12}$$

where: Cw is the concentration of the chemical in water; $Csediment$ is the concentration of the chemical in sediment; Koc is the chemical-specific organic carbon partition coefficient; OC is the organic carbon content of the sediment; DN is the sediment density (relative to water density).

Models can indeed be used for several purposes in the study of chemical exposure and risk characterization problems. In general, the models usually simulate the response of a simplified version of a more complex system. As such, the modeling results are imperfect. Nonetheless, when used in a technically responsible manner, models can provide a very useful basis for making technically sound decisions about a chemical exposure problem. In point of fact, models are particularly useful where several alternative scenarios are to be compared. In such comparative analyses/cases, all the alternatives are contrasted on a similar basis;

thus, whereas the numerical results of any single alternative may not be exact, the comparative results of showing that one alternative is superior to others will usually be valid.

8.5 Determination of the Level of a Chemical Hazard

In order to make an accurate determination of the level of hazard potentially posed by a chemical, it is very important that the appropriate set of exposure data is collected during the hazard identification and accounting processes. It is also imperative to use appropriate data evaluation tools in the processes involved; several of the available statistical methods and procedures finding widespread use in chemical exposure and risk characterization programs can be found in subject matter books on statistics (e.g., Berthouex and Brown 1994; Cressie 1994; Freund and Walpole 1987; Gibbons 1994; Gilbert 1987; Hipel 1988; Miller and Freund 1985; Ott 1995; Sachs 1984; Sharp 1979; Wonnacott and Wonnacott 1972; Zirschy and Harris 1986). In the final analysis, the process/approach used to estimate a potential receptor's EPC will comprise of the following key elements:

- Determining the distribution of the chemical exposure/sampling data, and fitting the appropriate distribution to the data set (e.g., normal, lognormal, etc.);
- Developing the basic statistics for the exposure/sampling data—to include calculation of the relevant statistical parameters, such as the upper 95% confidence limit (UCL95); and
- Calculating the EPC—usually defined as the minimum of either the UCL or the maximum exposure/sampling data value, and conceptually represented as follows: EPC = *min* [UCL95 *or* Max-Value].

Ultimately, the so-derived EPC (that may indeed be significantly different from any field-measured chemical concentrations) represents the 'true' or reasonable exposure level at the potential receptor location of interest—and this value is used in the calculation of the chemical intake/dose for the populations potentially at risk.

Chapter 9
Exposure Assessment: Analysis of Human Intake of Chemicals

Once a 'social' or environmental chemical has been determined to present a potential health hazard, the main concern then shifts to the likelihood for, and degree of, human exposure to such chemical. The exposure assessment phase of the human health risk assessment helps address this key concern; the process is used to estimate the rates at which chemicals are absorbed by potential receptors. In fact, since most potential receptors tend to be exposed to chemicals from a variety of sources and/or in different environmental media, an evaluation of the relative contributions of each medium and/or source to total chemical intake becomes a critical part of most exposure analyses. Ultimately, the accuracy with which exposures are characterized can undeniably become a major determinant of the validity of a risk assessment. This chapter discusses the principal exposure evaluation tasks that, upon careful implementation, should allow effective public health risk management decisions to be made about environmental contamination and/or chemical exposure problems.

9.1 Fundamental Concepts and Requirements in the Human Exposure Assessment Process

Broadly speaking, the human exposure assessment process is used to estimate the rates at which chemicals are absorbed by potential human receptors. More specifically, it is generally used to determine the magnitude of actual and/or potential receptor exposures to chemical constituents, the frequency and duration of these exposures, and the pathways via which the target receptor is potentially exposed to the chemicals that they contact from a variety of sources. The exposure assessment also involves describing the nature and size of the population exposed to a substance (i.e., the risk group, which refers to the actual or hypothetical exposed population), as well as the magnitude and duration of their exposure.

K. Asante-Duah, *Public Health Risk Assessment for Human Exposure to Chemicals*,
Environmental Pollution 27, DOI 10.1007/978-94-024-1039-6_9

All things considered, there are three fundamental steps for most exposure assessments—namely:

(i) Characterization of the exposure setting—to include the physical environment and potentially exposed populations;
(ii) Identification of the significant exposure pathways—to include sources or origins of release, exposure points, and exposure routes; and
(iii) Quantification of exposure—to include efforts directed at determining exposure concentrations and intake variables.

Accordingly, the exposure assessment process would typically involve several characterization and evaluation efforts—including the following key tasks:

- Determination of chemical distributions and behaviors—traced from a 'release' or 'originating' source to the locations for likely human exposure;
- Identification of significant chemical release, migration, and exposure pathways;
- Identification of potential receptors—i.e., the populations potentially at risk;
- Development of conceptual exposure model(s) and exposure scenarios—including a determination of current and future exposure patterns, and the analysis of the environmental fate and persistence of the CoPCs;
- Estimation/modeling of exposure point concentrations for the critical exposure pathways and media; and
- Estimation of chemical intakes for all potential receptors, and for all significant exposure pathways associated with the CoPCs.

In the end, as part of a consequential and holistic exposure characterization effort, populations potentially at risk are defined, and concentrations of the chemicals of potential concern (CoPCs) are determined in each medium to which potential receptors may be exposed. Then, using the appropriate case-specific exposure parameters, the intakes of the CoPCs can be estimated.

It is worth mentioning here that exposure pathways are one of the most important elements of the exposure assessment process; this consists of the routes that chemical constituents follow to reach potential receptors. Thus, failure to identify and address any significant exposure pathway may seriously detract from the usefulness of the concomitant risk assessment, since a complete pathway must be present for receptor exposures to occur; meanwhile, it is also notable that an exposure pathway is considered complete only if all of the following elements are present:

- Chemical hazard source(s), and mechanism of constituent release to the environment and/or target organism
- Mechanism(s) of chemical contacting by receptors and/or chemical release into the human environment
- A point of potential receptor contact with the contaminated medium
- Human exposure route(s) at the contact point (e.g., inhalation, ingestion, dermal contact)

- Receptor intake and/or exposure in the affected media, within the human environment.

On the whole, the interconnectivity of the exposure routes to the hazard sources are typically determined by integrating information from an initial environmental characterization with knowledge about potentially exposed populations and their likely behaviors. In the final analysis, the significance of the chemical hazard is evaluated on the basis of whether the target chemical could cause significant adverse exposures and impacts.

9.1.1 Factors Affecting Human Exposure to Chemical Hazards

The characterization of chemical exposure problems is a process used to establish the presence or absence of chemical hazards, to delineate the nature and degree of the hazards, and to determine possible human health threats posed by the exposure or hazard situation. The routes of chemical exposure (which may consist of inhalation, ingestion, and/or dermal contacts), as well as the duration of exposure (that may be short-term [acute], intermediate-term, or long-term [chronic]) will significantly influence the level of impacts on the affected receptors. The nature and behavior of the chemical substances of interest also form a very important basis for evaluating the potential for human exposures to its possible toxic or hazardous constituents.

By and large, the assessment of human receptor exposure to chemicals requires translating concentrations found in the target consumer product or human environment into quantitative estimates of the amount of chemical that comes into contact with the individual potentially at risk. Contact is expressed by the amount of material per unit body weight (mg/kg-day) that, typically, enters the lungs (for an inhalation exposure); enters the gastrointestinal tract (for an ingestion exposure); or crosses the stratum corneum of the skin (for a dermal contact exposure). This quantity is used as a basis for projecting the incidence of health detriment to the human receptor.

To accomplish the task of human exposure determination, several important exposure parameters and/or information will typically be acquired (Box 9.1)—also recognizing that, in terms of chemical exposures, the amount of contacted material that is bioavailable for absorption is a very important consideration [see Sect. 9.4.1]. At any rate, it is noteworthy that conservative estimates in the exposure evaluation oftentimes assume that a potential receptor is always in the same location, exposed to the same ambient concentration, and that there is 100% absorption upon exposure. These assumptions hardly represent any real-life situation. In fact, lower exposures will generally be expected under most circumstances—especially due to the fact that potential receptors will typically be

exposed to lower or even near-zero levels of the CoPCs for the period of time spent outside 'chemical-laden' settings.

In the final analysis, the extent of a receptor's exposure is estimated by identifying realistic exposure scenarios that describe the potential pathways of exposure to CoPCs, as well as the specific activities and behaviors of individuals that might lead to contact with the CoPCs encountered in the environment. The evaluation could indeed concern past or current exposures, as well as exposures anticipated in the future. In any case, it is also noteworthy that, because of the differences in activity patterns and sensitivity to exposures, multiple (typically three) age groups are normally considered in most evaluations—*e.g.*, young child age 1–6 years (i.e., from 1 up to the 7th birthday); older child age 7–18 years (i.e., from 7 up to the 19th birthday); and adult (>18 years of age) (USEPA 2014).

Box 9.1 Typical exposure parameters and information necessary for estimating potential receptor exposures

Exposure Route	*Relevant Exposure Parameters/Data*
• Inhalation	• airborne chemical concentrations (e.g., resulting from showering, bathing, and other uses of chemical-based consumer products; or from dust inhalation; etc.) • variation in air concentrations over time • amount of contaminated air breathed • fraction of inhaled chemical absorbed through lungs • breathing rate • exposure duration and frequency • exposure averaging time • average receptor body weight
• Ingestion	• concentration of chemical in consumed material (e.g., water, food, drugs/medicines, soils, etc.) • amount of chemical-based material ingested each day (e.g., water ingestion rate; food intake rate; soil ingestion rate; etc.) • fraction of ingested chemical absorbed through wall of gastrointestinal tract • exposure duration and frequency • exposure averaging time • average receptor body weight
• Dermal (Skin) Absorption	• concentration of chemical in contacted material (e.g., cosmetics, water, soils, etc.) • amount of daily skin contact (e.g., dermal contact with soil; dermal contact with water; dermal contact with cosmetics; etc.)

(continued)

Box 9.1 (continued)

Exposure Route	*Relevant Exposure Parameters/Data*
	• fraction of chemical absorbed through skin during contact period • period of time spent in contact with chemical-based material • average contact rate • receptor's contacting body surface area • exposure duration and frequency • exposure averaging time • average receptor body weight

9.1.2 Development of Human Conceptual Exposure Models and Exposure Scenarios

The human conceptual exposure model (CEM) provides the framework for the human health risk assessment; it is generally used to identify appropriate exposure pathways and receptors in order to engender a more focused evaluation during the risk assessment process. Indeed, the conceptual model generally enables a better and more comprehensive assessment of the nature and extent of exposure, as well as helps determine the potential impacts from such exposures. Consequently, in as early a stage as possible during a chemical exposure investigation, all available information should be compiled and analyzed to help develop a representative CEM for the problem situation. With that said, it is also notable that the CEM is generally meant to be a 'living paradigm' that can (and perhaps must) be updated and modified as appropriate when additional data or information become available—in order to properly exhibit its typically continuously evolving nature.

In essence, the purpose of the CEM is to identify: (1) potential chemical sources; (2) potential migration pathways of constituents from source areas to environmental media where exposure can occur; (3) potential human receptors; and (4) potential exposure pathways by which constituent uptake into the body may occur. Ultimately, potentially complete exposure pathways are identified for possible further evaluation within the risk assessment framework. Each potentially complete exposure pathway for any CoPC is generally evaluated quantitatively in the risk assessment—also recognizing that some receptor populations may be potentially exposed to CoPCs by more than one pathway. Further elaboration on this topic is provided in Chap. 6 of this book.

On the basis of the above CEM, a realistic set of exposure scenarios can be developed for a given chemical exposure or environmental characterization

problem. Several specific tasks are usually undertaken to facilitate the development of complete and realistic exposure scenarios; the critical tasks would typically include the following:

- Determine the sources of chemical hazards
- Identify the specific constituents of concern
- Identify the affected environmental or exposure media
- Delineate chemical release and migration pathways
- Identify potential receptors
- Determine potential exposure routes
- Delineate likely and significant chemical contacting rates by receptors, and/or chemical release rates into the human living and work environments
- Construct a representative conceptual exposure model (CEM) for the problem situation.

Additional discussion of this subject matter can be found in Chap. 6 of this title. At any rate, it is noteworthy that the exposure scenario associated with a given hazardous situation may be better defined if the exposure is known to have already occurred. In most cases associated with the investigation of potential chemical exposure problems, however, important decisions may have to be made about exposures that may not yet have occurred—in which case hypothetical exposure scenarios are generally developed to facilitate the problem solution. Ultimately, the type/nature of human exposure scenarios associated with a given exposure situation provides clear direction for the exposure assessment. Also, the exposure scenarios developed for a given chemical exposure problem can be used to support an evaluation of the risks posed by the situation, as well as facilitate the development of appropriate public health risk management decisions.

9.1.3 Chemical Intake Versus *Dose*

Intake (also commonly called 'exposure', or 'applied dose') is defined as the amount of chemical coming into contact with a receptor's visible exterior body (e.g., skin and openings into the body such as mouth and nostrils), or with the 'abstract/conceptual' exchange boundaries (such as the skin, lungs, or gastrointestinal tract); and *dose* (also commonly called 'absorbed dose', or 'internal dose') is the amount of chemical absorbed by the body into the bloodstream. In fact, the *internal dose* (i.e., absorbed dose) tends to differ significantly from the (externally) *applied dose* (i.e., exposure or intake)—recognizing that the *internal dose* of a chemical is the amount of a chemical that directly crosses the barrier at the absorption site into the systemic circulation.

The intake value quantifies the amount of a chemical contacted during each exposure event—where 'event' may have different meanings depending on the nature of exposure scenario being considered (e.g., each day's inhalation of an air contaminant may constitute one inhalation exposure event). The quantity of a

chemical absorbed into the bloodstream per event—represented by the dose—is calculated by further considering pertinent physiological parameters (such as gastrointestinal absorption rates). Overall, the internal dose of a chemical is considered rather important for predicting the potential toxic effects of the chemical; this is because, among other things, once in the systemic circulation, the chemical is able to reach all major target organ sites.

It is noteworthy that, in general, when the systemic absorption from an intake is unknown, or cannot be estimated by a defensible scientific argument, intake and dose are considered to be the same (i.e., a 100% absorption into the bloodstream from contact is assumed). Such an approach provides a conservative estimate of the actual exposures. In any case, intakes and doses are normally calculated during the same step of the exposure assessment; the former multiplied by an absorption factor yields the latter value.

9.1.4 *Chronic* Versus *Subchronic Exposures*

Event-based intake values are generally converted to final intake values by multiplying the intake per event by the frequency of exposure events, over the timeframe being considered in an exposure assessment. *Chronic daily intake* (CDI), which measures long-term (chronic) exposures, are based on the number of events that are assumed to occur within an assumed lifetime for potential receptors; *subchronic daily intake* (SDI), which represents projected receptor exposures over a short-term period, consider only a portion of a lifetime (USEPA 1989b). The respective intake values are calculated by multiplying the estimated exposure point chemical concentrations by the appropriate receptor exposure and body weight factors.

SDIs are generally used to evaluate subchronic non-carcinogenic effects, whereas CDIs are used to evaluate both carcinogenic risks and chronic non-carcinogenic effects. It is noteworthy that, the short-term exposures can result when a particular activity is performed for a limited number of years or when, for instance, a chemical with a short half-life degrades to negligible concentrations within several months of its presence in a receptor's exposure setting.

9.2 Potential Human Exposure Quantification: The Exposure Estimation Model

In order to determine human health risk arising from CoPCs for a given problem situation, it is invariably necessary to estimate the potential exposure dose for each CoPC. In fact, the exposure dose is estimated for each CoPC, and for each exposure pathway/route by which the likely receptor is assumed to be exposed. In the processes involved, exposure dose equations generally combine the estimates of

CoPC concentrations in the target medium of interest with assumptions regarding the type and magnitude of each receptor's potential exposure—so as to arrive at a numerical estimate of the exposure dose (intake); the exposure dose is defined as the amount of CoPC taken up into the receptor—and this is generally expressed in units of milligrams of CoPC per kilogram of body weight per day (mg/kg-day) (USEPA 1989a). Meanwhile, it is noteworthy that exposure doses are defined differently for potential carcinogenic versus non-carcinogenic effects. The 'chronic daily intake' is generally used to estimate a receptor's potential average daily dose from exposure to a CoPC with respect to non-carcinogenic effects—and generally calculated by averaging the exposure dose over the period of time for which the receptor is assumed to be exposed; thus, the averaging period is the same as the exposure duration for CoPCs with non-carcinogenic effects. For CoPCs with potential carcinogenic effects, however, the 'chronic daily intake' is calculated by averaging the exposure dose over the receptor's assumed lifetime (e.g., usually 70 years); therefore, the averaging period is the same as the receptor's assumed lifetime. Ultimately, these potential human receptor exposures can be evaluated via the calculation of the so-called *average daily dose* (ADD) and/or the *lifetime average daily dose* (LADD). The standardized equations for estimating a receptor's intake on this basis are presented later on, below.

On the whole, the analysis of potential human exposures to chemicals in the human environment often involves several complex issues. Invariably, potential receptors may become exposed to a variety of environmental chemicals via several different exposure routes—represented primarily by the inhalation, ingestion, and dermal exposure routes (illustrated by Fig. 9.1). The carcinogenic effects (and sometimes the chronic non-carcinogenic effects) associated with a chemical exposure problem involve estimating the LADD; for non-carcinogenic effects, the ADD is usually used. The ADD differs from the LADD in that the former is not averaged

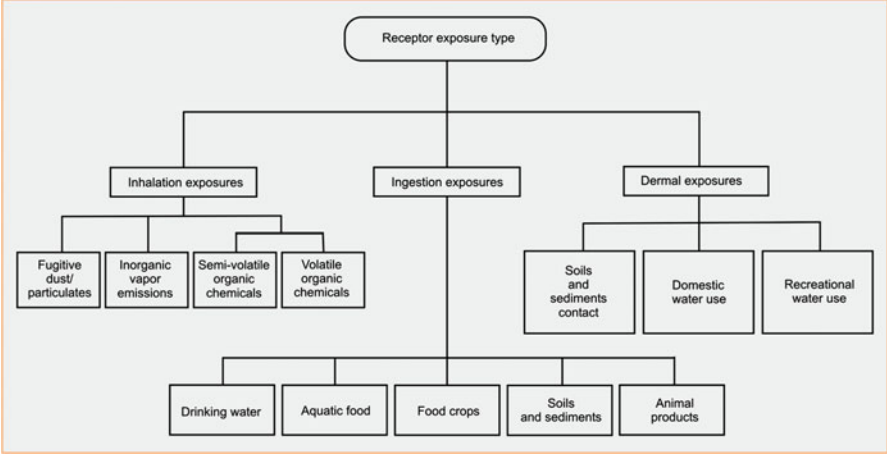

Fig. 9.1 Major routes for human exposures to chemicals

over a lifetime; rather, it is the average daily dose pertaining to the actual duration of exposure. The *maximum daily dose* (MDD) will typically be used in estimating acute or subchronic exposures.

At the end of the day, human exposures to chemical materials may be conservatively quantified according to the generic equation shown in Box 9.2. The various exposure parameters used in this model may be derived on a case-specific basis, or they may be compiled from regulatory guidance manuals and documents, and indeed other related scientific literature (e.g., Binder et al. 1986; Calabrese et al. 1989; CAPCOA 1990; DTSC 1994; Finley et al. 1994; Hrudey et al. 1996; Ikegami et al. 2014; LaGoy 1987; Lepow et al. 1974, 1975; OSA 1992; Sedman 1989; Smith 1987; Stanek and Calabrese 1990; Travis and Arms 1988; USEPA 1987, 1989a, b, 1991a, b, c, d, 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h, 1998a, b, c, d, 2000, 2011, 2014; Van Wijnen et al. 1990); these parameters are usually based on information relating to the maximum exposure level that results from specified categories of receptor activity and/or exposures.

Box 9.2 General equation for estimating potential human exposures to chemicals

$$EXP = \frac{(C_{medium} \times CR \times CF \times FI \times ABS_f \times EF \times ED)}{BW \times AT}$$

where:

EXP = intake (i.e., the amount of chemical at the exchange boundary), adjusted for absorption (mg/kg-day)

C_{medium} = average or reasonably maximum exposure concentration of chemical contacted by potential receptor over the exposure period in the medium of concern (e.g., μg/m^3 [air]; or μg/L [water]; or mg/kg [solid materials, such as food and soils])

CR = contact rate, i.e., the amount of 'chemical-based' medium contacted per unit time or event (e.g., inhalation rate in m^3/day [air]; or ingestion rate in mg/day [food; soil], or L/day [water])

CF = conversion factor (10^{-6} kg/mg for solid media, or 1.00 for fluid media)

FI = fraction of intake from 'chemical-based' source (dimensionless)

ABS_f = bioavailability or absorption factor (%).

EF = exposure frequency (days/years)

ED = exposure duration (years)

BW = body weight, i.e., the average body weight over the exposure period (kg)

AT = averaging time (period over which exposure is averaged – days)

= ED x 365 days/year, for non-carcinogenic effects of human exposure

= LT x 365 days/year =70 years × 365 days/year, for carcinogenic effects of human exposure (assuming an average lifetime, LT, of 70 years)

As a simple illustrative practical example, consider a situation where the average concentration of 1,2-dichlorobenzene in a domestic water supply has been recorded at 1.7 μg/L. Now, it is required to determine the intake for a 70-kg adult who consumes 2 L of water per day over a 30-year period. The requested chemical intake may be estimated by using the equation shown in Box 9.2. Assuming an exposure frequency of 365 days/year, and also $FI = 1$ and $ABS_f = 1$ for this non-carcinogenic contaminant, the required intake is estimated as follows:

$$EXP = \left[\frac{\left(C_{medium} \times CR \times CF \times FI \times ABS_f \times EF \times ED\right)}{(BW \times AT)}\right]$$

Substituting $C_{medium} = 1.7$ μg/L; $CR = 2$ L/day; $CF = 10^{-3}$ mg/μg; $FI = 1$; $ABS_f = 1$; $EF = 365$ d/year; $ED = 30$ years; $BW = 70$ kg; and $AT = (ED \times 365) = (30 \times 365)$ days yields:

$$EXP = \left[\frac{\left(1.7 \times 2 \times 10^{-3} \times 1 \times 1 \times 365 \times 30\right)}{(70 \times 30 \times 365)}\right] \cong 4.86 \times 10^{-5} mg/kg\text{-}day$$

The methods by which each specific type of chemical exposure (as depicted in Fig. 9.1) might be estimated—including the relevant exposure estimation algorithms/equations for specific major routes of exposure (*viz.*, inhalation, ingestion, and skin contacting)—are discussed in greater detail below. These algorithms and related ones are elaborated in an even greater detail elsewhere in the literature (e.g., Asante-Duah 1998; CAPCOA 1990; CDHS 1986; DTSC 1994; McKone 1989; McKone and Daniels 1991; NRC 1991a, b; USEPA 1986c, 1988a, b, 1989a, b, 1991a, b, c, d, 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h, 1998a, b, c, d, 2000, 2011, 2014). Further illustration of the computational steps involved in the calculation of human receptor intakes and doses is also presented below.

9.2.1 Potential Receptor Inhalation Exposures

Two major types of inhalation exposures are generally considered in the investigation of potential chemical exposure problems (see Fig. 9.1)—broadly categorized into the inhalation of airborne fugitive dust/particulates, in which all individuals within approximately 80 km (≅ 50 miles) radius of a chemical release source are potentially impacted; and the inhalation of volatile compounds (i.e., airborne, vapor-phase chemicals). In general, potential inhalation intakes may be estimated based on the length of exposure, the inhalation rate of the exposed individual, the concentration of constituents in the inhaled air, and the amount retained in the lungs; this is conservatively represented by the following generic relationship:

$$\text{Inhalation Exposure (mg/kg-day)} = \frac{\{\text{GLC} \times \text{RR} \times \text{CF}\}}{\text{BW}} \tag{9.1}$$

where: *GLC* is the ground-level concentration of constituents of concern (μg/m^3); *RR* is the respiration rate of exposed individual (m^3/day); *CF* is a conversion factor (= 1 mg/1000 μg = 1.0E-03 mg/μg); and *BW* is the body weight of exposed person (kg). Potential receptor inhalation exposures specific to chemical releases associated with wind-borne particulate matter/fugitive dust, and also volatile compounds from airborne vapor-phase emissions are elaborated below.

Finally, it must be acknowledged here that recent works call for variant approaches for determining exposure and risk from inhaled chemicals—especially in order for it to be consistent with inhalation dosimetry methodologies currently used by a number of institutions/agencies (such as the US EPA). Under this new paradigm noted here, it is generally recommended that when estimating risk via inhalation, risk assessors should use the concentration of the chemical in air as the exposure metric (e.g., mg/m^3)—i.e., rather than a use of inhalation intake of a contaminant in air based on IR and BW (e.g., mg/kg-day). In this case, the intake equations described above may not quite be consistent with the principles of the inhalation dosimetry methodology—especially because the amount of the chemical that reaches the target site is not a simple function of IR and BW; instead, the interaction of the inhaled contaminant with the respiratory tract is affected by factors such as species-specific relationships of exposure concentrations (ECs) to deposited/delivered doses and physiochemical characteristics of the inhaled contaminant. The inhalation dosimetry methodology also considers the target site where the toxic effect occurs (e.g., the respiratory tract or a location in the body remote from the portal-of-entry) when applying dosimetric adjustments to experimental concentrations (USEPA 1994a, b, c, d, e, f, g). In the end, it becomes necessary to appropriately characterize exposures in a manner that is consistent with the inhalation dosimetry methodology. Under this set of circumstances, the general approach involves the estimation of exposure concentrations (ECs) for each receptor exposed to contaminants via inhalation in the risk assessment—where the ECs are time-weighted average concentrations derived from measured or modeled contaminant concentrations in air at a locale or within an 'exposure object' (and possibly further adjusted based on the characteristics of the exposure scenario being evaluated). Representative equations for estimating ECs are presented in Chap. 11—with the ECs typically provided in units of μg/m^3. This matter is elaborated further in Chap. 11 of this book.

9.2.1.1 Receptor Inhalation Exposure to Particulates from Constituents in Fugitive/Airborne Dust

Box 9.3 shows an algorithm that can be used to calculate potential receptor intakes resulting from the inhalation of constituents in wind-borne fugitive dust (CAPCOA 1990; DTSC 1994; USEPA 1988a, b, 1989a, b, 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h, 1998a, b, c, d, 2000, 2004a, b, c, d, e, f, g, 2011, 2014). The constituent

concentration in air, *Ca*, is defined by the ground-level concentration (GLC)—usually represented by the respirable (PM-10) particles—expressed in $\mu g/m^3$. The PM-10 particles consist of particulate matter with physical/aerodynamic diameter of less than 10 microns (i.e., <10 μm)—and it represents the respirable portion of the particulate emissions; this portion is capable of being deposited in thoracic (tracheobronchial and alveolar) portions of the lower respiratory tract. It is noteworthy that, fine particulate matter has also been characterized by $PM_{2.5}$ (i.e., ≤ 2.5 μm aerodynamic diameter). Finally, it should be recognized that the total PM exposure for an individual during a given period of time usually consists of exposures to many different particles from various sources whiles the receptor is in different microenvironments. As such, these different human microenvironments should be carefully identified so that the corresponding exposures can be properly appraised.

9.2.1.2 Receptor Inhalation Exposure to Volatile Compounds

Box 9.4 shows an algorithm that can be used to calculate potential receptor intakes resulting from the inhalation of airborne vapor-phase chemicals (CAPCOA 1990; DTSC 1994; USEPA 1988a, b, 1989a, b, 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h, 1998a, b, c, d, 2000, 2004a, b, c, d, e, f, g, 2011, 2014). The vapor-phase contaminant concentration in air is assumed to be in equilibrium with the concentration in the release source. Meanwhile, it is noteworthy that, showering generally seems to represent a prominent activity that promotes the release of volatile organic chemicals (VOCs) from water—especially because of the high turbulence, high surface area, and small droplets of water involved. In fact, some contemporary studies have shown that risks from inhalation while showering can be comparable to—if not greater than—risks from drinking contaminated water (Jo et al. 1990a, b; Kuo et al. 1998; McKone 1987; Richardson et al. 2002; Wilkes et al. 1996). Thus, this exposure scenario represents a particularly important one to carefully examine/evaluate in a human health risk assessment, whenever applicable. For this scenario of volatile compounds released whiles bathing, the exposure relationship may be defined by the specific equation shown in Box 9.5 (USEPA 1988a, b; 1989a, b). In this case, the concentration of the contaminants in the shower air is assumed to be in equilibrium with the concentration in the water. Other assumptions used in this model include the following: there is no air exchange in the shower (this assumption tending to overestimate the concentration of contaminants in the air in the bathroom); there is perfect mixing within the bathroom (this assumption tending to underestimate the concentration of contaminants in the air in the shower); and the emission rate from water is independent of instantaneous air concentration.

Box 9.3 Equation for estimating inhalation exposure to chemical constituents in fugitive/airborne dust

$$INH_a = \frac{(C_a \times IR \times RR \times ABS_S \times ET \times EF \times ED)}{BW \times AT}$$

where:

INH_a = inhalation intake (mg/kg-day)

C_a = chemical concentration of airborne particulates (defined by the ground-levelconcentration [GLC], and represented by the respirable, PM-10 particles) (mg/m^3)

IR = inhalation rate (m^3/h)

RR = retention rate of inhaled air (%)

ABS_s = percent of chemical absorbed into the bloodstream (%)

ET = exposure time (h/day)

EF = exposure frequency (days/years)

ED = exposure duration (years)

BW = body weight, i.e., the average body weight over the exposure period (kg)

AT = averaging time (period over which exposure is averaged – days)

= ED x 365 days/year, for non-carcinogenic effects of human exposure

= LT x 365 days/year =70 years × 365 days/year, for carcinogenic effects of human exposure(assuming an average lifetime, LT, of 70 years)

Box 9.4 Equation for estimating inhalation exposure to vapor-phase chemical constituents

$$INH_{av} = \frac{(C_{av} \times IR \times RR \times ABS_S \times ET \times EF \times ED)}{BW \times AT}$$

where:

INH_{av} = inhalation intake (mg/kg-day)

C_{av} = chemical concentration in air (mg/m^3) [The vapor-phase contaminant concentration in airis assumed to be in equilibrium with the concentration in the release source.]

IR = inhalation rate (m^3/h)

RR = retention rate of inhaled air (%)

ABS_s = percent of chemical absorbed into the bloodstream (%)

ET = exposure time (h/day)

EF = exposure frequency (days/years)

ED = exposure duration (years)

(continued)

Box 9.4 (continued)

BW = body weight, i.e., the average body weight over the exposure period (kg)

AT = averaging time (period over which exposure is averaged – days)

= ED x 365 days/year, for non-carcinogenic effects of human exposure

= LT x 365 days/year =70 years × 365 days/year, for carcinogenic effects of human exposure(assuming an average lifetime, LT, of 70 years)

Box 9.5 Equation for estimating inhalation exposure to vapor-phase chemical constituents during showering activity

$$INH = \left[C_w \times FV \times \left\{\frac{ET_1}{VS \times 2} \times \frac{ET_2}{VB}\right\}\right] \times \frac{(IR \times RR \times VW \times ABS_S \times EF \times ED)}{BW \times AT}$$

$$= [ACB_{sh}] \times \frac{(IR \times RR \times VW \times ABS_S \times EF \times ED)}{BW \times AT}$$

where:

INH = inhalation intake whiles showering (mg/kg-day)

C_w = concentration of contaminant in water—adjusted for water treatment purification factor, T_f, which is the fraction remaining after treatment [i.e., $C_w = C_{w\text{-}source} \times T_f$] (mg/L)

FV = fraction of contaminant volatilized (unit less)

ET_1 = length of exposure in shower (h/day)

ET_2 = length of additional exposure in enclosed bathroom (h/day)

VS = volume of shower stall (m^3)

VB = volume of bathroom (m^3)

IR = breathing/inhalation rate (m^3/h)

RR = retention rate of inhaled air (%)

VW = volume of water used in shower (L)= water flow rate (Fw [L/h]) × shower duration (h)

ABS_s = percent of chemical absorbed into the bloodstream (%)

EF = exposure frequency (days/year)

ED = exposure duration (years)

BW = body-weight (kg)

AT = averaging time (period over which exposure is averaged—days)

ACB_{sh} = average air concentration in bathroom during a shower activity $= \left[C_w \times FV \times \left\{\frac{ET_1}{VS \times 2} \times \frac{ET_2}{VB}\right\}\right]$

(continued)

Box 9.5 (continued)

Note: The concentration of contaminants in water may be adjusted further for environmental degradation, by multiplying by a factor of e^{-kt}, where k (in $days^{-1}$) is the environmental degradation constant of the chemical and t (in days) is the average time of transit through the water distribution system. This yields a new C_w value to be used for the intakes computation, viz., $C_w^* = (C_w)(e^{-kt})$

9.2.2 Potential Receptor Ingestion Exposures

The major types of ingestion exposures that could affect chemical exposure decisions consist of the oral intake of constituents present in consumer products, food products, waters, and miscellaneous environmental materials (see Fig. 9.1). In general, exposure through ingestion is a function of the concentration of the constituents in the material ingested (e.g., soil, water, food products such as crops, or consumer products such as dairy/beef), the gastrointestinal absorption of the constituent in solid or fluid matrix, and the amount ingested. This can be conservatively estimated by using the following generic types of representative equations:

$$\text{Water(and other liquids) Ingestion Exposure (mg/kg)} = \frac{\{\text{CW} \times \text{WIR} \times \text{GI}\}}{\text{BW}} \tag{9.2}$$

$$\text{Soil Ingestion Exposure (mg/kg-day)} = \frac{\{\text{CS} \times \text{SIR} \times \text{GI}\}}{\text{BW}} \tag{9.3}$$

$$\text{Crop Ingestion Exposure (mg/kg-day)} = \frac{\{\text{CS} \times \text{RUF} \times \text{CIR} \times \text{GI}\}}{\text{BW}} \tag{9.4}$$

$$\text{Consumer Products (e.g., dairy and beef) Ingestion Exposure (mg/kg-day)} \times \frac{\{\text{CD} \times \text{FIR} \times \text{GI}\}}{\text{BW}} \tag{9.5}$$

where: *CW* is the chemical concentration in water (mg/L); *WIR* is the water consumption rate (L/day); *CS* is the chemical concentration in soil (mg/kg); *SIR* is the soil consumption rate (kg/day); *RUF* is the root uptake factor; *CIR* is the crop consumption rate (kg/day); *CD* is the concentration of chemical in diet (mg/kg)—for grazing animals, the concentration of chemicals in tissue, *CT*, is $CT = BCF \times F \times CD$, where *BCF* is the bioconcentration factor (fat basis) for the organism, expressed as [mg/kg fat]/[mg/kg of diet], and *F* is the fat content of tissues (in [kg fat]/[kg tissue]); *FIR* is the food (e.g., meat and dairy)

consumption (kg/day); *GI* is the gastrointestinal absorption factor; and *BW* is the body weight (kg).

The total dose received by the potential receptors from chemical ingestion will, in general, be very much dependent on the absorption of the chemical across the gastrointestinal (GI) lining. The scientific literature provides some estimates of such absorption factors for various chemical substances. For chemicals without published absorption values and for which absorption factors are not implicitly accounted for in toxicological parameters, absorption may conservatively be assumed to be 100%.

Potential receptor ingestion exposures specific to the oral intake of chemical-impacted waters, the consumption of chemicals in food products, and the incidental ingestion of other contaminated solid matrices (such as soils/sediments) are annotated below.

9.2.2.1 Receptor Exposure through Ingestion of Constituents in Drinking Water

Exposure to contaminants via the ingestion of contaminated fluids may be estimated using the algorithm shown in Box 9.6 (CAPCOA 1990; DTSC 1994; USEPA 1988a, b, 1989a, b, 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h, 1998a, b, c, d, 2000, 2004a, b, c, d, e, f, g, 2011, 2014). This is comprised of the applicable relationship for estimating the chemical exposure intake that occurs through the ingestion of drinking water.

As a special type of situation, receptor exposure through incidental ingestion of constituents in water *during swimming activities* (i.e., the result of the ingestion of contaminated surface water during recreational activities) may be estimated by using the algorithm shown in Box 9.7.

Box 9.6 Equation for estimating ingestion exposure to constituents in water used for culinary purposes

$$ING_{dw} = \frac{(C_W \times WIR \times FI \times ABS_S \times EF \times ED)}{BW \times AT}$$

where:
ING_{dw} = ingestion intake, adjusted for absorption (mg/kg-day)
C_W = chemical concentration in drinking water (mg/L)
WIR = average ingestion rate (L/day)
FI = fraction ingested from contaminated source (unitless)
ABS_s = bioavailability/gastrointestinal [GI] absorption factor (%).
EF = exposure frequency (days/year)
ED = exposure duration (years)

(continued)

Box 9.6 (continued)

BW = body-weight (kg)
AT = averaging time (period over which exposure is averaged—days)

Box 9.7 Equation for estimating incidental ingestion exposure to contaminated surface water during recreational activities

$$ING_r = \frac{(CW \times CR \times ABS_S \times ET \times EF \times ED)}{BW \times AT}$$

where:
ING_r = ingestion intake, adjusted for absorption (mg/kg-day)
CW = chemical concentration in water (mg/L)
CR = contact rate (L/h)
ABS_s = bioavailability/gastrointestinal [GI] absorption factor (%)
ET = exposure time (h/event)
EF = exposure frequency (days/year)
ED = exposure duration (years)
BW = body-weight (kg)
AT = averaging time (period over which exposure is averaged—days)

9.2.2.2 Receptor Exposure Through Ingestion of Constituents in Consumer/Food Products

Typically, exposure from the ingestion of food can occur via the ingestion of plant products, fish, animal products, and mother's milk. A general algorithm for estimating the exposure intake through the ingestion of foods is shown in Box 9.8—with corresponding relationships defined below for specific types of food products.

- *Ingestion of Plant Products*—Exposure through the ingestion of plant products, *INGp*, is a function of the type of plant, gastrointestinal absorption factor, and the fraction of plants ingested that are affected by the chemical constituents of concern. The exposure estimation is performed for each plant type in accordance with the algorithm presented in Box 9.9 (CAPCOA 1990; USEPA 1989a, 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h, 1998a, b, c, d, 2000, 2004a, b, c, d, e, f, g, 2011, 2014).
- *Bioaccumulation and Ingestion of Seafood*—Exposure from the ingestion of chemical constituents in fish (e.g., obtained from contaminated surface water bodies) may be estimated using the algorithm shown in Box 9.10 (USEPA 1987, 1988a, b, 1989a, 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h, 1998a, b, c, d, 2000, 2004a, b, c, d, e, f, g, 2011, 2014).

Box 9.8 Equation for estimating ingestion exposure to constituents in food products

$$ING_f = \frac{\left(C_f \times FIR \times CF \times FI \times ABS_S \times EF \times ED\right)}{BW \times AT}$$

where:
ING_f = ingestion intake, adjusted for absorption (mg/kg-day)
C_f = chemical concentration in food (mg/kg or mg/L)
FIR = average food ingestion rate (mg or L/meal)
CF = conversion factor (10^{-6} kg/mg for solids and 1.00 for fluids)
FI = fraction ingested from contaminated source (unitless)
ABS_s = bioavailability/gastrointestinal [GI] absorption factor (%).
EF = exposure frequency (meals/year)
ED = exposure duration (years)
BW = body weight (kg)
AT = averaging time (period over which exposure is averaged – days)

Box 9.9 Equation for estimating ingestion exposure to constituents in plant products

$$ING_p = \frac{(CP_Z \times PIR_Z \times FI_Z \times ABS_S \times EF \times ED)}{BW \times AT}$$

where:
ING_p = exposure intake from ingestion of plant products, adjusted for absorption (mg/kg-day)
CP_z = chemical concentration in plant type *Z* (mg/kg)
PIR_z = average consumption rate for plant type *Z* (kg/day)
FI_z = fraction of plant type *Z* ingested from contaminated source (unitless)
ABS_s = bioavailability/gastrointestinal [GI] absorption factor (%)
EF = exposure frequency (days/years)
ED = exposure duration (years)
BW = body weight (kg)
AT = averaging time (period over which exposure is averaged—days)

Box 9.10 Equation for estimating ingestion exposure to constituents in contaminated seafood

$$ING_{sf} = \frac{(CW \times FIR \times CF \times BCF \times FI \times ABS_S \times EF \times ED)}{BW \times AT}$$

where:
ING_{sf} = total exposure, adjusted for absorption (mg/kg-day)
CW = chemical concentration in surface water (mg/L)
FIR = average fish ingestion rate (g/day)
CF = conversion factor (= 10^{-3} kg/g)
BCF = chemical-specific bioconcentration factor (L/kg)
FI = fraction ingested from contaminated source (unitless)
ABS_s = bioavailability/gastrointestinal [GI] absorption factor (%)
EF = exposure frequency (days/years)
ED = exposure duration (years)
BW = body weight (kg)
AT = averaging time (period over which exposure is averaged – days)

- *Ingestion of Animal Products*—Exposure resulting from the ingestion of animal products, *INGa*, is a function of the type of meat ingested (including animal milk products and eggs), gastrointestinal absorption factor, and the fraction of animal products ingested that are affected by the constituents of concern. The exposure estimation is carried out for each animal product type by using the form of relationship shown in Box 9.11 (CAPCOA 1990; USEPA 1989a, 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h, 1998a, b, c, d, 2000, 2004a, b, c, d, e, f, g, 2011, 2014).
- *Ingestion of Mother's Milk*—Exposure through the ingestion of a mother's milk, *INGm*, is a function of the average chemical concentration in the mother's milk, the amount of mother's milk ingested, and gastrointestinal absorption factor—estimated according to the relationship shown in Box 9.12 (CAPCOA 1990; USEPA 1989a, 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h, 1998a, b, c, d, 2000, 2004a, b, c, d, e, f, g, 2011, 2014).

Box 9.11 Equation for estimating ingestion exposure to constituents in animal products

$$ING_a = \frac{(CAP_Z \times APIR_Z \times FI_Z \times ABS_S \times EF \times ED)}{BW \times AT}$$

where:
ING_a = exposure intake through ingestion of plant products, adjusted for absorption (mg/kg-day)

(continued)

Box 9.11 (continued)

CAP_z = chemical concentration in food type Z (mg/kg)
$APIR_z$ = average consumption rate for food type Z (kg/day)
FI_z = fraction of product type Z ingested from contaminated source (unitless)
ABS_s = bioavailability/gastrointestinal [GI] absorption factor (%)
EF = exposure frequency (days/years)
ED = exposure duration (years)
BW = body weight (kg)
AT = averaging time (period over which exposure is averaged – days)

Box 9.12 Equation for estimating ingestion exposure to chemicals in mother's milk used for breast-feeding

$$ING_m = \frac{(\text{CMM} \times \text{IBM} \times \text{ABS}_S \times \text{EF} \times \text{ED})}{\text{BW} \times \text{AT}}$$

where:
ING_m = exposure intake through ingestion of mother's milk, adjusted for absorption (mg/kg-day)
CMM = chemical concentration in mother's milk – which is a function of a mother's exposurethrough all routes and the contaminant body half-life (mg/kg)
IBM = daily average ingestion rate for breast milk (kg/day)
ABS_s = bioavailability/gastrointestinal [GI] absorption factor (%)
EF = exposure frequency (days/years)
ED = exposure duration (years)
BW = body weight (kg)
AT = averaging time (period over which exposure is averaged—days)

9.2.2.3 Receptor Exposure Through Pica and Incidental Ingestion of Soil/Sediment

Exposures that result from the incidental ingestion of contaminants sorbed onto soils is determined by multiplying the concentration of the constituent in the medium of concern by the amount of soil/material ingested per day and the degree of absorption. The applicable relationship for estimating the resulting exposures is shown in Box 9.13 (CAPCOA 1990; USEPA 1988a, b, 1989a, b, 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h, 1998a, b, c, d, 2000, 2004a, b, c, d, e, f, g, 2011, 2014). In general, it is usually assumed that all ingested soil during receptor exposures comes from a contaminated source, so that the FI term becomes unity.

Box 9.13 Equation for estimating pica and incidental ingestion exposure to contaminated soils/sediments

$$ING_S = \frac{(C_S \times SIR \times CF \times FI \times ABS_S \times EF \times ED)}{BW \times AT}$$

where:
ING_s = ingestion intake, adjusted for absorption (mg/kg-day)
C_s = chemical concentration in soil (mg/kg)
SIR = average soil ingestion rate (mg soil/day)
CF = conversion factor (10^{-6} kg/mg)
FI = fraction ingested from contaminated source (unitless)
ABS_s = bioavailability/gastrointestinal [GI] absorption factor (%)
EF = exposure frequency (days/years)
ED = exposure duration (years)
BW = body weight (kg)
AT = averaging time (period over which exposure is averaged—days)

9.2.3 Potential Receptor Dermal Exposures

The major types of dermal exposures that could affect chemical exposure decisions consist of dermal contacts with contaminants adsorbed onto or within solid matrices (e.g., cosmetics, soils, etc.), and also dermal absorption from contaminated waters and constituents in consumer products such as cosmetics (see Fig. 9.1). In general, dermal intake is a function of the chemical concentration in the medium of concern, the body surface area in contact with the medium, the duration of the contact, flux of the medium across the skin surface, and the absorbed fraction—conservatively estimated by the following representative relationships:

$$\text{Dermal Exposure to solid matrix (mg/kg-day)} = \frac{\{SS \times SA \times CS \times UF \times CF\}}{BW} \tag{9.6}$$

$$\text{Dermal Exposure to water (mg/kg-day)} = \frac{\{WS \times SA \times CW \times UF\}}{BW} \tag{9.7}$$

where: *SS* is surface dust/materials on skin (mg/cm^2/day); *CS* is chemical concentration in solid matrix (e.g., soil) (mg/kg); *CF* is conversion factor (= 1.00E-06 kg/mg); *WS* is water contacting skin (L/cm^2/day); *CW* is chemical concentration in water (mg/L); *SA* is exposed skin surface area (cm^2); *UF* is uptake factor; and *BW* is body weight (kg).

Potential receptor dermal exposures via dermal contacts with solid matrices containing chemical constituents, and from the dermal absorption of chemicals present in contaminated water media, are annotated below.

9.2.3.1 Receptor Exposure Through Contact/Dermal Absorption from Solid Matrices

The dermal exposures to chemicals in solid materials (e.g., soils and sediments) may be estimated by applying the equation shown in Box 9.14 (CAPCOA 1990; DTSC 1994; USEPA 1988a, b, 1989a, b, 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h, 1998a, b, c, d, 2000, 2004a, b, c, d, e, f, g, 2011, 2014).

Box 9.14 Equation for estimating dermal exposures through contacts with constituents in solid matrices (e.g., contaminated soils)

$$DEX_S = \frac{(C_S \times CF \times SA \times AF \times ABS_S \times SM \times EF \times ED)}{BW \times AT}$$

where:

DEX_s = absorbed dose (mg/kg-day).

C_s = chemical concentration in solid materials (e.g., contaminated soils) (mg/kg)

CF = conversion factor (10^{-6} kg/mg)

SA = skin surface area available for contact, i.e., surface area of exposed skin (cm^2/event)

AF = solid material to skin adherence factor (e.g., soil loading on skin) (mg/cm^2)

ABS_s = skin absorption factor for chemicals in solid matrices (e.g., contaminated soils) (%)

SM = factor for solid materials matrix effects (%)

EF = exposure frequency (events/year)

ED = exposure duration (years)

BW = body weight (kg)

AT = averaging time (period over which exposure is averaged – days)

9.2.3.2 Receptor Exposure Through Dermal Contact with Waters and Liquid Consumer Products

Dermal exposures to chemicals in water may occur during domestic use (such as bathing and washing), or through recreational activities (such as swimming or fishing). As a specific example, the dermal intakes of chemicals in groundwater or surface water, and/or in seeps from a contaminated site may be estimated by

using the type of equation shown in Box 9.15 (USEPA 1988a, b, 1989a, b, 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h, 1998a, b, c, d, 2000, 2004a, b, c, d, e, f, g, 2011, 2014).

Box 9.15 Equation for estimating dermal exposures through contacts with contaminated waters

$$DEX_w = \frac{(C_W \times CF \times SA \times PC \times ABS_S \times ET \times EF \times ED)}{BW \times AT}$$

where:

DEX_w = absorbed dose from dermal contact with chemicals in water (mg/kg-day)

C_w = chemical concentration in water (mg/L)

CF = volumetric conversion factor for water (1 L/1000 cm^3)

SA = skin surface area available for contact, i.e., surface area of exposed skin (cm^2)

PC = chemical-specific dermal permeability constant (cm/h)

ABS_s = skin absorption factor for chemicals in water (%).

ET = exposure time (h/day)

EF = exposure frequency (days/year)

ED = exposure duration (years)

BW = body weight (kg)

AT = averaging time (period over which exposure is averaged—days).

9.3 Establishing 'Exposure Intake Factors' for Use in the Computation of Chemical Intakes and Doses

Several exposure parameters are normally required so as to be able to model the various exposure scenarios typically associated with chemical exposure problems. Oftentimes, default values are obtainable from the scientific literature for some of the requisite parameters used in the estimation of chemical intakes and doses. Table 9.1 shows typical parameters that exemplify a generic set of values commonly used in some applications; indeed, this is by no means complete—and more detailed information on such parameters can be obtained from various scientific sources (e.g., Calabrese et al. 1989; CAPCOA 1990; Lepow et al. 1974, 1975; OSA 1992; USEPA 1987, 1988a, b, 1989a, b, 1991a, b, c, d, 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h, 1998a, b, c, d, 2000, 2004a, b, c, d, e, f, g, 2011, 2014).

A spreadsheet to help in automatically calculating exposure 'intake factors' for varying input parameters that reflect case-specific problem scenarios may be developed (based on the algorithms presented in the preceding sections) to facilitate the computational efforts involved in the exposure assessment (Table 9.2). Some example evaluations for potential receptor groups purportedly exposed through

Table 9.1 An example listing of case-specific exposure parameters

Parameter	Child aged up to 6 years	Child aged 6–12 years	Adult
Physical characteristics			
Average body weight (kg)	16	29	70
Average total skin surface area (cm^2)	6980	10470	18150
Average lifetime (yrs)	70	70	70
Average lifetime exposure period (yrs)	5	6	58
Activity characteristics			
Inhalation rate (m^3/h)	0.25	0.46	0.83
Retention rate of inhaled air (%)	100	100	100
Frequency of fugitive dust inhalation (days/yr)			
off-site residents, schools, and by-passers	365	365	365
off-site workers	–	–	260
Duration of fugitive dust inhalation (outside) (h/day)			
off-site residents, schools, and by-passers	12	12	12
off-site workers	–	–	8
Amount of incidentally ingested soils (mg/day)	200	100	50
Frequency of soil contact (days/yr)			
off-site residents, schools, and by-passers	330	330	330
off-site workers	–	–	260
Duration of soil contact (h/day)			
off-site residents, schools, and by-passers	12	8	8
off-site workers	–	–	8
Skin area contacted by soil (%)	20	20	10
Material characteristics			
Soil-to-skin adherence factor (mg/cm^2)	0.75	0.75	0.75
Soil matrix attenuation factor (%)	15	15	15

Note: The exposure factors represented here are considered to project potential maximum exposures (and therefore these are expected to produce conservative estimates). Indeed, these could be modified, as appropriate – to reflect the most reasonable exposure patterns anticipated for a project-specific situation; for instance, realistically, soil exposure is generally reduced from snow cover and rainy days – thus reducing potential exposures for children playing outdoors in a contaminated area. In any case, the sources and/or rationale for the choice of the exposure parameters should be very well supported and adequately documented

inhalation, soil ingestion (*viz.*, incidental or pica behavior), and dermal contact are discussed in the proceeding sections—albeit these are offered here only as an illustration of the computational mechanics involved in the exposure assessment process. The same set of units is maintained throughout these illustrative evaluations that follow as were used in the preceding sections.

Table 9.2 Example spreadsheet for calculating case-specific 'intake factors' for an exposure assessment

Fugitive Dust Inhalation Pathway								
Receptor Group	IR	RR	ET	EF	ED	BW	AT	INH factor
C(1–6)@NCancer	0.25	1	12	365	5	16	1825	1.88E-01
C(1–6)@Cancer	0.25	1	12	365	5	16	25,550	1.34E-02
C(6–12)@NCancer	0.46	1	12	365	6	29	2190	1.90E-01
C(6–12)@Cancer	0.46	1	12	365	6	29	25,550	1.63E-02
ResAdult@NCancer	0.83	1	12	365	58	70	21,170	1.42E-01
ResAdult@Cancer	0.83	1	12	365	58	70	25,550	1.18E-01
JobAdult@NCancer	0.83	1	8	260	58	70	21,170	6.76E-02
JobAdult@Cancer	0.83	1	8	260	58	70	25,550	5.60E-02
Soil Ingestion Pathway								
Receptor Group	IR	CF	FI	EF	ED	BW	AT	ING factor
C(1–6)@NCancer	200	1.00E-06	1	330	5	16	1825	1.13E-05
C(1–6)@Cancer	200	1.00E-06	1	330	5	16	25,550	8.07E-07
C(6–12)@NCancer	100	1.00E-06	1	330	6	29	2190	3.12E-06
C(6–12)@Cancer	100	1.00E-06	1	330	6	29	25,550	2.67E-07
ResAdult@NCancer	50	1.00E-06	1	330	58	70	21,170	6.46E-07
ResAdult@Cancer	50	1.00E-06	1	330	58	70	25,550	5.35E-07
JobAdult@NCancer	50	1.00E-06	1	260	58	70	21,170	5.09E-07
JobAdult@Cancer	50	1.00E-06	1	260	58	70	25,550	4.22E-07
Soil Dermal Contact Pathway									
Receptor Group	SA	CF	AF	SM	EF	ED	BW	AT	DEX factor
C(1–6)@NCancer	1396	1E-06	0.75	0.15	330	5	16	1825	8.87E-06
C(1–6)@Cancer	1396	1E-06	0.75	0.15	330	5	16	25,550	6.34E-07
C(6–12)@NCancer	2094	1E-06	0.75	0.15	330	6	29	2190	7.34E-06
C(6–12)@Cancer	2094	1E-06	0.75	0.15	330	6	29	25,550	6.30E-07
ResAdult@NCancer	1815	1E-06	0.75	0.15	330	58	70	21,170	2.64E-06
ResAdult@Cancer	1815	1E-06	0.75	0.15	330	58	70	25,550	2.19E-06
JobAdult@NCancer	1815	1E-06	0.75	0.15	260	58	70	21,170	2.08E-06
JobAdult@Cancer	1815	1E-06	0.75	0.15	260	58	70	25,550	1.72E-06

Notes:
Notations and units are same as defined in the text
INH factor = Inhalation factor for calculation of doses and intakes
ING factor = Soil ingestion factor for calculation of doses and intakes
DEX factor = Dermal exposure (via skin absorption) factor for calculation of doses and intakes
C(1–6)@NCancer; C(6–12)@NCancer; ResAdult@NCancer; JobAdult@NCancer = Non-carcinogenic effects for a child aged 1–6 years; child aged 6–12 years; resident adult; and adult worker, respectively
C(1–6)@Cancer; C(6–12)@Cancer; ResAdult@Cancer; JobAdult@Cancer = Carcinogenic effects for a child aged 1–6 years; child aged 6–12 years; resident adult; and adult worker, respectively

9.3.1 Illustrative Example for Inhalation Exposures

The daily inhalation intake of contaminated fugitive dust for various population groups is presented below for both carcinogenic and non-carcinogenic effects. The assumed parameters used in the computational demonstration are provided in Table 9.1, and the electronic spreadsheet automation process shown in Table 9.2.

9.3.1.1 Estimation of Lifetime Average Daily Dose (LADD) for Carcinogenic Effects

For the fugitive dust inhalation pathway, the LADD (also, the carcinogenic chronic daily intake [CDI]) is estimated for the different population groups (generally pre-selected as representative of the critical receptors in the risk assessment)—and the results are shown below.

- The carcinogenic CDI for children aged up to 6 years is calculated to be:

$$\begin{aligned}&\mathrm{CInh}_{(1-6)}\\&=\frac{(\mathrm{CA}\times\mathrm{IR}\times\mathrm{RR}\times\mathrm{ABS_S}\times\mathrm{ET}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&=\frac{([\mathrm{CA}]\times 0.25\times 1\times\mathrm{ABS_S}\times 12\times 365\times 5)}{(16\times(70\times 365))}=1.34\times 10^{-2}\times\mathrm{ABS_S}\times[\mathrm{CA}]\end{aligned}$$

- The carcinogenic CDI for children aged 6–12 years is calculated to be:

$$\begin{aligned}&\mathrm{CInh}_{(6-12)}\\&=\frac{(\mathrm{CA}\times\mathrm{IR}\times\mathrm{RR}\times\mathrm{ABS_S}\times\mathrm{ET}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&=\frac{([\mathrm{CA}]\times 0.46\times 1\times\mathrm{ABS_S}\times 12\times 365\times 6)}{(29\times(70\times 365))}=1.63\times 10^{-2}\times\mathrm{ABS_S}\times[\mathrm{CA}]\end{aligned}$$

- The carcinogenic CDI for adult residents is calculated to be:

$$\begin{aligned}&\mathrm{CInh}_{(\mathrm{adultR})}\\&=\frac{(\mathrm{CA}\times\mathrm{IR}\times\mathrm{RR}\times\mathrm{ABS_S}\times\mathrm{ET}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&=\frac{([\mathrm{CA}]\times 0.83\times 1\times\mathrm{ABS_S}\times 12\times 365\times 58)}{(70\times(70\times 365))}=1.18\times 10^{-1}\times\mathrm{ABS_S}\times[\mathrm{CA}]\end{aligned}$$

- The carcinogenic CDI for adult workers is calculated to be:

$$\begin{aligned}&\mathrm{CInh}_{(\mathrm{adultW})}\\&=\frac{(\mathrm{CA}\times\mathrm{IR}\times\mathrm{RR}\times\mathrm{ABS_S}\times\mathrm{ET}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&=\frac{([\mathrm{CA}]\times 0.83\times 1\times\mathrm{ABS_S}\times 8\times 260\times 58)}{(70\times(70\times 365))}=5.60\times10^{-2}\times\mathrm{ABS_S}\times[\mathrm{CA}]\end{aligned}$$

9.3.1.2 Estimation of Average Daily Dose (ADD) for Non-carcinogenic Effects

For the fugitive dust inhalation pathway, the ADD (also, the non-carcinogenic CDI) is estimated for the different population groups (generally pre-selected as representative of the critical receptors in the risk assessment)—and the results are shown below.

- The non-carcinogenic CDI for children aged up to 6 years is calculated to be:

$$\begin{aligned}&\mathrm{CInh}_{(1-6)}\\&=\frac{(\mathrm{CA}\times\mathrm{IR}\times\mathrm{RR}\times\mathrm{ABS_S}\times\mathrm{ET}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&=\frac{([\mathrm{CA}]\times 0.25\times 1\times\mathrm{ABS_S}\times 12\times 365\times 5)}{(16\times(5\times 365))}=1.88\times10^{-1}\times\mathrm{ABS_S}\times[\mathrm{CA}]\end{aligned}$$

- The non-carcinogenic CDI for children aged 6–12 years is calculated to be:

$$\begin{aligned}&\mathrm{NCInh}_{(6-12)}\\&=\frac{(\mathrm{CA}\times\mathrm{IR}\times\mathrm{RR}\times\mathrm{ABS_S}\times\mathrm{ET}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&=\frac{([\mathrm{CA}]\times 0.46\times 1\times\mathrm{ABS_S}\times 12\times 365\times 6)}{(29\times(6\times 365))}=1.90\times10^{-1}\times\mathrm{ABS_S}\times[\mathrm{CA}]\end{aligned}$$

- The non-carcinogenic CDI for adult residents is calculated to be:

$$\begin{aligned}&\mathrm{NCInh}_{(\mathrm{adultR})}\\&=\frac{(\mathrm{CA}\times\mathrm{IR}\times\mathrm{RR}\times\mathrm{ABS_S}\times\mathrm{ET}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&=\frac{([\mathrm{CA}]\times 0.83\times 1\times\mathrm{ABS_S}\times 12\times 365\times 58)}{(70\times(58\times 365))}=1.42\times10^{-1}\times\mathrm{ABS_S}\times[\mathrm{CA}]\end{aligned}$$

- The non-carcinogenic CDI for adult workers is calculated to be:

$$\begin{aligned}&\mathrm{NCInh}_{(\mathrm{adultW})}\\&=\frac{(\mathrm{CA}\times\mathrm{IR}\times\mathrm{RR}\times\mathrm{ABS_S}\times\mathrm{ET}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&=\frac{([\mathrm{CA}]\times 0.83\times 1\times\mathrm{ABS_S}\times 8\times 260\times 58)}{(70\times(58\times 365))}=6.76\times 10^{-2}\times\mathrm{ABS_S}\times[\mathrm{CA}]\end{aligned}$$

9.3.2 Illustrative Example for Ingestion Exposures

The daily ingestion intakes of contaminated soils for various population groups are calculated for both carcinogenic and non-carcinogenic effects. The assumed parameters used in the computational demonstration are provided in Table 9.1, and the electronic spreadsheet automation process shown in Table 9.2.

9.3.2.1 Estimation of Lifetime Average Daily Dose (LADD) for Carcinogenic Effects

For the soil ingestion pathway, the LADD (also, the carcinogenic CDI) is estimated for the different population groups (generally pre-selected as representative of the critical receptors in the risk assessment)—and the results are shown below.

- The carcinogenic CDI for children aged up to 6 years is calculated to be:

$$\begin{aligned}&\mathrm{CIng}_{(1-6)}\\&=\frac{(\mathrm{CS}\times\mathrm{IR}\times\mathrm{CF}\times\mathrm{FI}\times\mathrm{ABS_S}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&\frac{([\mathrm{CS}]\times 200\times 1.00\mathrm{E}\times 1\times\mathrm{ABS_S}\times 330\times 5)}{(16\times(70\times 365))}=8.07\mathrm{E}-07\times\mathrm{ABS_S}\times[\mathrm{CS}]\end{aligned}$$

- The carcinogenic CDI for children aged 6 to 12 years is calculated to be:

$$\begin{aligned}&\mathrm{CIng}_{(6-12)}\\&=\frac{(\mathrm{CS}\times\mathrm{IR}\times\mathrm{CF}\times\mathrm{FI}\times\mathrm{ABS_S}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&\frac{([\mathrm{CS}]\times 100\times 1.00\mathrm{E}-06\times 1\times\mathrm{ABS_S}\times 330\times 6)}{(29\times(70\times 365))}=2.67\mathrm{E}-07\times\mathrm{ABS_S}\times[\mathrm{CS}]\end{aligned}$$

- The carcinogenic CDI for adult residents is calculated to be:

$$\begin{aligned}&\mathrm{CIng}_{(\mathrm{adultR})}\\&=\frac{(\mathrm{CS}\times\mathrm{IR}\times\mathrm{CF}\times\mathrm{FI}\times\mathrm{ABS_S}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&\frac{([\mathrm{CS}]\times 50\times 1.00\mathrm{E}-06\times 1\times\mathrm{ABS_S}\times 330\times 58)}{(70\times(70\times 365))}=5.35\mathrm{E}-07\times\mathrm{ABS_S}\times[\mathrm{CS}]\end{aligned}$$

- The carcinogenic CDI for adult workers is calculated to be:

$$\begin{aligned}&\mathrm{CIng}_{(\mathrm{adultW})}\\&=\frac{(\mathrm{CS}\times\mathrm{IR}\times\mathrm{CF}\times\mathrm{FI}\times\mathrm{ABS_S}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&\frac{([\mathrm{CS}]\times 50\times 1.00\mathrm{E}-06\times 1\times\mathrm{ABS_S}\times 260\times 58)}{(70\times(70\times 365))}=4.22\mathrm{E}-07\times\mathrm{ABS_S}\times[\mathrm{CS}]\end{aligned}$$

9.3.2.2 Estimation of Average Daily Dose (ADD) for Non-carcinogenic Effects

For the soil ingestion pathway, the ADD (also, the non-carcinogenic CDI) is estimated for the different population groups (generally pre-selected as representative of the critical receptors in the risk assessment)—and the results are shown below.

- The non-carcinogenic CDI for children aged up to 6 years is calculated to be:

$$\begin{aligned}&\mathrm{NCIng}_{(1-6)}\\&=\frac{(\mathrm{CS}\times\mathrm{IR}\times\mathrm{CF}\times\mathrm{FI}\times\mathrm{ABS_S}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&\frac{([\mathrm{CS}]\times 200\times 1.00\mathrm{E}-06\times 1\times\mathrm{ABS_S}\times 330\times 5)}{(16\times(5\times 365))}=1.13\mathrm{E}-05\times\mathrm{ABS_S}\times[\mathrm{CS}]\end{aligned}$$

- The non-carcinogenic CDI for children aged 6 to 12 years is calculated to be:

$$\begin{aligned}&\mathrm{NCIng}_{(1-12)}\\&=\frac{(\mathrm{CS}\times\mathrm{IR}\times\mathrm{CF}\times\mathrm{FI}\times\mathrm{ABS_S}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&\frac{([\mathrm{CS}]\times 100\times 1.00\mathrm{E}-06\times 1\times\mathrm{ABS_S}\times 330\times 6)}{(29\times(6\times 365))}=3.12\mathrm{E}-06\times\mathrm{ABS_S}\times[\mathrm{CS}]\end{aligned}$$

- The non-carcinogenic CDI for adult residents is calculated to be:

$$\begin{aligned}&\mathrm{NCIng}_{(\mathrm{adultR})}\\&=\frac{(\mathrm{CS}\times\mathrm{IR}\times\mathrm{CF}\times\mathrm{FI}\times\mathrm{ABS_S}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&\frac{([\mathrm{CS}]\times 50\times 1.00\mathrm{E}-06\times 1\times\mathrm{ABS_S}\times 330\times 58)}{(70\times(58\times 365))}=6.46\mathrm{E}-07\times\mathrm{ABS_S}\times[\mathrm{CS}]\end{aligned}$$

- The non-carcinogenic CDI for adult workers is calculated to be:

$$\begin{aligned}&\mathrm{NCIng}_{(\mathrm{adultW})}\\&=\frac{(\mathrm{CS}\times\mathrm{IR}\times\mathrm{CF}\times\mathrm{FI}\times\mathrm{ABS_S}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&\frac{([\mathrm{CS}]\times 50\times 1.00\mathrm{E}-06\times 1\times\mathrm{ABS_S}\times 260\times 58)}{(70\times(58\times 365))}=5.09\mathrm{E}-07\times\mathrm{ABS_S}\times[\mathrm{CS}]\end{aligned}$$

9.3.3 Illustrative Example for Dermal Exposures

The daily dermal intakes of contaminated soils for various population groups are calculated for both carcinogenic and non-carcinogenic effects. The assumed parameters used in the computational demonstration are provided in Table 9.1, and the electronic spreadsheet automation process shown in Table 9.2.

9.3.3.1 Estimation of Lifetime Average Daily Dose (LADD) for Carcinogenic Effects

For the soil dermal contact pathway, the LADD (also, the carcinogenic CDI) is estimated for the different population groups (generally pre-selected as representative of the critical receptors in the risk assessment)—and the results are shown below.

- The carcinogenic CDI for children aged up to 6 years is calculated to be:

$$\begin{aligned}&\mathrm{CDEX}_{(1-6)}\\&=\frac{(\mathrm{CS}\times\mathrm{CF}\times\mathrm{SA}\times\mathrm{AF}\times\mathrm{ABS_S}\times\mathrm{SM}\times\mathrm{EF}\times\mathrm{ED})}{\mathrm{BW}\times\mathrm{AT}}\\&=\frac{([\mathrm{CS}]\times 1.00-06\times 1396\times 0.75\times\mathrm{ABS_S}\times 0.15\times 330\times 5)}{(16\times(70\times 365))}\\&=6.34\mathrm{E}-07\times\mathrm{ABS_S}\times[\mathrm{CS}]\end{aligned}$$

- The carcinogenic CDI for children aged 6 to 12 years is calculated to be:

$$\begin{aligned}
&\mathrm{CDEX}_{(6-12)} \\
&= \frac{(\mathrm{CS} \times \mathrm{CF} \times \mathrm{SA} \times \mathrm{AF} \times \mathrm{ABS_S} \times \mathrm{SM} \times \mathrm{EF} \times \mathrm{ED})}{\mathrm{BW} \times \mathrm{AT}} \\
&= \frac{([\mathrm{CS}] \times 1.00 - 06 \times 2094 \times 0.75 \times \mathrm{ABS_S} \times 0.15 \times 330 \times 6)}{(29 \times (70 \times 365))} \\
&= 6.30\mathrm{E} - 07 \times \mathrm{ABS_S} \times [\mathrm{CS}]
\end{aligned}$$

- The carcinogenic CDI for adult residents is calculated to be:

$$\begin{aligned}
&\mathrm{CDEX}_{(\mathrm{adultR})} \\
&= \frac{(\mathrm{CS} \times \mathrm{CF} \times \mathrm{SA} \times \mathrm{AF} \times \mathrm{ABS_S} \times \mathrm{SM} \times \mathrm{EF} \times \mathrm{ED})}{\mathrm{BW} \times \mathrm{AT}} \\
&= \frac{([\mathrm{CS}] \times 1.00 - 06 \times 1815 \times 0.75 \times \mathrm{ABS_S} \times 0.15 \times 330 \times 58)}{(70 \times (70 \times 365))} \\
&= 2.19\mathrm{E} - 06 \times \mathrm{ABS_S} \times [\mathrm{CS}]
\end{aligned}$$

- The carcinogenic CDI for adult workers is calculated to be:

$$\begin{aligned}
&\mathrm{CDEX}_{(\mathrm{adultW})} \\
&= \frac{(\mathrm{CS} \times \mathrm{CF} \times \mathrm{SA} \times \mathrm{AF} \times \mathrm{ABS_S} \times \mathrm{SM} \times \mathrm{EF} \times \mathrm{ED})}{\mathrm{BW} \times \mathrm{AT}} \\
&= \frac{([\mathrm{CS}] \times 1.00\mathrm{E} - 06 \times 1815 \times 0.75 \times \mathrm{ABS_S} \times 0.15 \times 260 \times 58)}{(70 \times (70 \times 365))} \\
&= 1.72\mathrm{E} - 06 \times \mathrm{ABS_S} \times [\mathrm{CS}]
\end{aligned}$$

9.3.3.2 Estimation of Average Daily Dose (ADD) for Non-carcinogenic Effects

For the soil dermal contact pathway, the ADD (also, the non-carcinogenic CDI) is estimated for the different population groups (generally pre-selected as representative of the critical receptors in the risk assessment)—and the results are shown below.

- The non-carcinogenic CDI for children aged up to 6 years is calculated as follows:

$$\begin{aligned}
&\mathrm{NCDEX}_{(1-6)} \\
&= \frac{(\mathrm{CS} \times \mathrm{CF} \times \mathrm{SA} \times \mathrm{AF} \times \mathrm{ABS_S} \times \mathrm{SM} \times \mathrm{EF} \times \mathrm{ED})}{\mathrm{BW} \times \mathrm{AT}} \\
&= \frac{([\mathrm{CS}] \times 1.00\mathrm{E}-06 \times 1396 \times 0.75 \times \mathrm{ABS_S} \times 0.15 \times 330 \times 5)}{(16 \times (5 \times 365))} \\
&= 8.87\mathrm{E}-06 \times \mathrm{ABS_S} \times [\mathrm{CS}]
\end{aligned}$$

- The non-carcinogenic CDI for children aged 6 to 12 years is calculated to be:

$$\begin{aligned}
&\mathrm{NCDEX}_{(6-12)} \\
&= \frac{(\mathrm{CS} \times \mathrm{CF} \times \mathrm{SA} \times \mathrm{AF} \times \mathrm{ABS_S} \times \mathrm{SM} \times \mathrm{EF} \times \mathrm{ED})}{\mathrm{BW} \times \mathrm{AT}} \\
&= \frac{([\mathrm{CS}] \times 1.00\mathrm{E}-06 \times 2094 \times 0.75 \times \mathrm{ABS_S} \times 0.15 \times 330 \times 6)}{(29 \times (6 \times 365))} \\
&= 7.34\mathrm{E}-06 \times \mathrm{ABS_S} \times [\mathrm{CS}]
\end{aligned}$$

- The non-carcinogenic CDI for adult residents is calculated to be:

$$\begin{aligned}
&\mathrm{NCDEX}_{(\mathrm{adultR})} \\
&= \frac{(\mathrm{CS} \times \mathrm{CF} \times \mathrm{SA} \times \mathrm{AF} \times \mathrm{ABS_S} \times \mathrm{SM} \times \mathrm{EF} \times \mathrm{ED})}{\mathrm{BW} \times \mathrm{AT}} \\
&= \frac{([\mathrm{CS}] \times 1.00\mathrm{E}-06 \times 1815 \times 0.75 \times \mathrm{ABS_S} \times 0.15 \times 330 \times 58)}{(70 \times (58 \times 365))} \\
&= 2.64\mathrm{E}-06 \times \mathrm{ABS_S} \times [\mathrm{CS}]
\end{aligned}$$

- The non-carcinogenic CDI for adult workers is calculated to be:

$$\begin{aligned}
&\mathrm{NCDEX}_{(\mathrm{adultW})} \\
&= \frac{(\mathrm{CS} \times \mathrm{CF} \times \mathrm{SA} \times \mathrm{AF} \times \mathrm{ABS_S} \times \mathrm{SM} \times \mathrm{EF} \times \mathrm{ED})}{\mathrm{BW} \times \mathrm{AT}} \\
&= \frac{([\mathrm{CS}] \times 1.00\mathrm{E}-06 \times 1815 \times 0.75 \times \mathrm{ABS_S} \times 0.15 \times 260 \times 58)}{(70 \times (58 \times 365))} \\
&= 2.08\mathrm{E}-06 \times \mathrm{ABS_S} \times [\mathrm{CS}]
\end{aligned}$$

9.4 Refining the Human Chemical Exposure Estimates

To be certain realistic human exposure estimates are generated to support public health risk assessments, a variety of refinements may have to be undertaken during an exposure determination phase of a study; this may be particularly important when one is carrying out comprehensive exposure assessments. Some of the key attributes recommended for serious consideration in any efforts to refine chemical exposure estimates (and therefore the consequential risk estimates) are discussed below.

9.4.1 Incorporating Chemical Bioavailability Adjustments into Exposure Calculations

Bioavailability is defined as the fraction of a chemical that is taken up by the body's circulatory system relative to the amount that an organism is exposed to during, for instance, the ingestion of a chemical-laden material of interest. Incontrovertibly, bioavailability is a rather important concept in risk determination—especially because exposure and risk are more closely related to the bioavailable fraction of a chemical than to its total concentration in any given media/matrix; thus, this would tend to have significant implications in determining any 'safe' levels of chemicals in an exposure medium. Invariably, the amount of contacted material that is bioavailable for absorption is very important in the evaluation of human exposure to chemicals.

Bioavailability can be influenced by external physical/chemical factors such as the form of a chemical in the exposure media, as well as by internal biological factors such as absorption mechanisms within a living organism. For example, the oral bioavailability of a chemical compound is often characterized as a function of two key elements—*bioaccessibility* and *absorption* (Paustenbach et al. 1997). *Bioaccessibility* describes the fraction of the chemical that desorbs from its matrix (e.g., soil, dust, wood, food, drinks, drugs/medicines, etc.) in the gastrointestinal (GI) tract and, therefore, is available for absorption; and *absorption* describes the transfer of a chemical across a biological membrane into the blood circulation. Broadly speaking, the bioavailability of a CoPC may be estimated by multiplying the fraction of the chemical that is bioaccessible and the fraction that is absorbed. Thus, as an example, a bioaccessibility of Pb in soil of 60%, combined with an absorption ratio of Pb in young children of 50% yields a total bioavailability of 30%; and similarly, a bioaccessibility of Pb in water of 100%, combined with an absorption fraction of Pb in young children of 50% yields a total bioavailability of 50%. Meanwhile, it is notable that bioavailablity can be media-specific; for instance, the bioavailability of metals ingested in a soil matrix is generally believed to be considerably lower than the bioavailability of the same metals ingested in water.

Overall, bioavailability has a direct and significant relationship to exposure dose and risk; among other things, a lower bioavailability means a decrease in exposure dose and risk—and, conversely, higher bioavailability implies an increased exposure dose and risk. Indeed, bioavailability generally refers to how much of a chemical is 'available' to have an adverse effect on humans or other organisms. Consequently, knowledge of chemical bioavailability can play key roles in risk management decisions. For example, bioavailability adjustments in risk assessment can help establish reduced time and cost necessary for site remediation; in this case, bioavailability would be inversely related to risk-based cleanup levels—i.e., lower bioavailability results in increased risk-based cleanup levels. In fact, when risk assessments are adjusted to account for lower case-specific bioavailability, the resulting increase in cleanup levels can, in some cases, reduce remediation costs substantially. This is because, determining the site-specific bioavailability can allow for a revising of the exposure estimates—so as to more realistically and pragmatically reflect the conditions at a project site.

9.4.2 Chemical Transformation Products in Risk Assessment: Incorporating Chemical Degradation into Exposure Calculations

Many chemicals are transformed to structurally related degradation/daughter products in the environment before they are mineralized (e.g., DDE formed out of DDT)—with each of the resultant transformation products tending to display their own toxicity and persistence characteristics. Indeed, when certain chemical compounds undergo degradation, potentially more toxic daughter products result (such as is the case when trichloroethylene (TCE) biodegrades to produce vinyl chloride). On the other hand, there are situations where the end-products of degradation are less toxic than the parent compounds. Consequently, it is often imperative to include pertinent data on such transformation products into chemical exposure and risk assessments—albeit this often adds another layer of complexity to the overall exposure and risk assessment process, especially because, among other things, toxicity data for the daughter products may often be lacking.

In fact, since receptor exposures could be occurring over long time periods, a more valid approach in exposure modeling will be to take chemical degradation (or indeed other transformation processes) into consideration during an exposure assessment. Under such circumstances, if significant degradation is likely to occur, then exposure calculations become much more complicated. In that case, chemical concentrations at exposure or release sources are calculated at frequent and short time intervals, and then summed over the exposure period.

To illustrate the concept of incorporating chemical degradation into exposure assessment, let us assume first-order kinetics for a hypothetical chemical exposure problem. An approximation of the degradation effects for this type of scenario can

be obtained by multiplying the chemical concentration data by a degradation factor, *DGF*, defined by:

$$DGF = \frac{1 - e^{-kt}}{kt} \tag{9.8}$$

where: k is a chemical-specific degradation rate constant [days^{-1}] and t is the time period over which exposure occurs [days]. For a first-order decaying substance, k is estimated from the following relationship:

$$T_{1/2}\,[\text{days}] = \frac{0.693}{k} \quad \text{or} \quad k\left[\text{days}^{-1}\right] = \frac{0.693}{T_{1/2}} \tag{9.9}$$

where $T_{1/2}$ is the chemical half-life, which is the time after which the mass of a given substance will be one-half its initial value.

It is noteworthy that, the degradation factor is usually ignored in most exposure calculations; this is especially justifiable if the degradation product is of potentially equal toxicity, and is present in comparable amounts as the parent compound. In any case, although it cannot always be proven that the daughter products will result in receptor exposures that are at comparable levels to the parent compound, the DGF term is still ignored in most screening-level exposure assessments. Anyhow, as necessary, various methods of approach may be utilized to incorporate transformation products into exposure and risk assessment of the parent compounds. For instance, Fenner et al. (2002) offer some elaborate procedures that integrate the chemical transformation kinetics into the overall assessment—by calculating the environmental exposure to parent compounds and daughter products as they are being formed in the degradation/transformation cascade, and then subsequently developing a corresponding risk quotient.

9.4.3 Receptor Age Adjustments to Human Exposure Factors

Age adjustments are often necessary when human exposures to a chemical occur from childhood through the adult life. Such adjustments are meant to account for the transitioning of a potential receptor from childhood (requiring one set of intake assumptions and exposure parameters) into adulthood (that requires a different set of chemical intake assumptions and exposure parameters). Indeed, in the processes involved in human exposure assessments, it frequently becomes very apparent that contact rates can be significantly different for children *vs.* adults. Consequently, carcinogenic risks (that are averaged over a receptor's lifetime) should preferably be calculated by applying the appropriate age-adjusted factors—such as shown in Box 9.16 (or similar ones). Further details on the development of age-adjusted factors are provided elsewhere in the literature (e.g., DTSC 1994; OSA 1992;

USEPA 1989b, 1997a, b, c, d, e, f, g, h, 1998a, b, c, d, 2000, 2004a, b, c, d, e, f, g, 2011, 2014).

The use of age-adjusted factors are especially important in certain specific situations—such as those involving human soil ingestion exposures, which are typically higher during childhood and decrease with age. For instance, because the soil ingestion rate is generally different for children and adults, the carcinogenic risk due to direct ingestion of soil should preferably be calculated using an age-adjusted ingestion factor. This takes into account the differences in daily soil ingestion rates, body weights, exposure fraction, and exposure duration for the two exposure groups—albeit exposure frequency may be assumed to be the same for the two 'quasi-divergent' groups. If calculated in this manner, then the estimated exposure/intake factor will result in a more realistic, yet health-protective, risk evaluation—compared to, for instance, using an 'adult-only' type of assumption. Indeed, in a refined and comprehensive evaluation, it is generally recommended to incorporate age-adjustment factors in the chemical exposure assessment, wherever appropriate. On the contrary, and for the sake of simplicity, such types of age adjustment will usually not be made part of most screening-level computational processes in an exposure/risk assessment.

9.4.4 Spatial and Temporal Averaging of Chemical Exposure Estimates

Oftentimes, in major public health policy decisions, it becomes necessary to evaluate chemical exposure situations for population groups—rather than for individuals only. In such type of more practical and realistic chemical exposure assessment, it usually is more appropriate (and indeed less conservative) to estimate chemical exposure to a specific population subgroup over an exposure duration of less than a lifetime, as illustrated by the exposure combination scenarios presented below.

Box 9.16 Age-adjustment factors to human exposure calculations

Ingestion (mg-yr./kg-d or L-yr./kg-d)

$$INGf_{adj} = \frac{(\mathrm{MIR_c} \times \mathrm{ED_c})}{\mathrm{BW_c}} + \frac{(\mathrm{MIR_a} \times [\mathrm{ED} - \mathrm{ED_c}])}{\mathrm{BW_c}}$$

$$= \left[\frac{(\mathrm{MIR}_c \times \mathrm{ED}_c}{BW_c}\right] + \left[\frac{(\mathrm{MIR}_a \times \mathrm{ED}_a}{BW_a}\right]$$

Dermal contact (mg-yr./kg-d)

(continued)

Box 9.16 (continued)

$$DERf_{adj} = \frac{(\mathrm{AF} \times \mathrm{SA_c} \times \mathrm{ED_c})}{\mathrm{BW_c}} + \frac{(\mathrm{AF} \times \mathrm{SA_a} \times [\mathrm{ED} - \mathrm{ED_c}])}{\mathrm{BW_a}}$$

Inhalation (m^3-yr./kg-d)

$$INHf_{adj} = \frac{(\mathrm{IRF} \times \mathrm{ED_c})}{\mathrm{BW_c}} + \frac{(\mathrm{IRA_a} \times [\mathrm{ED} - \mathrm{ED_c}])}{\mathrm{BW_a}}$$

where:
$INGf_{adj}$ = age-adjusted ingestion factor (mg-yr./kg-d)
$DERf_{adj}$ = age-adjusted dermal contact factor (mg-yr./kg-d)
$INHf_{adj}$ = age-adjusted inhalation factor (m^3-yr./kg-d)
$\mathrm{MIR_c}$ = material ingestion rate – child (mg/day or L/day)
$\mathrm{MIR_a}$ = material ingestion rate – adult (mg/day or L/day)
AF = material adherence factor (mg/cm^2)
$\mathrm{SA_c}$ = child's exposed surface area (cm^2)
$\mathrm{SA_a}$ = adult's exposed surface area (cm^2)
$\mathrm{IRA_c}$ = inhalation rate – child (m^3/day)
$\mathrm{IRA_a}$ = inhalation rate – adult (m^3/day)
ED = total exposure duration (years)
$\mathrm{ED_c}$ = exposure duration – child (years)
$\mathrm{ED_a}$ = exposure duration – adult (years)
$\mathrm{BW_c}$ = body weight – child, i.e., the average child body weight over the exposure period (kg)
$\mathrm{BW_a}$ = body weight – adult, i.e., the average adult body weight over the exposure period (kg)

- *Averaging exposure over population age groups—when chemical concentrations are constant in time*. For situations where chemical concentrations are assumed constant over time but for which exposure is to be averaged over population age groups, the chronic daily exposure may be estimated using the following model form (CDHS 1990; OSA 1992; USEPA 1992a, b, c, d, e):

$$CDI = \left\{ \frac{1}{\sum_{a=1}^{NG} AT_a} \right\} \times \left\{ \sum_{a=1}^{NG} \left[\frac{CR}{BW} \right]_a \times EF_a \times ED_a \right\} \times C_m \tag{9.10}$$

where: $\left[\frac{CR}{BW}\right]_a$ is the contact rate per unit body weight, averaged over the age group *a*; *EFa* is the exposure frequency of the exposed population in the age

group/category *a*; *EDa* is the exposure duration for the exposed population in the age group/category *a*; *ATa* is the averaging time for the age group *a*; *Cm* is the concentration in the 'chemical-based' medium contacted; and *NG* is the number of age groups used to represent the whole population.

- *Averaging exposure over time within a population group—when chemical concentrations vary in time*. For some chemical compounds present in consumer products and/or in the environment, the assumption that concentrations remain constant in time can result in significant overestimation of risks. Consequently, a model that accounts for time-varying concentrations may be utilized in the chemical exposure estimation process.

  Overall, if chemical concentrations in the source medium or material varies with time—such as for cases where there are chemicals volatilizing from a contaminated site, or are being transformed by degradational processes—then exposures or chronic daily intakes for the exposed population may be estimated using the following general model form (CDHS 1990; OSA 1992; USEPA 1992a, b, c, d, e, 1998a, b, c, d, 2000, 2004a, b, c, d, e, f, g, 2011, 2014):

$$CDI = \left\{ \frac{[CR_m \times EF \times ED]}{[BW \times AT]} \right\} \times \left\{ \int_{t=0}^{ED} C_m(t)dt \right\} \tag{9.11}$$

  where *CRm* is the contact rate in medium *m*; *EF* is the exposure frequency of the exposed population; *ED* is the exposure duration for the exposed population; *AT* is the averaging time for the population group; and *Cm(t)* is the time-varying concentration in the 'chemical-based' medium contacted. It should be noted, however, that when one chemical species is transformed such that its concentration decreases in time, then all decay products must also be identified and documented. Indeed, exposure to all toxic decay products must be modeled and accounted for under such circumstances—recognizing also that the concentrations of decay products could actually be increasing with time.

- *Averaging exposure over population age sub-groups—when chemical concentrations vary with time*. In some situations involving time-varying chemical concentrations, it may be decided to estimate the exposure to specific population subgroups over exposure duration of less than a lifetime, and then to use these age subgroups to calculate the lifetime equivalent chemical exposure to an individual drawn at random from the population. Under such circumstances, the following model form can be employed in the chemical exposure estimation (CDHS 1990; OSA 1992; USEPA 1992a, b, c, d, e, 1998a, b, c, d, 2000, 2004a, b, c, d, e, f, g, 2011, 2014):

$$CDI = \left\{ \frac{1}{\sum_{a=1}^{NG} AT_a} \right\} \times \left\{ \sum_{a=1}^{NG} \left[\frac{CR}{BW} \right]_a \times EF_a \times \int_{t=0}^{ED} C_m(t)dt \right\} \tag{9.12}$$

where: $\left[\frac{CR}{BW}\right]_a$ is the contact rate per unit body weight, averaged over the age group *a*; *EFa* is the exposure frequency of the exposed population in the age group/category *a*; *EDa* is the exposure duration for the exposed population in the age group/category *a*; *ATa* is the averaging time for the age group *a*; *Cm(t)* is the time-varying concentration in the 'chemical-based' medium contacted; and *NG* is the number of age groups used to represent the whole population.

Further details on the evaluation processes involved in the spatial and temporal averaging techniques for chemical exposure problems can be found elsewhere in the literature (e.g., CDHS 1990; OSA 1992; USEPA 1992a, b, c, d, e, 1998a, b, c, d, 2000, 2004a, b, c, d, e, f, g, 2011, 2014).

9.5 Contemporary and Emerging Concepts in Exposure Assessment: The 'Exposome' and 'Exposomics' Paradigm

Chemical exposure assessments can be a rather complex undertaking—particularly if it is being designed or formulated to serve as a reliable predictor of diseases in relation to public health risk assessment and management. Thus, novel concepts and models are often explored to help better support exposure determinations for various chemical exposure scenarios; of significant interest in this regard are the concepts of *exposome* and *exposomics*.

The concept of the *exposome* was developed to draw attention to the critical need for a more comprehensive environmental exposure assessment—particularly in the arena of epidemiological studies. The 'exposome' can be defined as the measure of all the exposures of an individual in a lifetime, and how those exposures relate to health; invariably, an individual's exposure generally begins before birth—and typically would include insults (or assaults for that matter) from environmental and occupational sources (Rappaport 2011; Wild 2005; Wild 2012). Accordingly, the concept of the 'exposome' is generally considered as being comprised of all the environmental exposures to which a person is exposed from the time of conception, and throughout the course of the individual's entire life—thus representing the totality of exposures throughout the lifetime. In fact, a good understanding of how exposures from our environment, diet, lifestyle, etc. interact with our own unique characteristics (such as genetics, physiology, and epigenetics) to ultimately impact our health is basically how the exposome paradigm is expressed. In other words, all of the things that humans are exposed to, taken together, make up what is called the

'exposome'—thus providing a holistic look at how environmental exposures can keep us healthy, or make us sick for that matter.

Exposomics is the study of the exposome—and this generally relies on the application of 'internal' and 'external' exposure assessment methods. Most of the internal exposure methods typically include the use of biomarkers to determine exposure, effect of exposure, disease progression, and susceptibility factors; also, the common methods tend to rely on the use of data mining techniques to find statistical associations between exposures, effect of exposures, and other factors such as genetics with disease. External exposure assessment relies on measuring environmental stressors; common approaches include using direct reading instruments, laboratory-based analysis, and survey instruments. The extent to which internal and external exposure assessment can contribute to our understanding of the exposome is still under debate, as each approach has certain merits.

At the end of the day, a key factor in describing the exposome is the ability to accurately measure exposures and effects of exposures. Indeed, some obvious challenges that may limit the progress in this field of study are quite evident—especially considering that, among several other things, an individual's exposome is generally highly variable and dynamic throughout their lifetime. The impact of exposures can also vary with the individual's stage of life; for example, exposure to lead in infants and early childhood can lead to cognitive deficiencies, and exposures during early years may also predispose an individual to certain chronic diseases later in life—all of which might present difficult accounting mechanics. By the same token, the impact of environmental or occupational exposures can be different for each individual because of differences in genetic and other personal factors; for instance, some people may develop a disease whiles another person with the same or greater exposure will not. Broadly speaking, the exposome may help an analyst/investigator to determine the underlying causes for the above-noted differences (and indeed such similar ones)—albeit mapping an entire exposome for an individual will likely be difficult, if not impossible because of the complexity of a lifetime of exposures; furthermore, specific exposures can be difficult to measure due to lack of sensitive methods, or simply to a lack of knowledge as to whether an exposure has hitherto occurred or not. In fact, even when the exposure is known, measuring that exposure can be a rather difficult task—since the indicators of exposure may be transient, such as for most chemicals that are rapidly excreted, and for which only a short time frame exists to directly measure them. In other cases, however, past exposure can be defined using legacy biomarkers; a common example of a legacy biomarker is antibodies produced by exposures to environmental or occupational insults or hazards.

Overall, the exposome—conceptually and practically—provides a holistic view of human health and disease. It includes exposures from our diets, our lifestyles, and our behaviors. It also includes how our bodies respond to these challenges. When coupled with advances in genetics and medicine, it is believed that the exposome might help develop improved strategies aimed at preventing and treating certain diseases. Indeed, the exposome can be said to put the primary focus of exposure determinations directly back on human health. It moves exposure science

away from studying the relationships between source and receptor, and closer to studying the relationships between exposure and some kind of health-related outcome (Rappaport 2011). Meanwhile, it is worth the mention here that developing the exposome will generally need input from many disciplines—including exposure science, epidemiology, molecular biology, analytic chemistry, bioinformatics, and engineering.

Chapter 10
Determination of Chemical Toxicity

In planning for public health protection from the likely adverse effects of human exposure to chemicals, a primary concern usually relates to whether or not the substance in question possesses potentially hazardous and/or toxic properties. In practice, an evaluation of the toxicological effects typically consists of a compilation of toxicological profiles of the chemicals of potential concern (including the intrinsic toxicological properties of the chemicals—which may include their acute, subchronic, chronic, carcinogenic, and/or reproductive effects), as well as a determination of the relevant toxicity indices. This chapter discusses the major underlying concepts, principles, and procedures that are often employed in the evaluation of the hazard effects or toxicity of various chemical constituents found in consumer products and/or in the human environments.

10.1 Fundamental Concepts and Principles in Toxicology

Toxicology, in a broad sense, is the study of poisons and their effects on living organisms. In the context of environmental or public health, toxicology embodies the study of how specific chemical substances cause injury or undesirable effects to living cells and/or whole organisms. It generally consists of studies that are conducted to determine several fate and behavior, as well as effects attributes of the chemical of interest/concern on an organism—including the following:

- How easily the chemical enters the organism;
- How the chemical behaves in the organism;
- How rapidly the chemical is removed from the organism;
- What cells are affected by the chemical; and
- What cell functions are impaired as a consequence of the chemical exposure.

It is noteworthy that the traditional definition of *toxicology* has simply been: "the science of poisons"; with the increased understanding of how various chemical

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stressors or agents can cause harm to humans (and indeed other organisms), however, a more descriptive definition of toxicology has evolved—*viz*., 'the study of the adverse effects of chemicals or physical agents on living organisms'. It is also notable that the nature and degree of adverse effects may be wide-ranging—such as the realization of immediate death on one end, through to varying degrees of relatively more subtle changes not realized until several days, weeks, months or even years later; the effects may also occur at various levels within the body—such as an organ, a cell type, etc. (often referred to as 'endpoints' or 'target organs').

10.1.1 Mechanisms of Toxicity

Toxicity represents the state of being poisonous—and therefore may be said to indicate the state of adverse effects or symptoms being produced by toxicants in an organism. In general, toxicity tends to vary according to both the duration and location of the receptor that is exposed to the toxicant, as well as the receptor-specific responses of the exposed organism (Hughes 1996; Renwick et al. 2001; WHO 2010a, b). The prototypical processes that would usually be anticipated following the exposure of an organism to a toxic substance, up through the realization of a toxic response on such organism, may be exhibited by the use of varying degrees/levels of detail appropriate for the case-specific study or program (Fig. 10.1). Indeed, the more detailed the discussion or display of the intermediary processes that occur between the 'external dose' and the consequential or potentially 'toxic response', the better the chance to foster clearer understanding amongst most audiences—further to facilitating a more comprehensive and comprehensible risk determination.

Invariably, toxicants exert their effects when they interact with cells; such cellular interaction may occur on the surface of the cell, within the cell, or in the underlying tissues and extracellular (interstitial) space. Chemical characteristics of both the toxicant and cell membrane determine whether any interaction occurs on the surface of the cell or whether the barrier will be effective in keeping the toxicant out of the organism (Hughes 1996)—all these helping to determine or define the nature of toxic response and related outcomes. In any event, after a chemical substance is absorbed following human contact or intake, it travels through the bloodstream. Subsequently, where binding occurs with organs (especially, the liver, the kidneys, and the blood) in the body, toxic effects may result. Depending on the partitioning behavior between the chemical and different biomolecules of the human body (including fat), storage may or may not occur. Chemicals (or their transformation products) that are highly water-soluble and do not have the tendency to partition into fats are rapidly eliminated in the urine. However, organic chemicals characterized by high octanol-water partition coefficients (K_{ow}) (i.e., the hydrophobic compounds) are stored in fat. It is noteworthy that metals may also be stored via binding to fat and other biological molecules of the body—albeit in a different manner from the hydrophobic organic compounds. For example, lead can complex

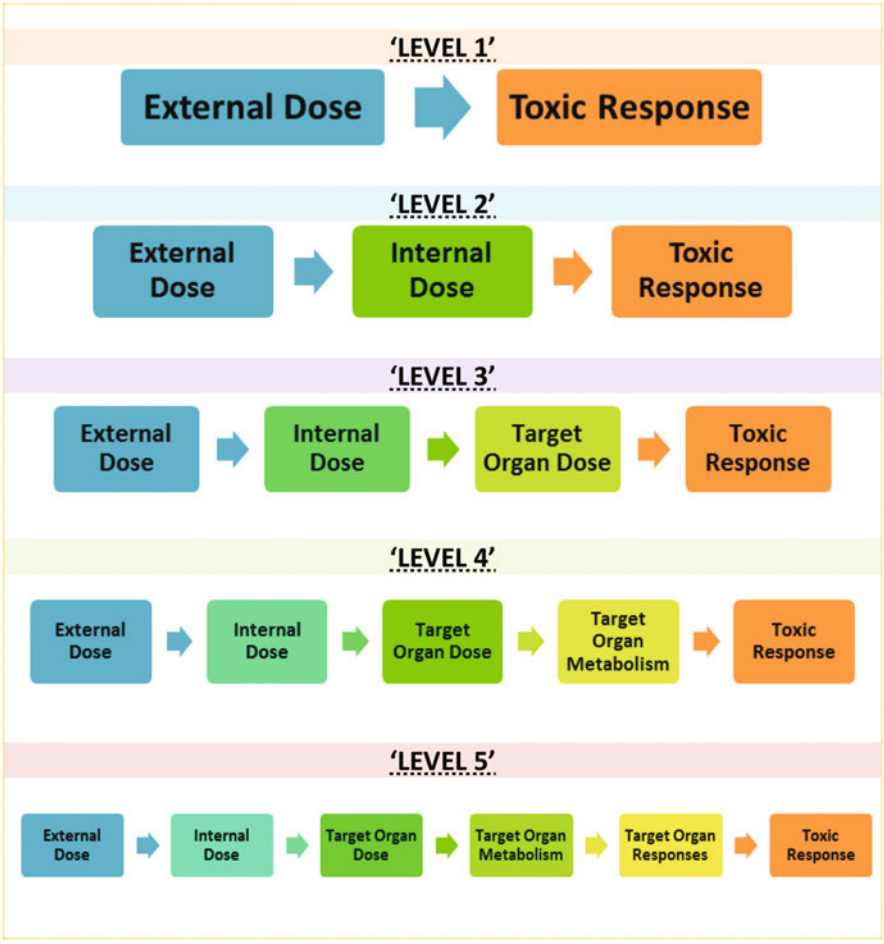

Fig. 10.1 Illustrative classic steps/pathways [from 'dose' to 'toxic response']—displaying varying degrees/levels of detail—that is typically assumed, upon exposure of an organism to a toxic substance

with biological molecules of the central nervous system; cadmium can bind to receptor molecules in the kidney, resulting in renal damage; etc.

In general, the important concepts relating to the mechanisms of toxicity for most toxic substances consider the following particularly relevant issues/attributes:

- Routes of chemical exposure and absorption;
- Distribution of the toxic chemical through the body;
- The biochemical transformation of the compound;
- Toxicant-receptor interactions;
- Storage of chemical; and
- Excretion of chemical.

Also, it is noteworthy that toxic effects could vary substantially depending on the location of contact and/or absorption of a chemical substance by the human receptor. For instance, whereas asbestos is highly toxic when inhaled, this material does not appear to exhibit any significant degree of toxicity when ingested—possibly attributable to its poor absorption in the gastrointestinal tract.

10.1.2 Categorization of Human Toxic Effects from Chemical Exposures: Carcinogenicity vs. *Non-carcinogenicity*

The toxic characteristics of a substance are usually categorized according to the organs or systems they affect (e.g., kidney, liver, nervous system, etc.), or the disease they cause (e.g., birth defects, cancer, etc.). In any case, chemical substances generally fall into one of the two broad categories of 'carcinogens' versus 'non-carcinogens'—customarily based, respectively, on their potential to induce cancer and their possession of systemic toxicity effects. Indeed, for the purpose of human health risk determination, chemical toxicants are usually distinctly categorized into carcinogenic and non-carcinogenic groups.

In general, chemicals that give rise to toxic endpoints other than cancer and gene mutations are often referred to as 'systemic toxicants' because of their effects on the function of various organ systems; the toxic endpoints are referred to as 'non-cancer' or 'systemic' toxicity. Most chemicals that produce non-cancer toxicity do not cause a similar degree of toxicity in all organs, but usually demonstrate major toxicity to one or two organs; these are referred to as the target organs of toxicity for the chemicals (Klaassen et al. 1986; USEPA 1989a, b, c, d, e, f). Also, it is apparent that chemicals that cause cancer and gene mutations would commonly evoke other toxic effects (*viz*., systemic toxicity) as well.

10.1.2.1 'Threshold' *vs*. 'Non-threshold' Concepts

Non-carcinogens commonly/traditionally are believed to operate by 'threshold' mechanisms—i.e., the manifestation of systemic effects requires a threshold level of exposure or dose to be exceeded during a continuous exposure episode. Thus, non-cancer or systemic toxicity is generally treated as if there is an identifiable exposure threshold below which there are no observable adverse effects—and this means that, in general, continuous exposure to levels below the threshold will produce no adverse or noticeable health effects. In fact, for many non-carcinogenic effects, protective mechanisms are believed to exist in the mammalian physiological system that must be overcome before the adverse effect of a chemical constituent is manifested. Consequently, a range of exposures exist from zero to some finite value—called the *threshold level*—that can be tolerated by the

exposed organism with essentially no likelihood of adverse effects. This characteristic distinguishes systemic endpoints from carcinogenic and mutagenic endpoints, which are often treated as 'non-threshold' processes; in other words, the threshold concept and principle is not quite applicable for carcinogens, since it is believed that no thresholds exist for this group. Indeed, carcinogenesis, unlike many non-carcinogenic health effects, is generally thought to be a phenomenon for which risk evaluation based on presumption of a threshold may be inappropriate (USEPA 1989a, b, c, d, e, f).

On the whole, it is usually assumed in risk assessments that, any finite exposure to carcinogens could result in a clinical state of disease. This hypothesized mechanism for carcinogenesis is referred to as 'non-threshold'—because it is believed that there is essentially no level of exposure to such a chemical that does not pose a finite probability, however small, of generating a carcinogenic response. Indeed, cancer effects have traditionally been considered to have no threshold—and thus, any exposure is associated with some risk. It is noteworthy, however, that among some professional groups, there is the belief that certain carcinogens require a threshold exposure level to be exceeded to provoke carcinogenic effects (e.g., Wilson 1996, 1997). In fact, opinion among regulatory scientists seems to have been returning to the somewhat 'ancient' presumption that at least some cancer-causing substances induce effects through a threshold process (Wilson 1997). This implies that, for such substances, there exists a finite level of exposure or dose at which no finite response is necessarily indicated. This perspective is based on the understanding among a number of toxicologists that most substances do not cause adverse effects unless exposures are sufficient to overwhelm the body's normal processes and defenses; under this view, the human body is able to accommodate various chemical, physical, and biological stresses at the subcellular and biochemical levels with control processes that adapt to and minimize the impact of chemical and other stressors—and only when the capacity of these protections is exceeded by high and sustained doses is an adverse impact to be expected. For instance, among others, Health Canada has noted the potential for a 'practical' threshold for genotoxic effects, for the most part attributable to the interplay between the genotoxicity and cellular DNA-repair mechanisms for the receptor/organism—albeit it is also assumed that all exposure levels have some concomitant risk.

Finally, it is noteworthy that cancer risks to humans are generally assessed differently for substances that act through a threshold mechanism compared to those acting via a non-threshold mechanism; yet still, most regulatory agencies in many different jurisdictions have only rarely considered the evidence to be strong enough to designate a threshold mechanism for carcinogens, and to support deviating from the conservative approach of assuming no-threshold for cancer risk assessments. As a case in point in relation to the 'no-threshold' concept, carcinogens have historically been regulated in the U.S. as though there is no dose below which there is zero risk of developing cancer. In fact, this seems to have remained the contemporary general practice despite the evidence that many substances probably contribute to cancer development only at doses above a certain threshold, i.e., at levels above low human exposures.

10.1.2.2 Mechanisms of Carcinogenicity

Carcinogenesis is the process by which normal tissue becomes cancerous—i.e., the production of cancer, most likely via a series of steps—*viz*., initiation, promotion, and progression; the carcinogenic event modifies the genome and/or other molecular control mechanisms of the target cells, giving rise to a population of altered cells. An important issue in chemical carcinogenesis relates to the concepts of 'initiators' and 'promoters.' An *initiator* is a chemical/substance or agent capable of starting but not necessarily completing the process of producing an abnormal uncontrolled growth of tissue, usually by altering a cell's genetic material; thus, initiated cells may or may not be transformed into tumors. A *promoter* is defined as an agent that results in an increase in cancer induction when it is administered some time after a receptor has been exposed to an *initiator*; thus, this represents an agent that is not carcinogenic in itself, but when administered after an initiator of carcinogenesis, serves to dramatically potentiate the effect of a low dose of a carcinogen—by stimulating the clonal expansion of the initiated cell to produce a neoplasm. Further yet, a *co-carcinogen* is an agent that is not carcinogenic on its own, but enhances the activity of another agent that is carcinogenic when administered together with the carcinogen; it is noteworthy that a *co-carcinogen* differs from a *promoter* only in that the former is administered at the same time as the initiator. It is believed that initiators, co-carcinogens, and promoters do not usually induce tumors when administered separately. Indeed, it has become apparent that a series of developmental stages is required for carcinogenesis—consisting of the following three key processes/steps (OSTP 1985):

1. *Initiation*, in which genetic damage occurs through a mutation to DNA; this involves a change in the capacity of DNA to function properly. This process basically refers to the first stage of carcinogenesis, and consists of the subtle alteration of DNA or proteins within target cells by carcinogens, which renders the cell capable of becoming cancerous.
2. *Promotion*, in which the genetic damage is expressed through the multiplication of cells in which initiation occurred previously. Basically this is the second hypothesized stage in a multistage process of cancer development, consisting of the conversion of initiated cells into tumorigenic cells; this occurs when initiated cells are acted upon by promoting agents to give rise to cancer.
3. *Progression,* which represents the spreading of cancer through an uncontrolled cell growth.

Many chemical carcinogens are believed to be *complete carcinogens*—i.e., chemicals that are capable of inducing tumors in animals or humans without supplemental exposure to other agents; thus, these chemicals function as both initiators and promoters. Generally speaking, the term 'complete' refers to the three stages of carcinogenesis (namely: initiation, promotion, and progression) that need to be present in order to induce a cancer. It should be acknowledged, however, that promoters themselves are usually not necessarily carcinogens; these

may include dietary fat, alcohols, saccharin, halogenated solvents, and estrogen. Even so, most regulatory agencies in many different jurisdictions do not usually distinguish between initiators and promoters, especially because it is often very difficult to confirm whether a given chemical acts by promotion alone, etc. (OSHA 1980; OSTP 1985; USEPA 1984b).

10.1.2.3 Identification of Carcinogens

Both human and animal studies are used in the evaluation of whether chemicals are possible human carcinogens. The strongest evidence for establishing a relationship between exposure to a given chemical and cancer in humans comes from epidemiological studies. These studies of human exposure and cancer must consider the latency period for cancer development, because apparently the exposure to the carcinogen often occurs many years (sometimes 20 to 30 years, or even more) before the first sign of cancer appears. On the other hand, the most common method for identifying substances as potential human carcinogens is by long-term animal bioassays. These bioassays provide accurate information about dose and duration of exposure, as well as interactions of the substance with other chemicals or modifiers. In these studies, the chemical, substance, or mixture is administered to one or, usually, two laboratory rodent species over a range of doses and durations of exposure with all experimental conditions carefully chosen to maximize the likelihood of identifying any carcinogenic effects (Huff 1993).

In general, experimental carcinogenesis research is based on the scientific assumption that chemicals causing cancer in animals will have similar effects in humans. It must be acknowledged, however, that it is not possible to predict with complete certainty from animal studies alone which agents, substances, mixtures, and/or exposure circumstances will be carcinogenic in humans. Conversely, all known human carcinogens that have been tested adequately also produce cancers in laboratory animals. In many cases, an agent was found to cause cancer in animals and only subsequently confirmed to cause cancer in humans (Huff 1993). In any event, it is noteworthy that, laboratory animals' adverse responses to chemicals (of which cancer is only one) do not always strictly correspond to similar or equivalent human responses. Yet still, laboratory animals remain the best tool for detecting potential human health hazards of all kinds, including cancer (OTA 1981; Tomatis et al. 1997).

10.1.3 Manifestations of Toxicity

Toxic responses, regardless of the organ or system in which they occur, can be of several types (USEPA 1985). For some, the *severity* of the injury increases as the dose increases. One of the goals of toxicity studies is to determine the 'no observed effect level' (NOEL)—which is the dose at which no toxic effect is seen in an

organism; this dose measure becomes an important input in the development of toxicity parameters for use in the risk assessment. For other cases, the severity of an effect may not necessarily increase with dose, but the *incidence* of the effects will increase with increasing dose; this type of response is properly characterized as probabilistic—since increasing the dose increases the probability (i.e., risk) that a specific abnormality or alteration will develop in the exposed population. In any event, with respect to toxic effects (including cancer), it is often to be expected that both the severity and the incidence would tend to increase as the level of exposure is raised. The increase in severity usually is a result of increased damage at higher doses, whereas the increase in incidence is a result of differences in individual sensitivity. Furthermore, the site at which a substance acts (e.g., kidney, liver, etc.) may change as the dose changes. In general, as the duration of exposure increases, both the NOEL and the doses at which effects appear decreases; in some cases, new effects not apparent upon exposure of short duration may additionally become manifest.

Toxic responses also vary in their degree of *reversibility*. In some cases, an effect will disappear almost immediately following cessation of exposure, whereas at the other extreme, exposures will result in a permanent injury. That is, *reversible* toxic effects are those that can be repaired, usually by a specific tissue's ability to regenerate or mend itself after a chemical exposure, whereas *irreversible* toxic effects are those that cannot be repaired. Most toxic responses tend to fall somewhere between these extremes.

Seriousness is yet another characteristic of a toxic response. Certain types of toxic damage are clearly adverse and are a definite threat to health, whereas other types of effects may not be of obvious health significance per se.

Finally, it is noteworthy that potential receptor populations (especially humans) tend to be exposed to mixtures of chemicals, as opposed to the single toxic agent scenario often presented in hazard evaluations. Consequently, several outcomes may result from chemical mixtures—including additive, synergistic, and antagonistic effects—that may have to be addressed differently, even if only qualitatively in some cases.

10.1.4 Dose-Response Relationships

The dose-response relationship is about the most fundamental concept in toxicology. A dose-response relationship exists when there is a consistent mathematical relationship that describes the proportion of test organisms responding to a specific dose of a toxicant/substance for a given exposure period. A number of assumptions usually will need to be considered when attempting to establish a dose-response relationship—most importantly, the following (Hughes 1996):

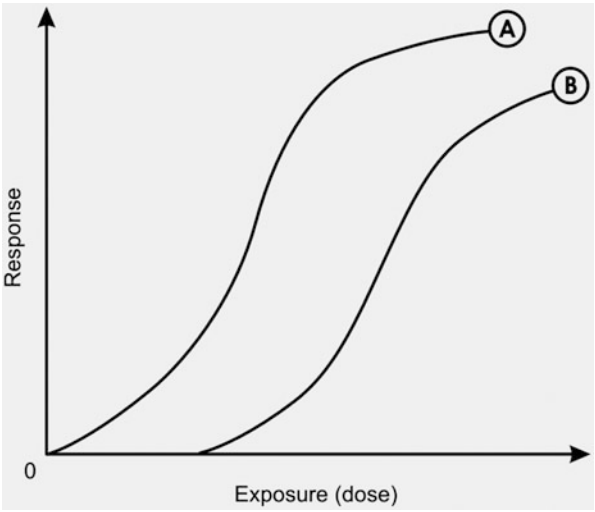

Fig. 10.2 Schematic representation of exposure-response relationships: Illustration of dose-response relationship for (**A**) = non-threshold chemicals (**B**) = threshold chemicals

- The observed response is caused by the substance administered to the organism;
- The magnitude of the response is directly related to the magnitude of the dose; and
- It is possible to correctly observe and measure a response.

In general, the relationship between the degree of exposure to a chemical (*viz*., the dose) and the magnitude of chemical-induced effects (*viz*., the response) is typically described by a dose-response curve. The typical dose-response curve is sigmoidal—but can also be linear, concave, convex, or bimodal; indeed, the general shape of the curve can offer clues as to the mechanism of action of the subject toxin, indicate multiple toxic effects, and identify the possible existence and extent of potentially sensitive sub-populations (Derelanko and Hollinger 1995).

Dose-response curves fall into the following two broad categories/groups (Fig. 10.2):

1. Those in which no response is observed until some minimum (i.e., threshold) dose is reached; and
2. Those in which no threshold is manifest—meaning that some type of response is expected for any dose, no matter how small.

In essence, for some chemicals, a very small dose causes no observable effects whereas a higher dose will result in some toxicity, and still higher doses cause even greater toxicity—up to the point of fatality; such chemicals are called *threshold chemicals* ('Curve B' in Fig. 10.2). For other chemicals, such as most carcinogens, the threshold concept may not be applicable—in which case no minimum level is required to induce adverse and overt toxicity effects ('Curve A' in Fig. 10.2).

Meanwhile, it should be acknowledged here that the most important part of the dose-response curve for a threshold chemical is the dose at which significant effects

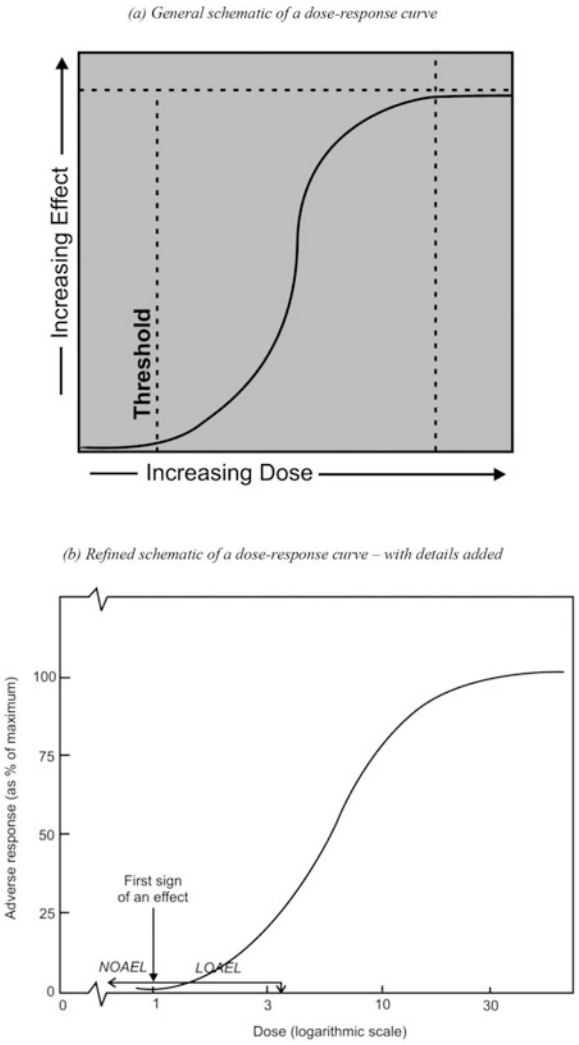

Fig. 10.3 Illustrative relationships of a typical dose-response curve for threshold chemicals. (**a**) General schematic of a dose-response curve. (**b**) Refined schematic of a dose-response curve—with details added

first begin to show (Fig. 10.3). The highest dose that does not produce an observable adverse effect is the 'no-observed-adverse-effect-level' (NOAEL), and the lowest dose that produces an observable adverse effect is the 'lowest-observed-adverse-effect-level' (LOAEL). For non-threshold chemicals, the dose-response curve behaves differently, in that there is no dose that is free of risk. Anyhow, at the end of the day, several important variables (Box 10.1) may help determine the characteristics of dose-response relationships—and these parameters should be given careful consideration when performing toxicity tests, and also when interpreting toxicity data (USEPA 1985). All these evaluations, however, may still be fraught with several uncertainties—best recapped in Rachel Carson's *Silent*

Spring, that: "When one is concerned with the mysterious and wonderful functioning of the human body, cause and effect are seldom simple and easily demonstrated relationships. They may be widely separated both in space and time. . . . . .The lack of sufficiently delicate methods to detect injury before symptoms appear is one of the great unsolved problems in medicine" (Carson 1962, 1994); indeed, although this observation was made several decades back, same concern will probably continue to hold true for some time to come.

Box 10.1 Important Parameters/Factors to Consider in Toxicity Assessments

- *Route of exposure:* The toxicity of some chemicals depends on whether the route of exposure is by inhalation, ingestion, or dermal contact. Also, there may be local responses at the absorption site (viz., lungs, gastrointestinal tract, and skin).
- *Duration/frequency of exposure:* The toxicity of many chemicals depends not only on dose (i.e., the amount of chemical contacted or absorbed each day) but also on the length of exposure (i.e., number of days, weeks, or years).
- *Test species characteristics:* Differences among species with respect to absorption, excretion or metabolism of chemicals, as well as several other factors (such as genetic susceptibility) should be carefully evaluated in the choice of appropriate animal test species.
- *Individual characteristics:* Individual members of a population (especially humans) are not identical, and usually do not respond identically to equal exposures to a chemical. It is therefore important to identify any subgroups that may be more sensitive to a chemical than the general population.
- *Toxicological endpoints:* This refers to the nature of toxic effects. The endpoints represent the changes detected in test animals, which become an index of the chemical's toxicity. Some commonly measured endpoints are carcinogenicity, hepatotoxicity (i.e., liver toxicity), mutagenicity, neurotoxicity, renal toxicity, reproductive toxicity, teratogenicity, etc. One of the most important parts of any toxicity study is the selection of the best endpoint to monitor—usually the most sensitive with respect to dose-response changes, the severity of effects, and whether effect is reversible or irreversible.

10.2 Carcinogen Classification Systems

Two prominent carcinogenicity evaluation philosophies—one based on 'weight-of-evidence' and the other on 'strength-of-evidence'—seem to have found the most common acceptance and widespread usage. Systems that employ the weight-of-

evidence evaluations consider and balance the negative indicators of carcinogenicity with those showing carcinogenic activity (Box 10.2); and schemes using the strength-of-evidence evaluations consider combined strengths of all positive animal tests (vis-à-vis human epidemiology studies and genotoxicity) to rank a chemical without evaluating negative studies, nor considering potency or mechanism (Huckle 1991). On the basis of the preceding, carcinogenic chemicals are generally classified into several categories, depending on the 'weight-of-evidence' or 'strength-of-evidence' available on a particular chemical's carcinogenicity (Hallenbeck and Cunningham 1988; Huckle 1991; IARC 1982, 2006; USDHS 1989, 2002; USEPA 1986a, b, c, d, e, f, 2005a, b, c, d, 2012).

Box 10.2 Summary of Pertinent/Comparative Factors Affecting the Weight-of-Evidence for Human Carcinogens

Factors increasing weight-of-evidence	*Factors decreasing weight-of-evidence*
• Evidence of human causality	• No evidence or relevant data showing human causality
• Evidence of animal effects relevant to humans	• No evidence or data on relevance of animal effects to humans
• Coherent inferences	• Conflicting data
• Comparable metabolism and toxicokinetics between species	• Metabolism and toxicokinetics between species not comparable
• Mode of action comparable across species	• Mode of action not comparable across species

A chemical's potential for human carcinogenicity is inferred from the available information relevant to the potential carcinogenicity of the chemical, and from judgments regarding the quality of the available studies. On the whole, carcinogens may be categorized into the following broad identifiable groupings (IARC 1982; Theiss 1983; USDHS 1989, 2002):

- *'Known human carcinogens'*—defined as those chemicals for which there exists sufficient evidence of carcinogenicity from studies in humans to indicate a causal relationship between exposure to the agent, substance, or mixture and human cancer.
- *'Reasonably anticipated to be human carcinogens'*—referring to those chemical substances for which there is limited evidence for carcinogenicity in humans and/or sufficient evidence of carcinogenicity in experimental animals. Sufficient evidence in animals is demonstrated by positive carcinogenicity findings in multiple strains and species of animals; in multiple experiments; or to an unusual

degree, with regard to incidence, site or type of tumor, or age of onset; or there is less than sufficient evidence of carcinogenicity in humans or laboratory animals.

- *'Sufficient evidence of carcinogenicity'* and *'Limited evidence of carcinogenicity'*—used in the criteria for judging the adequacy of available data for identifying carcinogens; it refers only to the amount and adequacy of the available evidence, and not to the potency of carcinogenic effect on the mechanisms involved.

Other varying carcinogen classification schemes also exist globally within various regulatory and legislative groups. Even so, it is apparent that the numerous agencies around the world and in various jurisdictions have schemes that are conceptually similar, but may vary in the specific descriptors and criteria used—e.g., as observed with systems maintained by the International Agency for Research on Cancer (IARC), US EPA, Health Canada, etc.; in actual fact, most of these nomenclatural systems are adapted or modified from the IARC classifications.

All in all, evidence of possible carcinogenicity in humans comes primarily from epidemiological studies and long-term animal exposure studies at high doses that have subsequently been extrapolated to humans. Results from these studies are supplemented with information from short-term tests, pharmacokinetic studies, comparative metabolism studies, molecular structure-activity relationships, and indeed other relevant information sources. Ultimately, conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment—with due consideration given to all relevant information. Characteristically, the relevant information includes, but is not limited to: dose-response, route-of-exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals—but then there also are compelling data indicating that the agent acts through mechanisms which do not operate in humans, and would therefore not reasonably be anticipated to cause cancer in humans.

In the final analysis, carcinogenicity classifications are used for a wide range of purposes—including human health risk assessments, regulatory decision-making, risk management, and cancer prevention measures. These classifications are based on an evaluation of both human and animal studies as well as supporting mechanistic data (i.e., studies at the cellular or molecular level). Because human evidence is scarce for most substances, animal studies generally provide most of the evidence for classification—albeit positive animal results are not always evidence of human carcinogenicity. At the end of it all, each of the classification schemes identifies the potential for a substance to cause cancer, but not necessarily how likely it is to occur at typical human exposure levels.

10.2.1 Weight-of-Evidence Classification and Narratives

A weight-of-evidence approach has been widely used by the US EPA regulatory body to classify the likelihood that an agent in question is a human carcinogen—ultimately producing a five-level classification scheme and corresponding narrative (USEPA 2012). This is a classification system for characterizing the extent to which available data indicate that an agent is a human carcinogen (or possesses some other toxic effects such as developmental toxicity). A three-stage procedure has typically been utilized in the process—namely:

- *Stage 1*—the evidence is characterized separately for human studies and for animal studies.
- *Stage 2*—the human and animal evidence are integrated into a presumptive overall classification.
- *Stage 3*—the provisional classification is modified (i.e., adjusted upwards or downwards), based on analysis of the supporting evidence.

The outcome of this process is that, chemicals are placed into one of five general categories—namely, Groups A-E (Box 10.3)—further discussed below. It is worth mentioning here that, the guidelines for classification of the weight-of-evidence for human carcinogenicity published by the US EPA (e.g., USEPA 1984b, 1986a, b, c, d, e, f, 2005a, b, c, d)—which basically consists of the categorization of the weight-of-evidence into the five groups—are indeed general adaptations from those maintained by the International Agency for Research on Cancer (IARC 1984, 1987, 1988).

Box 10.3 The US EPA Weight-of-Evidence Classification System and Descriptors for Potential Carcinogens

US EPA Group	*Reference Category*
A	Human carcinogen (*i.e.*, Carcinogenic—*or* known human carcinogen)
B	Probable human carcinogen (*i.e.*, Likely to be carcinogenic): B1 indicates limited human evidence B2 indicates sufficient evidence in animals and inadequate or no evidence in humans
C	Possible human carcinogen (*viz.*, Suggestive evidence)
D	Not classifiable as to human carcinogenicity (*viz.*, Inadequate information)
E	No Evidence of carcinogenicity in humans (or, Evidence of non-carcinogenicity for humans—*i.e.*, Not likely to be carcinogenic)

Further to the above, the following descriptors have more recently been recommended along with the corresponding weight-of-evidence narratives (USEPA 2005a, b, c, d):

- *Carcinogenic to Humans*—this descriptor indicates strong evidence of human carcinogenicity (including presence of convincing epidemiological evidence demonstrating causality between human exposure and cancer, or existence of compelling evidence of carcinogenicity in animals alongside mechanistic information that demonstrates a similar mode(s) of carcinogenic action in animals and in humans).
- *Likely to be Carcinogenic to Humans*—this descriptor is appropriate when the weight of evidence is adequate to demonstrate carcinogenic potential to humans.
- *Suggestive Evidence of Carcinogenic Potential*—this descriptor is appropriate when the weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion.
- *Inadequate Information to Assess Carcinogenic Potential*—this descriptor is appropriate when available data are judged inadequate for applying one of the other descriptors.
- *Not Likely to be Carcinogenic to Humans*—this descriptor is appropriate when the available data are considered robust for deciding that there is no basis for human hazard concern.

It is noteworthy that, more than one descriptor can indeed be used when the effects of a constituent differ by dose or exposure route. While these narrative descriptions represent important advances in carcinogen risk assessment, the alpha-numeric system still offers some very useful attributes.

Group A—Human Carcinogen, or 'Carcinogenic to Humans'.

For this group, there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agent and human cancer; in general, the following three criteria must be satisfied before a causal association can be inferred between exposure and cancer in humans (Hallenbeck and Cunningham 1988; USEPA 1986a, b, c, d, e, f, 2005a, b, c, d):

- No identified bias which could explain the association;
- Possibility of confounding factors (i.e., variables other than chemical exposure level which can affect the incidence or degree of the parameter being measured) has been considered and ruled out as explaining the association; and
- Association is unlikely to be due to chance.

Indeed, this group tends to be used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer—albeit, exceptionally, it may be used for lesser weight of epidemiological evidence, strengthened by other lines of evidence.

Group B—Probable Human Carcinogen, or 'Likely to be Carcinogenic to Humans'.

This group includes agents for which the weight-of-evidence of human carcinogenicity based on epidemiologic studies is 'limited'—and also includes agents for

which the weight-of-evidence of carcinogenicity based on animal studies is 'sufficient.' The category consists of agents for which the evidence of human carcinogenicity from epidemiologic studies ranges from almost sufficient to inadequate. Thus, there would be a demonstration of plausible (not definitively causal) association between human exposure and cancer.

Traditionally, this group has been divided into two subgroups—reflecting higher (Group B1) and lower (Group B2) degrees of evidence. Usually, category B1 is reserved for agents with which there is limited evidence of carcinogenicity to humans from epidemiologic studies; limited evidence of carcinogenicity indicates that a causal interpretation is credible—but then alternative explanations such as chance, bias, or confounding factors could not be excluded. Inadequate evidence indicates that one of the following two conditions prevailed: (1) there were few pertinent data; or (2) the available studies, while showing evidence of association, did not exclude chance, bias, or confounding factors (Hallenbeck and Cunningham 1988; USEPA 1986a, b, c, d, e, f, 2005a, b, c, d). When there are inadequate data for humans, it is reasonable to consider agents for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans. Therefore, agents for which there is 'sufficient' evidence from animal studies and for which there is 'inadequate' evidence from human (epidemiological) studies or 'no data' from epidemiologic studies would usually result in a classification as B2 (CDHS 1986; Hallenbeck and Cunningham 1988; USEPA 1986a, b, c, d, e, f, 2005a, b, c, d).

Group C—Possible Human Carcinogen, or 'Suggestive Evidence of Carcinogenic Potential'.

This group has been used for agents with limited evidence of carcinogenicity in animals in the absence of human data. Limited evidence means that the data suggest a carcinogenic effect, but are generally limited for the following reasons (Hallenbeck and Cunningham 1988; USEPA 1986a, b, c, d, e, f, 2005a, b, c, d):

- The studies involve a single species, strain, or experiment; or
- The experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or
- An increase in the incidence of benign tumors only.

On the whole, Group C classification essentially relies on a wide variety of evidence—including the following (Hallenbeck and Cunningham 1988; USEPA 1986a, b, c, d, e, f, 2005a, b, c, d): definitive malignant tumor response in a single well conducted experiment that does not meet conditions for 'sufficient' evidence; tumor response of marginal statistical significance in studies having inadequate design or reporting; benign but not malignant tumors, with an agent showing no response in a variety of short-term tests for mutagenicity; and responses of marginal statistical significance in a tissue known to have a high and/or variable background tumor rate.

Group D—Not Classifiable as to Human Carcinogenicity, or 'Inadequate Information to Assess Carcinogenic Potential'.

This group has generally been used for agents with inadequate animal evidence of carcinogenicity, and also inadequate evidence from human (epidemiological) studies. Inadequate evidence means that, because of major qualitative or quantitative limitations, the studies cannot necessarily be interpreted as showing either the presence or absence of a carcinogenic effect.

Group E—No Evidence of Carcinogenicity in Humans, or 'Not Likely to be Carcinogenic to Humans'.

This group has been used to describe agents indicating evidence of non-carcinogenicity for humans, together with no evidence of carcinogenicity in at least two adequate animal tests in different species, or no evidence in both adequate animal and human (epidemiological) studies. The designation of an agent as being in this group is based on the available evidence, and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

10.2.2 Strength-of-Evidence Classification

The International Agency for Research on Cancer (IARC) bases its classification on the so-called strength-of-evidence philosophy. Procedurally, the IARC assembles Working Groups for specific substances to make scientific judgments on the evidence for or against carcinogenicity (IARC 2006); the evidence from human and animal studies is evaluated separately, and then the full body of evidence is considered as a whole to categorize a substance into one of five groups. The corresponding IARC classification system (somehow comparable or equivalent to the US EPA system description presented above) is shown in Box 10.4—and further discussed below.

Box 10.4 The IARC Strength-of-Evidence Classification System and Descriptors for Potential Carcinogens

IARC Group	*Category*
1	Human carcinogen (i.e., Carcinogenic—Known human carcinogen)
2	Probable or Possible human carcinogen: 2A indicates limited human evidence (i.e., Probably carcinogenic) 2B indicates sufficient evidence in animals and inadequate or no evidence in humans (i.e., Possibly carcinogenic)
3	Not classifiable as to human carcinogenicity
4	No Evidence of carcinogenicity in humans (i.e., Probably *not* carcinogenic)

Group 1—Known Human Carcinogen.

This group is generally used for agents with sufficient evidence from human (epidemiological) studies as to human carcinogenicity. Thus, the Group 1 agent is essentially considered carcinogenic to humans.

Group 2—Probable or Possible Human Carcinogens.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient—as well as agents for which, at the other extreme, there are no human data but for which there is experimental evidence of carcinogenicity. Agents are assigned to either 2A (probably carcinogenic) or 2B (possibly carcinogenic) on the basis of epidemiological, experimental and other relevant data. These two subgroups are elaborated further in the proceeding sections below.

Group 2A—Probable Human Carcinogen. This group is generally used to represent agents for which there is sufficient animal evidence, evidence of human carcinogenicity, or at least limited evidence from human (epidemiological) studies. Indeed, these are probably carcinogenic to humans—and usually have at least limited human evidence.

On the whole, this category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. Exceptionally, an agent may be classified into this category solely on the basis of limited evidence of carcinogenicity in humans or of sufficient evidence of carcinogenicity in experimental animals, strengthened by supporting evidence from other relevant data.

Group 2B—Possible Human Carcinogen. This group is generally used to represent agents for which there is sufficient animal evidence but inadequate evidence from human (epidemiological) studies, or where there is limited evidence from human (epidemiological) studies in the absence of sufficient animal evidence. These are viewed as possibly carcinogenic to humans—but usually have no human evidence.

On the whole, this category is generally used for agents that indicate limited evidence in humans, in the absence of sufficient evidence in experimental animals. It may also be used when there is inadequate evidence of carcinogenicity in humans, or when human data are nonexistent but there is sufficient evidence of carcinogenicity in experimental animals. In some instances, an agent for which there is inadequate evidence or no data in humans but limited evidence of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

Group 3—Not Classifiable.

This group is generally used for agents for which there are inadequate animal evidence and inadequate evidence from human (epidemiological) studies—but where there is sufficient evidence of carcinogenicity in experimental animals. Overall, the Group 3 agent is not classifiable as to its carcinogenicity to humans—and agents are typically placed in this category when they do not fall into any other group.

Group 4—Non-carcinogenic to Humans.

This group is generally used for an agent or substance for which there is evidence to support a lack of carcinogenicity. The Group 4 agent is probably not carcinogenic to humans—and this category is essentially used for agents for which there is evidence suggesting lack of carcinogenicity in humans, together with evidence suggesting lack of carcinogenicity in experimental animals. Meanwhile, it is notable that under some circumstances, agents for which there is inadequate evidence of (or no data on) carcinogenicity in humans but for which there is evidence suggesting lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of other relevant data, may also be placed into this group.

10.3 Chemical Toxicity Assessment

Toxicity tests may reveal that a substance produces a wide variety of adverse effects on different organs or systems of the human body, or that the range of effects is narrow. Also, some effects may occur only at the higher doses used—and, in such cases, only the most sensitive indicators of a substance's toxicity may be manifest at the lower doses (USEPA 1985b). To help address these issues, toxicity studies are usually conducted to identify the nature of health damage produced by a substance, as well as the range of doses over which damage is produced (Box 10.5). In any event, the identification of toxic substances typically begins with the retrieval of a variety of pertinent information that is available on the suspected agent (Box 10.6); on the basis of such information, a more focused assessment protocol can be properly designed to meet both general and case-specific program or project objectives (CDHS 1986; Smith 1992).

Box 10.5 Summary Reasons for Conducting Toxicity Studies

- To identify the specific organs or systems of the body that may be damaged by a substance
- To identify specific abnormalities or diseases (such as cancer, birth defects, nervous disorders, or behavioral problems) that a substance may produce
- To establish the conditions of exposure and dose that give rise to specific forms of damage or disease
- To identify the specific nature and course of the injury or disease produced by a substance
- To identify the biological processes that underlie the production of observable damage or disease

Box 10.6 Typical Information Requirements for the Identification of Chemical Toxicity

- Physical and chemical properties
- Routes of exposure
- Metabolic and pharmacokinetic properties
- Structure-activity relationships
- Toxicological effects
- Short-term tests
- Long-term animal tests
- Human epidemiologic studies
- Clinical data

General methods of chemical toxicity assessment that are commonly used for determining the hazardous nature of substances include the following (Lave 1982; NRC 1991a, b, c; Talbot and Craun 1995):

- Case clusters
- Structural toxicology (structure-activity studies)
- Laboratory study of simple test systems
- Long-term animal bioassays
- Human (epidemiologic) studies

Case clusters are based on the identification of an abnormal pattern of disease. This procedure tends to be especially more powerful in identifying hazards when the resulting condition is extremely rare; the method is not very powerful in situations when the health condition is quite common in the general population. Since the population at risk is essentially never known in detail, the case cluster method necessarily yields no conclusive evidence—but only rather vague suspicions. *Structural toxicology* involves searching for similarities in chemical structure that might identify toxicological categories, such as carcinogens. The structure-activity studies seek to evaluate toxicity based on the substance's chemical structure; for instance, the close association between mutagens and carcinogens lead to a general presumption that mutagenic substances are also carcinogenic. *Animal bioassays* are laboratory experimentations, generally with rodents. In these types of studies, statistical models are used to extrapolate from animal bioassays to humans. *Epidemiologic studies* constitutes a more scientific, systematic form of case cluster analysis—with an attempt to control for confounding factors in the experimental design or statistical analysis. It examines the occurrence of disease in human populations and tries to determine the causes.

A comprehensive toxicity assessment with respect to chemical exposure problems is generally accomplished in two key steps, *viz*.: hazard effects assessment and dose-response assessment. These steps are elaborated below—and discussed in even greater detail elsewhere in the literature (e.g., Casarett and Doull 1975;

Klaassen et al. 1986, 1996; Lave 1982; NRC 1991a, b, c; Talbot and Craun 1995; USEPA 1989a, b, c, d, e, f).

10.3.1 Hazard Effects Assessment

Hazard effects assessment is the process used to determine whether exposure to an agent can cause an increased incidence of an adverse health effect (e.g., cancer, birth defects, etc.); it entails a characterization of the nature and strength of the evidence of causation. Broadly speaking, the process involves gathering and evaluating data on the types of health injury or disease that may be produced by a chemical, and on the conditions of exposure under which injury or disease is produced. Hazard assessment may also involve characterizing the behavior of a chemical within the receptor's body and the interactions it undergoes with organs, cells, or even parts of cells. Data of the latter types may be of value in answering the ultimate question of whether the forms of toxicity known to be produced by a substance in one population group or in experimental settings, are also likely to be produced in humans on a more 'global scale'.

The overall purpose of a hazard assessment is to review and evaluate data pertinent to answering questions relating to two key issues—namely:

1. Whether an agent may pose a hazard to potential receptors; and
2. Circumstances under which an identified hazard may be manifested.

To help address these issues, a comprehensive toxicity evaluation would typically become necessary; the assessment of the toxicity of a chemical substance involves identification of the adverse effects that the chemical causes, as well as a systematic study of how these effects depend upon dose, route and duration of exposure, and test organisms. This information is characteristically derived from studies falling into one of the following general protocols/categories (Cohrssen and Covello 1989; Derelanko and Hollinger 1995; Moeller 1997; USEPA 1985a, b):

- *Laboratory animal studies,* which evaluate the toxicity of a chemical with special reference and/or ultimate goal to predicting the toxicity in humans. Testing protocols in animals are designed to identify the principal adverse effects of a chemical as a function of dose, route of exposure, species and sex of test animals, and duration of exposure.
- *Clinical case studies in humans,* in which there are case-by-case investigations of the symptoms and diseases in humans who are exposed to a toxic substance at doses high enough to call for medical attention or intervention. Exposures may be accidental (e.g., a farmer applying pesticide without proper protection) or, in rare cases, intentional (e.g., suicide or homicide cases). Tragically, this sort of direct toxicological observation is especially valuable in characterizing toxic responses of clinical significance in humans—certainly far better than extrapolations from laboratory animals to humans.

- *Epidemiologic studies,* which seek to determine whether a correlation exists between chemical exposure and frequency of disease or health problems in large groups of human populations. It involves the examination of persons who have been inadvertently exposed to one or more chemical agents. Indeed, despite the many apparent problems inherent to epidemiological studies (especially with respect to the various biases, confounding factors, and inadequate quantitation of exposure), these studies offer a major advantage over those conducted with animals—chiefly because any consequential data are invariably derived from the direct observation of effects in humans. The major specific advantages of epidemiological studies are that they are based on large numbers of humans, and exposure levels are usually sub-clinical. Thus, the data are directly relevant—with no need to extrapolate from animal data, or to make projections from a small number of humans exposed to a high dose of the chemical (as necessary for clinical studies).

It is noteworthy that, since much of the uncertainty associated with most risk assessments arise from the extrapolation of animal data to humans, quality epidemiological studies can indeed significantly reduce or eliminate such uncertainty. Usually, however, the availability of quality epidemiological studies is limited—and, consequently, both human and animal data are preferably used together in the risk assessment process.

10.3.2 Dose-Response Assessment and Quantification

Dose-response assessment is the process of quantitatively evaluating toxicity information, and characterizing the relationship between the dose of the chemical administered or received (i.e., exposure to an agent) and the incidence of adverse health effects in the exposed populations. The process consists of estimating the potency of the specific compounds by the use of dose-response relationships. In the case of carcinogens, for example, this involves estimating the probability that an individual exposed to a given amount of chemical will contract cancer due to that exposure; potency estimates may be given as 'unit risk factor' (expressed in $\mu g/m^3$), or as 'potency slopes' (in units of $[mg/kg\text{-}day]^{-1}$). Data are generally derived from animal studies or, less frequently, from studies in exposed human populations.

The dose-response assessment first addresses the relationship of dose to the degree of response observed in an experiment or a human study. When chemical exposures are outside the range of observations, extrapolations are necessary—in order to be able to estimate or characterize the dose relationship. The extrapolations will typically be made from high to low doses, from animal to human responses, and/or from a specific route of exposure to a different one. The details of the extrapolation mechanics are beyond the scope of this discussion, but are briefly discussed below and elaborated at length elsewhere in the literature (e.g., Brown

1978; CDHS 1986; Crump 1981; Crump and Howe 1984; Gaylor and Kodell 1980; Gaylor and Shapiro 1979; Hogan 1983; Krewski and Van Ryzin 1981).

The dose-response relationships are typically used to determine what dose of a particular chemical causes specific levels of toxic effects to potential receptors. In fact, there may be many different dose-response relationships for any given substance if it produces different toxic effects under different conditions of exposure. In any case, the response of a given toxicant depends on the mechanism of its action; for the simplest scenario, the response, R, is directly proportional to its concentration, $[C]$, so that:

$$R = k \cdot [C] \tag{10.1}$$

where k is a rate constant. This would be the case for a chemical that metabolizes rapidly. Still, the response and the value of the rate constant would tend to differ for different risk groups of individuals and for unique exposures. If, for instance, the toxicant accumulates in the body, the response is better defined as follows:

$$R = k \cdot [C] \cdot t^n \tag{10.2}$$

where t is the time and n is a constant. For cumulative exposures, the response would generally increase with time. Thus, the cumulative effect may be shown as linear until a threshold is reached, after which secondary effects begin to affect and enhance the responses. Also, the cumulative effect may be related to what is referred to as the 'body burden' (BB). The body burden is determined by the relative rates of absorption (ABS), storage (STR), elimination (ELM), and biotransformation (BTF)—in accordance with the following relationship (Meyer 1983):

$$BB = ABS + STR - ELM - BTF \tag{10.3}$$

Each of the factors involved in the quantification of the body burden is dependent on a number of biological and physiochemical factors. In fact, the response of an individual to a given dose cannot be truly quantitatively predicted since it depends on many extraneous factors, such as general health and diet of individual receptors. Nonetheless, from the quantitative dose-response relationship, toxicity values can be derived and used to estimate the incidence of adverse effects occurring in potential receptors at different exposure levels.

In general, even if a substance is known to be toxic, the risks associated with the substance cannot be ascertained with any degree of confidence unless dose-response relationships are appropriately quantified. Meanwhile, it is noteworthy that, the fundamental principles underlying the dose-response assessment for carcinogenic chemicals remain arguable—especially in relation to the tenet that there is some degree of carcinogenic risk associated with every potential carcinogen, no matter how small the dose. This is because, the speculation and/or belief that chemically-induced cancer is a non-threshold process/phenomenon may be false after all—albeit it represents a conservative default policy necessary to ensure

adequate protection of human health; accordingly, this potential shortcoming should be kept in perspective in consequential policy decisions about the assessment.

10.3.2.1 The Nature of Dose-Response Extrapolation Models

Three major classes of mathematical extrapolation models are often used for relating dose and response in the sub-experimental dose range, namely:

- Tolerance Distribution models—including Probit, Logit, and Weibull;
- Mechanistic models—including One-hit, Multi-hit, and Multi-stage; and
- Time-to-Occurrence models—including Lognormal and Weibull.

Indeed, other independent models—such as linear, quadratic, and linear-cum-quadratic—may also be employed for this purpose. The details on all these wide-ranging types of models are beyond the scope of this discussion, but are elaborated elsewhere in the literature (e.g., Brown 1978; CDHS 1986; Crump 1981; Crump and Howe 1984; Gaylor and Kodell 1980; Gaylor and Shapiro 1979; Hogan 1983; Krewski and Van Ryzin 1981, Tan 1991). At any rate, the primary models typically used to extrapolate from non-threshold effects associated with carcinogenic responses that are observed at high doses to responses at low doses include the following (Derelanko and Hollinger 1995; Jolley and Wang 1993; Tan 1991):

- *Linearized multistage (LMS) model*—which assumes that there are multiple stages to cancer; it fits curve to the experimental data, and is linear from the upper confidence level to zero. Specifically, it is based on the assumption that the induction of irreversible self-replicating toxic effects is the result of a number of random biological events, the occurrence of each being in strict linear proportion to the dose rate.
- *One-hit model*—which assumes there is a single stage for cancer, and that one molecular or radiation interaction induces malignant change. This is indeed a very conservative model, and corresponds to the simplest mechanistic model of carcinogenesis. The model is based on the concept that a response will occur after the target has been 'hit' by a single biologically-effective unit of dose.
- *Multi-hit model*—which assumes several interactions are needed before a cell becomes transformed; indeed, it is the least conservative model. This model is based on an extension of the one-hit model, assuming that more than one 'hit' is required to induce a response.
- *Probit model*—which assumes probit (lognormal) distribution for tolerance of exposed population; it is appropriate for acute toxicity, but questionable for cancer.
- *Physiologically-based pharmacokinetic (PBPK) models*—which incorporate pharmacokinetic and mechanistic data into the extrapolation; for the most part, they possess data-rich requirements with continuing great promise for even more extensive utilization into the future, especially as more biological data becomes

available. Overall, this type of model quantifies the relationship between the exposure to a carcinogen and the dose of the biologically active component of the chemical—and then incorporates the kinetics of metabolic processes that may change a chemical's toxicity.

Finally, it is worth the mention here that, most of the techniques used to compensate for toxicity assessment uncertainties (such as the use of large safety factors, conservative assumptions, and extrapolation models) are designed to err on the side of safety. For these reasons, many regulatory agencies tend to use the so-called linearized multistage (LMS) model for the sake of maintaining conservatism in the overall process. Of course, alternative models that do not assume a linear relationship, and that are generally less conservative also exist; in fact, several models have been proposed for the quantitative extrapolations of carcinogenic effects to low dose levels—albeit, among these models, the LMS model (that conservatively assumes linearity at low doses) seems to be favored by regulatory agencies such as the US EPA (USEPA 1986a, b, c, d, e, f). Even so, it is notable that more recent guidelines seem to be favoring/incorporating the 'state-of-the-art' in carcinogenic risk assessment models. In general, however, the choice of model is determined by its consistency with the current understanding of the mechanisms of carcinogenesis.

10.3.2.2 Refining Dose-Response Model Outcomes

It must be acknowledged here that, there often is no sound basis (in a biological sense) for choosing one model over another. On the other hand, when applied to the same data, the various models can produce a wide range of risk estimates—and thus a need for being discerning in the choices we make. In general, the frequently recommended model—i.e., the LMS model—produces among the highest estimates of risk, and thus seems to provide a greater margin of protection for human health. However, this model does not provide a 'best estimate' or point estimate of risk, but rather an upper-bound probability that the actual risk will be less than the predicted risk 95 percent of the time. Indeed, using the LMS to extrapolate from high-dose to low-dose effects can lead to erroneous conclusions about risk for many animal carcinogens; in this light, the use of other appropriate extrapolation models is encouraged. Also, given that no single model will be applicable to all chemicals, perhaps a presentation of the best estimate of risk (or range, with an added margin of safety) from two or three appropriate models, or a single value based on 'weight-of-evidence'—rather than simply using the LMS model might be more appropriate (Huckle 1991).

In general, mathematical models fitted to high-dose experimental data are often used to help characterize the low-dose risks typically encountered in chemical risk quantifications; in such situations, different dose-response models are likely to yield substantially varying results for the same estimated effective dose. Thus, the concept of 'model averaging' has been suggested for use in contemporary times,

so as to provide some robustness under such circumstances; specifically, this approach will more likely provide outcomes that are generally better than attainable from the use of a single dose-response model during the processes involved in estimating an effective dose associated with a representative or pragmatic chemical exposure situation (i.e., the typical dose levels to which targeted human populations are potentially exposed)—especially in cases involving extremely small risks (Faes et al. 2007; Kim et al. 2014; Wheeler and Bailer 2007, 2009). Exceptions may occur, however, for cases of chemicals that have not been sufficiently studied.

10.4 Determination of Toxicological Parameters for Human Health Risk Assessments

In the processes involved in the assessment of human health risks arising from chemical exposures, it often becomes necessary to compare receptor chemical intakes with doses shown to cause adverse effects in humans or experimental animals. Correspondingly, the dose at which no effects are observed in human populations or experimental animals is referred to as the 'no-observed-effect-level' (NOEL); where data identifying a NOEL are lacking, a 'lowest-observed-effect-level' (LOEL) may be used as the basis for determining safe threshold doses.

For acute effects, short-term exposures/doses shown to produce no adverse effects characterize the parameters of interest needed to support the risk assessment process; this is called the 'no-observed-adverse-effect-level' (NOAEL). A NOAEL is an experimentally determined dose at which there has been no statistically or biologically significant indication of the toxic effect of concern. In cases where a NOAEL has not been demonstrated experimentally, the 'lowest-observed-adverse-effect level' (LOAEL) is used.

In general, for chemicals possessing carcinogenic potentials, the LADD is typically compared with the NOEL identified in long-term bioassay experimental tests; for chemicals with acute effects, the MDD is compared with the NOAEL observed in short-term animal studies. An elaboration on the derivation of the relevant toxicological parameters commonly used in human health risk assessments follows below, with further in-depth discussions to be found in the literature elsewhere (e.g., Dourson and Stara 1983; Faes et al. 2007; Kim et al. 2014; Wheeler and Bailer 2007, 2009; USEPA 1985b, 1986a, 1989a, 1989c, 1989d).

10.4.1 Toxicity Parameters for Non-carcinogenic Effects

Traditionally, risk decisions on systemic toxicity are made using the concept of 'acceptable daily intake' (ADI), or by using the so-called reference dose (RfD). The ADI is the amount of a chemical (in mg/kg body-weight/day) to which a receptor

can be exposed to on a daily basis over an extended period of time—usually a lifetime—without suffering a deleterious effect. The RfD is defined as the maximum amount of a chemical (in mg/kg body-weight/day) that the human body can absorb without experiencing chronic health effects. Thus, for exposure of humans to the non-carcinogenic effects of environmental chemicals, the ADI or RfD may be used as a measure of exposure that is considered to be without adverse effects. Meanwhile, it is worth the mention here that, although often used interchangeably, RfDs are based on a more rigorously defined methodology—and is therefore generally preferred over ADIs.

The reference concentration (RfC) of a chemical—like the RfD—represents an estimate of the exposure that can occur on a daily basis over a prolonged period, with a reasonable anticipation that no adverse effect will occur from that exposure. In contrast to RfDs, however, RfCs are expressed in units of concentration in an environmental medium (e.g., mg/m^3 or μg/L). RfCs customarily pre-suppose continuous exposure, with an average inhalation rate and body weight; it may therefore be inappropriate to use them in 'non-standard' exposure scenarios.

In general, both the RfD and RfC represent estimates of the exposure that can occur on a daily basis over a prolonged period, with a reasonable expectation that no adverse effect will occur from that exposure. In assessing the chronic and subchronic effects of non-carcinogens and also non-carcinogenic effects associated with carcinogens, the experimental dose value (e.g., NOEL) is usually divided by a safety (or uncertainty) factor to yield the RfD—as elaborated and illustrated further below.

Finally, it should be mentioned here that, when no toxicological information exists for a chemical of interest or concern, concepts of structure-activity relationships may have to be employed to help derive acceptable intake levels by influence and analogy analysis in comparison with closely related or similar compounds. In such cases, some reasonable degree of conservatism is typically recommended in any judgment call to be made.

10.4.1.1 Reference Doses (RfDs)

A reference dose, or RfD, is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily [oral] exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. In general, it provides an estimate of the continuous daily exposure of a non-carcinogenic substance for the general human population (including sensitive subgroups) which appears to be without an appreciable risk of deleterious effects. Indeed, RfDs are established as thresholds of exposure to toxic substances below which there should be no adverse health impact. Broadly speaking, these thresholds are established on a substance-specific basis for oral and inhalation exposures, taking into account evidence from both human epidemiologic and laboratory toxicologic studies. Correspondingly, subchronic

RfD is typically used to refer to cases involving only a portion of the lifetime, whereas chronic RfD is associated with lifetime exposures.

In general, RfDs can be derived from a NOAEL, LOAEL, or benchmark dose—or indeed by using categorical regression, with uncertainty factors commonly applied to reflect limitations of the data used. Various types of RfDs are available depending on the critical effect (developmental or other) and the length of exposure being evaluated (chronic or subchronic).

Chronic oral RfDs are specifically developed to be protective for long-term exposure to a compound. As a typical guideline for most risk assessments, chronic oral RfDs generally should be used to evaluate the potential noncarcinogenic effects associated with exposure periods greater than 7 years (approximately 10 percent of an average human lifetime). However, this is not a bright-line; for instance, it is noteworthy that the U.S. ATSDR defines chronic exposure as greater than 1 year for use of their typical decision values.

Subchronic oral RfDs are specifically developed to be protective for short-term exposure to a compound. As a typical guideline for most risk assessments, subchronic oral RfDs should generally be used to evaluate the potential noncarcinogenic effects of exposure periods between two weeks and seven years. However, this is not a bright-line; for instance, it is noteworthy that the U.S. ATSDR defines subchronic exposure as less than 1 year for use of their typical decision values.

10.4.1.2 Reference Concentrations (RfCs)

A reference concentration (RfC) is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL or, NOAEC, LOAEL or, LOAEC, or benchmark concentration—or indeed by using categorical regression with uncertainty factors generally applied to reflect limitations of the data used. Various types of RfCs are available depending on the critical effect (developmental or other) and the length of exposure being evaluated (chronic or subchronic).

The *chronic inhalation reference concentration* is generally used for continuous or near continuous inhalation exposures that occur for 7 years or more. However, this is not a bright-line—as, e.g., the U.S. ATSDR chronic equivalent values are based on exposures longer than 1 year. It is also noteworthy that the U.S. EPA chronic inhalation reference concentrations are typically expressed in units of (mg/m^3)—albeit other agencies present same values in $\mu g/m^3$.

The *subchronic inhalation reference concentration* is generally used for exposures that are between 2 weeks and 7 years. However, this is not a bright-line—as, e.g., the U.S. ATSDR subchronic equivalent values are based on exposures less than 1 year. It is also notable that the U.S. EPA subchronic inhalation reference

concentrations are usually expressed in units of (mg/m^3)—albeit some agencies present these in $\mu g/m^3$.

10.4.1.3 Derivation of RfDs and RfCs

The RfD is a 'benchmark' dose operationally derived from the NOAEL by consistent application of general 'order-of-magnitude' 'uncertainty factors' (UFs) (also called 'safety factors') that reflect various types of data sets used to estimate RfDs. In addition, a so-called modifying factor (MF) that is commonly based on professional judgment of the entire database associated with the specific chemical under review is sometimes applied. Broadly stated, RfDs (and ADIs) are calculated by dividing a NOEL (i.e., the highest level at which a chemical causes no observable changes in the species under investigation), a NOAEL (i.e., the highest level at which a chemical causes no observable adverse effect in the species being tested), or a LOAEL (i.e., that dose rate of chemical at which there are statistically or biologically significant increases in frequency or severity of adverse effects between the exposed and appropriate control groups) derived from human or animal toxicity studies by one or more uncertainty and modifying factors. Corresponding statements can also be made in relation to the derivation of RfCs.

Typically, to derive a RfD or RfC for a non-cancer critical effect, the common practice is to apply standard UFs to the NOAEL, LOAEL, or indeed a benchmark dose/concentration (BMD/BMC). The UFs are used to account for the extrapolation uncertainties (e.g., inter-individual variation, interspecies differences, exposure duration, etc.) and database adequacy. A modifying factor (MF) is also used to account for the general level of confidence in the critical study(s) used in the derivation of the RfD or RfC. Although a use of default values tends to be the norm, replacements for default UFs are used when chemical-specific data are available to modify such standard default values; this is known as the 'data-derived' approach. Also, the use of pharmacokinetic or dosimetry models can obviate the need for an UF to account for differences in toxicokinetics across species. Anyhow, it is noteworthy that, a number of related factors can indeed result in significant uncertainties in the RfD or RfC values. Among these is the selection of different observed effects as a critical effect—which may vary within and across available studies. Also significant is the choice of different data sets for the identification of the NOAEL, LOAEL, or benchmark dose analysis; the use of different values for the various UFs; and additional judgments that impact the MF.

On the whole, RfDs are usually calculated using a single exposure level together with uncertainty factors that account for specific deficiencies in the toxicological database. Both the exposure level and uncertainty factors are selected and evaluated in the context of the available chemical-specific literature. After all the toxicological, epidemiologic, and supporting data have been reviewed and evaluated, a key study is selected that reflects optimal data on the critical effect. Dose-response data points for all reported effects are typically examined as part of this review. Additional general and specific issues of particular significance in this

endeavor—including the types of response levels (ranked in order of increasing severity of toxic effects as NOEL, NOAEL, LOAEL, and FEL [the Frank effect level, defined as overt or gross adverse effects]) that are considered in deriving RfDs are discussed elsewhere in the literature (e.g., USEPA 1989b). Ultimately, the RfD (or ADI) can be determined from the NOAEL (or LOAEL, or BMD) for the critical toxic effect by consistent application of UFs and a MF, in accordance with the following relationship:

$$\text{Human dose}(\text{e.g., } ADI \text{ or } RfD) = \frac{\text{Experimental dose}(\text{e.g., NOAEL})}{(\text{UF} \times \text{MF})} \tag{10.4}$$

or, specifically:

$$RfD = \frac{\text{NOAEL}}{(\text{UF} \times \text{MF})} \tag{10.5}$$

or, more generally:

$$RfD = \frac{[NOAEL \text{ or } LOAEL \text{ or } BMD]}{\left[\sum_{i=1}^{n} UF_i \times MF\right]} \tag{10.6}$$

The derivation of a RfC is a parallel process that is appropriately based on a 'no-observed-adverse-effect-concentration' (NOAEC) or 'lowest-observed-adverse-effect-concentration' (LOAEC)—or indeed the 'benchmark dose concentration' (BMC). Alternatively, a RfC may be derived from a RfD, taking into account the exposure conditions of the study used to derive the RfD.

Determination of the Uncertainty and Modifying Factors. The uncertainty factors used in the derivation of an RfD generally reflect the scientific judgment regarding the various types of data used to estimate the RfD values; it is basically used to offset the uncertainties associated with extrapolation of data, etc. Generally speaking, the UF consists of multipliers of 10 (although values less than 10 could also be used)—each factor representing a specific area of uncertainty inherent in the extrapolations from the available data. For example, a factor of 10 may be introduced to account for the possible differences in responsiveness between humans and animals in prolonged exposure studies. Indeed, for interspecies extrapolation of toxic effects seen in experimental animals to what might occur in exposed humans, an UF of up to tenfold is generally recommended; this is usually viewed as consisting of two components, *viz*.: one that accounts for metabolic or pharmacokinetic differences between the species, and another that addresses pharmacodynamic differences (i.e., differences between the response of human and animal tissues to the chemical exposure). Next, a second factor of 10 may be used to account for variation in susceptibility among individuals in the human population; indeed, exposed humans are known to vary considerably in their response to toxic chemical and drug exposures due to age, disease states, and genetic makeup—

particularly in genetic polymorphisms for enzymes (isozymes) for detoxifying chemicals. In such types of cases, the resultant UF of 100 has been judged to be appropriate for many chemicals. For other chemicals with databases that are less complete (for example, those for which only the results of subchronic studies are available), an additional factor of 10 (leading to a UF of 1000) might be judged to be more appropriate. For certain other chemicals, such as those associated with well-characterized responses in sensitive humans (as, e.g., regarding the effect of fluoride on human teeth), an UF as small as 1 might be selected (Dourson and Stara 1983). Finally an additional tenfold UF may be used to account for possible carcinogenicity effects. Meanwhile, it is notable that, within the US EPA, the maximum cumulative UF for any given database tends to be 3000; thus, databases weaker than this are judged too uncertain to estimate RfDs or RfCs.

Box 10.7 provides the general guidelines for the process of selecting uncertainty and modifying factors during the derivation of RfDs (Dourson and Stara 1983; USEPA 1986b, 1989a, 1989b, 1993b); it is noteworthy that the uncertainty factors shown are as typically used by the US EPA—also recognizing that, although other health and environmental organizations or agencies may use similar guidelines, they do not necessarily subdivide these elements to the same extent. Additionally, it is worth mentioning here that the UFs can indeed include various 'chemical-specific adjustment factors' (CSAFs); CSAFs represent part of a broader continuum of approaches which incorporate increasing amounts of data to reduce uncertainty—generally ranging from default ('presumed protective') to more 'biologically-based predictive' methodologies (Meek 2001; WHO 2010a, b).

In general, the choice of the UF and MF values reflect the uncertainty associated with the estimation of a RfD from different human or animal toxicity databases. For instance, if sufficient data from chronic duration exposure studies are available on the threshold region of a chemical's critical toxic effect in a known sensitive human population, then the UF used to estimate the RfD may be set at unity (1); this is because, under such circumstances, these data are judged to be sufficiently predictive of a population sub-threshold dose—so that additional UFs are not needed after all (USEPA 1989b).

Box 10.7 General Guidelines for Selecting Uncertainty and Modifying Factors in the Derivation of RfDs
Standard Uncertainty Factors (UFs):

- Use a 10-fold factor when extrapolating from valid experimental results in studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population, due to heterogeneity in human populations, and is referenced as "10H". Thus, if NOAEL is based on human data, a safety factor of 10 is usually applied to the NOAEL dose to account for variations in sensitivities between individual humans.

(continued)

Box 10.7 (continued)

- Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty involved in extrapolating from animal data to humans and is referenced as "10A". Thus, if NOAEL is based on animal data, the NOAEL dose is divided by an additional safety factor of 10, to account for differences between animals and humans.
- Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there are no useful long-term human data. This factor is intended to account for the uncertainty involved in extrapolating from less than chronic (i.e., subchronic or acute) NOAELs to chronic NOAELs and is referenced as "10S".
- Use an additional 10-fold factor when deriving an RfD from a LOAEL, instead of a NOAEL. This factor is intended to account for the uncertainty involved in extrapolating from LOAELs to NOAELs and is referenced as "10 L".
- Use an additional up to 10-fold factor when extrapolating from valid results in experimental animals when the data are 'incomplete.' This factor is intended to account for the inability of any single animal study to adequately address all possible adverse outcomes in humans, and is referenced as "10D."

Modifying Factor (MF):

- Use professional judgment to determine the MF, which is an additional uncertainty factor that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the qualitative professional assessment of scientific uncertainties of the study and data base not explicitly treated above—e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

Illustrative Examples of the RfD Derivation Process. Some hypothetical example situations involving the determination of RfDs based on information on NOAEL, and then also on LOAEL, are provided below.

- *Determination of the RfD for a Hypothetical Example Using the NOAEL.* Consider the case involving a study carried out on 250 animals (e.g., rats) that is of subchronic duration—and subsequently yielding a NOAEL dosage of 5 mg/kg/day. Then, in this case

$$UF = 10\text{H} \times 10\text{A} \times 10\text{S} = 1{,}000$$

In addition, there is a subjective adjustment (represented by the MF), based on the high number of animals (250) per dose group, as follows:

$$\mathrm{MF} = 0.75$$

These factors then give UF x MF = 750, and consequently:

$$RfD = \frac{\mathrm{NOAEL}}{(\mathrm{UF} \times \mathrm{MF})} = \frac{5}{750} = 0.007(\mathrm{mg/kg/day})$$

- *Determination of the RfD for a Hypothetical Example Using the LOAEL.* If the NOAEL is not available, and if 25 mg/kg/day had been the lowest dose from the test that showed adverse effects, then

$$\mathrm{UF} = 10\mathrm{H} \times 10\mathrm{A} \times 10\mathrm{S} \times 10\mathrm{L} = 10{,}000$$

Using again the subjective adjustment of MF = 0.75, one obtains:

$$\mathrm{RfD} = \frac{\mathrm{LOAEL}}{(\mathrm{UF} \times \mathrm{MF})} = \frac{25}{7500} = 0.003(\mathrm{mg/kg/day})$$

10.4.1.4 The Benchmark Dose (BMD) Approach

The RfD or RfC for humans is often derived from animal experiments—with the NOAEL (which represent the highest experimental dose for which no adverse health effects have been documented) often being a starting point for its calculation. However, using the NOAEL in the derivation of RfDs and RfCs has long been recognized as having significant limitations—especially because: it is limited to only one of the doses in the study, and is also dependent on the particular study design; it does not account for variability in the estimate of the dose-response; it does not account for the slope of the dose-response curve; and it cannot be applied when there is no NOAEL, except through the application of an uncertainty factor (Crump 1984; Kimmel and Gaylor 1988; USEPA 1995a, b, c, d, e). As an alternative to the use of NOAEL and LOAEL in the determination of the RfD or RfC in the non-cancer risk evaluation, therefore, other methodologies have become increasingly popular—such as has happened with the so-called 'benchmark dose' (BMD) approach. An important goal of the BMD approach is to define a starting point of departure for the computation of a reference value (*viz.*, RfD or RfC), or a slope factor, that is more independent of study design.

The BMD is an estimate of the dose or concentration that produces a predetermined change in response rate of an adverse effect (called the 'benchmark response' or BMR) compared to background—and this is typically defined for a given exposure route and duration. The BMR generally should be near the low end

of the range of increased risk that can be detected by a bioassay; indeed, low BMRs can impart high model dependence. In general, if there is an accepted (minimum) level of change in the endpoint that is considered to be biologically significant, then that amount is the BMR—like, for instance, a 10% body weight decrease compared to the control; in the absence of any other idea of what level of response to consider as being adverse, a change in the mean that equals one standard deviation of the control from the mean of the control may be utilized in this case (Crump 1995).

Overall, the use of BMD methods involve fitting mathematical models to dose-response data, and then using the different results to select an appropriate BMD or BMC (as represented by, say, a $BMCL_x$) that is associated with a predetermined benchmark response (such as a 10% increase in the incidence of a particular lesion, or a 10% decrease in body weight changes). In practice, the BMD represents a lower confidence limit on the effective dose associated with some defined level of effect—e.g., a 5% or 10% increase in response. In other words, it is the confidence limit on the dose that elicits adverse responses in a fraction [often 5% or 10%] of the experimental animals; the confidence limits characterize uncertainty in the dose that affects a specified fraction of the animals. Thus, a $BMCL_x$ is defined as the lower 95% confidence limit of the dose that will result in a level of *x*% response; for example, $BMCL_{10}$ is the lower 95% confidence limit of a dose for a 10% increase in a particular response (USEPA 1995c).

Ultimately, a dose-response relationship is fitted to the bioassay data points, and a confidence limit for that relationship is determined. The BMD is the dose yielding the desired response rate [e.g., 5%, or 10%] based on the curve representing the confidence limit. Unlike the NOAEL, the BMD makes use of all the bioassay data and is not constrained to dose values administered in the experiment. On the other hand, there is no scientific basis for selecting a particular response rate for the BMD [e.g., 5% *vs*. 10%], and neither does the BMD easily address 'continuous' responses (e.g., as reflected by changes in body weight)—since it depends on identifying the dose at which a certain fraction of animals is 'affected' by the toxicant.

Deriving an RfD or RfC Using a BMD. In utilizing the BMD approach, the equation for an RfD or RfC becomes:

$$RfD = \frac{BMDL}{UF} \tag{10.7}$$

$$RfC = \frac{BMCL}{UF} \tag{10.8}$$

where, in this case, the lower confidence bound on the BMD (*viz*., the BMDL or BMCL) may be considered as simply being a procedural replacement for the NOAEL that gives the same 'comfort level' of minimal risk—albeit this may not necessarily be construed as the NOAEL equivalent *per se*. Also, in this case, there is no UF for LOAEL to NOAEL extrapolation, etc.

10.4.1.5 Inter-Conversions of Non-carcinogenic Toxicity Parameters

Usually, the RfD for inhalation exposure is reported both as a concentration in air (in units of, e.g., mg/m^3) and as a corresponding inhaled dose (mg/kg-day). Anyhow, when determining the toxicity value for inhalation pathways, the inhalation RfC [mg/m^3] should be used whenever available. Broadly speaking, the RfC can also be converted to equivalent RfD values (in units of dose [mg/kg-day]) via multiplying the RfC term by an average human inhalation rate of 20 m^3/day (for adults), and dividing it by an average adult body weight of 70 kg—as follows:

$$RfD_i[\text{mg/kg-day}] = \frac{\text{RfC}[\text{mg/m}^3] \times 20\,\text{m}^3/\text{day}}{70\,\text{kg}} = 0.286\,\text{RfC} \tag{10.9}$$

Correspondingly, RfD values associated with oral exposures (and reported in mg/kg-day) can also be converted to a corresponding concentration in drinking water (usually called the 'drinking water equivalent level', DWEL), as follows:

$$\begin{aligned} DWEL[\text{mg/L in water}] &= \frac{\text{oral RfD}(\text{mg/kg-day}) \times \text{body weight}(\text{kg})}{\text{ingestion rate}(\text{L/day})} \\ &= \frac{\text{RfD}_\text{o}(\text{mg/kg-day}) \times 70(\text{kg})}{2(\text{L/day})} = 35\,\text{RfD}_\text{o} \end{aligned} \tag{10.10}$$

The above derivation assumes a 2 L/day of water consumption by a 70-kg adult.

10.4.1.6 Tools for Making Risk Management Decisions

In a typical risk determination process, a comparison is essentially made between the RfD and an 'estimated exposure dose' (EED) (or a so-called 'regulatory dose' [RgD]); the EED characteristically would include all germane sources and routes of exposure. In general, as a risk management tool, if the EED is less than the RfD (i.e., EED $<$ RfD), then the need for regulatory concern may be small.

Another alternative measure that is also considered useful to risk managers is the so-called 'margin of exposure' (MOE)—which is the magnitude by which the NOAEL of the critical toxic effect exceeds the EED, where both are expressed in the same units; the MOE is defined as follows:

$$\text{MOE} = \frac{\text{NOAEL}}{\text{EED}} \tag{10.11}$$

As an example of the utility of the MOE concept and procedure, suppose the EED for humans exposed to a chemical substance (with a RfD of 0.005 mg/kg-day) under a proposed use pattern is 0.02 mg/kg-day (i.e., the EED is greater than the RfD), then:

$$\text{NOAEL} = \text{RfD} \times (\text{UF} \times \text{MF}) = 0.005 \times 1,000 = 5 \text{ mg/kg-day}$$

and

$$\text{MOE} = \frac{\text{NOAEL}}{\text{EED}} = \frac{5(\text{mg/kg/day})}{0.02(\text{mg/kg/day})} = 250$$

Now, because the EED exceeds the RfD (and the MOE is less than the [UF x MF] of 1,000), the risk manager may need to carefully look at the data set as well as the assumptions associated with both the RfD and the exposure estimates.

The MOE may indeed be used as a surrogate for measuring the levels of risk in chemical exposure situations. In general, as the MOE becomes larger, the risk becomes smaller.

10.4.2 Toxicity Parameters for Carcinogenic Effects

Under a no-threshold assumption for carcinogenic effects, exposure to any level of a carcinogen is considered to have a finite risk of inducing cancer. An estimate of the resulting excess cancer per unit dose (called the unit cancer risk, or the cancer slope factor/cancer potency factor) is typically used to develop risk decisions for chemical exposure problems. On the whole, two specific toxicity parameters for expressing carcinogenic hazards based on the dose-response function find common application in human health risk assessments, namely:

- Cancer slope factor ([C]SF)—that expresses the slope of the dose-response function in dose-related units (i.e., $[\text{mg/kg-day}]^{-1}$); and
- Unit risk factor (URF)—that expresses the slope in concentration-based units (i.e., $[\mu\text{g/m}^3]^{-1}$).

Typically, the [C]SFs are used when evaluating risks from oral or dermal exposures, whereas the URFs are used to evaluate risks from inhalation exposures. *Oral slope factors* are toxicity values for evaluating the probability of an individual developing cancer from oral exposure to contaminant levels over a lifetime; oral slope factors are expressed in units of $(\text{mg/kg-day})^{-1}$. Generally used for the inhalation exposure route, *inhalation unit risk* toxicity values are expressed in units of $(\mu\text{g/m}^3)^{-1}$.

It is noteworthy that cancer dose-response assessment generally involves many scientific judgments regarding the following: the selection of different data sets (e.g., benign and malignant tumors, or their precursor responses) for extrapolation; the choice of low dose extrapolation approach based on the interpretation and assessment of the mode of action for the selected tumorigenic response(s); the choice of extrapolation models and methods to account for differences in dose across species; and the selection of the point of departure for low dose

extrapolation. Indeed, many judgments usually have to be made in the many steps of the assessment process in the face of data variability. Also, different science policy choices and default procedures or methods are used to bridge data and knowledge gaps. Consequently, it is generally recognized that significant uncertainty exists in the cancer risk estimates.

Finally, it should be mentioned here that when no toxicological information exist for a chemical of interest or concern, structural similarity factors, etc. can be used to estimate cancer potency units for the chemicals that are suspected carcinogens but lack such pertinent values. For instance, in the case of a missing URF, this concept may be used to derive a surrogate parameter for the chemical with unknown URF—by, for example, estimating the geometric mean of a number of similar compounds with known URFs, and then using this as the surrogate value. Also, in contemporary times, PBPK modeling has become a preferred approach to both dose estimation and interspecies scaling of inhalation exposures, wherever data are available to support such efforts.

10.4.2.1 Slope Factors (SFs)

The SF, also called cancer potency factor (CPF) or potency slope, is a measure of the carcinogenic toxicity or potency of a chemical. It is a plausible upper-bound estimate of the probability of a response per unit intake of a chemical over a lifetime—represented by the cancer risk (proportion affected) per unit of dose (i.e., risk per mg/kg/day). In general, the CPF is used in human health risk assessments to estimate an upper-bound lifetime probability of an individual developing cancer as a result of exposure to a given level of a potential carcinogen. This represents a slope factor derived from a mathematical function (e.g., the LMS model) that is used to extrapolate the probability of incidence of cancer from a bioassay in animals using high doses to that expected to be observed at the low doses, likely to be found in chronic human exposures.

In general, slope factors should always be accompanied by the weight-of-evidence classification to indicate the strength of the evidence that the agent is a human carcinogen. A slope factor and the accompanying weight-of-evidence determination are the toxicity data most commonly used to evaluate potential human carcinogenic risks.

10.4.2.2 Inhalation Unit Risk (IUR)

The IUR is defined as the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 μg/m^3 in air. In evaluating risks from chemicals found in certain human environmental settings, dose-response measures may generally be expressed as risk per concentration unit—yielding the URF (also called unit cancer risk, UCR or unit risk, UR) values. These measures may include the unit risk factor for air (*viz.*, an inhalation URF),

and the unit risk for drinking water (*viz*., an oral URF). In essence, the continuous lifetime exposure concentration units for air and drinking water are usually expressed in micrograms per cubic meter ($\mu g/m^3$) and micrograms per liter ($\mu g/L$), respectively.

10.4.2.3 Derivation of SFs and URFs

The determination of carcinogenic toxicity parameters often involves the use of a variety of mathematical extrapolation models. In fact, scientific investigators have developed numerous models to extrapolate and estimate low-dose carcinogenic risks to humans from the high-dose carcinogenic effects usually observed in experimental animal studies. Such models yield an estimate of the upper limit in lifetime risk per unit of dose (or the unit cancer risk). On the whole, the nature of extrapolation employed for a given chemical during the estimation of carcinogenic potency very much depends on the existence of data to support linearity or nonlinearity—or indeed a biologically-based, or a case-specific model (USEPA 1996f). In any event, the more popular approach amongst major regulatory agencies (such as the US EPA) involves a use of the LMS model—particularly because of the conservative attributes of this model.

The Linearized Multistage Model. Mathematically, the multistage model may be expressed as follows:

$$P(d) = 1 - \exp\left[-\left(q_0 + q_1 d + q_2 d^2 + \ldots\ldots + q_k d^k\right)\right] \tag{10.12}$$

where: P(d) is the lifetime probability of developing a tumor at a given dose, *d*, of carcinogen; q_0 is a constant that accounts for the background incidence of cancer (i.e., occurring in the absence of the carcinogen under consideration); and q_1, q_2,. . q_k are coefficients that allow the data to be expressed to various powers of the dose of carcinogen, in order to obtain the best fit of the model to the data. To determine the extra risk above the background rate at dose, *d*, the above equation takes the following form:

$$Pe(d) = 1 - \exp\left[-\left(q_1 + q_2 d^2 + \ldots\ldots + q_k d^k\right)\right] \tag{10.13}$$

At low doses, the extra risk is approximated by:

$$Pe(d) = q_1 d \tag{10.14}$$

The linearized multistage model uses animal tumor incidence data to compute maximum likelihood estimates (MLE) and upper 95% confidence limits (UCL_{95}) of risk associated with a particular dose. In general, the true risk is very unlikely to be greater than the UCL, may be lower than the UCL, and could be even as low as zero. In fact, the linearized multistage model yields upper bound estimates of risks

that are a linear function of dose at low doses, and are frequently used as a basis for a number of regulatory decisions.

Overall, the linearized multistage model is known to make several conservative assumptions that result in highly conservative risk estimates—and thus yields overestimates of actual URFs for carcinogens; in fact, the actual risks may perhaps be substantially lower than that predicted by the upper bounds of this model (Paustenbach 1988). Even so, such approach is generally preferred since it allows analysts to err on the side of safety—and therefore would likely offer better protection of public health.

Deriving CSF Using a BMD. As presented earlier on in Sect. 10.4.1, the BMD is an estimate of the dose or concentration that produces a predetermined change in response rate of an adverse effect (called the 'benchmark response' or BMR) compared to background—and this is typically defined for a given exposure route and duration. The BMR generally should be near the low end of the range of increased risk that can be detected by a bioassay; indeed, low BMRs can impart high model dependence. In general, if there is an accepted (minimum) level of change in the endpoint that is considered to be biologically significant, then that amount is the BMR—like, for instance, a 10% body weight decrease compared to the control; in the absence of any other idea of what level of response to consider as being adverse, a change in the mean that equals one standard deviation of the control from the mean of the control may be utilized in this case (Crump 1995).

Overall, the use of BMD methods involve fitting mathematical models to dose-response data, and then using the different results to select an appropriate BMD or BMC (as represented by, say, a $BMCL_x$) that is associated with a predetermined benchmark response (such as a 10% increase in the incidence of a particular lesion, or a 10% decrease in body weight changes). In practice, the BMD represents a lower confidence limit on the effective dose associated with some defined level of effect—e.g., a 5% or 10% increase in response. In other words, it is the confidence limit on the dose that elicits adverse responses in a fraction [often 5% or 10%] of the experimental animals; the confidence limits characterize uncertainty in the dose that affects a specified fraction of the animals. Thus, a $BMCL_x$ is defined as the lower 95% confidence limit of the dose that will result in a level of x% response; for example, $BMCL_{10}$ is the lower 95% confidence limit of a dose for a 10% increase in a particular response (USEPA 1995c).

In utilizing the BMD approach here, the equation for an CSF becomes:

$$CSF = \frac{BMR}{BMDL} \tag{10.15}$$

As an illustrative example, this may be represented by: $CSF = 0.1/BMDL_{10}$.

10.4.2.4 Inter-conversion of Carcinogenic Toxicity Parameters

Generally speaking, the URF estimates the upper-bound probability of a 'typical' or 'average' person contracting cancer when continuously exposed to one microgram per cubic meter (1 μg/m^3) of the chemical over an average (70-year) lifetime. Potency estimates are also given in terms of the potency slope factor (SF), which is the probability of contracting cancer as a result of exposure to a given lifetime dose (in units of mg/kg-day). That said, the SF can be converted to URF (also, unit risk, UR or unit cancer risk, UCR), by adopting several assumptions. The most critical requirement here is that the endpoint of concern must be a systematic tumor—in order that the potential target organs will experience the same blood concentration of the active carcinogen, regardless of the method of administration. This implies an assumption of equivalent absorption by the various routes of administration. Lastly, the basis for such conversions is the assumption that, at low doses, the dose-response curve is linear—so that the following holds true:

$$\mathrm{P(d)} = \mathrm{SF} \times [\mathrm{DOSE}] \tag{10.16}$$

where: P(d) is the response (probability) as a function of dose; SF is the cancer potency slope factor ([mg/kg-day]$^{-1}$); and [DOSE] is the amount of chemical intake (mg/kg-day). The inter-conversions between URF and SF are expounded below.

- *Inter-conversions of the Inhalation Potency Factor*. Risks associated with a unit chemical concentration in air may be estimated in accordance with following mathematical relationship:

$$\begin{aligned}&\text{Air unit risk}\\&= \text{risk per } \mu\text{g/m}^3 \text{ (air)}\\&= [\text{slope factor (risk per mg/kg/day)}] \times \left[\frac{1}{\text{bodyweight(kg)}}\right]\\&\times \left[\text{inhalation rate}(\text{m}^3/\text{day}) \times 10^{-3} \text{ (mg/}\mu\text{g)}\right.\end{aligned}$$

Thus, the inhalation potency can be converted to an inhalation URF by applying the following conversion factor:

$$\begin{aligned}&[(\text{kg-day})/\text{mg}] \times [1/70 \text{ kg}] \times [20 \text{ m}^3/\text{day}]\\&\times [1 \text{ mg}/1,000\, \mu g] = 2.86 \times 10^{-4}\end{aligned}$$

Accordingly, the lifetime excess cancer risk from inhaling 1 μg/m^3 concentration for a full lifetime is estimated as:

$$URF_i \left(\mu g/\text{m}^3\right)^{-1} = \left(2.86 \times 10^{-4}\right) \times SF_i \tag{10.17}$$

Conversely, the SF_i can be derived from the URFi as follows:

$$SF_i = \left(3.5 \times 10^3\right) \times URF_i \tag{10.18}$$

The assumptions used in the above derivations involve a 70-kg body weight, and an average inhalation rate of 20 m^3/day.

- *Inter-conversions of the Oral Potency Factor*. Risks associated with a unit chemical concentration in water may be estimated in accordance with following mathematical relationship:

$$\begin{aligned}&\text{Water unit risk}\\&= \text{risk per } \mu\text{g/L(water)}\\&= [\text{slope factor (risk per mg/kg/day)}] \times \left[\frac{1}{\text{body weight(kg)}}\right]\\&\times \text{ingestion rate (L/day)} \times 10^{-3}\ (\text{mg/}\mu\text{g})\end{aligned}$$

Thus, the ingestion potency can be converted to an oral URF value by applying the following conversion factor:

$$[(\text{kg-day})/\text{mg}] \times [1/70\text{kg}] \times [2\text{L/day}] \times [1\text{mg}/1,000\,\mu\text{g}] = 2.86 \times 10^{-5}$$

Accordingly, the lifetime excess cancer risk from ingesting 1 μg/L concentration for a full lifetime is:

$$URF_o(\mu\text{g/L})^{-1} = \left(2.86 \times 10^{-5}\right) \times SF_o \tag{10.19}$$

Conversely, the potency, SFo, can be derived from the unit risk as follows:

$$SF_o = \left(3.5 \times 10^4\right) \times URF_o \tag{10.20}$$

The assumptions used in the above derivations involve a 70-kg body weight, and an average water ingestion rate of 2 L/day.

10.4.3 The Use of Surrogate Toxicity Parameters

Risk characterizations generally should consider every likely exposure route in the evaluation process. However, toxicity data may not always be available for each route of concern—and in which case the use of surrogate values might become necessary; the pertinent surrogate values may indeed include extrapolation from data for a different exposure route. Broadly speaking, extrapolations may be reasonable for some cases where there is reliable information on the degree of absorption of materials by both routes of exposure in question—and assuming the substance is not locally more active by one route.

In principle, it is generally not possible to extrapolate between exposure routes for some substances that produce localized effects dependent upon the route of exposure. For example, a toxicity value based on localized lung tumors that result only from inhalation exposure to a substance would not be appropriate for estimating risks associated with dermal exposure to the substance. Thus, it may be appropriate to extrapolate dermal toxicity values *only* from values derived for oral exposure. In fact, it is recommended that oral toxicity reference values *not* be extrapolated casually from inhalation toxicity values, although some such extrapolations may be performed on a case-by-case basis (USEPA 1989b). At any rate, these types of extrapolation can become useful approximations to employ—at least for preliminary risk assessments.

10.4.3.1 Exposure Route-Specificity of Toxicological Parameters

Toxicity parameters used in risk assessments are dependent on the route of exposure. However, as an example, oral RfDs and SFs have been used in practice for both ingestion and dermal exposures to some chemicals that affect receptors through a systemic action—albeit this will be inappropriate if the chemical affects the receptor contacts through direct local action at the point of application. In fact, in several (but certainly not all) situations, it is quite appropriate to use oral SFs and RfDs as surrogate values to estimate systemic toxicity as a result of dermal absorption of a chemical (DTSC 1994; USEPA 1989b, 1992a, b, c, d, e). It is noteworthy, however, that direct use of the oral SF or oral RfD does not account for differences in absorption and metabolism between the oral and dermal routes—leading to increasingly uncertain outcomes. Also, in the evaluation of the inhalation pathways, when an inhalation SF or RfD is not available for a compound, the oral SF or RfD may be used in its place—but mostly for screening-level types of analyses; similarly, inhalation SFs and RfDs may be used as surrogates for both ingestion and dermal exposures for those chemicals lacking oral toxicity values—also adding to the uncertainties in the evaluations.

In addition to the uncertainties caused by route differences, further uncertainty is introduced by the fact that the oral dose-response relationships are based on potential (i.e., administered) dose, whereas dermal dose estimates are absorbed doses. Ideally, these differences in route and dose type should be resolved via pharmacokinetic modeling. Alternatively, if estimates of the gastrointestinal absorption fraction are available for the compound of interest in the appropriate vehicle, then the oral dose-response factor, unadjusted for absorption, can be converted to an absorbed dose equivalent as follows:

$$\mathrm{RfD}_{\mathrm{absorbed}} = \mathrm{RfD}_{\mathrm{administered}} \times \mathrm{ABS}_{\mathrm{GI}} \tag{10.21}$$

$$SF_{absorbed} = \frac{SF_{administered}}{ABS_{GI}} \tag{10.22}$$

On the average, absorption fractions corresponding to approximately 10% and 1% are typically applied to organic and inorganic chemicals, respectively.

It is noteworthy that, for the most part, direct toxic effects on the skin have not been adequately evaluated for several chemicals encountered in the human work and living environments. This means that, it may be inappropriate to use the oral slope factor to evaluate the risks associated with a dermal exposure to carcinogens such as benz(*a*)pyrene, that are believed to cause skin cancer through a direct action at the point of application—i.e., unless proper adjustments are made accordingly. Indeed, depending on the chemical involved, the use of an oral SF or oral RfD for the dermal route is likely to result in either an over- or under-estimation of the risk or hazard. Consequently, the use of the oral toxicity value as a surrogate for a dermal value will usually tend to increase the uncertainty in the estimation of risks and hazards. However, this approach is not generally expected to significantly under-estimate the risk or hazard relative to the other routes of exposure that are evaluated in most risk assessments (DTSC 1994; USEPA 1992a, b, c, d, e).

Certainly, other methods of approach that are quite different from the above may be used to generate surrogate toxicity values. For instance, in some situations, toxicity values to be used in characterizing risks are available only for certain chemicals within a chemical class—and this may require a different evaluation approach. In such cases, rather than simply eliminating those chemicals without toxicity values from a quantitative evaluation, it usually is prudent to group data for such class of chemicals into well-defined categories (e.g., according to structure-activity relationships, or indeed other similarities) for consideration in the risk assessment. Such grouping should not be based solely on toxicity class or carcinogenic classifications. Regardless, it still must be acknowledged that significant uncertainties will likely result by using this type of approach as well. Hence, if and when this type of grouping is carried out, the rationale should be explicitly stated and adequately documented in the risk assessment summary—emphasizing the fact that the action may have produced over- or under-estimates of the true risk.

As a final point here, the introduction of additional uncertainties in an approach that relies on surrogate toxicity parameters cannot be over-emphasized—and such uncertainties should be properly documented and adequately elucidated as part of the overall risk evaluation process.

10.4.3.2 Route-to-Route Extrapolation of Toxicological Parameters

For systemic effects away from the site of entry, an inhalation toxicity parameter, TPinh [mg/m^3], may be converted to an oral value, TPoral [mg/kg-d], or vice versa, by using the following type of relationship (van Leeuwen and Hermens 1995):

$$TP_{inh} \times IR \times t \times BAF_{inh} = TP_{oral} \times BAF_{oral} \times BW \quad (10.23)$$

where: IR is the inhalation rate [m^3/h]; t is the time [h]; BAFr is the bioavailability for route r, for which default values should be used if no data exists [e.g., use 1 for oral exposure, 0.75 for inhalation exposure, and 0 (in the case of very low or very high lipophilicity or high molecular weight) or 1 (in the case of intermediate lipophilicity and low molecular weight) for dermal exposure]; and BW is the body weight [kg]. A dermal toxicity parameter for systemic effects, TPderm [mg/kg-d] can also be derived from the TP_{oral} [mg/kg-d] or the TP_{inh} [mg/m^3] values as follows (van Leeuwen and Hermens 1995):

$$TP_{derm} = TP_{oral} \times \frac{BAF_{oral}}{BAF_{derm}} \quad (10.24)$$

$$TP_{derm} = \frac{TP_{inh} \times IR \times t}{BW} \times \frac{BAF_{inh}}{BAF_{derm}} \quad (10.25)$$

It is noteworthy that, route-to-route extrapolation introduces additional uncertainty into the overall risk assessment process; such uncertainty can be reduced by utilizing physiologically-based pharmacokinetic (PBPK) models. Indeed, PBPK models are particularly useful for predicting disposition differences due to exposure route differences—i.e., if sufficient pharmacokinetic data is available (van Leeuwen and Hermens 1995).

Examples of the Route-to-route Extrapolation Process. As an illustrative example, some of the more common processes involved in route-to-route extrapolation exercises are provided below for both the carcinogenic and non-carcinogenic effects of chemical constituents.

- *Non-carcinogenic Effects*. Oftentimes, reference concentrations (RfCs) for inhalation exposures are extrapolated from oral reference doses (RfDs) for adults by using the following relationship:

$$\text{Extrapolated RfC}\left[\text{mg}/\text{m}^3\right] = \text{RfD}_{oral}[\text{mg/kg-day}] \times \frac{70[\text{kg}]}{20[\text{m}^3/\text{day}]} \quad (10.26)$$

  It should be noted here, however, that for this simplistic approximation, dosimetric adjustments have not been made to account for respiratory tract deposition efficiency and distribution; physical, biological, and chemical factors; and other aspects of exposure (e.g., discontinuous exposures) that affect chemical uptake and clearance (USEPA 1996a, b, c, d, e, f). Consequently, this simple extrapolation method relies on the implicit assumption that the route of administration is irrelevant to the dose delivered to a target organ—an assumption not supported by the principles of dosimetry or pharmacokinetics.

- *Carcinogenic Effects*. For carcinogens, unit risk factors (URFs) for inhalation exposures may be extrapolated from oral carcinogenic slope factors (SFs) for adults by using the following relationship (assuming a 100% absorption via inhalation):

$$\begin{aligned} &\text{Extrapolated URF}\left[(\mu g/\text{m}^3)^{-1}\right] \\ &= \text{SF}_{\text{oral}}\left[(\text{mg/kg-day})^{-1}\right] \times \frac{20[\text{m}^3/\text{day}]}{70[\text{kg}]} \\ &\times[\text{inhalation absorption rate}, 100\%] \times 10^{-3}\ [\text{mg}/\mu g] \end{aligned} \tag{10.27}$$

  Using the extrapolated URF, risk-specific air concentrations can be calculated as a lifetime average exposure concentration, as follows:

$$\text{Extrapolated air concentration}\left[\mu g/\text{m}^3\right] = \frac{\text{Target risk}\left[\text{e.g.}10^{-6}\right]}{\text{URF}\left[(\mu g/\text{m}^3)^{-1}\right]} \tag{10.28}$$

In general, insofar as possible, inhalation values should *not* be extrapolated from oral values—i.e., if at all avoidable. Yet, situations do sometimes arise when it becomes necessary to rely on such approximations to make effective environmental and public health risk management decisions.

10.4.3.3 Toxicity Equivalence Factors and Toxicity Equivalency Concentration

Some chemicals are members of the same family and exhibit similar toxicological properties; however, these chemicals would generally differ in their degrees of toxicity. To carry out a hazard effects assessment for such chemicals, a 'toxicity equivalence factor' (TEF) may first be applied to adjust the measured concentrations to a toxicity equivalent concentration—i.e., prior to embarking on the ultimate risk determination goal. In fact, the TEF approach has been extensively used for the hazard assessment of different classes of toxic chemical mixtures.

Broadly speaking, a toxicity equivalence factor (TEF) procedure is one used to derive quantitative dose-response estimates for substances that are members of a certain category or class of agents. The assumptions implicit in the utilization of the TEF approach include the following significant ones (NATO/CCMS 1988a, b; Safe 1998):

- The individual compounds all act through the same biologic or toxic pathway;
- The effects of individual chemicals in a mixture are essentially additive at sub-maximal levels of exposure;
- The dose-response curves for different congeners should be parallel; and
- The organotropic manifestations of all congeners must be identical over the relevant range of doses.

In essence, a basic premise of the TEF methodology is the presence of a common biologic end-point, or in the case of multiple end-points, a common mechanism of action. A second key assumption is the additivity of effects. In fact, these assumptions are inherent in all TEF-schemes—and thus, the accuracy of all TEF-schemes will be affected by situations where such assumptions are not applicable. It is also noteworthy that, for more complex mixtures containing compounds that act through multiple pathways to give both similar and different toxic responses, the TEF/TEQ approach may *not* be appropriate *per se* (Safe 1998).

On the whole, TEFs are based on shared characteristics that can be used to hierarchically rank-order the class members by carcinogenic potency when cancer bioassay and related data are inadequate for this purpose. The rank-ordering is by reference to the characteristics and potency of a well-studied member or members of the class under review. Other class members are then indexed to the reference agent(s) by using one or more shared characteristics to generate their TEFs. Examples of shared characteristics that may be used include: receptor-binding characteristics; results of biological activity assays related to carcinogenicity; or structure-activity relationships. The TEFs are usually indexed at increments of a factor of 10; very good data, however, may permit a smaller increment to be used.

Scope of Application for TEFs. It has to be acknowledged here that adequate data to support the use of TEFs has been found in only a limited class of compounds—most prominently, the dioxins (USEPA 1989c; 2010a, b). Dioxins are a group of compounds that share distinct chemical structures and characteristics. The term 'dioxin' commonly refers to the compound in this group considered most toxic—namely, 2,3,7,8-tetrachlorodibenzo-para-dioxin [or, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin] (TCDD); and 'dioxin-like' is a description used for compounds that have chemical structures, physico-chemical properties, and toxic responses similar to TCDD. Dioxin-like compounds (DLCs)—including polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like polychlorinated biphenyls (PCBs)—typically are found in mixtures with TCDD in potentially impacted/contaminated media or materials; indeed, TCDD and DLCs will characteristically occur as mixtures in the target environmental media.

In essence, dioxin and dioxin-like compounds represent structurally related groups of chemicals from the family of halogenated aromatic hydrocarbons. Depending on the number of chlorine-substituted positions, there are several congeners in each group. Ostensibly, the most toxic and the most studied congener is TCDD. Thus, TEFs have been developed to compare the relative toxicity of individual dioxin-like compounds to that of TCDD; the TEFs are numerical factors that express the toxicity of an individual PCDD or PCDF relative to the toxicity of TCDD, the highly toxic and best studied among the 210 congeners. This comparison is based on the assumption that dioxin and dioxin-like compounds act through the same mechanism of action. In this case, the TEF for TCDD is set at one (1), whereas TEF values for all other dioxin-like compounds are less than one. Ultimately, the toxicity equivalent (TEQ) (or the toxicity equivalency concentration) of TCDD is calculated by multiplying the exposure level of a particular dioxin-like compound by its TEF. A TEQ is defined by the product of the concentration, C_i, of

an individual 'dioxin-like compound' in a complex environmental mixture (i.e., concentration of the *i*-th congener) and the corresponding TCDD toxicity equivalency factor (TEF_i) for that compound (relative to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, i.e., 2,3,7,8-TCDD). The TEQs are generally used to assess the risk from exposure to a mixture of dioxin-like compounds.

Meanwhile, it is noteworthy that, even though they are distinctly different compounds, some PCBs also exhibit dioxin-like toxicity. Thus, a similar approach that utilizes the TEF concept for PCB congeners can also be found in the literature. Indeed, there are some 209 distinct PCB chemical compounds or congeners in reality—albeit, once released into the environment, PCBs are subject to a variety of photolysis and biodegradation processes, to the extent that only 50–75 congeners are routinely detected in higher trophic level species (van den Berg et al. 1995; 2006); also, it is notable that some twelve (12) of the 209 PCB congeners are considered dioxin-like. Anyhow, the PCBs are often classified into two broad categories—namely, 'dioxin-like' and 'non-dioxin-like'; the dioxin-like PCBs bind to the Ah receptor (AhR) and produce dioxin-like effects in experimental animals—with all other remaining PCBs then falling into the non-dioxin-like classification, and consequently behaving differently. Also quite important, it is remarkable that, although the dioxin-like PCBs are generally more potent at inducing biological effects, they tend to constitute only a minor portion of the mass of PCBs found in environmental and biological samples—with the non-dioxin-like PCBs accounting for a majority of the mass of the PCBs found in environmental and biological samples. At any rate, if dioxin-like PCBs are of concern for a PCB-impacted medium, the requisite PCB 'action/remedy level' will need to meet a case-specific dioxin TEQ 'action level'; in this case, two PCB action levels may have to be computed—*viz*., one for total PCBs (i.e., for all PCB congeners present) that is based on toxicity values for total PCBs, and the other calculated such that it meets a case-specific dioxin TEQ action level (that depends on the TEQ [i.e., concentration x TEF] of dioxin-like PCBs in the PCB-impacted media, along with any TCDD and other dioxin-like compounds (DLCs) present, as well as further considers toxicity values for TCDD). Ultimately, the more stringent of the set of the PCB action levels is then selected for any corrective action or remedy, as well as related risk management decisions. [By the way, when PCB congener concentrations are available, the usual PCB slope-factor approach can be supplemented by analysis of dioxin TEQs—in order to evaluate the dioxin-like toxicity. Subsequently, risk from the dioxin-like congeners is evaluated using TEFs—and this is then added to risks from the rest of the mixture.]

On the whole, the TEF scheme compares the relative toxicity of individual dioxin-like compounds to that of TCDD, which is the most toxic halogenated aromatic hydrocarbon—all the while recognizing that TEFs are based on congener-specific data and the assumption that the toxicity of dioxin-like chemicals is additive. Ultimately, the total TCDD equivalent (TEQ) is then used in conjunction with a cancer potency or reference exposure level to estimate cancer risk or non-cancer hazard index, respectively.

International TEFs (ITEFs). TEF schemes for PCDDs and PCDFs have been developed or adopted by many governmental institutions throughout much of the industrialized world. Of special interest, the International TEFs (ITEFs) scheme has been the result of an international conference, convened for the purpose of reaching a consensus for a uniform TEF scheme based on available whole animal non-cancer and cancer data, short term exposures, and *in vitro* data (NATO/CCMS, 1988a,b). To incorporate the results from many studies, the ITEF scheme used the assumption that all effects are initiated by the interaction of a PCDD or PCDF congener with a specific receptor protein, the *Ah* receptor. The rationale for this assumption comes from analyses in which biologic endpoints were found to be highly correlated with known *Ah* receptor associated effects. The ITEF scheme focuses on those congeners that are preferentially absorbed and accumulated in mammalian tissue over a long period of time and exhibit a similar spectrum of toxicities as 2,3,7,8 TCDD—namely, PCDDs/PCDFs in which positions 2-,3-,7-, and 8- are substituted by chlorine.

Essentially, the choice of an ITEF for each 2,3,7,8-PCDD/PCDF congener has been based on a synthesis of data from cancer studies, long-term toxicity studies, subchronic effects, acute toxicity studies, and receptor binding and enzyme induction. Greater weight has been given to results from long-term studies, but information of short-term studies has also been considered. In the absence of long-term studies, data from short-term whole animal and/or *in vitro* studies have been used. Meanwhile, it is noteworthy that a specific formula was not applied to the various data—but rather the final individual ITEF was based on the professional judgment of the aggregate data available for the individual congener.

The Calculus of TEQs: Fundamentals on the Practical Use of Dioxin TEFs to Calculate Dioxin TEQs. The toxicity of DLCs can be examined by considering their toxicity relative to TCDD. A TEF for a DLC is a measure of the compound's toxicity relative to TCDD (which is assigned a TEF of 1); thus, as an example, 1,2,3,4,7,8- hexachloro-dibenzo-*p*-dioxin is considered to be one tenth as toxic as TCDD—and has therefore been assigned a TEF of 0.1. Meanwhile, it is worth the mention here that the TEFs are generally most appropriate for dioxin exposures via the oral exposure route. In any event, in addition to the ingestion pathway, the TEFs may be applied to other exposure routes (i.e., dermal or inhalation) as well—but generally as a rough estimate, and whiles also assuming that exposures to DLCs via these routes can indeed be quantified. When included in an assessment, the fractional contribution of oral, dermal, and inhalation route exposures to the predicted TEQ should be identified.

For a single DLC, the dioxin toxicity equivalence [TCDD TEQ] is the product of the concentration of the DLC in an environmental mixture and its corresponding TEF; the total TEQ for the mixture is the sum of the individual TCDD TEQs across the DLCs. Looking at the bigger picture, a general equation for calculating the exposure concentration for n DLCs in a mixture, in TCDD TEQ, can be formulated; in this case, exposure to the i^{th} individual PCDD, PCDF, or PCB compound is expressed in terms of an equivalent exposure of TCDD by computing the product of the concentration of the individual compound (C_i) and its assigned TEF_i. Finally, the total TEQs is the sum of the TEQs for each of the congeners in a given

mixture—i.e., the total TEQ is calculated by summing these products across the n DLCs present in the mixture, as follows:

$$\text{Total TEQs} = \sum_{i=1}^{n} (C_i \times TEF_i) \tag{10.29}$$

where: TEQ is the TCDD toxicity equivalence; C_i is the individual TCDD or DLC concentration in the target environmental media; and TEF_i is the toxicity equivalence factor assigned for TCDD or the DLC. On the whole, the TCDD TEQ provides a means for determining the toxicity of a mixture of DLCs, in the absence of toxicity values for these DLCs. In this effort, the most current WHO-developed TEF values—which include dioxins, furans and dioxin-like PCBs—generally would serve as the recommended TEF values for use in most human health risk analyses, as and when applicable.

Finally, it is noteworthy that the overall TEF approach is based on the concept of dose addition, under which it is assumed that the toxicokinetics and toxicodynamics for all DLCs are similar (with the dose-response curves of the components of a mixture assumed to be similarly shaped), and that the DLCs act by a common toxic mode of action. Furthermore, this approach assumes that toxicological interactions do *not* occur among the DLCs within the environmental mixtures being assessed (e.g., that synergism and antagonism do *not* occur).

10.4.3.4 Relative Potency Factors

Another variation of the TEF concepts described above is often encountered in relation to other families of compounds. For example, although several polycyclic aromatic hydrocarbons (PAHs) have been classified as probable human carcinogens (*viz*., USEPA Group B or IARC Group 2A), cancer slope factors for this family is often associated with only one particular constituent—namely, benzo[*a*]pyrene (BaP). Consequently, quantitative risk estimates for PAH mixtures have often assumed that all carcinogenic PAHs are equipotent to BaP. A preferred approach, however, involves using an estimated order of potential potency relative to BaP. This allows a potency-weighted total concentration to be calculated, as follows:

$$PEC = \sum_{i=1}^{n} (RP_i \times C_i) \tag{10.30}$$

where PEC is the potency equivalency concentration; RP_i is the relative potency for the i-th PAH; and C_i is the concentration of the i-th PAH.

Indeed, considering the fact that PAHs seem almost ubiquitous in most environmental settings, it is important to be able to more accurately evaluate the risks arising from exposure to this family of compounds. On the other hand, there is *not* an adequate scientific data on which to base a cancer SF for all PAHs, other than

BaP for the most part. Consequently, the risk for PAHs has often been based on assessing all the PAHs found in an environmental sampling analysis by using the SF for BaP. Since BaP is one of the two most potent PAHs (with dibenz[*a,h*]anthracene being the other), assessing all PAHs as if they were BaP may significantly overestimate risks. The use of the relative potencies for PAHs, therefore, may offer enormous improvements in ensuring that risks are better represented. Even so, it must be cautioned that the applications of the TEFs concept to PAHs usually require a more detailed knowledge of the complete composition of these mixtures as well as the RPs of all active components. Thus, the approach may be most useful for defined PAH mixtures containing only parent hydrocarbons (Safe 1998).

10.5 The Dose-Response Assessment in Practice: A Recap of the Facts and Fallacies

The practical purpose of the dose-response assessment is to identify the types of adverse health effects that may be associated with potential exposure to a chemical, as well as to define the relationship between the dose of a chemical and the likelihood-cum-magnitude of an adverse effect (response) (USEPA 1989a); adverse effects are generally classified as potentially carcinogenic or noncarcinogenic (i.e., potential health effects, other than cancer). For the most part, the dose-response relationships are usually defined for oral exposure, and also for exposure via inhalation. However, because of the scarcity of toxicological data and established values for the dermal route of exposure, oral toxicity values are often used to evaluate dermal exposures—usually with appropriate adjustment for differences in absorption insofar as possible (USEPA 2004a). Ultimately, combining the results of the toxicity assessment with information on the magnitude of potential exposure (developed in an exposure assessment) provides an estimate of potential risk (as generated in a typical risk characterization).

For the evaluation of potential noncancer effects, oral reference doses (RfDs) and inhalation reference concentrations (RfCs) are generally available for effects known or assumed to be produced through a nonlinear mode of action (USEPA 2015a); the RfDs [expressed in units of milligrams of a chemical per kilogram of body weight per day (mg/kg-day)] and RfCs [expressed in units of milligrams of a chemical per cubic meter of air (mg/m^3)] are developed based on the assumption that thresholds exist for certain toxic effects (such as gastrointestinal effects). All in all, the RfDs and RfCs are estimates (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Meanwhile, it is worth recalling here that, for the evaluation of potential noncarcinogenic effects, exposures are generally characterized as chronic (i.e., lasting longer than 7 years) or subchronic (i.e., lasting 7 years or less)—albeit,

consistent with a Science Advisory Board (SAB) recommendation, a child of 1 to 6 years is considered to have a chronic exposure (USEPA 2002c).

For evaluation of potential cancer effects, the weight of evidence for human carcinogenicity is used alongside the target chemical's oral slope factors [presented as the risk per (mg/kg-day)], and oral and inhalation unit risks [presented as ingestion risk per μg/L drinking water or inhalation risk per $\mu g/m^3$ air breathed, as appropriate] in the risk characterization process (USEPA 2015a).

10.5.1 Basis for Dose-Response Relationships

The dose-response relationships, characterized by the toxicity values typically used in practice, are often established from studies of laboratory animals conducted under controlled conditions that are purposely designed to minimize responses due to confounding variables—and also are conducted at relatively high dose levels to ensure that responses can be observed using as few animals as possible in the experiments. Mathematical models and uncertainty factors are then used to extrapolate the relatively high doses administered to animals—in order to attempt to predict potential human responses at dose levels far below those tested in animals. Indeed, humans are typically exposed to chemicals in the environment at levels much lower than those tested in animals; these low doses may also be detoxified or rendered inactive by the myriad of protective mechanisms that are present in humans, but which may not function at the high dose levels used in animal experiments (Ames et al. 1987). Moreover, in the case of systemic toxicity, organic homeostatic, compensating, and adaptive mechanisms exist for humans that may have to be overcome before a toxic endpoint is manifested USEPA (1993b). Therefore, the results of these animal studies may only be of limited use in accurately predicting a dose-response relationship in humans (USEPA 1989a). In fact, many effects seen in laboratory animals at the high doses tested tend not to be seen in human exposures to chemicals *per se*; for example, while PCBs have been demonstrated to produce tumors in animals, human epidemiological data do not quite seem to wholly support the carcinogenicity of PCBs (Shields 2006; Golden et al. 2003, Golden and Kimbrough 2009). Notwithstanding these uncertainties, and with the goal of being protective of human health being a dominant decision factor, it is generally assumed that the results of animal toxicity studies are predictive of potential toxicity in humans. Moreover, based on the assumption that humans are more sensitive to chemicals than most laboratory animals, conservative assumptions and uncertainty factors are often incorporated into the processes used to derive numerical toxicity values from laboratory studies—albeit it is still prudent to explicitly recognize these extrapolations (e.g., from high doses to low doses, and from animal studies used to predict responses in humans) as significant sources of uncertainties to contend with; consequently it becomes important to properly ascertain that these issues are meticulously documented as an essential part of the overall risk assessment process (USEPA 1989a).

Next, it should be acknowledged here that in some cases, data from human exposure to chemicals are used to develop dose-response values. However, these data also have uncertainties because in most cases, it is not possible to determine from human exposure studies whether one or more chemicals are responsible for the observed effects; in fact, it is even more difficult to determine the precise exposure levels of interest (USEPA 1989a). Moreover, where effects are observed in humans, they generally occur at high exposure levels (often in industrial settings)—and it is difficult to predict potential human responses at the much lower dose levels that occur in typical or more 'representative'/'normal' environmental exposure scenarios (USEPA 1989a).

10.5.2 Options for Noncarcinogenic Toxicity Assessment

Constituents with known or potential noncarcinogenic effects are conventionally assumed to have a dose below which no adverse effect occurs or, conversely, above which an adverse effect may be seen; this dose is called the threshold dose. A conservative estimate of the true threshold dose is called a 'No Observed Adverse Effect Level' (NOAEL); the lowest dose at which an adverse effect has been observed is called a 'Lowest Observed Adverse Effect Level' (LOAEL). The NOAEL (or if not available, the LOAEL) would generally be used as the so-called 'point-of-departure' (POD) for extrapolating from experimental data to predict a threshold level for humans. By applying uncertainty factors to the NOAEL or the LOAEL, RfDs for chronic exposure to chemicals with noncarcinogenic effects can be developed for use in risk assessments (1997a, 2015a).

In more recent derivations, a benchmark dose (BMD) approach has been used to define the POD for an observed adverse outcome—or benchmark response—from experimental observations. The BMD approach provides a more quantitatively-rich alternative to the first step in the dose-response assessment than the classic NOAEL/LOAEL process for noncancer health effects. Broadly speaking, derivation of the BMD is a two-step process: first, response data are modeled in the range of empirical observation, and then extrapolation below the range of observation is subsequently achieved by modeling. The POD for BMD modeling is the BMDL, or the lower 95% bound on the dose/exposure associated with the benchmark response (i.e., adverse response)—typically 10% above the control response. Using the lower bound accounts for the uncertainty inherent in a given study, and assures (with 95% confidence) that the target benchmark response is likely not exceeded. Uncertainty factors are then applied to the BMDL, as in the case for the NOAEL/LOAEL approach, to derive an RfD.

In a typical regulatory toxicity assessment, it is often assumed that humans are as sensitive (or perhaps even more sensitive) to the toxic effects of a chemical as the most sensitive species used in the laboratory studies. Moreover, the RfD is developed based on the most sensitive or critical adverse health effect observed in the study population, with the assumption that if the most critical effect is prevented,

then all other potential toxic effects might be prevented. Uncertainty factors are applied to the BMDL or NOAEL (or LOAEL, when a NOAEL is unavailable) for this critical effect to account for uncertainties associated with the dose-response relationship. The key sources of uncertainties include the following:

- Using an animal study to derive a human toxicity value;
- Extrapolating from a LOAEL to a NOAEL;
- Extrapolating from a subchronic (partial lifetime) to a chronic lifetime exposure; and
- Evaluating sensitive subpopulations.

Generally, a tenfold factor is used to account for each of these uncertainties; thus, the total uncertainty factor can typically range from 10 to 10,000. In addition, another uncertainty factor—or a modifying factor—of up to 10 can be used to account for inadequacies in the database or other uncertainties.

Ultimately, the resulting RfDs generated tend to be conservative (i.e., reasonably health-protective) because of the use of often multiple uncertainty and modifying factors. Consequently, an RfD provides reasonable certainty that no noncarcinogenic health effects are expected to occur, even for sensitive individuals—and indeed even if daily exposures were to occur at the RfD level for a lifetime. Finally, it is notable that, since RfDs and exposure doses are expressed in units of milligrams of a chemical per kilogram of body weight per day (mg/kg-day), it becomes apparent that the lower the RfD value, the lower is the assumed threshold for effects, and the greater the assumed toxicity.

10.5.2.1 Closing Remarks on the Non-cancer Endpoint Appraisal Process

In appraising the non-cancer endpoint risks to human health arising from a given chemical exposure situation, it invariably becomes necessary to develop or utilize available reference dose (RfD) parameters for the chemical of concern. An RfD represents an 'estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime'; in general, the RfD is based on the assumption that a certain dose must be exceeded before toxicity is manifested (EPA 2012b). [It is noteworthy that a reference concentration (RfC) is typically developed for inhalation toxicants.]

The RfD is generally derived from a no-observed-adverse-effect level (NOAEL), a lowest-observed-adverse-effect level (LOAEL), or a benchmark dose from animal or epidemiological studies. The NOAEL is the 'highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control' (EPA 2012b). The LOAEL is the 'lowest exposure level at which there are biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group' (EPA 2012b).

The benchmark dose (BMD) is a 'dose or concentration that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background' (EPA 2012b). In general, NOAELs and LOAELs are derived from animal data; and benchmark doses are derived from epidemiologic studies. In developing the RfD, the NOAEL, LOAEL, or BMD is generally adjusted (downward) by uncertainty factors (UFs) which are usually multiples of 10—meant to account for limitations and incompleteness in the data used; these limitations could include knowledge of interspecies variability, and the expectation that variability in response in the general population is likely to be much greater than that present in the populations (human or animal) from which the NOAEL, LOAEL, or BMD is derived.

10.5.3 Carcinogenic Toxicity Assessment and Mutagenic Mode of Action

Constituents with known or potential carcinogenic effects are generally evaluated using the toxicity parameters or potency factors that differ from what is used in evaluating non-cancer effects. The potency estimate for oral and dermal exposure, called a cancer slope factor (CSF) is expressed in units of $(\text{mg/kg-day})^{-1}$; in consequence, the higher the CSF, the greater the carcinogenic potential.

It is noteworthy that, recent refinements in risk assessment methods have used 'mode-of-action' (MOA) evaluations in dose-response assessments. As found in the literature (see, *e.g.*, EPA 2005a), 'mode-of-action' is generally defined as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation; a 'key event' is an empirically observable precursor step that is itself a necessary element of the mode-of-action, or is a biologically-based marker for such an element. At any rate, and among several other things, regulatory guidance for early life exposure to carcinogens generally recommends that potential risks from chemicals that act by a mutagenic mode of action be calculated differently in comparison to those chemicals that do not act via a mutagenic mode of action (USEPA 2005b). For carcinogens presumed to act via a mutagenic mode of action, dose-response values are generally based on the linearized multistage (LMS) model—which assumes that cancer risks are linear in the low-dose region (USEPA 2005b, c).

10.5.4 Mechanisms of Action and the Determination of Human Health Hazard Effects

Mechanism of action is defined as the complete sequence of biological events that must occur to produce an adverse effect. In cases where only partial information is available, the term *mode of action* is used to describe only major (but not all) biological events that are judged to be sufficient to apprise the shape of the dose-response curve beyond the range of observation. For effects that involve the alteration of genetic material (e.g., most cancers and heritable mutations), there are theoretical reasons to believe that such mode of action would not show a threshold or dose below which there are no effects. On the other hand, a threshold is widely accepted for most other health effects, based on considerations of compensatory homeostasis and adaptive mechanisms. The threshold concept presumes that there exists a range of chemical exposures (from zero up to some finite value) that can be tolerated by an individual without adverse effects. Accordingly, different approaches have traditionally been used to evaluate the potential carcinogenic effects *versus* health effects other than cancer (namely, 'non-cancer' effects).

Overall, chemical hazard effects evaluation is characteristically conducted as part of a risk assessment in order to, qualitatively and/or quantitatively, determine the potential for adverse effects from receptor exposures to chemical stressor(s). For most chemical exposure problems, this usually will comprise of intricate toxicological evaluations, the ultimate goal of which is to derive reliable estimates of the amount of chemical exposure that may be considered 'tolerable' (or 'acceptable' or 'reasonably safe') for humans. The relevant toxicity parameters that are generated during this process usually will be dependent on the mechanism and/or mode of action for the particular toxicant, on the receptor of interest.

By and large, public health risk assessments for chemical exposure problems would typically rely heavily on 'archived' toxicity indices/information developed for specific chemicals. A summary listing of such toxicological parameters—predominantly represented by the cancer SF (for carcinogenic effects) and the RfD (for non-cancer effects)—is provided in Table C.1 (Appendix C) for some representative chemicals commonly found in consumer products and/or in the human living and work environments. A more complete and up-to-date listing may be obtained from a variety of toxicological databases—such as the Integrated Risk Information System (IRIS) database (developed and maintained by the US EPA); the International Register of Potentially Toxic Chemicals (IRPTC) database (from UNEP); the International Toxicity Estimates for Risks (ITER) database (from TERA); etc. [see Appendix D]. Where toxicity information does not exist at all, a decision may be made to estimate toxicological data from that of similar compounds (i.e., with respect to molecular weight and structural similarities; etc.).

10.6 A Call for a Unified Framework and Approach to Dose-Response Assessments

Traditionally, dose-response assessments for carcinogenic end points have generally been carried out very differently from noncancer assessments. For carcinogens, it has commonly been assumed that there is no threshold of effect, and dose-response assessments have focused on quantifying the risk at low doses. For instance, the contemporary US Environmental Protection Agency (EPA) approach usually derives a point-of-departure' (POD), such as the lower bound on the dose that results in an excess risk of 10% based on the fitting of a dose-response model to animal bioassay data (USEPA 2000a). After adjustment for animal-human differences in the dose metric, risk is assumed to decrease linearly with doses below the POD for carcinogens that are direct mutagens or are associated with large human body burdens (USEPA 2005a). The population burden of disease or the population risk at a given exposure can also be estimated. In practice, the US EPA carcinogen assessments do not account for differences among humans in cancer susceptibility other than from possible early-life susceptibility (NRC 2009). Next, for noncancer end points, it is assumed that homeostatic and defense mechanisms lead to a dose threshold (that is, there is low-dose nonlinearity) below which effects do not occur or are extremely unlikely. For these agents, risk assessments have focused on defining the reference dose (RfD) or reference concentration (RfC)—generally considered as a 'cut-off point' that is 'likely to be without an appreciable risk of deleterious effects' (USEPA 2002a; NRC 2009). As in cancer dose-response assessment, the RfD is also derived from a POD—which could be a no-observed-adverse-effect level (NOAEL) or a benchmark dose (BMD). However, instead of extrapolating to a low-dose risk, the POD is divided by 'uncertainty factors' to adjust for animal-human differences, human-human differences in susceptibility, and other factors (e.g., data gaps or study duration). Furthermore, in a variant of the RfD approach to noncancer or low-dose nonlinear cancer risk assessment, a 'margin of exposure' (MOE)—defined by the ratio of a NOAEL or POD to a projected environmental exposure—may be computed (USEPA 2000a, 2005b). The MOE is compared with the product of uncertainty factors; an MOE greater than the product is considered to be without appreciable risk or 'of low concern', and an MOE smaller than the product reflects a potential health concern (USEPA 2000b). MOEs and RfDs are typically specified for durations of exposure (for example, acute, subchronic, and chronic), and may also be defined for specific life stages (e.g., developmental) (USEPA 2002a).

On the other hand, the threshold-nonthreshold dichotomy seems to create an inconsistent approach for bringing toxicology and risk science into the decision-making process when dealing with carcinogens *versus* noncarcinogens (NRC 2009). Thus, there have been efforts in recent times to harmonize dose-response methods for cancer and noncancer end points. As an example of the efforts towards harmonization, for carcinogens with sufficient MOA data to conclude nonlinearity at low doses (such as those acting through a cytotoxic MOA), the RfD approach

noted above for noncancer end points may indeed be applied (USEPA 2005b); in this case, thresholds are assumed for noncarcinogens, as well as for carcinogens believed to operate through an MOA considered nonlinear at low doses. Another refinement in dose-response assessment has been the derivation of the RfD or low-dose cancer risk from a POD that is calculated using BMD methodology (USEPA 2000a); in noncancer risk assessment, this approach has the advantage of making better use of the dose-response evidence available from bioassays than do calculations based on NOAELs—and also provides additional quantitative insight into the risk presented in the bioassay at the POD (NRC 2009).

Indeed, a number of criticisms have been put forward as to the true validity of the 'traditionalist' approach to dose-response assessments (NRC 2009); for instance, the US National Academy of Science (NRC 2009) has suggested that the separation of cancer and noncancer outcomes in dose-response analysis is artificial because noncancer end points can occur without a threshold or low-dose nonlinearity on the population level, and in some cases even on the individual level. Also, it has been argued that the MOA for carcinogens varies and requires a flexible but consistent analytic framework. Overall, it is contended that the separation may not only be scientifically unjustified—but could also lead to undesirable risk management outcomes, including inadequate attention to noncancer end points. Consequently, it is believed that a new approach that incorporates the re-definition of the RfD as a 'risk-specific dose' may be in order (NRC 2009). To allow for a use of risk descriptors that are quantitative and probabilistic, the RfD could indeed be redefined as a risk-specific dose (for example, the dose associated with a 1 in 100,000 risk of a particular end point), and then the risk could be estimated at doses above and below the RfD. On the whole, the underlying scientific and risk management considerations seem to point to the need for unification of cancer and noncancer approaches in which chemicals are put into a common analytic framework regardless of type of outcome—i.e., despite the obvious core differences among endpoints.

Finally, and among several other things, a key part of the argument against segregating the cancer and noncancer risk assessment evaluation elements is the fact that the approach is believed to ignore possible contributions to ongoing carcinogenesis processes and the multifactorial nature of cancer. In other words, chemicals that may increase human cancer risk by contributing to an underlying process are handled essentially as noncarcinogens even though they may be integral to the carcinogenic process—and this dichotomy increases the burden of judging which chemicals are carcinogens rather than accepting the variety of carcinogenic MOAs and incorporating them into a comprehensive risk assessment (NRC 2009). This could indeed represent a significant shortcoming in the overall risk assessment process.

Chapter 11
Chemical Risk Characterization

Fundamentally, risk characterization consists of estimating the probable incidence of adverse impacts to potential receptors, under the various exposure conditions associated with a chemical hazard situation. It involves an integration of the hazard effects and exposure assessments—in order to arrive at an estimate of the health risk to the exposed population. In general, all information derived from each step of a chemical exposure-cum-hazard assessment are integrated and utilized during the risk characterization—so as to help project the degree and severity of adverse health effects in the populations potentially at risk.

Risk characterization is indeed the final step in the risk assessment process, and this also becomes the first input into risk management programs. Thus, risk characterization serves as a bridge between risk assessment and risk management—making it a key factor in the ultimate decision-making process that would often be undertaken to help address chemical exposure problems. Classically, risk characterization commonly will entail a statement regarding the 'response' or 'risk of harm' that is expected in the population under an associated set of exposure conditions, together with a description of uncertainties (NRC 1983). Through probabilistic modeling and analyses, uncertainties associated with the risk evaluation process can be assessed properly, and their effects on a given decision accounted for systematically. In this manner, the risks associated with given decisions may be delineated—and then appropriate corrective measures taken accordingly. This chapter elaborates the mechanics of the risk characterization process, together with example risk presentation modalities that would tend to, among several other things, facilitate effective risk management and/or risk communication efforts.

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11.1 Fundamental Issues and Considerations Affecting the Risk Characterization Process

The chemical risk characterization process generally consists of an integration of the toxicity and exposure assessments—resulting in a quantitative estimation of the actual and potential risks and/or hazards associated with a chemical exposure problem. Broadly stated, risk from human exposure to chemicals is a function of dose or intake and potency, viz.:

$$Risk\,from\,chemical\,exposure = [Dose\,of\,chemical] \times [Chemical\,potency] \quad (11.1)$$

Overall, chemical risk characterization is viewed as a process by which dose-response information is integrated with quantitative estimates of human exposure derived in an exposure assessment; the result is a quantitative estimate of the likelihood that humans will experience some form of adverse health effects under a given set of exposure assumptions. During the risk characterization, chemical-specific toxicity information is traditionally compared against both field measured and estimated chemical exposure levels (and in some cases, those levels predicted through fate and behavior modeling) in order to determine whether concentrations associated with a chemical exposure problem are of significant concern. In principle, the process should also consider the possible additive or cumulative and related effects of exposure to mixtures of the chemicals of potential concern.

Two general types of health risk are typically characterized for each potential exposure pathway considered—viz.: potential carcinogenic risk, and potential noncarcinogenic hazard. Broadly speaking, characterization of the potential health effects of potential carcinogenic versus noncarcinogenic chemicals are approached very differently. A key difference in the approaches arises from the conservative assumption that substances with possible carcinogenic action typically behave via a no-threshold mechanism, whereas other toxic actions may have a threshold (i.e., a dose below which few individuals would be expected to show a response of concern)—albeit this viewpoint has been challenged, and remains in debate. Thus, under the no-threshold assumption, it becomes necessary to calculate a risk number—whereas for chemicals with a threshold, it is possible to simply characterize an exposure as above or below the designated threshold level (generally termed a reference dose or reference concentration). Also, potential carcinogenic risk is evaluated by averaging exposure over a 'normal' human lifetime, whereas potential noncarcinogenic hazard is evaluated by averaging exposure over the total exposure period considered in practice. Indeed, depending on the nature of populations potentially at risk from a chemical exposure problem, different types of risk metrics or parameters may be employed in the risk characterization process. At any rate, the cancer risk estimates and hazard quotient-cum-hazard index estimates are the measures of choice typically used to define potential risks to human health [see Sects. 11.2 and 11.3]. Indeed, it is almost indispensable to have these measures available to support effectual public health risk management

programs. Consequently, the health risks to potentially exposed populations resulting from chemical exposures are characterized through a calculation of non-carcinogenic hazard quotients/indices and/or carcinogenic risks (CAPCOA 1990; CDHS 1986; USEPA 1986a, 1989a).

In the final analysis, an effective risk characterization should be carried out in such a manner that it fully, openly, and clearly characterize risks as well as disclose the scientific analyses, uncertainties, assumptions, and science policies that underlie decisions utilized throughout the risk assessment and risk management processes. In fact, every risk assessment should clearly delineate the strengths and weaknesses of the data, the assumptions made, the uncertainties in the methodology, and the rationale used in reaching the conclusions (e.g., similar or different routes of exposure, and metabolic differences between humans and test animals). Furthermore, the hazard and risk assessment of human exposure to chemicals must take a miscellany of other critical issues into account—especially as relates to scenarios whereby chemical interactions may significantly influence toxic outcomes; chemical interactions are indeed very important determinants in evaluating the potential hazards and risks of exposure to chemical mixtures (Safe 1998).

Lastly, it is noteworthy that, a health risk assessment/characterization is only as good as its component parts—i.e., the hazard characterization, the dose-response analysis, and the exposure assessment. Confidence in the results of a risk assessment is thus a function of the confidence in the results of the analysis of these distinct key elements, and indeed their corresponding ingredients. In the end, several important issues usually will have very significant bearing on the processes involved in completing risk characterization tasks designed to support effective public health risk management programs; a number of the particularly important topics/issues are discussed below.

11.1.1 Corrections for 'Non-standard' Population Groups

During the risk estimation, the exposure information is customarily combined with dose-response information. In the processes involved, care must be taken to ensure that the assumptions about population parameters in the dose-response analysis are consistent with the population parameters used in the exposure analysis; common procedures for assuring such consistency is provided in the literature elsewhere (e.g., USEPA 1997a, b, c, d, e, f, g, h; West et al. 1997). In general, when the population of interest is different in comparison with the 'standard' population assumed in the dose-response assessments, then the dose-response parameter may need to be adjusted accordingly. Furthermore, when the population of interest is different from the population from which the often-used default exposure factors were derived, then the exposure factor may also need to be adjusted accordingly. A good example of a 'non-standard' sub-population would be a sedentary hospital population with lower than 20 m^3/day air intake rates (as is often assumed for most 'standard' population groups). Also, an example of such a sub-population relates to

mean body weight (that is different from the often assumed standard of 70 kg); for instance, under some circumstances, females usually may be assumed to have an average body weight of 60 kg, and also children's body weights will be dependent on their age.

To exemplify the requisite procedures for modifying standard parameters for non-standard populations, consider a recommended value for the average consumption of tap water by adults in a population group to be 1.4 L/day. Assume the drinking water unit risk for chemical *X* is 8.3×10^{-6} per μg/L, and that this was calculated from the slope factor assuming the standard intake, I_{ws}, of 2 L/day. Then, for the population group drinking 1.4 L of tap water per day, the corrected drinking water unit risk should be (USEPA 1997a, b, c, d, e, f, g, h):

$$\left[8.3 \times 10^{-6}\right] \times \left[\frac{1.4}{2}\right] = 5.8 \times 10^{-6}\,\text{per}\,\mu\text{g/L}$$

Subsequently, the risk to the average individual can then be estimated by multiplying this value by the average concentration (in units of μg/L).

Another illustrative example using the procedures provided by the US EPA (USEPA 1997a, b, c, d, e, f, g, h) involves estimating the risk specifically for women drinking the water contaminated with chemical *X*. Now, if the body weight, W^p, of the population of interest differs from the body weight, W^s, of the population from which the standard exposure values were derived, then a modeling adjustment may have to be made in estimating the intake of food, water, and air in this population (USEPA 1997a, b, c, d, e, f, g, h; West et al. 1997). If it is assumed that this group of women has an average body weight of 60 kg, then the correction factor for the drinking water unit risk (disregarding the correction discussed above with respect to consumption rate) is:

$$\left[\frac{70}{60}\right]^{2/3} = 1.11$$

Thus, the corrected water unit risk for chemical *X* is:

$$\left[8.3 \times 10^{-6}\right] \times [1.11] = 9.2 \times 10^{-6}\,\text{per}\,\mu\text{g/L}$$

As indicated previously, the risk to the average individual is subsequently estimated by multiplying this value by the water concentration.

11.1.2 Adjustments for Chemical Absorption: Administered vs. Absorbed Dose

Oftentimes, absorption adjustments may become necessary during the risk estimation process—in order to ensure that the exposure estimate and the toxicity value

being compared during the risk characterization are both expressed as absorbed doses, or both expressed as administered doses (i.e., intakes). Adjustments may also be required for different vehicles of exposure (e.g., water, food, or soil)—albeit, in most cases, the unadjusted toxicity value will provide a reasonable or conservative estimate of risk. Furthermore, adjustments may be needed for different absorption efficiencies, depending on the medium of exposure; in general, correction for fractional absorption is particularly appropriate when interaction with environmental media or other chemicals may alter absorption from what would typically be expected for the pure compound. Correction may also be necessary when assessment of exposure is via a different route of contact than what was utilized in the experimental studies used to establish the toxicity parameters (i.e., the SFs, RfDs, etc. discussed in Chap. 10). For instance, only limited toxicity reference values generally exist for dermal exposure; consequently, oral values are frequently used to assess risks from dermal exposures (USEPA 1989d). On the other hand, most RfDs and some carcinogenic SFs usually are expressed as the amount of substance administered per unit time and unit body weight, *whereas* exposure estimates for the dermal route of exposure are eventually expressed as absorbed doses. Thus, for dermal exposures, it may become particularly important to adjust an oral toxicity value from an administered to an absorbed dose—generally carried out as indicated below (USEPA 1989d).

- *Adjustment of an 'administered dose' to an 'absorbed dose' for RfDs.* The 'administered dose'-based RfD (RfD_{adm}) of a chemical with oral absorption efficiency, ABS, in the species on which the RfD is based may be adjusted to an 'absorbed dose'-based RfD (RfD_{abs}); this is achieved by simply multiplying the unadjusted RfD by the absorption efficiency percent—as follows:

$$RfD_{abs} = RfD_{adm} \times ABS \tag{11.2}$$

  This can then be compared with the amount estimated to be absorbed dermally.

- *Adjustment of an 'administered dose' to an 'absorbed dose' for SFs.* The 'administered dose'-based SF (SF_{adm}) of a chemical with oral absorption efficiency, ABS, in the species on which the SF is based may be adjusted to an 'absorbed dose'-based SF (SF_{abs}); this is achieved by simply dividing the unadjusted SF by the absorption efficiency percent—as follows:

$$SF_{abs} = \frac{SF_{adm}}{ABS} \tag{11.3}$$

  This can then be used to estimate the cancer risk associated with the estimated absorbed dose for the dermal route of exposure.

- *Adjustment of an exposure estimate to an absorbed dose.* If the toxicity value is expressed as an absorbed rather than an administered dose, then it may become necessary to convert the exposure estimate from an intake into an absorbed dose

for comparability. The unadjusted exposure estimate or intake (CDI_{adm}) of a chemical with absorption efficiency, ABS, may be converted to an 'adjusted exposure' or absorbed dose (CDI_{abs}); this is achieved by simply multiplying the unadjusted CDI by the absorption efficiency percent—as follows:

$$CDI_{abs} = CDI_{adm} \times ABS \tag{11.4}$$

This can then be used in comparisons with the RfD or SF that has been developed based on an absorbed (*not* administered) dose.

Absorption efficiency adjustment procedures are elaborated further elsewhere in the literature (e.g., USEPA 1989d, 1992a, b, c, d, e). Meanwhile, it is noteworthy that, for evaluations of the dermal exposure pathway, if the oral toxicity value is already expressed as an absorbed dose, then it is not necessary to adjust the toxicity value. Also, exposure estimates should not be adjusted for absorption efficiency if the toxicity values are based on administered dose. Furthermore, in the absence of reliable information, 100% absorption is usually used for most chemicals; for metals, an approximately 10% absorption may be considered a reasonable upper-bound for other than the inhalation exposure route.

In general, absorption factors should not be used to modify exposure estimates in those cases where absorption is inherently factored into the toxicity/risk parameters used for the risk characterization. Thus, 'correction' for fractional absorption is appropriate only for those values derived from experimental studies based on absorbed dose. In other words, absorbed dose should be used in risk characterization only if the applicable toxicity parameter (e.g., SF or RfD) has been adjusted for absorption; otherwise, intake (unadjusted for absorption) are used for the calculation of risk levels.

11.1.3 Aggregate Effects of Chemical Mixtures and Multiple Exposures

Oftentimes in the study of human exposures to chemical hazards, it becomes necessary to carry out aggregate and cumulative exposure and risk assessments. In fact, in most situations, it is quite important to consider both aggregate and cumulative exposures—to facilitate the making of effectual risk assessment and risk management decisions, as well as help the process of setting chemical tolerance or safe levels for human exposures. In general, aggregate exposures may occur across different pathways and media that contribute to one or more routes of an individual receptor's exposure—which then becomes the basis for determining cumulative risks.

Cumulative risk refers to effects from chemicals that have a common mode of toxicological action—and thus have aggregate exposure considerations as part of the assessment process (Clayton et al. 2002). Indeed, whereas some chemical

hazard situations involve significant exposure to only a single compound, most instances of chemical exposure problems can involve concurrent or sequential exposures to a mixture of compounds that may induce similar or dissimilar effects over exposure periods ranging from short-term to a lifetime (USEPA 1984a, 1986b). Meanwhile, it is notable that evaluating mixtures of chemicals is one of the areas of risk assessment with obviously many uncertainties; this is especially so, because several types of interactions in chemical mixtures are possible—including the following key distinct attributes:

- Additive—wherein the effects of the mixture equals that of adding the effects of the individual constituents.
- Synergistic—wherein the effects of the mixture is greater than obtained by adding the effects of the individual constituents.
- Antagonistic—wherein the effects of the mixture is less than obtained by adding the effects of the individual constituents.

Of particular concern are those mixtures where the effects are synergistic. Unfortunately, the toxicology of complex mixtures is not very well understood—complicating the problem involved in the assessment of the potential for these compounds to cause various health effects. Nonetheless, there is the need to assess the cumulative health risks for the chemical mixtures, despite potential large uncertainties that may exist. The risk assessment process must, therefore, address the multiple endpoints or effects, and also the uncertainties in the dose-response functions for each effect.

Finally, in combining multi-chemical risk estimates for multiple chemical sources, it should be noted here that, if two sources do not affect the same individual or subpopulation, then the sources' individual risk estimates (and/or hazard indices) do not quite influence each other—and, therefore, these risks should not be combined. Thus, one should not automatically sum risks from all sources evaluated for a chemical exposure problem—i.e., unless if it has been determined/established that such aggregation is appropriate. On the other hand, potential receptors are typically exposed not to isolated chemical sources, but rather to a complex, dilute mixture of many origins. Considering how many chemicals are present in the wide array of consumer products, and in the human environments, there are virtually infinite number of combinations that could constitute potential synergisms and antagonisms. In the absence of any concrete evidence of what the interactive effects might be, however, an additive method that simply sums individual chemical effects on a target organ is usually employed in the evaluation of chemical mixtures.

11.1.3.1 Carcinogenic Chemical Effects

The common method of approach in the assessment of chemical mixtures assumes additivity of effects for carcinogens when evaluating multiple carcinogens—albeit alternative procedures that are more realistic and/or less conservative have been proposed for certain situations by some investigators (e.g., Bogen 1994; Chen et al.

1990; Gaylor and Chen 1996; Kodell and Chen 1994; Slob 1994). In any case, prior to a summation for aggregate risks, estimated cancer risks should perhaps be (preferably) segregated by weight-of-evidence (or strength-of-evidence) category for the chemicals of concern—the goal being to provide a clear understanding of the risk contribution of each category of carcinogen.

11.1.3.2 Systemic (Non-cancer) Chemical Effects

For multiple chemical exposures to non-carcinogens and the non-carcinogenic effects of carcinogens, constituents should be grouped by the same mode of toxicological action (i.e., those that induce the same physiologic endpoint—such as liver or kidney toxicity). Cumulative non-carcinogenic risk is evaluated through the use of a hazard index that is generated for each health or physiologic 'endpoint'. Physiologic/toxicological endpoints that will normally be considered with respect to chronic toxicity include: cardiovascular systems (CVS); central nervous system (CNS); gastrointestinal (GI) system; immune system; reproductive system (including teratogenic and developmental effects); kidney (i.e., renal); liver (i.e., hepatic); and the respiratory system.

In fact, in a strict sense, constituents should not be grouped together unless they induce/affect the same toxicological/physiologic endpoint. Thus, in a well-defined risk characterization exercise, it becomes necessary to segregate chemicals by organ-specific toxicity—since strict additivity without consideration for target-organ toxicities could over-estimate potential hazards (USEPA 1986b, 1989d). Accordingly, the 'true' hazard index is preferably calculated only after putting chemicals into groups with same physiologic endpoints. Listings of chemicals with their associated non-carcinogenic toxic effects on specific target organ/system can be found in such databases as IRIS (Integrated Risk Information System), as well as in the literature elsewhere (e.g., Cohrssen and Covello 1989a; USEPA 1996a, b, c, d, e, f).

11.1.4 Updating the Inhalation Exposure/Risk Paradigm

Traditionally, the inhalation exposure route has been evaluated by using the 'inhalation RfD' (expressed in units of mg/kg day) and the 'inhalation SF' (expressed in units of $[\text{mg/kg day}]^{-1}$) [see Chap. 10], integrated with the estimated intake values (generally expressed in units of mg/kg day) [see Chap. 9], to arrive at probable risk estimates. However, recent works call for variant approaches for determining exposure and risk from inhaled chemicals—especially in order for it to be consistent with inhalation dosimetry methodologies currently used by a number of institutions/agencies (such as the US EPA). Generally speaking, the 'inhalation dosimetry methodology' describes a refined recommended approach for interpreting inhalation toxicity studies in laboratory animals, or studies of

occupational exposures of humans to airborne chemicals; under this approach, the experimental exposures are typically extrapolated to a 'human equivalent concentration' (HEC)—and a 'reference concentration' (RfC) is typically calculated by dividing the HEC by appropriate uncertainty factors (UFs) [see Chap. 10]. The HEC, developed in accordance with the inhalation dosimetry methodology, typically is also used in developing an 'inhalation unit risk' (IUR) for cancer risk assessment (which may also be called an inhalation cancer slope factor) [see Chap. 10]. Ultimately, the procedure is used to calculate published RfCs and IURs—such as documented in USEPA's IRIS profiles, and indeed other similar toxicological reference documents, etc.

Under this new paradigm noted here, it is generally recommended that when estimating risk via inhalation, risk assessors/analysts should use the concentration of the chemical in air as the exposure metric (e.g., mg/m^3 or $\mu g/m^3$)—i.e., rather than a use of inhalation intake of a contaminant in air based on IR and BW (e.g., mg/kg day). In this case, some of the intake equations described in Chap. 9 may not quite be wholly consistent with the principles of the inhalation dosimetry methodology—especially because the amount of the chemical that reaches the target site is not a simple function of IR and BW; instead, the interaction of the inhaled contaminant with the respiratory tract is affected by factors such as species-specific relationships of exposure concentrations (ECs) to deposited/delivered doses and physiochemical characteristics of the inhaled contaminant. The inhalation dosimetry methodology also considers the target site where the toxic effect occurs (e.g., the respiratory tract or a location in the body remote from the portal-of-entry) when applying dosimetric adjustments to experimental concentrations (USEPA 1994a, b, c, d, e, f, g).

In the end, it becomes necessary to appropriately characterize exposures in a manner that is consistent with the inhalation dosimetry methodology. The general approach involves the estimation of exposure concentrations (ECs) for each receptor exposed to contaminants via inhalation in the risk assessment; ECs are time-weighted average concentrations derived from measured or modeled contaminant concentrations in air at a locale or within an 'exposure object'—and possibly further adjusted based on the characteristics of the exposure scenario being evaluated. Representative equations for estimating ECs are presented below—with the ECs typically provided in units of $\mu g/m^3$.

11.1.4.1 Estimating Exposure Concentrations for Use in Cancer Risk Assessments

The estimation of an EC when assessing cancer risks characterized by an IUR encompasses a contaminant concentration in air (CA) measured at an exposure point, and at an appropriate locale or within an 'exposure target', as well as scenario-specific parameters (such as the exposure duration and frequency); the ECs are typically based on either estimated (i.e., modeled) or measured contaminant concentrations in air. Ultimately, the EC characteristically takes the form of a

CA that is time-weighted over the duration of exposure, and incorporates information on activity patterns for the specific locale and/or further utilizes professional judgment as part of the overall process.

The general equation for estimating an EC for use with an IUR would be as follows (USEPA 2009):

$$\text{EC}\ \left(\mu g/m^3\right) = \frac{[CA \times ET \times EF \times ED]}{AT} \tag{11.5}$$

where: EC ($\mu g/m^3$) = exposure concentration; CA ($\mu g/m^3$) = contaminant concentration in air; ET (h/day) = exposure time; EF (days/year) = exposure frequency; ED (years) = exposure duration; and AT (lifetime in years × 365 days/year × 24 h/day) = averaging time (viz., lifetime in years × 365 days/year × 24 h/day).

11.1.4.2 Estimating Exposure Concentrations for Use in Non-cancer Risk Assessments

When estimating ECs for non-cancer or hazard effects characterized by a use of the RfC, varying EC equations would typically be used based on the scenario duration and frequency of exposure; overall, the following general equations would typically be utilized for estimating an EC for use with an RfC (USEPA 2009):

$$\text{EC}\ \left(\mu g/m^3\right) = CA \tag{11.6a}$$

where: EC ($\mu g/m^3$) = exposure concentration; CA ($\mu g/m^3$) = contaminant concentration in air.

$$\text{EC}\ \left(\mu g/m^3\right) = \frac{[CA \times ET \times EF \times ED]}{AT} \tag{11.6b}$$

where: EC ($\mu g/m^3$) = exposure concentration; CA ($\mu g/m^3$) = contaminant concentration in air; ET (h/day) = exposure time; EF (days/year) = exposure frequency; ED (years) = exposure duration; and AT (ED in years × 365 days/year × 24 h/day) = averaging time (viz., ED in years × 365 days/year × 24 h/day). It is notable that, if the duration of the exposure period is less than 1 year, the units in the above equation can be changed to the following: EF (days/week); ED (weeks/exposure period); and AT (hour/exposure period).

First, it is important to assess the duration of the exposure scenario at a locale or within a 'exposure target'; invariably, the decision has to be made as to whether the duration of the exposure scenario is generally acute, subchronic, or chronic—recognizing that effects from a single or short-term exposure can differ markedly from effects resulting from repeated exposures. The response by the exposed person depends upon factors such as whether the chemical accumulates in the body, whether it overwhelms the body's mechanisms of detoxification or elimination, or whether it produces irreversible effects (Eaton and Klaassen 2001). Thus,

ideally, the chemical-specific elements of metabolism and kinetics, reversibility of effects, and recovery time should be considered as part of this recommended process when defining the duration of a site-specific exposure scenario (USEPA 2009).

Next is the assessment of the exposure pattern for each exposure scenario at a site or locale; this generally entails comparing the exposure time and frequency for the subject case to that of a typical subchronic or chronic toxicity test (USEPA 2009).

The final step would consist of estimating the EC for the specific exposure scenario based on the preceding decisions. For each acute exposure period at a locale, the EC is equal to the CA—estimated by using Eq. (11.6a) provided above; by the way, exposure periods with significantly less frequency should be treated as acute exposures. For longer-term exposures, the exposure time, frequency, and duration for each receptor being evaluated as well as the period over which the exposure is averaged (i.e., the averaging time (AT)) to arrive at a time-weighted EC should be taken into consideration; thus, if there are one or more exposure periods that are generally as frequent as a subchronic toxicity test, Eq. (11.6b) should be used to estimate a subchronic EC for each of these exposure periods. If the exposure pattern is generally as frequent as a chronic toxicity test of an occupational study, Eq. (11.6b) should be used to estimate a single chronic EC for the duration of the exposure.

Ultimately, it is important to use the EC equation that most closely matches the exposure pattern and duration in relation to the problem on hand. For instance, if the exposure pattern for a given problem scenario consists of a series of short (e.g., 4-h) periods of high exposure separated by several days of no exposure, then perhaps estimating an acute EC for each acute exposure period might be the most appropriate modality to adopt. On the other hand, if the chronic EC equation (viz., Eq. (11.6b)) were to be used instead, then the result would be an average EC value that may lead to an underestimation of the risk since the inhaled concentrations could be higher than acute toxicity values during periods of exposure.

11.1.4.3 Estimating Exposure Concentrations in Multiple Microenvironments

When detailed information on the activity patterns of a receptor at a locale is available, risk assessors/analysts can use these data to estimate the EC for either non-carcinogenic or carcinogenic effects arising from a problem situation. The activity pattern data generally describe how much time a receptor spends, on average, in different microenvironments (MEs)—each of which may have a different contaminant concentration level; a microenvironment may be defined as a delineated space that can be treated as a well-characterized, relatively homogeneous location with respect to pollutant concentration for a specified time period (e.g., rooms in homes, restaurants, schools, offices, inside vehicles, or outdoors) (USEPA 2004a, b, c, d, e, f, g). By combining data on the contaminant

concentration level in each ME and the activity pattern data, the risk assessor can calculate a time-weighted average EC for a receptor. Meanwhile, because activity patterns (and hence, MEs) can vary over a receptor's lifetime, it is generally recommended that risk assessors pursuing the ME approach first calculate a time-weighted average EC for each exposure period characterized by a specific activity pattern (e.g., separate ECs for a school-aged child resident and a working adult resident); these exposure period-specific ECs can then be combined into a longer term or lifetime average EC by weighting the EC by the duration of each exposure period (USEPA 2004a, b, c, d, e, f, g).

Overall, the ME approach can be used to estimate an average EC *for a particular/specific exposure period* during which a receptor has a specified activity pattern. As a simplified example, consider the case of a residential receptor that may be exposed to a higher concentration of a contaminant in air in the bathroom for 30 min/day while showering, and then exposed to a lower concentration in the rest of the house for the remaining 23.5 h/day. In such cases, the CA value experienced in each ME weighted by the amount of time spent in each ME may be used to estimate an average EC for the period of residency in that house—using the following equation (USEPA 2004a, b, c, d, e, f, g, 2009):

$$\mathrm{EC_j}\ \left(\mu g/m^3\right) = \sum_{i=1}^{n} \left(CA_i \times ET_i \times EF_i\right) \times \frac{ED_j}{AT_j} \tag{11.7a}$$

where: EC_j ($\mu g/m^3$) = average exposure concentration for exposure period *j*; CA_i ($\mu g/m^3$) = contaminant concentration in air in ME *i*; ET_i (h/day) = exposure time spent in ME *i*; EF_i (days/year) = exposure frequency for ME *i*; ED_j (years) = exposure duration for exposure period *j*; and AT_j (h) = averaging time = $ED_j \times 24$ h/day $\times$ 365 days/year. It is noteworthy here that, if one or more MEs involve acute exposures, then a supplemental analysis should probably be carried out—comparing the CA for each of those MEs to a corresponding acute toxicity value, to ensure that receptors are protected from potential acute health effects. Indeed, this approach may also be used to address exposures to contaminants in outdoor and indoor environments at locations where both indoor and outdoor samples have been collected or where the vapor intrusion pathway has been characterized.

Furthermore, the ME approach may be used in estimating an average exposure concentration *across multiple exposure periods*. To derive an average EC for a receptor over multiple exposure periods, the average EC from each period (as calculated above in Eq. (11.7a)) can be weighted by the fraction of the total exposure time that each period represents, using the following equation (USEPA 2004a, b, c, d, e, f, g, 2009):

$$\mathrm{ECLT}\ \left(\mu g/m^3\right) = \frac{\sum \left(EC_j \times ED_j\right)}{AT_j} \tag{11.7b}$$

where: ECLT ($\mu g/m^3$) = long-term average exposure concentration; EC_j ($\mu g/m^3$) = average exposure concentration of a contaminant in air for exposure period *j*; ED_j

(years) = duration of exposure period *j*; and AT (years) = averaging time. For example, when estimating cancer risks, the risk assessor may calculate a lifetime average EC where the weights of the individual exposure periods are the duration of the period, ED_j, divided by the total lifetime of the receptor. Alternatively, when estimating an HQ, risk assessors/analysts can use Eq. (11.7b) to calculate less-than-lifetime average ECs across multiple exposure periods; in that case, the AT will equal the sum of the individual EDs for all of the exposure periods. Once again it is worth the mention here that when evaluating cancer risk, the AT is equal to lifetime in years, and when evaluating non-cancer hazard, the AT is equal to the sum of the EDs for each exposure period.

11.1.5 Fundamental Considerations in the Health Assessment of Carcinogens

Cancer risk assessment by necessity involves a number of assumptions—most of which reflect scientific and policy judgments. In general, in the absence of data to the contrary, a substance that has been shown to cause cancer in animals is presumed to pose a potential carcinogenic risk to humans. However, as more knowledge on particular agents and the oncogenic process in general becomes available, the position on these issues becomes subject to change. A number of fundamental but critical issues affecting the health risk assessment of carcinogens are enumerated below.

11.1.5.1 Qualitative Issues

Several qualitative issues affect the health assessment of carcinogens—most importantly, the topics identified below (IARC 1987; NTP 1991; USEPA 1986a, b, c, d, e, f).

- '*Weight/Strength of Evidence*'. A 'weight-of-evidence' or a 'strength-of-evidence' approach may be adopted in evaluating all the relevant case data available on a given carcinogenic chemical. The general types of evidence that may be used for qualitatively identifying carcinogens include: case studies, epidemiological studies, long-term animal bioassays, short-term tests, and structure-activity relationships. Specific factors that are typically evaluated in determining if a substance poses a carcinogenic risk to humans include, but are not limited to: the quality of the toxicity studies (namely, relating to the choice of appropriate control groups; sufficient number of animals; administration route; dose selection; tumor types; etc.), and the relevance of animal data to humans. Ultimately, a narrative statement may be used to incorporate the weight/strength-of-evidence conclusions—i.e., in lieu of alphanumeric designations alone being used to convey qualitative conclusions regarding the chemical carcinogenicity.

- *Mechanistic Inference and Species Concordance*. Carcinogenesis is generally viewed as a multistage process—proceeding from initiation, through promotion, and progression. Carcinogens may work through mechanisms that directly or indirectly affect the genome. Commonly, it is assumed that many or most carcinogens are characterized by the absence of a threshold in eliciting a tumorigenic response. On the other hand, the presence or absence of a threshold for one step in the multistage process of carcinogenesis does not necessarily imply the presence or absence of a threshold for other steps, or the entire process. For example, carcinogenic effects of some agents may result from non-physiological responses to the agents, such as extensive organ damage; under such circumstances, the relevance of the animal data to humans should be evaluated on a case-by-case basis—with a view towards extending its assessment effort beyond the dominant paradigm of carcinogenesis (i.e., initiation, promotion, and progression).
- *Exposure Route Specificity*. In the analysis of potential carcinogenic risk of chemical agents to humans, it is generally important to address the issue of exposure route specificity. In fact, for some agents, exposure might result in adverse health effects via one route only; for example, whereas chronic *oral* exposures to an agent may not result in cancer in animals and/or humans, the same agent may be carcinogenic via *inhalation* in the same species. Accordingly, the potential health risk of toxic substances should be evaluated by carefully taking into account the relevant route(s) of exposure. In the absence of data to the contrary, however, an agent that is carcinogenic via one route may be considered to be a potential carcinogen via alternate routes as well.
- *Role of Epidemiological Data*. Epidemiological studies generally provide direct information on the carcinogenic risk of chemical agents to humans. For this reason, in evaluating the potential human cancer risks, a higher weight may be assigned to well-designed and well-executed epidemiological studies than to animal studies of comparable quality. Even so, the observational nature of such studies, as well as the use of indirect measures of exposure, can sometimes constrain the overall interpretation of the data. In any case, it is noteworthy that, although an agent may not have been shown to be a carcinogen in a well-designed epidemiological study, a potential association between exposure to the agent and human cancer cannot be completely ruled out. Indeed, the potential for an association will remain—especially if relevant animal data suggest that a carcinogenic effect exist; this premise would also apply in the case of health effects other than cancer.

  On the whole, descriptive epidemiological studies may be useful in generating/refining hypotheses that suggest further in-depth studies. These studies also provide limited information on causal relationships. Alternatively, analytical epidemiological investigations, such as case-control or cohort studies, can provide the basis for testing causal associations—and these are an invaluable resource in public health decisions. In the end, the causal association of toxic chemical exposure and cancer is greatly enhanced when studies show: relationships without significant bias, a temporal sequence of exposure and response,

consistency with other studies, strength of association, a dose-response relationship, and biologic plausibility.

- *Sensitive and Susceptible Populations.* Certain populations may be at a higher risk of developing cancer due to several factors—including exposure to unusually high levels of carcinogens, genetic predisposition, age, and other host factors (such as physiological and nutritional status). Thus, it is quite important to carefully identify these susceptible populations and independently address the associated public health concerns for the particularly sensitive group(s).
- *Structure-Activity Relationships.* Information on the physical, chemical, and toxicological characteristics as well as the environmental fate of many hazardous substances exists amongst the scientific communities. Thus, some correlations can be made between the structures of some hazardous substances and the properties they exhibit. Indeed, the use of structure-activity relationships to derive preliminary estimates of both the environmental and toxicological characteristics of hazardous substances for which little or no information is available could become very crucial in some risk characterization programs. However, a great deal of scientific judgment may be required in interpreting these results, since these methods may need to be refined and validated a priori. Also, conclusions derived by such approaches may be inadequate as surrogates for human or other bioassay data.
- *Chemical Interactions.* Health evaluations are often complicated by the fact that multiple hazardous substances may be of concern at specific locales and/or occupied human environments. Given the paucity of empirical data and the complexity of this issue, it is often assumed that, in the absence of information regarding the interaction of these substances, their effects are additive. In any case, such assessments should also be accompanied by qualitative weight-of-evidence type of statement on the possibilities for interactive effects—whether they are potentiation, additivity, antagonism, and/or synergism. Ideally, these conclusions are based on insights regarding the mechanism of action of individual components—as relates to the potential for interaction among components of the mixture.

Indeed, the above is by no means a complete listing—as a number of other case-specific matters might become apparent during the risk appraisal of distinct problem situations/scenarios.

11.1.5.2 Quantitative Issues

Several quantitative issues affect the health assessment of carcinogens—most importantly, the topics identified below (IARC 1987; NTP 1991; USEPA 1986a, b, c, d, e, f).

- *Dose Scaling.* Conversion of exposure levels derived from experimental animal studies to humans is an equivocal process because of recognized differences among species—e.g., life span and body size, as well as pharmacokinetic and

genetic factors, among others. Although a number of default scaling factors have been proposed in various scientific works, no single scaling approach may be considered as being universally appropriate. Indeed, the use of any default approach to scaling is at best a crude approximation, and all factors responsible for interspecies differences must be considered in dose/exposure conversions among species when selecting extrapolation methods. Thus, empirically derived data relevant to dose scaling are preferred—and this should be used preferentially, whenever available. Meanwhile, it is noteworthy that extrapolation may not be necessary if epidemiological data are used to assess potential carcinogenic risk; however, differences in individual sensitivity must still be taken into account.

- *Pharmacokinetics and Pharmacodynamics*. Oftentimes, it becomes necessary to carry out health assessments in populations that have been exposed to carcinogens in the past, or that are currently exposed to such agents. In assessing the potential carcinogenic risks of chemical agents, information on the 'delivered' target dose—rather than the exposure dose—may help in developing a more accurate assessment of the possible carcinogenicity of the subject agent. Thus, the development and use of physiologically-based pharmacokinetic models that can be used for estimating the magnitude and time course of exposure to agents at target sites in animal models may be quite an important exercise to undertake. Overall, once data from the animal models have been appropriately validated, they can subsequently be used to estimate corresponding target tissue doses in humans. Meanwhile, it should be recognized that the estimation of lifetime cancer risks is further complicated when available data are derived from less-than-lifetime exposures, and that pharmacokinetic insights may be of great help in addressing these types of issues.
- *Mechanistic Considerations and Modeling*. Health assessment for potential carcinogens must take into consideration dose-response relationships from all available relevant studies. In chronic bioassays, animals are often exposed to levels of the chemical agent that are, for practical reasons, far higher than levels to which humans are likely to be exposed in the environment. Therefore, mathematical models are used to extrapolate from high to low dose; the selection of models depends on the known or presumed mechanism of action of the agent, and on science policy considerations. In the absence of sufficient information to choose among several equally plausible models, preference should perhaps be given to the more conservative (i.e., protective) of models.

  In general, the multistage model is widely used for low-dose extrapolation for genotoxic agents; it is based on the premise that a developing tumor proceeds through several different stages before it is clinically detectable. In the low-dose region, this multistage model is frequently linear, and it is assumed that a threshold, below which effects are not anticipated, does not exist. At any rate, it must be recognized that no single mathematical model is appropriate in all situations; furthermore, it is understandable that the incorporation of new information on mechanism and pharmacokinetics, among other factors, will increase the model's usefulness and facilitate the selection of the most appropriate

mathematical model. It must be acknowledged, however, that existing mathematical models for low-dose extrapolation may not quite be appropriate for non-genotoxic agents. Indeed, more information on biological mechanism is needed to determine if there are threshold exposure levels for non-genotoxic agents. For these reasons, where feasible, the presentation of a range of plausible potency estimates should be used to convey quantitative conclusions.

- *Individual vs. Population Risk—The Role of Molecular Epidemiology*. Biomarkers have the potential to serve as bridges between experimental and epidemiological studies of carcinogens, insofar as they reflect biochemical or molecular changes associated with exposure to carcinogens. Indeed, biomarkers, such as DNA adducts, may be used as indices of the biologically effective doses—reflecting the amount of the potential carcinogen or its metabolite that has interacted with a cellular macromolecule at the target site. Furthermore, markers of early biologic effect, such as activated oncogenes and their protein products, and/or loss of suppressor gene activity, may indicate the occurrence of possibly irreversible toxic effects at the target site. Also, genetic markers may suggest the presence of heritable predispositions or the effects of other host factors, such as lifestyle or prior disease. Thus, molecular epidemiology—that combines experimental models, molecular biology, and epidemiology—provides an opportunity to estimate individual cancer risk, and to better define the health implications of chemical exposure problems for members of exposed populations (NRC 1991a, b, c). It should be noted, however, that extensive work is needed before biomarkers can be truly used as prognostic indicators. Meanwhile, it is notable that fairly recent advances in biomolecular technology have resulted in the development of highly sensitive methods for measuring biomarkers of exposure, effects, and susceptibility (Shields and Harris 1991; Johnson and Jones 1992).

Indeed, the above is by no means a complete listing—since a number of other case-specific matters might become apparent during the risk appraisal of distinct problem situations/scenarios.

11.2 Carcinogenic Risk Effects: Estimation of Carcinogenic Risks to Human Health

For potential carcinogens, risk is defined by the incremental probability of an individual developing cancer over a lifetime as a result of exposure to a carcinogen. This risk of developing cancer can be estimated by combining information about the carcinogenic potency of a chemical and exposure to the substance. Specifically, carcinogenic risks are estimated by multiplying the route-specific cancer slope factor (which is the upper 95% confidence limit of the probability of a carcinogenic response per unit intake over a lifetime of exposure) by the estimated intakes; this yields the excess or incremental individual lifetime cancer risk.

Broadly speaking, risks associated with the 'inhalation' and 'non-inhalation' pathways may be estimated in accordance with some adaptations of the following generic relationships:

$$\begin{aligned}\text{Risk for 'inhalation pathways'} &= \text{Ground-level Concentration (GLC) or Exposure Concentration (EC)}\left[\mu g/m^3\right] \\ &\quad \times \text{Inhalation Unit risk}\left[\left(\mu g/m^3\right)^{-1}\right]\end{aligned} \tag{11.8}$$

$$\text{Risk for 'non-inhalation pathways'} = \text{Dose}\left[\text{mg/kg-day}\right] \times \text{Potency slope}\left[\left(\text{mg/kg-day}\right)^{-1}\right] \tag{11.9}$$

The resulting estimates can then be compared with benchmark criteria/standards in order to arrive at risk decisions about a given chemical exposure problem.

In practice, a customarily preferred first step in a cancer risk assessment (i.e., when appraising human health risks for cancer endpoints) is to characterize the hazard using a 'weight-of-evidence' (or perhaps a 'strength-of-evidence') narrative—e.g., by using one of the following five standard hazard descriptors: 'Carcinogenic to Humans'; 'Likely to Be Carcinogenic to Humans'; 'Suggestive Evidence of Carcinogenic Potential'; 'Inadequate Information to Assess Carcinogenic Potential'; and 'Not Likely to Be Carcinogenic to Humans'. The narrative describes the available evidence, including its strengths and limitations, and 'provides a conclusion with regard to human carcinogenic potential' (USEPA 2005a). Depending on how much is known about the 'mode-of-action' of the agent of interest, one of two methods is used for completing any pertinent extrapolations, viz.: linear or nonlinear extrapolation. A linear extrapolation is used in the 'absence of sufficient information on modes-of-action' or when 'the mode-of-action information indicates that the dose-response curve at low dose is or is expected to be linear'; for a linear extrapolation, the 'slope factor' is considered 'an upper-bound estimate of risk per increment of dose'—and this is used to estimate risks at different exposure levels (USEPA 2005a). A nonlinear approach would be used 'when there is sufficient data to ascertain the mode of action—with the conclusion that it is not linear at low doses, and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses'; details of the computational approaches are offered elsewhere (e.g., USEPA 2005a).

On the whole, the carcinogenic effects of the constituents associated with potential chemical exposure problems are typically calculated using the linear low-dose and one-hit models, represented by the following relationships (USEPA 1989d):

$$\textit{Linear low-dose model},\ \ CR = CDI \times SF \tag{11.10}$$

$$\textit{One-hit model}, \quad CR = 1 - \exp(-CDI \times SF) \tag{11.11}$$

where *CR* is the probability of an individual developing cancer (dimensionless); *CDI* is the chronic daily intake for long-term exposure (i.e., averaged over receptor lifetime) (mg/kg day); and *SF* is the cancer slope factor ([mg/kg day]$^{-1}$). The linear low-dose model is based on the so-called 'linearized multistage' (LMS) model—which assumes that there are multiple stages for cancer; the 'one-hit' model assumes that there is a single stage for cancer, and that one molecular or radiation interaction induces malignant change—making it very conservative. In reality, and for all practical purposes, the linear low-dose cancer risk model is valid only at low risk levels (i.e., estimated risks <0.01); for situations where chemical intakes may be high (i.e., potential risks >0.01), the one-hit model represents the more appropriate algorithm to use.

As a simple illustrative example calculation of human health carcinogenic risk, consider a situation where PCBs from abandoned electrical transformers have leaked into a groundwater reservoir that serves as a community water supply source. Environmental sampling and analysis conducted in a routine testing of the public water supply system showed an average PCB concentration of 2 μg/L. Thence, the pertinent question here is: 'what is the individual lifetime cancer risk associated with a drinking water exposure from this source?' Now, assuming that the only exposure route of concern here is from water ingestion, and using a cancer oral SF of 7×10^{-2} (obtained from Table C.1 in Appendix C) and applicable/appropriate 'intake factor' [see Chap. 9/Sect. 9.3], then the cancer risk attributable to this exposure scenario is estimated as follows:

$$\begin{aligned}\text{Cancer risk} &= \text{SF}_\text{o} \times \text{CDI}_\text{o} \\ &= \text{SF}_\text{o} \times \text{C}_\text{w} \times 0.0149 \\ &= \left(7 \times 10^{-2}\right) \times \left(2\mu g/\text{L} \times 10^{-3}\,\text{mg}/\mu g\right) \\ &\quad \times 0.0149 = 2.1 \times 10^{-6}\end{aligned}$$

Similar evaluations can indeed be carried out for the various media and exposure routes of potential concern or possible interest.

Anyway, as noted above in Sect. 11.1.3, the method of approach for assessing the cumulative health risks from chemical mixtures generally assumes additivity of effects for carcinogens when evaluating chemical mixtures or multiple carcinogens. Thus, for multiple carcinogenic chemicals and multiple exposure routes/pathways, the aggregate cancer risk for all exposure routes and all chemicals of concern associated with a potential chemical exposure problem can be estimated using the algorithms shown in Boxes 11.1 and 11.2. The combination of risks across exposure routes is based on the assumption that the same receptors would consistently experience the reasonable maximum exposure via the multiple routes. Hence, if specific routes do not affect the same individual or receptor group, risks should not be combined under those circumstances.

Finally, as a rule-of-thumb, incremental risks of between 10^{-4} and 10^{-7} are generally perceived as being reasonable and adequate for the protection of human health—with 10^{-6} often used as the 'point-of-departure'. In reality, however, populations may be exposed to the same constituents from sources unknown or unrelated to a specific study. Consequently, it is preferable that the estimated carcinogenic risk is well below the 10^{-6} benchmark level—in order to allow for a reasonable margin of protectiveness for populations potentially at risk. Surely, if a calculated cancer risk exceeds the 10^{-6} benchmark, then the health-based criterion for the chemical mixture has been exceeded, and the need for corrective measures and/or risk management actions must be given serious consideration.

Box 11.1 The Linear Low-Dose Model for the Estimation of Low-Level Carcinogenic Risks

Total Cancer Risk, $TCR_{lo\text{-}risk} = \sum_{j=1}^{p} \sum_{i=1}^{n} \left(\mathrm{CDI_{ij}} \times \mathrm{SF_{ij}}\right)$

and

Aggregate/Cumulative Total Cancer Risk, $ATCR_{lo\text{-}risk} = \sum_{k=1}^{s} \left\{ \sum_{j=1}^{p} \sum_{i=1}^{n} \left(CDI_{ij} \times SF_{ij}\right) \right\}$

where:

TCR = probability of an individual developing cancer (dimensionless)
CDI_{ij} = chronic daily intake for the ith chemical and jth route (mg/kg day)
SF_{ij} = slope factor for the ith chemical and jth route ([mg/kg day]$^{-1}$)
n = total number of carcinogens
p = total number of pathways or exposure routes
s = total number for multiple sources of exposures to receptor (e.g., dietary, drinking water, occupational, residential, recreational, etc.)

Box 11.2 The One-Hit Model for the Estimation of High-Level Carcinogenic Risks

$$\text{Total Cancer Risk, } TCR_{hi\text{-}risk} = \sum_{j=1}^{p} \sum_{i=1}^{n} \left[1 - \exp\left(-CDI_{ij} \times SF_{ij}\right)\right]$$

and

$$\text{Aggregate/Cumulative Total Cancer Risk, } ATCR_{hi\text{-}risk} = \sum_{k=1}^{s} \left\{ \sum_{j=1}^{p} \sum_{i=1}^{n} \left[1 - \exp\left(-\mathrm{CDI_{ij}} \times SF_{ij}\right)\right] \right\}$$

(continued)

Box 11.2 (continued)

where:
TCR = probability of an individual developing cancer (dimensionless)
CDI_{ij} = chronic daily intake for the ith chemical and jth route (mg/kg day)
SF_{ij} = slope factor for the *i*th chemical and *j*th route ([mg/kg day]$^{-1}$)
n = total number of carcinogens
p = total number of pathways or exposure routes
s = total number for multiple sources of exposures to receptor (e.g., dietary, drinking water, occupational, residential, recreational, etc.)

11.2.1 Population Excess Cancer Burden

The two important parameters or measures often used for describing carcinogenic effects are the individual cancer risk and the estimated number of cancer cases (i.e., the cancer burden). The individual cancer risk from simultaneous exposure to several carcinogens is assumed to be the sum of the individual cancer risks from each individual chemical. The risk experienced by the individual receiving the greatest exposure is referred to as the 'maximum individual risk'.

Now, to assess the population cancer burden associated with a chemical exposure problem, the number of cancer cases due to an exposure source within a given community can be estimated by multiplying the individual risk experienced by a group of people by the number of people in that group. Thus, if ten million people (as an example) experience an estimated cancer risk of 10^{-6} over their lifetimes, it would be estimated that 10 (i.e., 10 million $\times$ 10^{-6}) additional cancer cases could occur for this group. The number of cancer incidents in each receptor area can be added to estimate the number of cancer incidents over an entire region. Hence, the excess cancer burden, B_{gi}, is given by:

$$B_{gi} = \sum \left(R_{gi} \times P_g\right) \tag{11.12}$$

where: B_{gi} is the population excess cancer burden for *i*th chemical for exposed group, G; R_{gi} is the excess lifetime cancer risk for *i*th chemical for the exposed population group, G; P_g is the number of persons in exposed population group, G. Assuming cancer burden from each carcinogen is additive, the total population group excess cancer burden is given by:

$$B_g = \sum_{i=1}^{N} B_{gi} = \sum_{i=1}^{N} \left(R_{gi} \times P_g\right) \tag{11.13}$$

and the total population burden, B, is represented by:

$$B = \sum_{g=1}^{G} B_g = \sum_{g=1}^{G} \left\{ \sum_{i=1}^{N} B_{gi} \right\} = \sum_{g=1}^{G} \left\{ \sum_{i=1}^{N} \left(R_{gi} \times P_g \right) \right\} \tag{11.14}$$

Insofar as possible, cancer risk estimates are expressed in terms of both individual and population risk. For the population risk, the individual upper-bound estimate of excess lifetime cancer risk for an average exposure scenario is simply multiplied by the size of the potentially exposed population.

11.2.2 Carcinogenic Risk Computations: Illustration of the Processes for Calculating Carcinogenic Risks

The overall purpose of a carcinogenic risk characterization is to estimate the upper-bound likelihood, over and above the background cancer rate, that a receptor will develop cancer in his or her lifetime as a result of exposure to a constituent in an environmental medium of interest or concern. This likelihood is a function of the dose of a constituent (as determined during an exposure assessment) and the CSF (as documented from a dose-response assessment) for that constituent.

In accordance with the relationships presented earlier on in this chapter, the potential carcinogenic risks associated with chemical exposures can be systematically calculated for all relevant exposure routes. Illustrative example evaluations for potential receptor groups ostensibly exposed through inhalation, soil ingestion (i.e., incidental or pica behavior), and dermal contact are discussed in the proceeding sections. The examples shown below are used to demonstrate the computational mechanics for estimating chemical risks; the same set of units is maintained throughout as given above in related prior discussions.

11.2.2.1 Carcinogenic Effects for Contaminants in Water

The carcinogenic risk associated with a potential receptor exposure to chemical constituents in water can generally be estimated using the following type of relationship:

$$\begin{aligned} \text{Risk}_{\text{water}} &= [\text{CDI}_{\text{o}} \times \text{SF}_{\text{o}}] + [\text{CDI}_{\text{i}} \times \text{SF}_{\text{i}}] \\ &= \left[\left(\text{CDI}_{\text{ing}} + \text{CDI}_{\text{der}} \right) \times \text{SF}_{\text{o}} \right] + [\text{CDI}_{\text{i}} \times \text{SF}_{\text{i}}] \\ &= \{ [(\text{INGf} \times \text{C}_{\text{w}}) + (\text{DEXf} \times \text{C}_{\text{w}})] \times \text{SF}_{\text{o}}] \} \\ &\quad + \{ [(\text{INHf} \times \text{C}_{\text{w}}) \times \text{SF}_{\text{i}}] \} \end{aligned} \tag{11.15}$$

More generally, the carcinogenic risk may be calculated from 'first principles' as follows:

$$\begin{aligned}\text{Risk}_{\text{water}} = & \left\{\text{SF}_{\text{o}} \times \text{C}_{\text{w}} \times \frac{\left(\text{IR}_{\text{adult}} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{EF} \times \text{ED}_{\text{adult}}\right)}{\left(\text{BW}_{\text{adult}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\} \\ & + \left\{\text{SF}_{\text{o}} \times \text{C}_{\text{w}} \times \frac{\left(\text{IR}_{\text{child}} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{EF} \times \text{ED}_{\text{child}}\right)}{\left(\text{BW}_{\text{child}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\} \\ & + \left\{\text{SF}_{\text{o}} \times \text{C}_{\text{w}} \times \frac{\left(\text{SA}_{\text{adult}} \times \text{K}_{\text{p}} \times \text{CF} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{EF} \times \text{ED}_{\text{adult}} \times \text{ET}_{\text{adult}}\right)}{\left(\text{BW}_{\text{adult}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\} \\ & + \left\{\text{SF}_{\text{o}} \times \text{C}_{\text{w}} \times \frac{\left(\text{SA}_{\text{child}} \times \text{K}_{\text{p}} \times \text{CF} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{EF} \times \text{ED}_{\text{child}} \times \text{ET}_{\text{child}}\right)}{\left(\text{BW}_{\text{child}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\} \\ & + \left\{\text{SF}_{\text{i}} \times \text{C}_{\text{w}} \times \frac{\left(\text{IR}_{\text{adult}} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{EF} \times \text{ED}_{\text{adult}}\right)}{\left(\text{BW}_{\text{adult}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\} + \cdots \\ & + \left\{\text{SF}_{\text{i}} \times \text{C}_{\text{w}} \times \frac{\left(\text{IR}_{\text{child}} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{EF} \times \text{ED}_{\text{child}}\right)}{\left(\text{BW}_{\text{child}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\}\end{aligned} \tag{11.16}$$

As an example, substitution of the exposure assumptions presented in Box 11.3 into the above equation yields the following reduced form of Eq. (11.15):

$$\begin{aligned}\text{Risk}_{\text{water}} = & \left(\text{SF}_{\text{o}} \times \text{C}_{\text{w}} \times 0.0149\right) + \left(\text{SF}_{\text{o}} \times \text{C}_{\text{w}} \times 0.0325 \times \text{K}_{\text{p}}\right) \\ & + \left(\text{SF}_{\text{i}} \times \text{C}_{\text{w}} \times 0.0149\right)\end{aligned} \tag{11.17}$$

Subsequently, by substituting the chemical-specific parameters in the above reduced risk equation, potential carcinogenic risks associated with the particular constituent can be determined.

Box 11.3 Definitions and Exposure Assumptions for Example Risk Computations Associated with Exposure to Environmental Contaminants in Water and Soil

Parameter	Parameter Definition and Exposure Assumption
SF_{o}	Oral cancer potency slope (obtained from literature, or Appendix C) ($[\text{mg/kg day}]^{-1}$)
SF_{i}	Inhalation cancer potency slope (from the literature, or Appendix C) ($[\text{mg/kg day}]^{-1}$)
C_{w}	Chemical concentration in water (obtained from the sampling and/or modeling) (mg/L)
C_{s}	Chemical concentration in soil (obtained from the sampling and/or modeling) (mg/kg)
C_{a}	Chemical concentration in air (obtained from the sampling and/or modeling) (mg/m^3)
K_{p}	Chemical-specific dermal permeability coefficient from water (obtained from the literature, e.g., DTSC 1994) ($\text{cm}^2\text{/h}$)
AF	Soil to skin adherence factor (1 mg/cm^2)

(continued)

Box 11.3 (continued)

Parameter	Parameter Definition and Exposure Assumption
SA	Skin surface area available for water contact (adult = 23,000 cm^2; child = 7200 cm^2); Skin surface area available for soil contact (adult = 5800 cm^2; child = 2000 cm^2)
IR	Average water intake rate—where intake from inhalation of volatile constituents may be assumed as equivalent to the amount of ingested water (adult = 2 L/day; child = 1 L/day)
SIR	Average soil ingestion rate (adult = 100 mg/day; child = 200 mg/day)
IR_a	Inhalation rate (adult = 20 m^3/day; child = 10 m^3/day)
CF	Conversion factor for water (1 L/1000 cm^3); Conversion factor for soil (10^{-6} kg/mg)
FI	Fraction ingested from contaminated source (1)
ABS_{gi}	Bioavailability/gastrointestinal [GI] absorption factor (100%)
ABS_s	Chemical-specific skin absorption fraction of chemical from soil (%)
EF	Exposure frequency for water (350 days/year); Exposure frequency for soil (soil ingestion = 350 days/year; dermal contact—adult = 100 days/year, child = 350 days/year)
ED	Exposure duration (adult = 24 years; child = 6 years)
ET	Exposure time during showering/bathing (adult = 0.25 h/day; child = 0.14 h/day)
BW	Body weight (adult = 70 kg; child = 15 kg)
AT	Averaging time (period over which exposure is averaged = 70 years or [70 × 365] days)

11.2.2.2 Carcinogenic Effects for Contaminants in Soils

The carcinogenic risk associated with a potential receptor exposure to chemical constituents in soils can generally be estimated using the following type of relationship:

$$\begin{aligned} \text{Risk}_{\text{soil}} &= [\text{CDI}_o \times \text{SF}_o] + [\text{CDI}_i \times \text{SF}_i] \\ &= \left[\left(\text{CDI}_{\text{ing}} + \text{CDI}_{\text{der}}\right) \times \text{SF}_o\right] + [\text{CDI}_i \times \text{SF}_i] \\ &= \{[(\text{INGf} \times C_w) + (\text{DEXf} \times C_w)] \times \text{SF}_o\} \\ &\quad + \{[(\text{INHf} \times C_w) \times \text{SF}_i]\} \end{aligned} \tag{11.18}$$

More generally, the carcinogenic risk may be calculated from 'first principles' as follows:

$$\begin{aligned}\text{Risk}_{\text{soil}} = & \left\{\text{SF}_{\text{o}} \times \text{C}_{\text{s}} \times \frac{\left(\text{SIR}_{\text{adult}} \times \text{CF} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{EF} \times \text{ED}_{\text{adult}}\right)}{\left(\text{BW}_{\text{adult}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\} \\ & + \left\{\text{SF}_{\text{o}} \times \text{C}_{\text{s}} \times \frac{\left(\text{SIR}_{\text{child}} \times \text{CF} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{EF} \times \text{ED}_{\text{child}}\right)}{\left(\text{BW}_{\text{child}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\} \\ & + \left\{\text{SF}_{\text{o}} \times \text{C}_{\text{s}} \times \frac{\left(\text{SA}_{\text{adult}} \times \text{AF} \times \text{CF} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{ABS}_{\text{s}} \times \text{EF} \times \text{ED}_{\text{adult}}\right)}{\left(\text{BW}_{\text{adult}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\} \\ & + \left\{\text{SF}_{\text{o}} \times \text{C}_{\text{s}} \times \frac{\left(\text{SA}_{\text{child}} \times \text{AF} \times \text{CF} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{ABS}_{\text{s}} \times \text{EF} \times \text{ED}_{\text{child}}\right)}{\left(\text{BW}_{\text{child}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\} \\ & + \left\{\text{SF}_{\text{i}} \times \text{C}_{\text{a}} \times \frac{\left(\text{IR}_{\text{adult}} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{EF} \times \text{ED}_{\text{adult}}\right)}{\left(\text{BW}_{\text{adult}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\} \\ & + \left\{\text{SF}_{\text{i}} \times \text{C}_{\text{a}} \times \frac{\left(\text{IR}_{\text{child}} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{EF} \times \text{ED}_{\text{child}}\right)}{\left(\text{BW}_{\text{child}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\}\end{aligned} \tag{11.19}$$

As an example, substitution of the exposure assumptions previously shown in Box 11.3 into the above equation yields the following reduced form of Eq. (11.18):

$$\begin{aligned}\text{Risk}_{\text{soil}} = & \left(\text{SF}_{\text{o}} \times \text{C}_{\text{s}} \times \left[1.57 \times 10^{-6}\right]\right) \\ & + \left(\text{SF}_{\text{o}} \times \text{C}_{\text{s}} \times \left[1.88 \times 10^{-5}\right] \times \text{ABS}_{\text{s}}\right) \\ & + \left(\text{SF}_{\text{i}} \times \text{C}_{\text{a}} \times 0.149\right)\end{aligned} \tag{11.20}$$

Subsequently, by substituting the chemical-specific parameters in the reduced risk equation, potential carcinogenic risks associated with the particular constituent can be determined.

11.3 Non-cancer Risk Effects: Estimation of Non-carcinogenic Hazards to Human Health

The potential non-cancer health effects resulting from a chemical exposure problem are usually expressed by the hazard quotient (HQ) and/or the hazard index (HI). The HQ is defined by the ratio of the estimated chemical exposure level to the route-specific reference dose, represented as follows (USEPA 1989d):

$$\text{Hazard Quotient, } HQ = \frac{\text{E}}{\text{RfD}} \tag{11.21}$$

where E is the chemical exposure level or intake (mg/kg-day); and RfD is the reference dose (mg/kg-day). [Note that the HQ associated with the inhalation pathway may preferably be represented as follows: HQ = EC/RfC, where EC is the exposure concentration in μg/m^3 and RfC is the inhalation toxicity value in g/m^3.]

As a simple illustrative example calculation of human health non-carcinogenic risk, consider a situation where an aluminum container is used for the storage of

water meant for household consumption. Laboratory testing of the water revealed that some aluminum consistently gets leached and dissolved into this drinking water—with average concentrations of approximately 10 mg/L. The question here then is: 'what is the individual non-cancer risk for a person who uses this source for drinking water?' Now, assuming the only exposure route of concern is associated with water ingestion (a reasonable assumption for this situation), and using a non-cancer toxicity index (i.e., an RfD) of 1.0 (obtained from Table C.1 in Appendix C), then the non-cancer risk attributable to this exposure scenario is calculated to be:

$$\begin{aligned}\text{Hazard Index} &= (1/\text{RfD}_o) \times \text{CDI}_o \\ &= (1/\text{RfD}_o) \times C_w \times 0.0639 \\ &= 1.0 \times 10\,\text{mg/L} \times 0.0639 = 0.6\end{aligned}$$

Similar evaluations can indeed be carried out for the various media and exposure routes of potential concern or possible interest.

Anyway, as noted previously in Sect. 11.1.3, for multiple chemical exposures to non-carcinogens and the non-carcinogenic effects of carcinogens, constituents are normally grouped by the same mode of toxicological action. Cumulative non-cancer risk is then evaluated through the use of a hazard index that is generated for each health or toxicological 'endpoint'. Chemicals with the same endpoint are generally included in a hazard index calculation. Thus, for multiple non-carcinogenic effects of several chemical compounds and multiple exposure routes, the aggregate non-cancer risk for all exposure routes and all constituents associated with a potential chemical exposure problem can be estimated using the algorithm shown in Box 11.4. It is noteworthy that, the combination of hazard quotients across exposure routes is based on the assumption that the same receptors would consistently experience the reasonable maximum exposure via the multiple routes. Thus, if specific sources do not affect the same individual or receptor group, hazard quotients should not be combined under those circumstances. Furthermore, and in the strictest sense, constituents should not be grouped together unless the physiologic/toxicological endpoint is known to be the same—otherwise the efforts will likely over-estimate and/or over-state potential health effects.

Box 11.4 General Equation for Calculating Non-carcinogenic Risks to Human Health

$$\text{Total Hazard Index} = \sum_{j=1}^{p}\sum_{i=1}^{n}\frac{E_{ij}}{\text{RfD}_{ij}} = \sum_{j=1}^{p}\sum_{i=1}^{n}[\text{HQ}]_{ij}$$

and

(continued)

Box 11.4 (continued)

$$\text{Aggregate/Cumulative Total Hazard Index} = \sum_{k=1}^{s}\left\{\sum_{j=1}^{p}\sum_{i=1}^{n}\frac{E_{ij}}{RfD_{ij}}\right\} = \sum_{k=1}^{s}\left\{\sum_{j=1}^{p}\sum_{i=1}^{n}[\text{HQ}]_{\text{ij}}\right\}$$

where:
E_{ij} = exposure level (or intake) for the ith chemical and jth route (mg/kg day)
RfD_{ij} = acceptable intake level (or reference dose) for the ith chemical and jth exposure route (mg/kg day)
$[HQ]_{ij}$ = hazard quotient for the ith chemical and jth route
n = total number of chemicals showing non-carcinogenic effects
p = total number of pathways or exposure routes
s = total number for multiple sources of exposures to receptor (e.g., dietary, drinking water, occupational, residential, recreational, etc.)

Finally, in accordance with general guidelines on the interpretation of hazard indices, for any given chemical, there may be potential for adverse health effects if the hazard index exceeds unity (1)—albeit it is possible that no toxic effects may occur even if this benchmark level is exceeded, since the RfD incorporates a large margin of safety. At any rate, as a rule-of-thumb in the interpretation of the results from HI calculations, a reference value of less than or equal to unity (i.e., HI $\leq$ 1) should be taken as the acceptable benchmark. Also, it is noteworthy that, for HI values greater than unity (i.e., HI $>$ 1), the higher the value, the greater is the likelihood of adverse non-carcinogenic health impacts. In the final analysis, since populations may be exposed to the same constituents from sources unknown or unrelated to a case-problem, it is preferred that the estimated non-carcinogenic hazard index be well below the benchmark level of unity—in order to allow for additional margin of protectiveness for populations potentially at risk. Indeed, if any calculated hazard index exceeds unity, then the health-based criterion for the chemical mixture or multiple routes has been exceeded, and the need for corrective measures must be given serious consideration.

11.3.1 Chronic Versus Subchronic Non-carcinogenic Effects

Human receptor exposures to chemicals can occur over long-term periods (i.e., chronic exposures), or over short-term periods (i.e., subchronic exposures). Chronic exposures for humans usually range in duration from about 7 years to a lifetime;

sub-chronic human exposures typically range in duration from about 2 weeks to 7 years (USEPA 1989a)—albeit shorter-term exposures of less than 2 weeks could also be anticipated. Accordingly, appropriate chronic and subchronic toxicity parameters and intakes should generally be used in the estimation of non-carcinogenic effects associated with the different exposure duration—as reflected in the relationships shown below.

The chronic non-cancer hazard index is represented by the following modification to the general equation presented earlier on in Box 11.4:

$$\text{Total Chronic Hazard Index} = \sum_{j=1}^{p} \sum_{i=1}^{n} \frac{CDI_{ij}}{RfD_{ij}} \tag{11.22}$$

where: CDI_{ij} is chronic daily intake for the ith constituent and jth exposure route, and RfD_{ij} is chronic reference dose for ith constituent and jth exposure route.

The subchronic non-cancer hazard index is represented by the following modification to the general equation presented earlier on in Box 11.4:

$$\text{Total Subchronic Hazard Index} = \sum_{j=1}^{p} \sum_{i=1}^{n} \frac{SDI_{ij}}{RfD_{sij}} \tag{11.23}$$

where: SDI_{ij} is subchronic daily intake for the ith constituent and jth exposure route, and RfD_{sij} is subchronic reference dose for ith constituent and jth exposure route.

11.3.2 Non-carcinogenic Hazard Computations: Illustration of the Processes for Calculating Non-carcinogenic Hazards

The overall purpose of a non-carcinogenic hazard characterization is to estimate the likelihood that a receptor will experience systemic health effects as a result of exposure to a constituent in an environmental medium of interest or concern. This likelihood is a function of the dose of a constituent (as determined during an exposure assessment) and the RfD (as documented from a dose-response assessment) for that constituent.

In accordance with the relationships presented earlier on in this chapter, the potential non-cancer risks associated with chemical exposures can be systematically calculated for all relevant exposure routes. Illustrative example evaluations for potential receptor groups purportedly exposed through inhalation, soil ingestion (i.e., incidental or pica behavior), and dermal contact are discussed in the proceeding sections. The examples shown below for childhood exposure from infancy through age six are used to demonstrate the computational mechanics for estimating chemical risks; the same set of units is maintained throughout as given above in related prior discussions.

11.3.2.1 Non-carcinogenic Effects for Contaminants in Water

The non-carcinogenic risk associated with a potential receptor exposure to chemical constituents in water can generally be estimated using the following type of relationship:

$$\begin{aligned}\text{Hazard}_{\text{water}} &= \left[\text{CDI}_{\text{o}} \times \frac{1}{\text{RfD}_{\text{o}}}\right] + \left[\text{CDI}_{\text{i}} \times \frac{1}{\text{RfD}_{\text{i}}}\right] \\ &= \left[\left(\text{CDI}_{\text{ing}} + \text{CDI}_{\text{der}}\right) \times \frac{1}{\text{RfD}_{\text{o}}}\right] + \left[\text{CDI}_{\text{i}} \times \frac{1}{\text{RfD}_{\text{i}}}\right] \\ &= \left\{\left[\left(\text{INGf} \times \text{C}_{\text{w}}\right) + \left(\text{DEXf} \times \text{C}_{\text{w}}\right)\right] \times \frac{1}{\text{RfD}_{\text{o}}}\right\} + \left\{\left[\left[\text{INHf}_{\text{i}} \times \text{C}_{\text{w}}\right] \times \frac{1}{\text{RfD}_{\text{i}}}\right]\right\}\end{aligned} \tag{11.24}$$

More generally, the non-cancer risk may be calculated from 'first principles' as follows:

$$\begin{aligned}\text{Hazard}_{\text{water}} = &\left\{\frac{1}{\text{RfD}_{\text{o}}} \times \text{C}_{\text{w}} \times \frac{\left(\text{IR}_{\text{child}} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{EF} \times \text{ED}_{\text{child}}\right)}{\left(\text{BW}_{\text{child}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\} \\ &+\left\{\frac{1}{\text{RfD}_{\text{o}}} \times \text{C}_{\text{w}} \times \frac{\left(\text{SA}_{\text{child}} \times \text{K}_{\text{p}} \times \text{CF} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{EF} \times \text{ED}_{\text{child}} \times \text{ET}_{\text{child}}\right)}{\left(\text{BW}_{\text{child}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\} \\ &+\left\{\frac{1}{\text{RfD}_{\text{i}}} \times \text{C}_{\text{w}} \times \frac{\left(\text{IR}_{\text{child}} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{EF} \times \text{ED}_{\text{child}}\right)}{\left(\text{BW}_{\text{child}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\}\end{aligned} \tag{11.25}$$

As an example, substitution from the exposure assumptions presented in Box 11.5 into the above equation yields the following reduced form of Eq. (11.24):

$$\begin{aligned}\text{Hazard}_{\text{water}} = &\left(\frac{1}{\text{RfD}_{\text{o}}} \times \text{C}_{\text{w}} \times 0.0639\right) \\ &+ \left(\frac{1}{\text{RfD}_{\text{o}}} \times \text{C}_{\text{w}} \times 0.0644 \times \text{K}_{\text{p}}\right) \\ &+ \left(\frac{1}{\text{RfD}_{\text{i}}} \times \text{C}_{\text{w}} \times 0.0639\right)\end{aligned} \tag{11.26}$$

Subsequently, by substituting the chemical-specific parameters in the reduced risk equation, potential non-carcinogenic risks associated with the particular constituent can be determined.

Box 11.5 Definitions and Exposure Assumptions for the Example Hazard Computations Associated with Exposure to Environmental Contaminants in Water and Soil

Parameter	*Parameter Definition and Exposure Assumption*
RfD_o	Oral reference dose (obtained from the literature, or Appendix C) ([mg/kg day])
RfD_i	Inhalation reference dose (from the literature, or Appendix C) ([mg/kg day])
C_w	Chemical concentration in water (obtained from the sampling and/or modeling) (mg/L)
C_s	Chemical concentration in soil (obtained from the sampling and/or modeling) (mg/kg)
C_a	Chemical concentration in air (obtained from the sampling and/or modeling) (mg/m^3)
K_p	Chemical-specific dermal permeability coefficient from water (obtained from the literature, e.g., DTSC 1994) (cm^2/h)
AF	Soil to skin adherence factor (1 mg/cm^2)
SA	Skin surface area available for water contact (child = 7200 cm^2)
SA	Skin surface area exposed/available for soil contact (child = 2000 cm^2)
IR	Average water intake rate—where intake from inhalation of volatile constituents may be assumed as equivalent to the amount of ingested water (child = 1 L/day)
SIR	Average soil ingestion rate (child = 200 mg/day)
IR_a	Inhalation rate (child = 10 m^3/day)
CF	Conversion factor for water (1 L/1000 cm^3)
CF	Conversion factor for soil (10^{-6} kg/mg)
FI	Fraction ingested from contaminated source (1)
ABS_{gi}	Bioavailability/gastrointestinal [GI] absorption factor (100%)
ABS_s	Chemical-specific skin absorption fraction of chemical from soil (%)
EF	Exposure frequency (350 days/years)
ED	Exposure duration (child = 6 years)
ET	Exposure time during showering/bathing (child = 0.14 h/day)
BW	Body weight (child = 15 kg)
AT	Averaging time (period over which exposure is averaged = 6 years or [6 × 365] days)

11.3.2.2 Non-carcinogenic Effects for Contaminants in Soils

The non-carcinogenic risk associated with a potential receptor exposure to chemical constituents in soils can generally be estimated using the following type of relationship:

$$\begin{aligned}\text{Hazard}_{\text{soil}} &= \left[\text{CDI}_{\text{o}} \times \frac{1}{\text{RfD}_{\text{o}}}\right] + \left[\text{CDI}_{\text{i}} \times \frac{1}{\text{RfD}_{\text{i}}}\right] \\ &= \left[\left(\text{CDI}_{\text{ing}} + \text{CDI}_{\text{der}}\right) \times \frac{1}{\text{RfD}_{\text{o}}}\right] + \left[\text{CDI}_{\text{i}} \times \frac{1}{\text{RfD}_{\text{i}}}\right] \\ &= \left\{\left[\left(\text{INGf} \times \text{C}_{\text{w}}\right) + \left(\text{DEXf} \times \text{C}_{\text{w}}\right)\right] \times \frac{1}{\text{RfD}_{\text{o}}}\right\} \\ &\quad + \left\{\left[\left(\text{INHf}_{\text{i}} \times \text{C}_{\text{w}}\right) \times \frac{1}{\text{RfD}_{\text{i}}}\right]\right\}\end{aligned} \tag{11.27}$$

More generally, the carcinogenic risk may be calculated from 'first principles' as follows:

$$\begin{aligned}\text{Hazard}_{\text{soil}} = &\left\{\frac{1}{\text{RfD}_{\text{o}}} \times \text{C}_{\text{s}} \times \frac{\left(\text{SIR}_{\text{child}} \times \text{CF} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{EF} \times \text{ED}_{\text{child}}\right)}{\left(\text{BW}_{\text{child}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\} \\ &+\left\{\frac{1}{\text{RfD}_{\text{o}}} \times \text{C}_{\text{s}} \times \frac{\left(\text{SA}_{\text{child}} \times \text{AF} \times \text{CF} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{ABS}_{\text{s}} \times \text{EF} \times \text{ED}_{\text{child}}\right)}{\left(\text{BW}_{\text{child}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\} \\ &+\left\{\frac{1}{\text{RfD}_{\text{i}}} \times \text{C}_{\text{a}} \times \frac{\left(\text{IR}_{\text{child}} \times \text{FI} \times \text{ABS}_{\text{gi}} \times \text{EF} \times \text{ED}_{\text{child}}\right)}{\left(\text{BW}_{\text{child}} \times \text{AT} \times 365\,\text{day/year}\right)}\right\}\end{aligned} \tag{11.28}$$

As an example, substitution from the exposure assumptions presented in Box 11.5 into the above equation yields the following reduced form of Eq. (11.27):

$$\begin{aligned}\text{Hazard}_{\text{soil}} = &\left(\frac{1}{\text{RfD}_{\text{o}}} \times \text{C}_{\text{s}} \times \left[1.28 \times 10^{-5}\right]\right) \\ &+ \left(\frac{1}{\text{RfD}_{\text{o}}} \times \text{C}_{\text{s}} \times \left[1.28 \times 10^{-4}\right] \times \text{ABS}_{\text{s}}\right) \\ &+ \left(\frac{1}{\text{RfD}_{\text{i}}} \times \text{C}_{\text{a}} \times 0.639\right)\end{aligned} \tag{11.29}$$

Subsequently, by substituting the chemical-specific parameters in the reduced risk equation, potential non-carcinogenic risks associated with the particular constituent can be determined.

11.3.2.3 Interpreting the Non-cancer Risk Metric

The 'hazard quotient' (viz., the ratio of the environmental exposure to the RfD or RfC) and the 'hazard index' (viz., the sum of hazard quotients of chemicals to which a person is exposed—and that affect the same target organ, or operate by the same mechanism of action) are generally used as indicators of the likelihood of harm arising from the non-carcinogenic effects of chemicals encountered in human

environments (USEPA 2000b). In such usage, an HI less than unity (1) is commonly understood as being indicative of a lack of appreciable risk, whereas a value over unity (1) would indicate a likely increased risk; thus, the larger the HI, the greater the risk—albeit the index is not related to the likelihood of adverse effect except in qualitative terms. In fact, the HI cannot be translated into a probability realm that would necessarily suggest that adverse effects will occur—and also, is not likely to be proportional to risk *per se* (USEPA 2006a; NRC 2009). As such, this RfD-based risk characterization does not quite provide information on the fraction of a population adversely affected by a given dose, or on any other direct measure of risk for that matter (USEPA 2000a; NRC 2009).

Meanwhile, it is worth the mention here that, in more recent times, some investigators have been advocating for the development and use of a 'hazard range' concept (rather that the 'simplistic' point value) to facilitate better and more informed decision-making about exposures and likely effects to humans of the noncancer attributes of chemicals; this would somehow parallel the practices that already exist for the cancer effects from chemicals (viz., the 10^{-6} to 10^{-4} risk range concept for carcinogenicity). In fact, although the RfD and RfC have generally been defined in terms of metrics that carry with them uncertainties that perhaps span an order of magnitude, risk managers have generally not implemented their decisions by necessarily accounting for this implicit uncertainty; consequently, non-cancer hazards have frequently been evaluated and/or regulated in such a manner that the hazard quotient or index of one (1) is more or less interpreted as a 'bright line' for risk management decision-making.

11.4 A Holistic Approach to Risk Presentations

It is often imperative to offer a systematic framework for presenting risk computations and consequential outcomes. This is generally best done in a manner that also facilitates effectual risk management and any possible risk communication efforts that might become necessary.

To start off, consider the following illustrative practical example. Routine air monitoring at a housing development downwind of a chemical recycling facility has documented air contamination for the following chemicals (at the corresponding average concentrations indicated): Acetone = 12 $\mu g/m^3$; Benzene = 0.5 $\mu g/m^3$; and PCE = 2 $\mu g/m^3$. Now, it is required to determine the total health risk to a 70-kg adult in this housing estate, assuming an inhalation rate of 0.83 m^3/h. The computation process—consisting of a systematic presentation to this task—is provided below for this example problem.

Step 1—Intake Computations
The intakes for the non-carcinogenic risk contributions from Acetone and PCE are estimated as follows:

$$NCInh_{(adult\ R)} = \left[\frac{(CA \times IR \times RR \times ABS_s \times ET \times EF \times ED)}{(BW \times AT)}\right]$$

Substituting CA = 12 μg/m^3 = (12 × 10^{-3}) mg/m^3 [Acetone] and 2 μg/m^3 = (2 × 10^{-3}) mg/m^3 [PCE]; IR = 0.83 m^3/h; RR = 1; ABS_s = 1; ET = 12 h/day; EF = 365 day/year; ED = 58 years; BW = 70 kg; and AT = (ED × 365) = (58 × 365) days yields:

For Acetone:

$$NCInh_{(adult\ R)} = \left[\frac{\left(12 \times 10^{-3} \times 0.83 \times 12 \times 365 \times 58\right)}{(70 \times 58 \times 365)}\right]$$
$$\cong 1.71 \times 10^{-3}\, mg/kg\text{-}day$$

For PCE:

$$NCInh_{(adult\ R)} = \left[\frac{\left(2 \times 10^{-3} \times 0.83 \times 12 \times 365 \times 58\right)}{(70 \times 58 \times 365)}\right]$$
$$\cong 2.85 \times 10^{-4}\, mg/kg\text{-}day$$

Now, the intakes for the carcinogenic risk contributions from Benzene and PCE are estimated as follows:

$$CInh_{(adult\ R)} = \left[\frac{(CA \times IR \times RR \times ABS_s \times ET \times EF \times ED)}{(BW \times AT)}\right]$$

Substituting CA = 0.5 μg/m^3 = (0.5 × 10^{-3}) mg/m^3 [Benzene] and 2 μg/m^3 = (2 × 10^{-3}) mg/m^3 [PCE]; IR = 0.83 m^3/h; RR = 1; ABS_s = 1; ET = 12 h/day; EF = 365 day/year; ED = 58 years; BW = 70 kg; and AT = (70 × 365) = (70 × 365) days yields:

For Benzene:

$$CInh_{(adult\ R)} = \left[\frac{\left(0.5 \times 10^{-3} \times 0.83 \times 12 \times 365 \times 58\right)}{(70 \times 70 \times 365)}\right]$$
$$\cong 5.89 \times 10^{-5}\, mg/kg\text{-}day$$

For PCE:

$$CInh_{(adult\ R)} = \left[\frac{\left(2 \times 10^{-3} \times 0.83 \times 12 \times 365 \times 58\right)}{(70 \times 70 \times 365)}\right] \cong 2.36 \times 10^{-4}\, mg/kg\text{-}day$$

Step 2—Risk Computations

For the non-carcinogenic risk, assuming $\mathrm{RfD_i} = 1.00 \times 10^{-1}$ [Acetone] and 1.00×10^{-2} [PCE], the hazard quotients are calculated to be:

$$HQ_{(acetone)} = \left[\frac{NCInh_{(adultR)}}{RfD_i}\right] = \frac{1.71 \times 10^{-3}}{1.00 \times 10^{-1}} \cong 1.71 \times 10^{-2}$$

$$HQ_{(PCE)} = \left[\frac{NCInh_{(adultR)}}{RfD_i}\right] = \frac{2.85 \times 10^{-4}}{1.00 \times 10^{-2}} \cong 2.85 \times 10^{-2}$$

Thence, the total hazard index is given by:

$$\mathrm{HI} = \left(1.71 \times 10^{-2}\right) + \left(2.85 \times 10^{-2}\right) = 4.56 \times 10^{-2} = 0.05$$

For the carcinogenic risk, assuming $\mathrm{SF_i} = 2.90 \times 10^{-2}$ [Benzene] and 2.10×10^{-2} [PCE], the cancer risks are calculated to be:

$$CR_{(benzene)} = \left[CInh_{(adult)} \times SF_i\right] = \left[\left(5.89 \times 10^{-5}\right) \times \left(2.90 \times 10^{-2}\right)\right] \cong 1.71 \times 10^{-6}$$

$$CR_{(PCE)} = \left[CInh_{(adult)} \times SF_i\right] = \left[\left(2.36 \times 10^{-4}\right) \times \left(2.10 \times 10^{-2}\right)\right] \cong 4.96 \times 10^{-6}$$

Thence, the total cancer risk is given by:

$$\mathrm{TCR} = \left(1.71 \times 10^{-6}\right) + \left(4.96 \times 10^{-6}\right) = 6.67 \times 10^{-6}$$

After going through all the requisite computational exercises, the risk values are often stated simply as numerals—such as is expressed in the following statements:

- Risk probability of occurrence of additional cases of cancer—e.g., a cancer risk of 1×10^{-6}, which reflects the estimated number of excess cancer cases in a population.
- Hazard index of non-cancer health effects such as neurotoxicity or birth defects—e.g., a hazard index of 1, reflecting the degree of harm from a given level of exposure.

One of the most important points to remember in all cases of risk presentation, however, is that the numbers by themselves may not tell the whole story. For instance, a human cancer risk of 10^{-6} for an 'average exposed person' (e.g., someone exposed via food products only) may not necessarily be interpreted to be the same as a cancer risk of 10^{-6} for a 'maximally exposed individual' (e.g., someone exposed from living in a highly contaminated area)—i.e., despite the fact that the numerical risk values may be identical. In fact, omission of the qualifier terms—e.g., 'average' or 'maximally/most exposed'—could mean an incomplete description of the true risk scenarios, and this could result in poor risk management

strategies and/or a failure in risk communication tasks. Thus, it is very important to know, and to recognize such seemingly subtle differences in the risk summarization—or indeed throughout the risk characterization process.

To ultimately ensure an effective risk presentation, it must be recognized that the qualitative aspect of a risk characterization (which may also include an explicit recognition of all assumptions, uncertainties, etc.) may be as important as its quantitative component (i.e., the estimated risk numbers). The qualitative considerations are indeed essential to making judgments about the reliability of the calculated risk numbers, and therefore the confidence associated with the characterization of the potential risks.

11.4.1 Graphical Presentation of the Risk Summary Information

Several graphical representations may be employed in presenting a summary of the requisite risk information that has been developed from the risk characterization efforts. Examples of such graphical forms include the following:

- *Pie charts,* such as shown in Fig. 11.1a, b to illustrate the risk contributions from different chemical exposure sources.
- *Horizontal bar charts,* such as shown in Fig. 11.2 to illustrate the hazard index contributions associated with different exposure routes and receptor groups.
- *Vertical bar charts,* such as shown in Fig. 11.3a–c to illustrate the hazard index and cancer risk contributions from different exposure sources and CoPCs.
- *Variety of relational plots,* such as shown in Figs. 11.4, 11.5, and 11.6 to illustrate various graphical relationships used to characterize risk associated with chemical exposure problems.

This listing is by no means complete; other novel representations that may consist of variations or convolutions of the above may indeed be found to be more appropriate and/or useful for some case-specific applications.

11.5 Risk Characterization in Practice and the Cumulative Risk Assessment Paradigm

A primary aim of risk assessment should be to inform decision-makers about the public health implications of various strategies for reducing receptor/populations exposures to the totality of environmental stressors. And yet, oftentimes, risk assessment applications seem centered on simply evaluating risks associated with individual chemicals in the context of regulatory requirements or isolated actions.

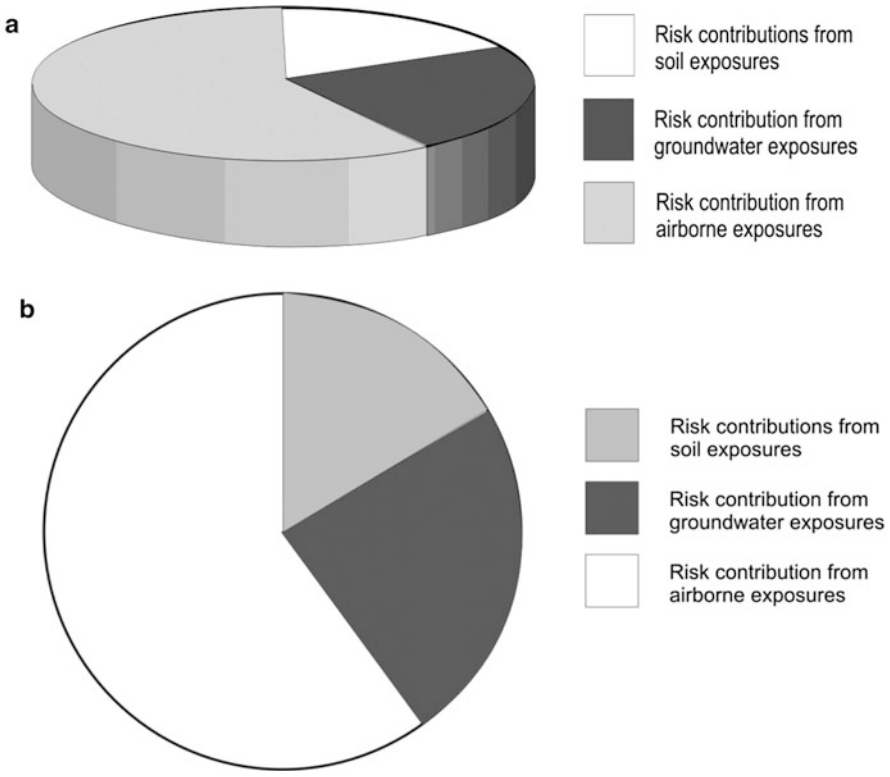

Fig. 11.1 (**a**) Pie chart illustration of risk summary results: a 3-D schematic. (**b**) Pie chart illustration of risk summary results: a 2-D sketch

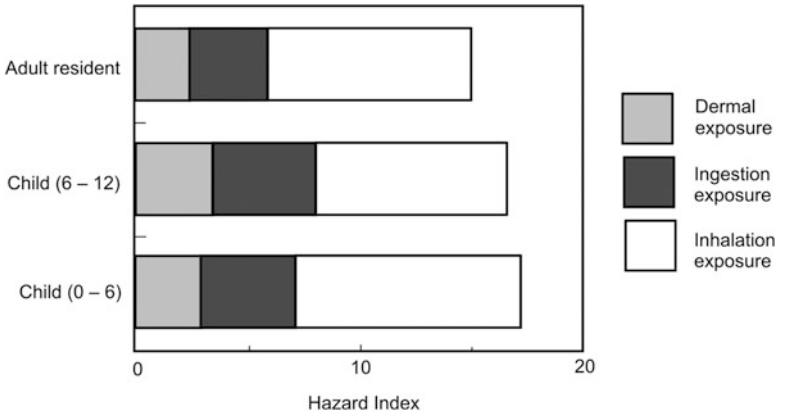

Fig. 11.2 Horizontal bar chart illustration of risk summary results

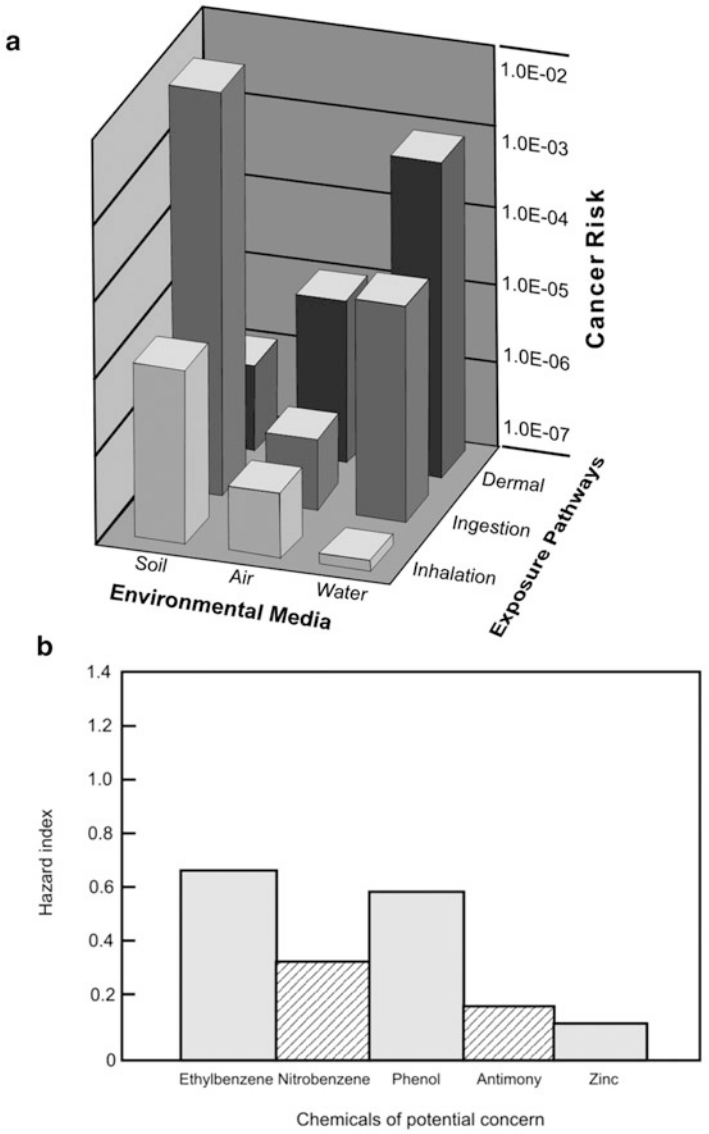

Fig. 11.3 (**a**) Vertical bar chart illustration of risk summary results. (**b**) Vertical bar chart illustration of risk summary results: illustrative presentation of the relative contribution of individual chemicals to overall hazard index estimates associated with a hypothetical public water supply system. (**c**) Vertical bar chart illustration of risk summary results: illustrative presentation of the relative contribution of individual chemicals to overall cancer risk estimates associated with a hypothetical public water supply system (semi-log plot)

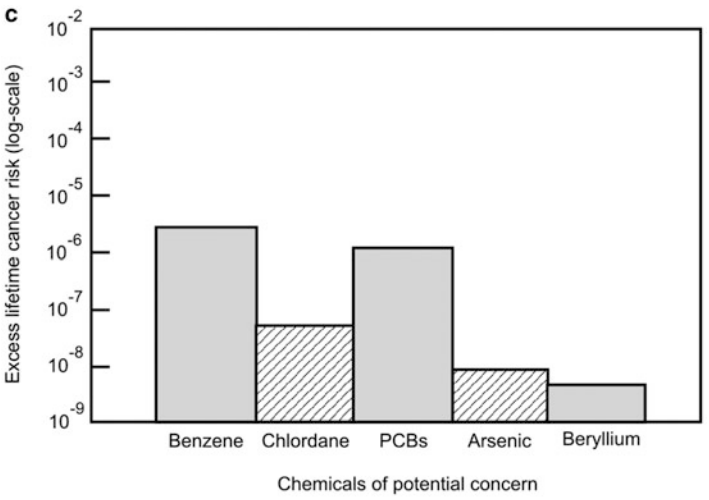

Fig. 11.3 (continued)

In fact, it has become apparent that such a narrow focus does not accurately capture the risks associated with true exposure, given that simultaneous exposure to multiple chemical and nonchemical stressors seems inevitable in contemporary societies—and of course further to other factors that could influence receptor or population vulnerability as well (NRC 2009). This, therefore, calls for the concept of 'cumulative risk assessment'—that may essentially be deemed as helping add a more holistic dimension to the risk characterization process.

Cumulative risk may be formally defined as the combination of risks posed by the aggregate exposure to multiple agents or stressors—whence *aggregate exposure* is exposure by all routes and pathways, and from all sources of each given agent or stressor (USEPA 2003a; NRC 2009). In this context, chemical, biologic, radiologic, physical, and psychological/psychosocial stressors are all recognized as affecting human health—and thus are potentially addressed in the multiple-stressor, multiple-effects assessments (Callahan and Sexton 2007; NRC 2009). *Cumulative risk assessment* may therefore be defined as the analysis, characterization, and possible quantification of the combined risks to health and/or the environment posed by multiple agents or stressors (USEPA 2003a; NRC 2009). That said, it is also noteworthy that cumulative risk assessment can involve qualitative analyses, and is not necessarily always wholly quantitative—recognizing that even limited or simple qualitative analyses may be sufficient at times to discriminate among competing risk management options (Callahan and Sexton 2007; USEPA 2003a; NRC 2009). Consequently, the cumulative risk assessment process would typically consist of the evaluation of an array of stressors (chemical and nonchemical) in order to characterize (quantitatively to the extent possible) human health or ecologic effects, taking account of such factors as vulnerability and background exposures (NRC 2009). [By the way, where this becomes the broader focus for particular program, 'cumulative *impact* assessment' would consider a wider array

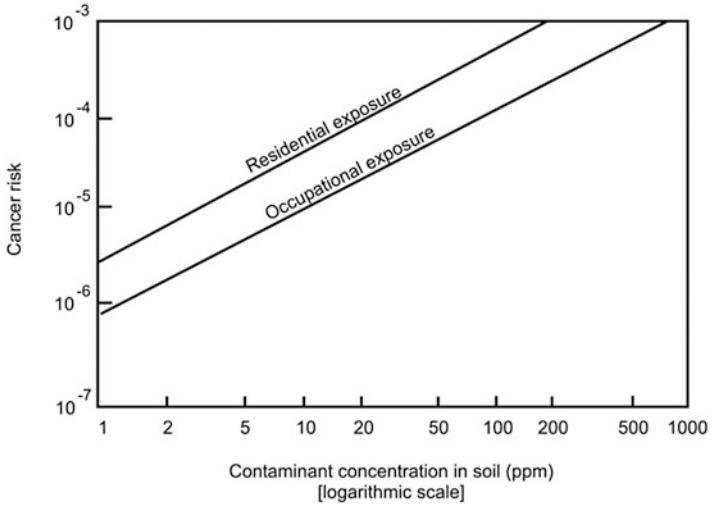

Fig. 11.4 Illustrative sketch of the effects of choice of exposure scenarios on dose and risk estimates

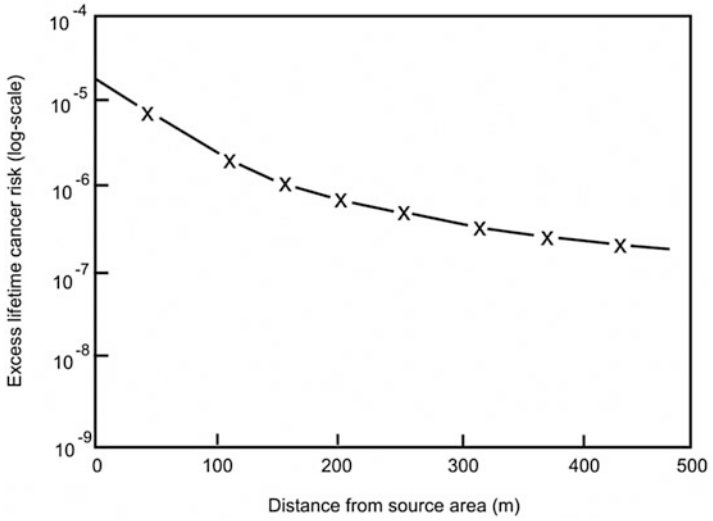

Fig. 11.5 Illustrative sketch of the variation of estimated cancer risks with distance from contaminant source: a semi-log plot of cancer risk estimates from receptor exposures to benzene in groundwater at several different locations downgradient of a release source

of end points, including effects on historical resources, quality of life, community structure, and cultural practices, some of which may not lend themselves to the 'traditional' quantification process/paradigm *per se* (CEQ 1989; NRC 1983).]

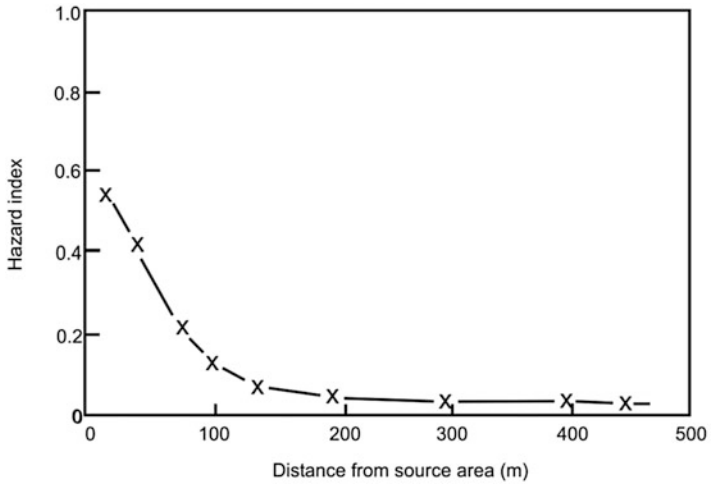

Fig. 11.6 Illustrative sketch of the variation of estimated hazard index with distance from contaminant source: an arithmetic-scale plot of hazard index estimates from receptor exposures to ethylbenzene in groundwater at several different locations downgradient of a release source

In spite of the fact that cumulative risk assessment by definition might consider psychosocial, physical, and other factors, most contemporary cumulative risk assessments do not tend to formally incorporate nonchemical stressors. Indeed, it is apparent that cumulative risk assessments have generally not quite attained the potential implied by the true definition—mainly because there has been less than optimal formal consideration of nonchemical stressors, aspects of vulnerability, background processes, and other factors that could be of interest to stakeholders concerned about effects of cumulative exposures (NRC 2009). All these may, in large part, be due to the fact that data tends to be inadequate to address most nonchemical stressors issues; but then, such omission also means that cumulative risk assessment will usually end up having a much narrower scope than could be expected or desired by many stakeholders (NRC 2009). Anyhow, despite all the apparent difficulties and/or complications to be anticipated in a typical problem situation, approaches to incorporate nonchemical stressors into cumulative risk assessment are not infeasible.

Meanwhile, cumulative risk assessments to date have mostly focused on aggregate chemical exposure assessment—and have generally not considered nonchemical stressors. Still, it should be explicitly recognized here that, analyses of chemical mixtures constitute only one component of cumulative risk assessment (even when the prospects for synergistic or antagonistic interactions that may affect the shape of the dose-response relationship of the individual chemicals are taken into consideration); indeed, for a truly comprehensive/holistic cumulative risk appraisal, other multiple stressors may have to be properly accounted for. That said, it is notable that the approach to evaluate cumulative risk posed by multiple

chemicals with similar MOAs has been developed reasonably well (although with generally modest treatment of synergistic and antagonistic effects).

Cumulative risk assessment has also been used to determine the risks posed by baseline exposures, rather than the benefits of various risk management strategies—and this use has implications for the methods developed and their interpretations; for instance, NRC (2009) notes that some of the omissions can be attributed to the fact that formal consideration of numerous simultaneous chemical, physical, and psychosocial exposures with evaluation of background disease processes and other dimensions of vulnerability could quickly become analytically intractable if the standard risk assessment paradigm is followed—both because of the computational burden, and because of the likelihood that important exposure and dose-response data will be missing. Indeed, cumulative risk assessment requires extensive information beyond chemical toxicity and MOAs, including aggregate exposure data and information on population characteristics and nonchemical stressors—albeit, in the long run, despite the fact that there may be numerous theoretical combinations of exposures, only a subset will be relevant in choosing among various intervention options for a well-defined problem (NRC 2009).

Finally, it is worth mentioning here that, although it is generally preferable to have quantitative information as the primary health risk characterization/assessment outputs, it will often be useful enough to provide qualitative information about potential health effects when risks cannot be fully quantified. Furthermore, it should prove quite useful to incorporate appropriate terminologies that distinguish the full discussion of possible health effects from the myriad other effects that may be considered in a cumulative impact assessment (NRC 2009); indeed, any such undertakings should be such that, at the end of the day, it would be seen as serving a reasonably important role with regards to the decision on hand.

Chapter 12
Uncertainty and Variability Issues in Public Health Risk Evaluation

Uncertainty and variability are almost an omnipresent aspect of risk assessments—and tackling these in a reasonably comprehensive manner is crucial to the overall risk assessment process. Broadly stated, *uncertainty* stems from lack of knowledge—and thus can be characterized and managed but not necessarily eliminated, whereas *variability* is an inherent characteristic of a population—inasmuch as people vary substantially in their exposures and their susceptibility to potentially harmful effects of exposures to the stressors of concern/interest (NRC 2009). In general, uncertainty can be reduced by the use of more or better data; on the other hand, variability cannot be reduced, but it can be better characterized with improved information. In any event, when all is said and done, uncertainty (alongside variability) analyses become key factors in the ultimate decision-making process that is typically developed to address chemical exposure problems. By way of probabilistic modeling and analyses, uncertainties associated with the risk evaluation process can be assessed properly and their effects on a given decision accounted for systematically. In this manner the risks associated with given decisions may be aptly delineated, and then appropriate corrective measures taken accordingly. This chapter discusses the key issues and evaluation modalities regarding uncertainty and variability matters that surround the overall risk assessment process.

12.1 Uncertainty and Variability Concerns in Risk Assessment

Risk assessments tend to be highly uncertain, as well as highly variable. In fact, due to the oftentimes limited availability of data for most scientific endeavors, uncertainty in particular tends to be rather pervasive in so many studies.

K. Asante-Duah, *Public Health Risk Assessment for Human Exposure to Chemicals*,
Environmental Pollution 27, DOI 10.1007/978-94-024-1039-6_12

Variability (or *stochasticity*) refers to the inherent lack of uniformity in a population—and this cannot be reduced with additional data, but can be better represented by providing ranges or distributions of the subject parameter in question; it arises from true heterogeneity or diversity in characteristics such as dose-response differences within a population, or differences in body weight, or differences in rates of food and water intakes/ingestion, or differences in chemical exposure levels in source materials, etc. Differences among individuals in a population are referred to as '*inter*-individual variability', and differences associated with a particular individual over time are referred to as '*intra*-individual variability'.

Uncertainty represents a lack of knowledge about factors such as adverse effects or chemical exposure levels—and this may potentially be reduced with additional studies or investigations. For instance, uncertainty in exposure estimates may be the result of limited data being available on significant exposure factors for a particular age group—or it may also be due to assumptions made in development of an exposure conceptual model; etc.

As an example of the intertwining relationships between uncertainty and variability, consider a situation involving the ingestion of contaminated drinking water; now, assume that it is possible to measure an individual's daily water consumption (and indeed the contaminant concentration) in exact terms—thereby eliminating uncertainty in the measured daily dose. Notwithstanding, the daily dose would still have an inherent day-to-day variability—due to changes in the individual's daily water intake, or the contaminant concentration in the water. Ultimately, since the individual's true average daily dose (ADD) is actually unknown, it becomes uncertain as to how close the estimate is to the true value. Accordingly, the variability across daily doses has been translated into uncertainty in the ADD. In this light, it becomes apparent that although the individual's true ADD has no variability *per se*, the estimate of the ADD has some uncertainty associated with it (USEPA 1997a, b, c, d, e, f, g, h). All together, uncertainty can indeed lead to inaccurate or biased estimates, whereas variability can affect the precision of the estimates and the degree to which they can be generalized.

On the whole, 'variability' encompasses any aspect of the risk assessment process that can produce varying results. This includes the potential interpretations of the available data, the availability of different data sets collected under different experimental protocols, and the availability of different models and methods—albeit several of these may also be considered as sources of uncertainty (NRC 1994a, b; USEPA 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h). Thus, the use of 'variability' to refer to differences attributable to diversity in biological sensitivity or exposure parameters means these differences can be better understood, but not reduced, by further research. On the other hand, 'uncertainty'—that refers to lack of knowledge about specific factors, parameters, or models—can generally be reduced through further study. Indeed, in principle, uncertainty can be reduced through the acquisition of more information, whereas variability is irreducible.

Finally, it is worth mentioning here that, some parameters used in risk assessments may reflect both variability and uncertainty under different sets of

circumstances or conditions. However, insofar as possible, stochastic variability and knowledge uncertainty should be segregated in the evaluation processes employed during the risk assessment. Ultimately, probabilistic assessments can become useful statistical tools for analyzing variability and uncertainty in risk assessments—particularly on the assumption that adequate data would be available for such undertaking.

12.1.1 Types and Nature of Variability

Three fundamental types of variability may be identified for most risk assessment exercises, namely (USEPA 1997a, b, c, d, e, f, g, h):

1. Spatial variability (i.e., variability across locations)
2. Temporal variability (i.e., variability over time)
3. Inter-receptor variability (i.e., variability amongst individual receptors)

Spatial variability can occur both at regional (macroscale) and local (microscale) levels. For example, fish intake rates can vary significantly depending on the region or locality of a country—with higher consumption more likely to occur among populations located near large water bodies or coastal areas (USEPA 1997a, b, c, d, e, f, g, h). In general, higher exposures tend to be associated with receptors in closer proximity to the pollutant source.

Temporal variability refers to variations that occur over time—and this may relate to both long- and short-term situations. For example, seasonal fluctuations in weather, pesticide applications, use of wood-burning appliances, and fraction of time spent outdoors relate to longer-term variability; and shorter-term variability may include differences in individual or personal activities on weekdays versus weekends, or even at different times of the day (USEPA 1997a, b, c, d, e, f, g, h).

Inter-receptor variability can be attributed or related to two major factors—namely: human characteristics (such as age or body weight) and human behaviors (such as location and activity patterns), each of which in turn may be related to several underlying phenomena that might vary as well (USEPA 1997a, b, c, d, e, f, g, h); for example, the natural variability in human weight may be attributed to a combination of genetic, nutritional, and other lifestyle or environmental factors. Congruently, it is notable that the common and significant 'inter-individual differences' in physical and pharmacokinetic characteristics include gender, body weight, rates of breathing, and metabolism; additionally, 'person-to-person differences' in behavioral attributes (such as dietary preferences, daily shower/bath duration, etc.) that govern route-specific exposures can be quite significant.

Variability may indeed be confronted and evaluated in a variety of ways (see, e.g., NRC 1994a, b; USEPA 1997a, b, c, d, e, f, g, h)—albeit a strategy that involves using both the appropriate maximum and minimum parameter values seems to be favored in most chemical exposure and risk assessments. Such approach allows for

the characterization of the variability by a range between the extreme values, as well as produces a measure of central tendency estimates.

12.1.2 Types and Nature of Uncertainty

Multiple sources of uncertainty exist in just about any type of risk evaluation. The uncertainties that typically arise in risk assessments can be of three general types—namely (see, e.g., USEPA 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h):

1. Uncertainties in parameter values (e.g., use of incomplete or biased values);
2. Uncertainties in parameter modeling (e.g., issue of model adequacy/inadequacy); and
3. Uncertainties in the degree of completeness (e.g., representativeness of evaluation scenarios).

Parameter uncertainties arise from the need to estimate parameter values from limited or inadequate data. Such uncertainties are inherent because the available data are usually incomplete, and the analyst must make inferences from a state of incomplete knowledge. Examples of uncertainties in parameter values relate to such issues as: incomplete or biased data; applicability of available data to the particular case on hand (i.e., generic vs. case-specific data); etc.

Modeling uncertainties stem from inadequacies in the various models used to evaluate hazards, exposures, and consequences—and also from the deficiencies of the models in representing reality. Examples of uncertainties in modeling relate to such issues as: model adequacy; whether uncertainty is introduced by the mathematical or numerical approximations that are made for convenience; use of models outside its range of validity; etc.

Completeness/scenario uncertainties relate to the inability of the analyst to evaluate exhaustively all contributions to risk. They refer to the problem of assessing what may have been omitted in the analysis. Examples of uncertainties in the degree of completeness may relate to such questions as to: whether the analyses have been taken to sufficient depth; whether all important hazard sources and exposure possibilities have been addressed; etc.

Depending on the specific aspect or component of the risk assessment being performed, the type of uncertainty that dominates at each stage of the analysis can be different. Anyhow, each type of uncertainty can be characterized either qualitatively or quantitatively. Various levels of uncertainty analysis can therefore be classified by the degree to which each type of uncertainty is quantitatively analyzed. Indeed, identification of the sources of uncertainty is an important first step in determining how to reduce the specific uncertainty. Furthermore, because the uncertainties tend to be fundamentally tied to a lack of knowledge concerning important evaluation factors/parameters, strategies for reducing uncertainty necessarily involve the concurrent reduction or elimination of knowledge gaps (USEPA 1997a, b, c, d, e, f, g, h).

Overall, uncertainties are inherent in just about all scientific undertakings—and this probably cannot be avoided. With that said, it should also be recognized that the extent to which uncertainties in data and analyses can be measured and expressed in highly quantitative terms depends very much on the types of investigations used to develop the scientific knowledge in the first place. For instance, highly controlled experiments, usually conducted in a laboratory or clinical setting, if well designed and conducted, can provide the clearest information regarding uncertainties—albeit it is still not always possible to quantify uncertainties in many experimental studies; indeed, controlled clinical trials, for example, still may come with uncertainties and variability that cannot necessarily be predicted or accurately quantified. As a matter of fact, using available knowledge with its inherent uncertainties to make predictions about an as-yet unobserved (and perhaps inherently unobservable) situation is even more uncertain—and yet such needs can be critical to the derivation of many important societal decisions (such as relates to human health protection efforts) (USEPA 2012). For instance, whereas, risk assessments can address such questions as to whether risk to health will be reduced if certain actions are taken, the scientific uncertainties associated with such predictive efforts include not only the uncertainty associated with the available knowledge, but also uncertainty related to the predictive nature of estimates.

Finally, it is noteworthy that uncertainty is invariably embedded in most risk evaluation processes. Indeed, many areas of science or scientific works involve uncertainty—and broadly speaking, uncertainty can become an obstacle to effective decision-making, i.e., unless effectually addressed. Anyhow, by acknowledging (and hopefully characterizing or addressing) uncertainty issues associated with a given project or undertaking, there just might be the chance of making a decision that would likely yield the greatest benefits for public health. Broadly stated in rather simplistic terms, the characterization of uncertainty during risk assessments generally implies that 'lower bounds', 'central estimates', and 'upper bounds' of risk can all be appropriately defined or identified and properly utilized in the risk-based decision-making processes—i.e., rather than a blind focus simply on so-called conservative or 'health protective' estimates of risk on only one end of the 'risk spectrum'. After all, uncertainty has to be seen more so as the characterization of our 'state of knowledge' of the problem on hand—and not as a barrier to effective decisions and actions. At any rate, for all practical purposes, uncertainties are generally propagated through the analysis under consideration. To the extent possible, a 'sensitivity analysis' provides insight into the possible range of results. *Sensitivity analysis* entails the determination of how rapidly the output of an analysis changes with respect to variations in the input. Meanwhile, it is also notable that sensitivity studies do not usually incorporate the error range or uncertainty of the input parameters—thus serving as a distinguishing element from uncertainty analyses.

12.1.3 Common Sources of Uncertainty in Public Health Endangerment Assessments

Inevitably, considerable uncertainty is inherent in the human risk assessment process; Box 12.1 identifies several major sources of uncertainty often associated with human health risk assessments. In particular, uncertainties arise due to the use of several assumptions and inferences necessary to complete a risk assessment. For instance, human health risk assessments usually involve extrapolations and inferences to predict the occurrence of adverse health effects under certain conditions of exposure to chemicals present in the environment. The extrapolations and inferences are typically based on knowledge of the adverse effects that occur under a different set of exposure conditions (e.g., different dose levels and/or species). As a consequence of these types of extrapolations and projections, there is considerable uncertainty in the resulting conclusions—due in part to the several assumptions that tend to be part of the overall evaluation process. Indeed, the dose-response analysis component of the chemical risk assessment process almost always raises questions about the likelihood that effects observed at the generally higher doses used in animal studies (or under conditions of workplace exposures) would actually or likely be observed at the generally lower doses expected in connection with environmental exposures; additionally, exposure assessment can involve an even broader range of uncertainties and related choice points—some associated with the fate and behavior of a chemical of interest in the environment or human tissue, others to data and uncertainties with respect to the metabolism, distribution, and ultimately fate of the chemical in the target population, etc. (NRC 2009).

Indeed, for most chemical substances for which there are insufficient data in humans, a major uncertainty in the evaluation of potential health effects to humans relates to the reliance on animal studies. Such applications involve the use of high exposure in animals to predict human response at lower exposure. Furthermore, this is often carried out in the absence of an understanding of how an agent causes the observed toxicological effects in the animals, and in the face of the varying results frequently obtained with different animal species under different exposure conditions. Even when there are human data, there is uncertainty about average response at lower exposures, and additionally, there is variability in individual response around this average. Still, risk assessment professionals frequently rely heavily on information generated from laboratory animal studies—i.e., despite the fact that biological differences among species and the use of high experimental doses often lead to significant uncertainties that are not easily resolved by traditional risk assessment methodologies.

On the whole, uncertainties are difficult to quantify, or at best, the quantification of uncertainty is itself uncertain. Thus, the risk levels generated in a risk assessment are useful only as a yardstick, and as a decision-making tool for the prioritization of problem situations—rather than to be construed as actual expected rates of disease, or adversarial impacts in exposed populations. For such reasons, it is used only as an estimate of risks, mostly based on current level of knowledge coupled with

several assumptions. Quantitative descriptions of uncertainty, which could take into account random and systematic sources of uncertainty in potency, exposure, intakes, etc. would usually help present the spectrum of possible true values of risk estimates, together with the probability (or likelihood) associated with each point in the spectrum.

Box 12.1 Major Sources of Uncertainty in Human Health Risk Assessments

- Uncertainty in health effects/toxicity data
  - Uncertainty in extrapolating from high dose to low dose
  - Uncertainty in extrapolating data from experimental animals to humans
  - Uncertainty due to differences between individuals
- Uncertainty in measuring or calculating exposure point concentrations
  - Uncertainty in transposing chemical source concentrations into exposure point concentrations
  - Uncertainty in assumptions used to model exposure point concentrations
- Uncertainty in calculating exposure dose
  - Uncertainty in source terms (i.e., chemical source sampling and monitoring data)
  - Uncertainty in estimating exposure dose using mathematical models

12.1.3.1 Archetypical Limitations and Uncertainties Often Encountered in Practice

In general, because of the various limitations and uncertainties often encountered in practice, the results of a risk assessment cannot be considered as an absolutely accurate determination of risks. In fact, this seems to present an almost contentious debate between various investigators—e.g., as eloquently articulated by Dr. Adam M. Finkel on one side of the argument, as follows: "If exposed to an identical concentration of a carcinogen, every human being would face a different level of risk, determined by his or her genetic, environmental, medical, and other uniquely individual characteristics. Various lines of evidence indicate that this susceptibility variable is distributed rather broadly in human populations, . . ., but cancer risk assessment at the EPA and elsewhere has always treated every (adult) human as identically susceptible. . ." (Finkel 2014). On the basis of the preceding argument, therefore, this has the potential for likely underestimation of risks. On the counter-argument side of the debate, however, other investigators do not appear to be in full agreement with the rationale offered by the opposition—and thus seem to disagree with (or at least minimize the impacts of) such assertions (e.g., Bogen 2014a, b).

Notwithstanding, commonly encountered limitations and uncertainties of considerable significance in relation to several components of the risk assessment process are enumerated below—each of which should perhaps be closely apprised for unique case-specific situations (see, e.g., Calabrese 1984; Clewell and Andersen 1985; Dourson and Stara 1983; USEPA 1989b).

- *Uncertainties in general extrapolations relevant to toxicity information*. Whereas some chemicals have been studied extensively under a variety of exposure conditions in several species (including humans), others may have only limited investigations done on them; this latter group will tend to have inherent limitations in toxicity data (arising for several reasons). Also, because data that specifically identify the hazards to humans as a result of their exposure to various chemicals of concern under the conditions of likely human exposure may not exist, it becomes necessary to infer such hazard effects by extrapolating from data obtained under different exposure conditions, usually in experimental animals. This introduces three major types of uncertainties—namely, that related to extrapolating from one species to another (i.e., uncertainties in inter-species extrapolation); those relating to extrapolation from a high-dose region curve to a low-dose region (i.e., uncertainties in intra-species extrapolation); and those related to extrapolating from one set of exposure conditions to another (i.e., uncertainties due to differences in exposure conditions).
- *Uncertainties from quantitative extrapolations and adjustments in dose-response evaluation*. Experimental studies to determine the likely carcinogenic effects due to low exposure levels often encountered in the environment generally are not feasible. This is because, such effects are not readily perceptible in the relatively short time frame over which it is usually possible to conduct such a study. Consequently, various mathematical models are used to extrapolate from the high doses used in animal studies to the doses likely to be encountered during exposure to ambient environmental concentrations. Extrapolating from a high dose (of animal studies) to a low dose (for human effects) introduces a level of uncertainty which could be significantly large, and which may have to be meticulously addressed. For instance, in human health risk assessments, no-observed-adverse-effect-levels (NOAELs) and cancer potency slope factors (SFs) from animal studies are usually divided by a factor of 10 to account for extrapolation from animals to humans, and by an additional factor of 10 to account for variability in human responses (see Chap. 10). Given the recognized differences among species in their responses to toxic insult, and between strains of the same species, it is apparent that additional uncertainties will likely be introduced when this type of quantitative extrapolations and adjustments are made in the dose-response evaluation.
- *Uncertainty associated with the toxicity of chemical mixtures*. The effects of combining two chemicals may be synergistic (effect when outcome of combining two chemicals is greater than the sum of the inputs), antagonistic (effect when the outcome is less than the sum of the two inputs), or under potentiation (i.e., when one chemical has no toxic effect but combined with another chemical

that is toxic, produces a much more toxic effect). Indeed, chemicals present in a mixture can interact to yield a new chemical; or one can interfere with the absorption, distribution, metabolism, or excretion of another. Notwithstanding all these possible scenarios, risk assessments often assume toxicity to be additive—resulting in a potentially significant source of uncertainty.

- *Limitations in model form*. Exposure scenarios, as well as fate and behavior models, usually can be a major contributor of uncertainty to risk assessments. Apart from general model imperfections, environmental and exposure models usually oversimplify reality—thus contributing one form of uncertainty or another. Also, the natural variability in environmental and exposure-related parameters causes variability in exposure factors, and therefore in exposure estimates developed on this basis. This, therefore, begs the question of how close to reality the model function and output are likely to be.
- *Consideration of ambient/'background' exposures*. For the most part, risk assessment methods used in practice tend to ignore background/ambient exposures; instead, the process considers only incremental risk estimates for the exposed populations. Consequently, such risk estimates do not address what constitutes the true health risks to the public—of which background or ambient exposures could be contributing in a very significant way. That said, it should also be acknowledged here that a good understanding of the role and influence of background levels of environmental chemicals can indeed involve several different typologies. Anyhow, to properly incorporate a consideration of background into environmental risk-based decision making, the multiple attributes of 'background' must be examined both individually and collectively.
- *Representativeness of sampling data*. Uncertainties may arise from random and systematic errors in the type of measurement and sampling techniques often used in environmental and exposure characterization activities. For instance, professional judgment (based on scientific assumptions) is frequently used for sampling design and also to make decisions on how to correct for data gaps—albeit this process has some inherent uncertainties associated with it.

In practice, very stage in the risk assessment process usually calls for a series of choices—each with the potential to influence, and in some cases determine, the outcome of the risk assessment. By and large, the data gaps and uncertainties inherent in the process might engender the need for a use of defaults and assumptions; in addition, utilization of alternative approaches with respect to each assumption may elicit the element of choice—and of course introduce its corresponding uncertainties (NRC 1994a, b, 2009).

12.1.4 The Need for Uncertainty and Variability Analyses

All risk estimates involve some degree of uncertainty and variability—especially because of the inability of the risk analyst to quantify all the requisite information

necessary to complete a credible study. Uncertainty analysis in particular should therefore become an integral part of all risk assessments, regardless of the scope or level of detail. Moreover, it is prudent and essential to the credibility of the risk assessment, to describe the relevant uncertainties in as great a detail as possible. But, as one strives to be more scientifically credible, it is also important not to attempt to infer levels of precision that clearly are not appropriate for quantitative risk assessments (Felter and Dourson 1998). After all, the acknowledgment of 'inexactness' is very much in line with a cautionary note that Aristotle is quoted to have sounded, once upon a time—that: "It is the mark of an instructed mind to rest satisfied with the degree of precision which the nature of the subject permits and not to seek an exactness where only an approximation of the truth is possible." Ultimately, the degree to which variability and uncertainty are addressed in a given study depends largely on the scope of the risk assessment and the resources available. For the study of variability, stochastic models are used as the more realistic representations of reality, rather than the use of deterministic models. In any case, as a guiding principle, the discussion of uncertainty and variability should, ideally, reflect the type and complexity of the risk assessment—with proportionate levels of effort dedicated to the risk assessment and the analysis or discussion of uncertainty and variability.

In the end, a number of factors—directly or indirectly related to uncertainties and variability—may undeniably cause a given analysis to either under-estimate or over-estimate true risks that are associated with a chemical exposure problem. For instance, it is always possible that a chemical whose toxic properties have not been thoroughly tested may be more toxic than originally believed or anticipated; a chemical not tested for carcinogenicity or teratogenicity may in fact display those effects; etc. Furthermore, an approach that limits an evaluation process to selected 'indicator chemicals' only may have some indeterminate (even if somehow insignificant) effects on the overall risk assessment exercise. Notwithstanding, a systematic and well-formulated presentation of uncertainty and variability analyses as part of the overall risk assessment process will generally help remove much of the concerns or doubts that could surround a given program.

12.1.4.1 General Degree and Scope of Uncertainty Analyses

Human health risk estimations that are customarily designed to potentially help decision makers reach the following feat in particular (IOM 2013):

- Evaluate alternative regulatory options;
- Assess how credible extreme risk estimates are, and how much to rely on them in decision making;
- Weigh the marginal decrease in risk against the effort made to reduce it;

- Clarify issues within a decision by using variant scenarios to characterize very 'different worlds'; and
- Identify regulatory solutions that are effective over a broad spectrum of scenarios—as may be applicable for some case-specific scenarios.

However, to assure credibility in the efforts involved, the characterization of all pertinent uncertainties becomes crucial; in this regard, the nature and sources of uncertainty are often seen as key determinants of the proper type of uncertainty analyses to be carried out. The appropriate extent or degree and scope of uncertainty analysis necessary for a given decision-making situation will generally depend on the types, source, and magnitude of the uncertainty as well as on the context of the decisions to be made—as, for example, the severity of the adverse effects and the timeframe within which a decision is needed.

At the end of the day, uncertainty analyses in human health risk estimates can help decision makers to weigh the marginal decrease in risk against the effort made to reduce such risks. In such efforts, decision makers need to understand—either quantitatively or qualitatively—the types and magnitude of the uncertainty that are present, in order to arrive at an informed decision. Meanwhile, it is noteworthy that the development and application of probabilistic techniques and Monte Carlo simulation methods to uncertainty analyses can add significant improvements to the overall risk estimation efforts.

12.1.4.2 The Uncertainty Analysis in Practice

Within any of the major steps of the human health risk assessment process, assumptions must be made due to a lack of absolute scientific knowledge. Some of the assumptions may be supported by reasonable amounts of scientific evidence, whiles others may not necessarily be supported to same level of confidence; regardless, every assumption likely introduces some degree of uncertainty into the risk assessment process. Traditionally, and especially in the regulatory realm of things, the risk assessment methodology tends to require that conservative assumptions be made throughout the risk assessment—at least to ensure that risks are not underestimated; on the other hand, when all of the conservative assumptions and approaches are combined, it is more likely that risk results/outcomes would be overestimated, rather than underestimated. Anyhow, insofar as possible, the assumptions that introduce the greatest amount of uncertainty in the risk assessment would tend be quantified and/or comprehensively discussed as part of the overall risk determination process; meanwhile, the assumptions for which there may not be enough information available to assign a numerical value to the uncertainty *per se* (and thus cannot be factored into the risk quantification/calculations) are typically discussed in qualitative terms. Ultimately, these uncertainties may also be properly incorporated into an overall risk management plan for pragmatic action.

Now, consider the following practical example discussion relating to the concepts offered in this chapter and elsewhere in the book; it is apparent that significant uncertainties exist in estimating dose-response relationships for potential carcinogens—due in part to experimental and epidemiologic variability, as well as uncertainty in extrapolating both from animals to humans, and from high to low doses. In exemplifying this type of case scenario, three major issues are identified as affecting the validity of toxicity assessments used to estimate potential excess lifetime cancer risks, namely: (1) the selection of a study (i.e., data set, animal species, matrix the constituent is administered in) upon which to base the calculations; (2) the conversion of the animal dose used to an equivalent human dose; and (3) the mathematical model used to extrapolate from experimental observations at high doses to the very low doses more likely to be encountered in the environment. *Study selection* involves the identification of a data set (experimental species and specific study) that provides sufficient, well-documented dose-response information to enable the derivation of a valid CSF. In this case, human data (e.g., from epidemiological studies) are preferable to animal data—albeit adequate human data sets are relatively rare. Therefore, it is often necessary to develop dose-response information from a laboratory species, ideally one that biologically resembles humans (e.g., with respect to metabolism, physiology, and pharmacokinetics), and where the route of administration is similar to the expected mode of human exposure (e.g., inhalation and ingestion). Next, assumptions for *dose conversions* involve standardized scaling factors to account for differences between humans and experimental animals with respect to lifespan, body size, breathing rates, and other physiological parameters. Moreover, evaluation of risks associated with one route of administration (e.g., inhalation) when tests in animals involve a different route (e.g., ingestion) requires additional assumptions with corresponding additional uncertainties. In regards to *high-to-low dose extrapolation*, it should be recognized that the concentration of constituents to which humans are potentially exposed in the environment is usually much lower than the levels used in the studies from which dose-response relationships are developed. Estimating potential health effects, therefore, requires the use of models that allow extrapolation of health effects from high experimental doses in animals to low environmental doses; these models are generally statistical in character and have uncertain biological basis—and thus the use of such models for dose extrapolation inevitably introduce uncertainty in the dose-response estimates. In addition, these models contain assumptions that may also introduce a large amount of additional uncertainty arising from a miscellany of sources. At the end of the day, these models typically would have been developed to err on the side of overestimating, rather than underestimating, potential health risks.

12.2 Characterization of Data Variability and Uncertainties

An uncertainty analysis consists of a process that translates uncertainties about models, variables and input data, as well as the random variability in measured parameters into uncertainties in output variables (Calabrese and Kostecki 1992; Finkel 1990; Iman and Helton 1988). The overall goal of an analysis of uncertainties is to provide decision-makers with the complete spectrum of information concerning the quality of an assessment—including the potential variability in the estimated parameters, the major data gaps, and the effect that such data gaps have on the accuracy and reasonableness of the estimates that are developed (Bogen 1990; Covello et al. 1987; Cox and Ricci 1992; Finkel and Evans 1987; Helton 1993; Hoffmann and Hammonds 1992; IOM 2013; Morgan and Henrion 1991; USEPA 1989a). Proper analysis and presentation of the uncertainties allow analysts or decision-makers to better evaluate the risk assessment results in the context of other factors being considered. This, in turn, will generally result in a more sound and open decision-making process.

The analysis of uncertainties will typically involve the following fundamental elements:

- Evaluation of uncertainties in the input of each of the relevant tasks;
- Propagation of input uncertainties through each task;
- Combination/convolution of uncertainties in the output from the various tasks; and
- Display and interpretation of the uncertainties in the final results.

On the whole, premium should be placed on a critical evaluation and presentation of all environmental, biological, and statistical uncertainties in the situation-specific assessment. Furthermore, it may be useful to carefully reexamine the quality of the studies used to support all conclusions, and to compare data across similar studies that are relevant to specific assessments. When appropriate, policy makers may employ plausible ranges associated with default exposure, as well as toxicological and other assumptions/policy positions; these may include, for instance, ranges of typical default values—such as the range of pulmonary ventilation rates (e.g., of 8–20 m^3/day), human body weight (e.g., of 10–60 or 70 kg), or ranges based on the use of low-dose extrapolation models (such as logit, probit, multistage, etc. models).

In the end, uncertainty analyses can have both qualitative and quantitative components/dimensions; accordingly, an uncertainty analysis can be performed qualitatively and/or quantitatively. But, whether qualitative or quantitative in nature, the analysis considers: uncertainties in every available database; uncertainties arising from assumptions in modeling; and the completeness of the analysis. Anyhow, the uncertainty analysis must be designed on a case-by-case basis—with the choice of uncertainty analysis protocol depending on the context of the decision, including the nature or type of uncertainty, and the factors that are considered in the

decision, as well as on the data that are available (IOM 2013). Indeed, most environmental problems will require the use of multiple approaches to uncertainty analysis; consequently, a mix of statistical analyses and expert judgments may be needed—albeit, in general, quantitative uncertainty analyses should probably be undertaken only when they are important and relevant to a given decision (e.g., such that at the end of the day, these quantitative uncertainty analyses would truly affect the environmental decision on hand). For that reason, if an environmental decision would stay the same for all states of information and analysis results, then it would not be worth conducting the identified type of analysis after all (IOM 2013).

12.2.1 Qualitative Analysis of Uncertainties

The qualitative analysis of uncertainties typically involves a determination of the general quality and reasonableness of the risk assessment data, parameters, and results. Qualitative analysis is usually most important to 'screening', 'preliminary', and 'intermediate' level types of assessments (USEPA 1989a).

As part of the qualitative analysis, the cause(s) of uncertainty is initially determined. The basic general cause of uncertainty is a lack of knowledge on the part of the analyst because of inadequate, or even nonexistent, experimental and operational data on key processes and parameters. The specific causes of uncertainty that are typically addressed here can be categorized as follows (USEPA 1989a, 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h):

- Measurement errors (resulting from measurement techniques employed in the study that could yield imprecise or biased measurements).
- Sampling errors (arising from the degree of representativeness of sampled data to actual population—e.g., small or unrepresentative samples).
- Aggregation errors (such as results from spatial and temporal approximations).
- Incomplete analysis (such as results from overlooking an important exposure scenario).
- Natural variability—e.g., in time, space, or activities.
- Model limitations (reflecting on how close to reality the models employed prove).
- Application and quality of generic or indirect empirical data.
- Professional/expert judgment (reflecting on the possible unreliability of scientific assumptions that may have been invoked or used—e.g., selection of an inappropriate model or surrogate data).

In general, once the causes of the uncertainties have been identified, the impact that these uncertainties have on the assessment results would then have to be determined. Insofar as possible, measures to minimize the impacts of such uncertainties on the results or final outcomes should be clearly expounded. Ultimately, the explicit presentation of the qualitative analysis results will transmit the requisite

level of confidence in the results to the decision-maker—facilitating the implementation of appropriate environmental and public health risk management actions.

12.2.2 Quantitative Analysis of Uncertainties

In addition to a qualitative analysis (as noted above), most detailed risk assessments may also require quantitative uncertainty analysis techniques to be used in chemical exposure studies. The quantitative analysis of uncertainties, often employed in detailed assessments, usually will proceed via sensitivity analysis and/or probabilistic analysis (e.g., Monte Carlo simulation techniques); the technique of choice normally depends on the availability of input data statistics. But, regardless of the technique of choice, the approach will generally allow for a deviation from the conservative and rather unrealistic approach of generating point estimates for risks, as has 'traditionally' been done in most risk assessment programs. Indeed, point estimates tend to confer a false sense of precision and population homogeneity—and thus may subsequently disguise the basis for rational decision-making. On the other hand, techniques such as Monte Carlo simulation provides a more complete description of risks—allowing risk managers and other stakeholders to appreciate/understand the level of protection offered by various risk management alternatives in an explicit manner. Ultimately, the Monte Carlo simulation approach helps the risk manager avoid making decisions based on implausible and unrealistic risk estimates.

In general, quantitative analysis of uncertainty becomes very important and necessary when prior risk screening calculations indicate a potential problem, or when risk control actions may result in excessively high costs, or when it is necessary to establish the relative importance of chemicals and exposure routes in a comparative analysis. Conversely, if estimated chemical intakes or risks are most obviously small and/or if the consequence of a 'wrong' prediction/decision based on the calculated risk is negligible, then perhaps quantitative analysis of uncertainty may neither be necessary nor a worthwhile effort.

12.2.2.1 Probabilistic Analysis: The Application of Monte Carlo Simulation Techniques

Various probabilistic analysis techniques can be employed/used to quantify uncertainties in risk assessment (e.g., Burmaster 1996; Finley and Paustenbach 1994; Finley et al. 1994a, b; Lee and Kissel 1995; Lee et al. 1995a, b; Macintosh et al. 1994; Power and McCarty 1996; Richardson 1996; Smith et al. 1992). The driving force behind the development and use of probabilistic risk assessment techniques has been the desire to more completely reveal the complexity in exposure conditions and toxicological responses that are present in the real world (Boyce 1998). Probabilistic risk analyses may indeed serve several purposes—including being

used to: propagate uncertainty in the estimate of exposure dose and risk; properly prioritize resources for risk reduction activities; and simulate stochastic variability among individuals in a population. Probabilistic analysis may surely be applied to the evaluation of risks in order that uncertainties are accounted for systematically.

In general, probabilistic analyses require data on the range and probability function (or distribution) of each model parameter. In fact, a central part of probabilistic risk analyses is the selection of probability distributions for the uncertain input variables (Haas 1997; Hamed and Bedient 1997a, b). Thus, it is usually recommended to undertake a formal selection among various distributional families, along with a formal statistical goodness-of-fit test, in order to obtain the most suitable family of statistical distributions appropriate for characterizing the case-specific data set. Ultimately, the favored probabilistic approach for assessing uncertainty is via 'Monte Carlo Simulation' (e.g., McKone 1994; McKone and Bogen 1991; Price et al. 1996; Smith 1994; Thompson et al. 1992). *Monte Carlo simulation* is a statistical technique by which a quantity is calculated repeatedly, using randomly selected/generated scenarios for each calculation cycle—and typically presenting the results in simple graphs and tables. The results from the simulation process approximate the full range of possible outcomes, and the likelihood of each.

The Monte Carlo simulation process involves assigning a joint probability distribution to the input variables; the procedure yields a concomitant distribution that is strictly a consequence of the assumed distributions of the model inputs and the assumed functional form of the model (Fig. 12.1). Meanwhile, it is noteworthy that several considerations may be important in the selection of appropriate probability distribution used to represent the relevant input parameters (Box 12.2) (Finley et al. 1994a; USEPA 1989a). In any event, unless specific information on the relationships between the relevant parameters is available, values for the required input parameters will normally be assumed to be independent.

Box 12.2 Important Considerations in the Selection of Appropriate Probability Distribution in a Monte Carlo Simulation

- A *uniform distribution* would be used to represent a factor/parameter when nothing is known about the factor except its finite range. The use of a uniform distribution assumes that all possible values within the range are equally likely.
- A *triangular distribution* would be used if the range of the parameter and its mode are known.
- A *Beta distribution* (scaled to the desired range) may be most appropriate if the parameter has a finite range of possible values and a smooth probability function is desired.
- A *Gamma, Log-Normal,* or *Weibull distribution* may be an appropriate choice if the parameter only assumes positive values. The Gamma

(continued)

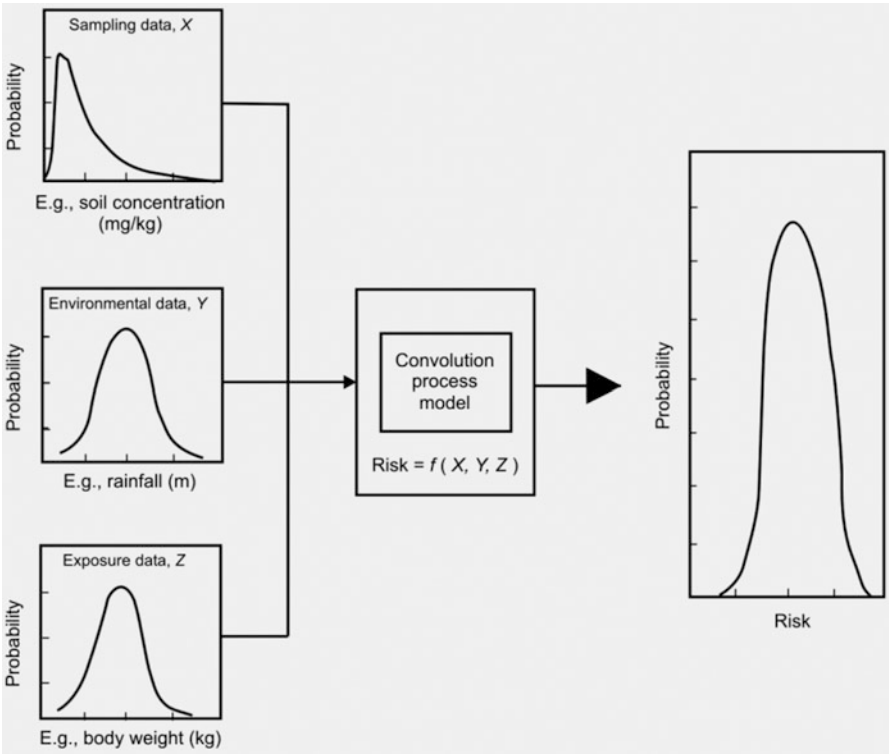

Fig. 12.1 Conceptual illustration of the Monte Carlo simulation procedure

Box 12.2 (continued)

distribution is probably the most flexible, especially because its probability function can assume a variety of shapes by varying its parameters, and it is mathematically tractable.

- A *Normal distribution* may be an appropriate choice if the parameter has an unrestricted range of possible values and is symmetrically distributed around its mode.

Monte Carlo simulations can indeed be used to develop numerical estimates of uncertainties that allow efficient ways to extend risk assessment methods to the estimation of both point values as well as distributional values of risks posed by chemical exposure problems. In using Monte Carlo techniques, most or all input variables to the risk assessment models become random variables with known or estimated probability density functions (pdfs). Within this framework, a variable can take on a range of values with a known probability. In general, when Monte Carlo Simulation is applied to risk assessment, the risk presentation appears as

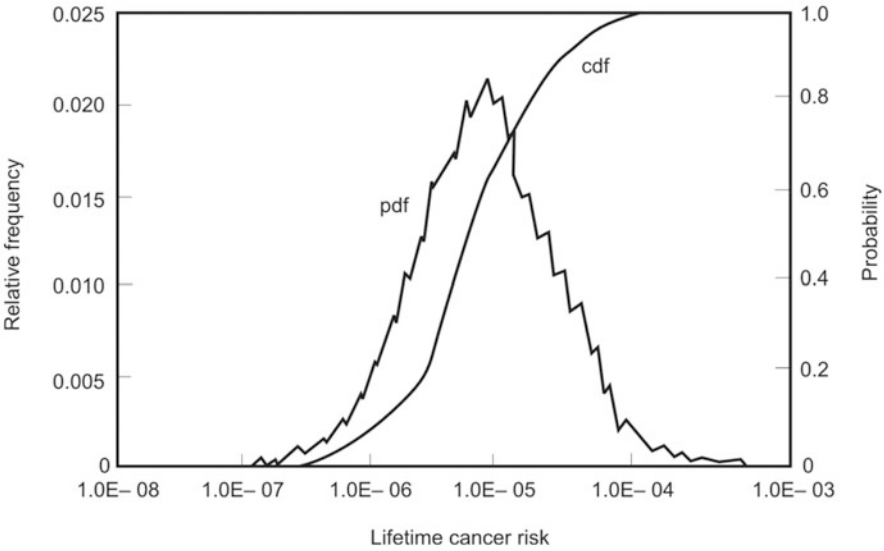

Fig. 12.2 An illustrative sketch of a plot from a Monte Carlo simulation analysis (showing probability density function [pdf] and cumulative distribution function [cdf] for lifetime cancer risks from a contaminated site)

frequency or probability distribution graphs—as illustrated by the sketch shown in Fig. 12.2—from which the mean, median, variance, and/or percentile levels/values can be extracted.

12.2.3 Presentation Formats for Uncertainty in Risk Estimates

The most widely used 'formal language' of uncertainty in risk estimates is probability (IOM 2013; Morgan 2009)—albeit it is generally recognized that 'probabilities are notoriously difficult to communicate effectively to lay audiences' (Spiegelhalter et al. 2011); yet still, these layperson groups are likely to form a significant portion of the stakeholder pool for the types of programs envisaged for most public health risk assessment/management situations. Alternatively, probabilistic information, and the uncertainties associated with those probabilities, can usually be communicated using numeric, verbal, or graphic formats—forms likely to be more amenable to effective risk communication to broad-spectrum audience. At least for the aforementioned reasons, careful consideration should generally be given to the most appropriate approach for the circumstances being evaluated (Fagerlin et al. 2007; Lipkus 2007; Nelson et al. 2009; Spiegelhalter et al. 2011; Visschers et al. 2009). In any event, regardless of the format in which the uncertainty is presented, it is important to bound the uncertainty and to describe the effect

it might have on the ultimate decision; presenting the results/outcomes via sensitivity analyses scenarios is one way to provide some boundaries on the effects of those uncertainties, and to educate stakeholders about how those uncertainties might affect a given decision (IOM 2013).

12.2.3.1 Numeric Vs. Verbal/'Linguistic' Vs. Graphical Presentations of Uncertainty

Risk probabilities and associated uncertainties may typically be presented in various formats—most commonly as numeric values, 'verbal statements', and/or graphically. Somehow, it is believed that numeric presentations of probabilistic information can eventually (even if conditionally) lead to better perceptions of risk than verbal and graphic formats (Budescu et al. 2009; IOM 2013).

Numeric presentations of probabilistic information—such as in terms of percentages and frequencies—often become the preferred approach for most analysts. Percentage and frequency formats have indeed been found to be (conditionally) more effective than most other formats for a number of circumstances because they more readily allow the stakeholder pool to conduct simple mathematical operations (such as comparisons) on risk probabilities (Cuite et al. 2008). Among the key disadvantages of numeric presentations are that, they are only useful if the primary stakeholders being communicated with are capable of interpreting the numeric information presented; also, they may not particularly hold certain groups of people's attention as well as verbal and graphic presentations (Krupnick et al. 2006; IOM 2013; Lipkus 2007).

Verbal presentations of risk—for example, messages containing words such as 'likely' or 'unlikely'—can be used as calibrations of numeric risk; such representations may indeed do a better job of capturing people's attention than numeric presentations, and they are also effective for portraying 'directionality' (IOM 2013). Furthermore, verbal expressions of uncertainty can be better adapted to the level of understanding of an individual or group than can numeric and graphic presentations (IOM 2013; Kloprogge et al. 2007). A major weakness of 'verbal' or 'linguistic' presentations of risk is that some studies have shown that the probabilities attributed to words such as 'likely' or 'very likely' varies among individuals—and indeed can even vary for a single individual depending on the scenario being presented (see, e.g., Erev and Cohen 1990; Morgan 1998; Morgan 2003; Wallsten and Budescu 1995; Wallsten et al. 1986). Thus, qualitative descriptions of probability—that is, those that include a description or definition for a category of certainty—are sometimes used instead of such subjective calibrations as 'very likely' or 'unlikely' which are open for individual interpretations, etc. (Budescu et al. 2009; IARC 2006; IPCC 2001, 2007; Moss and Schneider 2000; Smithson et al. 2011).

Graphical displays of probabilistic information—such as bar charts, pie charts, and line graphs—can usually summarize more information than other presentation modes, as well as can capture and hold people's attention, and can show patterns

and 'whole-to-part' relationships (Budescu et al. 1988; IOM 2013; Spiegelhalter et al. 2011). Furthermore, uncertainties about the outcomes of an analysis can also be depicted using graphical displays, such as bar charts, pie charts, probability density functions, cumulative density functions, and box-and-whisker plots—among others. For instance, probability density functions can be a sensitive indicator of variations in probability density, and thus their use may be advantageous when it is important to emphasize small variations; on the other hand, this sensitivity may sometimes be a disadvantage—in that small variations attributed to random sampling may be present as 'noise', and are of no intrinsic interest, etc. Cumulative distribution functions (CDFs) seem to have the advantage of not showing as much small variation noise as a probability density function does, so that the shape of the distribution may appear much smoother—albeit this has its own shortcomings as a tool for a broad stakeholder base (Ibrekk and Morgan 1987; IOM 2013). Box-and-whisker plots are effective in displaying summary statistics (medians, ranges, fractiles), but they provide no information about the shape of the distribution except for the presence of asymmetry in the distribution (Krupnick et al. 2006). Anyway, despite their advantages, graphic displays do not always explicitly describe conclusions—and they can indeed require more effort to extract information, particularly for people who are not familiar with the mode of presentation or who lack skills in interpreting graphs or in cases where the graphic presents complex data (Boduroglu and Shah 2009; IOM 2013; Kloprogge et al. 2007; Lipkus 2007; Shah and Freedman 2009; Slovic and Monahan 1995; Slovic et al. 2000; Spiegelhalter et al. 2011; Stone et al. 1997).

In the final analysis, perhaps using a mix of verbal terms, numerical values, and graphical displays to communicate uncertainty might portray a relatively better overall picture.

12.3 Presenting and Managing Uncertain Risks: The Role of Sensitivity Analyses

Inevitably, some degree of uncertainties remains in quantitative risk estimates in virtually all fields of applied risk analysis. A carefully executed analysis of uncertainties therefore plays a very important role in all risk assessments. On the other hand, either or both of a comprehensive qualitative analysis and a rigorous quantitative analysis of uncertainties will be of little value if the results of such analysis are not clearly presented for effective use in the decision-making process. To facilitate the design of an effectual process, a number of methods of approach have been suggested by some investigators (e.g., Cox and Ricci—see, Paustenbach 1988) for presenting risk analysis results to decision-makers, including the following:

- Risk assessment results should be presented in a sufficiently disaggregated form (to show risks for different subgroups) so that key uncertainties and heterogeneities are not lost in the aggregation.
- Confidence bands around the predictions of statistical models can be useful, but uncertainties about the assumptions of the model itself should also be presented.
- Both individual (e.g., the typical and most threatened individuals in a population) and population/group risks should be presented, so that the equity of the distribution of individual risks in the population can be appreciated and taken into account.
- Any uncertainties, heterogeneities, or correlations across individual risks should be identified.
- Population risks can be described at the 'micro' level (namely, in terms of frequency distribution of individual risks), and/or at the 'macro' level (namely, by using decision-analytic models, in terms of attributes such as equivalent number of life-years).

On the whole, uncertainty is typically expressed in terms of the probability or likelihood of an event, and can indeed be presented numerically, verbally, and/or graphically—with each approach having its unique advantages and disadvantages (IOM 2013). It is noteworthy that, the uncertainty analysis can also be achieved via sensitivity analyses for key assumptions.

Sensitivity analysis is generally defined as the assessment of the impact of changes in input values on model outputs. Often a useful adjunct to the traditional uncertainty analysis, sensitivity analysis is comprised of a process that examines the relative change or response of output variables caused by variation of the input variables and parameters (Calabrese and Kostecki 1992; Iman and Helton 1988; USEPA 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h). It is indeed a technique that tests the sensitivity of an output variable to the possible variation in the input variables of a given model. Accordingly, the process serves to identify the sensitivity of the calculated result vis-à-vis the various input assumptions—and thus identify key uncertainties, as well as help bracket potential risks so that policy-makers can make more informed decisions or choices.

Typically, the performance of sensitivity testing requires data on the range of values for each relevant model parameter. The intent of sensitivity analysis is then to identify the influential input variables, and to develop bounds on the model output. When computing the sensitivity with respect to a given input variable, all other input variables are generally held fixed at their 'nominal' values. By identifying the influential or critical input variables, more resources can then be directed to reduce their uncertainties—and thence reduce the output uncertainty. Thus, as an example, the main purpose of sensitivity analyses in an exposure characterization would be to determine which variables in the applicable model equations, as well as the specific pathways or scenarios, would likely affect the consequential exposure estimates the most. These techniques can also be used to assess key sources of variability and uncertainty for the purpose of prioritizing additional data collection and/or research efforts.

In the end, notwithstanding the added value of sensitivity analyses, several factors may still contribute to the over- or under-estimation of risks. For example, in human health risk assessments, some factors will invariably underestimate health impacts associated with the chemicals evaluated in the assessment. These may include: lack of potency data for some carcinogenic chemicals; risk contributions from compounds produced as transformation byproducts, but that are not quantified; and the fact that all risks are assumed to be additive, although certain combinations of exposure may potentially have synergistic effects. Conversely, another set of factors would invariably cause the process to overestimate risks. These may include the fact that: many unit risk and potency factors are often considered plausible upper-bound estimates of carcinogenic potency, when indeed the true potency of the chemical could be considerably lower; exposure estimates are often very conservative; and possible antagonistic effects, for chemicals whose combined presence reduce toxic impacts, are not accounted for properly.

12.4 Coming to Terms with Uncertainty and Variability Issues in Risk Assessment

Uncertainty seems foremost among the recurring themes in risk assessment; in quantitative assessments, *uncertainty* relates to lack of information, incomplete information, or incorrect information (NRC 2009). Uncertainty in a risk assessment depends on the quantity, quality, and relevance of data—as well as on the reliability and relevance of models and inferences used to fill data gaps; for example, the quantity, quality, and relevance of data on dietary habits and a pesticide's fate and transport will affect the uncertainty of parameter values used to assess population variability in the consumption of the pesticide in food and drinking water (NRC 2009). As to variability, it can be said that there are important variations among individuals in a population with respect to susceptibility and exposure.

Characterizing uncertainty and variability is crucial to the human health risk assessment process; among other things, the analytical protocols used in the risk determination efforts must engage the best available science in the presence of uncertainties, as well as often difficult-to-characterize variability—in order to properly inform risk management and related decisions (NRC 2009). Indeed, proper characterization of each stage in the risk assessment process—starting from environmental release or hazard realization through to chemical exposure, and onto the recognition of health effect(s)—invariably poses significant analytic challenges that cannot quite be ignored *per se*. Thus, each component of a risk assessment should strive to include uncertainty and variability considerations—preferably in an explicitly characterized manner. Meanwhile, it is noteworthy that many of the statistical techniques and general concepts used in relation to uncertainty analysis are also applicable to variability analysis; however, the key difference between uncertainty analysis and variability analysis relates to the fact that

variability can only be better characterized, not reduced—and thus it often must be addressed with strategies somewhat different from those used to address uncertainty (NRC 2009).

In the end, the following guiding principles are recommended in the efforts at addressing the likely wide-ranging issues pertaining to uncertainty and variability in risk assessments (NRC 2007a, b, 2009; IOM 2013):

1. Risk assessments should provide a quantitative, or at least qualitative, description of uncertainty and variability consistent with available data—recognizing that the information required or necessary to carry out detailed uncertainty analyses may not be available in many situations.
2. In addition to characterizing the broader population group at risk, special attention should be directed to vulnerable individuals and subpopulations that may be particularly susceptible or relatively more highly exposed.
3. The depth, extent, and detail of the uncertainty and variability analyses should be commensurate with the importance and nature of the decision to be informed by the risk assessment, and with what is considered as the valued assets in a decision. This may best be achieved by early engagement of risk assessors/analysts, risk managers, and other stakeholders with respect to the nature and objectives of the risk assessment, as well as the terms of reference—all of which must be clearly defined upfront.
4. The risk assessment should systematically compile or otherwise characterize the types, sources, extent, and magnitude of variability and substantial uncertainties associated with the overall assessment. To the extent feasible, there should be homologous treatment of uncertainties among the different components of a risk assessment, as well as among different policy options being compared.
5. To maximize public understanding of, and participation in, risk-related decision-making, a risk assessment should endeavor to explain the basis and results of the uncertainty analysis with sufficient clarity to be understood by the general (layperson) public and decision-makers.
6. Uncertainty and variability should preferably be kept conceptually separate in the risk characterization.
7. The uncertainty assessment should not be a significant source of delay in the release of a given project's risk assessment.

When all is said and done, depending on the risk management options being considered, a quantitative treatment of uncertainty and variability may be needed to differentiate among the options—in order to arrive at well-informed decisions. Uncertainty analysis is indeed important for both data-rich and data-poor situations—albeit confidence in the analysis will vary according to the amount of information available (NRC 2009).

In closing, it must be accentuated here that the results of deterministic risk assessments should be interpreted with caution, and never construed as absolute measures of risk—especially when uncertainty and variability factors may not have been properly taken into account. Even so, the resultant point estimates of risk so-generated may still be useful in a qualitative sense for the ranking of different

public health risk management programs or issues. At any rate, probabilistic methods must be encouraged as the logical evolution of the risk assessment process—and perhaps this should be accompanied by the development of risk management methods that can utilize the richness of information provided by Monte Carlo assessments and other similar techniques (Zemba et al. 1996). In fact, it is believed that, the danger of mischaracterizing high-end, central tendency, and surely other statistical exposure levels can only be properly alleviated via the development and utilization of full probabilistic analyses.

Part IV
Development of Public Health Risk Management Strategies for Human Exposure to Chemicals

This part of the book consists of the following three specific chapters:

- Chapter 13, *Determination of 'Acceptable' and 'Safe' Levels for Human Exposure to Chemicals*, presents discussions of how risk assessment may facilitate a determination of what constitutes a reasonably 'safe' or 'acceptable' concentration of chemicals appearing in a variety of consumer products and in the human environments. This also includes an elaboration of a number of analytical relationships that can be adapted or used to estimate such 'safe' levels that are necessary for public health risk management decisions.
- Chapter 14, *Designing Public Health Risk Management Programs*, elaborates the key elements and steps necessary for the effectual design of typical public health risk assessment and risk management programs. Such risk management programs are typically directed at: risk reduction (i.e., taking measures to protect humans and/or the environment against previously identified risks); risk mitigation (i.e., implementing measures to remove risks); and/or risk prevention (i.e., instituting measures to completely prevent the occurrence of risks). Ultimately, the risk management (i.e., reduction, mitigation, and preventative) programs can generally help engender an increase in the level of protection to public health and enhance safety, as well as assist in the reduction of liability.
- Chapter 15, *Utility of Risk Assessment in Public Health Policy Decisions,* details the general role and scope for the application of risk assessment, as pertains to the management of potential chemical exposure problems—recognizing that, invariably, risk-based decision-making will generally result in the design of better environmental and public health risk management programs; it also discusses specific practical example situations for the utilization of the risk assessment paradigm.

Chapter 13
Determination of 'Acceptable' and 'Safe' Levels for Human Exposure to Chemicals

An important and yet perhaps controversial issue that comes up in attempts to establish 'safe' or 'tolerable' levels for human exposure to chemical constituents relates to the notion of an 'acceptable chemical exposure level' (ACEL). The *ACEL* may be considered as the concentration of a chemical in a particular medium or product that, when exceeded, presents significant risk of adverse impact to potential receptors. In fact, in a number of situations, the ACEL concept tends to drive the public health risk management decision made about several consumer products. However, the ACELs may not always result in 'safe' or 'tolerable' risk levels *per se*—in part due to the nature of the critical exposure scenarios, receptor-specific factors, and other conditions that are specific to the particular hazard situation. Under such circumstances, and insofar as possible, it becomes necessary to develop more stringent and health-protective levels that will meet the 'safe' or 'tolerable' risk level criteria.

This chapter presents discussions of how risk assessment may facilitate a determination of what constitutes a reasonably 'safe' or 'acceptable' concentration of chemicals appearing in a variety of consumer products and in the human environments. This also includes an elaboration of a number of analytical relationships that can be adapted or used to estimate such 'safe' levels that are necessary for public health risk management decisions.

13.1 General Consideration in Determining 'Safe' Doses for Chemicals of Interest

Traditionally, as a default assumption, most analysts have worked on the premise that for most types of chemical effects, there is a dose level below which a response is unlikely—mainly because homeostatic, compensation, and adaptive mechanisms in the cell of the affected organism will protect against toxic effects. For such

K. Asante-Duah, *Public Health Risk Assessment for Human Exposure to Chemicals*,
Environmental Pollution 27, DOI 10.1007/978-94-024-1039-6_13

reasons then, all chemical effects excluding cancer/genotoxicity have conventionally been assumed to have a 'threshold'—i.e., a dose below which there is no probability of harm. Consequently, a so-called 'safe-dose' has often been derived for these types of threshold effects. Indeed, even for the so-called 'non-threshold' chemicals, a 'quasi-safe-dose' may be derived based on the specific level of risk that is considered acceptable to the target populace.

13.1.1 Requirements and Criteria for Establishing Risk-Based Chemical Exposure Levels

Risk-based chemical exposure levels (RBCELs) may generally be derived for various chemical sources by manipulating the exposure and risk models previously presented in Chaps. 9 and 11. Basically, this involves a 'back-calculation' process that yields a media concentration predicated on health-protective exposure parameters; as an example, the RBCEL generally should result in a target cumulative non-cancer hazard index of ≤ 1 and/or a target cumulative carcinogenic risk $\leq 10^{-6}$. On the whole, since risk is a function of both the exposure to a chemical and the toxicity of that chemical, a complete understanding of the exposure scenarios together with an accurate determination of the constituent toxicity is key to developing 'permissible' exposure levels that will be protective of human health.

By and large, the target RBCELs are typically established for both the carcinogenic and non-carcinogenic effects of the constituents of concern—with the more stringent value or outcome usually being selected as a public health criterion (Fig. 13.1); invariably, the carcinogenic limit tends to be more stringent in most situations where both values exist—albeit this is not necessarily true in all situations. Indeed, until recently, cancer risk was typically the driver in risk management decisions for any chemical evaluated with respect to both cancer risk and non-cancer hazard, particularly when risk management decisions emphasized the lower end of the excess lifetime cancer risk spectrum. However, some more recent experiences indicate that risk managers should be cognizant of the fact that there can be situations where risk management decisions could be driven by non-cancer endpoints; for instance, the RfD and RfC values of some chemicals (e.g., trichloroethylene, or TCE) had to be revised to lower levels (i.e., indicative of potentially greater toxicity) in recent times. Anyhow, within the general procedural framework, the following criteria and general guidelines may additionally be used to facilitate the process of establishing media-specific RBCELs and/or public health goals:

- Assuming dose additivity, $\sum_{j=1}^{p} \sum_{i=1}^{n} \frac{CMAX_{ij}}{RBCEL_{ij}} < 1$

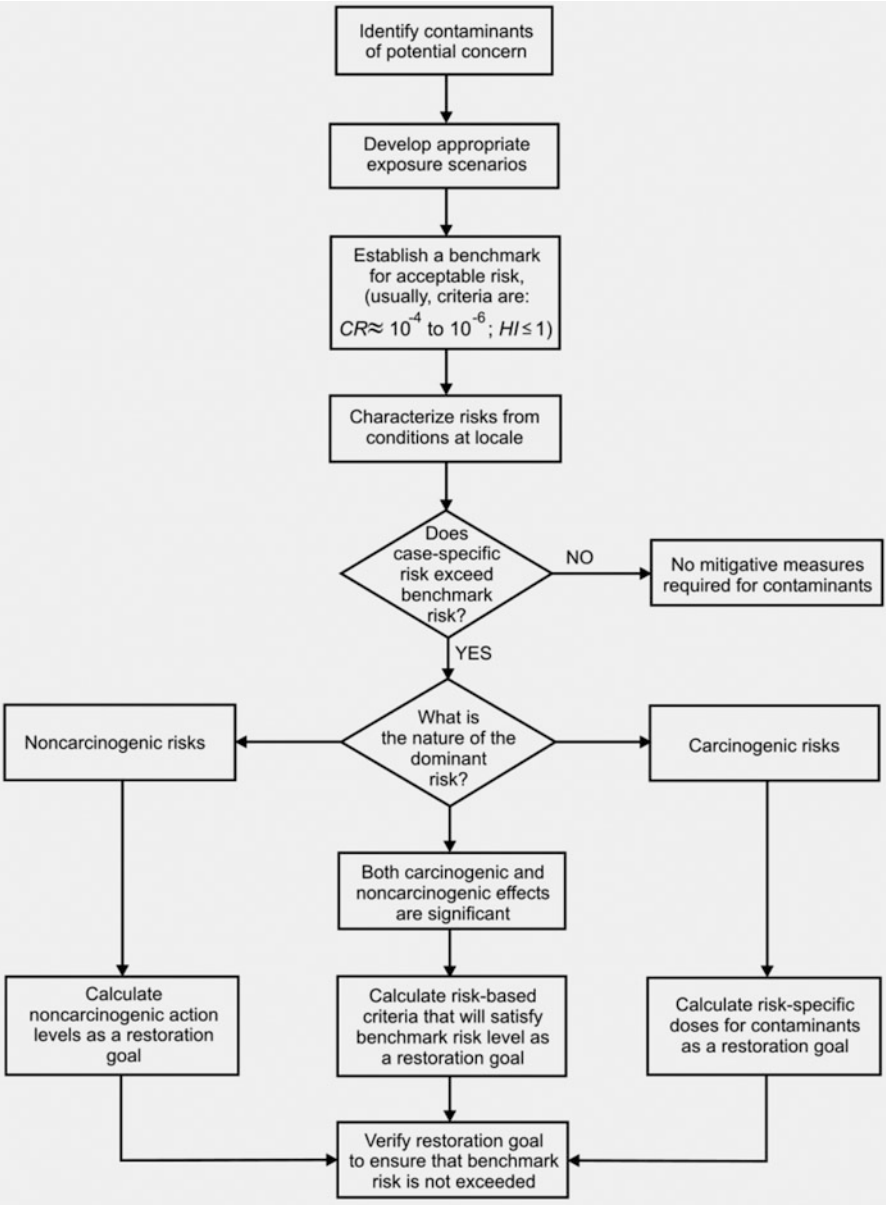

Fig. 13.1 General protocol for developing risk-based chemical exposure levels and public health goals

where: $CMAX_{ij}$ is the prevailing maximum concentration of constituent *i* in product or matrix *j*, and $RBCEL_{ij}$ is the risk-based chemical exposure level for constituent *i* in product or matrix *j*.

- In developing public health goals, it usually is necessary to establish a target level of risk for the constituents of concern; such standards are generally established within the cancer risk range of 10^{-7} to 10^{-4} (with a lifetime excess cancer risk of 10^{-6} normally used as a point-of-departure) and a non-cancer hazard index of 1.
- It is recommended that the cumulative risk posed by multiple chemical constituents not exceed a 10^{-4} cancer risk and/or a hazard index of unity.
- If sensitive populations (including vulnerable persons, such as children and the sick) are to be protected, then more stringent standards may be required.
- If nearby populations are exposed to hazardous constituents from other sources, lower target levels may generally be required than would ordinarily be necessary.
- If exposures to certain hazardous constituents occur through multiple routes, lower target levels should generally be prescribed.

Indeed, if/when the above conditions are satisfied, then the corresponding RBCEL may be viewed as representing a maximum acceptable constituent level that will likely be sufficiently protective of public health. In general, exceeding the RBCEL will usually call for the development and implementation of a corrective action and/or public health risk management plan.

13.1.2 Miscellaneous Methods for Establishing Environmental Quality Goals

Several possibilities exist to use various analytical tools in the development of alternative or media-specific chemical exposure concentration limits and environmental quality goals. Some select general procedures commonly employed in establishing environmental quality goals are briefly annotated below. Broadly speaking, these approaches represent reasonably conservative ways of setting environmental quality goals. Thus, the use of such methods will generally ensure that risks are not underestimated—which tantamount to situations that result in reasonably adequate protection of public health.

13.1.2.1 Determination of Risk-Specific Concentrations in Air

The estimation of health-protective concentrations of chemical constituents in air must generally take into account the toxicity of the chemicals of potential concern, as well as the potential exposure scenarios and parameters of individuals breathing the impacted air. By employing the risk assessment concepts and methodologies discussed in Chaps. 9 through 11, risk-specific concentrations of chemicals in air may be estimated from the unit risk in air as follows:

$$\text{Air concentration } [\mu g/\text{m}^3] = \frac{[\text{specified risk level}] \times [\text{body weight}]}{\text{SF}_\text{i} \times [\text{inhalation rate}] \times 10^{-3}} = \frac{[\text{specified risk level}]}{\text{URF}_\text{i}} = \frac{1 \times 10^{-6}}{\text{URF}_\text{i}}. \tag{13.1}$$

The assumptions generally used for such computations involve a stipulated risk level of 10^{-6}, a 70-kg body weight, and an average inhalation rate of 20 m^3/day.

13.1.2.2 Determination of Risk-Specific Concentrations in Water

The estimation of health-protective concentrations of chemical constituents in drinking water must generally take into account the toxicity of the chemicals of potential concern, as well as the potential exposure scenarios and parameters of individuals using the water. By employing the risk assessment concepts and methodologies discussed in Chaps. 9 through 11, risk-specific concentrations of chemicals in drinking water can be estimated from the oral slope factor. The water concentration corrected for an upper-bound increased lifetime risk of R ($=10^{-6}$) is given by:

$$\text{Water concentration } [\text{mg/L}] = \frac{[\text{specified risk level}] \times [\text{body weight}]}{\text{SF}_\text{o} \times [\text{ingestion rate}]} = \frac{\text{specified risk level}}{\text{URF}_\text{o}} \tag{13.2}$$

The assumptions generally used for such computations involve a stipulated risk level of 10^{-6}, a 70-kg body weight, and an average water ingestion rate of 2 L/day—so that:

$$\text{Water concentration } [\text{mg/L}] = \frac{1 \times 10^{-6} \times 70\,\text{kg}}{\text{SF}_\text{o}\,(\text{mg/kg/day})^{-1} \times 2\,\text{L/day}} = \frac{3.5 \times 10^{-5}}{\text{SF}_\text{o}}$$

It is noteworthy that, in general, the estimation of health-protective concentrations of chemical constituents in drinking water that results in negligible risk outcomes must also account for the fact that tap water is typically used directly as drinking water, as well as for preparing foods and beverages, etc. Indeed, the water may also be typically used for bathing/showering, in washing clothes and dishes, flushing of toilets, and in a variety of other household uses—some of which could result in potential dermal and inhalation exposures as well. To allow for these additional exposures, therefore, the assumed daily volume of water consumed by an adult may typically be increased from the default value of 2 L/day indicated above, to say 3 L-equivalents/day (Leq/day).

13.2 Assessing the Safety of Chemicals in Consumer Products

Through the use of a variety of consumer products, numerous groups of peoples around the world are exposed to a barrage of chemical compounds on a daily basis. Typically, risk assessments (which allow the consumer exposures to be estimated by measurements and/or models) assist in the determination and management of potential health problems that could be expected or anticipated from the use of such consumer products. It is noteworthy, however, that the exposure assessment component of the processes involved tends to be particularly complicated, though not insurmountable—especially because of the huge diversity in usage and composition of consumer products at large. There is also the additional issue of intermittent exposures to variable amounts and types of products containing varying concentrations of chemical compounds (van Veen 1996; Vermeire et al. 1993). Notwithstanding all the apparent complexities, risk-based analyses can be carefully designed to help evaluate the safety of chemicals that appear in various consumer goods.

Consumer product safety is indeed a function of exposure and toxicity—determined primarily based on the exposure patterns/rates and the toxicity of the chemical components of concern or interest. This can be represented by the following conceptual expressions:

$$\text{Risk} = \mathfrak{f}(\text{Exposure}, \text{Toxicity}) \tag{13.3}$$

or,

$$\text{Safety} \propto \frac{1}{\text{Risk}} = \frac{1}{f(\text{Exposure}, \text{Toxicity})} \tag{13.4}$$

At the end of the day, for a particular consumer product to be classified as reasonably safe, the relatable chemical-specific exposure dose should generally be less than the chemical's 'acceptable' daily intake—defined as the daily intake level for a chemical that represents no anticipated significant risk to the consumer or exposed individual.

13.2.1 Determination of 'Tolerable' Chemical Concentrations

Chemicals in consumer products (including that occurring in dietary materials or foods) may be classified into two broad categories—viz.: carcinogenic and non-carcinogenic materials. The methods for deriving the 'acceptable' daily intakes and/or 'tolerable' concentrations for such chemicals are generally based on procedures/protocols presented earlier on in Chaps. 9 through 11; the general concepts are briefly annotated below.

13.2.1.1 'Acceptable' Daily Intake and 'Tolerable' Concentration for Carcinogens

The 'acceptable' daily intake for carcinogenic materials appearing in a consumer product may be estimated by using the following approximate relationships:

$$\mathrm{ADI}_{\mathrm{carcinogen}} = \frac{[\mathrm{TR} \times \mathrm{AT} \times 365\,\mathrm{day/year}]}{[\mathrm{ED} \times \mathrm{EF} \times \mathrm{SF}]}. \tag{13.5}$$

Thence, the 'tolerable' chemical concentration for carcinogens [$\mathrm{TC}_{\mathrm{carcinogen}}$] (mg/kg or mg/L) in the consumer product will be defined by,

$$\mathrm{TC}_{\mathrm{carcinogen}} = \frac{[\mathrm{ADI}_{\mathrm{carcinogen}} \times \mathrm{BW}]}{[\mathrm{FR} \times \mathrm{CR} \times \mathrm{ABS}]} \times \mathrm{CF} \tag{13.6}$$

where: $\mathrm{ADI}_{\mathrm{carcinogen}}$ is the 'acceptable' daily intake for the carcinogenic materials (mg/kg day); TR is the generally acceptable risk level (usually set at 10^{-6}); AT is the averaging time (years); ED is the exposure duration (year); EF is the exposure frequency (day/year); SF is the cancer potency or slope factor ($[\mathrm{mg/kg\ day}]^{-1}$); BW is the average body weight (kg); FR is the fraction of consumed material that is assumed to be contaminated; CR is the consumption rate (kg/day or L/day); ABS is the % absorption rate; and CF is a conversion factor to help maintain the dimensional tractability of the algorithm.

13.2.1.2 'Acceptable' Daily Intake and 'Tolerable' Concentration for Non-carcinogens

The 'acceptable' daily intake for non-carcinogenic materials appearing in a consumer product may be estimated by using the following approximate relationship:

$$\mathrm{ADI}_{\mathrm{non\text{-}carcinogen}} = \frac{[\mathrm{HQ} \times \mathrm{AT} \times 365\,\mathrm{day/year} \times \mathrm{RfD}]}{[\mathrm{ED} \times \mathrm{EF}]} \tag{13.7}$$

Thence, the 'tolerable' chemical concentration for non-carcinogens [$\mathrm{TC}_{\mathrm{non\text{-}carcinogen}}$] (mg/kg or mg/L) in the consumer product will be defined by,

$$\mathrm{TC}_{\mathrm{non\text{-}carcinogen}} = \frac{[\mathrm{ADI}_{\mathrm{noncarcinogen}} \times \mathrm{BW}]}{[\mathrm{FR} \times \mathrm{CR} \times \mathrm{ABS}]} \times \mathrm{CF} \tag{13.8}$$

where: $\mathrm{ADI}_{\mathrm{non\text{-}carcinogen}}$ is the 'acceptable' daily intake for the non-carcinogenic materials (mg/kg day); HQ is the generally acceptable hazard level (usually set at 1); AT is the averaging time (years); ED is the exposure duration (year); EF is the exposure frequency (day/year); RfD is the non-cancer reference dose or acceptable

daily intake (mg/kg day); BW is the average body weight (kg); FR is the fraction of consumed material that is assumed to be contaminated; CR is the consumption rate (kg/day or L/day); ABS is the % absorption rate; and CF is a conversion factor to help maintain the dimensional tractability of the algorithm.

13.3 Determination of Risk-Based Chemical Exposure Levels

After defining the critical exposure routes and exposure scenarios appropriate for a given a chemical exposure problem, it generally becomes possible to estimate a corresponding RBCEL that would likely not pose significant risks to an exposed population. To determine the RBCEL for a given chemical compound, algebraic manipulations of the hazard index and/or carcinogenic risk equations, together with the exposure estimation equations, discussed in Chaps. 9 through 11 can be used to arrive at the appropriate analytical relationships. The step-wise computational efforts involved in this exercise consist of a 'back-calculation' process that yields a media/material concentration predicated on health-protective exposure parameters; as an example, the RBCEL generally results in a cumulative non-cancer hazard index of ≤ 1 and/or a cumulative carcinogenic risk $\leq 10^{-6}$.

The processes involved in the determination of the RBCELs are summarized in the proceeding sections. In practice, for chemicals with carcinogenic effects, a target risk of (1×10^{-6}) is typically used in the 'back-calculation' exercise, and a target hazard index of 1.0 is typically used for non-carcinogenic effects; for substances that are both carcinogenic as well possess systemic toxicity properties, the lower of the resulting carcinogenic or non-carcinogenic criterion would typically be used for the relevant public health risk management action or decision.

13.3.1 RBCELs for Carcinogenic Constituents

As discussed in Chaps. 9 through 11, the cancer risk (CR) associated with the principal human exposure routes (comprised of inhalation, ingestion, and dermal exposures) may be represented by the following equation:

$$\begin{aligned} CR &= \left\{ \sum_{i=1}^{p} CDI_p \times SF_p \right\} = [CDI_i \times SF_i]_{\text{inhalation}} \\ &\quad + [CDI_o \times SF_o]_{\text{ingestion}} + [CDI_d \times SF_o]_{\text{dermal contact}} \\ &\equiv C_m \{ [INHf \times SF_i] + [INGf \times SF_o] + [DEXf \times SF_o] \} \end{aligned} \tag{13.9}$$

where: the CDIs represent the chronic daily intakes, adjusted for absorption (mg/kg day); INHf, INGf, and DEXf represent the inhalation, ingestion, and dermal contact 'intake factors', respectively (see Chap. 9); C_m is the chemical concentration in environmental/exposure matrix of concern; and the SFs are the route-specific cancer slope factors; and the subscripts *i, o* and *d* refer to the inhalation, oral ingestion, and dermal contact exposures, respectively.

The above model can indeed be re-formulated to calculate the carcinogenic RBCEL (viz., $RBCEL_c$) for the environmental/exposure media of interest. This involves 'back-calculating' from the chemical intake equations presented in Chap. 9 for inhalation, ingestion, and dermal contact exposures. Hence,

$$RBCEL_c = C_m = \frac{CR}{\{[INHf \times SF_i] + [INGf \times SF_o] + [DEXf \times SF_o]\}} \quad (13.10)$$

For illustrative purposes, let us assume that there is only one chemical constituent present in soils at a hypothetical contaminated land; furthermore, assume that exposures via the dermal and ingestion routes are the only pathways contributing to, or at least dominating, the total target carcinogenic risk (of, say $CR = 10^{-6}$). Thence,

$$CDI = \frac{CR}{SF_o} = RSD$$

or,

$$\left(CDI_{ing} + CDI_{der}\right) = \frac{CR}{SF_o}$$

i.e.,

$$\frac{(RBC_c \times SIR \times CF \times FI \times ABS_{si} \times EF \times ED)}{(BW \times AT \times 365)} + \frac{(RBC_c \times CF \times SA \times AF \times ABS_{sd} \times SM \times EF \times ED)}{(BW \times AT \times 365)} = \frac{CR}{SF_o}$$

Consequently,

$$RBCEL_c = \frac{(BW \times AT \times 365) \times (RSD)}{(CF \times EF \times ED)\{(SIR \times FI \times ABS_{si}) + (SA \times AF \times ABS_{sd} \times SM)\}}$$

where RSD represents the risk-specific dose—defined by the ratio of the target risk to the slope factor. Indeed, the estimated RBCEL may serve as surrogate for a health-based acceptable chemical exposure level (ACEL)—albeit some case-specific adjustments will usually be required, in order to arrive at a true ACEL used in public health risk management decisions.

13.3.1.1 Health-Based ACELs for Carcinogenic Chemicals

As health-based criteria, ACELs for carcinogens may be determined in a similar manner to the so-called 'virtually safe dose' (VSD) of a carcinogenic chemical constituent. A *VSD* is the daily dose of a carcinogenic chemical that, over a lifetime, will result in an incidence of cancer at a stipulated risk level; usually, this is calculated based on the appropriate *de minimis* risk level.

The governing equation for calculating ACELs for carcinogenic constituents is shown in Box 13.1. This model—developed from algorithms and concepts presented earlier on in Chaps. 9 through 11—assumes that there is only one chemical constituent involved in the problem situation. In other situations where several chemicals may be of concern, it is assumed (for simplification purposes) that each carcinogen has a different mode of biological action and target organs. Each of the carcinogens is, therefore, assigned 100% of the 'acceptable' excess carcinogenic risk (typically equal to $[1 \times 10^{-6}]$) in calculating the health-based ACELs; in other words, the excess carcinogenic risk is not allocated among the carcinogens.

Box 13.1 General Equation for Calculating Acceptable Chemical Exposure Levels for Carcinogenic Constituents

$$ACEL_c = \frac{(R \times BW \times LT \times CF)}{(SF \times I \times A \times ED)}$$

where:

$ACEL_c$ = acceptable chemical exposure level (equivalent to the VSD) in medium of concern (e.g., mg/kg in food; mg/L in water)
R = specified benchmark risk level, usually set at 10^{-6} (dimensionless)
BW = body weight (kg)
LT = assumed lifetime (years)
CF = conversion factor (equals 10^6 for ingestion exposure from solid materials; 1.00 for ingestion of fluids)
SF = cancer slope factor ($[mg/kg\ day]^{-1}$)
I = intake assumption (mg/day for solid material ingestion rate; L/day for fluid ingestion)
A = absorption factor (dimensionless)
ED = exposure duration (years)

Example Calculations. Consider a hypothetical situation whereby some human receptors may be consuming water contaminated with methylene chloride. Thenceforth, the allowable human exposure due to ingestion of 2 L of the water containing methylene chloride (with oral SF = 2.0×10^{-3} $[mg/kg/day]^{-1}$) by a 70-kg weight adult over a 70-year lifetime is given by:

$$ACEL = \frac{(R \times BW \times LT \times CF)}{(SF \times I \times A \times ED)}$$

i.e.,

$$ACEL_{methchl} = \frac{\left[10^{-6} \times 70 \times 70 \times 1\right]}{\left[\left(2.0 \times 10^{-03}\right) \times 2 \times 1 \times 70\right]} \approx 0.0175\,\text{mg/L} = 17.5\,\mu g/\text{L}$$

Thus, the health-based ACEL for methylene chloride, based on an acceptable excess lifetime cancer risk of 10^{-6}, is estimated to be 17.5 μg/L.

Next, consider another situation of a contaminated land impacting a multipurpose surface water-body due to overland flow. This surface water body is used both as a culinary water supply source and for recreational purposes. Assuming—in addition to the drinking water intake—an average daily consumption of aquatic organisms, DIA, of 6.5 g/day, and a BCF of 0.91 L/kg for methylene chloride, then the health-based exposure levels for the ingestion of both water and fish is determined from the following modified equation:

$$\begin{aligned} ACEL_{methchl} &= \frac{\text{R} \times \text{BW} \times \text{LT} \times \text{CF}]}{[\text{SF} \times (\text{I} + (\text{DIA} \times \text{BCF})) \times \text{A} \times \text{ED}]} \\ &= \frac{\left[10^{-6} \times 70 \times 70 \times 1\right]}{\left[\left(2.0 \times 10^{-03}\right) \times (2 + (0.0065 \times 0.91)) \times 1 \times 70\right]} \\ &\approx 0.0174\,\text{mg/L} = 17.4\,\mu g/\text{L} \end{aligned}$$

Thus, in this particular case, the allowable exposure level in relation to a drinking water intake, together with the eating of aquatic organisms contaminated with methylene chloride, is also approximately 17.5 μg/L.

13.3.2 RBCELs for Non-carcinogenic Effects of Chemical Constituents

As discussed in Chaps. 9 through 11, the hazard index (HI) associated with the principal human exposure routes (comprised of inhalation, ingestion, and dermal exposures) may be represented by the following equation:

$$\begin{aligned} \text{HI} &= \left\{ \sum_{\text{i}=1}^{\text{p}} \frac{\text{CDI}_\text{p}}{\text{RfD}_\text{p}} \right\} \\ &= \left[\frac{\text{CDI}_\text{i}}{\text{RfD}_\text{i}}\right]_{\text{inhalation}} + \left[\frac{\text{CDI}_\text{o}}{\text{RfD}_\text{o}}\right]_{\text{ingestion}} + \left[\frac{\text{CDI}_\text{d}}{\text{RfD}_\text{o}}\right]_{\text{dermal contact}} \\ &\equiv \text{C}_\text{m}\left\{ \left[\frac{\text{INHf}}{\text{RfD}_\text{i}}\right] + \left[\frac{\text{INHf}}{\text{RfD}_\text{o}}\right] + \left[\frac{\text{DEXf}}{\text{RfD}_\text{o}}\right] \right\} \end{aligned} \tag{13.11}$$

where: the CDIs represent the chronic daily intakes, adjusted for absorption (mg/kg day); INHf, INGf, and DEXf represent the inhalation, ingestion, and dermal contact 'intake factors', respectively (see Chap. 9); C_m is the chemical concentration in environmental/exposure matrix of concern; and the RfDs are the route-specific reference doses; the subscripts *i, o* and *d* refer to the inhalation, oral ingestion and dermal contact exposures, respectively.

The above model can indeed be re-formulated to calculate the non-carcinogenic RBCEL (viz., $RBCEL_{nc}$) for the environmental/exposure media of interest. This is derived by 'back-calculating' from the chemical intake equations presented in Chap. 9 for inhalation, ingestion, and dermal contact exposures. Hence,

$$RBCEL_{nc} = C_m = \frac{1}{\left\{\left[\frac{INHf}{RfD_i}\right] + \left[\frac{INGf}{RfD_o}\right] + \left[\frac{DEXf}{RfD_o}\right]\right\}} \tag{13.12}$$

For illustrative purposes, assume that there is only one chemical constituent present in soils at a hypothetical contaminated land; furthermore, assume that exposures via the dermal and ingestion routes are the only pathways contributing to, or at least dominating, the total target hazard index (of HI = 1). Then,

$$CDI = RfD$$

or,

$$\left(CDI_{ing} + CDI_{der}\right) = RfD_o$$

i.e.,

$$\frac{RBC_{nc} \times SIR \times CF \times FI \times ABS_{si} \times EF \times ED)}{(BW \times AT \times 365)} + \frac{(RBC_{nc} \times CF \times SA \times AF \times ABS_{sd} \times SM \times EF \times ED)}{(BW \times AT \times 365)} = RfD_o$$

Consequently,

$$RBCEL_{nc} = \frac{(BW \times AT \times 365) \times (RfD_o)}{(CF \times EF \times ED)\{(SIR \times FI \times ABS_{si}) + (SA \times AF \times ABS_{sd} \times SM)\}}$$

assuming a benchmark hazard index of unity. Indeed, the estimated RBCEL may serve as surrogate for a health-based acceptable chemical exposure level (ACEL)—albeit some case-specific adjustments will usually be required, in order to arrive at a true ACEL used in public health risk management decisions.

13.3.2.1 Health-Based ACELs for Non-carcinogenic Chemicals

As health-based criteria, ACELs for non-carcinogens may be determined in a similar manner to the so-called 'allowable daily intakes' (ADIs) of the non-carcinogenic effects from a chemical constituent. The *ADI* represents the threshold exposure limit below which no adverse effects are anticipated.

The governing equation for calculating ACELs for non-carcinogenic effects (i.e., the systemic toxicity) of chemical constituents is shown in Box 13.2. This model—derived from algorithms and concepts presented earlier on in Chaps. 9 through 11—assumes that there is only one chemical constituent involved. In situations where several chemicals may be of concern, it is assumed (for simplification purposes) that each chemical has a different organ-specific non-carcinogenic effect. Otherwise, the right hand side may be multiplied by a 'percentage factor' to account for contribution to hazard index by each non-carcinogenic chemical subgroup—or may indeed be appropriately manipulated by other methods.

Box 13.2 General Equation for Calculating Acceptable Chemical Exposure Levels for Non-carcinogenic Effects of Systemic Toxicants

$$ACEL_{nc} = \frac{\mathrm{RfD} \times \mathrm{BW} \times \mathrm{CF})}{(\mathrm{I} \times \mathrm{A})}$$

where:
$ACEL_{nc}$ = acceptable chemical exposure level in medium of concern (e.g., mg/kg in food; mg/L in water)
RfD = reference dose (mg/kg day)
BW = body weight (kg)
CF = conversion factor (equals 10^6 for ingestion exposure from solid materials; 1.00 for fluid ingestion)
I = intake assumption (mg/day for solid material ingestion rate; L/day for fluid ingestion)
A = absorption factor (dimensionless)

Example Calculations. Consider a hypothetical situation whereby some human receptors may be consuming water contaminated with ethylbenzene. Then, the allowable human exposure concentration associated with the ingestion of 2 L of water containing ethylbenzene (with RfD of 0.1 mg/kg/day) by a 70-kg weight adult is given by:

$$ACEL = \frac{[\mathrm{RfD} \times \mathrm{BW}]}{[\mathrm{DW} \times \mathrm{A}]}$$

i.e.,

$$ACEL_{ebz} = \frac{[0.1 \times 70]}{[2 \times 1]} = 3500 \mu g/\mathrm{L}$$

Next, consider another situation of a contaminated land impacting a multipurpose surface water-body due to overland flow. This surface water body is used both as a culinary water supply source and for recreational purposes. Assuming—in addition to the drinking water intake—an average daily consumption of aquatic organisms, DIA, of 6.5 g/day, and a BCF of 37.5 L/kg for ethylbenzene, then the health-based exposure levels for the ingestion of both water and fish is determined from the following modified equation:

$$ACEL_{ebz}\ [\mathrm{mg/L}] = \frac{[\mathrm{RfD} \times \mathrm{BW}]}{[2 + (0.0065 \times \mathrm{BCF})] \times 1} = \frac{[0.1 \times 70]}{[2 + (0.065 \times 37.5)]}$$
$$= 3120 \mu g/\mathrm{L}$$

Thus, the allowable exposure concentration (represented by the water ACEL) for drinking water and eating aquatic organisms contaminated with ethylbenzene is approximately 3120 μg/L.

13.4 Establishing Risk-Based Cleanup Limits for Contaminated Lands as a Classic Example

In addressing potentially contaminated land problems, soils can become the major focus of attention in the risk management decisions involved; this is because soils at such sites could serve as a major long-term reservoir for chemical contaminants—with the capacity to release contamination into several other environmental media. As such, the importance of soil cleanup for such contaminated lands cannot be overemphasized. In fact, the soil media typically requires a particularly close attention in most risk-based evaluations carried out for contaminated lands—albeit groundwater contaminant plumes underlying such sites are proving to be equally, if not more, problematic in some situations.

Risk assessment has indeed become particularly useful in determining the level of cleanup most appropriate for potentially contaminated lands. By utilizing methodologies that establish cleanup criteria based on risk assessment principles, corrective action programs can be conducted in a cost-effective and efficient manner. Once realistic risk reduction levels potentially achievable by various remedial alternatives are known, the decision-maker can then use other scientific criteria (such as implementability, reliability, operability, and cost) to select a final design alternative. Subsequently, an appropriate corrective action plan can be developed and implemented for the contaminated land. In fact, a major consideration in developing a remedial action plan for a contaminated land is the level of cleanup to be achieved—which could become the driving force behind remediation costs. The site cleanup limit concept generally facilitates decisions as to the effective use of limited funds to clean up a site to a level appropriate/safe for its intended use. It is

therefore be prudent to allocate adequate resources to develop the appropriate and defensible cleanup criteria.

In principle, the cleanup criteria selected for a potentially contaminated land may vary significantly from one site to another—due especially to the prevailing site-specific conditions. Similarly, mitigation measures may be case-specific for various hazardous situations and problems. In general, preliminary remediation goals (PRGs) are usually established as part of the cleanup objectives early in a site characterization process. The development of PRGs typically requires site-specific data relating to the impacted media of interest, the chemicals of potential concern (CoPCs), and the probable future land uses. It is noteworthy that an early determination of remediation goals tends to facilitate the development of a range of feasible corrective action decisions, which in turn helps focus remedy selection on the most effective remedial alternative(s). It is also notable that an initial list of PRGs may have to be revised when new data becomes available during the site characterization process. In fact, PRGs may have to be refined into final remediation goals throughout the process leading up to the final remedy selection. Consequently, it is important to iteratively review and re-evaluate the media and CoPCs, future land uses, and exposure assumptions originally identified during project formulation.

Now, consider for illustrative purposes, a potentially contaminated land that is being envisioned for remediation so that it could possibly be re-developed for either residential or industrial purposes. Contaminant levels in residential soils in which children might play (which allows for pica behavior in toddlers and other infants) must necessarily be lower than the same contaminant levels in soils present at a site designated for large industrial complexes (which effectively prevent direct exposures to contaminated soils). Also, the release potential of several chemical constituents will usually be different from sandy soils vs. clayey soils—and this will invariably affect the possible exposure scenarios, and therefore the acceptable soil contaminant levels that are designated for the different types of soils. Consequently, it is generally preferable to establish and use site-specific cleanup criteria for contaminated land problems encountered in practice, especially where soil exposures is critical to the site restoration decisions.

In order to determine the risk-based cleanup level for a chemical compound present in soils at a contaminated land, algebraic manipulations of the hazard index and/or carcinogenic risk equations together with the exposure estimation equations discussed in Chaps. 9 through 11 can be used to arrive at the appropriate analytical relationships. The step-wise computational efforts involved in this exercise consist of a 'back-calculation' process that yields an acceptable soil concentration (ASC) predicated on health-protective exposure parameters; as a classic example, the ASC generally results in a target cumulative non-cancer hazard index of ≤ 1 and/or a target cumulative carcinogenic risk $\leq 10^{-6}$. Indeed, for chemicals with carcinogenic effects, a target risk of $[1 \times 10^{-6}]$ is typically used in the 'back-calculation', and a target hazard index of 1.0 is typically used for non-carcinogenic effects. The processes involved in the determination of the ASCs are summarized in the sections

that follow directly below. For substances that are both carcinogenic and possess systemic toxicity properties, the lower of the carcinogenic or non-carcinogenic criterion would characteristically be used for the relevant site restoration and/or risk management decisions.

13.4.1 Soil Chemical Limits for Carcinogenic Contaminants

Box 13.3 shows a general equation for calculating the risk-based site restoration criteria for a single carcinogenic chemical present in soils at a contaminated land. This has been derived by 'back-calculating' from the risk and chemical exposure equations associated with the inhalation of soil emissions, ingestion of soils, and dermal contact with soils. It is noteworthy that, where appropriate and necessary, this general equation may also be re-formulated to incorporate the receptor age-adjustment exposure factors developed and presented earlier on in Chap. 9.

13.4.1.1 An Illustrative Example

In a simplified example of the application of the ASC equation (for calculating media-specific ASC for a carcinogenic chemical), consider a hypothetical site located within a residential setting where children might become exposed to site contamination during recreational activities. It has been found that soil at this playground for young children in the neighborhood is contaminated with methylene chloride. It is expected that children aged 1–6 years could be ingesting approximately 200 mg of the contaminated soils per day during outdoor activities at the impacted playground. The ASC associated with the *ingestion only exposure* of 200 mg of soil (contaminated with methylene chloride, with an oral SF of 2.0×10^{-3} $[\text{mg/kg day}]^{-1}$) on a daily basis, by a 16-kg child, over a 5-year exposure period is conservatively estimated to be:

$$ASC_{mc} = \frac{\left[10^{-6} \times 16 \times 70 \times 365\right]}{\left[0.002 \times 200 \times 1 \times 1 \times 365 \times 5 \times 10^{-6}\right]} \approx 560\,\text{mg/kg}$$

That is, the allowable exposure concentration (represented by the ASC) for methylene chloride in soils within this residential setting, assuming a benchmark excess lifetime cancer risk level of 10^{-6}, is estimated to be approximately 560 mg/kg. Thus, if environmental sampling and analysis indicates contamination levels in excess of 560 mg/kg at this residential playground, then immediate risk control action (such as restricting access to the playground as an interim measure) should probably be implemented.

Box 13.3 General Equation for Calculating Risk-Based Soil Cleanup Level for a Carcinogenic Chemical Constituent

$$ASC_c = \frac{\text{TCR}}{\left(\frac{\text{EF} \times \text{ED} \times \text{CF}}{\text{BW} \times \text{AT} \times 365}\right) \times \{[\text{SF}_\text{i} \times \text{IR} \times \text{RR} \times \text{ABS}_\text{a} \times \text{AEF} \times \text{CF}_\text{a}] + [\text{SF}_\text{o} \times \text{SIR} \times \text{FI} \times \text{ABS}_\text{si}) + (\text{SF}_\text{o} \times \text{SA} \times \text{AF} \times \text{ABS}_\text{sd} \times \text{SM})]\}}$$

$$= \frac{(\text{TCR}) \times (\text{BW} \times \text{AT} \times 365)}{(\text{EF} \times \text{ED} \times \text{CF}) \times \{[\text{SF}_\text{i} \times \text{IR} \times \text{RR} \times \text{ABS}_\text{a} \times \text{AEF} \times \text{CF}_\text{a}] + \text{SF}_\text{o}[(\text{SIR} \times \text{FI} \times \text{ABS}_\text{si}) + (\text{SA} \times \text{AF} \times \text{ABS}_\text{sd} \times \text{SM})]\}}$$

where:

ASC_c = acceptable soil concentration (i.e., acceptable risk-based cleanup level) of carcinogenic contaminant in soil (mg/kg)

TCR = target cancer risk, usually set at 10^{-6} (dimensionless)

SF_i = inhalation slope factor ($[\text{mg/kg day}]^{-1}$)

SF_o = oral slope factor ($[\text{mg/kg day}]^{-1}$)

IR = inhalation rate (m^3/day)

RR = retention rate of inhaled air (%)

ABS_a = percent chemical absorbed into bloodstream (%)

AEF = air emissions factor, i.e., PM_{10} particulate emissions or volatilization (kg/m^3)

CF_a = conversion factor for air emission term (10^6)

SIR = soil ingestion rate (mg/day)

CF = conversion factor (10^{-6} kg/mg)

FI = fraction ingested from contaminated source (dimensionless)

ABS_si = bioavailability absorption factor for ingestion exposure (%)

ABS_sd = bioavailability absorption factor for dermal exposures (%)

SA = skin surface area available for contact, i.e., surface area of exposed skin (cm^2/event)

AF = soil to skin adherence factor, i.e., soil loading on skin (mg/cm^2)

SM = factor for soil matrix effects (%)

EF = exposure frequency (days/year)

ED = exposure duration (years)

BW = body weight (kg)

AT = averaging time (i.e., period over which exposure is averaged) (years)

It is noteworthy that, other potentially significant exposure routes (e.g., dermal contact and inhalation) as well as other sources of exposure (e.g., via drinking water and food) have not been accounted for in this illustrative example. Meanwhile, all such other exposure routes and sources may require the need to further lower the

calculated ASC for any site restoration decisions. Indeed, regulatory guidance would probably require reducing the contaminant concentration, ASC_{mc}, to only a fraction (e.g., 20%) of the calculated value in view of the fact that there could be other sources of exposure (e.g., air, food, etc.). Anyhow, this kind of thinking should generally be factored into the overall risk management decisions about contaminated land management problems.

13.4.2 Soil Chemical Limits for the Non-carcinogenic Effects of Site Contaminants

Box 13.4 shows a general equation for calculating the risk-based site restoration criteria for the non-carcinogenic effects of a single chemical constituent found in soils at a contaminated land. This has been derived by 'back-calculating' from the hazard and chemical exposure equations associated with the inhalation of soil emissions, ingestion of soils, and dermal contact with soils.

13.4.2.1 An Illustrative Example

In a simplified example of the application of the ASC equation (for calculating media-specific ASC for the non-carcinogenic effects of a chemical constituent), consider a hypothetical site located within a residential setting where children might become exposed to site contamination during recreational activities. It has been found that soil at this playground for young children in the neighborhood is contaminated with ethylbenzene. It is expected that children aged 1–6 years could be ingesting approximately 200 mg of contaminated soils per day during outdoor activities at the impacted playground. The ASC associated with the *ingestion only exposure* of 200 mg of soil (contaminated with ethylbenzene, with an oral RfD of 0.1 mg/kg day) on a daily basis, by a 16-kg child, over a 5-year exposure period is conservatively estimated to be:

$$ASC_{ebz} = \frac{0.1 \times [1 \times 16 \times 5 \times 365]}{[200 \times 1 \times 1 \times 365 \times 5 \times 10^{-6}]} \approx 8000\,\text{mg/kg}.$$

That is, the allowable exposure concentration (represented by the ASC) for ethylbenzene in soils within this residential setting is estimated to be approximately 8000 mg/kg. Thus, if environmental sampling and analysis indicates contamination levels in excess of 8000 mg/kg at this residential playground, then immediate risk control action (such as restricting access to the playground as an interim measure) should probably be implemented.

It is noteworthy that, other potentially significant exposure routes (e.g., dermal contact and inhalation) as well as other sources of exposure (e.g., via drinking water

and food) have not been accounted for in this illustrative example. Meanwhile, all such other exposure routes and sources may require the need to further lower the calculated ASC for any site restoration decisions. Indeed, regulatory guidance would probably require reducing the contaminant concentration, ASC_{ebz}, to only a fraction (e.g., 20%) of the calculated value in view of the fact that there could be other sources of exposure (e.g., air, food, etc.). Anyhow, this kind of thinking should generally be factored into the overall risk management decisions about contaminated land management problems.

Box 13.4 General Equation for Calculating Risk-Based Soil Cleanup Level for the Non-carcinogenic Effects of a Chemical Constituent

$$ASC_{nc} = \frac{\text{Target Hazard Quotient}}{\left(\frac{EF \times ED \times 10^{-6}}{BW \times AT \times 365}\right) \times \left\{\left[\frac{IR \times RR \times ABS_a}{RfD_i} \times AEF \times CF_a\right] + \left[\left(\frac{SIR}{RfD_o} \times FI \times ABS_{si}\right)\right] + \left[\frac{SA \times AF \times ABS_{sd} \times SM}{RfD_o}\right]\right\}}$$

$$= \frac{(THQ) \times (BW \times AT \times 365)}{(EF \times ED \times CF) \times \left\{\left[\frac{IR \times RR \times ABS_a}{RfD_i} \times AEF \times CF_a\right] + \frac{1}{RfD_o}[(SIR \times FI \times ABS_{si}) + (SA \times AF \times ABS_{sd} \times SM)]\right\}}$$

where:

ASC_{nc} = acceptable soil concentration (i.e., acceptable risk-based cleanup level) of non-carcinogenic contaminant in soil (mg/kg)
THQ = target hazard quotient (usually equal to 1) (unitless)
RfD_i = inhalation reference dose (mg/kg day)
RfD_o = oral reference dose (mg/kg day)
IR = inhalation rate (m^3/day)
RR = retention rate of inhaled air (%)
ABS_a = percent chemical absorbed into bloodstream (%)
AEF = air emission factor, i.e., PM_{10} particulate emissions or volatilization (kg/m^3)
CF_a = conversion factor for air emission term (10^6)
SIR = soil ingestion rate (mg/day)
CF = conversion factor (10^{-6} kg/mg)
FI = fraction ingested from contaminated source (dimensionless)
ABS_{si} = bioavailability absorption factor for ingestion exposure (%)
ABS_{sd} = bioavailability absorption factor for dermal exposures (%)
SA = skin surface area available for contact, i.e., surface area of exposed skin (cm^2/event)

(continued)

Box 13.4 (continued)

AF = soil to skin adherence factor, i.e., soil loading on skin (mg/cm^2)
SM = factor for soil matrix effects (%)
EF = exposure frequency (days/year)
ED = exposure duration (years)
BW = body weight (kg)
AT = averaging time (i.e., period over which exposure is averaged, equals ED for non-carcinogens) (years)

13.5 Establishing Risk-Based Cleanup Limits for Contaminated Waters as a Practical Example

To determine the risk-based cleanup level for a chemical compound present in water, algebraic manipulations of the hazard index and/or carcinogenic risk equations together with the exposure estimation equations discussed in Chaps. 9 through 11 can be used to arrive at the appropriate analytical relationships. The step-wise computational efforts involved in this exercise consist of a 'back-calculation' process that yields an acceptable water concentration (AWC) predicated on health-protective exposure parameters; as a classic example, the AWC generally results in a target cumulative non-cancer hazard index of ≤ 1 and/or a target cumulative carcinogenic risk $\leq 10^{-6}$. Indeed, for chemicals with carcinogenic effects, a target risk of $[1 \times 10^{-6}]$ is typically used in the 'back-calculation', and a target hazard index of 1.0 is typically used for non-carcinogenic effects. The processes involved in the determination of the AWCs are summarized in the sections that follow directly below. For substances that are both carcinogenic and possess systemic toxicity properties, the lower of the carcinogenic or non-carcinogenic criterion would characteristically be used for the relevant corrective action and/or risk management decisions.

13.5.1 Water Chemical Limits for Carcinogenic Contaminants

Box 13.5 shows a general equation for calculating the risk-based restoration criteria for a single carcinogenic constituent present in potable water. This has been derived by 'back-calculating' from the risk and chemical exposure equations associated with the inhalation of contaminants in water (for volatile constituents only), ingestion of water, and dermal contact with water. It is noteworthy that, where appropriate and necessary, this general equation may also be re-formulated to incorporate the receptor age-adjustment exposure factors developed and presented earlier on in Chap. 9.

13.5.1.1 An Illustrative Example

In a simplified example of the application of the AWC equation (for calculating media-specific AWC for a carcinogenic chemical), consider the case of a contaminated site that is impacting an underlying water supply aquifer as a result of contaminant migration into groundwater. This groundwater resource is used for culinary water supply purposes. The AWC associated with the *ingestion only exposure* to 2 L of water (contaminated with methylene chloride, with an oral SF of 2.0×10^{-3} [mg/kg-day]$^{-1}$) on a daily basis, by a 70-kg adult, over a 70-year lifetime is given by the following approximation:

$$AWC_{mc} = \frac{\left[10^{-6} \times 70 \times 70 \times 365\right]}{[0.002 \times 2 \times 1 \times 365 \times 70]} \approx 0.0175\,\text{mg/L} = 17.5\,\mu g/\text{L}$$

That is, assuming a benchmark excess lifetime cancer risk level of 10^{-6}, the allowable exposure concentration for methylene chloride (represented by the AWC) is estimated at 17.5 μg/L. Obviously, the inclusion of other pertinent exposure routes (such as inhalation of vapors, and dermal contacts during showering/bathing activities, etc.) would likely call for a lower AWC in any aquifer restoration decision. Indeed, regulatory guidance would probably require reducing the contaminant concentration, AWC_{mc}, to only a fraction (e.g., 20%) of the calculated value in view of the fact that there could be other sources of exposure (e.g., air, food, etc.). Anyhow, this kind of thinking should generally be factored into the overall risk management decisions about contaminated water management problems.

Box 13.5 General Equation for Calculating Risk-Based Water Cleanup Level for a Carcinogenic Chemical Constituent

$$\begin{aligned} AWC_c &= \frac{\text{TCR}}{\left(\frac{\text{EF} \times \text{ED}}{\text{BW} \times \text{AT} \times 365}\right) \times \{[\text{SF}_\text{i} \times \text{IR}_\text{w} \times \text{RR} \times \text{ABS}_\text{a} \times \text{CF}_\text{a}] + \\ &\quad \left[\text{SF}_\text{o} \times \text{WIR} \times \text{FI} \times \text{ABS}_\text{si}\right) + \left(\text{SF}_\text{o} \times \text{SA} \times \text{K}_\text{p} \times \\ &\quad \text{ET} \times \text{ABS}_\text{sd} \times \text{CF})]\} \\ &= \frac{\text{TCR} \times (\text{BW} \times \text{AT} \times 365)}{(\text{EF} \times \text{ED}) \times \{[\text{SF}_\text{i} \times \text{IR}_\text{w} \times \text{RR} \times \text{ABS}_\text{a} \times \text{CF}_\text{a}] \\ &\quad + \text{SF}_\text{o}[(\text{WIR} \times \text{FI} \times \text{ABS}_\text{si}) + \\ &\quad \left(\text{SA} \times \text{K}_\text{p} \times \text{ET} \times \text{ABS}_\text{sd} \times \text{CF}\right)]\} \end{aligned}$$

(continued)

Box 13.5 (continued)

where:
AWC_c = acceptable water concentration (i.e., acceptable risk-based cleanup level) of carcinogenic contaminant in water (mg/L)
TCR = target cancer risk, usually set at 10^{-6} (dimensionless)
SF_i = inhalation slope factor ($[mg/kg\ day]^{-1}$)
SF_o = oral slope factor ($[mg/kg\ day]^{-1}$)
IR_w = intake from the inhalation of volatile compounds (sometimes equivalent to the amount of ingested water) (m^3/day)
RR = retention rate of inhaled air (%)
ABS_a = percent chemical absorbed into bloodstream (%)
CF_a = conversion factor for volatiles inhalation term (1000 L/1 $m^3 = 10^3$ L/m^3)
WIR = water ingestion rate (L/day)
CF = conversion factor (1 L/1000 $cm^3 = 10^{-3}$ L/cm^3)
FI = Fraction ingested from contaminated source (unitless)
ABS_{si} = bioavailability absorption factor for ingestion exposure (%)
ABS_{sd} = bioavailability absorption factor for dermal exposures (%)
SA = skin surface area available for contact, i.e., surface area of exposed skin (cm^2/event)
K_p = chemical-specific dermal permeability coefficient from water (cm^2/h)
ET = exposure time during water contacts (e.g., during showering/bathing activity) (h/day)
EF = exposure frequency (days/years)
ED = exposure duration (years)
BW = body weight (kg)
AT = averaging time (i.e., period over which exposure is averaged) (years).

13.5.2 Water Chemical Limits for the Non-carcinogenic Effects of Site Contaminants

Box 13.6 shows a general equation for calculating the risk-based restoration criteria for a single non-carcinogenic constituent present in potable water. This has been derived by 'back-calculating' from the risk and chemical exposure equations associated with the inhalation of contaminants in water (for volatile constituents only), ingestion of water, and dermal contact with water.

Box 13.6 General Equation for Calculating Risk-Based Water Cleanup Level for Non-carcinogenic Effects of a Chemical Constituent

$$AWC_{nc} = \frac{\mathrm{THQ}}{\left(\frac{\mathrm{EF}\times\mathrm{ED}}{\mathrm{BW}\times\mathrm{AT}\times 365}\right)\times\left\{\left[\frac{\mathrm{IR_w}\times\mathrm{RR}\times\mathrm{ABS_a}\times\mathrm{CF_a}}{\mathrm{RfD_i}}\right]+\left[\left(\frac{\mathrm{WIR}}{\mathrm{RfD_o}}\times\mathrm{FI}\times\mathrm{ABS_{si}}\right)\right]+\left[\frac{\mathrm{SA}\times\mathrm{K_P}\times\mathrm{ET}\times\mathrm{ABS_{sd}}\times\mathrm{CF}}{\mathrm{RfD_o}}\right]\right\}}$$

$$= \frac{\mathrm{THQ}\times(\mathrm{BW}\times\mathrm{AT}\times 365)}{(\mathrm{EF}\times\mathrm{ED})\times\left\{\left[\frac{\mathrm{IR_w}\times\mathrm{RR}\times\mathrm{ABS_a}\times\mathrm{CF_a}}{\mathrm{RfD_i}}\right]+\frac{1}{\mathrm{RfD_o}}\left[(\mathrm{WIR}\times\mathrm{FI}\times\mathrm{ABS_{si}})+\mathrm{SA}\times\mathrm{K_p}\times\mathrm{ET}\times\mathrm{ABS_{sd}}\times\mathrm{CF})\right]\right\}}$$

where:

AWC_{nc} = acceptable water concentration (i.e., acceptable risk-based cleanup level) of non-carcinogenic contaminant in water (mg/L)
THQ = target hazard quotient (usually equal to 1)
$\mathrm{RfD_i}$ = inhalation reference dose (mg/kg day)
$\mathrm{RfD_o}$ = oral reference dose (mg/kg day)
$\mathrm{IR_w}$ = inhalation intake rate ($\mathrm{m^3}$/day)
RR = retention rate of inhaled air (%)
$\mathrm{ABS_a}$ = percent chemical absorbed into bloodstream (%)
$\mathrm{CF_a}$ = conversion factor for volatiles inhalation term (1000 L/1 $\mathrm{m^3} = 10^3$ $\mathrm{L/m^3}$)
WIR = water intake rate (L/day)
CF = conversion factor (1 L/1000 $\mathrm{cm^3} = 10^{-3}$ $\mathrm{L/cm^3}$)
FI = fraction ingested from contaminated source (dimensionless)
$\mathrm{ABS_{si}}$ = bioavailability absorption factor for ingestion exposure (%)
$\mathrm{ABS_{sd}}$ = bioavailability absorption factor for dermal exposures (%)
SA = skin surface area available for contact, i.e., surface area of exposed skin ($\mathrm{cm^2}$/event)
$\mathrm{K_p}$ = chemical-specific dermal permeability coefficient from water ($\mathrm{cm^2}$/h)
ET = exposure time during water contacts (e.g., during showering/bathing activity) (h/day)
EF = exposure frequency (days/years)
ED = exposure duration (years)
BW = body weight (kg)
AT = averaging time (i.e., period over which exposure is averaged) (years).

13.5.2.1 An Illustrative Example

In a simplified example of the application of the AWC equation (for calculating media-specific AWC for a non-carcinogenic chemical), consider the case of a contaminated site that is impacting an underlying water supply aquifer as a result of contaminant migration into groundwater. This groundwater resource is used for culinary water supply purposes. The AWC associated with the *ingestion only exposure* to 2 L of water (contaminated with ethylbenzene, with an oral RfD of 0.1 mg/kg day) on a daily basis, by a 70-kg adult is approximated by:

$$AWC_{ebz} = \frac{0.1 \times [1 \times 70 \times 70 \times 365]}{[2 \times 1 \times 1 \times 365 \times 70]} \approx 3500\,\mu g/\mathrm{L}$$

That is, the allowable exposure concentration (represented by the AWC) for ethylbenzene is estimated to be 3500 μg/L. Of course, additional exposures via inhalation and dermal contacts during showering/bathing and washing activities may also have to be incorporated to yield an even lower AWC, in order to arrive at a more responsible water restoration decision. Indeed, regulatory guidance would probably require reducing the contaminant concentration, AWC_{ebz}, to only a fraction (e.g., 20%) of the calculated value in view of the fact that there could be other sources of exposure (e.g., air, food, etc.). Anyhow, this kind of thinking should generally be factored into the overall risk management decisions about contaminated water management problems.

13.6 Towards a 'Desirable' Health-Protective Chemical Exposure Level

Oftentimes, the RBCEL that has been established based on an acceptable risk level or hazard index are for a single contaminant in one environmental matrix or exposure medium. Consequently, the risk and hazard associated with multiple contaminants in a multi-media setting are not fully accounted for during the 'back-modeling' process used to establish the RBCELs. In contrast, the evaluation of risks associated with a given chemical exposure problem usually involves a set of equations designed to estimate hazard and risk for several chemicals, and for a multiplicity of exposure routes. Under this latter type of scenario, the computed 'acceptable' risks could indeed exceed the health-protective limits; accordingly, it becomes necessary to establish a modified RBCEL for the requisite environmental or public health risk management decision. To obtain the 'modified RBCEL', the 'acceptable' chemical exposure level is estimated in the same manner as elaborated earlier on in Sect. 13.3—but with the cumulative effects of multiple chemicals being taken into account through a process of apportioning the target risks and hazards among all the CoPCs.

13.6.1 *The 'Modified* RBCEL*' for Carcinogenic Chemicals*

A modified RBCEL for carcinogenic constituents may be derived by the application of a 'risk disaggregation factor'—that allows for the apportionment of risk amongst all CoPCs. That is, the new RBCEL may be estimated by proportionately aggregating (or perhaps rather disaggregating) the target cancer risk amongst the CoPCs, and then using the corresponding target risk level in the equation presented earlier on in Box 13.1. The assumption used for apportioning the excess carcinogenic risk may be one that considers all carcinogens as having the same mode of biological actions and target organs; otherwise, excess carcinogenic risk is not apportioned among carcinogens, but rather each assumes the same value in the computational efforts. A more comprehensive approach to 'apportioning' or 'allotting' risks would involve more complicated mathematical manipulations—such as by the use of linear programming algorithms.

In general, the acceptable risk level may be apportioned between the chemical constituents contributing to the overall target risk by assuming that each constituent contributes equally or proportionately to the total acceptable risk. The 'risk fraction' obtained for each constituent can then be used to derive the modified RBCEL—by working from the relationships established previously for the computation of RBCELs (Sect. 13.3); by utilizing the approach for estimating media RBCELs, the modified RBCEL is derived in accordance the following approximate relationship:

$$RBCEL_{c-\mathrm{mod}} = \frac{[\%] \times \mathrm{CR}}{\{[\mathrm{INHf} \times \mathrm{SF_i}] + [\mathrm{INGf} \times \mathrm{SF_o}] + [\mathrm{DEXf} \times \mathrm{SF_o}]\}} \qquad (13.13)$$

All the terms are the same as defined previously in Sect. 13.3, and [%] represents the proportionate contribution from a specific chemical constituent to the overall target risk level. One may also choose to use 'weighting factors' in apportioning the chemical contributions to the target risk levels; for instance, this could be based on carcinogenic classes—such that 'Class A' carcinogens are given twice as much weight as 'Class B', etc., or chemicals posing carcinogenic risk via all exposure routes are given more weight than those presenting similar risks via specific routes only. Overall, the use of the modified RBCEL approach will likely ensure that the sum of risks from all the chemicals involved over all exposure pathways is less than or equal to the set target *de minimis* risk (e.g., $\leq 10^{-6}$).

13.6.2 *The 'Modified* RBCEL*' for Non-carcinogenic Constituents*

A modified RBCEL for non-carcinogenic constituents may be derived by application of a 'hazard disaggregation factor'—that allows for the apportionment of target

hazard index amongst all CoPCs. That is, the new RBCEL may be estimated by proportionately aggregating (or perhaps rather disaggregating) the non-cancer hazard index amongst the CoPCs, and then using the corresponding target hazard level in the equation presented earlier on in Box 13.2.

In general, the acceptable hazard level may be apportioned between the chemical constituents contributing to the overall hazard index by assuming that each constituent contributes equally or proportionately to the total acceptable hazard index—all the while accounting for commonality in endpoint effects as well. The 'hazard fraction' obtained for each constituent can then be used to derive the modified RBCEL—by working from the relationships established previously for the computation of RBCELs (Sect. 13.3). By using the approach to estimating media RBCELs, the modified RBCEL is derived in accordance the following approximate relationship for non-carcinogenic effects of chemicals having the same toxicological endpoints:

$$RBCEL_{nc-\mathrm{mod}} = \frac{[\%] \times 1}{\left\{ \left[\frac{\mathrm{INHf}}{\mathrm{RfD_i}}\right] + \left[\frac{\mathrm{INGf}}{\mathrm{RfD_o}}\right] + \left[\frac{\mathrm{DEXf}}{\mathrm{RfD_o}}\right] \right\}}. \tag{13.14}$$

All the terms are the same as defined previously in Sect. 13.3, and [%] represents the proportionate contribution from a specific chemical constituent to the overall target hazard index for the non-carcinogenic effects of chemicals with same physiologic endpoint. Overall, the use of the modified RBCEL approach will ensure that the sum of hazard quotients over all exposure pathways for all chemicals (with the same physiologic endpoints) is less than or equal to the hazard index criterion of 1.0.

13.6.3 Incorporating Degradation Rates into the Estimation of Environmental Quality Criteria

The effect of chemical degradation is not incorporated into estimated RBCELs often enough. However, since exposure scenarios used in calculating the RBCELs or similar criteria usually make the assumption that exposures could be occurring over long time periods (up to a lifetime of 70 years), it is prudent, at least in a detailed analysis, to consider the fact that degradation or other transformation of the CoPC could occur. Under such circumstances, the degradation properties of the CoPCs should be carefully evaluated. Subsequently, an adjusted RBCEL (or its equivalent) can be estimated—that is based on the original RBCEL (or equivalent), a degradation rate coefficient, and the specified exposure duration. The new adjusted RBCEL is then given by:

$$RBCEL_a = \frac{\mathrm{RBCEL}}{\mathrm{degradation\ factor\ (DGF)}}. \tag{13.15}$$

where $RBCEL_a$ is the adjusted RBCEL or its equivalent, and this incorporates a degradation rate coefficient. Now, assuming first-order kinetics, as an example, an approximation of the degradation effects can be obtained as follows:

$$\mathrm{DGF} = \frac{\left(1 - \mathrm{e}^{-\mathrm{kt}}\right)}{\mathrm{kt}} \tag{13.16}$$

where: k is a chemical-specific degradation rate constant (days^{-1}), and t is time period over which exposure occurs (days). For a first-order decaying substance, k is estimated from the following relationship:

$$\mathrm{T}_{1/2}\ [\mathrm{days}] = \frac{0.693}{\mathrm{k}} \quad \text{or} \quad \mathrm{k}\left[\mathrm{days}^{-1}\right] = \frac{0.693}{\mathrm{T}_{1/2}}. \tag{13.17}$$

where $\mathrm{T}_{1/2}$ is the half-life, which is the time after which the mass of a given substance will be one-half its initial value. Consequently,

$$RBCEL_a = RBCEL \times \frac{\mathrm{kt}}{\left(1 - \mathrm{e}^{-\mathrm{kt}}\right)} \tag{13.18}$$

This relationship assumes that a first-order degradation/decay is occurring during the complete exposure period; decay/degradation is initiated at time, $t = 0$ years; and the RBCEL is the average allowable concentration over the exposure period. In fact, if significant degradation is likely to occur, the $RBCEL_a$ calculations become much more complicated; in that case, predicted source chemical levels must be calculated at frequent intervals and summed over the exposure period.

13.7 Sifting Through the Maze: Public Health Goals vs. Risk-Based Chemical Exposure Levels

Pre-established public health goals (PHGs) are often used in practice to define acceptable chemical exposure limits for human exposure—i.e., if they are determined to represent 'safe' or 'tolerable' benchmark levels for the case-specific situation. However, such generic PHGs may not always be available, or may not even offer adequate public health protection under certain circumstances. For instance, the presence of multiple constituents, multiple exposure routes, or other extraneous factors could result in 'unacceptable' aggregate risk being associated with a PHG for the particular situation. Under such circumstances, a new 'acceptable' or 'safe' level may be better represented by the RBCEL—that are derived for the various exposure routes, and from elaborately defined exposure scenarios. As the preferred risk-based benchmark, the RBCEL can then be used as a surrogate or replacement for the PHG of the CoPC.

In general, health-protective risk-based benchmarks are usually developed by 'back-modeling' from a target risk level that produces an acceptable RBCEL—which can then serve as a surrogate PHG. Invariably, the type of exposure scenarios envisioned as well as the exposure assumptions used may determine the new benchmark level—also recognizing that when the calculated RBCEL based on non-cancer toxicity is less protective of public health than the cancer-based value, the surrogate PHG for the CoPC is set at the lower of the two, which is usually the one based on the cancer effects. Meanwhile, it is noteworthy that, for criteria predicated on the cancer toxicity, the pre-established PHG is generally considered to contain an adequate margin of safety for the potential non-carcinogenic adverse effects, such as adverse effects on the renal, neurological and reproductive systems.

In so many ways, the use of risk assessment principles to establish case-specific benchmarks for chemical exposure problems represent an even better and more sophisticated approach to designing cost-effective public health risk management programs—i.e., in comparison with the use of generic benchmarks. In general, the risk-based benchmarks predicated on RBCELs may be used to:

- Determine the degree of chemical exposures;
- Evaluate the need for intervention and receptor monitoring;
- Provide guidance on the need for risk control and/or corrective actions;
- Establish safer PHGs; and
- Verify the adequacy of possible remedial/corrective actions.

Ultimately, the use of such an approach aids in the development and/or selection of appropriate public health risk management strategies capable of achieving a more impressive set of performance goals—such that public health is not jeopardized.

Chapter 14
Designing Public Health Risk Management Programs

Risk management is a decision-making process that entails weighing policy alternatives, and then selecting the most appropriate regulatory action. This is accomplished by integrating the results of risk assessment with scientific data, as well as with social, economic, and political concerns—in order to arrive at an appropriate decision on a potential hazard situation (Cohrssen and Covello 1989; NRC 1994a, b; Seip and Heiberg 1989; van Leeuwen and Hermens 1995). Risk management may also include the design and implementation of policies and strategies that result from this decision-making process.

This chapter elaborates the key elements and steps necessary for the effectual design of typical public health risk assessment and risk management programs. Such risk management programs are typically directed at: risk reduction (i.e., taking measures to protect humans and/or the environment against previously identified risks); risk mitigation (i.e., implementing measures to remove risks); and/or risk prevention (i.e., instituting measures to completely prevent the occurrence of risks). Ultimately, the risk management (i.e., reduction, mitigation, and preventative) programs can generally help engender an increase in the level of protection to public health and enhance safety, as well as assist in the reduction of liability.

14.1 Risk Assessment as a Cost-Effective Tool in the Formulation of Public Health and Environmental Management Decisions

Risk assessment is a systematic technique that can be used to generate estimates of significant and likely risk factors associated with chemical exposure problems. Oftentimes, risk assessment is used as a management tool to facilitate effective decision-making on the control of chemical exposure problems. In fact, the chief

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purpose of risk assessment is to aid decision-making—and this focus should be maintained throughout any environmental or public health risk management program. On the whole, the application of risk assessment to chemical exposure problems can likely remove some of the ambiguities in the decision-making process. It can also aid in the selection of prudent, technically feasible, and scientifically justifiable risk control or corrective actions that will help protect public health and the environment in a cost-effective manner.

Risk assessments do indeed provide decision-makers with scientifically defensible information for determining whether a chemical exposure problem poses a significant threat to human health or the environment. Congruently, it would typically be conducted to assist in the development of cost-effective strategies for the management of chemical exposure problems. Among other things, the risk assessment process can be used to define the level of risk—and which will in turn assist in determining the level of analysis and the type of risk management actions to adopt for a given chemical exposure or environmental management problem. The level of risk considered in such applications can be depicted in a risk-decision matrix (Fig. 14.1)—in a manner that will help distinguish between imminent health hazards and risks. In general, this can be used as an aid for policy decisions, in order

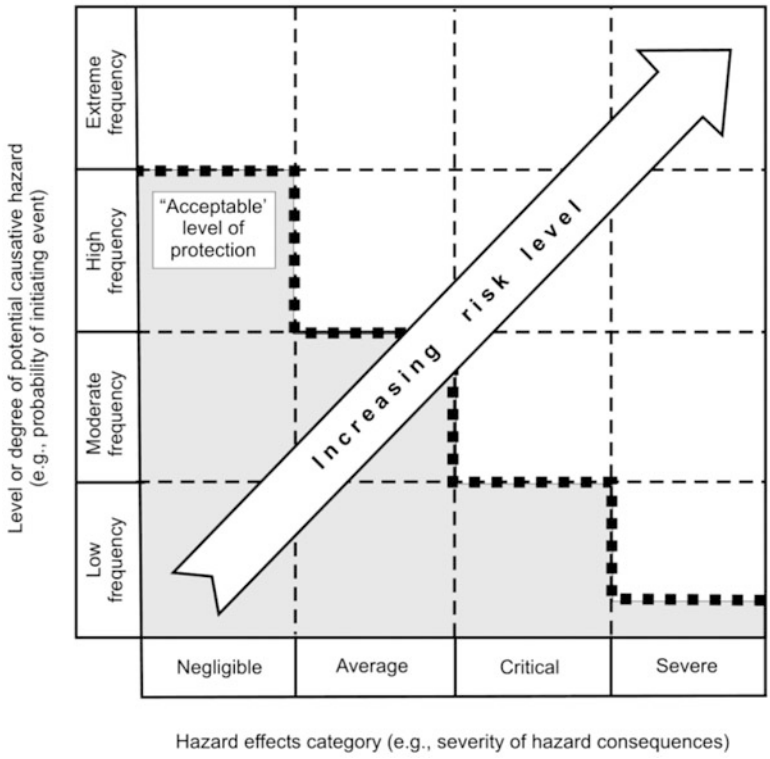

Fig. 14.1 A conceptual representation defining risk profiles in a risk-decision matrix

to develop variations in the scope of work necessary for case-specific public health risk management programs. At any rate, the procedures utilized in these efforts must reflect current/state-of-the-art methods for conducting risk assessments; for all intents and purposes, the following are noteworthy recommendations in the exercises typically involved:

- Performing risk assessment to incorporate all likely scenarios envisaged rather than for the 'worst-case' alone allows better comparison to be made between risk assessments performed by different scientists and analysts whose views on what represents a 'worst-case' may be very subjective, and therefore may vary significantly.
- Risk assessments performed for chemical exposure problems usually will, among other things, depend on an understanding of the fate and behavior of the chemical constituents of concern. Consequently, the fate and behavior issues in the various exposure settings should be carefully analyzed with the best available scientific tools.
- Exposure scenarios and chemical fate and behavior models may contribute significant uncertainty to the risk assessment. The uncertainties, heterogeneities, and similarities should be identified and well documented throughout the risk assessment.
- Whenever possible, the synergistic, antagonistic, and potentiation (i.e., the case of a non-hazardous situation becoming hazardous due to its combination with others) effects of chemicals and other hazardous situations should be carefully evaluated for inclusion in the risk decisions.
- It is prudent to appraise what the 'baseline' (no-action) risks are for a potentially hazardous situation or chemical exposure problem. This will provide a reflection on what the existing situation is, which can then be compared against future improved situations.
- An evaluation of the 'post-remedy' risks (i.e., residual risks remaining after the implementation of corrective actions) for a potentially hazardous situation or chemical exposure problem should generally be carried out for alternative mitigation measures. This will provide a reflection of what the anticipated improved situation is vis-à-vis the prior conditions associated with the problem situation.

Ultimately, the risk assessment efforts can help minimize or eliminate potential long-term problems or liabilities that could result from hazards associated with chemical exposure problems.

On the whole, the benefits of risk assessment designed to facilitate public health risk management decisions outweigh any possible disadvantages; still, it must be recognized that this process will not be without tribulations. Indeed, risk assessment is by no means a panacea. Its use, however, is an attempt to widen and extend the decision-maker's knowledge-base—and thus improve the decision-making capability. In conclusion, the method deserves the effort required for its continual refinement as a public health risk management tool.

14.2 Comparative Risk Analysis: Application of Environmental Decision Analysis Methods to Public Health Risk Management Programs

Decision analysis is a management tool comprised of a conceptual and systematic procedure for rationally analyzing complex sets of alternative solutions to a problem—in order to improve the overall performance of the decision-making process. Decision theory provides a logical and systematic framework to structure the problem objectives, and to evaluate and rank alternative potential solutions to the problem. Environmental decision analyses typically involve the use of a series of techniques to comprehensively develop risk control or corrective action plans, and to evaluate appropriate mitigative alternatives in a technically defensible manner.

As part of a corrective action assessment program, it is almost inevitable that the policy analyst will often have to make choices between alternative remedial options. These are based on: an evaluation of risk tradeoffs and relative risks that exist among feasible decision alternatives; evaluation of the cost-effectiveness of corrective action plans; or a risk-cost-benefit comparison of several management options. In fact, comparing risks, benefits, and costs amongst various risk management strategies can become very important in the appraisal of most environmental and public health risk management programs—since this could ultimately facilitate better optimization of proposed solutions to the problem on hand. A number of analytical tools may generally be used to assist with the processes involved here (see, e.g., Ashford and Caldart 2008; Bentkover et al. 1986; Clemen 1991; Finkel 2003; Haimes 1981; Haimes et al. 1990; Hattis and Goble 2003; Keeney 1990; Lave et al. 1988; Lave and Omenn 1986; Lind et al. 1991; Nathwani et al. 1990; Raiffa 1968; Seip and Heiberg 1989; USEPA 1984a, b; Weinstein et al. 1996); examples of the relevant tools are annotated below.

14.2.1 Cost-Effectiveness Analysis

Cost-effectiveness analysis involves a comparison of the costs of alternative methods to achieve some set goal(s) of risk reduction, such as an established benchmark risk or environmental cleanup criteria. The process compares the costs associated with different methods of achieving a specific risk management goal. All in all, the analysis involved can be used to allocate limited resources among several risk abatement programs—aimed at achieving the maximum positive results per unit cost. The procedure may also be used to project and compare total costs of several risk management plans.

In the application of cost-effective analyses to risk management actions, a fixed goal is established, and then policy options are evaluated on the ability to achieve that goal in a most cost-effective manner. The goal generally consists of attaining a specified level of ‘acceptable’ risk—with the risk management options being

compared on the basis of the monetary costs necessary to reach the benchmark risk. Cost constraints can also be imposed so that the options are assessed on their ability to control the risk most effectively for a fixed cost. The efficacy of the risk management action alternatives in the hazard reduction process can subsequently be assessed, and the most cost-effective course of action (i.e., one with minimum cost that meets the constraint of a benchmark risk/hazard level) can then be implemented. This would then guarantee the objective of meeting the overarching goal in concert with the constraints at the lowest feasible cost.

14.2.2 Risk-Cost-Benefit Optimization

Risk-cost-benefit analysis is a generic term for techniques encompassing risk assessment and the inclusive evaluation of risks, costs, and benefits of alternative projects or policies. In performing risk-cost-benefit analysis, one attempts to measure risks, costs and benefits; to identify uncertainties and potential tradeoffs; and then to present this set of information coherently to decision-makers. A general form of objective function for use in a risk-cost-benefit analysis that treats the stream of benefits, costs, and risks in a net present value calculation is given by (Crouch and Wilson 1982; Massmann and Freeze 1987):

$$\Phi = \sum_{t=0}^{T} \frac{1}{(1+r)^t} [B(t) - C(t) - R(t)] \tag{14.1}$$

where: Φ = objective function ($); t = time, spanning 0 to T (years); T = time horizon (years); r = discount rate; B(t) = benefits in year t ($); C(t) = costs in year t ($); R(t) = risks in year t ($). The risk term is defined as the expected cost associated with the probability of significant impacts or failure, and is a function of the costs due to the consequences of failure in year t. In general, tradeoff decisions made in the process will be directed at improving both short- and long-term benefits of the program.

In closing, it is noteworthy here that, subjective and controversial as it might appear to express certain hazards in terms of cost, especially where public health and/or safety is concerned, it nevertheless has been used to provide an objective way of evaluating risk management actions/problems. This is particularly true where risk factors are considered in the overall study.

14.2.3 Multi-attribute Decision Analysis and Utility Theory Applications

Multi-attribute decision analysis and utility theory have been suggested (e.g., Keeney and Raiffa 1976; Lifson 1972) for the evaluation of problems involving multiple conflicting objectives—such as is the case for a number of decisions on environmental and public health risk management programs. Indeed, environmental and public health risk management tend to be complicated and multidisciplinary in nature—such that the typical issues involved can be quite difficult to resolve analytically; multi-criteria/attribute decision analysis usually would provide a more effectual framework by which the appropriate types of critical decisions can be made. As typical in such situations, the decision-maker is usually faced with the problem of having to trade-off the performance of one objective for another. In addressing these types of problem, a mathematical structure may be developed around utility theory that presents a deductive philosophy for risk-based decisions (Keeney 1984; Keeney and Raiffa 1976; Lifson 1972; Starr and Whipple 1980).

For instance, risk tradeoffs between increased expenditure of a risk management action and the hazard reduction achieved upon implementation may be assessed by the use of multi-attribute decision analysis and utility theory methods. Multi-attribute decision analysis and utility theory can indeed be applied in the investigation and management of environmental contamination and chemical exposure problems, in order to determine whether one set of risk management action alternatives is more or less desirable than another set. With such a formulation, an explicitly logical and justifiable solution can be assessed for the complex decisions involved in environmental and public health risk management programs. In using expected utility maximization, the preferred alternative will be the one that maximizes the expected utility—or equivalently, the one that minimizes the loss of expected utility. In a way, this is a nonlinear generalization of cost-benefit or risk-benefit analysis.

On the whole, the use of structured decision support systems has proven to be efficient and cost-effective in making sound environmental and public health risk management decisions. Such tools can indeed play vital roles in improving the decision-making process. It should be acknowledged, however, that despite the fact that decision analysis presents a systematic and flexible technique that incorporates the decision-maker's judgment, it does not necessarily provide a complete analysis of the public's perception of risk. Also, it is worth mentioning here that, even though utility theory offers a rational procedure for evaluating environmental and public health risk management measures, it may transfer the burden of decision to the assessment of utility functions. Additionally, several subjective assumptions are used in the application of utility functions that are a subject of debate. Anyhow, the details of the paradoxes surrounding key conclusions derived from expected utility applications are beyond the scope of this elaboration, and are not discussed here.

14.2.3.1 Utility-Attribute Analysis

In its application to environmental contamination and chemical exposure management problems, both hazards and costs can be converted to utility values, as measured by the relative importance that the decision-maker attaches to either attribute. Attributes measure how well a set of objectives is being achieved. Through the use of multiple attributes scaled in the form of utilities, and weighted according to their relative importance, a decision analyst can describe an expanded set of consequences associated with an environmental or public health risk management program. Adopting utility as the criterion of choice among alternatives allows a multifaceted representation of each possible consequence.

Although it may conceptually be viewed as a more-or-less linear-type relationship, in practice, the utility function need not be linear since the utility is not necessarily proportional to the attribute. Thus, curves of the forms shown in Fig. 14.2 can be generated for the utility function. An arbitrary value [e.g., *0* or *1*] of *1* can be assigned to the 'ideal' situation (i.e., a 'no hazard/no cost scenario')—and the 'dooms-day' scenario (i.e., 'high hazard/high cost') is then assigned a corresponding relative value [e.g., -1 or *0*] of *0*. The shape of the curves is determined by the relative value given each attribute. The range in utilities is the same for each attribute, and attributes should, strictly speaking, be expressed as specific functions of system characteristics.

In assigning utility value to hazard, it is a commonplace to rely on various social and environmental or public health goals that can help determine the threats posed by the hazard, rather than use the direct concept of hazard. These utility values can then be used as the basis for selection among the environmental and public health risk management action alternatives.

14.2.3.2 Preferences and Evaluation of Utility Functions

Preferences are directly incorporated in the utility functions by assigning an appropriate weighting factor to each utility term. The weighting factors are changed to reflect varying tradeoff values associated with alternative decisions. For instance, if minimizing hazards is k times as important as minimizing costs, then weighting factors of $[k/(k+1)]$ and $[1/(k+1)]$ would be assigned to the hazard utility and the cost utility, respectively. These weighting factors would reflect, or give a measure of, the preferences for a given utility function. Past decisions can help provide empirical data that can be used for quantifying the tradeoffs, and therefore the k values. In the end, the given utilities are weighted by their preferences, and are summed over all the objectives. For n alternatives, the value of the i-th alternative would be determined as follows:

$$V_i = \frac{\mathrm{k}}{(\mathrm{k}+1)} U(H_i) + \frac{1}{(\mathrm{k}+1)} U(\$i) \tag{14.2}$$

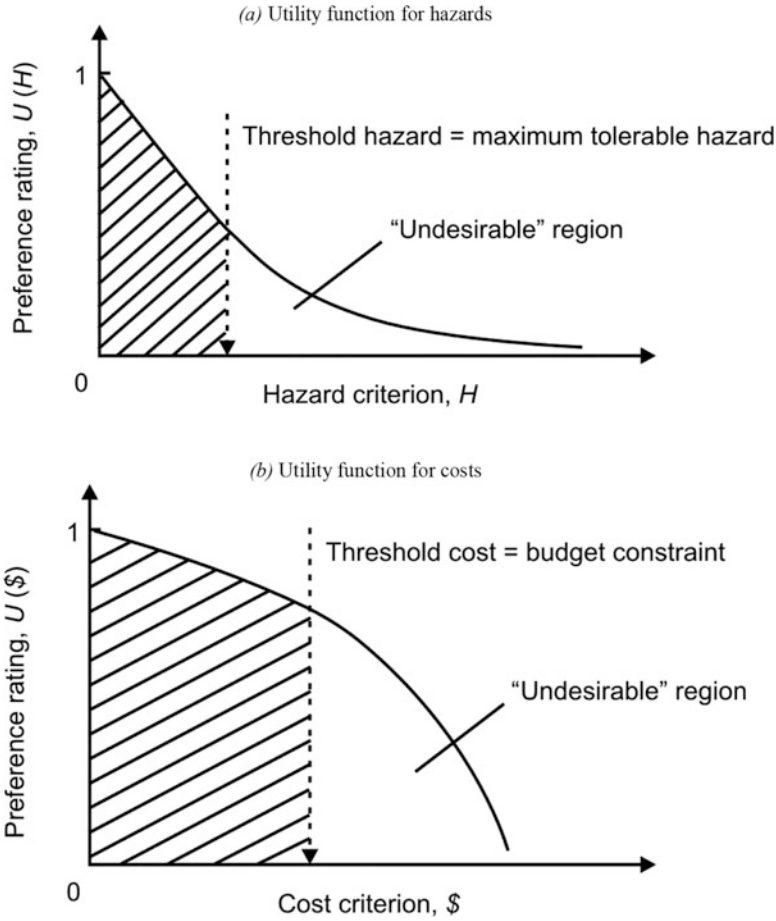

Fig. 14.2 Utility functions giving the relative values of hazards and costs in similar (dimensionless) terms. (**a**) Utility function for hazards. (**b**) Utility function for costs

where:

V_i = the total relative value for the i-th alternative
$U(H_i)$ = the hazard utility, H, for the i-th alternative
$U(\$_i)$ = the cost utility, $\$$, associated with alternative i.

In general, the largest total relative value would ultimately be selected as the best alternative.

On the whole, evaluation of utility functions requires skill, and when the utility function represents the preferences of a particular interest group, additional difficulties arise. Nonetheless, risk tradeoffs may be determined by reasonably applying weighting factors of preferences in a utility-attribute analysis.

14.2.3.3 Utility Optimization

To facilitate the development of an optimal risk management program, the total relative value can be plotted against the cost (Fig. 14.3). From this plot, the optimum cost is that cost value which corresponds to the maximum total relative value. The optimum cost is equivalently obtained, mathematically, as follows:

$$\frac{dV}{(d\$)} = \frac{d}{(d\$)}\left[\frac{k}{(k+1)}U(H) + \frac{1}{(k+1)}U(\$)\right] = 0$$
$$\text{or,} \qquad (14.3)$$
$$k\frac{dU(H)}{(d\$)} = -\frac{dU(\$)}{(d\$)}$$

where: $\frac{dU(H)}{(d\$)}$ is the derivative of hazard utility relative to cost, and $\frac{dU(\$)}{(d\$)}$ is the derivative of cost utility relative to cost. The optimum cost is obtained by solving this equation for *$*; this would represent the most cost-effective option for project execution.

In an evaluation similar to the one presented above, a plot of total relative value against hazard provides a representation of the 'optimum hazard' (Fig. 14.4). Again, this result can be evaluated in an analytical manner similar to that presented above for cost; the 'optimum hazard' is given, mathematically, by:

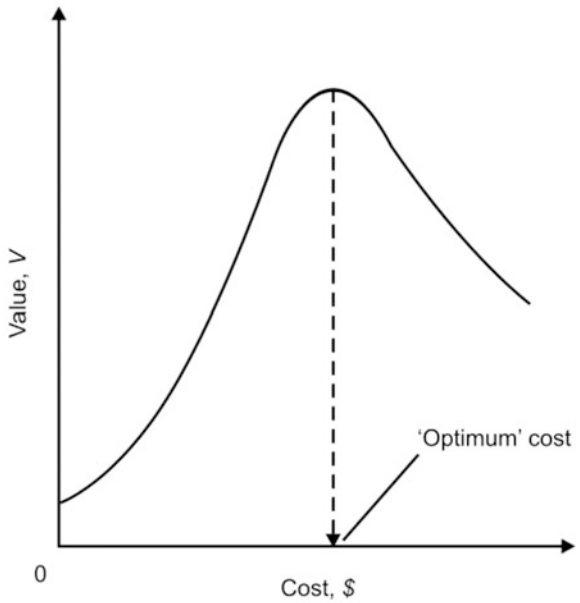

Fig. 14.3 Value function for costs

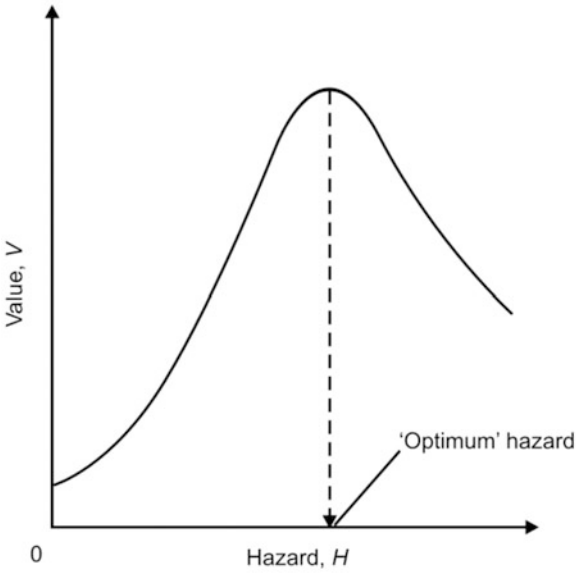

Fig. 14.4 Value function for hazards

$$\begin{aligned} &\frac{dV}{(dH)} = \frac{d}{(dH)}\left[\frac{k}{(k+1)}U(H) + \frac{1}{(k+1)}U(\$)\right] = 0 \\ &\text{or} \\ &k\frac{dU(H)}{dH} = -\frac{dU(\$)}{(dH)} \end{aligned} \tag{14.4}$$

where: $\frac{dU(H)}{(dH)}$ is the derivative of hazard utility relative to hazard, and $\frac{dU(\$)}{(dH)}$ is the derivative of cost utility relative to hazard. Solving for H yields the 'optimum' value for the hazard.

14.3 A Framework for Risk Management Programs

Risk management decisions generally consist of complex processes that involve a variety of technical, political, and socioeconomic considerations. Notwithstanding the complexity and the fuzziness of the issues involved, the ultimate goal of public health risk management programs is to protect public health—and this can be effectively accomplished in a reasonable manner. The application of risk assessment can indeed remove some of the ambiguity in the decision-making process—albeit the relationship between risk assessment and risk management can itself be quite ambiguous and disagreeable; it can also aid in the selection of prudent, technically feasible, and scientifically justifiable risk management actions that will help protect public health in a cost-effective manner. To successfully apply

the risk assessment process to a potential chemical exposure problem, however, the process must be tailored to the case-specific conditions and relevant regulatory constraints. In the end, based on the results of a risk assessment, decisions can then be made relating to the types of risk management actions needed for a given chemical exposure problem. If unacceptable risk levels are identified, the risk assessment process can further be employed in the evaluation of remedial or risk control action alternatives. This will ensure that net risks to human health are truly reduced to acceptable levels via the remedial or risk management action of choice.

Figure 14.5 provides a framework that may be used or adapted to facilitate the environmental and public health risk management decision-making process involved in chemical exposure programs. The process will generally incorporate a consideration of the complex interactions existing between the exposure setting, regulatory policies, and technical feasibility of risk management options. Ultimately, the tasks involved should help public health risk analysts to: identify, rank/categorize, and monitor the status of potential chemical exposure problems; identify field data needs and decide on the best investigation or sampling strategy; establish appropriate public health goals; and choose the risk management action that is most cost-effective in controlling or abating the risks associated with the chemical exposure problem.

In the arena of chemical exposure problems, it is noteworthy that, public health risk management decisions should typically be based on a wide range of issues relevant to a holistically-designed risk analysis—including medical opinion, epidemiology, and professional judgment, along with socioeconomic factors and technical feasibility. It is also imperative to: systematically identify hazards throughout an entire public health risk management system; assess the potential consequences due to any associated hazards; and examine corrective measures for dealing with the case-specific type of problem. Risk management—used in tandem with risk assessment—offers the necessary mechanism for achieving such goals.

14.3.1 Hazard Characterization as a Foundational Basis for Environmental and Public Health Risk Management

Hazard accounting and characterization usually represents a very fundamental activity that needs to be undertaken before any credible risk management decisions and/or actions can take place. The general purpose of a hazard characterization is to make a qualitative judgment of the effect(s) caused by an agent or stressor under consideration and its relevance to a target population of interest. In translating hazard characterization into corresponding risk value or indicator, the processes involved need to consider, among other things, the severity of critical effects and the specific affected population groups, etc.; for instance, in determining ‘safe exposure limits’ associated with human exposure to nitrate, it is important to

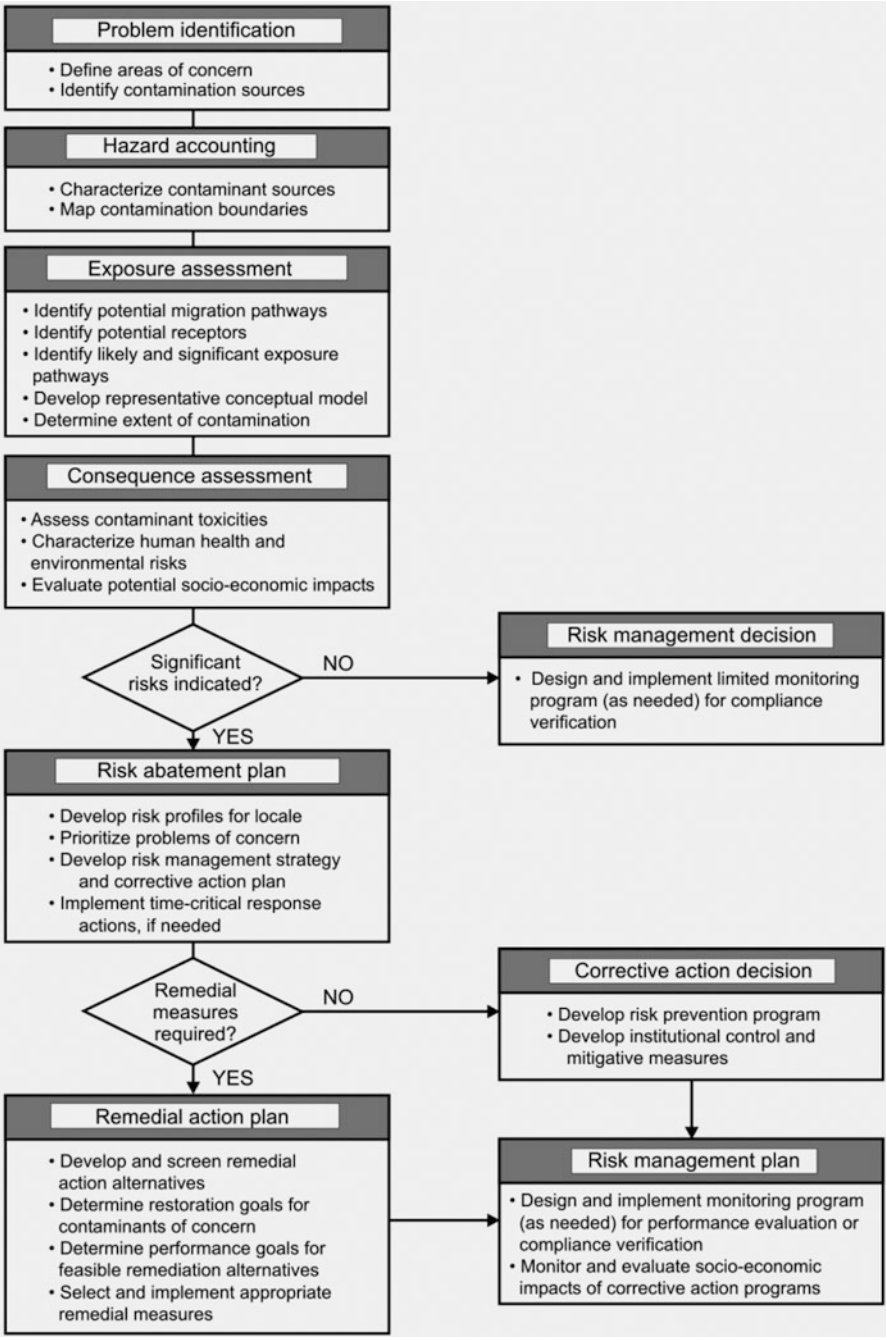

Fig. 14.5 A risk management decision framework for the management of chemical exposure problems

recognize the fact that infants are very sensitive to nitrate exposures (related to methemoglobinemia)—whereas, in general, this critical effect would not be relevant to the development of an occupational exposure limit. Overall, it is important to carefully consider the scenarios of interest (with respect to population, duration, exposure routes, etc.) in such characterization efforts—in order to arrive at realistic and pragmatic risk conclusions.

Meanwhile, it is worth the mention here that, to ensure that risk assessments are maximally useful for risk management decisions, the questions that risk assessments need to address must be raised before the process begins—also recognizing that the more complex and multifaceted the problem to be dealt with, the more important the need to operate in this manner; indeed, by focusing on early and careful problem formulation, and on the options for managing the problem, implementation of this type of paradigm or structural framework can do much to improve the utility of risk assessment (NRC 1996; NRC 2009).

In the final analysis, the levels and complexity of hazard and risk assessments (especially with regards to planning efforts and design elements) should generally be consistent with the goals of the overarching and/or anticipated decisions to be made in the long run. Indeed, one could argue that risk assessments should not be conducted unless it is clear that they are designed to answer very specific questions, and that the level of technical detail along with uncertainty and variability analysis is appropriate to the decision context; such attention to planning should probably assure the most efficient use of resources, as well as affirm the relevance of the risk assessment to decision-makers (NRC 2009).

14.4 Risk Communication as a Facilitator of Risk Management

Risk management combines socioeconomic, political, legal, and scientific approaches to manage risks. Risk assessment information is used in the risk management process to help in deciding how to best protect public health. Thus, essentially, risk assessment provides *information* on the risks—and risk management develops and implements an *action* based on that information. This means that, risk assessment can in principle be carried out objectively, whereas risk management usually involves preferences and attitudes, and should therefore be considered a subjective activity (Seip and Heiberg 1989; NRC 1983; USEPA 1984a, b). The subjectivity of the risk management task calls for the use of very effective facilitator tools/techniques—with good risk communication being the logical choice; risk communication is an interactive process or exchange of information and opinions among interested parties or stakeholders concerning risk, potential risk, or perceived risk.

Risk communication has formally been defined as the process of conveying or transmitting information among interested parties about the following types of

issues: levels of health and environmental risks; the significance or meaning of health or environmental risks; and decisions, actions, or policies aimed at managing or controlling health or environmental risks (Cohrssen and Covello 1989). It offers a forum at which various stakeholders discuss the nature, magnitude, significance, or control of risks and related consequences with one another. Effective risk communication is indeed important for the implementation of an effectual risk management program. It is therefore quite important to give adequate consideration to risk communication issues when developing a risk management agenda. As a matter of fact, in many a situation, even credible risk assessment and risk management decisions may never get implemented unless they are effectively communicated to all interested stakeholders. Thus, risk communication should be viewed as rather vital to the risk assessment and risk management processes—and, ultimately, to the success of most risk management actions.

In practice, to be able to design an effectual risk management program, a variety of qualitative issues—such as relates to sound risk communication—become equally important in addition to any prior risk quantification. Risk communication may indeed dictate public perception, and therefore public acceptance of risk management strategies and overall environmental and public health risk management decisions. One paramount goal of risk communication is to improve the agreement between the magnitude of a risk and the public's political and behavioral response to this risk—necessitating researchers to investigate a number of message characteristics and risk communication strategies (Weinstein et al. 1996; Weinstein and Sandman 1993). The process involved provides information to a concerned public about potential health risks from exposure to toxic chemicals or similar environmental hazards. In fact, because the perception of risks often differs widely, risk communication typically requires a somehow perceptive approach, and should involve genuine dialogue (van Leeuwen and Hermens 1995). Among several other factors, trust and credibility are believed to be key determinants in the realization of any risk communication goals. Apparently, defying a negative stereotype is crucial to improving perceptions of trust and credibility (Peters et al. 1997). Anyway, the literature available on the subject addresses several other important elements/issues—including checklists for improving both the process and content of risk communication efforts. Meanwhile, only limited presentation on the risk communication topic is given in this book—with more detailed elaboration/discussions to be found elsewhere in the literature (e.g., Cohrssen and Covello 1989; Covello 1992, 1993; Covello and Allen 1988; Fisher and Johnson 1989; Freudenburg and Pastor 1992; Hance et al. 1990; Kasperson and Stallen 1991; Laird 1989; Leiss 1989; Leiss and Chociolko 1994; Lundgren 1994; Morgan and Lave 1990; NRC 1989a, b; Pedersen 1989; Peters et al. 1997; Renn 1992; Silk and Kent 1995; Slovic 1993; van Leeuwen and Hermens 1995; Vaughan 1995; Weinstein et al. 1996; Weinstein and Sandman 1993).

14.4.1 *Designing an Effectual Risk Communication Program*

Several rules and guidelines have been suggested/proposed to facilitate effective risk communication (e.g., Cohrssen and Covello 1989; Covello and Allen 1988)—albeit there are no easy prescriptions *per se*. In fact, it is very important that risk communication should consider and embrace several important elements (Box 14.1)—in order to minimize or even prevent suspicion/outrage from a usually cynical public. Thoughtful consideration of the relevant elements should generally help move a potentially charged atmosphere to a responsible one, and one of cooperation and dialog. Ultimately, a proactive, planned program of risk communication will—at the very least—usually place the intended message in the public eye in advance of negative publicity and sensational media headlines. Under all circumstances, a reliable tool and channel of communication should be identified to ensure effective and timely transmittal of all relevant information. Overall, a systematic evaluation using structured decision methods—such as the use of the event tree approach (see, e.g., Asante-Duah 1998)—can greatly help in this direction. The event tree illustrates the cause and effect ordering of event scenarios, with each event being shown by a branch of the event tree in the context of the decision problem. The event tree model structure can indeed aid risk communicators in improving the quality and effectiveness of their performance and presentations.

Box 14.1 Important Strategic Considerations in Developing an Effective Risk Communication Program

- Accept and involve the public as a legitimate partner—especially all parties that have an interest or direct stake in the particular risk situation.
- Involve all stakeholders as early as possible—via taking a proactive stance, based on a coherent strategy, sound tactics, and careful planning of community relations and actions.
- Listen to your audience—recognizing communication is a two-way activity, and take note of the public's specific concerns.
- Ensure an effective two-way discourse/dialogue, to ensure adequate flow of information in both directions between the risk communication team and the interested public/parties. That is, flow of information should be from, and to all stakeholders.
- Be honest, frank, and open—since lost trust and credibility are almost impossible to regain.
- Focus should be on what the risks are, and what is already being done to keep these risks as low as reasonably possible.

(continued)

Box 14.1 (continued)

- Have an even greater focus on long-term implication of risk management decisions/strategies, without necessarily discounting potential short-term consequences.
- Have an elaborate evaluation of alternative choice of proposed risk management strategies.
- Anticipate or investigate the affected party's likely perception to the prevailing or expected risks, since this could be central to any response to proposed actions or risk management strategies.
- Speak clearly and with compassion—especially minimizing excessive use of technical language and jargon.
- Avoid use of unnecessary jargon and excessive technical details, in order to allow the community to focus on the real/practical issues of interest to the PARs.
- Anticipate controversy, request for changes to proposed risk management plans, and then offer positive response that may form a basis for consensus between all stakeholders.
- Keep the needs and perceptions of the 'outsider' stakeholders in perspective, to ensure a balanced and equitable program needs.
- Focus more on psychological needs of community, rather than economic realities/interests of project.
- Plan carefully and evaluate performance—to help re-focus, if necessary.
- Coordinate and collaborate with other credible sources—such as by issuing communication jointly with other trustworthy sources like credible university scientists, area physicians, trusted local officials, and opinion leaders.
- Meet the needs of the media—recognizing that they tend to play a critical role in setting agendas and determining outcomes.
- Clarify who the risk assessment protects—i.e., the community and/or stakeholders.
- Identify potentially overlooked stakeholder project knowledge—and incorporate such useful information in the overall strategic plan.
- Give credit for stakeholder roles and contributions in a decision—also explaining how and why stakeholder input has or has not been used in the process.

Ultimately, scientific information about health and environmental risks is generally communicated to the public through a variety of channels—ranging from warning labels on consumer products to public meetings/forums involving representatives from government, industry, the media, the populations potentially at risk, and other sectors of the general public (Cohrssen and Covello 1989). Important traditional techniques of risk communication usually consist of community public

health education programs, 'fact sheets', newsletters, public notices, workshops, focus groups, public meetings, and similar forum types—all of which seem to work very well if rightly implemented or utilized. Anyhow, irrespective of the approach or technique adopted, however, it must be acknowledged that hazard perception and risk thresholds tend to be quite different in different parts of the world—and maybe, at times, even between different communities within the same region, etc. In fact, there could also be variations within different sectors of a community or society within the same locale or region. Even so, such variances should not affect the general design principles when one is developing a risk communication program.

14.5 The Use of Contemporary Risk Mapping Tools: GIS in Public Health Risk Management Applications

A Geographic Information System (GIS) is a computer-based tool used to capture, manipulate, process, and display spatial or geo-referenced data (Bernhardsen 1992; Gattrell and Loytonen 1998; Goodchild et al. 1993, 1996). It is a tool that can serve a wide range of research and surveillance purposes; it allows the layering of health, demographic, environmental and other traditional data sources to be analyzed by their location on the earth's surface. Indeed, the GIS technology has become an important tool for public health professionals—as this generally allows for the efficacious mapping and analysis of public health and environmental management data.

It is apparent that, recent advances in the application of GIS technology have significantly improved, and will continue to revolutionize the spatial analysis of diseases, environmental contamination, and social/demographic information. In a way, the unlimited future of GIS in public health risk management is derived from comparable situations from centuries ago, whereby public health surveillance activities by health professionals have relied on maps to locate and identify changes in patterns of human disease. The GIS of today provides a relatively easy tool for overlaying and analyzing disparate data sets that relate to each other by location on the earth's surface. The growing availability of health, demographic, and environmental databases containing local, regional, national, and international information are further propelling major advances in the use of GIS and computer mapping with spatial statistical analyses.

Broadly speaking, understanding and communicating the association between environmental hazards and disease incidence are essential requirements of an effective environmental health policy. For instance, in the United States, routine public health surveillance programs generate massive amounts of information. Environmental monitoring and simulation modeling projects also provide an equally large volume of data. But, due to the lack of a coordinated framework to organize, manage, analyze, and display the data, majority of this information had been poorly utilized in the past. This is one reason why the advances in the

geospatial information technologies, such as GIS, have become so very useful in a whole wide range of public health risk management functions.

14.5.1 Utilization of GIS in Public Health Risk Assessment and Environmental Management Programs

Invariably, use of a GIS can allow for the processing of geo-referenced data and provide answers to such questions as relate to the particulars of a given location, the distribution of selected phenomena and their temporal changes, the impact of a specific event, or the relationships and systematic patterns of a region (Bernhardsen 1992). In fact, it has been suggested that, as a planning and policy tool, the GIS technology could be used to 'regionalize' (or perhaps even 'globalize') the risk analysis process—moving it from its traditional focus on a micro-scale (i.e., site-specific problems) to a true macro-scale (e.g., urban or regional risk analysis, comparative risk analysis, risk equity analysis) (D. Rejeski, in Goodchild et al. 1993).

GIS is indeed a rapidly developing technology for handling, analyzing, and modeling geographic information. It is not a source of information *per se*, but only a way to manipulate information. Overall, when the manipulation and presentation of data relates to geographic locations of interest, then our understanding of the real world is enhanced. Example application types for the utilization of GIS in environmental and public health risk management decisions are briefly discussed below.

- *Exposure Assessment of Population Groups*. The exposure assessment of population groups is usually made through the linkage of environmental and health data. However, environmental and exposure data are generally referred to scattered and instantaneous samples, while epidemiological data integrate periods of time within administrative territories. GIS can be used as an organizing tool of health and environmental data sets. For example, in a case for a water supply system, potential health risk in a locality or supply area can be examined via the overlay of information layers containing data on the presence and quality of water supply service vs. the primary georeferenced data such as: the census tract which contains information on the manner of how the household is supplied; the water distribution system; and the water quality data derived from a monitoring program. The population groups potentially at risk can then be identified, and then appropriate corrective actions can subsequently be undertaken.
- *Development of Thematic Map Layers for Risk Management*. By combining population density information with ambient concentrations for a specific chemical ($\mu g/m^3$), and the unit risk factor for that chemical ($risk/\mu g/m^3$), a map showing the risk per unit of population may be produced—that could be used to facilitate risk management decisions.

- *Data Improvement for Source/Pathway Characterization*. It is recognized that, in general, an adequate characterization of the exposure pathways that affect the fate and behavior of risk-inducing agents can help improve risk estimates significantly. Thus, more spatial data could be added to a GIS model to empirically describe the environmental medium and its effects on the distribution or dispersion of risk agents.
- *Community Health and Environmental Assessments*. GIS is an effective tool that can be used by local environmental community health departments to perform health and environmental assessments, improve public access to environmental health information, and increase organizational effectiveness and efficiency. In fact, in the daily work activities required to protect public health and welfare, environmental health departments usually collect large amounts of useful data. Much of this data has a geographic component. These data, while integral to daily environmental health tasks, can have many additional applications—especially as the field of environmental health grows more assessment-oriented. Indeed, a trend for regulatory and public health agencies to track their activities with GIS offers environmental health departments a unique opportunity to join in sharing information while serving the public's interest in health and environmental needs.
- *Potential Risk Cataloging System*. A potential risk cataloging system may be designed to serve as a screening methodology that ranks key areas of concern (e.g., hazardous facilities, industrial sectors, etc.) vis-à-vis multimedia chemical releases, chemical toxicities, and selected demographics of surrounding populations. The system can utilize GIS technologies to display vast quantities of data to assist users in cumulative risk analysis and other decision-making processes. A 'vulnerability index' is used to characterize potentially exposed populations—highlighting those that may be more vulnerable. In this manner, the screening can include population characteristics without using broad assumptions about exposure conditions. The 'chemical release index' and the 'vulnerability index' can then be overlaid to identify potential incidence of highly toxic and large release combinations within areas with relatively high percentage of vulnerable populations, or the like.
- *Characterization and Mapping of Public Health Concerns and Problems Associated with Various Industrial Sectors in a Region*. An important aspect of public health risk management with growing interest relates to the coupling of environmental health data and environmental models with information systems—such as GIS—in order to allow for effectual risk mapping of a study area. GIS can indeed be used to map the location and proximity of risk to identified or selected populations. The GIS can process geo-referenced data and provide answers to such questions as the distribution of selected phenomena and their temporal changes, the impact of a specific event, or the relationships and systematic patterns of a region. In fact, it has been suggested that, as a planning and policy tool, the GIS technology could be used to 'regionalize' a risk analysis process. For the characterization and mapping of public health concerns and problems associated with various industrial sectors, a typical study could consist

of a survey of workers and communities within major industrial bases, and an investigation of the pattern of likely environmental health problems borne by such communities. GIS can then be used to examine the spatial distribution of risks around toxic sources (such as hazardous waste sites or incinerators and smelters). This would incorporate the development of thematic map layers for public health risk management.

- *Design of Risk Reduction Strategies*. Once risks have been mapped using GIS, it may be possible to match estimated risks to risk reduction strategies, and also to delineate spatially, the regions where resources should be invested, as well as the appropriate strategies to adopt for various geographical dichotomies.
- *Utilization in Remediation Planning and Design*. GIS may be used to examine the spatial distribution of risks around toxic sources, such as hazardous waste sites or incinerators and smelters. The ability of GIS to aid in the calculation of volumes, for instance, would allow soil removal and transport costs to be estimated, and for an optimal remedial action decision to be made.
- *Investigation of Risk Equity Assurance Issues*. Considering the fact that the notion of environmental justice, based on an equitable distribution of risks, is emerging as a critical theme in environmental and public health risk decision-making, GIS could become a powerful tool of choice for exploring such risk equity issues. This type of application moves beyond simply calculating risks based on somehow abstract and subjective probabilities, and actually presents comparative analyses for all stakeholders and 'contesting' regions or neighborhoods.

In general, the evaluation of possible exposures to environmental chemicals requires the integration of information from several and various sources.Oftentimes, environmental sampling and chemical exposure data is analyzed to determine the magnitude and extent of contamination and/or human exposures; GIS provides a means of viewing spatial characteristics of such contamination or exposures. As an illustrative example, the sampling data may be overlayed with geographical features such as roads, streams, schools, and census data. During the assessment of possible exposures, a user may define locations of concern (such as areas within a groundwater plume, or areas with contaminated soil) by drawing a polygon. Environmental sampling data contained within the polygon is then summarized, and population characteristics for residents within the polygon are estimated from census data. The user may also define an exposure pathway by tying together the sampling data and population characteristics, along with other information such as the exposure route (e.g., oral ingestion), the period of time over which the exposure occurred, and characteristics of different groups within the exposed population (e.g., the body weight of children). All this information may then be used to estimate exposure doses—and subsequently, the potential for adverse health effects to occur. GIS has indeed proven to be a valuable tool during these types of evaluation. It provides the means to visually assess large quantities of environmental and public health information, and to relate that information to locations where exposures might occur. Overall, the GIS technology provides a

way to manage and analyze information—and perhaps even more importantly allows users to visualize information using combinations of different map layers.

14.5.2 The General Role of GIS Applications in Public Health Risk Assessment and Environmental Management Decisions

Every field of environmental and exposure modeling is increasingly using spatially distributed approaches, and the use of GIS methods will likely become even more widespread. Notwithstanding, it is noteworthy that models lacking a spatial component clearly have no significant use for GIS. That said, it is apparent that the specific role of environmental and exposure models integrated with GIS would largely be in their ability to communicate effectively—i.e., via the use of maps as a well-understood and accepted form of information display, as well as by generating a widely accepted and familiar format for the sharing of information (Goodchild et al. 1993). In general, the GIS would describe the spatial environment, and the environmental and risk modeling simulates the functioning of exposure processes (Goodchild et al. 1996). Thus, GIS can serve as a common data and analysis framework for environmental and exposure models. Even so, however, it must be acknowledged that, although linkage of environmental and exposure models with GIS has frequently been encountered in the past, in the majority of the cases, the GIS and environmental/risk models had not been truly integrated—but simply used together (Goodchild et al. 1993). The GIS has often been used as pre-processors to prepare spatially distributed input data, and as post-processors to display and possibly analyze model results further. Compared to maps, however, GIS has the inherent advantage that the data storage and data presentation aspects are separate. Consequently, data may be presented and viewed in a variety of ways.

Finally, it is notable that in typical application scenarios, the GIS will generally form a central framework and integrating component that provides a variety of map types for use in an overall environmental and public health risk management system. Maps or overlays include simple line features (such as residential boundaries) or complex topical maps serving as background for the spatially distributed environmental models. A simple example of such a representation is concentration fields of pollutants from air, groundwater or surface water models stored as grid cell files. Ultimately, the integration of GIS into risk assessment and environmental management programs can generally result in the following particularly important uses for GIS:

- Serves as a tool in environmental and exposure modeling;
- Serves as a tool for hazard, exposure and risk mapping; and
- Serves as a tool for risk communication.

Indeed, exposure analysis as an overlay of sources and receptor represents an almost classical GIS application. After all, GIS have the ability to integrate spatial variables into risk assessment models—yielding maps that are powerful visual tools to communicate risk information (Goodchild et al. 1993). In principle, the conceptual mapping of risk makes it much easier to communicate hazard and risk levels to potentially affected society and other stakeholders.

14.6 The General Nature of Risk Management Programs

The management of chemical exposure problems usually involves competing and contradictory objectives—with the prime objective being to minimize both hazards and risk management action costs under multiple constraints. Typically, once a minimum acceptable and achievable level of protection has been established via hazard assessment, alternative courses of action can be developed that weigh the magnitude of adverse consequences against the cost of risk management actions. Anyhow, in general, reducing hazards would tend to require increasing costs—and cost minimization during hazard abatement will likely leave higher degrees of unmitigated hazards (Fig. 14.6). At the end of the day, a decision is usually made based on the alternative that accomplishes the desired objectives at the least total cost—total cost here being the sum of hazard cost and risk management cost.

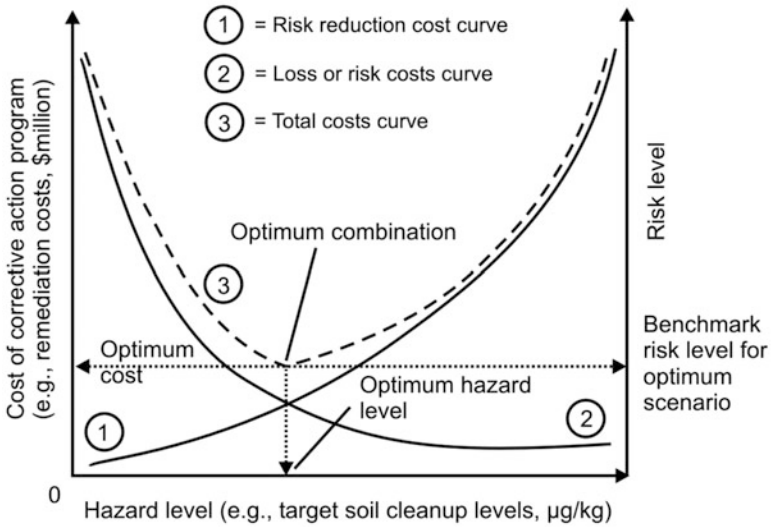

Fig. 14.6 Risk reduction vs. costs: a schematic of corrective action costs (e.g., cleanup or remediation costs) for varying hazard levels (e.g., chemical concentrations in environmental media or residual risk)

Invariably, risk management uses information from hazard analyses and/or risk assessment—along with information about: technical resources; social, economic, and political values; and regulatory control or response options—to determine what actions need to be taken in order to reduce or eliminate a risk. It is comprised of actions evaluated and implemented to help in risk reduction policies, and may indeed include concepts for prioritizing the risks, as well as an evaluation of the costs and benefits of proposed risk reduction programs. Examples of risk management actions that are commonly encountered in environmental and public health risk management programs include:

- Deciding on how much of a chemical a manufacturing company may discharge into a river;
- Deciding on which substances may be handled at a hazardous waste treatment, storage, and disposal facilities (TSDF);
- Deciding on the extent of cleanup warranted at a hazardous waste site;
- Setting general permit levels for discharge, storage, or transport of hazardous materials;
- Establishing levels for air contaminant emissions for air pollution control purposes;
- Determining allowable levels of contamination in drinking water or food;
- Deciding on the use of specific chemicals in manufacturing processes and related industrial activities;
- Determining hazardous waste facility design and operation requirements;
- Consideration of the harmful effect of chemical pollutants that need to be controlled; and
- Determining the relinquished benefits of using a pesticide or other toxic chemical.

In fact, risk management decisions associated with these types of issues are made based on inputs from a prior risk assessment conducted for the applicable case-specific problem. Ultimately, risk assessment results, serving as input to risk management, generally help in the setting of priorities for a variety of chemical exposure problems—further to producing more efficient and consistent risk reduction policies. Risk management does indeed provide a context for balanced analysis and decision-making—with public health risk management programs generally designed with the goal to minimize potential negative impacts associated with chemical exposure problems.

Chapter 15
Utility of Risk Assessment in Public Health Policy Decisions

Risk assessment has become a vital decision-making tool for informing risk managers and the public about the different prospective policy options for protecting public health and the environment; in particular, it seems to be gaining wider grounds in making public health policy decisions on the control of risks associated with human exposures to chemicals. This state of affairs may be attributed to the fact that, the very process of performing a risk assessment can lead to a better understanding and appreciation of the nature of the risks inherent in a study—and it further helps develop steps that can be taken to reduce these risks. Overall, the application of risk assessment to chemical exposure problems helps identify critical receptor exposure routes, as well as expose other extraneous factors contributing most to total risks. It also facilitates the determination of cost-effective risk reduction policies. Indeed, the risk assessment process is intended to give the risk management team the best possible evaluation of all available scientific data—in order to arrive at justifiable and defensible decisions on a wide range of issues. For example, to ensure public safety in chemical exposure situations, receptor exposures must not exceed some stipulated risk-based exposure levels or acceptable public health goals—typically established through a risk assessment process. On the whole, it is apparent that, some form of risk assessment is inevitable if public health and environmental management programs are to be conducted in a sensible and deliberate manner. Ultimately, based on the results of a risk assessment, a more effectual decision can be made in relation to the types of risk management actions that might be necessary to address a given chemical exposure problem or a hazardous situation.

Invariably, risk-based decision-making will generally result in the design of better environmental and public health risk management programs. This is because risk assessment can produce more efficient and consistent risk reduction policies. It can also be used as a screening device for the setting of policy priorities. This chapter details the general role and scope for the application of risk assessment, as pertains to the management of potential chemical exposure problems; it also

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discusses specific practical example situations for the utilization of the risk assessment paradigm.

15.1 General Role and Scope of Public Health Risk Assessment Practice

Risk assessment has several specific applications that might affect the type of decisions to be made in relation to environmental and public health risk management programs. A number of practical examples of the potential application of risk assessment principles, concepts, and techniques—including the identification of key decision issues associated with specific problems—abound in the literature of risk analysis. Some of the broad applications often encountered in chemical exposure situations include the following uses:

- Analysis of human health impacts from chemical residues found in food products (such as contaminated fish and pesticide-treated produce), as well as a variety of consumer products—including cosmetics and pharmaceuticals.
- Addressing the health and safety issues associated with environmental chemicals—i.e., to determine 'safe' exposure limits for toxic chemicals used or found in the workplace and residences.
- Facilitation of decisions about the use of specific chemicals in manufacturing processes and industrial activities.
- Implementation of general risk management and risk prevention programs for public health and environmental management planning.
- Evaluation and management of potential risks due to toxic air emissions from industrial facilities and incinerators.
- Evaluation of potential risks associated with the migration of contaminant vapors into building structures.
- Facilitation of property transactions by assisting developers, lenders, and buyers in the 'safe' acquisition of both residential and commercial properties.
- Determination of potential risks associated with industrial, commercial, and residential properties—to facilitate land-use decisions and/or restrictions.

Undeniably, the classic application of the risk assessment process to chemical exposure problems will generally serve to document the fact that risks to human health and the environment have been evaluated and incorporated into a set of applicable response actions. In fact, almost invariably, every process for developing effectual environmental and public health risk management programs should probably incorporate some concepts or principles of risk assessment. In particular, all decisions on corrective action plans for potential chemical exposure problems will include, implicitly or explicitly, some elements of risk assessment.

In the final analysis, when appropriately applied, risk assessment techniques can indeed be used to estimate the risks posed by chemical hazards under various

exposure scenarios—as well as to further estimate the degree of risk reduction achievable by implementing various scientific remedies. Invariably, a risk assessment will generally provide the decision-maker with scientifically defensible procedures for determining whether or not a potential chemical exposure problem could represent a significant adverse health and environmental risk, and if it should therefore be considered a candidate for mitigative actions. In fact, several issues that—directly or indirectly—affect public health and environmental management programs may be addressed by using some form of risk assessment.

15.1.1 Designing Effectual Risk Assessment Protocols/ Programs: Important Design Considerations and Challenges

As lucidly noted by the U.S. National Academy of Sciences, the process of risk assessment has been used to help us understand and manage a wide variety of hazards and corresponding risks that surround us in our contemporary societies; from protecting air and water to ensuring the safety of food, drugs, and consumer products (such as toys), risk assessment is considered an important public-policy tool for informing regulatory and scientific decisions—often setting priorities among research needs, and developing approaches for costs and benefits considerations of regulatory policies (NRC 2009). Still, for maximum value-addition to its utilization in risk management and related efforts, risk assessments carried out for a given program should be more closely tied to the key questions to be answered—and indeed so should the technical analyses supporting it; this, therefore, calls for a good design of the overall process—especially in the formative stages, such as in regards to the planning, scoping, and problem formulations aspects. Indeed, it has become apparent that 'planning and scoping' as well as 'problem formulation' may well constitute significantly important steps in the risk assessment process—and thus a need to incorporate these all-important elements as part of the traditional stages/elements of the risk assessment process; what is more, without adequate 'planning and scoping' and/or proper 'problem formulation', most risk assessments will not succeed in providing the type of information needed or necessary for risk management purposes—and thus fail to support credible or well-founded decisions in the long run. In fact, it appears that many of the shortcomings or failures of some past risk assessments could possibly be traced to a weakness in, or complete lack of, a problem formulation and similarly related efforts (CENR 1999; NRC 2009).

The 'planning and scoping', as well as the 'problem-formulation' stages of the risk assessment framework are indeed necessary to ensure that the general form and content of a risk assessment are determined by the nature of the target decision to be supported. Among other things, both stages offer opportunities to reach some level of consensus on how to proceed in an assessment so that its results will be useful and informative to decision-makers; those stages also offer excellent opportunities

to give risk communication an early and pivotal role in the overall risk assessment process—i.e., rather than allow it to become an afterthought (NRC 2009). Ultimately, the use of such an approach or procedural framework should allow for risk assessments that are more useful insofar as serving the risk management and/or abatement needs, and one that would generally be better accepted by decision-makers and other stakeholders.

Overall, increased emphasis on planning and scoping, as well as on problem formulation, has been shown to characteristically engender risk assessments that are more useful and better accepted by decision-makers (USEPA 2002a, b, c, d, e, f, 2003a, b, c, 2004a, b, c, d, e, f, g; NRC 2009); even so, incorporation of these stages in risk assessment oftentimes seem inconsistent in most evaluations (NRC 2009). In any event, it is noteworthy that the rather important features of planning and scoping would have to include a clear set of options for consideration in decision-making, where appropriate—and this notion ought to be reinforced by the upfront involvement of decision-makers, stakeholders, and risk assessors/analysts who, together, can gage whether the design of the assessment protocol will truly address the identified problems (NRC 2009). Thus, increased attention to the design of risk assessment in its formative stages is quite important—and which therefore calls for the proper/systematic formalization and implementation of the planning and scoping components, as well as the problem formulation elements mentioned here. Undoubtedly, the tasks of 'planning and scoping', as well as 'problem formulation' constitute key roles of design in risk assessments. In fact, it has been suggested that a more aggressive formative design stage is critical for the future success of risk assessments—with the design generally reflecting the many objectives of the decision-making function, and indeed even helping maintain this focus throughout the life cycle of the assessment (NRC 2009).

Next, it should be recognized that addressing uncertainty and variability is also a critical aspect of the overall risk assessment process [see Chap. 12]. Uncertainty stems from lack of knowledge—and thus can be characterized and managed, but not necessarily eliminated; generally speaking, uncertainty can be reduced by the use of more or better data. Variability is an inherent characteristic of a population, inasmuch as people vary substantially in their exposures and their susceptibility to potentially harmful effects of the exposures; variability generally cannot be reduced, but it can be better characterized with improved information. Anyhow, developing a consistent approach to determine the level of sophistication or the extent of uncertainty and variability analyses needed to address a particular problem situation is invariably a welcome effort—especially considering the fact that the level of detail for characterizing uncertainty tends to be adequate only to the extent that it is needed to inform specific risk management decisions appropriately (NRC 2009). On the whole, a critical challenge to risk assessment is to evaluate risks in ways that are consistent among chemicals—all the while accounting adequately for variability and uncertainty, as well as provide information that is timely, efficient, and maximally useful for risk characterization and risk management (NRC 2009).

Lastly, it is worth the mention here that, in efforts to address broader public health and environmental health questions involving multiple exposures, complex mixtures, and vulnerability of exposed populations, there is an inevitable need for the design and implementation of cumulative risk assessment protocols—i.e., evaluations that include combined risks posed by aggregate exposure to multiple agents or stressors; concurrently, the aggregate exposure would include all routes, pathways, and sources of exposure to a given agent or stressor (Callahan and Sexton 2007; USEPA 2003a, b, c; NRC 2008, 2009).

15.1.2 Illustrative Examples of Public Health Risk Assessment in Practice

In the broad applications of risk assessment to typical real-life issues, it is important to adequately characterize the exposure and physical settings for the problem situation, in order to allow for a proper application of appropriate risk assessment methods of approach. Unfortunately, there tends to be several unique complexities associated with real-life chemical exposure scenarios, and this can seriously overburden the overall process. Also, the populations potentially at risk from chemical exposure problems are usually heterogeneous—and this can greatly influence the anticipated impacts/consequences. Critical receptors should therefore be carefully identified with respect to numbers, location (areal and temporal), sensitivities, etc.—in order that risks are neither underestimated nor conservatively overestimated.

Invariably, the determination of potential risks associated with chemical exposure problems plays a rather important role in public health risk mitigation and/or risk management strategies—as demonstrated by the hypothetical example problems that follow below. Meanwhile, it is noteworthy that, risk assessments may be formulated quite differently for differing situations or circumstances—as, for example, one that might be purely qualitative in nature, and on through semi-qualitative/semi-quantitative to completely quantitative evaluations.

15.1.2.1 Evaluation of Human Health Risks Associated with Airborne Exposures to Asbestos

Processed asbestos has typically been fabricated into a wide variety of materials that have been used in consumer products (such as cigarette filters, wine filters, hair dryers, brake linings, vinyl floor tiles, and cement pipe), and also in a variety of construction materials (e.g., asbestos-cement pipe, flooring, friction products, roofing, sheeting, coating and papers, packaging and gaskets, thermal insulation, electric insulation, etc.). Notwithstanding the apparent useful commercial ascribes, asbestos has emerged as one of the most complex, alarming, costly, and tragic

environmental health problems (Brooks et al. 1995). It is notable that, there are two sub-divisions of asbestos: the serpentine group containing only chrysotile (which consists of bundles of curly fibrils); and the amphibole group containing several minerals (which tend to be more straight and rigid). Asbestos is neither water-soluble nor volatile—and so the form of concern is generally the microscopic fibers (usually reported as, or measured in the environment in units of fibers per m^3 or fibers per cc).

A case in point regarding the possibility of a target group being exposed and/or impacted arises from the fact that asbestos materials are frequently removed and discarded during building renovations and demolitions; to ensure safe ambient conditions under such circumstances, it often becomes necessary to conduct an asbestos sampling and analysis—which results can be used to support a risk assessment. This section presents a discussion of the investigation and assessment of the human health risks associated with worker exposures to asbestos in the ventilation systems of a commercial/office building.

Study Objective. The primary concern of the risk assessment for the ventilation systems in the case building is to determine the level of asbestos exposures that potential receptors (especially workers cleaning the ventilation systems) could experience, and whether such exposure constitutes significant potential risks.

Summary Results of Environmental Sampling and Analysis. Standard air samples are usually collected on a filter paper, and fibers >5 μm long are counted with a phase contrast microscope; alternative approaches include both scanning and transmission electron microscopy and X-ray diffraction. It is generally believed that fibers that are 5 μm or longer are of potential concern (USEPA 1990a, b). Anyway, following an asbestos identification survey of the case structure, air samples collected from suspect areas in the building's ventilation systems were analyzed using phase contrast microscopy (PCM), and highly suspect ones further analyzed by using transmission electron microscopy (TEM). The TEM analytical results are important because the method used provides a means for distinguishing asbestos particles from other fibers or dust particles.

On the whole, the PCM analysis produced concentration of asbestos fibers in the range of <0.002 to a maximum of 0.008 fibers/cm^3. From the TEM, chrysotile asbestos was determined to be at <0.004 structures per cm^3 (str/cm) in all the environmental air samples.

The Risk Estimation. For asbestos fibers to cause any disease in a potentially exposed population, they must gain access to the potential receptor's body. Since they do not pass through the intact skin, their main entry routes are by inhalation or ingestion of contaminated air or water (Brooks et al. 1995)—with the inhalation pathway apparently being the most critical in typically-encountered exposure scenarios. That is, for asbestos exposures, inhalation is expected to be the only significant exposure pathway. Consequently, intake is based on estimates of the asbestos concentration in air, the rate of contact with the contaminated air, and the duration of exposure. Subsequently, the intake is integrated with the toxicity index to determine the potential risks associated with any exposures.

Individual excess cancer risk is a function of the airborne contaminant concentration, the probability of an exposure causing risk, and the exposure duration. By using the cancer risk equations presented earlier in Chap. 11, the cancer risk from asbestos exposures may be estimated in accordance with the following relationship:

$$\begin{aligned}\text{Cancer Risk} = &[\text{airborne fiber concentration (fibers/m}^3)] \\ &\times [\text{exposure constant (unitless)}] \\ &\times \left[\text{inhalation unit risk } \left((100\ \text{PCM fibers/m}^3)^{-1}\right)\right]\end{aligned} \tag{15.1}$$

or,

$$\text{Risk Probability} = \text{Intake} \times \text{UR} = [\text{C}_\text{a} \times \text{INHf}] \times \text{UR} \tag{15.2}$$

The following exposure assumptions are used to facilitate the intake computation for this particular problem noted above:

- It is assumed that workers cleaning the ventilation system will complete this task within 2 weeks for a 5-day work-week. Hence, the maximum exposure duration is taken as, ED = 10 days—in comparison to a 70-year lifetime daily exposure.
- Assumed exposure time is 40 min per working hour, for an 8-hour work-day.
- Inhalation rate is 20 m^3/day (or 0.83 m^3/h).

The exposure evaluation utilizes the information obtained from the airborne fiber samples collected and analyzed during the prior air sampling activities; to be conservative, the maximum concentrations measured from the analytical results are used in the risk estimation. Thence, the fraction of an individual's lifetime for which exposure occurs—represented by the 'inhalation factor'—is estimated to be:

$$\text{INHf} = (40/60) \times (8/24) \times (10/365) \times (1/70) = 8.7 \times 10^{-5}$$

Next, asbestos is considered carcinogenic—with a suggested unit risk of approximately 1.9×10^{-4} $(100\ \text{PCM fibers/m}^3)^{-1}$ in this case (see Appendix C—Table C. 1). Consequently, potential risk associated with the 'possible' but unlikely (represented by an evaluation based on the PCM analysis results) and the reasonable/likely (represented by an evaluation based on TEM analysis results) asbestos concentrations are determined, respectively, as follows:

- Risk associated with results of the PCM analyses is estimated by properly integrating the following information:
  - PCM-based airborne fiber concentration (maximum) = 0.008 fibers/cm^3 = 8×10^3 fibers/m^3
  - INHf = 8.7×10^{-5}
  - UR = 1.9×10^{-4} $(100\ \text{PCM fibers/m}^3)^{-1} \equiv 1.9 \times 10^{-6}$ per fibers/m^3

  Hence,

$$\text{Cancer Risk (based on PCM concentration)} = 1.32 \times 10^{-6}$$

- Risk associated with results of the TEM analyses is estimated by appropriately integrating the following information:
  - TEM-based airborne asbestos concentration (maximum) = 0.004 structures/cc = 4×10^3 str/m^3
  - INHf = 8.7×10^{-5}
  - UR = 1.9×10^{-4} (100 PCM fibers/m^3)$^{-1}$ $\equiv 1.9 \times 10^{-6}$ per fibers/m^3

  Hence,

$$\text{Cancer Risk (based on TEM concentration)} = 6.6 \times 10^{-7}$$

A Risk Management Decision. All risk estimates indicated here are near the lower end of the generally acceptable risk range/spectrum (i.e., 10^{-4} to 10^{-6}). Thence, it may be concluded that asbestos in the subject building should represent minimal potential risks of concern for workers entering the ventilation system to clean up any released materials. Nonetheless, it is generally prudent to incorporate adequate worker protection through the use of appropriate respirators, etc. By and large, any asbestos abatement or removal program should indeed conform to strict health and safety requirements—with on-site enforcement of the specifications being carried out by a qualified health and safety officer or industrial hygienist.

15.1.2.2 A Human Health Risk Assessment Associated with PCB Release into the Environment

PCBs (polychlorinated biphenyls) are mixtures of synthetic organic chemicals; different mixtures can take on forms ranging from oily liquids to waxy solids. Although their chemical properties vary widely, different mixtures can have many common components. At any rate, because of their non-inflammability, chemical stability, and insulating properties, commercial PCB mixtures had been used in many industrial applications—especially in capacitors, transformers, and other electrical equipment. These same useful chemical properties, however, also contribute to the persistence of PCBs after they are released into the environment. In fact, because of the rather widespread evidence that PCBs do indeed persist in the environment and cause harmful effects, the manufacture of commercial mixtures of PCBs was halted in the late 1970s—albeit the use of existing PCBs continued beyond this date.

Overall, PCBs are absorbed through ingestion, inhalation, and dermal exposure—after which they are transported similarly through the circulation system. This provides a reasonable basis to expect similar internal effects from different routes of human exposure. Meanwhile, it is noteworthy that PCBs can ultimately persist in the body—thus providing a continuing source of internal exposure even

after external exposure stops. In fact, there may be greater-than-proportional effects from less-than-lifetime exposure, especially for persistent mixtures and for early-life exposures. It is also notable that toxic effects have been observed from acute and chronic exposures to PCB mixtures with varying chlorine content. Indeed, extensive review of various cancer studies and environmental processes leads to a conclusion that environmental PCB mixtures are highly likely to pose a risk of cancer to humans. But apart from the cancer effects, PCBs also have significant human health systemic effects—including neurotoxicity, reproductive and developmental toxicity, immune system suppression, liver damage, skin irritation, and endocrine disruption.

Problem Scenario. Consider a release of PCBs onto the ground near a lake. Potential pathways of human exposure have been determined to include: vapor inhalation; drinking water ingestion; fish ingestion; and skin contact with ambient water and contaminated soil.

The specific population group of interest here includes anglers who consume an average of two 105 g portions of local fish each week; this translates into 30 g of fish ingestion per day (i.e., [2 × 105 g per week]/7 days per week = [210/7] = 30 g per day). This target group also spends most of their time in the area—on average, breathing 20 m^3 of air, and drinking 2 L of water each day. Skin contact with ambient water and soil is assumed to be negligible for this population. Next, an 30-year human exposure duration is assumed, along with a representative lifespan of 70 years and an average body weight of 70 kg.

Environmental samples acquired for this project indicate long-term average concentrations of 0.01 μg/m^3 in ambient air, 5 μg/L in drinking water, and 110 μg/kg in the edible portion of local fish. Meanwhile, issues pertaining to dust in ambient air and sediment in drinking water are considered negligible.

The Exposure Scenarios. Three different exposure pathways are assumed for the above-noted problem situation—namely: vapor inhalation, water ingestion, and fish consumption. It is recognized here that, because of partitioning, transformation, and bioaccumulation, different fractions of the original mixture are encountered through these pathways—and hence use of different potency values should be appropriate. Vapor inhalation is associated with 'low risk' (because evaporating congeners tend to have low chlorine content, and likely susceptible to metabolism and elimination), so the low end of the range [viz., upper-bound slope of 0.4 per mg/kg day] is used for vapor inhalation (USEPA 1996a, b, c, d, e, f). Similarly, ingestion of water-soluble congeners is associated with 'low risk' (because dissolved congeners tend to have low chlorine content, and likely predisposed to metabolism and elimination)—so the low end (of 0.07 per mg/kg day) is also used for drinking water (USEPA 1996a, b, c, d, e, f). [By the way, it is noteworthy here that, if ambient air or drinking water had contained significant amounts of contaminated dust or sediment, then the high-end potency values would probably be more appropriate—since adsorbed congeners tend to have high chlorine content and persistence.] Finally, food chain exposure is more realistically associated with 'high risk' (because aquatic organisms and fish selectively accumulate congeners of high chlorine content and persistence—and these tend to be more resistant to

metabolism and elimination); thus, the high end of the range [viz., upper-bound slope of 2 per mg/kg day] is used for fish ingestion (USEPA 1996a, b, c, d, e, f).

Risk Calculation. The lifetime average daily dose (LADD) is calculated as the product of concentration (C), intake rate (IR), and exposure duration (ED)—and then divided by body weight (BW) and lifetime (LT), as follows:

$$\text{Pathway Exposure, LADD} = [\text{C} \times \text{IR} \times \text{ED}]/[\text{BW} \times \text{LT}] \tag{15.3}$$

Thence,

$$\begin{aligned}\text{Vapor Inhalation LADD} &= \left[0.01\,\mu g/\text{m}^3 \times 20\,\text{m}^3/\text{day} \times 30\,\text{year}\right]/[70\,\text{kg} \times 70\,\text{year}] \\ &= 1.2 \times 10^{-6}\,\text{mg/kg-day} \\ \text{Drinking Water LADD} &= [5.0\,\mu g/\text{L} \times 2\,\text{L/day} \times 30\,\text{year}]/[70\,\text{kg} \times 70\,\text{year}] \\ &= 6.1 \times 10^{-5}\,\text{mg/kg-day} \\ \text{Fish Ingestion LADD} &= [110\,\mu g/\text{kg} \times 30\,\text{g/day} \times 30\,\text{year}]/[70\,\text{kg} \times 70\,\text{yr}] \\ &= 2.0 \times 10^{-5}\text{mg/kg-day}\end{aligned}$$

Subsequently, for each pathway, the lifetime average daily dose is multiplied by the appropriate slope factor to arrive at the estimated risk, as follows:

$$\text{Pathway Risk} = [\text{LADD}] \times [\text{Cancer Slope Factor}] \tag{15.4}$$

Thence,

$$\begin{aligned}\text{Vapor Inhalation Risk} &= 1.2 \times 10^{-6}\,\text{mg/kg-day} \times 0.4\,\text{per mg/kg-day} \\ &= 4.8 \times 10^{-7} \\ \text{Drinking Water Risk} &= 6.1 \times 10^{-5}\,\text{mg/kg-day} \times 0.07\,\text{per mg/kg-day} \\ &= 4.3 \times 10^{-6} \\ \text{Fish Ingestion Risk} &= 2.0 \times 10^{-5}\text{mg/kg-day} \times 2\,\text{per mg/kg-day} = 4.0 \times 10^{-5}\end{aligned}$$

Thus,

$$\text{Total LADD} = 8.2 \times 10^{-5}\text{mg/kg-day}$$

and

$$\text{Total Risk} = 4.5 \times 10^{-5}$$

A Risk Management Decision. The above evaluation leads to a conclusion that fish ingestion is the principal pathway contributing to risk, and that drinking water and vapor inhalation are of lesser consequence. Indeed, in practice, it probably would be prudent to examine variability in fish consumption rates and fish tissue concentrations to determine whether some individuals are at much higher risk. In any case, it also is important to be cognizant of the fact that the specific site exposure may indeed be adding to a background level of exposure from other sources—as this could potentially sway the ultimate risk management decision to be made about this problem situation.

15.1.2.3 Determination of 'Threshold'/'Acceptable' Risk-Based Exposure Concentration for Tetrachloroethylene Within Child Daycare Center Indoor Air Environments

Because of widespread mixed uses of commercial properties in some metropolitan jurisdictions/locales in the United States, it has become apparent that some child daycare centers are co-located with, or adjacent to, dry-cleaning facilities that use tetrachloroethylene [*also known as*, perchloroethylene, Perc, or PCE] in their operational activities. Furthermore, in other situations, some child daycare centers may indeed be found in residential homes located in close proximity to mixed-use commercial properties, etc. Thus, occupants of such buildings that house child daycare centers are susceptible to the impacts of likely chemical releases originating from the commercial facilities in the neighborhood—in this case, the potential for exposure to PCE releases from dry-cleaning facilities. In fact, historically, there have been situations involving PCE releases that have permeated some child daycare center breathing environments found in a number of urban areas—and this type of scenario is probably not about to end anytime soon. Consequently, it becomes necessary to establish some 'action level guidelines' to facilitate likely response actions that might become necessary in such situations; this type of exercise is discussed in this section.

Purpose. The purpose of this effort is to offer 'threshold'/'acceptable' risk-based exposure concentration information on Tetrachloroethylene [*also known as*, Perchloroethylene, Perc, or PCE] permeating into child daycare center indoor air environments, in an urban neighborhood in the eastern US. The estimated risk-based exposure concentration could then serve as a 'cut-off'/screening level above which some form of response action may become imminent or necessary, if encountered.

Risk-based Computational Approach for Deriving 'Threshold' Concentration Values or Action Levels. Risk-based chemical exposure levels may generally be derived for various chemical exposure situations by manipulating the well-established exposure and risk models found in the risk assessment literature [see, e.g., Chaps. 9 and 11 of this volume, as well as Chap. 13]. This typically involves a 'back-calculation' process that yields a media concentration predicated on health-protective exposure parameters and chemical toxicity information; as an example,

the 'acceptable' risk-based exposure concentration will characteristically result in a non-cancer hazard index of ≤ 1 and/or a carcinogenic risk in the range of $\leq 10^{-6}$ to 10^{-4}.

Overall, since risk is a function of both the exposure to a chemical and the toxicity of that chemical, a complete understanding of the exposure scenarios together with an accurate determination of the constituent toxicity is key to developing permissible exposure levels that will be protective of human health—as reflected in discussions below. Ultimately, the target risk-based exposure concentrations are typically established for both the carcinogenic and non-carcinogenic effects of the constituents of concern—with the more stringent value usually being selected as a 'public health criterion' or 'threshold concentration'; frequently (but not necessarily always), the carcinogenic limit tends to be more stringent in most situations, where both values exist.

Toxicity Information on PCE: PCE exhibits both carcinogenic and non-carcinogenic effects upon exposure via a variety of exposure routes. Consequently, important threshold concentrations should generally be reviewed by considering both tendencies.

Regarding the noncarcinogenic effects of tetrachloroethylene (PCE), the US EPA has calculated a Reference Concentration (RfC) of 0.04 milligrams per cubic meter (0.04 mg/m^3) based on neurotoxicity in occupationally-exposed adults; the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious noncancer effects during a lifetime. It is not an estimator of risk but rather a reference point to gauge the potential for effects. At exposures increasingly greater than the RfC, the potential for adverse health effects increases. In any event, lifetime exposure above the RfC does not necessarily imply that an adverse effect would occur.

As to the potential cancer effects, the US EPA has classified PCE as likely to be carcinogenic to humans by all routes of exposure based on suggestive evidence in epidemiological studies and conclusive evidence in rats (mononuclear cell leukemia) and mice (increased incidence of liver tumors). [It is noteworthy here that the International Agency for Research on Cancer (IARC) has also classified PCE as probably carcinogenic to humans (Group 2A).] The US EPA uses mathematical models, based on animal or human studies, to estimate the probability of a person developing cancer from breathing air containing a specified concentration of a chemical; in this case, the US EPA has derived an inhalation unit risk estimate of 2.6×10^{-7} $(\mu g/m^3)^{-1}$ for PCE. In fact, the US EPA estimates that, if an individual were to continuously breathe air containing PCE at an average of 4 $\mu g/m^3$ (4×10^{-3} mg/m^3) over his or her entire lifetime, that person would theoretically have no more than a one-in-a-million increased chance of developing cancer as a direct result of breathing air containing this chemical. Similarly, the US EPA estimates that continuously breathing air containing 40 $\mu g/m^3$ (4×10^{-2} mg/m^3) would result in no greater than a one-in-a-hundred thousand increased chance of developing cancer, and air containing 400 $\mu g/m^3$ (4×10^{-1} mg/m^3) would result in not greater than a one-in-ten thousand increased chance of developing cancer.

Anyhow, the most recent IRIS toxicity values are used in this presentation to derive target risk-based exposure concentration for indoor air contaminated by PCE. [See also, Appendix C—Table C.1.]

Modeling Scenarios and Assumptions: The following exposure scenarios are utilized to provide a range of possible threshold concentration values or action levels for PCE potentially present within child daycare center indoor air environments:

1. General 'Commercial-Based' Daycare for Children Aged 0–6 years, Under 'Chronic Conditions';
2. 'Residential-Based' Child Daycare, Under 'Chronic Conditions';
3. General 'Commercial-Based' Daycare for Children Aged 0–6 years Under 'Sub-Chronic Conditions'; and
4. 'Residential-Based' Child Daycare, Under 'Sub-Chronic Conditions'.

The following corresponding key exposure assumptions are utilized to provide a range of possible threshold concentration values or action levels for PCE potentially present within child daycare center indoor air environments:

(a) Exposure frequency—assumed to be 250 days per year for a general 'commercial-based' child daycare center, and 350 days per year for a 'residential-based' child daycare center;
(b) Exposure duration—assumed up to 6 years for a general 'commercial-based' child daycare center, and up to 30 years for a 'residential-based' child daycare center; and
(c) Exposure time—assumed 8 h per day for a general 'commercial-based' child daycare center, and up to 24 h per day for a 'residential-based' child daycare center.

Modeling Approach: Typically, carcinogenic risks and noncarcinogenic hazards may be calculated according to the following general equations:

$$\text{Risk} = \frac{\text{PCE}_{\text{air}} \times \text{URF} \times \text{EF} \times \text{ED} \times \text{ET}}{\text{AT} \times 365 \frac{\text{day}}{\text{year}}} \times 1000 \mu g/\text{mg} \tag{15.5}$$

and

$$\text{HQ} = \frac{\text{PCE}_{\text{air}} \times \ 10^3 \frac{\mu g}{\text{mg}} \times \text{EF} \times \text{ED} \times \text{ET}}{\text{RfC} \times \text{AT} \times 365 \frac{\text{day}}{\text{year}}} \tag{15.6}$$

where:

Risk = probability of contracting cancer (unitless)
HQ = hazard quotient or non-cancer risk (unitless)
PCE_{air} = threshold/acceptable indoor air concentration of PERC ($\mu g/m^3$)—e.g., for a child daycare center occupant
URF = chemical-specific unit risk factor $(\mu g/m^3)^{-1}$

RfC = chemical-specific reference concentration (mg/m^3)
EF = exposure frequency (day/year)—e.g., assumed 250 days per year for a typical child daycare center
ED = exposure duration (year)—e.g., assumed 5 years for a typical child daycare center
ET = exposure time (h/day)—e.g., assumed 8 h per day for a typical child daycare center
AT = averaging time (days)—365 days × ED

By rearranging and 'manipulating' the above risk equations, the target risk-based exposure concentration, PCE_{air}, may be appropriately derived to represent the 'acceptable/threshold concentration' for human health protection.

Modeling Results: Two fundamentally similarly-designed models that can assist in calculating site-specific screening levels—namely: (1) the "Risk Assessment Information System (RAIS) Preliminary Remediation Goals (PRGs) Calculator" [from Oak Ridge National Laboratory (ORNL)], and (2) the "RSL/Screening Level Calculator" [from US EPA]—were both adapted and utilized in the evaluation scenarios presented here, in order to offer 'comparative verification' of the output of risk-based concentrations generated herein. The outcomes—i.e., the estimated risk-based threshold/acceptable concentration of PCE for child daycare center exposures—are summarized in tabular presentations shown below for both chronic and sub-chronic exposure conditions, relative to the general exposure scenarios and assumption stated above.

Scenario 1 Risk-based threshold concentration of PCE for child daycare center exposures under '*Chronic Conditions*'

Risk group	Threshold/acceptable concentration (μg/m^3)			
	Target HQ = 1	Target cancer risk = 1×10^{-6}	Target cancer risk = 1×10^{-5}	Target cancer risk = 1×10^{-4}
Type I: general daycare for children aged 0–6 years	**175**	197	1970	19,700
Type II: 'Residential' child daycare	**41.7**	**9.36**	93.6	936

NB: Bolded numerals represent the estimated 'trigger concentration/level' for possible imminent response action.

Scenario 2 Risk-based threshold concentration of PCE for child daycare center exposures under '*Sub-Chronic Conditions*'

Risk group	Threshold/acceptable concentration (μg/m^3)			
	Target HQ = 1	Target cancer risk = 1×10^{-6}	Target cancer risk = 1×10^{-5}	Target cancer risk = 1×10^{-4}
Type I: general daycare for children aged 0–6 years	**175**	197	1970	19,700
Type II: 'Residential' child daycare	**41.7**	**9.36**	93.6	936

NB: Bolded numerals represent the estimated 'trigger concentration/level' for possible imminent response action.

It is apparent that the evaluation in this case produced the same risk-based concentrations for both the chronic and sub-chronic exposure conditions. However, a 'residential-type' child daycare center would tend to require lower threshold levels for indoor air impacted by PCE, i.e., in comparison to a 'commercial-based' child daycare center.

Conclusions and Recommendations. It is understandable that a 'residential-based' child daycare center would produce the most conservative evaluation scenario, and thus generate the most stringent risk-based concentrations—i.e., in comparison to a typical 'commercial-based' child daycare center.

For a 'commercial-based' child daycare center, a PERC trigger concentration of approximately 175 $\mu g/m^3$ (corresponding to a HQ of unity) may serve as a 'cut-off'/screening level above which some form of response action should probably become imminent or necessary.

For a 'residential-based' child daycare center, a PERC trigger concentration of approximately 9 $\mu g/m^3$ (corresponding to a target cancer risk of 10^{-6}) may serve as a 'cut-off'/screening level above which some form of response action may become imminent or necessary—i.e., assuming the utilization of a generally acceptable risk level of 1×10^{-6} in the risk management decision. However, under less stringent acceptable risk criterion of 1×10^{-5} or higher, a PERC trigger concentration of approximately 42 $\mu g/m^3$ (corresponding to a HQ of unity) would become the 'cut-off'/screening level above which some form of response action could become imminent or necessary. Regardless, it may be important to integrate a 'life cycle assessment/thinking' into any overall (anticipated) regulatory program directed at managing these types of potential exposure scenarios, in order for an effective implementation strategy to become feasible.

Finally, it is noteworthy that, there has been an increasing awareness in recent years that children may be more susceptible than adults to the harmful effects of air pollutants—and thus the key focus here being on the potential child exposures as a basis for establishing a trigger action level in this case. After all, among other things, children are often more susceptible to the health effects of air pollution because their immune systems and developing organs are still immature.

15.2 The Public Health Risk Assessment Paradigm in Practice: Illustrative Examples of Public Health Study Designs

In our attempts to shape public health risk management policy decisions, one must appreciate what Rachel Carson notes in her book, *Silent Spring*, that: "As the tide of chemicals born of the Industrial Age has arisen to engulf our environment, a drastic change has come about in the nature of the most serious public health problems" (Carson 1962, 1994). Indeed, chemicals have become an integral part of modern ways of life—with the capacity to improve as well as endanger public health.

Globally, the general population is typically exposed to chemicals in air, water, foods, cosmetics, household products, and a variety of therapeutic drugs. In everyday life, a person may experience a multitude of exposure to potentially toxic substances, singly and in combination, and both synthetic and natural. Levels of exposure tend to vary and may or may not pose a hazard—depending on the dose, route, and duration of exposure. The consequences of human exposure to chemicals have therefore become (or should become) a very important driving force in public health policy decisions. To effectively address this situation, the traditional approach to dealing with public health risk management issues may not suffice in this day and age. Contemporary risk assessment methods of approach may therefore be used to facilitate the design of more reliable public health risk management strategies/schemes. But it must also be recognized that, a given risk assessment provides only a snapshot in time (and indeed in space as well) of the estimated risk of a given toxic agent at a particular phase of our understanding of the issues and problems. What is more, as Moeller (1997) points out, unless care is exercised and all interacting factors are considered, risk assessments directed at single issues, followed by ill-conceived risk management strategies, can create problems worse than those the management strategies were designed to correct. The single-issue approach can also create public myopia by excluding the totality of alternatives and consequences needed for an informed public choice (Moeller 1997). Indeed, to be truly instructive and constructive, therefore, risk assessments will usually be conducted on an iterative basis—being updated as new information and knowledge become available. Ultimately, it is quite important to examine the total system to which a given risk assessment is being applied.

In the end, it is expected that there will be growing applications of the risk assessment paradigm to several specific chemical exposure problems—and this could affect the type of decisions made in relation to public health risk management programs. Such applications may cover a wide range of diverse problem situations—as exemplified by the illustrative application scenarios annotated below. This listing of public health study designs is by no means complete and exhaustive, since variations or even completely different and unique problems may be resolved by use of one form of risk assessment principle and methodology or another.

- *Investigation of blood lead (Pb) distribution amongst population groups*. This type of public health risk assessment study may be used to help determine the likely impacts of Pb exposures on various population groups.
  - *Study Rationale*. For young children, Pb can cause lower levels of intelligence, behavioral problems, and school failures. In fact, among others, contemporary studies conducted by the Harvard School of Public Health in the United States have determined that, a woman's lead exposure during pregnancy can threaten the fetus' nervous system and other developing organs. Also, it has been noted that women of child-bearing age who were exposed to lead as children usually will have this lead accumulated in their bones, threatening the health of their babies many years later. The pre-natal exposure scenario is articulated as follows: if a little girl is exposed to lead,

the lead is stored in her bones as she grows, and when she becomes a pregnant adult, the lead moves from her bones—exposing her fetus to lead. Furthermore, lead acquired pre-natally can contribute to the lead burden in young children, implying a potential concern for pregnant women. Further yet, fairly recent studies (e.g., Tellez-Rojo et al. 2002) designed to evaluate the impact of breast-feeding on the mobilization of lead from bone seem to confirm the hypothesis that lactation stimulates lead release from bone to blood. Lactation has indeed been recognized as a powerful stimulus for bone resorption; thus, Pb accumulated in bone from past exposures may be released into the bloodstream and excreted in breast milk, constituting an important source of lead exposure for the breast-fed infant (see, e.g., Silbergeld 1991; Tellez-Rojo et al. 2002). Also of significant interest, reasonably recent studies document the impact of low level lead exposure on blood pressure in adults (Schwartz 1991). The significance of investigating lead exposure to a community can therefore not be underestimated, since it will ultimately threaten infant development as well as adult welfare.

- *Scientific Design*. A classic study may be designed to determine the presence of, and the degree of population group exposures and impacts in different regions. The study may document results with respect to gender differences, age categories and even the different socioeconomic classes of a community.
- *Significance of Study*. Considering the frequent occurrence of lead in several environmental settings, and in view of the dangers associated with lead exposures—especially to children—it is important to adequately document this kind of information, and then help develop strategies to deal with likely problems associated with the lead contamination and exposure situations.

  It is noteworthy that Pb is naturally occurring, but often is released into the environment from a variety of human-made sources; it has indeed been mined, smelted, refined, and used for hundreds of years. For example, Pb has been used as an additive in paint and gasoline, and in leaded pipes, solder, crystal, and ceramics. Mining, smelting, and refining activities have resulted in substantial increases in Pb levels in the environment, especially near mining and smelting sites, near some types of industrial and municipal facilities, and adjacent to highways. In general, Pb particles in the environment can attach to dust and be carried long distances in the air. Such Pb-containing dust can be removed from the air by rain and deposited on surface soil, where it may remain for many years. In addition, heavy rains may cause Pb in surface soil to migrate into ground water and eventually into water systems. Given its widespread distribution, everyone is potentially exposed to 'background' levels of Pb. In fact, there are many possible ways to be exposed to Pb—including ingestion of Pb-contaminated water, soil, paint chips, and dust; inhalation of Pb-containing particles of soil or dust in air; and ingestion of foods that contain Pb from soil or water.

  Pb poisoning is indeed a particularly insidious public health threat because there may be no unique signs or symptoms. Early symptoms of Pb exposure may include persistent fatigue, irritability, loss of appetite, stomach

discomfort, reduced attention span, insomnia, and constipation. Failure to treat Pb poisoning in the early stages can cause long-term or permanent health damage, but because of the general nature of symptoms at this stage, Pb poisoning is often not suspected. In adults, Pb poisoning can cause irritability, poor muscle coordination, and nerve damage to the sense organs and nerves controlling the body. It may cause increased blood pressure, hearing and vision impairment, and reproductive problems (such as a decreased sperm count). It also can retard fetal development even at relatively low levels of Pb. In children, Pb poisoning can cause brain damage, mental retardation, behavioral problems, anemia, liver and kidney damage, hearing loss, hyperactivity, developmental delays, other physical and mental problems, and in extreme cases, death. Although the effects of Pb exposure are a potential concern for all humans, young children (0–7 years old) are the most at risk. This increased vulnerability results from a combination of factors—particularly the following:

- Children typically have higher intake rates per unit body weight for environmental media such as soil, dust, food, water, air, and paint, than adults since they are more likely to play in dirt and to place their hands and other objects in their mouths;
- Children tend to absorb a higher fraction of ingested Pb from the gastrointestinal tract than adults;
- Children tend to be more susceptible to the adverse neurological and developmental effects of Pb than adults; and
- Nutritional deficiencies of iron or calcium, which tend to be prevalent in children, may facilitate Pb absorption and exacerbate the toxic effects of Pb. Indeed, it is reasonably well-established that iron deficiency tends to be associated with increased blood lead levels. Conversely, certain vitamins and minerals—especially calcium, iron and vitamin C—play a specific role in minimizing lead absorption.

Finally, it is notable that the typical blood Pb level of significant concern in children has for some time been 10 micrograms (μg) of Pb per deciliter (dL) of blood (i.e., 10 μg/dL). However, since adverse effects may occur even at far lower levels than previously thought, various agencies [e.g., the US Centers for Disease Control and Prevention's Advisory Committee for Childhood Lead Poisoning Prevention] had been considering whether this level should be lowered further—resulting a in a more recent recommended 'cut-off' level or 'elevated blood lead level of significant concern' being set at 5 micrograms (μg) of Pb per deciliter (dL) of blood (i.e., 5 μg/dL) [called the '*blood lead level reference value*']. Indeed, since no safe blood lead level in children has been identified per se, a so-called 'blood lead level of concern' cannot necessarily be used to truly define individuals in need of intervention; consequently, the best way to stop childhood lead poisoning is to prevent, control, or eliminate lead exposures in the first place.

- *Assessment of risks from chemical contaminants in nursing mothers' breast milk.* This kind of archetypical public health risk assessment study may be designed to help determine the potential chemical exposure risks associated with the breast-feeding of infants.
  - *Study Rationale*. It is apparent that human breast milk is an important primary source of infant nutrition—especially in most developing countries. But a number of investigations into the levels of chemical contaminants in human milk in some locales elucidate the potential risks of such contaminants to the health of breast-fed infants—and who are indeed more susceptible to chemical exposure effects. With that in mind, vis-à-vis the fact that 'child welfare' establishments or institutions have been encouraging mothers to breast-feed more often, the question needs to be raised as to whether this is always 'safe' for all children—especially considering the fact that some nursing mothers may have high accumulation of dangerous environmental chemicals in their breast milk, and also recognizing that pre-natal exposures to PCBs in foods, etc. can be passed on to newborn infants.
  - *Scientific Design*. An archetypical study may be so-designed to identify and quantify the presence and levels of select chemicals (e.g., Pb, PCBs, dioxins, and organochlorine pesticides such as DDT, dieldrin, lindane, aldrin, hexachlorobenzene, chlordane, etc.) in mothers' milk for nursing mothers in different locales, and from different socioeconomic classes of a community. Subsequently, the toxicological implications to the health status of both the nursing mother and the breast-fed infants can be determined.
  - *Significance of Study*. The toxicological implications derived from this study can become a very important guide for health care providers—especially at post-natal health care facilities.
- *Analysis of human health impacts from chemical residues in food and consumer products.* This type of public health risk assessment study may be designed to help determine the potential risks associated with population exposures to chemical residues that might be present in food (including contaminated fish and pesticide-treated produce) and a variety of consumer products.
  - *Study Rationale*. It is almost indisputable that all peoples around the world consume a whole variety of plant and animal products, some of which have—directly or indirectly—been exposed to chemical substances at one time or another. Also, a variety of consumer products abound on the world markets today—some of which have questionable origins, and several containing potentially toxic chemicals.
  - *Scientific Design*. A prototypical study may be so-designed in a manner that consists of an investigation into the occurrence, and the measurement of the levels of selected chemical contaminants (including organochlorine pesticides residues and various inorganic chemicals) that may be present in typical staple food products of the average person in a case-study area—especially relating to fish, meat, and chicken eggs. In implementing this type of

program, food samples can be collected and analyzed for selected chemical contaminants warranting investigation for the particular setting/location. Also, information can be collected on food consumption patterns of the various communities to facilitate realistic risk assessments. The relevant studies may also consist of an investigation into the types of toxic chemicals found in selected consumer products (such as hair products, skin care products, processed and canned food items, etc.) commonly found on the market for a case-study area—especially for those with widespread usage among various sectors of society. Based on an examination of the consumer use patterns and exposures, risks to human health from the widely used consumer products may be determined. As part of this kind of study, a comparative look can be made for the urban populace vs. the rural dweller, etc.

- *Significance of Study*. Results of this type of investigation can help develop an effectual public health education and awareness program about the potential harms from toxic chemicals—such as PCBs and DDT—potentially present in common food and various other consumer products finding widespread use in a region. It can also help national or regional governments in establishing long-term national food contamination monitoring program—as part of the comparable United Nations/WHO programs.

- *Investigating the health impacts of mining activities on a community*. This type of public health risk assessment study may be used to help determine the potential impacts associated with mining activities.

  - *Study Rationale*. As part of the recent economic rejuvenation programs in a number of nations, mining activities seem to have become one of the most popular ventures attracting a wide spectrum of investors. But even long before the recent additions to the mining sector, in some regions (especially in the newly emerging economies), environmental degradation from mining activities has always been a critical but neglected issue.
  - *Scientific Design*. A comprehensive tiered study may be so-designed that consists of both general and specific investigations of the health implications of the various mining sectors in the case region. This study may also include a look at the distribution of likely health problems associated with the different mining sectors and communities. For the mining communities selected for more detailed investigations, attention could be focused on issues such as water quality problems, levels of various chemicals in the blood of the target populations, etc. that are postulated or believed to be associated with particular mining activities. For example, mercury will generally be of particular interest in the gold-mining areas (since it is often used to extract gold); this becomes even more important in situations where when fishing streams can be found within the watershed. Also, the study may be so-designed to cover all seasons, in order to ensure accurate measurements and that will assure effective policy decisions. Among other things, the complete seasonal investigation is deemed necessary, in part because, as an example, certain studies by some Canadian scientists in the Brazilian Amazon found a link between

the seasons and methyl mercury (a highly toxic form of mercury created when the metal is released into streams and modified by bacteria) levels found in a village population in that region; in that case, it was proven that the contamination levels in the Amazon were highest during the rainy season. Whereas this seasonal variation in contaminant levels may not be universally true, it will seem prudent to extend such types of investigation to cover all the seasons—at least to give representative database for statistical analysis purposes.

For practicability, this type of somewhat extensive project can be carried out in phases—albeit each phase can be designed to yield project outputs/results that can individually be used to make important public health policies and to guide risk management programs. For example, a 'Phase 1' may consist of a survey to identify the prominent types of toxic chemicals found to originate from mining activities; the collection of chemical and exposure data, based on the nature of mining activities; and a statistical compilation of common health problems in the target communities. The information from this initial phase can be analyzed (both qualitatively and quantitatively) in order to determine the potential risks to the exposed populations. A 'Phase 2' may aim at collecting specific material samples that can undergo appropriate laboratory analyses (to facilitate a more accurate quantification of the likely risks to populations exposed to mining-related environmental chemicals under a variety of conditions). The 'Phase 2' sampling program may involve taking blood and other biomarker samples from representative residents of the target community, to be analyzed for the suspect chemicals of concern, and also the sampling and analysis of potable water supplies and selected dietary/farm produce of the target communities.

- *Significance of Study*. Results from each of the project phases can be used to design appropriate mitigative and public health risk management programs in relation to the impacts of mining activities on various sectors of the populations in the study locale. The results of the study can also be used to help develop effectual corrective measures for current and future mining practices in a locale or region. Ultimately, such a project can be expected to help improve risk mitigation and public health risk management programs associated with mining activities in a region.

- *Health implications of pesticide use in agricultural communities*. This type of public health risk assessment study may be used to facilitate public policy decisions on pesticide applications.

  - *Study Rationale*. The pervasive use of a wide range of chemical pesticides seems to be an inescapable aspect of much of modern agricultural practice worldwide. But then, such increased use of pesticides is of grave concern due to their potential effects on human health. In fact, the situation is particularly worrisome in the newly emerging economies, where lesser protective measures are generally taken, and also where reliable data on the population exposures to pesticides (and indeed several other environmental and 'social'

chemicals) is lacking. As has been affirmed by the World Health Organization (WHO) and the United Nations Environment Programme (UNEP), pesticides currently in use tend to involve a wide variety of chemicals—with great differences in their mode of action, uptake by the body, metabolism, elimination (from the body), and toxicity to humans. Also, it seems like an undisputed fact that, the health effects will depend on the health status of the individual exposed. Thus, malnutrition and dehydration—situations fairly prevalent in developing economies in particular—are likely to increase sensitivity to pesticides. In addition, several environmental factors—such as temperature and humidity—will tend to affect the absorption of pesticides by exposed individuals.

– *Scientific Design*. A typical research study that could be designed for this kind of scenario may consist of both general and specific investigations with respect to the health implications of pesticide use in the selected agricultural (or other pesticide applicator) communities. For instance, the levels of pesticides in potentially exposed farmers can be investigated. The study may also cover issues such as recorded miscarriages and the prevalence of birth defects in the target region, in order to determine any possible association with pesticide usage in particular communities.

  As part of the overall program, information can be collected on the pesticide use/application patterns for major farming communities. Blood samples can be collected from farmers and surrogates, and analyzed for organochlorine pesticide residues, and indeed other related chemical contaminants warranting investigation for the particular setting/location. The study can also include an investigation of possible pesticide contamination of rural drinking water supplies located near farmlands, etc.

  Indeed, such type of project may be carried out in phases—albeit each phase can be designed to yield project outputs/results that can individually be used to make important public health policies, and to guide broader risk management programs. For example, in a two-phase design, ‘Phase 1’ may consist of a survey to identify the prominent types of pesticides in general use; the collection of chemical and exposure data, based on the pesticide use patterns; and a statistical compilation of common health problems in the target communities. The information from this initial phase can be analyzed (both qualitatively and quantitatively) in order to determine the potential risks to the exposed populations. ‘Phase 2’ may then aim at collecting specific material samples that can undergo appropriate laboratory analyses (to facilitate a more accurate quantification of the likely risks to populations exposed to pesticides under a variety of conditions). The ‘Phase 2’ sampling program may, for example, involve taking blood and other biomarker samples from farmers, to be analyzed for organochlorine pesticide residues—and perhaps the sampling and analysis of potable water supplies and selected dietary/farm produce of the target communities as well. Results from each of the project phases can then be used to design appropriate mitigative and

public health risk management programs in relation to pesticide usage in the region.
  - *Significance of Study*. Results from such a study can be used to help develop an effectual public education program about the potential harms from pesticide usage in region, by providing a basis for public education on pesticides use. Ultimately, such a project can be expected to help improve risk mitigation actions and public health risk management programs involving pesticide usage in a region, particularly for the 'pesticide applicator' areas.

- *Evaluation of selected urban occupational worker exposure risks*. So many innocent and unsuspecting workers in numerous countries are exposed to a variety of toxic substances on a daily basis—but most of these likely represent preventable situations, achievable by possibly using appropriate protective equipment and clothing. In fact, chronic worker exposure for select categories of workers who often work with dangerous chemicals without personal protective tools/equipment/clothes is becoming an even more serious problem in a number developing and newly industrializing countries—especially because of the mushrooming of several small businesses and mini-industries.
  - *Study Rationale*. A study may be undertaken that consists of an investigation into the types of toxic chemicals widely used in consumer products (such as hair products, select food items, etc.); examination of the consumer use patterns and exposures (to include chronic worker exposure for select categories of workers who often work with dangerous chemicals without personal protective tools/equipment/clothes); and the assessment of human health risks from the use of various consumer products commonly found on the market in the region of concern, and that have widespread use among various sectors of society.
  - *Scientific Design*. Typically, the study will focus on select 'high-risk' urban occupational groups—to include, e.g., hairdressers and beauticians (for various chemicals found in cosmetics, etc.); auto mechanics/automotive shop workers (for various solvents and metals); and fuel station attendants (especially for benzene and possible fuel additives)—all of whom are exposed to specific chemicals on an almost daily basis. The study may consist of an investigation into occupational hazards associated with the types of toxic chemicals widely used by these worker groups.
  - *Significance of Study*. Results from this study can help develop an effectual public education program and worker protection campaign about the potential harms from toxic chemicals often encountered by various worker groups.

- *Morbidity effect of particulate matter (PM) exposures: an epidemiologic study of the human health effects from ambient particulate matter*. Epidemiologic studies that link population ambient PM exposures to adverse health effects can provide an indication of the measurable excesses in pulmonary function decrements, respiratory symptoms, hospital and emergency department

admissions, and indeed mortality associated with ambient levels of $PM_{2.5}$, PM_{10}, and other probable indicators of PM exposures.

- *Study Rationale*. Epidemiology studies can be used to establish causal inferences about PM health effects. Subsequently, the causal inference methodology can play a key role in evaluating the effectiveness of proposed interventions (such as changes in regulatory standards for ambient PM). Ultimately, this would help clarify the predicted effect of reductions in ambient PM on public health.
- *Scientific Design*. Typically, epidemiologic studies are divided into *morbidity studies* and *mortality studies*. In general, the morbidity studies would include a wide range of health endpoints—such as changes in pulmonary function test, reports of respiratory symptoms, self-medication in asthmatics, medical visits, low birth-weight infants, and hospitalization.

  A typical study design may consist of the so-called 'cross-sectional' studies—that evaluates subjects at a 'point' in time, where measurements of health status, pollution exposure, and individual covariates are observed simultaneously. In general, studies with individual-level outcome data, covariates, and PM exposure indices should be preferred—albeit individual-level exposure data are the most commonly missing component. Anyhow, in this type of study, the hypothesis being tested will consist of the null hypothesis, H_0: exposure to ambient PM at current levels cannot cause adverse health effects in susceptible sub-populations or individuals vs. the alternate hypothesis, H_A: exposure to ambient PM or some component at current levels is associated with adverse health effects in some susceptible sub-populations or individuals.
- *Significance of Study*. Past epidemiologic studies strongly implicate respirable particles in increased morbidity and mortality in the general population. Specific epidemiologic studies can provide information on pertinent health issues such as the following:

  Short-term PM exposure effects on lung function and respiratory symptoms in asthmatics and non-asthmatics;
  Long-term PM exposure effects on lung function and respiratory symptoms;
  Relationships of short-term PM exposure to the incidence of respiratory and other medical visits, as well as hospitalization (i.e., hospital admissions over limited to extended duration); and
  Effects of ambient PM exposure on acute cardiovascular morbidity.

  Meanwhile, it is noteworthy that mortality studies from many causes tend to provide the most unambiguous evidence of a clearly adverse endpoint.

For most of the types of applications identified above, studies using various epidemiological designs would commonly be employed; the various epidemiological studies may include both observational and experimental study designs—and these may consist of ordinary descriptive study designs, case control studies, prospective studies, and indeed various types of experimental studies. Overall,

these types of public health risk assessment studies will seek to increase the understanding and preventative strategies to be adopted by public health policy makers, and also by community healthcare providers, in relation to chemical exposure problem situations. Moreover, the specific projects or investigations could arrange to actively involve students/trainees from the appropriate institutions dedicated to the teaching of health-related sciences in the pertinent studies—and thus help bring early awareness to the would-be healthcare providers at an earlier stage of their training. Ultimately, such projects are expected to help improve risk mitigation and public health risk management programs associated with various chemical exposure problems.

Finally, it must be recognized that a clear understanding and effective communication about the association between environmental hazards (such as chemical exposures) and disease incidence are indeed essential requirements of an effective environmental and public health risk management policy. With that in mind, it is apparent that findings from the types of projects exemplified here will likely help develop effectual preventative and remedial strategies that can be adopted and/or adapted by public health policy makers, as well as community healthcare providers.

Appendix A
Glossary of Selected Terms and Definitions

Some scientific and environmental terminologies that are commonly found to be pertinent to the evaluation of environmental contamination and chemical exposure problems are provided below.

Absorption Generally used to refer to the uptake of a chemical by a cell or an organism following exposure through the skin, lungs, and/or gastrointestinal tract. *Systemic absorption*—refers to the flow of chemicals into the bloodstream. In general, chemicals can be absorbed through the skin into the bloodstream, and then transported to other organs; chemicals can also be absorbed into the bloodstream after breathing or oral intake.

Absorption barrier Any of the exchange barriers of the human body that allow differential diffusion of various substances across a boundary—i.e., any exposure surface that may retard the rate of penetration of an agent into a target organism; examples of absorption barriers are the skin, the respiratory tract lining (or lung tissue), and the gastrointestinal tract wall.

Absorption fraction Refers to the percent or fraction of a chemical in contact with an organism that becomes absorbed into the receptor—i.e., the relative amount of a substance at the exchange barrier that actually penetrates into the body of an organism. Typically, this is reported as the unitless fraction of the applied dose or as the percent absorbed—e.g., relative amount of a substance on the skin that penetrates through the epidermis into the body.

Acceptable daily intake (ADI) An estimate of the maximum amount of a chemical/agent, expressed on a body mass basis (*viz*., in mg/kg body weight/day), to which a potential receptor (or individuals in a [sub]population) can be exposed to on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, or without anticipating an adverse effect.

Acceptable risk A risk level generally deemed by society to be acceptable or tolerable. This is commonly considered as a risk management term—with the acceptability of the risk being dependent on: available scientific data; social,

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economic, and political factors; and the perceived benefits arising from exposure to an agent/stressor/chemical.

Action level (AL) The limit of a chemical in selected media of concern above which there are potential adverse health and/or environmental effects. On the whole, this represents the environmental chemical concentration above which some corrective action (e.g., monitoring or remedial action) is typically required by regulation.

Acute Of short-term duration—i.e., occurring over a short time, usually a few minutes or hours. *Acute exposure*—refers to a single large exposure or dose to a chemical, generally occurring over a short period (usually lasting <24 to 96 hours), in relation to the lifespan of the exposed organism. In general, this would typically address contact between an agent and a target occurring over a relatively short period of time—usually less than a day. An acute exposure can result in short-term or long-term health effects. *Acute effect*—generally takes place a short time (up to 1 year) after exposure. *Acute toxicity*—refers to the development of symptoms of poisoning or the occurrence of adverse health effects after exposure to a single dose or multiple doses of a chemical within a short period of time. It represents the sudden onset of adverse health effects that are of short duration—generally resulting in cellular changes that are reversible.

Additivity (of chemical effects) A pharmacologic or toxicologic interaction in which the combined effect of two or more chemicals is approximately equal to the sum of the effect of each chemical acting alone.

Administered dose The mass of substance administered to an organism, and that is in contact with an exchange boundary (e.g., gastrointestinal tract) per unit body weight per unit time (e.g., mg/kg-day). It actually is a measure of exposure only—since it does *not* account for absorption. [See also, *applied dose*.]

Adsorption The removal of contaminants from a fluid stream via a mechanism of concentrating the constituents onto a solid material. It consists of the physical process of attracting and holding molecules of other chemical substances on the surface of a solid, usually by the formation of chemical bonds. A substance is considered *adsorbed* if the concentration in the boundary region of a solid (e.g., soil) particle is greater than in the interior of the contiguous phase.

Adverse effect A biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to a future environmental challenge. It is often exhibited by a change in the morphology, physiology, growth, development, reproduction, or life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.

Aerosol A suspension of liquid or solid particles in air.

Agent (or Stressor) A chemical, biological, or physical entity that contacts a target material or organism.

Aliphatic compounds Organic compounds in which the carbon atoms exist as either straight or branched chains; examples include pentane, hexane, and octane.

Ambient Pertaining to surrounding conditions or area. *Ambient medium*—one of the basic categories of material surrounding or contacting an organism (e.g.,

outdoor air, indoor air, water, or soil) through which chemicals or pollutants can move and reach the organism.

Analyte A chemical component of a sample that is to be investigated or measured; for example, if the *analyte of interest* in an environmental sample is mercury, then the laboratory testing or analysis will determine the likely amount of mercury in the sample. The *analytical method* defines the sample preparation and instrumentation procedures or steps that must be performed to estimate the quantity of analyte in a given sample.

Antagonism (*or, *antagonistic chemical effect) A pharmacologic or toxicologic interaction in which the combined effect of two chemicals is less than the sum of the effect of each chemical acting alone. This phenomenon is the result of interference or inhibition of the effects of one chemical substance by the action of other chemicals—and reflects the general counteracting effect of one chemical on another, thus diminishing their additive effects.

Anthropogenic Caused or influenced by human activities or actions.

Applied dose The amount of a substance in contact with the primary absorption boundaries of an organism (e.g., skin, lung, gastrointestinal tract), and that is available for absorption. This actually is a measure of exposure only—since it does *not* take absorption into account. [See also, *administered dose*.]

Arithmetic mean (*also, *average) A statistical measure of central tendency for data from a normal distribution—defined, for a set of n values, as the sum of the values divided by n, as follows:

$$X_m = \frac{\sum_{i=1}^{n} X_i}{n}$$

Aromatic compounds Organic compounds that contain carbon molecular ring structures (i.e., a benzene ring); examples include benzene, toluene, ethylbenzene, xylenes (BTEX).

Attenuation Any decrease in the amount or concentration of a pollutant in an environmental matrix as it moves in time and space. It represents the reduction or removal of contaminant constituents by a combination of physical, chemical, and/or biological factors acting upon the contaminated 'parent' media.

Attributable risk (also, ***incremental risk***) The difference between risk of exhibiting a certain adverse effect in the presence of a toxic substance in comparison with that risk to be expected in the absence of the substance. [See also, *excess lifetime risk*.]

Average concentration A mathematical average of chemical concentration (s) from more than one sample—typically represented by the 'arithmetic mean' or the 'geometric mean' for environmental samples.

Average daily dose (ADD) The average dose calculated for the duration of receptor exposure, defined by:

$$\mathrm{ADD}(mg/kg\text{-}day) = \frac{[chemical\ \ concentration] \times [contact\ \ rate]}{[body\ \ weight]}$$

This is used to estimate risks for chronic non-carcinogenic effects of environmental chemicals.

Averaging time The time period over which a function (e.g., human exposure concentration of a chemical) is measured—yielding a time-weighted value.

Background (threshold) level The normal, or typical, average ambient environmental concentration of a chemical constituent. It represents the amount of an agent in a medium (e.g., air, water, soil) that is not attributed to the source (s) under investigation in an exposure assessment. Overall, two types of background levels may exist for chemical substances—namely, naturally-occurring concentrations and elevated anthropogenic levels resulting from non-site-related human activities. *Anthropogenic background levels*—refer to concentrations of chemicals that are present in the environment due to human-made, non-site sources (e.g., lead depositions from automobile exhaust and 'neighboring' industry). *Naturally occurring background levels*—refer to ambient concentrations of chemicals that are present in the environment and yet have not been influenced by human activities (e.g., natural formations of aluminum, arsenic, and manganese).

Benchmark concentration (BMC) A statistical lower confidence limit on the concentration that produces a predetermined change in response rate of an adverse effect (called the 'benchmark response' or BMR) compared to background. It is represented by the concentration calculated to be associated with a given incidence (e.g., 5% or 10% incidence) of effect estimated from all toxicity data on that effect within that study; in actuality, BMCL is the statistical lower confidence limit of the BMC.

Benchmark dose (BMD) A statistical lower confidence limit on the dose that produces a predetermined change in response rate of an adverse effect (called the 'benchmark response' or BMR) compared to background. It is represented by the dose calculated to be associated with a given incidence (e.g., 5% or 10% incidence) of effect estimated from all toxicity data on that effect within that study; in actuality, BMDL is the statistical lower confidence limit of the BMD.

Benchmark response (BMR) An adverse effect, used to define a benchmark dose from which an RfD (or RfC) can be developed. The change in response rate over background of the BMR is usually in the range of 5–10%, which is the limit of responses typically observed in well-conducted animal experiments.

Benchmark risk A threshold level of risk, typically prescribed by regulations, and above which corrective measures will almost certainly have to be implemented to mitigate the risks.

Bioaccessibility A term used in describing an event that relates to the absorption process upon exposure of an organism—and generally refers to the fraction of the administered substance that becomes solubilized in the gastrointestinal fluid. For the most part, solubility is a prerequisite of absorption, although small amounts of some chemicals in particulate or suspended/emulsified form may be absorbed by pinocytosis. Moreover, it is not simply the fraction dissolved that determines bioavailability, but also the rate of dissolution, which has physiological and geochemical influences. In and of itself, bioaccessibility is not a direct measure of the movement of a substance across a biological membrane (i.e., absorption or bioavailability). Indeed, the relationship of bioaccessibility to

bioavailability is ancillary and the former need not be known in order to measure the latter. However, bioaccessibility (i.e., solubility) may serve as a surrogate for bioavailability if certain conditions are met.

Bioaccumulation The progressive increase in amount of a chemical in an organism or part of an organism that occurs because the rate of intake exceeds the organism's ability to remove the substance from the body. This represents the retention and concentration of a chemical by an organism—that is the result of a build-up of the chemical in the organism as a consequence of the organism taking in more of the chemical than it can rid of in the same length of time, and therefore ends up storing the chemical in its tissue, etc. [See also, *bioconcentration*.]

Bioassay Measuring the effect(s) of environmental exposures by intentional exposure of living organisms to a chemical. It consists of tests used to evaluate the relative potency of a chemical by comparing its effects on a living organism with the effect of a standard preparation on the same type of organism.

Bioavailability A measure of the degree to which a dose of a chemical substance becomes physiologically available to the body target tissues after being administered, or upon exposure. It refers to the fraction of the total amount of material in contact with a body portal-of-entry (*viz*., lung, gut, skin) that actually enters the blood—and this depends on the absorption, distribution, metabolism and excretion rates. On the whole, bioavailability involves both release from a medium (if present) and absorption by an organism; ultimately, this is defined by the rate and extent to which an agent can be absorbed by an organism, and is available for metabolism or interaction with biologically significant receptors. *Absolute bioavailability*—refers to the fraction or percentage of a compound that is ingested, inhaled, or applied on the skin surface that actually is absorbed and reaches the systemic circulation. In other words, this is the amount of the substance entering the blood via a particular route of exposure (e.g., gastrointestinal) divided by the total amount administered (e.g., soil lead ingested). *Relative bioavailability*—refers to a measure of the extent of absorption among two or more forms of the same chemical (e.g., lead carbonate *vs*. lead acetate), different vehicles (e.g., food, soil, water, etc.), or different doses. In the context of environmental risk assessment, relative bioavailability is the ratio of the absorbed fraction from the exposure medium in the risk assessment (e.g., food or soil) to the absorbed fraction from the dosing medium used in the critical toxicity study. It is indexed by measuring the bioavailability of a particular substance relative to the bioavailability of a standardized reference material, such as soluble lead acetate.

Bioconcentration The accumulation of a chemical substance in tissues of organisms (such as fish) to levels greater than levels in the surrounding media (such as water) for the organism's habitat; this is often used synonymously with bioaccumulation. *Bioconcentration factor (BCF)*—is the ratio of the concentration of a chemical substance in an organism, at equilibrium to the concentration of the substance in the surrounding environmental medium. It is a measure of the

amount of selected chemical substances that accumulate in humans or in biota. [See also, *bioaccumulation*.]

Biologically-based dose response model A predictive tool used to estimate potential human health risks by describing and quantifying the key steps in the cellular, tissue, and organism responses as a result of chemical exposure.

Biological uptake The transfer of hazardous substances from the environment to plants, animals, and humans. This may be evaluated through environmental measurements, such as measurement of the amount of the substance in an organ known to be susceptible to that substance. More commonly, *biological dose measurements* are used to determine whether exposure has occurred. The presence of a chemical compound, or its metabolite, in human biologic specimens (such as blood, hair, or urine) is used to confirm exposure—and this can be an independent variable in evaluating the relationship between the exposure and any observed adverse health effects.

Biomagnification The serial accumulation of a chemical by organisms in the food chain—with higher concentrations occurring at each successive trophic level.

Biomarker (or, Biological marker) Biological markers of exposure refer to cellular, biochemical, analytical, or molecular measures that are obtained from biological media such as tissues, cells, or fluids and are indicative of exposure to an agent. This would generally be an indicator of changes or events in biological systems. *Biomarker of exposure*—refers to the exogenous chemicals, their metabolites, or products of interactions between a xenobiotic chemical and some target molecule or cell that is measured in a compartment within an organism to verify suspected exposures or degree of known exposures.

Biomedical testing Biological testing of persons to evaluate a qualitative or quantitative change in a physiologic function that may be predictive of health impairment resulting from exposure to hazardous substance(s).

Body burden The total amount of a particular chemical substance stored in the body (usually in fatty tissue, blood, and/or bone) at a particular time—especially relating to a potentially toxic chemical in the body that follows from exposure. Some chemicals build up in the body because they are stored in fat or bone, or are eliminated very slowly—e.g., the amount of metals such as lead in the bone; the amount of lipophilic compounds such as PCBs in the adipose tissue; etc. Indeed, body burdens can be the result of both long-term and short-term storage.

Cancer Refers to the development of a malignant tumor or abnormal formation of tissue. It is a disease characterized by malignant, uncontrolled invasive growth of body tissue cells. *Tumor*—an uncontrolled growth of tissue cells forming an abnormal mass. *Benign tumor*—refers to a tumor that does not spread to a secondary location, but may still impair normal biological function through obstruction, or may progress to malignancy later. *Malignant tumor*—refers to an abnormal growth of tissue that can invade adjacent or distant tissues. *Neoplasm*—an abnormal growth of tissues that may be benign or malignant. This relates to a genetically altered, relatively autonomous growth of tissue; it is

composed of abnormal cells, the growth of which is more rapid than that of other tissues, and is not coordinated with the growth of other tissues.

Cancer slope factor (CSF) **(also,** ***slope factor, SF, cancer potency factor, CPF, or cancer potency slope, CPS*****)** Health effect information factor commonly used to evaluate health hazard potentials for carcinogens. It is a plausible upper-bound estimate of the probability of a response per unit intake of a chemical over a lifetime—represented by the slope of the dose-response curve in the low-dose region. This parameter is used to estimate an upper-bound probability for an individual to develop cancer as a result of a lifetime of exposure to a particular level of a carcinogen. Generally, cancer slope factors are available from databases such as US EPA's Integrated Risk Information System (IRIS) [See, Appendix D].

Carcinogen A cancer-producing chemical or substance. It represents any substance that is capable of inducing a cancer response in living organisms. *Co-carcinogen*—refers to an agent that is not carcinogenic on its own, but enhances the activity of another agent that is carcinogenic when administered together with the carcinogen. *Complete carcinogen*—refers to chemicals that are capable of inducing tumors in animals or humans without supplemental exposure to other agents; the term 'complete' refers to the three stages of carcinogenesis (namely: initiation, promotion, and progression) that need to be present in order to induce a cancer.

Carcinogenesis The process by which normal tissue becomes cancerous; i.e., the production of cancer, most likely via a series of steps—*viz*., initiation, promotion, and progression. The carcinogenic event modifies the genome and/or other molecular control mechanisms of the target cells, giving rise to a population of altered cells. *Initiator*—a chemical/substance or agent capable of starting but not necessarily completing the process of producing an abnormal uncontrolled growth of tissue, usually by altering a cell's genetic material. Initiated cells may or may not be transformed into tumors. *Initiation*—refers to the first stage of carcinogenesis, and consists of the subtle alteration of DNA or proteins within target cells by carcinogens, which then renders the cell capable of becoming cancerous. *Promoter*—a chemical that, when administered after an initiator has been given, promotes the change of an initiated cell, culminating in a cancer. This generally represents a substance that may not be carcinogenic by itself, but when administered after an initiator of carcinogenesis, serves to dramatically potentiate the effect of a low dose of a carcinogen—by stimulating the clonal expansion of the initiated cell to produce a neoplasm. *Promotion*—the second hypothesized stage in a multistage process of cancer development, consisting of the conversion of initiated cells into tumorigenic cells; this occurs when initiated cells are acted upon by promoting agents to give rise to cancer.

Carcinogenic Capable of causing, and tending to produce or incite cancer in living organisms. That is, a substance able to produce malignant tumor growth.

Carcinogenicity The power, ability, or tendency of a chemical, physical, or biological agent to produce cancerous tissues from normal tissue—in order to cause cancer in a living organism.

Case-control study A retrospective epidemiologic study in which individuals with the disease under study (cases) are compared with individuals without the disease (controls) in order to contrast the extent of exposure in the diseased group with the extent of exposure in the controls. The study typically consists of an investigation in which select cases with a specific diagnosis (such as cancer) are compared to individuals from the same or related population(s) without that specific diagnosis. In chemical exposure problems, this type of (retrospective) epidemiologic study looks back in time at the exposure history of individuals who have the health effects (cases) and at a group who do not (controls), in order to ascertain whether they differ in the proportion exposed to the chemical (s) under investigation.

Cell The basic units of structure and function in a living organism. It consists of the complex assemblages of atoms, molecules, and complex molecules.

Central nervous system (CNS) The part of the nervous system that includes the brain and the spinal cord, and their connecting nerves.

Chemical-specific adjustment factor (CSAF) A factor based on quantitative chemical-specific toxicokinetic or toxicodynamic data, which replaces the classical default uncertainty factor.

Chronic Of long-term duration—i.e., occurring over a long period of time (usually more than 1 year). *Chronic daily intake (CDI)*—refers to the receptor exposure, expressed in mg/kg-day, averaged over a long period of time. *Chronic effect*—refers to an effect that is manifest after some time has elapsed from an initial exposure to a substance. *Chronic exposure*—refers to the long-term, low-level exposure to chemicals, i.e., the repeated exposure or doses to a chemical over a long period of time (usually lasting six months to a lifetime). It is generally used to define the continuous or intermittent long-term contact between an agent and a target. It is noteworthy that this may cause latent damage that does not appear until a later period in time. *Chronic toxicity*—refers to the occurrence of symptoms, diseases, or other adverse health effects that develop and persist over time, following exposure to a single dose or multiple doses of a chemical delivered over a relatively long period of time. This represents the adverse health effects that are of a long and continuous duration—generally resulting in cellular changes that are irreversible. Chronic toxicity usually consists of a prolonged health effect that may not become evident until many years after exposure.

Cleanup Actions taken to abate a situation involving the release or threat of release of contaminants that could potentially affect human health and/or the environment. This typically involves a process to remove or attenuate contamination levels, in order to restore the impacted media to an 'acceptable' or usable condition. *Cleanup level*—refers to the contaminant concentration goal of a remedial action, i.e., the concentration of media contaminant level to be attained through a remedial action.

Cluster investigation A review of an unusual numbers (real or perceived) of health events (e.g., reports of cancer) grouped together in time and location. Cluster investigations are designed to confirm case reports; determine whether the

reported cases represent an unusual disease occurrence; and, if possible, explore possible causes and environmental factors that are producing the cases.

***Cohort study* (or, *Prospective study*)** An epidemiologic study comparing those with an exposure of interest to those without the exposure. It involves observing subjects in differently exposed groups and comparing the incidence of symptoms; these two cohorts are then followed over time to determine the differences in the rates of disease between the exposure subjects. The *relative risk* (or *risk ratio*)—defined as the rate of disease among the exposed divided by the rate of the disease among the unexposed—provides a relative measure of the difference in risk between the exposed and unexposed populations in a cohort study; thus, a relative risk of two means that the exposed group has twice the disease risk as the unexposed group.

Community health investigation Medical or epidemiologic evaluation of a descriptive health information about individual persons or a population group that is used to evaluate and determine observed health concerns, and to assess the likelihood that such prevailing conditions may be linked to exposure to hazardous substances.

Compliance To conduct or implement an activity in accordance with stipulated legislative or regulatory requirements.

Concentration Broadly refers to the amount/quantity of a material or agent dissolved or contained in unit quantity/volume in a given medium or system.

Confidence interval (CI) A statistical parameter used to specify a range, and the probability that an uncertain quantity falls within this range. *Confidence limits*—the upper and lower boundary values of a range of statistical probability numbers that define the CI. *95 percent confidence limits (95% CL)*—refers to the limits of the range of values within which a single estimation will be included 95% of the time. For large samples sizes (i.e., $n > 30$),

$$95\%CL = X_m \pm \frac{1.96s}{\sqrt{n}}$$

where CL is the confidence level, and s is the estimate of the standard deviation of the mean (X_m). For a limited number of samples ($n < 30$), a confidence limit or confidence interval may be estimated from,

$$95\%CL = X_m \pm \frac{ts}{\sqrt{n}}$$

where t is the value of the Student t-distribution [refer to standard textbooks of statistics] for the desired confidence level and degrees of freedom, $(n - 1)$. [See also, *upper confidence limit, 95% (95% UCL).*]

***Confounder* (or, *confounding factor*)** A condition or variable that may be a factor in producing the same response as the agent under study. This association between the exposure of interest and the confounder (a true risk factor for disease) may make it falsely appear that the exposure of interest is associated with disease. The effects of such factors may be discerned through careful design and analysis.

Consequence The impacts resulting from the response associated with specified exposures, or loading or stress conditions.

Conservative assumption Used in exposure and risk assessment, this expression refers to the selection of assumptions (when real-time data are absent) that are unlikely to lead to under-estimation of exposure or risk. Conservative assumptions are those which tend to maximize estimates of exposure or dose—such as choosing a value near the high end of the concentration or intake rate range. [See also, *worst case*.]

Contact rate Amount of an exposure or environmental medium (e.g., air, groundwater, surface water, soil, cosmetics, etc.) contacted per unit time or per event (e.g., liters of groundwater ingested or milligrams of soil ingested per day).

Contaminant (*or, *pollutant) Any substance or material that enters a system (the environment, human body, food, etc.) where it is not normally found—as, e.g., any undesirable substance that is not naturally-occurring, and therefore not normally found in the environmental media of concern. This typically consists of any potentially harmful physical, chemical, biological, or radiological agent occurring in the environment, in consumer products, or at the workplace as a result of human activities. Such materials can potentially have adverse impacts upon exposure to an organism, and/or could adversely impact public health and the environment simply by their presence in the ambient setting. *Contaminant release*—refers to the ability of a contaminant to enter into other environmental media/matrices (e.g., air, water or soil) from its source(s) of origin. *Contaminant migration*—refers to the movement of a contaminant from its source through other matrices/media such as air, water, or soil. *Contaminant migration pathway*—is the path taken by the contaminants as they travel from the contaminated source through various environmental media.

Control group (*or, *reference group) A group used as the baseline for comparison in epidemiologic or laboratory studies. This group is selected because it either lacks the disease of interest—i.e., there is absence of an adverse response (case-control group), or lacks the exposure of concern—i.e., there is absence of exposure to agent (cohort study).

Corrective action Action taken to correct a problematic situation. A typical/common example involves the remediation of chemical contamination in soil and groundwater.

Critical effect The first adverse effect, or its known precursor, that occurs in the dose/concentration scale.

Data quality objectives (DQOs) Qualitative and quantitative statements developed by analysts to specify the quality of data that, at a minimum, is needed and expected from a particular data collection activity (or hazard source characterization activity). This is determined based on the end use of the data to be collected.

Decision analysis A process of systematic evaluation of alternative solutions to a problem where the decision is made under uncertainty. The approach is comprised of a conceptual and systematic procedure for analyzing complex sets of

alternatives in a rational manner so as to improve the overall performance of a decision-making process.

Decision framework Management tool designed to facilitate rational decision-making.

Default value Pragmatic, fixed or standard, value used in the absence of relevant case-specific data.

Degradation The physical, chemical or biological breakdown of a complex compound into simpler compounds and byproducts.

Delayed toxicity The development of disease states or symptoms a long-time (i.e., many months or years) after exposure to a given toxicant.

de Minimus A legal doctrine dealing with levels associated with insignificant versus significant issues relating to human exposures to chemicals that present very low risk. In general, this represents the level below which one need not be concerned—and, therefore, is of no public health consequence.

Dermal absorption The absorption of materials/substances through the skin. *Dermally absorbed dose*—refers to the amount of the applied material (i.e., the 'external dose') which becomes absorbed into the body.

Dermal adsorption The process by which materials come into contact with the skin surface, but are then retained and adhered to the permeability barrier without being taken into the body.

Dermal exposure Exposure of an organism or receptor through skin adsorption and possible absorption.

Dermatotoxicity Adverse effects produced by toxicants contacting or entering the skin of an organism.

Detection limit (DL) The minimum concentration or weight of analyte that can be detected by a single measurement with a known confidence level. *Instrument detection limit (IDL)*—represents the lowest amount that can be distinguished from the normal 'noise' of an analytical instrument (i.e., the smallest amount of a chemical detectable by an analytical instrument under ideal conditions). *Method detection limit (MDL)*—represents the lowest amount that can be distinguished from the normal 'noise' of an analytical method (i.e., the smallest amount of a chemical detectable by a prescribed or specified method of analysis).

Deterministic model A model that provides a single solution for a given set of stated variables. This type of model does not explicitly simulate the effects of uncertainty or variability, as changes in model outputs are due solely to changes in model components.

Developmental toxicity Adverse effects on the developing organism that may result from exposure prior to conception (in either parent), during prenatal development, or post-natally until the time of sexual maturation. The major manifestations of developmental toxicity include death of the developing organism, structural abnormality, altered growth, and functional deficiency.

Diffusion The migration of molecules, atoms, or ions from one fluid to another in a direction tending to equalize concentrations.

Digestive system The organ system that is responsible for the conversion of ingested food into simple molecules that can be absorbed by the blood and lymph, and then used by cells. It is made up of the digestive tract and related accessory organs, such as the liver and pancreas.

Dispersion The overall mass transport process resulting from both molecular diffusion (which always occurs if there is a concentration gradient in the system) and the mixing of the constituent due to turbulence and velocity gradients within the system.

DNA (Deoxyribonucleic acid) A nucleic acid molecule with the shape of a double helix that is present in chromosomes and that contains the genetic information. It is the repository of hereditary characteristics (genetic code).

Domain (spatial and temporal) The limits of space and time that are specified in a risk assessment, or components thereof.

Dose A stated quantity or concentration of a substance to which an organism is exposed over a continuous or intermittent duration of exposure; thus this provides a measure of the amount of a chemical substance received or taken in by potential receptors upon exposure—typically expressed as an amount of exposure (in mg) per unit body weight of the receptor (in kg). More specifically, it consists of the amount of agent that enters a target organ(ism) after crossing an exposure surface; if the exposure surface is an absorption barrier, the dose is an absorbed dose/uptake dose—otherwise it is considered an intake dose. *Total dose*—is the sum of chemical doses received by an individual from multiple exposure sources in a given interval as a result of interaction with all exposure or environmental media that contain the chemical substances of concern. Units of dose and total dose (mass) are often converted to units of mass per volume of physiological fluid or mass of tissue. *Exposure dose* (also referred to as *applied dose* or *potential dose*)—is the amount of an agent presented to an absorption barrier and available for absorption (i.e., the amount ingested, inhaled or applied to the skin); this amount may be the same as or greater than the absorbed dose. *Absorbed dose* (also called, *internal dose*)—is the amount or the concentration of a chemical substance (or its metabolites and adducts) actually entering an exposed organism (or pertinent biological matrices) via the lungs (for inhalation exposures), the gastrointestinal tract (for ingestion exposures), and/or the skin (for dermal exposures). It represents the amount of chemical that, after contact with the exchange boundaries of an organism (*viz*., skin, lungs, gut), actually penetrates the exchange boundary and enters the circulatory system—i.e., the amount of a substance penetrating across an absorption barrier (represented by the exchange boundaries such as the skin, lung, and gastrointestinal tract) of an organism, via either physical or biological processes. The amount may be the same as or less than the applied dose. *Delivered dose*—denotes the amount of a substance available for biologically significant interactions in a target organ. *Biologically effective dose*—represents the amount of the chemical available for interaction with any particular organ, cell or macromolecular target. *Effective dose (ED_{10})*—refers to the dose corresponding to a 10% increase in an adverse

effect, relative to the control response. *Lower limit on effective dose (LED_{10})*—the 95% lower confidence limit of the dose of a chemical needed to produce an adverse effect in 10% of those exposed to the chemical, relative to control.

Dose metric The target tissue dose that is closely related to ensuing adverse responses. Dose metrics used for risk assessment applications should reflect the biologically-active form of the chemical, its level, duration of internal exposure as well as intensity.

Dose-response (or dose-effect) The quantitative relationship between the dose of a chemical substance and an effect caused by exposure to such substance. *Dose-response relationship*—refers to the relationship between a quantified exposure (dose), and the proportion of subjects demonstrating specific biological changes (response). *Dose-response curve*—refers to the graphical representation of the relationship between the degree of exposure to a chemical substance and the observed or predicted biological effects or response. *Dose-response assessment*—consists of a determination of the relationship between the magnitude of an administered, applied, or internal dose and a specific biological response. Response can be expressed as measured or observed incidence, percent response within groups of subjects (or populations), or as the probability of occurrence within a population. *Dose-response evaluation*—refers to the process of quantitatively evaluating toxicity information, and then characterizing the relationship between the dose of a chemical administered or received and the incidence of adverse health effects in the exposed population.

Effect The response arising from a chemical-contacting episode. In general, this represents the change in the state or dynamics of an organism, system, or (sub) population caused by the exposure to an agent. *Local effect*—refers to the response that occurs at the site of first contact. *Systemic effect*—refers to the response that requires absorption and distribution of the chemical, and this tends to affect the receptor at sites farther away from the entry point(s).

Effect assessment Consists of the combination of analysis and inference of possible consequences of the exposure to a particular stressor/agent based on knowledge of the dose-effect relationship associated with that particular stressor/agent in a specific target organism, system, or (sub)population.

Embryotoxicity Any toxic effect on the *conceptus* as a result of prenatal exposure during the embryonic stages of development. These effects may include malformations and variations, altered growth, *in-utero* death, and altered postnatal function.

Empirical model A model with a structure that is based on experience or experimentation, and does not necessarily have a structure informed by a causal theory of the modeled process. This type of model can be used to develop relationships that are useful for forecasting and describing trends in behavior but may not necessarily be mechanistically relevant. Empirical dose-response models can be derived from experimental or epidemiologic observations.

Endangerment assessment A case-specific risk assessment of the actual or potential danger to human health and welfare, and also the environment, that is

associated with the release of hazardous chemicals into various exposure or environmental media or matrices.

Endpoint (toxic) An observable or measurable biological or biochemical effect (e.g., metabolite concentration in a target tissue) used as an index of the impacts of a chemical on a cell, tissue, organ, organism, etc. This is usually referred to as *toxicological endpoint* or *physiological endpoint* in the context of chemical toxicity assessments.

Environmental fate The 'destination' or 'destiny' of a chemical after release or escape from a given source into the environment, and following transport through various environmental compartments. For example, in a contaminated land situation, it may consist of the movement of a chemical through the environment by transport in air, water, sediment, and soil—culminating in exposures to living organisms. It represents the disposition of a material in the various environmental compartments (e.g., soil, sediment, water, air, biota) as a result of transport, transformation, and degradation.

Environmental medium A part of the environment for which reasonably distinct boundaries can be specified. Typical environmental media addressed in chemical risk assessments may include air, surface water, groundwater, soil, sediment, fruits, vegetables, meat, dairy, and fish—or indeed any other parts of the environment that could contain contaminants of concern.

Environmental toxicant Agents present in the surroundings of an organism that are harmful to the health of such organisms.

Epidemiology The study of the occurrence of disease, injury and other health effect patterns in human populations, as well as the causes and means of prevention or preventative strategies. An *epidemiological study* often compares two groups of people who are alike except for one factor—such as exposure to a chemical, or the presence of a health effect; the investigators endeavor to determine if any particular factor(s) is associated with observed health effect (s). *Descriptive epidemiology*—consists of a study of the amounts and distributions of diseases within a population by person, place, and time.

Erythrocytes Red blood cells.

Estimated exposure dose (EED) The measured or calculated dose to which humans are likely to be exposed—considering all sources and routes of exposure.

Event-tree analysis A procedure, utilizing deductive logic, often used to evaluate a series of events that lead to an upset or accident scenario. It offers a systematic approach for analyzing the types of exposure scenarios that can result from a chemical exposure problem.

Excess (*or *incremental) lifetime risk The additional or extra risk (above normal background rate) incurred over the lifetime of an individual as a result of exposure to a toxic substance. [See also, *attributable risk*.]

Exposure The situation of receiving a dose of a substance, or coming in contact with a hazard. It represents the contact of an organism with a chemical, biological, or physical agent available at the exchange boundary (e.g., lungs, gut, or

skin) during a specified time period. This is typically expressed by the concentration or amount of a particular agent that reaches a target organism, system, or (sub)population at a specific frequency for a defined duration. *Exposure conditions*—refer to factors (such as location, time, etc.) that may have significant effects on an exposed population's response to a hazard situation. *Exposure period*—refers to the time of continuous contact between an agent and a target receptor. *Exposure duration*—refers to the length of time over which continuous or intermittent contacts occur between an agent and a target receptor; it is generally represented by the length of time that a potential receptor is exposed to the hazards or contaminants of concern in a defined exposure scenario. *Exposure event*—refers to an incident or occurrence of continuous contact between a chemical or physical agent and a target receptor, usually defined by time (e.g., number of days or hours of contact). *Exposure frequency*—refers to the number of exposure events within a given exposure duration; it is generally represented by the number of times (per year or per event) that a potential receptor would be exposed to contaminants of concern in a defined exposure scenario. *Exposure parameters (or factors)*—refer to the variables used in the calculation of intake (e.g., exposure duration, breathing rate, food ingestion rate, and average body weight); these may consist of standard exposure factors that may be needed to calculate a potential receptor's exposure to toxic chemicals (in the environment).

Exposure assessment The qualitative or quantitative estimation, or the measurement, of the dose or amount of a chemical to which potential receptors have been exposed, or could potentially be exposed to. This process comprises of the determination of the magnitude, frequency, duration, route, and extent of exposure (to the chemicals or hazards of potential concern). This generally corresponds to the process of estimating or measuring the magnitude, frequency, and duration of exposure to an agent, along with the number and characteristics of the population exposed; ideally, this should describe the sources, pathways, routes, and the uncertainties in the assessment. *Exposure activity pattern data*—relates to information on human activities used in exposure assessments. These may include a description of the activity, frequency of activity, duration of time spent performing the activity, and the microenvironment in which the activity occurs.

Exposure (point) concentration (EPC) The concentration of a chemical (in its transport or carrier medium) at the point of receptor contact. *Exposure point*—refers to a location of potential contact between an organism and a hazardous (*viz*., biological, chemical or physical) agent.

Exposure investigation The collection and analysis of site-specific information to determine if human populations have been exposed to hazardous substances. The site-specific information may include environmental sampling, exposure-dose reconstruction, biologic or biomedical testing, and evaluation of medical information. The information from an exposure investigation can be used to

support a complete public health risk assessment and subsequent risk management programs.

Exposure model A conceptual or mathematical representation of the exposure process.

Exposure pathway The course a chemical, biological, or physical agent takes from a source to an exposed population or organism. It describes a unique mechanism by which an individual or population is exposed to chemical, biological, or physical agents at or originating from a contaminant release source.

Exposure route The avenue or path (such as inhalation, ingestion, and dermal contact) by which a chemical/agent enters a target receptor or organism after contact. It represents the way in which a potential receptor may contact a chemical substance; for example, drinking (ingestion) and bathing (skin contact) are two different routes of exposure to contaminants that may be found in water.

Exposure scenario A set of conditions or assumptions about hazard sources, exposure pathways, concentrations of chemicals, and potential receptors or exposed organisms that facilitates the evaluation and quantification of exposure(s) in a given situation. Broadly, it represents the combination of facts, assumptions, and inferences that define a discrete situation where potential exposures may occur; these may include the source, the exposed population(s), the timeframe of exposure occurrence, the microenvironment(s), and related activities. *Potentially exposed*—refers to the situation where valid information, usually analytical environmental data, indicates the presence of chemical(s) of a public health concern in one or more environmental media contacting humans (e.g., air, drinking water, soil, food chain, surface water), and where there is evidence that some of the target populations have well-defined route(s) of exposure (e.g., drinking contaminated water, breathing contaminated air, contacting contaminated soil, or eating contaminated food) associated with them. Although actual exposure is generally not confirmed for a 'potentially exposed' receptor, this type of exposure scenario would typically have to be adequately evaluated during the exposure assessment.

Extrapolation An estimate of response or quantity at a point outside the range of the experimental data, usually via the use of a mathematical model. This consists of the estimation of unknown numerical values of an empirical (measured) function by extending or projecting from known values/observations to points outside the range of data that were used to calibrate the function. In chemical exposure situations, this may comprise of the estimation of a measured response in a different species, or by a different route than that used in the experimental study of interest—i.e., species-to-species; route-to-route; acute-to-chronic; high-to-low dose; etc. For instance, the quantitative risk estimates for carcinogens are generally low-dose extrapolations based on observations made at higher doses.

Fate The pattern of distribution of an agent/chemical, its derivatives, or metabolites in an organism, system, compartment, or (sub)population of concern as a result of transport, partitioning, transformation, and/or degradation.

Frank effect level (FEL) A level of exposure or dose which produces irreversible adverse effects (such as irreversible functional impairment or mortality) and a statistically or biologically significant increase in frequency or severity between those exposed and those not exposed (i.e., the appropriate control).

Fugitive dust Atmospheric dust arising from disturbances of particulate matter exposed to the air. Fugitive dust emissions typically consist of the release of chemicals from contaminated surface soil into the air, attached to dust particles.

Genetic toxicity* (or, *genotoxicity) An adverse event resulting in damage to genetic material; damage may occur in exposed individuals or may be expressed in subsequent generations. *Genotoxic*—is a broad term that usually refers to a chemical that has the ability to damage DNA or the chromosomes.

Geographic Information System (GIS) Computer-based tool used to capture, manipulate, process, and display spatial or geo-referenced data for solving complex resource, environmental, and social problems. GIS is indeed a rapidly developing technology for handling, analyzing, and modeling geographic information. It is not a source of information *per se*, but only a way to manipulate information. When the manipulation and presentation of data relates to geographic locations of interest, then our understanding of the real world is enhanced.

Geometric mean A statistical measure of the central tendency for data from a positively skewed distribution (*viz*., lognormal), given by:

$$\mathrm{X_{gm}} = [(X_1)(X_2)(X_3)\ldots(X_\mathrm{n})]^{1/\mathrm{n}}$$

or,

$$X_{gm} = anti\log\left\{\frac{\sum_{i=1}^{n} ln[X_i]}{n}\right\}$$

Hazard That innate character or property which has the potential for creating adverse and/or undesirable consequences. It represents the inherent adverse effect that a chemical or other object poses—and defines the chance that a particular substance will have an adverse effect on human health or the environment under a particular set of circumstances that creates an exposure to that substance. Thus, hazard is simply a source of risk that does not necessarily imply actual potential for occurrence; a hazard produces risk only if an exposure pathway exists, and if exposures create the possibility of adverse consequences.

Hazard assessment The process of determining whether exposure to an agent can cause an increase in the incidence of a particular adverse health effect (e.g., cancer, birth defects, etc.), and whether the adverse health effect is likely to occur in the target receptor populations potentially at risk. This involves gathering and evaluating data on types of injury or consequences that may be produced by a hazardous situation or substance. The process includes hazard identification and hazard characterization.

Hazard characterization The qualitative and, wherever possible, quantitative (or - semi-quantitative) description of the inherent property of an agent/stressor or situation having the potential to cause adverse effects. Wherever possible, this would tend to include a dose-response assessment and its attendant uncertainties.

Hazard identification The systematic identification of potential accidents, upset conditions, etc.—consisting of a process of determining whether or not, for instance, a particular substance or chemical is causally linked to particular health effects. This is generally comprised of the identification of the type and nature of adverse effects that an agent has with respect to its inherent capacity to affect an organism, system, or (sub)population. Thus, the process involves determining whether exposure to an agent or hazard can cause an increase in the incidence of a particular adverse response or health effect in receptors of interest.

Hazard quotient (HQ) The ratio of a single substance exposure level for a specified time period to the 'allowable' or 'acceptable' intake limit/level of that substance derived from a similar exposure period. For a particular chemical and mechanism of intake (e.g., oral, dermal, inhalation), the hazard quotient is defined by the ratio of the average daily dose (ADD) of the chemical to the reference dose (RfD) for that chemical; or the ratio of the exposure concentration to the reference concentration (RfC). A value of less than 1.0 indicates the risk of exposure is likely insignificant; a value greater than 1.0 indicates a potentially significant risk. *Hazard index (HI)*—is the sum of several hazard quotients (HQs) for multiple substances and/or multiple exposure pathways.

Hazardous substance Any substance that can cause harm to human health or the environment whenever excessive exposure occurs. *Hazardous waste*—is that byproduct which has the potential to cause detrimental effects on human health and/or the environment if it is not managed in an effectual manner. Typically, this refers to wastes that are ignitable, explosive, corrosive, reactive, toxic, radioactive, pathological, or has some other property that produces substantial risk to life.

Heavy metals Members of a group of metallic elements that are recognized as toxic, and are generally bioaccumulative. The term arises from the relatively high atomic weights of these elements.

Hematotoxicity Adverse effects or diseases in the blood as produced by toxicants contacting or entering an organism. *Hematotoxins*—refer to agents that produce toxic symptoms or diseases in the blood of an organism.

Hemoglobin The respiratory compound of red blood cells. It consists of the oxygen-carrying protein in red blood cells.

Hepatotoxicity Adverse effects or diseases in the liver, as produced by toxicants contacting or entering an organism. *Hepatotoxins*—refer to agents that produce toxic symptoms or diseases in the liver of an organism.

'Hot-spot' Term often used to denote zones where contaminants are present at much higher concentrations than the immediate surrounding areas. It tends to represent a relatively small area that is highly contaminated within a study area.

Human-equivalent concentration or dose The human concentration (for inhalation exposure) or dose (for oral exposure) of an agent that is believed to induce the same magnitude of toxic effect as the exposure concentration or dose in experimental animal species. Generally speaking, the *human equivalent dose* represents the dose that, when administered to humans, produces effects comparable to that produced by a dose in experimental animals. This adjustment may incorporate toxicokinetic information on the particular agent, if available, or use a default procedure.

Human health risk The likelihood (or probability) that a given exposure or series of exposures to a hazardous substance will cause adverse health impacts on individual receptors experiencing the exposures.

Hydrocarbon Organic chemicals/compounds, such as benzene, that contain atoms of both hydrogen and carbon.

Hydrophilic Having greater affinity for water—or 'water-loving'. Hydrophilic compounds tend to become dissolved in water.

Hydrophobic Tending *not* to combine with water—or less affinity for water. Hydrophobic compounds tend to avoid dissolving in water and are more attracted to non-polar liquids (e.g., oils) or solids.

Incidence The number of new cases of a disease that develop within a specified population over a specified period of time. *Incidence rate*—is the ratio of new cases within a population to the total population at risk given a specified period of time.

Individual excess lifetime cancer risk An upper-bound estimate of the increased cancer risk, expressed as a probability that an individual receptor could expect from exposure over a lifetime.

Ingestion exposure An exposure type whereby chemical substances enter the body through the mouth, and into the gastrointestinal system. After ingestion, chemicals can be absorbed into the blood and then distributed throughout the body.

Inhalation exposure The intake of a substance by receptors through the respiratory tract system. Exposure may occur from inhaling contaminants—which become deposited in the lungs, taken into the blood, or both.

Initiating event A specific trigger action that could potentially give rise to some degree of risk being incurred.

Intake The amount of material inhaled, ingested or dermally absorbed during a specified time period. It is a measure of exposure—often expressed in units of mg/kg-day. More broadly, it may be viewed as the process by which an agent crosses an outer exposure surface of a target without passing an absorption barrier—as typically happens through ingestion or inhalation.

Integrated Risk Information System (IRIS) A US EPA database containing verified toxicity parameters (*e.g.*, reference doses [RfDs] and slope factors [SFs]), and also up-to-date health risk and EPA regulatory information for numerous chemicals. It does indeed serve as a very important source of toxicity information for health and environmental risk assessment. [See, Appendix D.]

Interspecies Between different species. *Interspecies dose conversion*—the process of extrapolating from animal doses to human equivalent doses.

Intraspecies Within a particular species.

In vitro Processes or reactions occurring in an artificial environment—outside of a living organism. For example, *in vitro* laboratory studies refer to studies conducted in a laboratory setup that do not use live animals (i.e., tests conducted outside the whole body in an artificially maintained environment)—as in a test tube, culture dish, or bottle.

In vivo Processes or reactions occurring within a living organism. For example, *in vivo* laboratory studies refer to those tests conducted using live animals, or whole living body—i.e., tests conducted within the whole living body.

Latency period A seemingly inactive period—such as the time between the initial induction of a health effect from first exposures to a chemical agent and the manifestation or detection of actual health effects of interest. This is often used to identify the period between exposure to a carcinogen and development of a tumor.

LC_{50} (Mean lethal concentration) The lowest concentration of a chemical in air or water that will be fatal to 50% of test organisms living in that media, under specified conditions.

LD_{50} (Mean lethal dose) The single dose (ingested or dermally absorbed) that is required to kill 50% of a test animal group. Also represents the median lethal dose value.

Leukocytes White blood cells.

Lifetime average daily dose (LADD) The exposure, expressed as mass of a substance contacted and absorbed per unit body weight per unit time, averaged over a lifetime. It is usually used to calculate carcinogenic risks—and takes into account the fact that, whereas carcinogenic risks are determined with an assumption of lifetime exposure, actual exposures may be for a shorter period of time. Indeed, the LADD may be derived from the ADD—to reflect the difference between the length of the exposure period and the exposed person's lifetime, as follows:

$$\text{LADD} = \text{ADD} \times \frac{\text{Exposure period}}{\text{Lifetime}}$$

Lifetime exposure The total amount of exposure to a substance or hazard that a potential receptor would be subjected to in a lifetime.

Lifetime risk Risk that arises from lifetime exposure to a chemical substance or hazard.

Linear dose-response A pattern of frequency or severity of biological response that varies proportionately with the amount of dose of an agent. *Non-linear dose-response*—shows a pattern of frequency or severity of biological response that does not vary proportionately with the amount of dose of an agent. When mode of action information indicates that responses may not follow a linear pattern below the dose range of the observed data, non-linear methods for determining risk at low dose may be justified.

Lipophilic The property of a chemical/substance to have a strong affinity for lipid, fats, or oils—i.e., being highly soluble in nonpolar organic solvents. Also, refers to a physicochemical property that describes a partitioning equilibrium of solute molecules between water and an immiscible organic solvent that favors the latter.

Lipophobic The property of a chemical to be antagonistic to lipid—i.e., incapable of dissolving in or dispersing uniformly in fats, oils, or nonpolar organic solvents.

LOAEC (Lowest-observed-adverse-effect-concentration) The lowest concentration in an exposure medium in a study that is associated with an adverse effect on the test organisms. It represents the lowest concentration of a substance, found by experiment or observation, that causes an adverse alteration of morphology, functional capacity, growth, development or lifespan of the target organisms distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure.

LOAEL (Lowest-observed-adverse-effect level) The lowest dose or exposure level, expressed in mg/kg body weight/day, at which adverse effects are noted in the exposed population. It represents the chemical dose rate or exposure level causing statistically or biologically significant increases in frequency or severity of adverse effects between the exposed and control groups. In practice, this consists of the lowest amount of a substance, found by experiment or observation, that causes an adverse alteration of morphology, functional capacity, growth, development or lifespan of the target organisms distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure. $LOAEL_a$—refers to the LOAEL values adjusted by dividing by one or more safety factors.

Local effect A biological response occurring at the site of first contact between the toxic substance and the organism.

LOEL (Lowest-observed-effect-level) The lowest exposure or dose level to a substance at which effects are observed in the exposed population; the effects may or may not be serious. In a given study, it is the lowest dose or exposure level at which a statistically or biologically significant effect is observed in the exposed population compared with an appropriate unexposed control group.

Margin-of-exposure (MOE) Defined by the ratio of the no-observed-adverse-effect-level (NOAEL) for the critical effect to the estimated (or theoretical, or predicted) human exposure.

Matrix (or, medium) The predominant material (e.g., food, consumer products—such as cosmetics, soils, water, and air) surrounding or containing a constituent or agent of interest—and generally comprising the environmental or exposure sample being investigated.

Maximum daily dose (MDD) The maximum dose calculated for the duration of receptor exposure—and used to estimate risks for subchronic or acute non-carcinogenic effects from chemical exposures.

Maximum Likelihood Estimate (MLE) Statistical method for estimating model parameters. It generally provides a mean or central tendency estimate, as opposed to a confidence limit on the estimate.

Mechanism of action A detailed description of the precise chain of events from the molecular level to gross macroscopic or histopathological toxicity.

Minimal risk level (MRL) An estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse (non-cancer) effects over a specified duration of exposure. *MRLs* are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration via a given route of exposure. *MRLs* are based on non-cancer health effects only—and can be derived for acute, intermediate, and chronic duration exposures by the inhalation and oral routes.

Mitigation The process of reducing or alleviating a hazard or problem situation.

Mode of action (MOA) A series of key events that may lead to induction of the relevant end-point of toxicity for which the weight of evidence supports plausibility.

Model A simplification of reality that is constructed to gain insights into select attributes of a particular physical, biologic, economic, or social system. *Mathematical models* express the simplification in quantitative terms—and generally would consist of mathematical function(s) with parameters that can be adjusted so that the function closely describes a set of empirical data. A *mechanistic model*—usually reflects observed or hypothesized biological or physical mechanisms, and has model parameters with real world interpretation. In contrast, *statistical or empirical models* selected for particular numerical properties are fitted to a given data—and model parameters in this case may or may not have real world interpretation. When data quality is otherwise equivalent, extrapolation from mechanistic models (e.g., biologically-based dose-response models) often carries higher confidence than extrapolation using empirical models (e.g., logistic model—representing a dose-response model used for low-dose extrapolation). *Model evaluation*—refers to the process of establishing confidence in a model on the basis of scientific principles, quality of input parameters, and ability to reproduce independent empirical data. For instance, in the context of PBPK models, evaluation is purpose-specific and focuses on the following aspects: biological basis of the model, model simulations of data and reliability of dose metric predictions. *Model verification*—refers to the process of examining the model structure, parameters, units, equations and model codes to ensure accuracy.

Modeling Refers to the use of mathematical equations to simulate and predict real events and processes.

Monitoring Process involving the measurement of concentrations of chemicals in environmental media, or in tissues of human receptors and other biological organisms. *Biological monitoring*—consists of measuring chemicals in biological materials (e.g., blood, urine, breath, etc.) to determine whether chemical exposure in living organisms (e.g., humans, animals, or plants) has occurred.

Monte Carlo simulation A process in which outcomes of events or variables are determined by selecting random numbers—subject to a defined probability law. In practice, Monte Carlo simulation with PBPK models can provide population distributions of dose metric of relevance to risk assessment. The technique is used to obtain information about the propagation of uncertainty in mathematical simulation models. The *Monte Carlo technique* involves a repeated random sampling from the distribution of values for each of the parameters in a calculation (e.g., lifetime average daily dose), in order to derive a distribution of output estimates (of exposures) in the population. *Markov chain Monte Carlo*—comprises a simulation approach that considers a model's parameters as random variables with a probability distribution for describing each parameter. The distribution based only on prior information and assumptions is called the prior distribution. Analysis of new data yields a posterior distribution of parameters that reconciles the prior information and assumptions with the new data.

Morbidity Illness or disease state. *Morbidity rate*—is the number of illnesses or cases of disease in a population.

Mortality The number of individual deaths in a population.

Multi-hit models Dose-response models that assume more than one exposure to a toxic material as necessary before effects are manifested.

Multi-stage models Dose-response models that assume there are a given number of biological stages through which the carcinogenic agent must pass, without being deactivated, for cancer to occur. The multistage model consists of a mathematical function that is used to extrapolate the probability of cancer from animal bioassay data. A *linearized multistage model*—is a derivation of the multistage model for which the data are assumed to be linear at low doses. The linearized multistage procedure consists of a modification of the multistage model, used for estimating carcinogenic risk—and that incorporates a linear upper bound on extra risk for exposures below the experimental range. A *multistage Weibull model*—is a dose-response model for low-dose extrapolation that includes a term for decreased survival time associated with tumor incidence.

Mutagen A substance that can cause an alteration in the structure of the DNA of an organism. *Mutagenic compounds*—have the ability to induce structural changes in genetic material.

Neuron Nerve cells.

Neurotoxicity Adverse effects or diseases in the nervous system as produced by toxicants contacting or entering an organism—i.e., the hazard effects that are poisonous to the nerve cells. *Neurotoxic*—having toxic effect on any aspect of the central or peripheral nervous system. *Neurotoxins*—refers to agents that have the ability to damage nervous tissues (i.e., produce toxic symptoms or diseases in the nervous system of an organism).

NOAEC (No-observed-adverse-effect-concentration) The highest concentration of a substance, found by experiment or observation, that causes no detectable adverse alteration of morphology, functional capacity, growth, development or lifespan of the target organisms under defined conditions of exposure. This

generally represents the highest concentration in an exposure medium in a study that is *not* associated with an adverse effect on the test organisms. Meanwhile, alterations may be detected that are judged not to be adverse.

NOAEL (No-observed-adverse-effect level) The highest amount of a substance, found by experiment or observation, that causes no detectable adverse alteration of morphology, functional capacity, growth, development or lifespan of the target organisms under defined conditions of exposure. That is, the highest level at which a chemical causes no observable adverse effect in the species being tested or the exposed population. It represents chemical intakes or exposure levels at which there are no statistically or biologically significant increases in frequency or severity of adverse effects between the exposed and control groups—meaning statistically significant effects are observed at this level, but they are not considered to be adverse nor precursors to adverse effects. Meanwhile, alterations may be detected that are judged not to be adverse. $NOAEL_a$—refers to NOAEL values adjusted by dividing by one or more safety factors.

NOEL (No-observed-effect level) The highest level at which a chemical causes no observable changes in the species or exposed populations under investigation. In a given study, this represents the dose rate or exposure level of chemical at which there are no statistically or biologically significant increases in frequency or severity of any effects between the exposed and control groups.

Nonparametric statistics Statistical techniques whose application is independent of the actual distribution of the underlying population from which the data were collected.

Non-threshold toxicant A chemical for which there is no dose or exposure concentration below which the critical effect will not be observed or expected to occur.

One-hit model A dose-response mathematical model that assumes a single biological event can initiate a response. It is represented by a dose-response model of the form $P(d) = [1 - e^{-\lambda d}]$, where $P(d)$ is the probability of cancer from a lifetime continuous exposure at a dose rate, d, and λ is a constant. The one-hit model is based on the concept that a tumor can be induced after a single susceptible target or receptor has been exposed to a single effective unit dose of an agent. *Gamma (Multi-hit) model*—is a generalization of the one-hit model for low-dose extrapolation. It defines the probability, $P(d)$, that an individual will respond to lifetime, continuous exposure to dose, d, by the use of a gamma function.

Organ A group of several tissue types that unite to form structures to perform a special function within an organism.

Parameters Terms in a model that determine the specific model form. For computational models, these terms are fixed during a model run or simulation, and they define the model output. They can be changed in different runs as a method of conducting sensitivity analysis or to achieve calibration goals.

Particulate matter Small/fine, discrete, solid or liquid particles/bodies, especially those suspended in a liquid or gaseous medium—such as dust, smoke, mist, fumes, or smog suspended in air or atmospheric emissions.

Partitioning Refers to the state of separation or division of a given substance into two or more compartments. This consists of a chemical equilibrium condition in which a chemical's concentration is apportioned between two different phases, according to the partition coefficient. *Partition coefficient*—is a term used to describe the relative amount of a substance partitioned between two different phases, such as a solid and a liquid or a liquid and a gas. It is the ratio of the chemical's concentration in one phase to its concentration in the other phase. For instance, a *blood-to-air partition coefficient* is the ratio of a chemical's concentration between blood and air when at equilibrium.

Pathway Any specific route via which environmental chemicals or stressors take in order to travel away from the source in order to reach potential receptors or individuals.

PEL (Permissible exposure limit) A maximum (legally enforceable) allowable level for a chemical in workplace air.

Persistence Attribute of a chemical substance which describes the length of time that such substance remains in a particular environmental compartment before it is physically removed, chemically modified, or biologically transformed.

pH A measure of the acidity or alkalinity of a material or medium.

Pharmacodynamic (PD) models Mathematical descriptions simulating the relationship between a biologically effective dose and the occurrence of a tissue response over time. [NB: These may also be referred to by *'toxicodynamic (TD) models'*.]

Pharmacokinetic (PK) models Mathematical descriptions simulating the relationship between external exposure level and chemical concentration in biological matrices over time. PK models take into account absorption, distribution, metabolism and elimination of the administered chemical and its metabolites. [NB: These may also be referred to as *'toxicokinetic (TK) models'*.]

Pharmacokinetics Study of changes in toxicant or substance characteristics (e.g., via absorption, distribution, metabolism/biotransformation, and excretion) in parts of the body of an organism over time.

Physiologically-based pharmacokinetic (PB-PK) models Models that estimate the dose to target tissue by taking into account the rate of absorption into the body, distribution and storage in tissues, as well as metabolism and excretion on the basis of interplay among critical physiological, physicochemical and biochemical determinants. They are indeed the type of models that find broad usefulness especially in predicting specific tissue dose under a range of exposure conditions. Physiologically-based compartmental models are used in characterizing the pharmacokinetic behavior of a chemical; in general, available data on blood flow rates, and on metabolic and other processes that the chemical undergoes within each compartment, are used to construct a mass-balance

framework for the PB-PK model. [NB: These may also be referred to as *'physiologically-based toxicokinetic (PB-TK) models'*.]

Pica The behavior in children and toddlers (usually under age 6 years) involving the intentional eating/mouthing of large quantities of dirt and other objects. More broadly stated, it may be seen as a behavior characterized by deliberate ingestion of non-nutritive substances (such as contaminated soil) by anyone in a (sub)population.

Plume (*or *contaminant plume) A zone containing predominantly dissolved (or vapor phase) and sorbed contaminants that usually originates from a given contaminant or pollution source areas. It refers to an area of chemicals in a particular medium (such as air or groundwater), moving away from its source in a long band or column. A plume can be a column of smoke from a chimney, or chemicals moving with groundwater; common examples may consist of a body of contaminated groundwater or vapor originating from a specific source and spreading out due to influences of environmental factors such as local groundwater conditions or soil vapor flow patterns, or wind directions.

PM-10, PM_{10} Particulate matter with physical/aerodynamic diameter <10 μm. It represents the respirable particulate emissions. *Aerodynamic diameter*—is the diameter of a particle with the same settling velocity as a spherical particle with unit density (1 g/cm^3); this parameter, which depends on particle density, is often used to describe particle size. *Respirable fraction (of dust) (*also, *respirable particulate matter)*—is the fraction of dust particles that enter the respiratory system because of their size distribution; generally, the size of these particles correspond to aerodynamic diameter of ≤ 10 μm.

Point of departure (POD) The dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence, or a change in response level from a dose response model (benchmark dose or concentration), or a no observed-adverse-effect level or lowest-observed-adverse effect level for an observed incidence or change in level or response.

Pollution (*or *contamination) Refers to the release of a physical, chemical, or biological agent into an environment; this typically has the potential to impact human and/or ecological health.

Population-at-risk (PAR) A population group or subgroup that is more susceptible or sensitive to a hazard or chemical exposure than is the general population.

Population excess cancer burden An upper-bound estimate of the increase in cancer cases in a population as a result of exposure to a carcinogen.

Potency A measure of the relative toxicity of a chemical.

Potentiation (of chemical effects) The effect of a chemical that enhances the toxicity of another chemical.

ppb (parts per billion) An amount of substance in a billion parts of another material—also expressed by μg/kg or μg/liter, and equivalent to (1×10^{-9}). [NB: A billion is often used to represent a thousand millions, i.e., 10^{-9}, in some places, such as in the USA and France; whereas a billion represents a

million millions, i.e., 10^{-12}, in some other places, such as in the UK and Germany.]

ppm (parts per million) An amount of substance in a million parts of another material—also expressed by mg/kg or mg/L, and equivalent to (1×10^{-6}).

ppt (parts per trillion) An amount of substance in a trillion parts of another material—also expressed by *ng*/kg or *ng*/L and equivalent to (1×10^{-12}). [NB: A trillion is often used to represent a million times a million or a thousand billions, i.e., 10^{-12}, in some places, such as in the USA and France; whereas a trillion represents a million billions, i.e., 10^{-18}, in some other places, such as in the UK and Germany.]

Prevalence The proportion of disease cases that exist within a population at a specific point in time, relative to the number of individuals within that population at the same point in time.

Probability The likelihood of an event occurring—numerically represented by a value between 0 and 1; a probability of 1 means an event is certain to happen, whereas a probability of 0 means an event is certain *not* to happen.

Probit model A dose-response model that can be derived under the assumption that individual tolerance is a random variable following a lognormal distribution. A probit, or probability unit, is obtained by modifying the standard variate of the standardized normal distribution; this transformation can then be used in the analysis of dose-response data used in a risk characterization.

Proxy concentration Assigned chemical concentration value for situations where sample data may not be available, or when it is impossible to quantify accurately.

Public health education A program of activities to promote health and provide information and training about hazardous substances in the human environments that will result in the reduction of exposure, illness, and/or disease. This type of program may include diagnosis and treatment information for health care providers, as well as activities in communities to enable them to prevent or mitigate the health effects from exposure to hazardous substances in the human environments.

Public health risk management Action designed to prevent exposures and/or to mitigate or prevent adverse health effects in populations experiencing chemical exposure problems. Public health mitigation actions can be identified from information developed in public health exposure and risk assessments, as well as from environmental and public health monitoring activities. These actions may be comprised of the removal or separation of individuals from exposure sources (as for example, by providing an alternative water supply); conducting biologic indicators of exposure studies to assess exposure; and providing health education for health care providers and community members.

Pulmonotoxicity Adverse effects or disease states produced by toxicants in the respiratory system of an organism.

Qualitative Description of a situation without numerical specifications.

Quality assurance (QA) A system of activities designed to assure that the quality control system in a study or investigation is performing adequately. It typically would consist of the management of information and data sets from an investigation, to ensure that they meet the data quality objectives. *Quality control (QC)*—a system of specific efforts designed to test and control the quality of data obtained in an investigation. This comprises of the management of activities involved in the collection and analysis of data to assure they meet the data quality objectives—and it also represents the system of activities required to provide information as to whether the quality assurance system is performing adequately.

Quantitation limit (QL) The lowest level at which a chemical can be accurately and reproducibly quantitated. It usually is equal to the instrument detection limit (IDL) multiplied by a factor of 3 to 5, but varies for different chemicals and different samples.

Quantitative Description of a situation that is presented in reasonably exact numerical terms.

Reasonable maximum exposure (RME) A concept that attempts to identify the highest exposure (and, therefore, the greatest risk) that could reasonably be expected to occur in a given population.

Receptor Members of a potentially exposed population, such as persons or organisms that are potentially exposed to concentrations of a particular chemical compound of concern. *Sensitive receptor*—individual in a population who is particularly susceptible to health impacts due to exposure to a chemical substance.

Reference concentration (RfC) An estimate of a daily inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious non-cancer effects during a lifetime. It represents a concentration of a non-carcinogenic chemical substance in an environmental medium to which exposure can occur over a prolonged period without expected adverse effect; the medium in this case is usually air—with the concentration expressed in mg of chemical per m^3 of air. Generally, RfCs are available from databases such as US EPA's Integrated Risk Information System (IRIS) – and serves as the toxicity value for a chemical in human health risk assessment used for evaluating the non-carcinogenic effects that could result from exposures to chemicals of concern [See, Appendix D].

Reference dose (RfD) The estimate of lifetime daily oral exposure of a non-carcinogenic substance for the general human population (including sensitive receptors) which appears to be without an appreciable risk of deleterious effects, consistent with the threshold concept. This constitutes the maximum amount of a chemical that the human body can absorb without experiencing chronic health effects, expressed in mg of chemical per kg body weight per day. Generally, RfDs are available from databases such as US EPA's Integrated Risk Information System (IRIS)—and serves as the toxicity value for a chemical in

human health risk assessment used for evaluating the non-carcinogenic effects that could result from exposures to chemicals of concern. [See, Appendix D.]

Regulatory standard A general term used to describe legally-established values above which regulatory action will usually be required. *Regulatory limit*—refers to an estimated chemical concentration in specific media that is not likely to cause adverse health effects, given a standard daily intake rate and standard body weight. The regulatory limits are calculated using information and data from the scientific literature available on exposure and health effects. *Regulatory dose*—refers to the daily exposure to the human population, as reflected in a final risk management decision.

Reliability In the context of PBPK modelling in risk assessment, refers to the trustworthiness of the model for its prediction of dose metrics. The reliability is assessed on the basis of how well the model has been tested against real data, and whether adequate sensitivity and uncertainty analyses have been conducted to support the model's ability to provide prediction of dose metrics.

Representative sample A sample that is assumed *not* to be significantly different from the population of samples available.

Respiratory system The organ system that functions to distribute air and gas exchange in an organism.

Response (toxic) The reaction of a body or organ to a chemical substance or other physical, chemical, or biological agent. This is generally reflected in the change (s) developed in the state or dynamics of an organism, system, or (sub)population in reaction to exposure to an agent.

Risk The probability or likelihood of an adverse consequence/effect from a hazardous situation or hazard, or the potential for the realization of undesirable adverse consequences from impending events. In chemical exposure situations, it is generally used to provide a measure of the probability and severity of an adverse effect to health, property, or the environment under specific circumstances of exposure to a chemical agent or a mixture of chemicals. In quantitative probability terms, risk may be expressed in values ranging from zero (representing the certainty that harm will not occur) to one (representing the certainty that harm will occur). In risk assessment practice, the following represent examples of how risk is typically expressed: 1E-4 or 10^{-4} = a risk of 1/10,000; 1E-5 or 10^{-5} = 1/100,000; 1E-6 or 10^{-6} = 1/1,000,000; 1.3E-3 or 1.3×10^{-3} = a risk of 1.3/1000 = 1/770; 8E-3 or 8×10^{-3} = a risk of 1/125; and 1.2E-5 or 1.2×10^{-5} = a risk of 1/83,000. *Individual risk*—refers to the probability that an individual person in a population will experience an adverse effect from exposures to hazards. It is used to define the frequency at which an individual may be expected to sustain a given level of harm from the realization of specified hazards. In general, this is identical to 'population' or 'societal' risk—unless if specific population subgroups can be identified that have different (i.e., higher or lower) risks. *Societal (*or *population) risk*—refers to the relationship between the frequency and the number of people suffering from a specified level of harm in a given population, as a result of the realization of

specified hazards. *Relative risk*—refers to the ratio of incidence or risk among exposed individuals to incidence or risk among non-exposed individuals. *Residual risk*—refers to the risk of adverse consequences that remains after corrective actions have been implemented. *Cumulative risk*—refers to the total added risks from all sources and exposure routes that an individual or group is exposed to. *Aggregate risk*—refers to the sum total of individual increased risks of an adverse health effect in an exposed population.

Risk acceptability/acceptance Refers to the willingness of an individual, group, or society to accept a specific level of risk in order to obtain some reward or benefit.

Risk analysis A process for controlling situations where an organism, system, or (sub)population could be exposed to a hazard. The risk analysis process is generally viewed as consisting of three key components—namely, risk assessment, risk management, and risk communication.

Risk appraisal A review of whether existing or potential biologic receptors are presently, or may in the future, be at risk of adverse effects as a result of exposures to chemicals originating or found in the human environments.

Risk assessment The determination of the type and degree of hazard posed by an agent; the extent to which a particular group of receptors have been or may become exposed to the agent; and the present or potential future health risk that exists due to the agent. It generally comprises of a methodology that combines exposure assessment with health and environmental effect data to estimate risks to human or environmental target organisms that may arise from exposure to various hazardous substances. The process is intended to calculate or estimate the risk to a given target organism, system, or (sub)population—including the identification of attendant uncertainties, following exposure to a particular agent, and taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system. In the context of human exposure to chemical substances, risk assessment involves the determination of potential adverse health effects from exposure to the chemicals of potential concern—including both quantitative and qualitative expressions of risk. Overall, the process of risk assessment involves four key steps, namely: hazard identification, dose-response assessment (or hazard characterization), exposure assessment, and risk characterization.

Risk-based concentration A chemical concentration determined based on an evaluation of the compound's overall risk to health upon exposure.

Risk characterization The qualitative and, wherever possible, quantitative determination (including attendant uncertainties) of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub)population, under defined exposure conditions. It generally would consist of the estimation of the incidence and severity of the adverse effects likely to occur in a human population or ecological group due to actual or predicted exposure to a substance or hazard.

Risk communication Activities carried out to ensure that messages and strategies designed to prevent exposure, adverse health effects, and diminished quality of

life are effectively communicated to the public and/or stakeholders. As part of a broader risk prevention strategy, risk communication supports education efforts by promoting public awareness, increasing knowledge, and motivating individuals to take action to reduce their exposure to hazardous substances.

Risk control The process of managing risks associated with a hazard situation. It may involve the implementation, enforcement, and re-evaluation of the effectiveness of corrective measures from time to time.

Risk decision The complex public policy decision relating to the control of risks associated with hazardous situations.

Risk determination An evaluation of the environmental and health impacts associated with chemical releases and/or exposures.

Risk estimation The process of quantifying the probability and consequence values for a hazard situation. In general, it is comprised of the quantification of the probability, including attendant uncertainties, that specific adverse effects will occur in an organism, system, or (sub)population due to actual or predicted exposure. The process is used to determine the extent and probability of adverse effects of the hazards identified, and to produce a measure of the level of health, property, or environmental risks being assessed. A *risk estimate* is comprised of a description of the probability that a potential receptor exposed to a specified dose of a chemical will develop an adverse response.

Risk evaluation This generally refers to the establishment of a qualitative or quantitative relationship between risks and benefits of exposure to an agent—involving the complex process of determining the significance of the identified hazards and estimated risks to the system concerned or affected by the exposure, as well as the significance of the benefits brought about by the agent. The effort is made up of the complex process of developing acceptable levels of risk to individuals or society. It is the stage at which values and judgments enter into the decision-making process.

Risk group A real or hypothetical exposure group composed of the general or specific population groups.

Risk management The steps and processes taken to reduce, abate, or eliminate the risk that has been revealed by a risk assessment. For chemical exposure situations, it consists of measures or actions taken to ensure that the level of risk to human health or the environment as a result of possible exposure to the chemicals of concern does not exceed the pre-established acceptable limit (e.g., 1E-06). The process focuses on decisions about whether an assessed risk is sufficiently high to present a public health concern, and also about the appropriate means for controlling the risks that are judged to be significant. The decision-making process involved takes account of political, social, economic, and engineering constraints, together with risk-related information, in order to develop, analyze, and compare management options and then select the appropriate managerial or regulatory response to a potential hazard situation.

Risk perception Refers to the magnitude of a risk as is perceived by an individual or population. It consists of a convolution of the measured risk together with the pre-conceptions of the observer.

Risk reduction The action of lowering the probability of occurrence and/or the value of a risk consequence, thereby reducing the magnitude of the risk.

Risk-specific dose (RSD) An estimate of the daily dose of a carcinogen which, over a lifetime, will result in an incidence of cancer equal to a given specified (usually the acceptable) risk level.

Risk tolerability A willingness to 'live with' a risk, and to keep it under review. 'Tolerances' refer to the extent to which different groups or individuals are prepared to tolerate identified risks.

Sample quantitation limit (SQL) **(also called** ***practical quantitation limit, PQL)*** The lowest level that can be reliably achieved within specified limits of precision and accuracy during routine laboratory operating conditions. It represents a detection limit that has been corrected for sample characteristics, sample preparation, and analytical adjustments such as dilution. Typically, the PQL or SQL will be about 5 to 10 times the chemical-specific detection limit.

Sampling and analysis plan (SAP) Documentation that consists of a quality assurance project plan (QAPP) and a field sampling plan (FSP). The *QAPP*—contains documentation of all relevant QA and QC programs for the case-specific project. The *FSP*—is a documentation that defines in detail, the sampling and data gathering activities to be used in the investigation of a potential environmental contamination or chemical exposure problem.

Sensitivity The degree to which the outputs of a quantitative assessment are affected by changes in selected input parameters or assumptions.

Sensitivity analysis A method used to examine the operation of a system by measuring the deviation of its nominal behavior due to perturbations in the performance of its components from their nominal values. In risk assessment, this may involve an analysis of the relationship of individual factors (such as chemical concentration, population parameter, exposure parameter, and environmental medium) to variability in the resulting estimates of exposure and risk. Typically, it consists of a quantitative evaluation of how input parameters influence the model output (e.g. dose metrics).

Simulation System behavior (e.g. blood kinetic profile in exposed organism) predicted by solving the differential and algebraic equations constituting a model.

Skin adherence The property of a material which causes it to be retained on the surface of the epidermis (i.e., adheres to the skin).

Skin (or dermal) permeability coefficient Denoted by K_p (cm/hr), this is a flux value (normalized for concentration) that represents the rate at which a chemical penetrates the skin.

Solubility A measure of the ability of a substance to dissolve in a fluid.

Sorption The processes that remove solutes from the fluid phase and concentrate them on the solid phase of a medium.

Standard deviation The most widely used statistical measure to describe the dispersion of a data set—defined for a set of n values as follows:

$$s = \sqrt{\frac{\sum_{i=1}^{n} (X_i - X_m)^2}{(n-1)}}$$

where X_m is the arithmetic mean for the data set of n values. The higher the value of this descriptor, the broader is the dispersion of data set about the mean.

Statistical Significance The probability that a result is likely to be due to chance alone. By convention, a difference between two groups is usually considered statistically significant if chance could explain it only 5% of the time or less—albeit study design considerations may influence the *a priori* choice of a different statistical significance level.

Stochastic model A model that involves random variables. [See also, *variable*.]

Stochasticity Variability in parameters (or in models containing such parameters) that may be attributed to the inherent variability of the system under consideration.

Stressor (*also, *Agent) Any physical, chemical, or biological entity that can induce an adverse response in an organism. *Stressor-response profile*—summarizes the data on the effects of a stressor and the relationship of the data to the assessment endpoint.

Structure-activity relationship Relationships of biological activity or toxicity of a chemical to its chemical structure or sub-structure.

Subchronic Relating to intermediate duration, and usually used to describe studies or exposure levels spanning 5 to 90 days duration. *Subchronic daily intake (SDI)*—refers to the exposure, expressed in mg/kg-day, averaged over a portion of a lifetime. *Subchronic exposure*—refers to the short-term, high-level exposure to chemicals, i.e., the maximum exposure or doses to a chemical over a portion (approximately 10%) of a lifetime of an organism. In general, this represents a contact between an agent and a target of intermediate duration between acute and chronic.

Surrogate data A substitute data or measurement on a given substance or agent that is used to estimate analogous or corresponding values of another substance/agent.

Susceptibility Generally refers to the capacity to be affected. Variation in risk reflects susceptibility; in this regard, person can be at greater or less risk relative to the person in the population who is at median risk because of such characteristics as age, sex, genetic attributes, socioeconomic status, prior exposure to harmful agents, and stress.

Synergism (of chemical effects) A pharmacologic or toxicologic interaction in which the combined effect of two or more chemicals is greater than the sum of the effect of each chemical acting alone. In other words, it is the aspect of two or more agents interacting to produce an effect greater than the sum of the agents' individual effects. More generally, this represents the effects arising from a

combination of two or more events, efforts, or substances that are greater than would be expected from adding the individual effects.

Systemic Pertaining to, or affecting, the body as a whole—or acting in a portion of the body other than the site of entry; generally used to refer to non-cancer effects. *Systemic effect*—relates to those effects that require absorption and distribution of the toxicant to a site distant from its original entry point, and at which distant point any effects are produced. Most chemical substances that produce systemic toxicity do not cause a similar degree of toxicity in all organs, but usually demonstrate major toxicity to one or two organs; these are referred to as the *target organs* of toxicity for that chemical. *Systemic toxicity*—relates to toxic effects as a result of absorption and distribution of a toxicant to a site distant from its entry point, at which distant point any effects are produced. It is noteworthy that not all chemicals that produce systemic effects cause the same degree of toxicity in all organs.

Target organ (or, Tissue) The biological organ(s) that are most adversely affected by exposure to a chemical substance or physical agent. That is, the organ affected by a specific chemical in a particular species. *Target organ toxicity*—the adverse effects or disease states manifested in specific organs of the body of an organism.

Teratogenic Structural developmental defects due to exposure to a chemical agent during formation of individual organs.

Threshold The lowest dose or exposure of a chemical at which a specified measurable/deleterious effect is observed, and below which such effect is not observed. *Threshold dose*—is the minimum exposure dose of a chemical that will evoke a stipulated toxicological response. *Toxicological threshold*—refers to the concentration at which a compound begins to exhibit toxic effects. *Threshold limit*—a chemical concentration above which adverse health and/or environmental effects may occur. *Threshold hypothesis*—refers to the assumption that no chemical injury occurs below a specified level of exposure or dose.

Threshold chemical/toxicant **(also, *nonzero threshold chemical)*** Refers to a substance that is known or assumed to have no adverse effects below a certain dose—i.e., a chemical for which the critical effect is observed or expected to occur only above a certain dose or exposure concentration. *Non-threshold chemical* (also called, *zero threshold chemical*)—refers to a substance that is known, suspected, or assumed to potentially cause some adverse response or toxic effect at any dose above zero. Thus, any level of exposure is deemed to involve some risk—and this has traditionally been used only in regard to carcinogenesis.

Thrombocytes (**also, *Platelets)*** The smallest cellular components of blood in an organism.

Tissue A collection of cells that together perform a similar function within an organism. This may also be identified as *target organ*.

Tolerable intake is the estimated maximum amount of an agent, expressed on a body mass basis, to which each individual in a (sub)population may be exposed over a specified period without appreciable risk.

Tolerance limit The level or concentration of a chemical residue in a media of concern above which adverse health effects are possible, and above which levels corrective action should therefore be undertaken.

Toxic Harmful or deleterious with respect to the effects produced by exposure to a chemical substance. *Toxic substance*—refers to any material or mixture that is capable of causing an unreasonable threat or adverse effects to human health and/or the environment.

Toxicant Any synthetic or natural chemical with an ability to produce adverse health effects.

Toxicity The inherent property of a substance to cause any adverse physiological effects (on living organisms). It represents the degree to which a chemical substance elicits a deleterious or adverse effect upon the biological system of an organism exposed to the substance over a designated time period. This generally indicates the harmful effects produced by a chemical substance—and reflects on the quality or degree of being poisonous or harmful to human or ecological receptors. *Delayed toxicity*—refers to the development of disease states or symptoms long (usually several months or years) after exposure to a toxicant. *Immediate toxicity*—refers to the rapid development or onset of disease states or symptoms following exposure to a toxicant.

Toxicity assessment Evaluation of the toxicity of a chemical based on all available human and animal data. It consists of the characterization of the toxicological properties and effects of a chemical substance, with special emphasis on the establishment of dose-response characteristics.

Toxicity equivalency factors (TEFs) Toxicity parameters that are based on congener-specific data and the assumption that the toxicity of dioxin and dioxin-like compounds is mediated by the *Ah* receptor, and is additive. The TEF scheme compares the relative toxicity of individual dioxin-like compounds to that of TCDD (i.e., 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and related compounds), which is the known most toxic halogenated aromatic hydrocarbon in that family.

Toxicity equivalent (TEQ) Is defined as the product of the concentration, CI, of an individual 'dioxin-like compound' in a complex environmental mixture and the corresponding TCDD toxicity equivalency factor (TEF_i) for that compound. The total TEQs is the sum of the TEQs for each of the congeners in a given mixture, *viz*.,

$$Total\ \ TEQs = \sum_{i=1}^{n} (CI_i \times TEF_i)$$

Toxicodynamics The study of the mechanisms by which toxicants produce their unique effects within an organism—i.e., the study of how a toxic chemical (or metabolites derived from it) interacts with specific molecular components of cellular processes in the body. Overall, it is comprised of the process of

interaction of chemical substances with target sites and the subsequent reactions leading to adverse effects. The term has essentially the same meaning as *pharmacodynamics*, but the latter term is frequently used in reference to pharmaceutical substances.

Toxicokinetics The study of the time-dependent processes of toxicants in their interactions with living organisms—i.e., the study of how a toxic chemical is absorbed, distributed, metabolized, and excreted into and from the body. Thus, this includes the study of the absorption, distribution, storage, biotransformation, and elimination processes taking place within an organism. *Distribution*—refers to a toxicokinetic process that occurs after absorption, when toxicants enter the lymph or blood supply for transport to other regions of the body. *Storage*—is the accumulation of toxicants or their metabolites in specific tissues of an organism or as bound to circulating plasma proteins in the organism. *Elimination*—refers to the toxicokinetic processes responsible for the removal of toxicants or their metabolites from the body. By and large, the subject of toxicokinetics is comprised of the process of the uptake of potentially toxic substances by the body, the biotransformation they undergo, the distribution of the substances and their metabolites in the tissues, and the elimination of the substances and their metabolites from the body. Both the amounts and the concentrations of the substances and their metabolites are studied. The term has essentially the same meaning as *pharmacokinetics*, but the latter term tends to be restricted to the study of pharmaceutical substances.

Toxicological profile A documentation about a specific substance in which scientific interpretation is provided from all known information on the substance; this also includes specifying the levels at which individuals or populations may be harmed if exposed. The toxicological profile may also identify significant gaps in knowledge on the substance, and serves to initiate further research, where needed.

Toxicology The study of the adverse effects of chemical, biological, and physical agents on living organisms.

Uncertainty The lack of confidence in the estimate of a variable's magnitude or probability of occurrence. It refers to lack of knowledge—and is generally attributable to the lack or incompleteness of information. Thus, uncertainty can often be reduced with greater knowledge of the system, or by collecting more and better experimental or simulation data. Quantitative uncertainty analysis attempts to analyze and describe the degree to which a calculated value may differ from the true value; it sometimes uses probability distributions. Uncertainty depends on the quality, quantity, and relevance of data—as well as on the reliability and relevance of models and assumptions.

Uncertainty factor (UF) **(also called, *safety factor*)** In toxicological evaluations, this refers to a factor that is used to provide a margin of error when extrapolating from experimental animals to estimate human health risks. Broadly, it consists of a product of several single factors by which the NOAEL or LOAEL of the critical effect is divided to derive a tolerable intake. These factors account for

adequacy of the pivotal study, interspecies extrapolation, inter-individual variability in humans, adequacy of the overall database, and nature of toxicity. Indeed, the term uncertainty factor is considered to be a more appropriate expression than 'safety factor' since it avoids the notion of absolute safety, and because the size of this factor is proportional to the magnitude of uncertainty rather than safety. Ultimately, the choice of uncertainty factor should be based on the available scientific evidence. In practice, it represents one of several, generally tenfold factors, used to operationally derive the reference dose (RfD) and reference concentration (RfC) from experimental data. Basically, the UFs are intended to account for: (1) the variation in sensitivity among the members of the human population, i.e., inter-human or intraspecies variability; (2) the uncertainty in extrapolating animal data to humans, i.e., interspecies variability; (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure, i.e., extrapolating from subchronic to chronic exposure; (4) the uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and (5) the uncertainty associated with extrapolation from animal data when the data base is incomplete. A *modifying factor (MF)*—serving as a companion parameter to the UF, refers to a factor used in the derivation of an RfD or RfC. The magnitude of the MF reflects the scientific uncertainties of the study and database not explicitly treated with standard uncertainty factors (e.g., completeness of the overall database). A MF is greater than zero and less than, or equal to 10—with a typical default value of 1.

Unit cancer risk (UCR) The excess lifetime risk of cancer due to a continuous lifetime exposure/dose of one unit of carcinogenic chemical concentration (caused by one unit of exposure in the low exposure region). It is a measure of the probability of an individual developing cancer as a result of exposure to a specified unit ambient concentration.

Unit risk (UR) The upper-bound (plausible upper limit) estimate of the probability of contracting cancer as a result of constant/continuous exposure to an agent at a concentration of 1 μg/L in water, or 1 $\mu g/m^3$ in air over the individual lifetime. The interpretation of unit risk would be as follows: if unit risk $= 5.5 \times 10^{-6}$ μg/L, 5.5 excess tumors are expected to develop per 1,000,000 people, if exposed daily for a lifetime to 1 μg of the chemical in 1-L of drinking water.

Upper-bound estimate The estimate not likely to be lower than the true (risk) value. That is, an estimate of the plausible upper limit to the true value of the quantity.

Upper confidence limit, 95% (95% UCL) The upper limit on a normal distribution curve below which the observed mean of a data set will occur 95% of the time. This is also equivalent to stating that, there is at most a 5% chance of the true mean being greater than the observed value. In other words, it is a value that equals or exceeds the true mean 95% of the time. Thus, assuming a random and normal distribution, this is the range of values below which a given value will fall 95% of the time. [See also, *confidence interval*.]

Validation Process by which the reliability and relevance of a particular approach (or model) is established for a defined purpose.

Variability Variability refers to true differences in attributes due to heterogeneity or diversity. Differences among individuals in a population are referred to as *inter-individual variability*; differences for one individual over time are referred to as *intra-individual variability*. Variability is usually not reducible by further measurement or study, although it can be better characterized.

Variable In mathematics, a variable is used to represent a quantity that has the potential to change. In the physical sciences and engineering, a variable is a quantity whose value may vary over the course of an experiment (including simulations), across samples, or during the operation of a system. In statistics, a *random variable* is that whose observed outcomes may be considered products of a stochastic or random experiment; their probability distributions can be estimated from observations. Generally, when a variable is fixed to take on a particular value for a computation, it is referred to as a *parameter*.

Volatile organic compound (VOC) Any organic compound that has a great tendency to vaporize, and is susceptible to atmospheric photochemical reactions. Such chemical volatilizes (evaporates) relatively easily when exposed to air. VOCs generally consist of substances containing carbon and different proportions of other elements such as hydrogen, oxygen, fluorine, chlorine, bromine, sulfur, or nitrogen—and these substances easily become vapors or gases. A significant number of the VOCs found in human environments are commonly used as solvents (e.g., paint thinners, lacquer thinner, degreasers, and dry cleaning fluids). In general, volatile compounds are amenable to analysis by the purge and trap techniques.

Volatilization The transfer of a chemical from the liquid or solid into the gaseous phase. *Volatility*—is a measure of the tendency of a compound to vaporize or evaporate, usually from a liquid state.

Vulnerability The intrinsic predisposition of an exposed element (person, community, population, or ecologic entity) to suffer harm from external stresses and perturbations; it is based on variations in disease susceptibility, psychological and social factors, exposures, and adaptive measures to anticipate and reduce future harm, and to recover from an insult.

Weight-/Strength-of-evidence for carcinogenicity The extent to which the available biomedical and related data support the hypothesis that a substance causes cancer in humans.

Worst case A semi-qualitative term that refers to the maximum possible exposure, dose, or risk to an exposed person or group, that could conceivably occur—i.e., regardless of whether or not this exposure, dose, or risk actually occurs or is observed in a specific population. Typically, this should refer to a hypothetical situation in which everything that can plausibly happen to maximize exposure, dose, or risk actually takes place. This worst case may indeed occur (or may even be observed) in a given population; however, since this is usually a very unlikely set of circumstances, in most cases, a worst-case estimate will be somewhat

higher than actually occurs in a specific population. In most health risk assessments, a worst-case scenario is essentially a type of bounding estimate. [See also, *conservative assumption*.]

Xenobiotics Substances noticeably foreign to an organism—i.e., substances that are not naturally produced within the organism. Also, substances not normally present in the environment—such as a pesticide or other environmental pollutant. Most xenobiotics are considered pollutants.

Appendix B
Some Key Fate and Behavior Properties Affecting Environmental Chemicals

Some examples of important physical and chemical properties, processes, and parameters affecting the environmental fate and/or cross-media transfers of chemical substances often encountered in the human environments are briefly annotated below—with further detailed discussions offered in the literature elsewhere (e.g., Devinny et al. 1990; Evans 1989; Hemond and Fechner 1994; Lindsay 1979; Lyman et al. 1990; Mahmood and Sims 1986; Mansour 1993; Neely 1980; Samiullah 1990; Swann and Eschenroeder 1983; Thibodeaux 1979, 1996; USEPA 1985a, 1989; Yong et al. 1992). This is in recognition of the fact that, proper understanding of a chemical's fate and behavior/transport is generally necessary to help characterize the potential risks associated with a chemical release or environmental contamination problem – and indeed to further develop appropriate risk management and/or remedial action plans for chemical exposure problems.

Physical State

Chemical substances often encountered in the human environments may exist in any or all of three major physical states—*viz*.: solid (e.g., solids adsorbed onto and/or embedded in consumer products or materials), liquid (e.g., free product or dissolved chemicals) and vapor states (e.g., vapor phase substances). Chemical substances in the solid phase are generally less susceptible to release and migration than the fluids—albeit certain processes (such as leaching and physical transport of chemical constituents) can act as significant release mechanisms, irrespective of the physical state of a chemical substance.

K. Asante-Duah, *Public Health Risk Assessment for Human Exposure to Chemicals*,
Environmental Pollution 27, DOI 10.1007/978-94-024-1039-6

Water Solubility

The solubility of a chemical in water is the maximum amount of the chemical that will dissolve in pure water at a specified temperature. Solubility is an important factor affecting a chemical constituent's release and subsequent migration and fate in various human environments. In fact, among the various parameters affecting the fate and transport of organic chemicals in the environment, water solubility is one of the most important, especially with regards to hydrophilic compounds.

Typically, solubility affects mobility, leachability, availability for biodegradation, and the ultimate fate of a given constituent. For instance, highly soluble chemicals tend to be more easily and quickly distributed by the hydrologic system; overall, such chemicals tend to have relatively low adsorption coefficients for soils and sediments, and also relatively low bioconcentration factors in aquatic biota. Furthermore, they tend to be more readily biodegradable. Indeed, substances that are more soluble are more likely to desorb from soils and less likely to volatilize from water.

In combination with vapor pressure, water solubility yields a chemical's *Henry's Law Constant* [see below]—which determines whether or not the chemical will volatilize from water into air. In combination with the chemical's solubility in fats (obtained from the octanol-water partition coefficient), water solubility predicts whether or not a chemical will tend to concentrate in living organisms, and also whether a chemical substance will remain bound to solid materials or will leach from solid matrix into other matrices and/or offer wider opportunities for human exposures.

Diffusion

Diffusivity describes the movement of a molecule in a liquid or gas medium as a result of differences in concentrations. Diffusive processes create mass spreading due to molecular diffusion, in response to concentration gradients. Thus, diffusion coefficients are used to describe the movement of a molecule in a liquid or gas medium as a result of differences in concentration; it can also be used to calculate the dispersive component of chemical transport. In general, the higher the diffusivity, the more likely a chemical is to move in response to concentration gradients.

Dispersion

Dispersive processes create mass mixing due to system heterogeneities (e.g., velocity variations). Consequently, as a pulse of contaminant plume migrates through a soil matrix for example, the peaks in concentration become decreased through spreading. Dispersion is indeed an important attenuation mechanism that generally results in the dilution of a contaminant—with the degree of spreading or dilution being proportional to the size of the dispersion coefficients.

Volatilization

Volatilization is the process by which a chemical compound evaporates from one environmental compartment into the vapor phase. The volatilization of chemicals is indeed a very important mass-transfer process. The transfer process from the source (e.g., water-body, sediments, or soils) into the atmosphere is dependent on the physical and chemical properties of the compound in question, the presence of other pollutants, the physical properties of the source media, and the atmospheric conditions.

Knowledge of volatilization rates is important in the determination of the amount of chemicals entering the atmosphere or ambient air, and indeed the change of pollutant concentrations in the source media. Volatility is therefore considered a very important parameter for chemical hazard assessments. Some of the most important measures of a chemical's volatility or volatilization rate are enumerated below.

Boiling Point

Boiling point (BP) is the temperature at which the vapor pressure of a liquid is equal to the atmospheric pressure on the liquid. At this temperature, a substance transforms from the liquid into a vapor phase. Indeed, besides being an indicator of the physical state of a chemical, the BP also provides an indication of its volatility. Other physical properties, such as critical temperature and latent heat (or enthalpy) of vaporization may be predicted by use of a chemical's normal BP as an input.

Henry's Law Constant

Henry's Law Constant (H) provides a measure of the extent of chemical partitioning between air and water at equilibrium. It indicates the relative tendency of a constituent to volatilize from aqueous solution into the atmosphere, based on the competition between its vapor pressure and water solubility.

This parameter is particularly important to determining the potential for cross-media transport into air. In general, contaminants with low Henry's Law Constant values will tend to favor the aqueous phase, and will therefore volatilize into the atmosphere more slowly than would constituents with high values. As a general guideline: H values in the range of 10^{-7} to 10^{-5} (atm-m^3/mol) represent low volatilization; H between 10^{-5} and 10^{-3} (atm-m^3/mol) means volatilization is not rapid, but possibly significant; and $H > 10^{-3}$ (atm-m^3/mol) implies volatilization is rapid. The variation in H between chemicals is indeed quite extensive.

Vapor Pressure

Vapor pressure is the pressure exerted by a chemical vapor in equilibrium with its solid or liquid form at any given temperature. It is a relative measure of the volatility of a chemical in its pure state, and is an important determinant of the rate of volatilization. The vapor pressure of a chemical can be used to calculate the rate of volatilization of a pure substance from a surface, or to estimate a Henry's Law Constant for chemicals with low water solubility.

In general, the higher the vapor pressure, the more volatile a chemical compound, and therefore the more likely the chemical is to exist in significant quantities in a gaseous state. Thus, as an example, constituents with high vapor pressure are more likely to migrate from soil and groundwater, for onward transport into air.

The Partitioning Phenomena: Partition Coefficients

The partitioning of a chemical between several phases within a variety of environmental matrices is considered a very important fate and behavior property for the migration of chemical substances in the human environment. As an example, the *partition coefficient* (also called the *distribution coefficient*) is viewed as one of the most important parameters used in estimating the migration potential of contaminants present in aqueous solutions in contact with surface, subsurface and suspended solids (USEPA 1999). The *partition coefficient* is a measure of the distribution of a given compound in two phases, and is expressed as a concentration ratio. Several important measures of the partitioning phenomena are enumerated below.

Water/Air Partition Coefficient

The water/air partition coefficient (K_w) relates the distribution of a chemical between water and air. It consists of an expression that is equivalent to the reciprocal of Henry's Law constant (H), i.e.,

$$K_w = \frac{C_{water}}{C_{air}} = \frac{1}{H} \tag{B.1}$$

where: C_{air} is the concentration of the chemical in air (expressed in units of μg/L), and C_{water} is the concentration of the chemical in water (in μg/L).

Octanol/Water Partition Coefficient

The octanol/water partition coefficient (K_{ow}) is defined as the ratio of a chemical's concentration in the octanol phase (organic) to its concentration in the aqueous phase of a two-phase octanol/water system, represented by:

$$K_{ow} = \frac{concentration\ in\ octanol\ phase}{concentration\ in\ aqueous\ phase} \tag{B.2}$$

This dimensionless parameter provides a measure of the extent of chemical partitioning between water and octanol at equilibrium. It has indeed become a particularly important parameter in studies of the environmental fate of organic chemicals.

In general, K_{ow} can be used to predict the magnitude of an organic constituent's tendency to partition between the aqueous and organic phases of a two-phase system, such as surface water and aquatic organisms. For instance, the higher the value of a K_{ow}, the greater would be the tendency of an organic constituent to adsorb to soil or waste matrices that contain appreciable organic carbon, or to accumulate in biota. Indeed, this parameter has been found to relate to water solubility, soil/sediment adsorption coefficients, and bioaccumulation factors for aquatic life.

Broadly speaking, chemicals with low K_{ow} (<10) values may be considered relatively hydrophilic, whereas those with high K_{ow} ($>10{,}000$) values are very hydrophobic. Thus, the greater the K_{ow}, the more likely a chemical is to partition to octanol than to remain in water. In fact, high K_{ow} values are generally indicative of a chemical's ability to accumulate in fatty tissues and therefore bioaccumulate in the foodchain. It is also a key variable in the estimation of skin permeability for chemical constituents. All in all, the hydrophilic chemicals tend to have high water solubilities, small soil or sediment adsorption coefficients, and small bioaccumulation factors for aquatic life.

Organic Carbon Adsorption Coefficient

The sorption characteristics of a chemical may be normalized to obtain a sorption constant based on organic carbon that is essentially independent of any solid or soil material. For instance, the organic carbon adsorption coefficient (K_{oc}) provides a measure of the extent of partitioning of a chemical constituent between soil or sediment organic carbon and water at equilibrium.

Also called the organic carbon partition coefficient, K_{oc} is a measure of the tendency for organics to be adsorbed by soil and sediment, and is expressed by the following relationship:

$$K_{oc}[mL/g] = \frac{mg\ chemical\ adsorbed\ per\ g\ weight\ of\ soil\ or\ sediment\ organic\ carbon}{mg\ chemical\ dissolved\ per\ mL\ of\ water} \quad (B.3)$$

As an example, the extent to which an organic constituent partitions between the solid and solution phases of a saturated or unsaturated soil, or between runoff water and sediment, is determined by the physical and chemical properties of both the constituent and the soil (or sediment). It is notable that the K_{oc} is chemical-specific and largely independent of the soil or sediment properties. The tendency of a constituent to be adsorbed to soil is, however, dependent on its properties and also on the organic carbon content of the soil or sediment.

Values of K_{oc} typically range from 1 to 10^7—and the higher the K_{oc}, the more likely a chemical is to bind to soil or sediment than to remain in water. In other words, constituents with a high K_{oc} have a tendency to partition to the soil or sediment. In fact, this value is also a measure of the hydrophobicity of a chemical; in general, the more highly sorbed, the more hydrophobic (or the less hydrophilic) a substance.

Soil-Water Partition Coefficient

The mobility of contaminants in soil depends not only on properties related to the physical structure of the soil, but also on the extent to which the soil material will retain, or adsorb, the pollutant constituents. The extent to which a constituent is adsorbed depends on the physico-chemical properties of the chemical constituent and of the soil. The sorptive capacity must therefore be determined with reference to a particular constituent and soil pair.

The soil-water partition coefficient (K_d), also called the soil/water distribution coefficient, is generally used to quantify soil sorption. K_d is the ratio of the adsorbed contaminant concentration to the dissolved concentration at equilibrium, and for most environmental concentrations, it can be approximated by the following relationship:

$$K_d[mL/g] = \frac{concentration\ of\ adsorbed\ chemical\ in\ soil\ (mg\ chemical\ per\ g\ soil)}{concentration\ of\ chemical\ in\ solution\ in\ water\ (mg\ chemical\ per\ mL\ water)} \quad (B.4)$$

Invariably, the distribution of a chemical between water and an adjoining soil or sediment may be described by this equilibrium expression that relates the amount of chemical sorbed to soil or sediment to the amount in water at equilibrium. As an example, it is notable that the K_d parameter is very important in estimating the

potential for the adsorption of dissolved contaminants in contact with soils or similar geologic materials. K_d provides a soil- or sediment-specific measure of the extent of chemical partitioning between soil or sediment and water, unadjusted for dependence on organic carbon. On this basis, K_d describes the sorptive capacity of the soil and allows estimation of the concentration in one medium, given the concentration in the adjoining medium. For hydrophobic contaminants:

$$K_d = f_{oc} K_{oc} \tag{B.5}$$

where: f_{oc} is the fraction of organic carbon in the soil.

In general, the higher the value of K_d, the less mobile is a contaminant; this is because, for large values of K_d, most of the chemical remains stationary and attached to soil particles due to the high degree of sorption. Thus, the higher the K_d the more likely a chemical is to bind to soil or sediment than to remain in water. [By the way, to minimize the degree of uncertainties in contaminant behavior assessment and risk computations, site-specific K_d values should generally be utilized whenever possible.]

Bioconcentration Factor

The bioconcentration factor (BCF) is the ratio of the concentration of a chemical constituent in an organism or whole body (e.g., a fish) or specific tissue (e.g., fat) to the concentration in its surrounding medium (e.g., water) at equilibrium, expressed as follows:

$$\begin{aligned} \mathrm{BCF} &= \frac{[\textit{concentration in biota}]}{[\textit{concentration in surrounding medium}]} \\ &= \frac{[\textit{mg of chemical per g of biota}(e.g.,\ \textit{fish})]}{[\textit{mg of chemical per mL medium material}\ (e.g.,\ \textit{water})]} \end{aligned} \tag{B.6}$$

As a general example, the BCF indicates the degree to which a chemical residue may accumulate in aquatic organisms, coincident with ambient concentrations of the chemical in water; it is a measure of the tendency of a chemical in water to accumulate in the tissue of an organism. In this regard, the concentration of the chemical in the edible portion of the organism's tissue can be estimated by multiplying the concentration of the chemical in surface water by the fish BCF for that chemical. Thus, the average concentration in fish or biota is given by:

$$C_{fish-biota}(\mu g/kg) = C_{water}(\mu g/L) \times BCF \tag{B.7}$$

where: C_{water} is the concentration in water. This parameter is indeed an important determinant for human exposure to chemicals via ingestion of aquatic foods. The

partitioning of a chemical between water and biota (e.g., fish) also gives a measure of the hydrophobicity of the chemical.

Values of BCF typically range from 1 to over 10^6. In general, constituents that exhibit a BCF greater than unity are potentially bioaccumulative, but those exhibiting a BCF greater than 100 cause the greatest concern (USEPA, 1987a). Ranges of BCFs for various constituents and organisms can be used to predict the potential for bioaccumulation, and therefore to determine whether, as an example, the sampling of biota is really a necessary part of an environmental characterization program. The accumulation of chemicals in aquatic organisms is indeed of increased concern as a significant source of environmental and health hazard.

Sorption and the Retardation Factors

Sorption, which collectively accounts for both adsorption and absorption, is the partitioning of a chemical constituent between the solution and solid phases. In this partitioning process, molecules of the dissolved constituents leave the liquid phase and attach to the solid phase; this partitioning continues until a state of equilibrium is reached. As an example of its real world application, the practical result of the partitioning process gives rise to a phenomenon called *retardation*—in which the effective velocity of the chemical constituents in a groundwater system is less than that of a 'pure' groundwater flow.

Retardation is the chemical-specific, dynamic process of adsorption to, and desorption from aquifer materials. It is typically characterized by a parameter called the *retardation factor* or *retardation coefficient*. In the assessment of the environmental fate and transport properties of chemical contaminants, reversible equilibrium and controlled sorption may be simulated by the use of the retardation factor or coefficient.

Retardation Factor

A contaminant retardation factor is the parameter commonly used in environmental transport models to describe the chemical interaction between the contaminant and typically the 'surrounding'/'embedding' geological materials (such as soils, sediments and similar geological formations). It includes processes such as surface adsorption, absorption into the soil structure or geological materials matrix, precipitation, and the physical filtration of colloids (USEPA 1999). Specifically, it describes the rate of contaminant transport relative to that of groundwater.

Mathematically, the retardation factor, R_f, is defined as the ratio of $[C_{mobile} + C_{sorbed}]$ to C_{mobile}, where C_{mobile} and C_{sorbed} are the mobile and sorbed chemical concentrations, respectively. Thus,

$$R_f = 1 + \frac{C_{sorbed}}{C_{mobile}} \tag{B.8}$$

It is noteworthy that, the chemical retardation term does not equal unity when the solute interacts with the soil. Indeed, the retardation term is almost always greater than unity (1) due to solute sorption to soils—albeit there are extremely rare cases when the retardation factor is actually less than 1, and such circumstances are thought to be caused by anion exclusion (USEPA 1999).

R_f can be calculated for a contaminant as a function of the chemical's soil-water partition coefficient (K_d), and also the bulk density (β) and porosity (n) of the medium through which the contaminant is moving. Typically, the retardation factors are calculated for linear sorption, in accordance with the following relationship:

$$R_f = 1 + \frac{bK_d}{n} = \left[1 + \frac{bK_{oc}f_{oc}}{n}\right] \tag{B.9}$$

where: $K_d = K_{oc} \times f_{oc}$, and f_{oc} is the organic carbon fraction.

It is notable that the velocity of a contaminant is one of the most important variables in any groundwater quality modeling study. Sorption affects the solute seepage velocity through retardation, which is a function of R_f. Estimating R_f is therefore very important if solute transport is to be adequately represented. In the aquifer system, the retardation factor gives a measure of how fast a compound moves in relation to groundwater (Hemond and Fechner 1994; Nyer 1993; USEPA 1999). Defined in terms of groundwater and solute concentrations, therefore,

$$R_f = \frac{groundwater\ \ velocity[v]}{solute\ \ velocity\ \ [v^*]} \tag{B.10}$$

As an illustrative example, a retardation factor of two (2) indicates that the specific compound is traveling at one-half the groundwater flow rate, and a retardation factor of five (5) means that a plume of the dissolved compound will advance only one-fifth as fast as the groundwater parcel. In consequence, this will usually become a very important parameter in the design of groundwater remediation systems; in particular, sorption can have major effects on pump-and-treat cleanup times and volumes of water to be removed from a contaminated aquifer system. That is, the retardation factor may be used to determine how much the cleanup time might increase. Thus, if it would have taken 1 year to clean up a site under a 'no-sorption' scenario, then this is going to take 2 years (for R_f of 2) or 5 years (for R_f of 5) due to the sorption effects. Similarly, if it would have taken 10 years to clean up the site under a 'no-sorption' scenario, then this is now going to take 20 years (for R_f of 2) or 50 years (for R_f of 5) due to the sorption effects.

Sorption

Under equilibrium conditions, a sorbing solute will partition between the liquid and solid phases according to the value of R_f. The fraction of the total contaminant mass contained in an aquifer that is dissolved in the solution phase, $F_{dissolved}$, and the sorbed fraction, F_{sorbed}, can be calculated as follows:

$$F_{dissolved} = \frac{1}{R_f} \tag{B.11}$$

$$F_{sorbed} = 1 - \left[\frac{1}{R_f}\right] \tag{B.12}$$

In general, if a compound is strongly adsorbed, then it also means this particular compound will be highly retarded.

Degradation

Degradation, whether biological, physical or chemical, is often reported in the literature as a half-life—and this is typically measured in days. It is generally expressed as the time it takes for one-half of a given quantity of a compound to be degraded. A number of important measures of the degradation phenomena are described below.

Chemical Half-Lives

Half-lives are used as measures of persistence, since they indicate how long a chemical will remain in various environmental media; long half-lives (e.g., greater than a month or a year) are characteristic of persistent constituents.

In general, media-specific half-lives provide a relative measure of the persistence of a chemical in a given medium, although actual values can vary greatly depending on case-specific conditions. For example, the absence of certain microorganisms at a site, or the number of microorganisms, can influence the rate of biodegradation, and therefore, the half-life for specific compounds. As such, half-life values should be used only as a general indication of a chemical's persistence in the environment. On the whole, however, the higher the half-life value, the more persistent a chemical is likely to be.

Biodegradation

Biodegradation is one of the most important environmental processes affecting the breakdown of organic compounds. It results from the enzyme-catalyzed transformation of organic constituents, primarily by microorganisms. As a result of biodegradation, the ultimate fate of a constituent introduced into several environmental systems (e.g., soil, water, etc.) may be that of any compound other than the parent compound that was originally released into the environment. Biodegradation potential should therefore be carefully evaluated in the design of environmental monitoring programs—in particular for contaminated site assessment programs. It is noteworthy that biological degradation may also initiate other chemical reactions—such as oxygen depletion in microbial degradation processes, creating anaerobic conditions and the initiation of redox-potential-related reactions.

Chemical Degradation

Similar to photodegradation [see section below] and biodegradation [see preceding section], chemical degradation—primarily through hydrolysis and oxidation/reduction (redox) reactions—can also act to change chemical constituent species from what the parent compound used to be when it was first introduced into the environment. For instance, oxidation may occur as a result of chemical oxidants being formed during photochemical processes in natural waters. Similarly, reduction of constituents may take place in some surface water environments (primarily those with low oxygen levels). Hydrolysis of organics usually results in the introduction of a hydroxyl group (–OH) into a constituent structure; hydrated metal ions (particularly those with a valence ≥ 3) tend to form ions in aqueous solution, thereby enhancing species solubility.

Photolysis

Photolysis (or photodegradation) can be an important dissipative mechanism for specific chemical constituents in the environment. Similar to biodegradation [noted above], photolysis may cause the ultimate fate of a constituent introduced into an environmental system (e.g., surface water, soil, etc.) to be different from the constituent originally released. Hence, photodegradation potential should be carefully evaluated in designing sampling and analysis plans, as well as environmental monitoring programs.

Miscellaneous Equilibrium Constants from Speciation

Several equilibrium constants will usually be important predictors of a compound's chemical state in solution—and such parameters may indeed play key roles in appraising the fate and behavior attributes of chemicals often encountered in human environments. For example, a constituent that is dissociated (ionized) in solution will be more soluble, and therefore more likely to be released into the environment—and thence more likely to migrate in a surface water body, etc.; it is also noteworthy that ionic metallic species are likely to have a tendency to bind to particulate matter, if present in a surface water body, and to settle out to the sediment over time and distance.

In general, many inorganic constituents, such as heavy metals and mineral acids, can occur as different ionized species depending on the ambient pH—and organic acids, such as the phenolic compounds, do indeed exhibit similar behavior. In the end, heavy metals are removed in natural attenuation by ion exchange reactions, whereas trace organics are removed primarily by adsorption. Anyway, it is notable that metallic species also generally exhibit bioaccumulative properties; consequently, when metallic species are present in the environment, a study design that incorporates both sediment and biota sampling would typically be appropriate—perhaps even critical.

Further Reading

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Appendix C
Toxicological Parameters for Selected Environmental Chemicals

Carcinogenic and non-carcinogenic toxicity indices relevant to the estimation of human health risks—generally represented by the cancer slope factor (SF)-cum-'inhalation unit risk' (IUR) factor and reference dose (RfD)-cum-'reference concentration' (RfC), respectively—are presented in Table C.1 for selected chemical constituents that may be encountered in the human environments. A more complete and up-to-date listing may be obtained from a variety of toxicological databases—such as the Integrated Risk Information System (IRIS), developed and maintained by the US EPA [see Appendix D].

K. Asante-Duah, *Public Health Risk Assessment for Human Exposure to Chemicals*,
Environmental Pollution 27, DOI 10.1007/978-94-024-1039-6

Table C.1 Toxicological parameters of selected environmental chemicals

Chemical name	Toxicity index			
	Oral *SF* $(mg/kg\text{-}day)^{-1}$	Inhalation *UR* $(\mu g/m^3)^{-1}$	Oral *RfD* (mg/kg-day)	Inhalation *RfC* (mg/m^3)
Inorganic Chemicals				
Aluminum (Al)			1.0E + 00	5.0E-03
Antimony (Sb)			4.0E-04	
Arsenic (As)	1.5E + 00	4.3E-03	3.0E-04	1.5E-05
Barium (Ba)			2.0E-01	5.0E-04
Beryllium (Be)		2.4E-03	2.0E-03	2.0E-05
Cadmium (Cd)		1.8E-03	5.0E-04	1.0E-05
Chromium (Cr—total)			1.5E + 00	
Chromium VI (Cr^{+6})[a]	5.0E-01	1.2E-02	3.0E-03	1.0E-04
Cobalt (Co)		9.0E-03	3.0E-04	6.0E-06
Cyanide (CN)—free			6.0E-04	8.0E-04
Manganese (Mn)			1.4E-01	5.0E-05
Mercury (Hg)			3.0E-04	3.0E-04
Molybdenum (Mo)			5.0E-03	
Nickel (Ni)		2.6E-04	2.0E-02	9.0E-05
Selenium (Se)			5.0E-03	2.0E-02
Silver (Ag)			5.0E-03	
Thallium (Tl)			1.0E-05	
Vanadium (V)			5.0E-03	1.0E-04
Zinc (Zn)			3.0E-01	
Organic Compounds				
Acetone			9.0E-01	3.1E + 01
Alachlor	5.2E-02		1.0E-02	
Aldicarb			1.0E-03	
Anthracene			3.0E-01	
Atrazine	2.3E-01		3.5E-02	
Benzene	5.5E-02	7.8E-06	4.0E-03	3.0E-02
Benzo(*a*)anthracene	7.3E-01	1.1E-04		
Benzo(*a*)pyrene [BaP]	7.3E + 00	1.1E-03		
Benzo(*b*)fluoranthene	7.3E-01	1.1E-04		
Benzo(*k*)fluoranthene	7.3E-02	1.1E-04		
Benzoic acid			4.0E + 00	
Bis(2-ethylhexyl)phthalate	1.4E-02	2.4E-06	2.0E-02	
Bromodichloromethane	6.2E-02	3.7E-05	2.0E-02	
Bromoform	7.9E-03	1.1E-06	2.0E-02	
Carbon disulfide			1.0E-01	7.0E-01
Carbon tetrachloride	7.0E-02	6.0E-06	4.0E-03	1.0E-01
Chlordane	3.5E-01	1.0E-04	5.0E-04	7.0E-04
Chlorobenzene			2.0E-02	5.0E-02
Chloroform	3.1E-02	2.3E-05	1.0E-02	9.8E-02

(continued)

Table C.1 (continued)

Chemical name	Toxicity index			
	Oral *SF* $(mg/kg\text{-}day)^{-1}$	Inhalation *UR* $(\mu g/m^3)^{-1}$	Oral *RfD* (mg/kg-day)	Inhalation *RfC* (mg/m^3)
2-Chlorophenol			5.0E-03	
Chrysene	7.3E-03	1.1E-05		
o-Cresol [2-Methylphenol]			5.0E-02	6.0E-01
m-Cresol [3-Methylphenol]			5.0E-02	6.0E-01
Cyclohexanone			5.0E + 00	7.0E-01
1,4-Dibromobenzene			1.0E-02	
Dibromochloromethane	8.4E-02		2.0E-02	
1,2-Dibromomethane [EDB]	2.0E + 00	6.0E-04	9.0E-03	9.0E-03
1,2-Dichlorobenzene			9.0E-02	2.0E-01
Dichlorodifluoromethane			2.0E-01	1.0E-01
p,*p*′-Dichlorodiphenyl-dichloroethane [DDD]	2.4E-01	6.9E-05		
p,*p*′-Dichlorodiphenyl-dichloroethylene [DDE]	3.4E-01	9.7E-05		
p,*p*′-Dichlorodiphenyl-trichloroethane [DDT]	3.4E-01	9.7E-05	5.0E-04	
1,1-Dichloroethane	5.7E-03	1.6E-06	2.0E-01	
1,2-Dichloroethane	9.1E-02	2.6E-05	6.0E-03	7.0E-03
1,1-Dichloroethene			5.0E-02	2.0E-01
cis-1,2-Dichloroethene			2.0E-03	
trans-1,2-Dichloroethene			2.0E-02	
2,4-Dichlorophenol			3.0E-03	
Dieldrin	1.6E + 01	4.6E-03	5.0E-05	
Di(2-ethylhexyl)phthalate [DEHP]	1.4E-02	2.4E-06	2.0E-02	
Diethyl phthalate			8.0E-01	
2,4-Dimethylphenol			2.0E-02	
2,6-Dimethylphenol			6.0E-04	
3,4-Dimethylphenol			1.0E-03	
m-Dinitrobenzene			1.0E-04	
1,4-Dioxane	1.1E-01	5.0E-06	3.0E-02	3.0E-02
Endosulfan			6.0E-03	
Endrin			3.0E-04	
Ethylbenzene	1.1E-02	2.5E-06	1.0E-01	1.0E + 00
Ethyl chloride (Chloroethane)				1.0E + 01
Ethyl ether			2.0E-01	
Ethylene glycol			2.0E + 00	
Fluoranthene			4.0E-02	
Fluorene			4.0E-02	
Formaldehyde		1.3E-05	2.0E-01	9.8E-03

(continued)

Table C.1 (continued)

Chemical name	Toxicity index			
	Oral *SF* $(mg/kg\text{-}day)^{-1}$	Inhalation *UR* $(\mu g/m^3)^{-1}$	Oral *RfD* (mg/kg-day)	Inhalation *RfC* (mg/m^3)
Furan			1.0E-03	
Heptachlor	4.5E + 00	1.3E-03	5.0E-04	
Hexachlorobenzene	1.6E + 00	4.6E-04	8.0E-04	
Hexachlorodibenzo-*p*-dioxin [HxCDD]	6.2E + 03	1.3E + 00		
Hexachloroethane	4.0E-02	1.1E-05	7.0E-04	3.0E-02
n-Hexane				7.0E-01
Indeno(1,2,3-*c*,*d*)pyrene	7.E-01	1.1E-04		
Isobutyl alcohol			3.0E-01	
Lindane [gamma-HCH]	1.1E + 00	3.1E-04	3.0E-04	
Malathion			2.0E-02	
Methanol			2.0E + 00	2.0E + 01
Methyl mercury			1.0E-04	
Methyl parathion			2.5E-04	
Methylene chloride [Dichloromethane]	2.0E-03	1.0E-08	6.0E-03	6.0E-01
Methyl ethyl ketone [MEK]			6.0E-01	5.0E + 00
Methyl isobutyl ketone [MIBK]				3.0E + 00
Mirex	1.8E + 01	5.1E-03	2.0E-04	
Nitrobenzene		4.5E-05	2.0E-03	9.0E-03
n-Nitroso-di-*n*-butylamine	5.4E + 00	1.6E-03		
n-Nitroso-di-*n*-methylethylamine	2.2E + 01	6.3E-03		
n-Nitroso-di-*n*-propylamine	7.0E + 00	2.0E-03		
n-Nitrosodiethanolamine	2.8E + 00	8.0E-04		
n-Nitrosodiethylamine	1.5E + 02	4.3E-02		
n-Nitrosodimethylamine	5.1E + 01	1.4E-02		
n-Nitrosodiphenylamine	4.9E-03	2.6E-06		
Pentachlorobenzene			8.0E-04	
Pentachlorophenol	4.0E-01	5.1E-06	5.0E-03	
Phenol			3.0E-01	2.0E-01
Polychlorinated biphenyls [PCBs][b]	7.0E-02 *to* 2.0E + 00	2.0E-05 *to* 5.7E-04		
Pyrene			3.0E-02	
Styrene			2.0E-01	1.0E + 00
1,2,4,5-Tetrachlorobenzene			3.0E-04	
1,1,1,2-Tetrachloroethane	2.6E-02	7.4E-06	3.0E-02	
1,1,2,2-Tetrachloroethane	2.0E-01	5.8E-05	2.0E-02	
Tetrachloroethene	2.1E-03	2.6E-07	6.0E-03	4.0E-02

(continued)

Table C.1 (continued)

Chemical name	Toxicity index			
	Oral *SF* $(mg/kg\text{-}day)^{-1}$	Inhalation *UR* $(\mu g/m^3)^{-1}$	Oral *RfD* (mg/kg-day)	Inhalation *RfC* (mg/m^3)
2,3,4,6-Tetrachlorophenol			3.0E-02	
Toluene			8.0E-02	5.0E + 00
Toxaphene	1.1E + 00	3.2E-04		
1,2,4-Trichlorobenzene	2.9E-02		1.0E-02	2.0E-03
1,1,1-Trichloroethane			2.0E + 00	5.0E + 00
1,1,2-Trichloroethane	5.7E-02	1.6E-05	4.0E-03	2.0E-04
Trichloroeth[yl]ene	4.6E-02	4.1E-06	5.0 E-04	2.0E-03
1,1,2-Trichloro-1,2,2-trifluoroethane [CFC-113]			3.0E + 01	
Trichlorofluoromethane			3.0E-01	
2,4,5-Trichlorophenol			1.0E-01	
2,4,6-Trichlorophenol	1.1E-02	3.1E-06	1.0E-03	
1,1,2-Trichloropropane			5.0E-03	
1,2,3-Trichloropropane	3.0E + 01		4.0E-03	3.0E-04
Triethylamine				7.0E-03
1,3,5-Trinitrobenzene			3.0E-02	
2,4,6-Trinitrotoluene [TNT]	3.0E-02		5.0E-04	
o-Xylene			2.0E-01	1.0E-01
Xylenes (mixed)			2.0E-01	1.0E-01
Others				
Asbestos (*units of per fibers/mL*)[c]		2.3E-01		
Hydrazine	3.0E + 00	4.9E-03		3.0E-05
Hydrogen chloride				2.0E-02
Hydrogen cyanide			6.0E-04	8.0E-04
Hydrogen sulfide				2.0E-03

[a]Inhalation unit risk $= 8 \times 10^{-6}$ mg/m^3 (for exposure to Cr^{+6} acid mists and dissolved aerosols); and inhalation unit risk $= 1 \times 10^{-4}$ mg/m^3 (for exposure to Cr^{+6} particulate matter)

[b]Tiers of human potency and slope estimates exist for environmental mixtures of PCBs. For instance, for high risk and persistent PCB congeners or isomers, an upper-bound slope of 2.0E + 00 per mg/kg-day and a central slope of 1.0E + 00 per mg/kg-day may be used for the oral SF, etc.; for low risk and persistent PCBs, an upper-bound slope of 4E-01 per mg/kg-day and a central slope of 3E-01 per mg/kg-day may be used for the oral SF, etc.; and for the lowest risk and persistent PCBs, an upper-bound slope of 7E-02 per mg/kg-day and a central slope of 4E-02 per mg/kg-day may be used for the oral SF, etc.

[c]Note the different set of units applied here; also, 2.3E-01 per fibers/mL ≡ 2.3E-07 per fibers/m^3. It is also noteworthy that, regulatory agencies (such as the California EPA) have used a significantly more restrictive value of 1.9 per fibers/mL (≡1.9E-06 per fibers/m^3) as the inhalation SF for asbestos in some risk management and remedy decisions

Appendix D
Selected Databases, Scientific Tools, and Information Library Germane to Public Health Risk Assessment and Environmental Management Programs

Oftentimes, a variety of scientific and analytical tools are employed to assist decision-makers with various issues associated with the management of chemical exposure problems. Indeed, several databases containing important information on numerous chemical substances exist within the scientific community that may find extensive useful applications in the management of various types of chemical exposure and related problems. Overall, the variety of decision-making tools and logistics, as well as computer databases and information libraries, may find several useful applications in public health risk assessment and risk management programs designed to address variant chemical exposure problems. A limited number and select examples of such logistical application tools, computer software, scientific models, and database systems of general interest to environmental assessments and risk management programs are featured below in this appendix; this select list is of interest, especially because of their international appeal and/or their wealth of risk assessment support information—albeit it is not at all meant to be wholly representative of the comprehensive and diverse number of resources containing important risk information that are available in practice. In actual fact, the presentation here is only meant to demonstrate the overall wealth of scientific information that already exists—and which should therefore be consulted whenever possible, in order to obtain the relevant chemical exposure and risk assessment support information necessary for risk determinations and/or public health risk management actions.

On the whole, a diversity of information sources are available to facilitate various types of risk assessment and/or risk management tasks—with only a partial listing provided below. It must be emphasized that the list provided here is by no means complete and exhaustive—and neither does it cover the broad spectrum of what is available to the scientific communities and/or the general public. Indeed, several other similar logistical and scientific tools are available that can be used to support environmental and risk management programs, in order to arrive at informed decisions on chemical exposure and related problems. Further listings and/or information may generally be obtainable on the *internet*—which serves as a

K. Asante-Duah, *Public Health Risk Assessment for Human Exposure to Chemicals*, Environmental Pollution 27, DOI 10.1007/978-94-024-1039-6

very important and contemporary international network search system. Also, traditional libraries and directories of environment- and risk-related professional groups/associations may provide the necessary up-to-date contacts.

Finally, it is noteworthy that the choice of one particular model or tool over another—some of which are proprietary or a registered trademark—will generally be problem-specific. Furthermore, the mention of any particular database, model or software in this title does not necessarily constitute an endorsement of such product as being the most preferred, since each has its own merits and limitations. In the end, it is quite important that extra care be exercised in the choice of an appropriate tool for specific problems.

The 'UNEP Chemicals'/International Register of Potentially Toxic Chemicals (IRPTC) Database

In 1972, the United Nations Conference on the Human Environment, held in Stockholm, recommended the setting up of an international registry of data on chemicals likely to enter and damage the environment. Subsequently, in 1974, the Governing Council of the United Nations Environment Programme (UNEP) decided to establish both a chemicals register and a global network for the exchange of information that the register would contain. The definition of the register's ultimate objectives was subsequently expounded to address the following:

- Make data on chemicals readily available to those who need it, by facilitating access to existing data on the production, distribution, release and disposal of chemicals, and their effects on humans and their environments—and thereby contribute to a more efficient use of national and international resources available for the evaluation of the effects of the chemicals and their control.
- On the basis of information in the Register, identify and draw attention to the major/important gaps in existing knowledge on the effects of chemicals and related available information—and then encourage research to fill those gaps.
- Identify, or help identify the potential hazards originating from chemicals and waste materials—and then improve people awareness of such hazards.
- Assemble information on existing policies for control and regulation of hazardous chemicals at national, regional and global levels—by ultimately providing information about national, regional and global policies, regulatory measures and standards, and recommendations for the control of potentially toxic chemicals.
- Facilitate the implementation of policies necessary for the exchange of information on chemicals in possible international trades.

In 1976, a central unit for the register—named the International Register of Potentially Toxic Chemicals (IRPTC)—was created in Geneva, Switzerland, with the main function of collecting, storing and disseminating data on chemicals, and

also to operate a global network for information exchange. IRPTC network partners (i.e., the designation assigned to participants outside the central unit) consisted of National Correspondents appointed by governments, national and international institutions, national academies (of sciences), industrial research centers, and specialized research institutions.

Chemicals examined by the IRPTC have generally been chosen from national and international priority lists. The key selection criteria used include the quantity of production and use, the toxicity to humans and ecosystems, persistence in the environment, and the rate of accumulation in living organisms.

As a final point, it is noteworthy that the IRPTC database has essentially been 'transformed' into what is also known as the '*UNEP Chemicals*'—which has more or less become the focus for all activities undertaken by UNEP to ensure the globally sound management of hazardous chemicals; indeed, it is built upon the same solid technical foundation of the IRPTC—and aims to promote chemicals safety by providing countries with access to information on toxic chemicals, facilitate or catalyze global actions to reduce or eliminate chemicals risks, and to assist countries in building their capacities for safe production, use and disposal of hazardous chemicals. At any rate, for all intents and purposes, the discussion provided here for UNEP's original IRPTC may reasonably be used interchangeably with '*UNEP Chemicals*'.

General Types of Information in the [Original] IRPTC Databases

IRPTC stores information that would aid in the assessment of the risks and hazards posed by a chemical substance to human health and environment. The major types of information collected include that relating to the behavior of chemicals, and information on chemical regulations. Information on the behavior of chemicals is obtained from various sources such as national and international institutions, industries, universities, private databanks, libraries, academic institutions, scientific journals and United Nations bodies such as the International Programme on Chemical Safety (IPCS). Regulatory information on chemicals is largely contributed by IRPTC National Correspondents. Specific criteria are used in the selection of information for entry into the databases. Whenever possible, IRPTC uses data sources cited in the secondary literature produced by national and international panels of experts to maximize reliability and quality. The data are then extracted from the primary literature. Validation is performed prior to data entry and storage on a computer at the United Nations International Computing Centre (ICC).

Overall, the complete IRPTC file structure consists of databases relating to the following key subject matter and areas of interest: Legal; Mammalian and Special Toxicity Studies; Chemobiokinetics and Effects on Organisms in the Environment;

Environmental Fate Tests, and Environmental Fate and Pathways into the Environment; and Identifiers, Production, Processes and Waste.

The IRPTC *Legal* database contains national and international recommendations and legal mechanisms related to chemical substances control in environmental media such as air, water, wastes, soils, sediments, biota, foods, drugs, consumer products, etc. This set-up allows for rapid access to the regulatory mechanisms of several nations, and to international recommendations for safe handling and use of chemicals.

The *Mammalian Toxicity* database provides information on the toxic behavior of chemical substances in humans; toxicity studies on laboratory animals are included as a means of predicting potential human effects. The *Special Toxicity* databases contain information on particular effects of chemicals on mammals, such as mutagenicity and carcinogenicity, as well as data on non-mammalian species when relevant for the description of a particular effect.

The *Chemobiokinetics and Effects on Organisms in the Environment* databases provide data that will permit the reliable assessment of the hazard of chemicals present in the environment to man. The absorption, distribution, metabolism and excretion of drugs, chemicals and endogenous substances are described in the *Chemobiokinetics* databases. *The Effects on Organisms in the Environment* databases contain toxicological information regarding chemicals in relation to ecosystems and to aquatic and terrestrial organisms at various nutritional levels.

The *Environmental Fate Tests, and Environmental Fate and Pathways into the Environment* databases assess the risk presented by chemicals to the environment.

The *Identifiers, Production, Processes and Waste* databases contain miscellaneous information about chemicals—including physical and chemical properties; hazard classification for chemical production and trade statistics of chemicals on worldwide or regional basis; information on production methods; information on uses and quantities of use for chemicals; data on persistence of chemicals in various environmental compartments or media; information on the intake of chemicals by humans in different geographical areas; sampling methods for various media and species, as well as analytical protocols for obtaining reliable data; recommendable methods for the treatment and disposal of chemicals; etc.

The Role of the [Original] IRPTC in Risk Assessment and Environmental Management

The IPRTC, with its carefully designed database structure, serves as a sound model for national and regional data systems. More importantly, it brings consistency to information exchange procedures within the international community. Indeed, the IPRTC serves as an essential international tool for chemicals hazard assessment, as well as a mechanism for information exchange on several chemicals. The wealth of

scientific information contained in the IRPTC can serve as an invaluable database for a variety of environmental and public health risk management programs.

Further information on the IRPTC (and related tools or databases) may be obtained from the National Correspondent to the IRPTC and scientific bodies/institutions (such as a country's National Academy of Sciences)—as well as via UNEP and related internet websites. [By the way, it is noteworthy that, following the successful implementation of the IRPTC databases, a number of countries created National Registers of Potentially Toxic Chemicals (NRPTCs) that is completely compatible with the IRPTC system.]

The Integrated Risk Information System (IRIS) Database

The Integrated Risk Information System (IRIS), that has been prepared and maintained by the Office of Health and Environmental Assessment of the United States Environmental Protection Agency (US EPA), is an electronic database containing health risk and regulatory information on several specific chemicals. The IRIS database was created by the USEPA in 1985 (and made publicly available in 1988) as a mechanism for developing consistent consensus positions on potential health effects of chemical substances. Indeed, IRIS was originally developed for the US EPA staff—in response to a growing demand for consistent risk information on chemical substances for use in decision-making and regulatory activities. On the whole, it serves as an on-line database of chemical-specific risk information; it is also a primary source of EPA health hazard assessment and related information on several chemicals of broad environmental concern. It is noteworthy that each IRIS assessment can cover a chemical, a group of related chemicals, or a complex mixture. It is also notable that the information in IRIS is generally accessible to even those without extensive training in toxicology, but with some rudimentary knowledge of health and related sciences.

Broadly speaking, the IRIS database provides information on how chemicals affect human health, and is a primary source of EPA risk assessment information on chemicals of environmental and public health concern. It serves as a guide for the hazard identification and dose-response assessment steps of EPA risk assessments. More importantly, IRIS makes chemical-specific risk information readily available to those who must perform risk assessments—and also increases consistency in risk management decisions. The information in IRIS generally represents expert Agency consensus; in fact, this Agency-wide agreement on risk information is one of the most valuable aspects of IRIS. Chemicals are added to IRIS on a regular basis—with chemical file sections in the system being updated as new information is made available to the responsible review groups.

General Types of Information in IRIS

The IRIS database consists of a collection of computer files covering several individual chemicals. To aid users in accessing and understanding the data in the IRIS chemical files, the following key supportive documentation is provided as an important component of the system:

- Alphabetical list of the chemical files in IRIS and list of chemicals by Chemical Abstracts Service (CAS) number.
- Background documents describing the rationales and methods used in arriving at the results shown in the chemical files.
- A user's guide that presents step-by-step procedures for using IRIS to retrieve chemical information.
- An example exercise in which the use of IRIS is demonstrated.
- Glossaries in which definitions are provided for the acronyms, abbreviations, and specialized risk assessment terms used in the chemical files and in the background documents.

The chemical files contain descriptive and numerical information on several subjects—including oral and inhalation reference doses (RfDs) for chronic non-carcinogenic health effects, as well as oral and inhalation cancer slope factors (SFs) and unit cancer risks (UCRs) for chronic exposures to carcinogens. It also contains supplementary data on acute health hazards and physical/chemical properties of the chemicals. In fact, the primary types of health assessment information in IRIS are oral reference doses (RfDs) and inhalation reference concentrations (RfCs) for non-carcinogens, as well as oral and inhalation carcinogen assessment parameters. Reference doses and concentrations are estimated human chemical exposures over a lifetime, and that are just below the expected thresholds for adverse health effects. The carcinogen assessments include: a weight-of-evidence classification, oral and inhalation quantitative risk information, including slope factors, along with unit risks calculated from those slope factors. [A slope factor is the estimated lifetime cancer risk per unit of the chemical absorbed, assuming lifetime exposure.]

Overall, summary information in IRIS consists of three components: derivation of oral chronic RfD and inhalation chronic RfC, for non-cancer critical effects, cancer classification (and cancer hazard narrative for the more recent assessments) and quantitative cancer risk estimates. Indeed, the IRIS information has generally focused on the documentation of toxicity values (i.e., RfD, RfC, cancer unit risk and slope factor) and cancer classification; the bases for these numerical values and evaluative outcomes are typically provided in an abbreviated and succinct manner. Anyhow, details for the scientific rationale can be found in supporting documents, and references for these assessment documents, and key studies are provided in the bibliography sections. Meanwhile, it is notable that since 1997, IRIS summaries and accompanying support documents, including a summary and response to external peer review comments, have been publicly available in full text on the

IRIS website—with the internet site now being EPA's primary repository for IRIS (comprising the 'IRIS assessment' for a given chemical substance as a whole). By and large, prevailing information on IRIS at any one time generally represents the state-of-the-science and state-of-the-practice in risk assessment—i.e., as existed when each assessment was prepared.

Finally, it is noteworthy that, because exposure assessment pertains to exposure at a particular place, IRIS cannot provide situation-specific information on exposure. However, IRIS can be used with an exposure assessment to characterize the risk of chemical exposure. This risk characterization can then be used to decide on what actions to take to protect human health.

The Role of IRIS in Risk Assessment and Environmental Management

IRIS is a tool that provides hazard identification and dose-response assessment information, but does not provide situation- or problem-specific information on individual instances of exposure. It is a computerized library of current information that is updated periodically. Combined with site-specific or national exposure information, the summary health information in IRIS could thenceforth be used by risk assessors/analysts and others to evaluate potential public health risks from environmental chemicals. Also, combined with specific exposure information, the data in IRIS can be used to characterize the public health risks of a chemical of potential concern under specific scenarios, which can then facilitate the development of effectual corrective action decisions designed to protect public health. The information in IRIS can indeed be used to develop corrective action and risk management decision for chemical exposure problems—such as achieved via the application of risk assessment and risk management procedures.

The IRIS Program is located within EPA's National Center for Environmental Assessment (NCEA) in the Office of Research and Development (ORD). Further information on, and access to the IRIS database may be obtained via the US EPA internet website. Alternatively, the following groups may be contacted for pertinent needs: IRIS User Support, US EPA, Environmental Criteria and Assessment Office, Cincinnati, Ohio, USA; and National Library of Medicine [NLM], Bethesda, Maryland, USA.

The International Toxicity Estimates for Risks (*ITER*) Database

International Toxicity Estimates for Risk (ITER) is a database of human health risk values and supporting information—generally comprised of data to aid human health risk assessments. Overall, the database consists of chemical files containing data with information that come mostly from: the US Environmental Protection Agency (EPA), the US Agency for Toxic Substances and Disease Registry (ATSDR)/CDC, Rijksinstituut Voor Volksgezondheid en Miliouhygiene (RIVM) [National Institute of Public Health and the Environment] of the Netherlands, Health Canada, the International Agency for Research on Cancer (IARC), and indeed a number of independent parties offering peer-reviewed risk values. Among other things, this includes direct links to EPA's IRIS, and to ATSDR's 'Toxicological Profiles' for each chemical file—and also has the ability to print reports. Meanwhile, it is worth the mention here that the data in the ITER database are presented in a comparative fashion—allowing the user to view what conclusions each organization has reached; in addition, a brief explanation of differences is provided. The database is typically updated several times a year.

In general, the values and text in the ITER database would have been extracted from credible published documents and data systems of the original author organizations. Independently-derived values, which have undergone external peer review at a TERA-sponsored peer-review meeting, are also listed in the ITER database. The risk values are compiled into a consistent format, so that comparisons can be made readily by informed users. The necessary conversions are performed so that direct comparisons can be made—and the synopsis text is written so as to help the user better understand the similarities and differences between the values of the different organizations. At the end of each so-identified 'Level 3' summary in the ITER database, the user will find a source and/or link for further information about that particular assessment listed.

The ITER database is compiled by 'Toxicology Excellence for Risk Assessment' (TERA), a non-profit corporation "with a mission dedicated to the best use of toxicity data for the development of risk values" (according to the organization). It is noteworthy that TERA is said to prevent conflicts of interest in part through its nonprofit status, as well as policy of informed and neutral guidance. Consequently, TERA generally helps environmental, industry, and government groups find common ground through the application of good science to risk assessment. Apparently, the general motivation has been that, in fostering successful partnerships, improvements in the science and practice of risk assessment will follow.

General Types of Information in ITER

ITER is considered a toxicology data file on the 'National Library of Medicine' (NLM)'s 'Toxicology Data Network' (TOXNET)—containing data in support of human health risk assessments. It is compiled by TERA, and contains over 650 chemical records—with key data coming from a number international establishments (such as ATSDR/CDC; Health Canada; RIVM—The Netherlands; U.S. EPA; IARC; NSF International; and independent parties whose risk values have undergone peer review). As an example, RIVM develops human-toxicological risk limits (i.e., maximum permissible risk levels, MPRs) for a variety of chemicals based on chemical assessments that are compiled in the framework of the Dutch government program on risks in relation to soil quality. As another example, information on the toxic effects of chemical exposure in humans and experimental animals is contained in the ATSDR 'Toxicological Profiles'; these documents also contain dose-response information for different routes of exposure—and when information is available, the Toxicological Profiles also contain a discussion of toxic interactive effects with other chemicals, as well as a description of potentially sensitive human populations. All these sources may indeed serve as a basis for some of the values reported in the ITER database. All in all, the ITER data, focusing on hazard identification and dose-response assessment, is extracted from each agency's assessment—and contains links to the source documentation.

Among the key data provided in ITER are: ATSDR's minimal risk levels; Health Canada's tolerable intakes/concentrations and tumorigenic doses/concentrations; EPA's carcinogen classifications, unit risks, slope factors, oral reference doses, and inhalation reference concentrations; RIVM's maximum permissible risk levels; NSF International's reference doses and carcinogen risk levels; IARC's cancer classifications; and noncancer and/or cancer risk values (that have undergone peer review) derived by independent parties. Finally, it is notable that ITER provides comparison charts of international risk assessment information in a side-by-side format, and explains differences in risk values derived by different organizations.

The Role of ITER in Risk Assessment and Environmental Management

ITER consists of a compilation of human health risk values for chemicals of environmental and/or public health concern from several health organizations worldwide. These values are developed for multiple purposes depending on the particular organization's function. They are principally used as guidance or regulatory levels against which human exposures from chemicals in the air, food, soil, and water can be compared.

As of the early part of the year 2016, ITER contained values mostly from the following major organizations: Health Canada; RIVM; US ATSDR/CDC; US EPA;

IARC; NSF International; and other independent parties offering peer-reviewed risk values. Anyhow, in the future, it is expected that the ITER database will include additional chemicals and health information from various other organizations such as the World Health Organization/International Programme on Chemical Safety (WHO/IPCS), etc. On the whole, the information in the ITER database is useful to risk assessors and risk managers needing human health toxicity values to make risk-based decisions. ITER allows the user to compare a number of key organizations' values and to determine the best value to use for the human exposure situation being evaluated.

Further information on, and access to, the ITER database may be obtained via the ITER and/or TERA internet websites—as well as the NLM and TOXNET websites, among others.

eChemPortal: The Global Portal to Information on Chemical Substances

eChemPortal represents a significant step towards achieving long-standing international commitments to identify and make information on chemical properties publicly available. The main objectives of eChemPortal are to:

(1) Make information on existing chemicals publicly available and free of charge;
(2) Enable quick and efficient use of this information; and
(3) Enable efficient exchange of the accrued information.

Although the eChemPortal web site exists fundamentally in English, eChemPortal recognizes chemical names or synonyms in several other languages same.

To give a brief historical perspective here, in June 1992, the United Nations Conference on Environment and Development in Rio de Janeiro, Brazil confronted the issue of environmentally sound management of toxic chemicals—covering, among other things, the 'information exchange on toxic chemicals and chemical risks...' Then, in September 2002, the World Summit on Sustainable Development advocated for the 'development of coherent and integrated information on chemicals...' Subsequently, the Intergovernmental Forum on Chemical Safety (IFCS) at 'Forum IV' in Bangkok in November 2003 adopted a priority for action on improving the availability of hazard data on chemicals—and then invited the Organisation for Economic Co-operation and Development (OECD), among others, to undertake certain tasks in this regard. Consequently, the OECD initiated an activity to develop a globally accessible data repository for hazard data, assessments and other information to assist countries and others with hazard identification and national priority setting on existing chemicals—ultimately giving birth to 'eChemPortal'. Indeed, eChemPortal is also a contribution to the 'Strategic Approach to International Chemicals Management' (SAICM), and especially its

recommendation to 'facilitate public access to appropriate information and knowledge of chemicals throughout their life cycle...'

The OECD is responsible for the development and maintenance of eChemPortal and it is hosted by the European Chemicals Agency (ECHA). The data sources accessed through eChemPortal are maintained by, and remain the responsibility of, the organizations that create them; thus, the data and information stored in each data source are the responsibility of the data owner. Participating data sources are responsible for ensuring links from eChemPortal to their local data sources are updated. In general, holders of internet-accessible databases or report collections containing peer-reviewed information on physical-chemical properties, environmental fate and pathways, ecotoxicity or toxicity of chemicals, as well as their use and exposure, are invited to participate in eChemPortal.

The eChemPortal tool is an effort of the OECD in collaboration with the European Commission (EC), the European Chemicals Agency (ECHA), the United States, Canada, Japan, the International Council of Chemical Associations (ICCA), the Business and Industry Advisory Committee (BIAC), the World Health Organization's (WHO) International Program on Chemical Safety (IPCS), the United Nations Environment Programme (UNEP) and indeed a number of environmental non-governmental organisations. The vision is for eChemPortal to be the preferred worldwide source of information about chemicals from authorities and international organizations.

General Types of Information in eChemPortal

First launched in 2007, eChemPortal has gone through major re-developments—with major changes occuring in 2010 and 2015. Anyhow, eChemPortal provides free public access to information on chemical properties, as well as direct links to collections of chemical hazard and risk information that have generally been prepared/compiled for governmental agencies to support pertinent 'chemical review programs' at national, regional, and international levels—including physical and chemical properties; ecotoxicity; environmental fate and behavior; and toxicity.

On the whole, eChemPortal allows simultaneous searching of reports and datasets by chemical name and number, by chemical property, and by a so-called 'GHS classification'. [It is noteworthy that classifications according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) for the same chemical can differ across countries/regions. The main reasons for diverging classifications are the use of different underlying datasets, a difference in interpretation of the underlying data (e.g. due to difference in data availability or a different rationale for selecting a study over another), a different application of the classification criteria, or a mix of these reasons. Also, classifications can be based on different forms of a substance, or on classification of an analogous substance.] Access to information on existing chemicals, new industrial chemicals, pesticides

and biocides is provided. Insofar as possible, eChemPortal also makes available national/regional classification results in accordance with national/regional hazard classification schemes—or according to the GHS. In addition, eChemPortal provides exposure and use information on chemicals.

The Role of eChemPortal in Risk Assessment and Environmental Management

eChemPortal is an Internet gateway to information on the properties, hazards and risks of chemicals found in the environment, homes and workplaces, and in everyday products. Users can simultaneously search data from multiple data sources prepared for government chemical review programs at national, regional, and international levels. eChemPortal provides descriptions of the sources and review of data stored in these participating data sources.

Overall, eChemPortal provides direct access to critical scientific information needed to meet public health and environmental objectives for the safe use of chemicals under proper conditions. Indeed, improving accessibility to these data typically increases understanding of chemical hazards and risks, changes behaviors, and reduces—or even eliminates—adverse health effects from exposures to chemicals.

Other Miscellaneous Tools and Information Sources

A variety of other information sources are available to facilitate various risk assessment and/or public health risk management tasks—such as the additional listing provided below.

- *ATSDR 'Toxicological Profiles'*. The US Agency for Toxic Substances and Disease Registry (ATSDR) 'Toxicological Profiles' contain information on the toxic effects of chemical exposure in humans and experimental animals. These documents also contain dose-response information for different routes of exposure. When information is available, the Toxicological Profiles also contain a discussion of toxic interactive effects with other chemicals, as well as a description of potentially sensitive human populations. Overall, the ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance of interest or concern. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties; other pertinent literature is also presented, but is described in less detail than the key studies. All in all, the focus of the profile is on health and toxicologic information; thus, each profile

begins with a 'Public Health Statement' that summarizes in nontechnical language, a substance's relevant properties.

Further information on, and access to the ATSDR toxicological profiles, may be obtained via the ATSDR internet website, or by contacting the Agency for Toxic Substances and Disease Registry (ATSDR), US Department of Health and Human Service, Atlanta, GA, USA.

- *Benchmark Dose Software (BMDS)*. The U.S. EPA's Benchmark Dose Software (BMDS) fits mathematical models to dose-response or exposure-response data. The EPA developed the BMDS as a tool to facilitate the application of benchmark dose (BMD) methods to EPA's hazardous pollutant risk assessments. This software can help EPA risk assessors estimate the dose or response of a chemical or chemical mixture, with confidence limits, that is associated with a given response level; this dose or exposure estimate can then be used as a benchmark for establishing guidelines that help protect against the adverse health effects associated with the chemical or chemical mixture.

  In general, EPA uses BMD methods to estimate reference doses (RfDs) and reference concentrations (RfCs)—which are used along with other scientific information to set standards for noncancer human health effects. A goal of the BMD approach is to define a starting point of departure (POD) for the computation of a reference value (RfD or RfC) or slope factor that is more independent of study design. Using BMD methods involves fitting mathematical models to dose-response data and using the different results to select a BMD that is associated with a predetermined benchmark response (BMR), such as a 10% increase in the incidence of a particular lesion or a 10% decrease in body weight gain. Ultimately, BMDS facilitates the risk assessment operations by providing simple data-management tools and an easy-to-use interface to run multiple models on the same dose-response dataset. Results from all models include a reiteration of the model formula and model run options chosen by the user, goodness-of-fit information, the BMD, and the estimate of the lower-bound confidence limit on the BMD (BMDL). Model results are presented in textual and graphical output files that can be printed or saved and incorporated into other documents.

  It is noteworthy that BMDS has been continually improved and enhanced since its initial release in 1999; most recently, it has been known to contain thirty (30) different models that are appropriate for the analysis of dichotomous (quantal) data, continuous data, nested developmental toxicology data, multiple tumor analysis, and concentration-time data. Further information on the BMDS Software may be obtained from EPA's National Center for Environmental Assessment (NCEA), USEPA, USA.
- *The CALTOX Model*. CalTOX is a multimedia, multi-pathway risk assessment model that allows stochastic simulation to be carried out. The CalTOX spreadsheet encompasses a multimedia transport and transformation model that uses equations based on conservation of mass and chemical equilibrium; it calculates the gains and losses in each environmental compartment over time, by accounting for both transport from one compartment into another, and also chemical

biodegradation and transformation. Overall, it is an innovative spreadsheet model that relates the concentration of a chemical in soil to the risk of an adverse health effect for a person living or working on or near a contaminated soil source. The model computes site-specific health-based soil clean-up concentrations for specified target risk levels, and/or estimates human health risks for given soil concentrations at the site. It is a fugacity model for evaluating the time dependent movement of contaminants in various environmental media. A noteworthy feature is that, the model makes the distinction between the environmental concentration and the exposure concentration.

On the whole, the CalTOX model predicts the time-dependent concentrations of a chemical in seven environmental compartments—comprised of air, water, three soil layers, sediment, and plants at a site. After partitioning the concentration of the chemical to these environmental compartments, CalTOX determines the chemical concentration in the exposure media of breathing zone air, drinking water, food, and soil that people inhale, ingest, and contact dermally. CalTOX then uses the standard equations (such as found in the US Environmental Protection Agency Risk Assessment Guidance for Superfund [USEPA, 1989]) to estimate exposure and risk.

CalTOX has the capability to carry out Monte Carlo simulations with a spreadsheet add-in program. It quantitatively addresses both uncertainty and variability by allowing the presentation of both the risks and the calculated cleanup goals as probability distributions—allowing for a clearer distinction between the risk assessment and risk management steps in site remediation decisions. Used in this manner, CalTOX will produce a range of risks and/or health-based soil target clean-up levels that reflect the uncertainty/variability of the estimates.

CalTOX was developed by the California EPA, and is available for free downloading from their website. In addition to the site-specific risk assessments, results from CalTOX can be exported to other programs (such as *Crystal Ball*) for Monte Carlo Simulation.

Further information on CalTOX may be obtained from the following: California Environmental Protection Agency (Cal EPA), Department of Toxic Substances Control (DTSC), Sacramento, California, USA; and Lawrence Livermore National Laboratory, Berkeley, California, USA.

- *CatReg Software for Categorical Regression Analysis*. *CatReg* is a computer program, written in the R-programming language, to support the conduct of exposure-response analyses by toxicologists and health scientists. It can be used to perform categorical regression analyses on toxicity data after effects have been assigned to ordinal severity categories (e.g., no effect, adverse effect, severe effect) and bracketed with up to two independent variables corresponding to the exposure conditions (e.g., concentration and duration) under which the effects occurred. *CatReg* calculates the probabilities of the different severity categories over the continuum of the variables describing exposure conditions. The categorization of observed responses allows expression of dichotomous,

continuous, and descriptive data in terms of effect severity—and supports the analysis of data from single studies or a combination of similar studies.

CatReg reads data from ordinary text files in which data are separated by commas. A query-based interface guides the user through the modeling process. Simple commands provide model summary statistics, parameter estimates, diagnostics, and graphical displays. The special features offered by *CatReg* include options for the following:

- Stratifying the analysis by user-specified covariates (e.g., species, sex, etc.);
- Choosing among several basic forms of the exposure-response curve;
- Using effects assigned to a range of severity categories, rather than a single category;
- Using cluster-correlated data;
- Incorporating user-specified weights;
- Using aggregate data; and
- Query-based exclusion of user-specified data (i.e., filtering) for sensitivity analysis.

Indeed, there are many potential applications of the *CatReg* program in the analysis of health effects studies and other types of data. Although the software was developed to support toxicity assessment for acute inhalation exposures, the US Environmental Protection Agency (EPA) encourages a broader application of this software. The user manual, which contains illustrated examples, provides ideas on adapting *CatReg* for situation-specific applications.

Further information on, and access to, *CatReg* is obtainable from USEPA, Office of Research and Development, National Center for Environmental Assessment, Research Triangle Park, NC, USA.

- *ConsExpo.* Consumers are frequently exposed to chemical substances contained in or released from everyday consumer products like paint, cosmetics, deodorant, cleaning products, etc.; generally speaking, chemical substances found in these products should be so-constituted in manner that would not make them pose significant concern to human health when used properly – albeit this is not always the case in practice. At any rate, to assess the risk associated with a given consumer product, it is very important to understand the nature of the receptor exposure arising from chemicals in these products – all the while recognizing that exposure to chemical substances during normal use of consumer products is essentially determined by the specific ways in which the product is used (*viz.*, the nature of exposure scenario), the concentration of the ingredient in the product, and the release of the substance of interest or concern from the product during its usage. Yet, in practice, the relevant 'measurement data' are usually not readily or directly available for such determinations *per se*. Consequently, Rijksinstituut Voor Volksgezondheid en Miliouhygiene (RIVM) [the Dutch National Institute for Public Health and the Environment] has developed some germane methods to help determine the safety of chemical substances under a variety of scenarios; for consumer products, RIVM offers the 'ConsExpo Model' – a model that

mathematically predicts human exposure associated with the use of consumer products. With the use of *ConsExpo*, manufacturers and consumer product safety experts or advocates as well as researchers are able to predict the amounts or levels of chemical substances that consumers are exposed to during use of a consumer product. On the whole, *ConsExpo* can be used for the safety assessment of various industrial chemicals (such as defined in the EU's 'REACH' program) as well as biocides and indeed related or similar environmental chemicals.

ConsExpo is a computer program that enables/facilitates the estimation and assessment of exposure to substances found in consumer products such as paint, cleaning agents and personal care products (e.g., cosmetics). The model in its original form was developed by RIVM – and then in October 2016, an 'upgraded' web-based version [*viz*., 'ConsExpo Web'] was also launched following additional works carried out by RIVM in collaboration with its counterpart European institutions in France, Germany and Switzerland, as well as with Health Canada; all in all, exposure calculations from *ConsExpo Web* provide information needed to assess the safety of chemical substances in consumer products. In the end, by using *ConsExpo Web*, exposure assessments for a consumer can generally be performed in a transparent and standardized way by governments, as well as various institutions and industries working to address human exposure problems. It is anticipated that, in the future, *ConsExpo Web* can easily be expanded with various new applications – as for example, with the inclusion of an exposure assessment for short-term exposures, etc.

It is notable that *ConsExpo* has typically been used within and outside Europe by governments, as well as by various institutions and industries, to assess human exposure to chemical substances found in everyday consumer products; the program provides insight to exposure via multiple exposure routes – particularly with respect to exposure via inhalation, as well as dermally (via the skin) or by oral intake/ingestion. In these efforts, users would normally choose the most appropriate scenario, and then provide input of default or user-specified exposure parameters (such as body weight and exposure duration) – in order to arrive at applicable exposure estimates; it is worth mentioning here that the program does indeed consist of both 'screening' and 'higher tier' models for the exposure estimations of interest.

Further information on, and access to, *ConsExpo* is obtainable online via the internet or directly from RIVM [consexpo@rivm.nl], The Netherlands.

- *EPA-Expo-Box*. The U.S. EPA's 'EXPOsure toolBOX' (EPA-Expo-Box) was developed by the Office of Research and Development, as a compendium of exposure assessment tools that links to exposure assessment guidance documents, databases, models, key references materials, and other related resources. Overall, the toolbox provides a variety of exposure assessment resources organized into six 'Tool Sets'—each containing a series of modules.

The EPA's EXPOsure toolBOX (EPA-Expo-Box) is indeed a toolbox created to assist individuals from within government, industry, academia, and the general public with assessing exposure. The toolbox allows the user to navigate from different starting points, depending on the problem-specific needs. Further information on EPA-Expo-Tox may be obtained from Office of Research and Development, USEPA, USA.

- *The IEUBK Model*. Lead (Pb) poisoning seems to present potentially significant risks to the health and welfare of children all over the world in this day and age. The Integrated Exposure Uptake Biokinetic (IEUBK) model for lead in children attempts to predict blood-lead concentrations (PbBs) for children exposed to Pb in their environment. Meanwhile, it is worth the mention here that measured PbB concentration is not only an indication of exposure, but is a widely used index to discern potential future health problems.

  The IEUBK model for lead in children is a menu-driven, user-friendly model designed to predict the probable PbB concentrations (via pharmacokinetic modeling) for children aged between six months and seven years who have been exposed to Pb in various environmental media (*e.g.*, air, water, soil, dust, paint, diet and other sources). The model has the following four key functional components:

  – *Exposure component*—compares Pb concentrations in environmental media with the amount of Pb entering a child's body.
  – *Uptake component*—compares Pb intake into the lungs or digestive tract with the amount of Pb absorbed into the child's blood.
  – *Biokinetic component*—shows the transfer of Pb between blood and other body tissues, or the elimination of Pb from the body altogether.
  – *Probability distribution component*—shows a probability of a certain outcome (*e.g.*, a PbB concentration greater than 10 μgPb/dL in an exposed child based on the parameters used in the model).

  It is noteworthy that, in the United States, the US EPA and the Centers for Disease Control and Prevention (CDC) have determined that childhood PbB concentrations at or above 5 micrograms of Pb per deciliter of blood (i.e., $\geq$5μgPb/dL) present risks to children's health. The IEUBK model can calculate the probability of children's PbB concentrations exceeding 5 μgPb/dL (or other user-entered value). By varying the data entered into the model, the user can evaluate how changes in environmental conditions may affect PbB levels in exposed children.

  The IEUBK model allows the user to input relevant absorption parameters, (e.g., the fraction of Pb absorbed from water) as well as rates for intake and exposure. Using these inputs, the IEUBK model then swiftly calculates and recalculates likely outcomes using a complex set of equations to estimate the potential concentration of Pb in the blood for a hypothetical child or population of children (6 months to 7 years). Overall, the model is intended to:

- Estimate a typical child's long-term exposure to Pb in and around his/her residence;
- Provide an accurate estimate of the geometric average PbB concentration for a typical child aged 6 months to 7 years;
- Provide a basis for estimating the risk of elevated PbB concentration for a hypothetical child;
- Predict likely changes in the risk of elevated PbB concentration from exposure to soil, dust, water, or air following rigorous efforts/actions to reduce such exposure;
- Provide assistance in determining target cleanup levels at specific residential sites for soil or dust containing high amounts of Pb; and
- Provide assistance in estimating PbB levels associated with the Pb concentration of soil or dust at undeveloped sites that may be developed at a later date.

A major advantage of the IEUBK model is the fact that it takes into consideration the several different media through which children can be exposed.

Further information on IEUBK may be obtained from the US EPA's Office of Emergency and Remedial Response, Washington, DC, USA.

- *INTEGRA*. It is apparent that non-occupational exposure to chemical agents originates either from environmental contamination (e.g., air, water, soil, transfer through food chain), or from consumer products (e.g., food contact materials, construction materials, cosmetics, clothes, etc.) via multiple routes – namely inhalation, ingestion and dermal contact. To make credible predictions of the degree of consequential exposures to a given chemical of interest, it becomes inevitable to determine the likely 'aggregate exposure' for a target receptor; aggregate exposure – represented by the quantitative exposure assessment to a single agent from all potential exposure pathways (i.e., the physical course taken by an agent as it moves from a source to a point of contact with a person) – and the related exposure routes, generally present specific questions that need to be addressed, especially in relation to the following:

  - Identification of contamination sources;
  - Estimation of the different environmental media contamination, including inter-media exchange;
  - Exposure based on media concentrations and contact duration;
  - Identification of exposure mechanisms (*viz*., pathways and relevant routes);
  - Internal dose in target tissue(s) based on temporal variation of exposure and contribution of exposure routes;
  - Exposure distribution in relation to the wider population or specific susceptible groups (e.g., infants);
  - Identification of contribution of sources to exposure, or possible exposure patterns when biological indices of exposure (biomarkers) are measured (reverse modeling);
  - Risk characterization based on worst case as well as to realistic exposure estimates; and

– Direct evaluation of available biomonitoring data relative to toxicological/legislative thresholds (biomonitoring equivalents).

In any event, refined aggregate exposure assessment tends to be data-intensive, requiring detailed information at every step of the source-to-dose pathway; typically, this would require a methodology to allow for calculating the aggregate exposure systematically, as well as a computational platform to disaggregate the exposure into the different contributing sources. Based on the aforementioned needs, *INTEGRA* (Integrated External and Internal Exposure Modelling Platform) was born/developed – to serve as a unified computational/software platform that seeks to bring together all available relevant information within a coherent methodological framework; this then allows for a comprehensive assessment of the source-to-dose continuum over the entire life cycle of substances – all the while covering an extensive chemical space through the use of QSARs. Hence, the major component of INTEGRA consists of a **unified computational platform** that integrates environmental fate, exposure and internal dose dynamically in time. In this way, the platform can differentiate between biomonitoring data corresponding to steady exposure patterns as opposed to acute, one-off or rare exposures. The platform is by and large validated using human biomonitoring data from Europe and the USA.

On the whole, INTEGRA encompasses a comprehensive computational platform that integrates multimedia environmental and micro-environmental fate, exposure and internal dose within a dynamic framework in time. The platform allows multimedia interactions across different spatial scales, taking into account environmental releases and related processes at global, regional and local scale – and indeed even up to the level of personal microenvironments. By seamlessly coupling exposure models with refined computational tools for internal dosimetry, the process essentially transforms risk assessment of environmental chemicals – since it allows risk characterization to be based on internal dosimetry metrics. Consequently, this opens the way towards a higher level of assessment that incorporates refined exposure (tissue dosimetry) and toxicity testing associated with environmental contamination at different scales. In the end, INTEGRA more or less facilitates the shift from hazard-based risk assessment to exposure-based risk assessment.

Further information on *INTEGRA* is obtainable directly from Centre for Research and Technology Hellas (CERTH), Chemical Process and Energy Resources Institute, Thessaloniki, GR 57001, Greece; or Institute for Occupational Medicine (IOM), UK.

- *The LEADSPREAD Model.* LEADSPREAD, the CalEPA/DTSC Lead Risk Assessment Spreadsheet, is a tool for evaluating exposure and the potential for adverse health effects that could result from exposure to lead in the environment. Basically, it consists of a mathematical model for estimating blood lead concentrations as a result of contacts with lead-contaminated environmental media. The model can be used to determine blood levels associated with multiple pathway exposures to lead. A distributional approach is used with this

model—allowing estimation of various percentiles of blood lead concentration associated with a given set of inputs.

Overall, the LEADSPREAD model provides a computer spreadsheet methodology for evaluating exposure and the potential for adverse health effects resulting from multipathway exposure to inorganic lead via dietary intake, drinking water, soil and dust ingestion, inhalation, and dermal contact. Each of these pathways is represented by an equation relating incremental blood lead increase to a concentration in an environmental medium, using contact rates and empirically determined ratios. The contributions via all pathways are added to arrive at an estimate of median blood lead concentration resulting from the multipathway exposure. 90th, 95th, 98th, and 99th percentile concentrations are estimated from the median by assuming a log-normal distribution with a geometric standard deviation (GSD) of 1.6.

'LeadSpread 8' is the most current version (as of the time of this writing) of the DTSC Lead Risk Assessment Spreadsheet. Among other things, the risk-based soil concentration developed in 'LeadSpread 8' is generally based on the CalEPA Office of Environmental Health Hazard Assessment (OEHHA)'s more recent developments—consisting of a new toxicity evaluation of lead that replaces the previous 10 μg/dL threshold blood concentration with a source-specific "benchmark change" of 1 μg/dL incremental blood lead criterion; this is meant to be implemented as an estimate of the 'Exposure Point Concentration' (EPC), usually based on the 95 percent confidence limit on the arithmetic mean—not as a 'not to exceed' soil concentration. Further information on LEADSPREAD may be obtained from the Office of Scientific Affairs, Department of Toxic Substances Control (DTSC), California EPA, Sacramento, California, USA.

- *The MERLIN-Expo Tool*. At this moment in time, exposure assessment is generally recognized as a somewhat weak element/link in health risk assessments – especially for the following reasons:

  – A general lack of integrated approaches for combined stressors (i.e., mixtures);
  – Widespread use of overly-conservative so-called 'worst-case' scenarios;
  – Commonly, a focus on the estimation of external exposures rather than the more desirable/relevant internal exposures (all the while recognizing that the actual targets of interest in terms of chemical toxicity are the internal tissues where toxic effects arise); and
  – Generally, a lack of comprehensive uncertainty and sensitivity analysis for the identification of key exposure drivers.

  On the other hand, to assure credible outcomes, such considerations as noted in the aforementioned have been identified as essential in most current health risk assessment guidelines – among several other things. In response, consequently, successive European Union (EU) projects set out to develop the 'MERLIN-Expo' software – which contains a library of models for exposure assessment that includes the coupling of environmental multimedia and

pharmacokinetic models; this is aimed at delivering a **standardized tool** for **human exposure assessment to chemicals**.

MERLIN-Expo is a library of models that has been developed within the framework of an EU project in order to provide an integrated assessment tool that represents state-of-the-art exposure assessment, as well as allows for the explicit recognition of scientific uncertainties at each step of the exposure process. The MERLIN-Expo tool contains a set of models for simulating the fate of chemicals in the main environmental systems, and in the human body. Among several other things, in the MERLIN-Expo tool, the exposure concept is extended from the environment to the internal tissues of the human body so that the full exposure chain can be considered in a comprehensive health effects evaluation. In this case, the main challenges in exposure modeling that MERLIN-Expo tackles are: (1) the integration of multimedia models that simulate the fate of chemicals in environmental media, and of physiologically-based pharmacokinetic (PBPK) models simulating the fate of chemicals in human body – and then determining internal effective chemical concentrations; (2) the incorporation of a set of functionalities for uncertainty/sensitivity analysis – from screening to variance-based approaches; and (3) the integration of human and wildlife biota targets with common fate modeling in the environment.

Key features of the MERLIN-Expo tool are reflected in the following important attributes that form the basis for the overall design:

- Integrated multimedia and PBPK models;
- Coverage of the total exposure assessment chain;
- Estimation of internal exposures for different human populations;
- Functionalities for uncertainty and sensitivity analysis (from screening semi-quantitative methods to quantitative variance-based approaches), in line with the tiered approach recommended by the World Health Organization (WHO);
- Ability to perform both deterministic and probabilistic simulations;
- Consideration of multiple exposure pathways for multiple chemicals to estimate combined exposure of humans and biota;
- Ability to perform steady-state as well as time-varying simulations;
- A modular structure allowing the easy construction of complex scenarios;
- A robust, transparent ('difficult-to-abuse') platform that is amenable to further development;
- Quality-assured and standardized documentation (generally developed in collaboration with CEN – the 'European Committee for Standardisation'); and
- A comprehensive package of on-line training materials.

On the whole, MERLIN-Expo features powerful numerical solvers in combination with state of the art methods for uncertainty and sensitivity analysis. MERLIN-Expo can indeed be used to carry out tiered risk assessments of increasing complexity (initial, or screening, intermediate, or refined stages of assessment) – and the availability of such options for uncertainty and sensitivity analysis should also facilitate the consideration of such issues in future decision-

making efforts. Meanwhile, it is noteworthy here that the fate models typically used in exposure assessments for predicting the distribution of chemicals among physical and biological media are essentially dictated by the intrinsic properties of the chemical substances in question. In the end, the MERLIN-Expo tool allows a more comprehensive lifetime risk assessments (i.e., rather than just plain/simple daily intakes) to be carried out for different human populations (such as a general population; children at different ages; pregnant women; etc.) – and with due consideration also given to exposure through multiple pathways. Additionally, to enable the software to be used by a wide range of end-users (including governmental agencies, industry, regulators, policy makers, academics, etc.), it was designed to allow flexible construction of exposure scenarios by linking the models available in the library.

Broadly, MERLIN-Expo is composed of a library of chemical fate models meant to assess environmental and human exposure to chemicals. These models can be linked together to create flexible scenarios relevant for both human and wildlife biota exposure evaluations. The MERLIN-Expo tool does indeed integrate multimedia, PBPK, and dose-response models on the same platform – allowing for the coverage of the complete exposure assessment chain (*viz*., from concentration in various environmental matrices such as water, air and/or soil, etc., to internal dose, to target organs, and eventually on to pathology risks). Standardized documentation for each model, as well as training materials, have been prepared to support an accurate use of the tool by end-users.

Models available in the MERLIN-Expo library are implemented on a common 'easy-to-use' and 'difficult-to-abuse' platform – to facilitate integrated full-chain assessments for combined exposures; thus, alerts are included in the tool to prevent irrelevant or nonsensical calculations *(viz*., the 'difficult-to-abuse' criteria). In fact, a number of fate and exposure problems can be addressed by the MERLIN-Expo tool with 'customized' scenarios easily constructed on account of its flexible, modular format. Also, it has been argued that other features such as the embedded holistic uncertainty and sensitivity analysis, as well as the consideration of pharmacokinetics, have helped put this tool at the forefront of regulatory science. Indeed, use of this tool should typically enable robust, regulatory-relevant environmental fate and exposure assessments to be performed with more ease and transparency. Ultimately, complex scenarios can be generated by combining independent modules that are available in the library.

Further information on *The MERLIN-Expo Tool* is obtainable online via the internet.

- *MEPAS (Multimedia Environmental Pollutant Assessment System).* MEPAS (Multimedia Environmental Pollutant Assessment System) is an analytical model that has been developed to address problems at hazardous waste sites. It is a versatile tool that can handle a diversity of different types of source terms. MEPAS couples contaminant release, migration and fate for environmental media (groundwater, surface water, air) with exposure routes (inhalation, ingestion, dermal contact, external dose) and risk/health consequences for radiological and non-radiological carcinogens and noncarcinogens.

Overall, MEPAS develops an integrated, site-specific, multimedia environmental assessment. It can simulate the transport and distribution of contaminants over time and space within air, water, soil, and foodchain pathways. MEPAS incorporates a sector-averaged Gaussian plume algorithm to simulate the atmospheric transport of contaminants; simulates groundwater transport using a three-dimensional algorithm; uses a simplistic approach to modeling the surface water pathway; and includes foodchains as an integral part of its exposure-dose component. It can model both onsite and offsite contaminant exposures. It estimates long-term health effects at receptor locations, as well as normalized maximum hourly concentrations for determining acute effects.

In the end, MEPAS integrates and evaluates transport and exposure pathways for chemicals and radioactive releases according to their potential human health impacts. It takes the nontraditional approach of combining all major exposure pathways into a multimedia computational tool for public health impact.

Further information on MEPAS may be obtained from the following: Battelle—Pacific Northwest National Laboratory, Richland, Washington, USA.

- *Physiological Information Database (PID)*. The U.S. EPA has developed a physiological information database (created using Microsoft ACCESS) intended to be used in physiologically-based pharmacokinetic (PBPK) modeling efforts. The database contains physiological parameter values for humans from early childhood through senescence, as well as similar data for laboratory animal species (primarily rodents). The database information has been collected through extensive literature search; to date, all of the data entries have been verified by an independent contractor as a means of quality assurance and quality control (QA/QC).

  It is noteworthy that PBPK models have increasingly been employed in chemical health risk assessments carried out by the U.S. Environmental Protection Agency (EPA)—and it is anticipated that their use will continue to increase. Because relevant physiological parameter values (e.g. alveolar ventilation, blood flow and tissue volumes, glomerular filtration rate) are critical components of these models but are oftentimes scattered among various sources in the scientific literature, EPA has sponsored several efforts to compile these data into an electronic relational database that is intended to be suitable for use by researchers and risk assessors. Indeed, as an important class of dosimetry models, PBPK models are useful for predicting internal dose at target organs for risk assessment applications. Dose-response relationships that appear unclear or confusing at the administered dose level can become more understandable when expressed on the basis of internal dose of the chemical. To predict internal dose level, PBPK models use physiological data to construct mathematical representations of biological processes associated with the absorption, distribution, metabolism, and elimination of compounds. With the appropriate data, these models can be used to extrapolate across species, lifestages, and exposure scenarios, as well as address various sources of uncertainty in risk assessments. The PID contains a collection of physiological data relevant for parameterizing PBPK models for children, adults, and the elderly. In addition, the database

contains physiological data for parameterizing PBPK models for young (i.e., developing) and adult rodents.

Further information on PID may be obtained from Office of Research and Development, USEPA, USA.

- *The RBCA (Risk-Based Corrective Action) Tool Kit*. The RBCA (risk-based corrective action) spreadsheet system/tool kit is a complete step-by-step package for the calculation of site-specific risk-based soil and groundwater cleanup goals, which will then facilitate the development of site remediation plans. The system includes fate and transport models for major and significant exposure pathways (i.e. air, groundwater, and soil), together with an integrated chemical/toxicological library of several chemical compounds (i.e. over 600, and also expandable by the user).

  RBCA is indeed a standardized approach to designing remediation strategies for contaminated sites. It was developed by the American Society for Testing and Materials (ASTM) to help prioritize sites according to the urgency and type of corrective action needed to protect human health and the environment. The RBCA process allows for the calculation of baseline risks and cleanup standards, as well as for remedy selection and compliance monitoring at petroleum release sites. The user simply provides site-specific data to determine exposure concentrations, average daily intakes, baseline risk levels, and risk-based cleanup levels.

  Further information on the RBCA tool kit/spreadsheet system may be obtained from the following source: ASTM (American Society for Testing and Materials), Philadelphia, Pennsylvania, USA.
- *Regional Screening Levels (RSLs)*. The RSL tables provide comparison values for residential and commercial/industrial exposures to soil, air, and tap-water (drinking water). Included here are tables of risk-based screening levels—calculated using the latest toxicity values, default exposure assumptions, and physical and chemical properties; also included is a calculator where default parameters can be changed to reflect site-specific risks.

  Overall, this tool presents standardized risk-based screening levels and variable risk-based screening level calculation equations for chemical contaminants. The risk-based screening levels for chemicals are based on the carcinogenicity and systemic toxicity of the analytes of interest. In the end, screening levels are presented in the default tables for residential soil, outdoor worker soil, residential indoor air, worker indoor air and tap water. In addition, the calculator provides a fish ingestion equation. The standardized or default screening levels used in the tables are based on default exposure parameters, and incorporate exposure factors that present 'Reasonable Maximum Exposure' (RME) conditions.

  Further information on the RSLs is obtainable from USEPA, Office of Research and Development, National Center for Environmental Assessment, Arlington, VA, USA.
- *The Stochastic Human Exposure and Dose Simulation (SHEDS) Models*. The SHEDS Models are considered probabilistic models that can estimate the

exposures that people typically confront from chemicals encountered in everyday activities. The models are able to generate predictions of aggregate and cumulative exposures over time—in order to engender risk assessments that are protective of human health.

SHEDS can estimate the range of total chemical exposures in a population from different exposure pathways over different time periods, given a set of demographic characteristics. SHEDS can also help identify critical exposure pathways, factors and uncertainties. Overall, the SHEDS models estimate the range of total chemical exposures in a population from four exposure pathways, *viz*.: inhalation, skin contact, and dietary and non-dietary ingestion. These estimates are calculated using available data—such as dietary consumption surveys; human activity information; and observed or modeled levels in food, water, air and on surfaces like counters and floors. The data on chemical concentrations and exposure factors used in SHEDS are typically based on measurements collected in field studies and published literature.

Among other things, SHEDS models have been successfully used by the U.S. EPA to help:

- Improve pesticide-related risk assessments;
- Evaluate risks to children posed by chemically-treated play-sets;
- Improve risk assessment for chemicals in food;
- Prioritize chemicals for further study on the basis of risk; and
- Prioritize data needs.

In the end, SHEDS enhances estimates of exposure in many contexts; for instance, it has been used to better inform EPA human health risk assessments and risk management decisions. Indeed, the SHEDS models are generally used by representatives from academia, industry, government, and consulting firms globally.

The U.S. EPA has developed a number of different SHEDS models and modules that address specific research questions about chemical exposure. Further information on SHEDS may be obtained from Office of Research and Development, USEPA, USA.

Further listings of variant tools of potential interest to environmental and public health risk management programs may generally be accessed on the *internet*—which serves as a very important and contemporary international network search system.

Appendix E
Selected Units of Measurement and Noteworthy Expressions

Some selected units of measurements and noteworthy expressions (of potential interest to the environmental professional, analyst, or decision-maker) are provided below.

Mass/Weight Units

g	gram(s)
ton (metric)	tonne $= 1 \times 10^6$ g
Mg	Megagram(s), metric ton(s) $= 10^6$ g
kg	kilogram(s) $= 10^3$ g
mg	milligram(s) $= 10^{-3}$ g
μg	microgram(s) $= 10^{-6}$ g
ng	nanogram(s) $= 10^{-9}$ g
pg	picogram(s) $= 10^{-12}$ g
mol	mole, molecular weight (mol. wt.) in grams

Volumetric Units

cc or cm^3	cubic centimeter(s) ≈ 1 mL $= 10^{-3}$ L
mL	milliliter(s) $= 10^{-3}$ L
L	liter(s) $= 10^3$ cm^3
m^3	cubic meter(s) $= 10^3$ L

Environmental/Chemical Concentration Units

ppm	parts per million
ppb	parts per billion
ppt	parts per trillion

These are used for expressing/specifying the relative masses of contaminant within a given exposure matrix/medium. It is worth mentioning here that, because

K. Asante-Duah, *Public Health Risk Assessment for Human Exposure to Chemicals*,
Environmental Pollution 27, DOI 10.1007/978-94-024-1039-6

water is necessarily assigned a mass of 1 kilogram per liter, mass-to-mass and mass-to-volume measurements are interchangeable for this particular medium.

NB: (1) A billion is often used to represent a thousand millions [i.e., 10^9] in some regions, such as in the USA and France; whereas a billion represents a million millions [i.e., 10^{12}] in some other jurisdictions, such as in the UK and Germany. (2) A trillion is often used to represent a million times a million or a thousand billions [i.e., 10^{12}] in some regions, such as in the USA and France; whereas a trillion represents a million billions [i.e., 10^{18}] in some other jurisdictions, such as in the UK and Germany.

Concentration Equivalents

1 ppm	≡	mg/kg or mg/L ≡ 10^{-6}
1 ppb	≡	µg/kg or µg/L ≡ 10^{-9}
1 ppt	≡	ng/kg or ng/L ≡ 10^{-12}

Concentrations in solid media [e.g., soils, etc.]:

Mg/kg	mg chemical per kg weight of sampled solid medium
µg/kg	µg chemical per kg weight of sampled solid medium

Concentrations in water or other liquid media:

Mg/L	mg chemical per liter of total liquid volume
µg/L	µg chemical per liter of total liquid volume

Concentrations in air media:

Mg/m^3	mg chemical per m^3 of total fluid volume
µg /m^3	µg chemical per m^3 of total fluid volume

Unit Conversions

To convert from ppm to mg/m^3, use the following conversion relationship:

$$\left[\mathrm{mg/m^3}\right] = [\mathrm{ppm}] \times \frac{[\text{molecular weight of substance, in g/mol}]}{24.45}$$

To convert from ppm to $\mu g/m^3$, use the following conversion relationship:

$$\left[\mu\mathrm{g/m^3}\right] = [\mathrm{ppm}] \times [\text{molecular weight of substance, in g/mol}] \times 40.9$$

Note: The above conversion relationships assume standard temperature and pressure (STP), i.e., temperature of 25 °C and barometric pressure of 760 mmHg (or 1 atm). More generally, to convert from ppm to mg/m^3, the following equation can be used:

$$\mathrm{mg/m^3} = \frac{[\mathrm{ppm} \times \mathrm{MW}]}{V}$$

where: MW is the molecular weight of the gas, and V is the volume of 1 gram molecular weight of the airborne contaminant under review. This is further derived by using the formula: V = RT/P, where R is the ideal gas constant, T is the temperature in Kelvin (K = 273.16 + T°C), and P is the pressure in mmHg. The value of R is 62.4 when T is in Kelvin, the pressure is expressed in units of mmHg, and the volume is in liters. The value of R differs if the temperature is expressed in degrees Fahrenheit (°F), or if other units of pressure are used (e.g., atmospheres, kilopascals).

Units of Chemical Intake and Dose

mg/kg-day = milligrams of chemical exposure per unit body weight of exposed receptor per day

Typical Expressions Commonly Used in Risk Assessment and Environmental Management Programs

- '*Order of Magnitude'*. Reference to an 'order of magnitude' means a tenfold difference or a multiplicative factor of ten—i.e., the base parameter may vary by a factor of 10. Hence, 'two orders of magnitude' means a factor of about 100; 'three orders of magnitude' implies a factor of about 1000; etc. For example, 'three orders of magnitude' may be used to describe the difference between 3 and 3000 ($=3 \times 10^3$). The expression is often used in reference to the calculation of environmental quantities or risk probabilities.
- *Exponentials denoted by* 10^{κ}. Superscript refers to the number of times that ***10*** is multiplied by itself. For example, $10^2 = 10 \times 10 = 100$; $10^3 = 10 \times 10 \times 10 = 1000$; $10^6 = 10 \times 10 \times 10 \times 10 \times 10 \times 10 = 1{,}000{,}000$. [*NB: It is notable that* 10^0 *is equivalent to 1.*]
- *Exponentials denoted by* $10^{-\kappa}$. Negative superscript is equivalent to the reciprocal of the positive term, i.e., $10^{-\kappa}$ is equivalent to $1/10^{\kappa}$. For example, $10^{-1} = 1/10^1 = 1/10 = 0.1$; $10^{-2} = 1/10^2 = 1/(10 \times 10) = 0.01$; $10^{-3} = 1/10^3 = 1/(10 \times 10 \times 10) = 0.001$; $10^{-6} = 1/10^6 = 1/(10 \times 10 \times 10 \times 10 \times 10 \times 10) = 0.000001$.
- *Exponentials denoted by X.YZ E +* κ. Number after the ***E*** indicates the power to which *10* is raised, and then multiplied by the preceding term (i.e., the number of times 10^{κ} is multiplied by preceding term, or $\mathrm{X.YZ} \times 10^{\kappa}$). For example, $1.00\mathrm{E}{-}01 = 1.00 \times 10^{-1} = 0.1$; $1.23\mathrm{E}{+}04 = 1.23 \times 10^{+4} = 12{,}300$; $4.44\mathrm{E}{+}05 = 4.44 \times 10^5 = 444{,}000$.
- *'Conservative assumption'*. Used in exposure and risk assessment, this expression refers to the selection of assumptions (when real-time data are absent) that are unlikely to lead to under-estimation of exposure or risk. Conservative assumptions are those which tend to maximize estimates of exposure or dose—such as choosing a value near the high end of the concentration or intake rate range.

- *'Worst case'*. A semi-qualitative term that refers to the maximum possible exposure, dose, or risk to an exposed person or group that could conceivably occur—i.e., regardless of whether or not this exposure, dose, or risk actually occurs or is observed in a specific population. Typically, this would refer to a hypothetical situation in which everything that can plausibly happen to maximize exposure, dose, or risk actually takes place. Under some circumstances, this worst case may indeed occur (or may even be observed) in a given population; however, since this is usually a very unlikely set of circumstances, in most cases, a worst-case estimate will tend to be somewhat higher than what actually occurs in a specific population. In most health risk assessments, a 'worst-case scenario' is essentially a type of 'upper-bounding' estimate.
- *'Risk of* 1×10^{-6} *(or simply,* 10^{-6}*)'*. Also written as 0.000001, or one in a million, means that one additional case of cancer risk is projected in a population of one million people exposed to a certain level of chemical X over their lifetimes. Similarly, a risk of 5×10^{-3} corresponds to 5 in 1000 or 1 in 200 persons; and a risk of 2×10^{-6} means two chances in a million of the exposure causing cancer.

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Index

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