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.

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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.

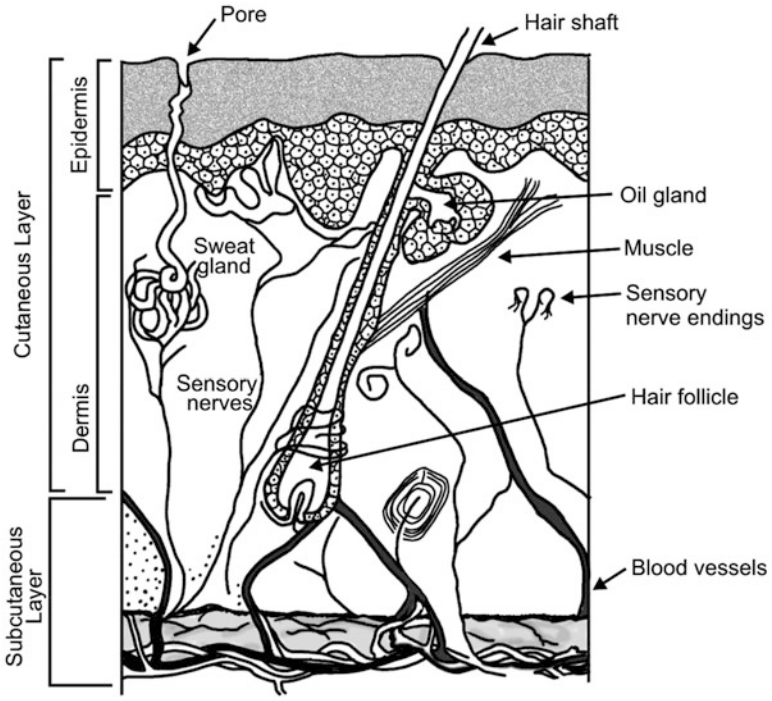

Fig. 2.1 Illustrative sketch of the general structure of the human skin (as a dermal contact exposure route for chemical materials)

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

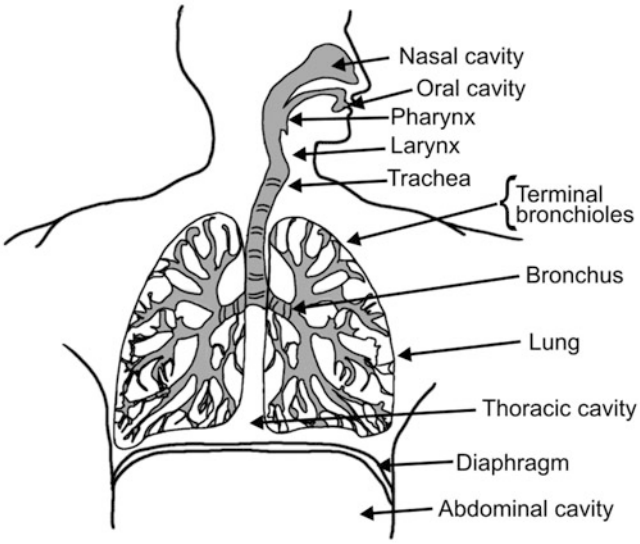

Fig. 2.2 Illustrative sketch of the general structure of the human respiratory system (as an inhalation exposure route for chemical materials)

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

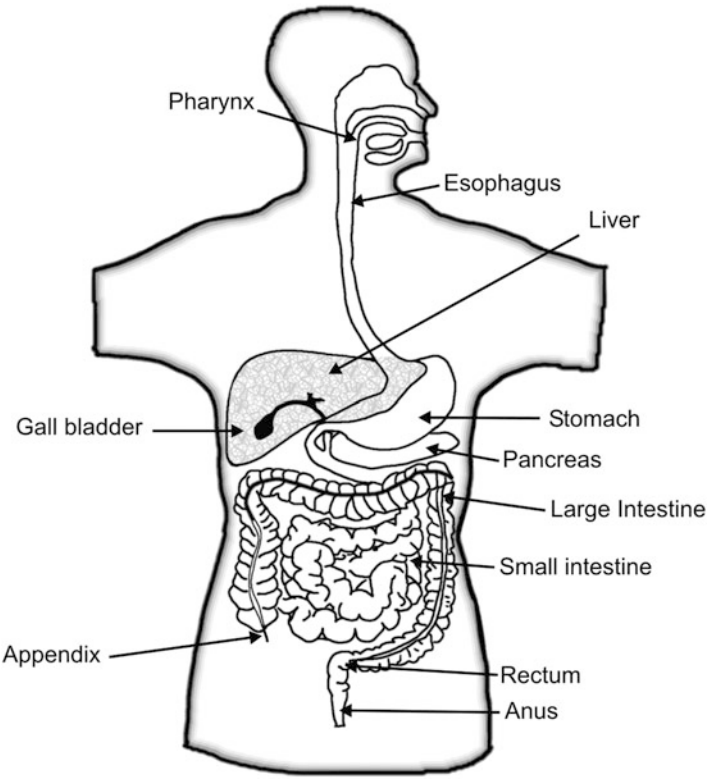

Fig. 2.3 Illustrative sketch of the general structure of the human digestive system (as an ingestion exposure route for chemical materials)

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.

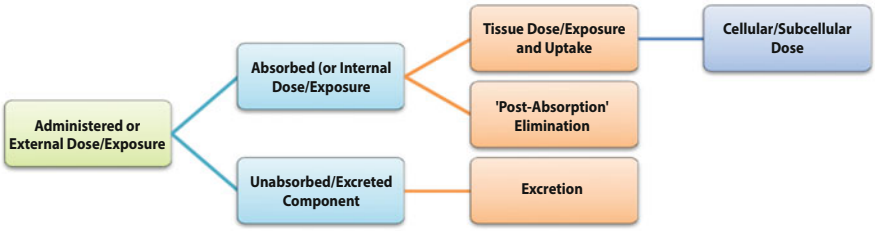

Fig. 2.4 Basics of toxicokinetics: mass balance concepts in chemical exposure situations

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

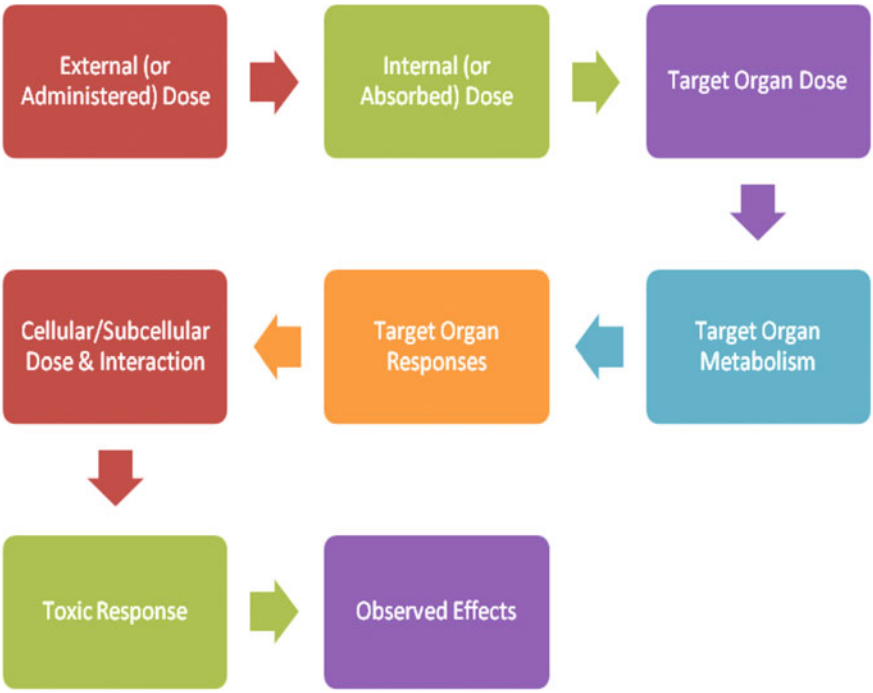

Fig. 2.5 Relationship between 'administered dose' and 'observed effects': Representation of the general pathways leading from 'external dose' to 'toxic response'/'observed effects' for a typical chemical exposure problem

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.