Occupational Causes of Cancer

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Abstract

Many recognized human carcinogens are chemicals or physical agents found in the occupational environment. The present chapter is intended to summarize current information on occupational carcinogens. Most discoveries have been based on epidemiologic research; however, animal experimentation and basic science research have also contributed to this body of knowledge. Establishing a list of occupational carcinogens is not straightforward; since many occupational agents are also found in consumer products and the general environment, it requires judgment as to what should be considered an occupational agent. It is important to synthesize this information for both scientific and public health purposes. The International Agency for Research on Cancer (IARC) publishes lists of human carcinogens based on evaluations conducted by expert panels. Based largely on the evaluations published by IARC, and supplemented by our knowledge of the occupations and industries in which they are found, and their target organs, we list 50 definite occupational carcinogens and 51 probable occupational carcinogens. The evidence base for some of these is described. In various countries it has been estimated that between 4% and 14% of all cancer deaths among males are attributable to occupational exposures, and the corresponding range is from 1% to 3% of cancer deaths among females.

Introduction

Occupational carcinogens occupy a special place among the different classes of modifiable risk factors for cancer. The occupational environment has been a most fruitful one for investigating the etiology of human cancer. Indeed, nearly half of all recognized human carcinogens are occupational carcinogens. Although it is important to discover occupational carcinogens for the sake of preventing occupational cancer, the potential benefit of such discoveries goes beyond the factory walls since most occupational exposures find their way into the general environment, sometimes at higher concentrations than in the workplace, and, for some agents, with more people exposed in the general environment than in the workplace.

Early Discoveries

From the late eighteenth century to the early twentieth century, there were some reports of clusters of various types of cancer (scrotum, lung, bladder) among workers in certain occupations (chimney sweeps, coal tar and shale oil workers, metal miners, dyestuff production). These discoveries were usually sparked by a clinician

observing a cluster of cases in his clinical practice and following it up with some documentation of a case series which made a persuasive case for a causal association, particularly because the background incidence of cancer was very low at the time.

Rigorous scientific investigation of cancer etiology began in the early twentieth century with experimental animal research. It was found that skin tumors could be induced in rabbits by applying coal tar, and it was found that the active carcinogenic components were in the family of polycyclic aromatic hydrocarbons (PAHs). These compounds may have been responsible for many of the excess risks of scrotal cancer in various groups exposed to soot and oils. Several other PAHs were subsequently shown to be carcinogenic to laboratory animals, but so were substances of many other chemical families. For instance, 2-naphthylamine, an aromatic amine, was shown to cause bladder tumors in dogs, and this was thought to explain the bladder cancers seen earlier among dyestuff workers.

The era of modern cancer epidemiology began around 1950 with several studies of smoking and lung cancer, and with the conduct of some important studies of occupational cohorts such as nickel refinery workers, coal carbonization workers, chromate workers, asbestos products manufacture, and workers producing dyestuffs in the chemical industry (Siemiatycki 2014). The findings of these early studies highlighted some significant workplace hazards. Indeed, until the 1970s, virtually the only proven causes of human cancer were smoking and various occupational exposures.

In the 1960s and 1970s, there was a sharp increase in the amount of research aimed at investigating links between the environment and cancer. Particular attention was paid to the occupational environment for several reasons. Most of the historic observations of environmental cancer risks were discovered in occupationally exposed populations. As difficult as it is to characterize and study groups of workers, it is much harder to study groups of people who share other characteristics, such as diet or general environmental pollution. Not only are working populations easier to delineate, but, often, company personnel and industrial hygiene records permit some, albeit crude, forms of quantification of individual workers' exposure to workplace substances. Also, the pressure of organized labor was an important force in attracting attention to the workplace. Finally, the workplace is a setting where people have been exposed to high levels of many substances which could potentially be harmful.

Sources of Evidence on Risk to Humans due to Chemicals

Direct evidence concerning human carcinogenicity of a substance comes from epidemiologic studies. Experimental studies of animals (usually rodents) provide evidence of carcinogenicity, but the interspecies differences preclude automatic inferences regarding human carcinogenicity. Complementary evidence comes from

the results of studies of mutagenicity, genotoxicity, and other studies of biological mechanisms.

Epidemiology

Epidemiologic research provides the most relevant data for identifying occupational carcinogens and characterizing their effects in humans. Such research requires the juxtaposition of information on illness or death due to cancer among workers and information on their past occupations, industries, and/or occupational exposures. A third, optional data set which would improve the validity of inferences drawn from that juxtaposition is the set of concomitant risk factors which may confound the association between occupation and disease. Confounding is a well-known potential problem in all nonexperimental empirical research, including in epidemiology. It refers to the possible distortion of the relationship between a factor and a disease by another factor. For instance, in estimating the relationship between an occupational chemical and lung cancer, it is important to consider whether the people exposed to the occupational chemical are more often smokers than the people unexposed to the chemical. That would distort the true relationship between the chemical under investigation and lung cancer.

Each human experiences, over his or her lifetime, an idiosyncratic and bewildering pattern of exposures. Not only is it impossible to completely and accurately characterize the lifetime exposure profile of an individual, but even if we could it is a daunting statistical task to tease out the effects of a myriad of specific substances. The possibility of mutual confounding among different occupational chemicals is sometimes particularly challenging in occupational epidemiology because of some highly correlated chemical co-exposures in the occupational environment. Blue-collar workers tend to be exposed to many different chemicals, not just one. Because of long induction periods for most cancers, it is necessary to ascertain exposure information about workers many years before cancer onset. The statistical power of a study to detect hazards depends among other things on the number of people in the study, and this is often limited by the size of a workforce in a given company or plant. Despite all of these challenges, epidemiology has made significant contributions to our knowledge of occupational carcinogens.

Epidemiologic investigation of occupation-cancer associations has usually been conducted by one of the following research designs: retrospective cohort study of a group of workers in a certain company or workplace or a case-control study in the population. Each of these designs has pros and cons in regard to ability to ascertain exposure histories, relevant confounder information, valid cancer incidence data, and statistical power.

An occupational retrospective cohort study is one in which the investigator obtains a list of workers from a company or union who worked in the company at some point in the past. Using the worker's employment history, the investigator reconstructs an employment history and, if there are historic industrial hygiene records, a history of exposure to agents in that company's workplace. With the

worker's identification, the investigator could trace the worker through national mortality or cancer incidence registers to determine if the worker had a cancer diagnosis since starting to work there. This can be used to estimate risks of different types of cancer in relation to the exposure circumstances of the worker. One weakness of this design is that it usually does not involve communication with workers, and thus the investigator rarely has access to information about nonoccupational potential confounding variables like smoking.

A case-control study is one where the investigator starts with a series of cancer cases, typically identified through a cancer registry or a hospital, and a series of controls who do not have cancer, chosen from the general population or from among hospital patients with other conditions, and the investigator contacts each person to obtain information about the work they have done and about potential confounding variables. When carried out properly, the results from a case-control study should be of equivalent validity to those of a well-conducted cohort study.

Recently there have been increasing numbers of prospective cohort studies in the general population that collect occupational information and information on potential confounders, from initially cancer-free study subjects, and follow them over time to ascertain the incidence of cancer among study participants. This type of cohort study is potentially very valid, but it might take decades of follow-up time and huge investments of resources to conduct such studies. Few such studies have thus far produced useful results on occupational carcinogens.

Since the revolution in genomics research, there has been considerable effort and investment to integrate genetic markers in occupational cancer studies to estimate so-called gene-environment interactions. While this is an interesting and worthwhile pursuit, it has not yet led to a significant increase in knowledge of new carcinogens.

Animal Experimentation

Partly in consequence of the difficulty of generating adequate data among humans and partly because of the benefits of the experimental approach, great efforts have been devoted to studying the effects of substances in controlled animal experiments. Results generated by animal studies do bear on carcinogenicity among humans. Certain fundamental genetic and cellular characteristics are similar among all mammalian species. Most recognized human carcinogens have been reported to be carcinogenic in one or more animal species; and there is some correlation between species in the target organs affected and in the carcinogenic potency.

Still, there are several reasons for caution in extrapolating from animal evidence to humans. The animal experiment is not designed to emulate the human experience but rather to maximize the sensitivity of the test to detect animal carcinogens. Doses administered are usually orders of magnitude higher than levels to which humans are exposed. The route of exposure is sometimes unrealistic (e.g., injection or implantation), and the controlled and limited pattern of co-exposures is unlike the human situation. The "lifestyle" of the experimental animal is not only different

from that of humans, but it is unlike that of its species in the wild. Animals used are typically from pure genetic strains, and susceptibility to carcinogens may be higher in such populations than in genetically heterogeneous human populations. Metabolism, immunology, DNA repair systems, life spans, and other physiologic characteristics differ between species. Tumors seen in animals often occur at sites that do not have a counterpart among humans or that are much more rarely affected among humans. Some experimental carcinogens operate via mechanisms which may not be relevant to humans. While there remain disagreements about the predictive value of animal experimentation (Cohen 1995; Gold et al. 1998), it remains an important arm in the effort to identify human carcinogens.

Short-Term Tests and Understanding of Mechanisms

A number of rapid in vitro tests have been developed to detect presumed correlates of or predictors of carcinogenicity (Ashby and Tennant 1988). However, neither alone nor in combination have these approaches proven to be consistently predictive of animal carcinogenicity, much less human carcinogenicity (Huff et al. 1996; Kim and Margolin 1999).

Deeper understanding of mechanisms of carcinogenesis has provided insight into the plausibility of a specified chemical having a carcinogenic effect on particular sites of cancer, and this can be useful in complementing the results on carcinogenicity that come from epidemiology or animal experimentation (International Agency for Research on Cancer 2006).

Listing of Occupational Carcinogens

This chapter includes a tabular listing of known occupational carcinogens, the occupations and industries in which they are found, and their target organs. Although seemingly simple, drawing up an unambiguous list of occupational carcinogens is challenging. The first challenge is define what is meant by an "occupational carcinogen." Exposures to most occupational carcinogens also occur in the general environment and/or in the course of using consumer products, and reciprocally, most environmental exposures and those associated with using certain consumer products, including medications, foods, and others, also occur in some occupational context. For instance, whereas exposures to tobacco smoke, sunlight, and immunosuppressive medications are generally not identified as occupational exposures, there are people whose occupation results in them being in contact with these agents to a degree that would not otherwise occur. Also, whereas asbestos, benzene, diesel engine emissions, and radon gas are considered to be occupational carcinogens, exposure to these agents is also experienced by the general population, and indeed many more people are probably exposed to these substances in the course of day-to-day life than are exposed at work. Given the definitional ambiguity, we adopt the following operational rule: a carcinogen is considered to be "occupational"

if there is significant human exposure to the agent in the workplace, as measured in terms of prevalence of exposure or level of exposure, or if the main epidemiological studies that led to the identification of an elevated risk of cancer were undertaken among workers. Even this operational definition requires judgment in its implementation.

The strength of the evidence for an association can vary. For some associations the evidence of excess risk seems incontrovertible (e.g., liver angiosarcoma and vinyl chloride monomer (IARC 2012b); bladder cancer and benzidine (IARC 2012b)). For some associations the evidence is suggestive (e.g., breast cancer and shift work (Hansen and Stevens 2012); bladder cancer and employment as a painter (IARC 2012b)). Among the many substances in the industrial environment for which there are no human data concerning carcinogenicity, there are hundreds that have been shown to be carcinogenic in some animal species and thousands that have been shown to have some effect in assays of mutagenicity or genotoxicity. These considerations complicate the attempt to devise a list of occupational carcinogens.

IARC Monographs

One of the key sources of information for listing of occupational carcinogens is the monograph program of the International Agency for Research on Cancer (IARC) – Evaluation of the Carcinogenic Risk of Chemicals to Humans. The objective of the IARC program, which has been operating since 1971, is to publish critical reviews of epidemiological and experimental data on carcinogenicity for chemicals, groups of chemicals, industrial processes, other complex mixtures, physical agents, and biological agents to which humans are known to be exposed and to evaluate the data in terms of human risk.

Once it is decided to evaluate a given agent or set of related agents, an international working group of experts, usually numbering between 15 and 25, is convened by IARC, and all relevant data on the topic is assembled. The meetings may evaluate only one agent, such as silica, they may address a set of related agents, or they may even address exposure circumstances such as an occupation or an industry. The working group is comprised of experts covering the following domains: (i) exposure and occurrence of the substances being evaluated, (ii) human evidence of cancer risk (i.e., epidemiology), (iii) animal carcinogenesis, and (iv) other data relevant to the evaluation of carcinogenicity and its mechanisms. They determine whether the epidemiological evidence supports the hypothesis that the substance causes cancer and, separately, whether the animal evidence supports the hypothesis that the substance causes cancer. The judgments are not simply dichotomous (yes/no), but rather they allow the working group to express a range of opinions on each of the dimensions evaluated. (In the IARC jargon, these are labeled sufficient evidence of carcinogenicity; limited evidence of carcinogenicity; inadequate evidence of carcinogenicity; evidence indicating lack of carcinogenicity.)

The overall evaluation of human carcinogenicity is based on the epidemiological and animal evidence of carcinogenicity, plus any other relevant evidence on

genotoxicity, mutagenicity, metabolism, mechanisms, or others. Epidemiological evidence, where it exists, is given greatest weight. Direct animal evidence of carcinogenicity is next in importance, with increasing attention paid to mechanistic evidence that can inform the relevance of the animal evidence for human risk assessment.

Table 1 shows the categories for the overall evaluation and how they are derived from humans, animals, and other evidence. In the end, each substance is classified into one of the following classes (which IARC refers to as "groups": carcinogenic (Group 1), probably carcinogenic (Group 2A), possibly carcinogenic (Group 2B), not classifiable (Group 3), probably not carcinogenic (Group 4)). However, the

Table 1 Classifications and guidelines used by IARC working groups in evaluating human carcinogenicity based on the synthesis of epidemiological, animal, and other evidence[a]

| Group | Definition of group | Combinations which fit in this group | | |
		Epidemiological evidence	Animal evidence	Other evidence
1	The agent, mixture, or exposure circumstance is carcinogenic to humans	Sufficient	Any	Any
		Less than sufficient	Sufficient	Strongly supportive
2A	The agent, mixture, or exposure circumstance is probably carcinogenic to humans	Limited	Sufficient	Less than strongly supportive
		Inadequate or not available	Sufficient	Strongly supportive
2B	The agent, mixture, or exposure circumstance is possibly carcinogenic to humans	Limited	Less than sufficient	Any
		Inadequate or not available	Sufficient	Less than strongly supportive
		Inadequate or not available	Limited	Strongly supportive
3	The agent, mixture, or exposure circumstance is not classifiable as to its carcinogenicity to humans	Inadequate or not available	Limited	Less than strongly supportive
		Not elsewhere classified		
4	The agent, mixture, or exposure circumstance is probably not carcinogenic to humans	Suggesting lack of carcinogenicity	Suggesting lack of carcinogenicity	Any
		Inadequate or not available	Suggesting lack of carcinogenicity	Strongly nonsupportive

[a]This table shows our interpretation of the IARC guidelines used by the working groups to derive the overall evaluation from the combined epidemiological, animal, and other evidence. However, the working group can, under exceptional circumstances, depart from these guidelines in deriving the overall evaluation. For example, the overall evaluation can be downgraded if there is less than sufficient evidence in humans and strong evidence that the mechanism operating in animals is not relevant to humans. For details of the guidelines, refer to the Preamble of the IARC Monographs (International Agency for Research on Cancer 2006)

algorithm implied by Table 1 is only indicative, and the working group may derive an overall evaluation that departs from the strict interpretation of the algorithm. For example, neutrons have been classified as human carcinogens (Group 1) despite the absence of epidemiological data, because of overwhelming experimental evidence and mechanistic considerations (IARC 2000). The IARC process relies on consensus, and this is usually achieved, but sometimes, differing opinions among experts lead to split decisions. The published evaluations reflect the views of at least a majority of participating experts. The results of IARC evaluations are published in readily available and user-friendly volumes, and summaries are published on a web site (IARC 2013).

As of 2018, over 120 meetings have been held and almost 1100 agents have been evaluated, many of which are occupational. IARC evaluations are respected worldwide and are widely used by government regulatory agencies.

Occupational Agents or Exposure Circumstances Evaluated as Carcinogenic or Probably Carcinogenic

We used the IARC Monographs as the basis for listing of occupational carcinogens. There are some limitations to bear in mind. First, IARC does not provide any explicit indication as to whether the substance evaluated should be considered as an "occupational" exposure. We have made these judgments. Second, the evaluations are anchored in the time that the working group met and reviewed the evidence; it is possible that evidence that appeared after the IARC review could change the evaluation. Third, the evaluation is a qualitative hazard evaluation; it is not a quantitative risk assessment. This means that IARC does not quantify the potency of the carcinogen or indicate what the risks may be at different levels of exposure.

Table 2 lists 50 occupational agents, occupations, and industries that have been classified as Group 1, carcinogenic to humans. The table explicitly distinguishes 38 chemical or physical agents from 12 occupations and industries that involve an increased risk of cancer but for which the responsible agent has not yet been identified.

Some of the carcinogens listed occur naturally, such as wood dust or solar radiation, whereas some are man-made, such as 1,3-butadiene or vinyl chloride. Some are single chemical compounds, such as benzene or trichloroethylene; others are families of compounds that include some carcinogens, and still others are mixtures of varying chemical composition, of which diesel engine emissions and mineral oils are examples. Most known human carcinogens have been shown to induce only one or a few different types of cancer.

Among the high-risk occupations and industries shown in Table 2 for which the agents responsible for the excess cancer risk have not yet been identified, most are industries in which the number of workers is quite small, at least in developed countries. But one occupational group – painters – stands out as an occupation that is very prevalent. Aromatic amines may be responsible for some of the excess bladder cancer risk among painters, and some of the dusts in the construction

Table 2 Occupational exposures, occupations, industries, and occupational circumstances classified as definite carcinogenic exposures (Group 1) by the *IARC Monographs*, Volumes 1–123

Agent, occupation, or industry	Target organ	Main industry or use
Chemical or physical agent		
Acid mists, strong inorganic	Larynx, lung	Pickling operations; steel and petrochemical industries; phosphate fertilizer manufacturing
4-Aminobiphenyl	Bladder	Rubber
Arsenic and inorganic arsenic compounds	Lung, skin, bladder	Glass, metals, pesticides
Asbestos (all forms)	Larynx, lung, mesothelioma, ovary	Insulation, construction, renovation
Benzene	Leukemia (acute nonlymphocytic), leukemia (acute myeloid)	Starter and intermediate in chemical production, solvent
Benzidine	Bladder	Pigments
Benzo[*a*]pyrene	Uncertain	Coal liquefaction and gasification, coke production, coke ovens, coal-tar distillation, roofing, paving, aluminum production, and others
Beryllium and beryllium compounds	Lung	Aerospace, metals
Bis(chloromethyl) ether; chloromethyl methyl ether	Lung	Production of BCME; manufacturing of plastics, resins, and polymers
1,3-Butadiene	Leukemia and/or lymphoma	Plastics, rubber
Cadmium and cadmium compounds	Lung	Pigments, batteries
Chromium (VI) compounds	Lung	Metal plating, pigments
Coal-tar pitch	Lung, skin	Construction, electrodes
1,2-Dichloropropane	Biliary tract	Production of chlorinated chemicals
Diesel engine exhaust	Lung	Transportation, mining
Ethylene oxide	Uncertain	Many, including chemical, sterilizing agent
Formaldehyde	Nasopharynx, leukemia	Formaldehyde production; plastics, textiles
Ionizing radiation (including radon-222 progeny)	Thyroid, leukemia, salivary gland, lung, bone, esophagus, stomach, colon, rectum, skin, breast, kidney, bladder, brain	Radiology, nuclear industry, underground mining

(continued)

Table 2 (continued)

Agent, occupation, or industry	Target organ	Main industry or use
Leather dust	Nasal cavity	Shoe manufacture and repair
Lindane	Non-Hodgkin's lymphoma	Pesticide
4,4′-Methylenebis(2-chloroaniline) (MOCA)	Uncertain	Rubber
Mineral oils, untreated or mildly treated	Skin	Lubricant
2-Naphthylamine	Bladder	Pigments
Nickel compounds	Nasal cavity, lung, paranasal sinus	Metal alloy
Outdoor air pollution	Lung	Outdoor workers
Pentachlorophenols	Non-Hodgkin's lymphoma	Pesticide
Pentachlorobiphenyl (PCBs)	Melanoma of skin	Transformer manufacturing, electric power workers
Shale oils	Skin	Lubricant, fuel
Silica dust, crystalline, in the form of quartz or cristobalite	Lung	Construction, mining
Solar radiation	Skin, melanoma	Outdoor work
Soot	Lung, skin	Chimney sweeps, masons, firefighters
Tobacco smoke, second-hand	Lung	Bars, restaurants, offices
Ortho-Toluidine	Bladder	Pigments
Trichloroethylene	Kidney	Solvent, dry cleaning
Ultraviolet radiation from welding	Melanoma of eye	Welding
Vinyl chloride	Liver	Plastics
Welding fumes	Lung	Welders, construction workers
Wood dust	Nasal cavity, nasopharynx	Wood sawing, construction, furniture
Occupation or industry, without specification of the responsible agent		
Acheson process	Lung	Production of silicon carbide fibers
Aluminum production	Lung, bladder	–
Auramine production	Bladder	–
Coal gasification	Lung	–
Coal-tar distillation	Skin	–
Coke production	Lung	–
Hematite mining (underground)	Lung	–

Table 2 (continued)

Agent, occupation, or industry	Target organ	Main industry or use
Iron and steel founding	Lung	–
Isopropyl alcohol manufacture using strong acids	Nasal cavity	–
Magenta production	Bladder	–
Painter	Bladder, lung, mesothelioma	–
Rubber manufacture	Stomach, bladder, leukemia	–

Table 3 Occupational exposures, occupations, industries, and occupational circumstances classified as probable carcinogenic exposures (Group 2A) by the *IARC Monographs*, Volumes 1–123

Agent, occupation, or industry	Suspected target organ	Main industry or use
Chemical or physical agent		
Acrylamide	–	Plastics
Bitumens (combustion products)	Lung	Roofing
Captafol	–	Fungicide
α-Chlorinated toluenes combined with benzoyl chloride	–	Pigments, chemicals
4-Chloro-*ortho*-toluidine	Bladder	Pigments, textiles
Cobalt metal with tungsten carbide	Lung	Hard-metal production
Creosotes	Skin	Wood preserving, brick making
Diazinon	Lung, non-Hodgkin lymphoma	Insecticide
4,4′-Dichlorodiphenyltrichloroethane (DDT)	Liver, testis, non-Hodgkin lymphoma	Biocide
Dichloromethane (Methylene chloride)	–	Organic solvent
Dieldrin and aldrin metabolized to dieldrin	–	Pesticides
Diethyl sulfate	–	Production of dyes, pigments, textiles
Dimethylcarbamoyl chloride	–	Production and manufacture of pharmaceuticals, pesticides, and dyes
Dimethylformamide	–	Solvent in production of acrylic fibers, plastics, pharmaceuticals, pesticides, adhesives, synthetic leathers, and surface coatings

(continued)

Table 3 (continued)

Agent, occupation, or industry	Suspected target organ	Main industry or use
1,2-Dimethylhydrazine	–	Laboratory use only – DNA methylation
Dimethyl sulfate	–	Used in methylation of phenols, amines, and thiols – plastics, pharmaceuticals, herbicides
Epichlorohydrin	–	Plastics
Ethylene dibromide	–	Fumigant
Glycidol	–	Pharmaceutical industry
Glyphosate	Non-Hodgkin's lymphoma	Herbicide, agriculture
Hydrazine	Lung	Production of gases, propellants, pharmaceuticals, pesticides, solvent
Indium phosphide	–	Semiconductors
Lead compounds, inorganic	Lung, stomach	Metals, pigments
Malathion	Prostate, non-Hodgkin lymphoma	Organophosphate insecticide
2-Mercaptobenzothiazole	–	Sulphur vulcanization of rubber
Methyl methanesulfonate	–	Methylating agent
6-Nitrochrysene	–	Transportation, vehicle mechanic
1-Nitropyrene	–	Transportation, vehicle mechanic
2-Nitrotoluene	–	Production of dyes
Non-arsenical insecticides	–	Agriculture
Polybrominated biphenyls	–	Plastics
Polychlorinated biphenyls	Non-Hodgkin lymphoma	Electrical components

Polycyclic aromatic hydrocarbons
    Cyclopenta[cd]pyrene
    Dibenz[a,h]anthracene
    Dibenz[a,j]acridine
    Dibenzo[a,l]pyrene
	–	Combustion of organic matter, coal liquefaction and gasification, coke production, coke ovens, coal-tar distillation, roofing, paving, aluminum production, foundries; steel mills; firefighters; vehicle mechanics

1-3-Propane sultone	–	Laboratory use, photographic chemicals, pharmaceuticals, insecticides, dyes, chemical industry
Silicon carbide whiskers	–	Mineral, abrasives
Styrene	–	Plastics
Styrene-7,8-oxide	–	Plastics
Tetrabromobisphenol A	–	Fire retardant
3,3′,4,4′-Tetrachloroazobenzene	–	Contaminant in the production of some commonly used herbicides
Tetrachloroethylene (perchloroethylene)	–	Solvent

Table 3 (continued)

Agent, occupation, or industry	Suspected target organ	Main industry or use
Tetrafluoroethylene	–	Alkylating agent used in production of polymers, nonstick coatings, resistant tubing
1,2,3-Trichloropropane	–	General purpose solvent
Tris(2,3-dibromopropyl) phosphate	–	Plastics, textiles
Vinyl bromide	–	Plastics, textiles
Vinyl fluoride	–	Production of various polymers, solar panels
Occupation or industry, without specification of the responsible agent		
Art glass, glass containers, and pressed ware (manufacture of)	Lung, stomach	–
Carbon electrode manufacture	Lung	–
Hairdressers or barbers	Bladder, lung	–
Petroleum refining	–	–
Occupational circumstance, without specification of the responsible agent		
Food frying at high temperature	–	–
Shift work involving circadian disruption	Breast	Nursing, others

industry (e.g., asbestos, silica) may be responsible for some of the excess lung cancer risk.

Table 3 lists occupational agents, occupations, and industries that have been classified as Group 2A, probably carcinogenic to humans. The table explicitly distinguishes 45 chemical or physical agents from 4 occupations and industries that have been found to present a probable risk but for which a causative agent has not been identified and the two other at-risk occupational circumstances – food frying and shift work. Whereas most agents in Table 2 (definite carcinogens) have been evaluated in several epidemiologic studies, most agents in Table 3 do not have a large body of epidemiologic evidence but rather have been found to be carcinogenic in animal experiments.

Interpreting the Lists

The designation of an agent as carcinogenic is an important public health statement, as well as a scientific one.

The determination that a substance or circumstance is carcinogenic depends on the strength of evidence at a given point in time. The evidence is sometimes clear-cut, but more often it is not. The balance of evidence can change in either direction as new data emerge.

The characterization of an occupation or industry group as a "high-risk group" is strongly rooted in time and place. For instance, the fact that some groups of nickel refinery workers experienced excess risks of nasal cancer does not imply that all workers in all nickel refineries will be subject to such risks. The particular circumstances of the industrial process, raw materials, impurities, and control measures may produce risk in one nickel refinery but not in another or in one historic era but not in another. The same can be said of rubber production facilities, aluminum refineries, and other industries and occupations. Labeling a chemical substance as a carcinogen in humans is a more timeless statement than labeling an occupation or industry as a high-risk group. A determination of carcinogenicity of a specified chemical is a statement about the properties of that chemical that is invariant in time and place; conditional on the amount of exposure to the agent, it should always be considered that a carcinogenic chemical is capable of causing cancer.

Different carcinogens produce different levels of risk, and for a given carcinogen, there may be vast differences in the risks incurred by different people exposed under different circumstances. Indeed there may also be interactions with other factors, environmental or genetic, that produce no risk for some exposed workers and high risk for others.

This raises the issue of quantitative risk assessment, which is an important tool in prevention of occupational cancer. While it would be valuable to have such information, for many agents, the information base on dose-response to support such quantification is fragmentary. As much as the designation of an agent as carcinogenic should raise flags that could lead to changes in industrial processes or regulations, we must be careful to avoid needless panic in regard to the presence of carcinogens. For most carcinogens, exposure to low concentrations for brief periods of time is unlikely to measurably influence a person's risk of cancer. Many of the already recognized carcinogens are very widespread and even ubiquitous in the occupational or general environment, and this has not been shown to lead to epidemics of cancer.

Illustrative Examples and Controversies

In this section, we present a few examples to illustrate some of the difficulties inherent in research to evaluate occupational carcinogens.

Polycyclic Aromatic Hydrocarbons (PAHs)

PAHs comprise a large family of chemical compounds which are produced during incomplete combustion of organic material and in particular fossil fuels. PAHs are found in many occupations and industries, and they are found in such non-occupational settings as vehicle roadways, homes heated by burning fuel, barbequed foods, cigarette smoke, and many more.

As described above, the earliest known occupational carcinogens were coal-derived soots, oils, and fumes that caused skin cancers. Animal experiments

showed that several of the chemicals found in these complex mixtures were carcinogenic. These chemicals were in the family of PAHs. When epidemiologic evidence accumulated on lung cancer risks among workers exposed to complex mixtures derived from combustion of coal, petroleum, and wood, it was widely felt that the responsible agents were likely to be PAHs. Several of the complex mixtures (coal tars and pitch, mineral oils, shale oils, soot) which are classified as IARC Group 1 carcinogens include PAHs, and several of the industries in which cancer risks have been identified (coal gasification, coke production, aluminum production, iron and steel founding) are industries in which PAHs are prevalent. Paradoxically, however, there is only one specific PAH on the Group 1 list – benzo (a)pyrene. Some others are classed in Group 2A. This is because it is virtually impossible to epidemiologically isolate the effect of one versus another of the components of these carcinogenic mixtures. Because of the non-feasibility of measuring all PAHs when they are measured for industrial hygiene purposes, benzo(a)pyrene has typically been considered a representative marker of PAHs. While this marker may be available for epidemiologic purposes, it cannot be assumed that this is the only PAH present or how its presence is correlated with those of other PAHs. It is possible that biomarker and genetic studies will provide the additional information that would permit the determination that specific PAHs are definite human carcinogens.

Diesel and Gasoline Engine Emissions

Engine emissions are common in many workplaces and are ubiquitous environmental pollutants. Engine emissions are complex and variable mixtures of chemicals, including many PAHs. There has long been suspicion that emissions from diesel-powered engines may be lung carcinogens; but, until recently, the epidemiologic evidence was considered inconclusive (Boffetta et al. 1997; Katsouyanni and Pershagen 1997; Nauss et al. 1995). The difficulty of drawing inferences was partly due to the crudeness of the use of the job titles of truck driver as a proxy for occupational exposure to diesel exhaust and partly because few studies were able to control for the potential confounding effect of cigarette smoking and of other occupational exposures. Also, many of the studies had low statistical power and/or insufficient follow-up time. Finally, the relative risk estimates in most studies ranged from 1.0 to 1.5, making it difficult to exclude the possibility of chance or bias. The number of diesel-powered vehicles is increasing in many countries. Because of the significant scientific and public policy implications, it is important to derive more definitive inferences regarding the potential human carcinogenicity of diesel emissions. Recently some studies of diesel-exposed mine workers and railroad workers have provided more definitive evidence that the associations previously observed are probably true (Attfield et al. 2012; Garshick et al. 2004; Silverman et al. 2012) and IARC classified diesel engine emissions as a human carcinogen.

By contrast, there is no evidence for a carcinogenic effect of exposure to gasoline engine emissions (IARC 2014; Xu et al. 2018).

Engine emission provides an example of a common dilemma in occupational and environmental cancer risk assessment. A chemical analysis of both gasoline and diesel exhaust shows the presence of many substances which are considered carcinogenic, notably some nitro-PAHs which are classed by IARC as 2A and 2B. Should the presence of a carcinogen within a complex mixture automatically trigger a labeling of the mixture as carcinogenic, irrespective of the epidemiologic evidence on the mixture? There is no wide consensus on this issue, but it has important consequences. For instance, it would have meant that both diesel and gasoline engine emissions would have been classified long ago as probable or definite human carcinogens.

Asbestos

Few health issues have sparked as much public concern, controversy, and expense as has asbestos-related cancer risk. Asbestos is a term describing a family of naturally occurring fibrous silicates which have varied chemical and physical compositions and which have been widely used in industrial and consumer products for over a century. The main fiber types are called chrysotile and amphibole. Exposure to asbestos fibers has occurred in many occupations, including mining and milling, manufacture of asbestos-containing products, and use of these products. Currently, in developed countries, construction and maintenance workers constitute the largest group of asbestos-exposed workers, resulting from application and removal of asbestos products and building demolition. Asbestos was one of the most ubiquitous workplace exposures in the twentieth century. Not only is asbestos found in occupational environments, but it is found, albeit at lower concentrations, in the air of urban centers and even rural areas.

Case reports linking asbestos with lung cancer started to appear in the 1930s and 1940s, but the first formal investigations were published in the 1950s and 1960s (Selikoff 1990). In the early 1960s, reports appeared linking asbestos exposure to a hitherto unrecognized tumor of the pleura and peritoneum called mesothelioma. By the mid-1960s, it was clear that the very high and virtually uncontrolled exposure conditions prevalent up to then could induce lung cancer and mesothelioma.

While asbestos production and use has declined dramatically in most industrialized countries since 1975, public concern and controversy have not (IPCS (International Programme on Chemical Safety) 1998; Upton et al. 1991). Asbestos fibers are highly persistent and widespread in the environment, partly because of its widespread industrial use in the past and partly because it is a natural geological component of outcroppings in many areas of the world. Measurements carried out in all kinds of non-occupational settings have detected asbestos fibers, and it has become clear that asbestos is a widespread environmental pollutant, albeit at much lower levels than in some workplaces. Also, because of long latency periods, we are still seeing the cancer impact of high occupational exposure levels experienced 30 to 50 years ago, and we will for some time to come. Since exposure levels are much lower than they used to be, it is of interest to determine the risk due to low levels of

asbestos exposure. Risk assessment models have been developed to extrapolate from high to low exposure levels, but these models have not been validated.

Many countries have banned use of asbestos, while some others have instituted regulatory limits orders of magnitude below levels that had been known to produce harmful effects. The availability of alternative non-asbestos substitution products makes such strategies feasible. Perhaps because they are not carcinogenic, or perhaps because exposure levels to the substitution products is much lower than that experienced by asbestos-exposed workers in the past, there has been no demonstrated cancer risk related to the substitution products.

While asbestos use has declined in developed countries, its use has been increasing in some developing countries.

Cadmium and Cadmium Compounds

Cadmium has been produced and used in alloys and various compounds for several end products including batteries, pigments, electroplating, and some plastics (IARC 2012a). Exposure varies widely between industries in both types of cadmium compounds and level of exposure. Following reports in a few small cohorts of excess cases of prostate cancer among workers in battery plants, an early IARC working group concluded that there was moderately persuasive evidence of an excess risk of prostate cancer as a result of cadmium exposure (IARC 1976). They noted in passing that one of the cohorts also reported an excess of lung cancer. In the following decade, a number of additional cohort studies were undertaken in cadmium-exposed workers (IARC 1993). There was no additional evidence of an increase in prostate cancer risk. But the evidence on lung cancer, which was unremarkable in the first few studies, became much more pronounced as additional data were accumulated. By 1993, another IARC working group pronounced cadmium a Group 1 carcinogen but solely on the basis of its association with lung cancer. Still, the assessment of carcinogenicity of cadmium highlighted several methodological problems. The number of long-term, highly exposed workers was small, the historical data on exposure to cadmium was limited, and the ability to define and examine a gradient of exposure was limited to one study. Confounding by cigarette smoking in relation to lung cancer was difficult to address, as was possible confounding by other occupational chemicals.

Styrene

Styrene is one of the most important industrial chemicals. The major uses are in plastics, latex paints and coatings, synthetic rubbers, polyesters, and styrene-alkyd coatings. These products are used in construction, packaging, boats, automotive (tires and body parts), and household goods (e.g., carpet backing). Nearly 18 million tons were used worldwide in 1998, with millions of workers exposed in different industries. In addition, there is widespread low-level environmental exposure.

The first evidence of a possible cancer risk came from case reports of leukemia and lymphoma among workers in various styrene-related industries. A number of cohort studies have been carried out since then in Europe and the USA in various industries (Bond et al. 1992). The interpretation of these studies has been bedeviled by four main problems: the different types of industries in which these studies were carried out make it difficult to compare results across studies; within most industries, styrene is only one of several chemical exposures, and these tend to be highly correlated with styrene exposure; the pattern of results has been unpersuasive, though there are a couple of hints of excess risk of leukemia in some subgroups of some cohorts; and finally, the classification of hematopoietic malignancies is complicated (IARC 2002).

The substantial body of epidemiologic evidence can reasonably be interpreted as showing no cancer risk, or it can be interpreted as showing suggestions of risk of leukemia in some subgroups of some cohorts. The IARC working group leaned in the latter direction as they categorized the human evidence as "limited" rather than "inadequate." The studies already conducted have been large and there have been several of them. It is not clear that another study would resolve the issue (Boffetta et al. 2009).

Nor does the experimental evidence provide clear guidance. The animal experimental evidence is equivocal and human biomarker studies show some signs of DNA adduct formation.

Vinyl Chloride

Vinyl chloride is a large-volume industrial chemical with many practical applications. In the early 1970s, clinicians observed a cluster of cases of a rare type of liver cancer called angiosarcoma among a group of workers in a plant using vinyl chloride (Creech and Johnson 1974). Within a very short time of the initial publication, other similar clusters were reported in other plants using vinyl chloride, and the association was quickly accepted as causal. The discovery was facilitated by the rarity of the tumor, the strength of the association, and the fact that there are no other known risk factors for this tumor and thus little danger of confounding. Early cohort studies confirmed the strong effect of vinyl chloride on risk of angiosarcoma of the liver and also raised questions about a possible association with lung cancer. In fact the data were suggestive enough in the 1980s that an effect on lung cancer was considered likely (Doll 1988). However, subsequent studies have failed to demonstrate such an effect, and it is likely that the early reports were distorted by confounding or by chance (Boffetta et al. 2003). While there is growing evidence that lung cancer is not a target organ for vinyl chloride, it is becoming more plausible that exposure to vinyl chloride may cause other types of liver cancer as well as angiosarcoma (Boffetta et al. 2003). Detecting an association of low to moderate strength with a fairly rare tumor which has a long latency is difficult. Because of the drastic decrease in exposure levels that took place in the vinyl chloride industry after the discovery of its carcinogenic activity, it is unlikely that there will be new cohorts of highly

exposed workers to investigate. It is conceivable that new data can be generated from further follow-up of existing cohorts; however, the maximum latent period for most cancers has likely passed, and additional cancers are increasingly likely to reflect background risk factors for liver cancer.

Occupational Cancer Risk Factors Among Women

Until quite recently, in most countries, blue-collar jobs involving significant and long-term exposure to chemicals were mainly held by men. Consequently, most research on cancer risks among workers focused on male workers. Almost all the evidence that has led to the identification of occupational cancer risk factors has been derived from studies among male workers. However, and increasingly with the shift in workplace roles of women, many women are exposed at work to agents identified as carcinogens among men. In the absence of contrary empirical evidence, it is assumed that occupational carcinogens identified among males, and listed in Tables 2 and 3, are dangerous for female workers as they are for male workers when the exposure circumstances are similar. This general assumption has not been validated, but it is reasonable to accept it as a precaution.

What is more troubling is the possibility that there may be occupational agents that are carcinogenic among women but not among men or that there are exposures experienced predominantly by women workers that have not been evaluated at all because there are few men exposed. A well-known historic example of the latter possibility is the discovery in the early 1930s that radium exposure is a risk factor for bone cancer. This was discovered because of a cluster of bone cancer among young women working as radium dial painters (Winkelstein 2002).

Although there have been few studies of cancer risks among female workers, and those that have been conducted tended to be rather small, we nevertheless enumerate here some of the findings that have hinted at cancer risks to female workers. This review is not based on a consensus process such as those conducted by IARC, and it should not be interpreted as a listing of established or probable causal associations. Some evidence of increased risk of lung cancer was observed among female workers exposed to asbestos, arsenic, chromium, nickel, and mercury or in industries including motor vehicle manufacturing, food service, or cosmetology (Zahm and Blair 2003). Some evidence of leukemia risk was observed among female workers exposed to solvents, vinyl chloride, antineoplastic drugs, radiation, and pesticides and in women who worked in food processing or textile industry (Zahm and Blair 2003). For bladder cancer, an increase in risk was observed among women who worked as painters, dry cleaners, and health-care workers, as well as women who worked in the textile and dyestuff, rubber and plastic, and leather industries (Zahm and Blair 2003). A higher risk of breast cancer was observed in female white-collar workers (Kullberg et al. 2017) and shift workers (Yuan et al. 2018). Most of the associations listed above were based on limited number of studies with small study sample, and thus further investigations are warranted to strengthen the current evidence on occupational cancer risk factors among women.

Fraction of Cancer Attributable to Occupation

Given the lengthy list of established occupational carcinogens, it is natural to wonder how much of the total number of cancers in our society could be prevented if we eliminated all occupational carcinogens. Such a fraction is referred to as an attributable fraction, and it can be estimated for any known carcinogen. By far the most important risk factor for cancer is smoking; in North America, about 85% of lung cancers and about 30% of all cancers are attributable to smoking (Jacobs et al. 2015).

To estimate the fraction of cancers attributable to occupational exposures, it is necessary to have a list of occupational carcinogens, to know what the potency of each is (as measured by relative risk), and to know the prevalence of each one in the population. Conducting such analyses is complicated and is beyond the scope of this chapter. However other investigators have conducted such analyses. We compile in Table 4 a set of estimates that have been made since 2001 in various countries. The results depend on various features of the analysis, including which chemical agents are included and which types of cancer are included in the analysis, as well as whether the focus is on incident cases or deaths. The different analyses have been based on different decisions and assumptions, but they largely coincide.

In the various analyses, it has been estimated that between 4% and 14% of all cancer deaths among males are attributable to occupational exposures, and the corresponding range is from 1% to 3% of cancer deaths among females. In many countries this would translate to thousands of deaths per year. The WHO Global Burden of Disease project estimated that in 2017, approximately 334,000 cancer deaths worldwide were due to occupational exposures (Stanaway et al. 2018). The most detailed and extensive of the national analyses was that of Rushton et al. in

Table 4 Population attributable fraction (PAF) of cancer due to occupation: selected national estimates

Lead author (year)	Country	Nbr agents[a]	Nbr types of cancer	Incidence or mortality	PAF (%) M	F
Nurminen (2001) (Nurminen and Karjalainen 2001)	Finland	>40	26	Mortality	14	2
Steenland (2003) (Steenland et al. 2003)	USA	>40	9	Mortality	4	1
Fritschi (2006) (Fritschi and Driscoll 2006)	Australia	>40	26	Incidence	11	2
Boffetta (2010) (Boffetta et al. 2010)	France	17	7	Mortality	4	1
Rushton (2012) (Rushton et al. 2012)	UK	>40	24	Mortality	8	2
Labrèche (2014) (Labrèche et al. 2014)	Canada (Quebec)	>40	28	Mortality	12	3

[a]For the most part, these agents were IARC Group 1 and Group 2A agents

Britain; there it was estimated that the occupational agents that led to the greatest numbers of attributable cancers were (in descending order) asbestos, shift/night work, mineral oils, solar radiation, silica, and diesel engine exhaust.

Additional Considerations

In the 1960s and 1970s, the field of occupational cancer research was one of the most thriving areas of epidemiological research. This was fed by the social trends which raised the profile of environmentalism and workers' health and by important discoveries of occupational carcinogens such as asbestos. Workers' organizations were active and vocal in calling for improved working conditions and for the research that would support such action. Many young investigators, influenced by the zeitgeist of the 1960s, were ideologically drawn to a research area which would dovetail with their political and social interests. Over time there has been a waning of interest and enthusiasm.

The reasons for this decline are complex but may well include the following. The political/social climate that fostered research on occupational health has greatly changed. In western countries, the economies and workforces have shifted, and there are fewer blue-collar industrial workers than there were 30 years ago. Union membership, especially in blue-collar unions, has declined, and the unions have become less militant and influential. These trends have been fostered by technology (e.g., computerization and robotization) and by globalization. Many "dirty jobs" have been eliminated or exported from western to developing countries. The bottom line is that a smaller fraction of the western workforce is involved in traditional "dirty jobs." Another factor is that most large workplaces have become much cleaner, at least in some industrialized countries. But this should not be exaggerated. There remain many industries and hundreds of thousands of workers in industrialized countries who are in jobs that involve exposure to dusts and fumes to agents that may be dangerous. This is particularly the case of small companies.

There are many thousands of chemicals in workplaces. Many of them are obscure and involve relatively few workers; but many involve exposure for thousands of workers. Of these, only a small fraction has been adequately investigated in epidemiological studies. One of the foremost problems in occupational epidemiology is to reveal as-yet-unrecognized carcinogens and carcinogenic risks.

In the past, epidemiological research of occupational risk factors has largely focused on occupational exposures associated with "dirty" industrial environments. In recent decades, however, occupational hygiene in many industries has improved, or different technologies have been adopted such that the historical circumstances no longer apply, at least in developed countries. Increasing attention is now being paid to nonchemical agents in the work environment. Physical agents such as solar

radiation and electromagnetic fields have been investigated, as have behavioral and ergonomic characteristics of particular occupations, such as physical activity and shift work. For almost all these risk factors, the distinction between occupational and non-occupational exposure is becoming more blurred.

Industries and occupations are constantly evolving. Even if we knew all there was to know about the cancer risks in today's occupational environments – which we do not – continuing to monitor cancer risks in occupational settings would remain an important activity because occupational exposure circumstances change over time and novel exposures may be introduced. Recent examples of "new" exposures are nanoparticles and indium phosphide in the semiconductor industry.

As much as the occupational environment in industrialized countries remains an area of concern, the problem in developing countries is much more precarious. Occupational hygiene conditions in developing countries are generally not subject to the same levels of regulation as those in industrialized countries. Enormous numbers of people are now working in insalubrious conditions. As life expectancy in these populations rises with improved living conditions and medical care, the numbers of cancer cases and most likely the numbers of occupationally related cancers will increase.

Many chemicals in the workplace find their way into the general environment, either via industrial effluent or via their use in consumer products. Hazards identified in the workplace often have an importance that goes beyond the factory walls.

Prevention and Compensation

The listing of occupational carcinogens in Tables 2 and 3 is useful in occupational medicine, in compensation, and in prevention. Approaches to preventing workplace exposures to occupational carcinogens include eliminating the production or use of such agents or reducing exposure levels. For some agents, reduction of exposure levels is feasible and appropriate; for others, more draconian measures, like banning use, may be appropriate. Education of workers and industries and regulators is an important component of prevention.

Where a worker has been diagnosed with a cancer known to be linked to the occupation he or she exercised, it is appropriate to look into the possibility of compensation, depending on the national policies for compensation. We offer the listing of occupational carcinogens as a tool that can be used for such a purpose.

Cross-References

▶ Cancer Survivors at the Workplace
▶ Surveillance, Monitoring, and Evaluation

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