Historical Overview of Occupational Cancer Research

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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 pathogenesis 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

In 1775, Sir Percivall Pott, one of the leading British surgeons of the day, described some cases of cancer of the scrotum among English chimney sweeps. He ascribed this condition, which was known in the trade as "soot wart," to the chimney sweeps' pitifully dirty working conditions and to the "lodgment of soot in the rugae of scrotum" [1]. In the ensuing century, the syndrome became widely known, but it remained the only recognized occupationally caused cancer until the latter part of the nineteenth century. In 1875, Volkmann described a syndrome identical to "chimney sweeps cancer" of the scrotum among a group of coal tar and paraffin workers [2]. Apparent clusters of scrotal cancer were thereafter reported among shale oil workers [3] and mule spinners in the cotton textile industry [4, 5]. By 1907 the belief in the carcinogenicity of "pitch, tar, and tarry substances" was widespread enough that skin cancers among exposed workers were officially recognized as compensable in the UK. Other types of cancer were also implicated as occupationally induced. In the late nineteenth century, following several centuries of informal observations of unusually high incidence of lung tumors in residents of Joachimsthal, Czechoslovakia, and Schneeberg, Germany, it was shown that these risks were related to work in local metal mines [6–8]. At about the same time, Rehn [9] reported a striking cluster of bladder cancer cases among workers from a German plant which produced dyestuffs from coal tar.

Following the accumulation of several of these clinical case reports of high-risk occupations, the scientific investigation of cancer etiology began in earnest at the beginning of the twentieth century with experimental animal research. A major breakthrough came with the experiments of Yamagiwa and Ichikawa [10], in which they succeeded in inducing skin tumors in rabbit ears by applying coal tar. Several important experimental discoveries were made in the next 20 years, particularly by an English group led by Kennaway. In a series of experiments, they managed to isolate dibenz(*a*,*h*)anthracene and benzo(*a*)pyrene, both polycyclic aromatic hydrocarbons (PAHs) and active ingredients in coal tar [11–13]. These compounds may have been responsible for many of the excess risks of scrotal cancer in various groups exposed to soot and oils [14]. 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 was shown to cause bladder tumors in dogs, and this was thought to explain the bladder cancers seen earlier among dyestuffs workers.

During the first half of the twentieth century, there were additional reports of high-risk occupation groups. Respiratory cancer risks were reported in such diverse occupational settings as nickel refineries [15], coal carbonization processes [16], chromate manufacture [17], manufacture of sheep-dip containing inorganic arsenicals [18], and asbestos products manufacture [19]. This occurred before the smoking-induced epidemic of lung cancer was at its peak, when the background risks of lung cancer were low.

The era of modern cancer epidemiology began around 1950 with several studies of smoking and lung cancer. In the

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field of occupational cancer epidemiology, this era saw the conduct of some important studies of gas workers [20], asbestos workers [21], and workers producing dyestuffs in the chemical industry [22]. The findings of these early studies were important in highlighting significant workplace hazards, and the methods that these pioneering investigators developed for studying occupational cohorts have strongly influenced the conduct of occupational cancer research.

Subsequently, and especially with the flowering of "environmentalism" in the 1960s as a component of social consciousness, 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, form 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. Nonetheless, since many occupational exposures can also occur in the general environment, the cancer risks borne by workers have implications well beyond the workplace.

The burst of epidemiologic research on cancer and environment was accompanied by extensive experimental work aimed at testing the carcinogenic potential of different substances. Whereas this was carried out in an uncoordinated fashion in the early years, national bodies, most notably the National Toxicology Program in the USA, have implemented systematic strategies to test large numbers of substances with standardized state-of-the-art long-term animal studies [23].

How Evidence Has Been Accumulated on Selected Associations

Table 1.1 shows the evolution of evidence regarding 8 recognized occupational risk factors [56]. For each association, the table indicates when the first suspicions were published and some of the significant pieces of evidence that came into play subsequently. The tables also give some synthetic information about the nature of the epidemiologic findings. Typically, the association was first suspected on the basis of a clinical observation, which was followed up by suggestive but inconclusive cohort studies and then by more rigorous and more persuasive cohort studies.

For most recognized carcinogens, the interval between the first clinical report and the general acceptance of the association was measured in decades. The length of the interval was great in the early period, in part because of the lack of expertise in epidemiologic research and resources to conduct such studies. For three more recent "discoveries," those relating asbestos to mesothelioma, vinyl chloride to angiosarcoma of the liver, and chloroethers to lung cancer, the interval between the first publication of a suspicious cluster and the general acceptance of a causal association was only a matter of a few years. As a rule, early reports tended to manifest higher relative risk estimates than more recent reports. This is likely due to several reasons, including the greater likelihood that outlier results will get noticed and reported and real improvements in the industrial hygiene conditions that have indeed had the effect of decreasing risks of cancer.

While it is instructive to study the history of the evolution of knowledge for recognized carcinogens, it is just as useful to understand that the trajectories of suspicion and recognition are not necessarily monotonic. That is, there are also examples of associations that have been considered possible or likely in the past that are now considered as unlikely. One such example concerns the risk of prostate cancer following exposure to cadmium. Early studies hinted at an association [57–60], but more recent and stronger studies have tended to refute the hypothesis [61–63]. For the possible association between man-made mineral fibers (MMMF) and lung cancer, the impetus and suspicion came from the similarity in physical characteristics between MMMF and asbestos. But large American and European cohort studies have failed to demonstrate an excess risk [64–66]. Still, the absolute exposure levels to MMMF have been so much lower than they have been to asbestos, that it may justly be asked whether the differential evidence of lung carcinogenicity between asbestos and MMMF is likely due to exposure levels rather than to inherent carcinogenic properties of the two classes of fibers. A third example is that of ethylene oxide and leukemia. There were reports from Sweden among producers and some users of ethylene oxide that hinted at excess risks of leukemia [67, 68]. But larger American studies have subsequently shown no such risk [69, 70]. A fourth example is that concerning acrylonitrile and lung cancer. Some American and British studies published in the early 1980s indicated possible excess risks [71–73]. But a series of large studies from Europe and the USA subsequently failed to demonstrate any risk of lung cancer. Finally, suspicions have been voiced for a long time about the possible association between formaldehyde and lung cancer. But a series of large studies have failed to demonstrate such an effect [74–78].

It is certainly clear that reports of case clusters or suspicions based on experimental findings or individual epidemiologic studies are not sufficient to predict the ultimate

Table 1.1 Selected milestone publications illustrating the development of information in humans on selected well-established occupational cancers

Material/cancer	Reference	Location	Study population	Study type	Evidence of effect
Radon/lung	Härting and Hesse [6]	Germany	Miners	Case series	Moderate
	Peller [8]	Czechoslovakia	Miners	Cohort	Moderate
	Archer et al. [24]	USA	Uranium miners	Cohort	Strong
	Archer et al. [25]	USA	Uranium miners	Cohort	Strong
	Howe et al. [26]	Canada	Uranium miners	Cohort	Strong
Benzidine/bladder	Rehn [9]	Germany	Dye workers	Case series	Weak
	Scott [27]	England	Dye workers	Case series	Moderate
	Case et al. [22]	Great Britain	Dye workers	PMR	Strong
	Meigs et al. [28]	Connecticut	Benzidine makers	Cohort	Strong
Nickel and nickel compounds/nasal	Annual Report [29]	Wales	Nickel refineries	Case series	Moderate
	Doll [30]	Wales	Nickel refineries	PMR	Strong
	Kaldor et al. [31]	Wales	Nickel refineries	Cohort	Strong
Arsenic/respiratory	Henry [32]	England	Sheep-dip makers	Case series	Weak
	Hill and Faning [18]	England	Arsenical packers	PMR	Moderate
	Lee and Fraumeni [33]	Montana	Smelter workers	Cohort	Strong
	Lee-Feldstein [34]	Montana	Smelter workers	Cohort	Strong
	Pinto et al. [35]	Washington	Smelter workers (urine index)	Cohort	Strong
	Enterline et al. [36]	Washington	Smelter workers (air index)	Cohort	Strong
Asbestos/lung	Lynch and Smith [37]	South Carolina	Asbestos textile workers	Single case	Weak
	Doll [21]	England	Asbestos workers	Cohort	Weak
	Selikoff et al. [38]	USA	Insulation workers	Cohort	Moderate
	McDonald et al. [39]	Canada	Chrysotile miners	Cohort	Strong
	Dement et al. [40]	USA	Asbestos textile workers	Cohort	Strong
	Seidman et al. [41]	USA	Amosite workers	Cohort	Strong
Benzene/leukemia	Mallory et al. [42]	UK	Various occupations	Case series	Weak
	Vigliani and Saita [43]	Italy	Various occupations	Case series	Weak
	Ishimaru et al. [44]	Japan	Various occupations	Case series	Moderate
	Aksoy et al. [45]	Turkey	Shoemakers	Case series	Moderate
	Infante et al. [46]	Ohio	Pliofilm makers	Cohort	Moderate
	Rinsky et al. [47]	Ohio	Pliofilm makers	Cohort	Strong
	Yin et al. [48]	China	Benzene producers	Cohort	Strong
Chloroethers/lung	Figueroa et al. [49]	Philadelphia	Chemical workers	Case series	Moderate
	DeFonso and Kelton [50]	Philadelphia	Chemical workers	Cohort	Moderate
	McCallum et al. [51]	UK	Chloroether makers	Cohort	Strong
Vinyl chloride/liver angiosarcoma	Creech and Johnson [52]	Kentucky	PVC makers	Case series	Weak
	Monson et al. [53]	Kentucky	PVC makers	PMR	Strong
	Waxweiler et al. [54]	USA	PVC makers	Cohort	Strong
	Fox and Collier [55]	Great Britain	PVC makers	Cohort	Moderate

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judgment regarding an association. Since random chance and error, supplemented by publication bias, will inevitably lead to the publication of some false-positive results, it is important to seek replication of findings.

Sources of Evidence on Risk to Humans Due to Chemicals

Direct evidence concerning carcinogenicity of a substance can come from epidemiologic studies among humans or from experimental studies of animals (usually rodents). Additional evidence comes from the results of studies of chemical structure–activity analysis, pharmacokinetics, mutagenicity, cytotoxicology, and other aspects of toxicology.

Epidemiology

Epidemiologic research provides the most relevant data for identifying occupational carcinogens and characterizing their effects in humans. It can also contribute to the understanding of the mechanism of action of occupational carcinogens. 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 conditions. 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.

Because of long induction periods for most cancers, current epidemiologic studies would not provide direct evidence on carcinogenic risk that might be caused by recently introduced industrial agents. Even for substances which have been with us for a long time, there are obstacles. 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 also even if we could, it is a daunting statistical task to tease out the effects of a myriad of specific substances. The ascertainment of valid cancer diagnoses is also problematic since subjects are often traced via routine record sources (notably, death certificates), which may be error prone or in which cancers with long survival are poorly represented. Confounding by factors other than the one under investigation is of course an issue in occupational cancer epidemiology, as it is in other areas of epidemiology. But the problem is sometimes particularly acute in occupational epidemiology because of some highly correlated co-exposures in the occupational environment. The number of subjects available for epidemiologic study is often limited, and this compromises the statistical power to detect hazards. Despite these challenges, epidemiology has made significant contributions to our knowledge of occupational 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 [79–87].

Still, there are several reasons for caution in extrapolating from animal evidence to humans. The animal experiment is designed not 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 (e.g., forestomach or Zymbal’s glands) or that are much more rarely affected among humans (e.g., pituitary gland). The behavior of many tumors generated in experimental animals does not mimic that of malignant neoplasms in humans, and the malignant phenotype is sometimes unclear. Quantitative extrapolation of effects from rodents to humans depends on unverifiable mathematical assumptions concerning dose equivalents, dose–response curves, safety factors, etc. Different reasonable assumptions can lead to wildly divergent estimates. Some experimental carcinogens operate via mechanisms which may not be relevant to humans. A case in point is that of kidney tumors in male rats following exposure to various organic chemicals and mixtures including gasoline; these tumors are apparently caused by precipitation of α_2-microglobulin, a gender- and species-specific protein [88]. Gold et al. [89] have shown that even between two species as close on the phylogenetic scale as mice and rats, the predictive value of carcinogenicity is only in the range of 75%.

Despite efforts to investigate the scientific basis for interspecies extrapolation and despite resources that have been devoted to testing chemicals in animal systems, there remain serious disagreements about the predictive value of animal experimentation [23, 87, 90–97].

Short-Term Tests and Structure–Activity Relationships

To mitigate the lengthy and costly process of animal carcinogenesis testing, a number of rapid, inexpensive, and ingenious tests have been developed, to detect presumed correlates of or predictors of carcinogenicity [82, 98–101]. However, neither alone nor in combination has these approaches proven to be consistently predictive of animal carcinogenicity, much less human carcinogenicity [99, 102–104]. Their role is in screening chemicals for animal testing and in complementing the results of animal experiments.

Listing Occupational Carcinogens

Although it seems like a simple enough task, it is very difficult to draw up an unambiguous list of occupational carcinogens. The first source of ambiguity concerns the definition of an *occupational* carcinogen. Most occupational exposures are also found in the general environment and/or in consumer products; most general environmental exposures and consumer products, including medications, foods, and others, are found in some occupational environments. The distinctions can be quite arbitrary. For instance, while tobacco smoke, sunlight, and immunosuppressive medications are not primarily considered to be occupational exposures, there certainly are workers whose occupations bring them into contact with these agents. Also, while asbestos, benzene, and radon gas are considered to be occupational carcinogens, they are also found widely among the general population, and indeed it is likely that many more people are exposed to these substances outside than inside the occupational environment. There is no simple rule to earmark "occupational" carcinogens as opposed to "nonoccupational" ones. Further, some carcinogens are chemicals that are used for research purposes and to which few people would ever be exposed, whether occupationally or nonoccupationally.

A second source of ambiguity derives from the rather idiosyncratic nature of the evidence. In some instances, we know that an occupational or industrial group is at excess risk of cancer, and we have a good idea of the causative agent (e.g., scrotal cancer among chimney sweeps and PAHs in soot [14]; and lung cancer among asbestos miners and asbestos fibers [63]). 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 [105]; and bladder cancer and benzidine [105]). For some associations, the evidence is suggestive (e.g., breast cancer and shift work [106]; and bladder cancer and employment as a painter [105]). 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 occupational carcinogens is the Monograph Programme of the International Agency for Research on Cancer (IARC)—Evaluation of the Carcinogenic Risk of Chemicals to Humans. The objective of the IARC Programme, 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.

IARC evaluations are carried out during specially convened meetings that typically last a week. The meetings may evaluate only one agent such as silica, may address a set of related agents, or may even address exposure circumstances such as an occupation or an industry. For each such meeting, and there have typically been three per year, IARC convenes an international working group, usually involving from 15 to 30 experts on the topic(s) being evaluated from four perspectives: (1) exposure and occurrence of the substances being evaluated, (2) human evidence of cancer risk (i.e., epidemiology), (3) animal carcinogenesis, and (4) other data relevant to the evaluation of carcinogenicity and its mechanisms. The working group is asked to review all of the literature relevant to an assessment of carcinogenicity. In the first part of the meeting, four subgroups (based on the four perspectives mentioned above) review and revise drafts prepared by members of the subgroup, and each subgroup develops a joint review and evaluation of the evidence on which they have focused. Subsequently, the entire working group convenes in plenary and proceeds to derive a joint text. 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

Table 1.2 Classifications used in the IARC Monographs to characterize evidence of carcinogenicity

Category of evidence	In humans	In animals
Sufficient evidence of carcinogenicity	A causal relationship has been established between exposure to the agent, mixture, or exposure circumstance and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias, and confounding could be ruled out with reasonable confidence	A causal relationship has been established between the agent or mixture and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols
Limited evidence of carcinogenicity	A positive association has been observed between exposure to the agent, mixture, or exposure circumstance and cancer for which a causal interpretation is considered to be credible, but chance, bias, or confounding could not be ruled out with reasonable confidence	The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g., (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct, or interpretation of the study; or (c) the agent or mixture increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential or of certain neoplasms which may occur spontaneously in high incidences in certain strains
Inadequate evidence of carcinogenicity	The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available	The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available
Evidence suggesting lack of carcinogenicity	There are several adequate studies covering the full range of levels of exposure that human beings are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent, mixture, or exposure circumstance and any studied cancer at any observed level of exposure	Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent or mixture is not carcinogenic

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evaluated. Table 1.2 shows the categories into which the working groups are asked to classify each substance, when examining only the epidemiological evidence and when examining only the animal experimental evidence [56]. The operational criteria for making these decisions leave room for interpretation, and the scientific evidence itself is open to interpretation. It is not surprising then that the evaluations are sometimes difficult and contentious.

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 1.3 shows the categories for the overall evaluation and how they are derived from human, animal, and other evidence [56]. 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), and probably not carcinogenic (Group 4). However, the algorithm implied by Table 1.3 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 [108]. The IARC process relies on consensus, and this is usually achieved, but sometimes, differing opinions among experts lead to split decisions. In the end, 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 website [109].

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. 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. Siemiatycki et al. [110] provided a consolidation of occupational carcinogens identified by the IARC Monographs up to 2003, including identification of target organs. We use their operational definition of occupational agents. In 2008 and 2009, a series of IARC Monograph meetings were held to reevaluate evidence regarding agents that had previously been considered to be Group 1 carcinogens. The evidence of carcinogenicity was reevaluated, and where appropriate the target organs were identified.

Table 1.3 Classifications and guidelines used by IARC working groups in evaluating human carcinogenicity based on the synthesis of epidemiological, animal, and other evidence

Combinations which fit in this class				
Group	Description of 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 positive
2A	The agent, mixture, or exposure circumstance is probably carcinogenic to humans	Limited	Sufficient	Less than strongly positive
		Inadequate or not available	Sufficient	Strongly positive
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 positive
		Inadequate or not available	Limited	Strongly positive
3	The agent, mixture, or exposure circumstance is not classifiable as to its carcinogenicity to humans	Inadequate or not available	Limited	Less than strongly positive
		Not elsewhere classified		
4	The agent, mixture, or exposure circumstance probably not carcinogenic to humans	Suggesting lack of carcinogenicity	Suggesting lack of carcinogenicity	Any
		Inadequate or not available	Suggesting lack of carcinogenicity	Strongly negative

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 [107] From Siemiatycki et al. [56]. By permission of Oxford University Press, USA

Definite and Probable Occupational Risk Factors for Cancer

Table 1.4 shows a list of 32 agents which have been classified as Group 1 (i.e., definite) causes of cancer and which we consider to be occupational exposures. It shows the target organs at risk, and it shows the main occupations or industries in which the agents are found. The table also shows 11 occupations and industries which have been found to be at risk, but for which the responsible agent has not been identified.

Some of these carcinogens are naturally occurring substances or agents (e.g., asbestos, wood dust, solar radiation), while some are man-made (e.g., mineral oils, TCDD, vinyl chloride). Some are well-defined chemical compounds (e.g., benzene, trichloroethylene), while others are families of compounds which may include some carcinogens and some noncarcinogens (e.g., nickel compounds, acid mists, wood dust), while yet others are mixtures of varying chemical composition (e.g., diesel engine emissions, mineral oils).

Among the 11 high-risk occupations and industries shown in Table 1.3, most are industries in which the number of workers is quite small, in developed countries at least. But one occupation group, painters, stands out as an occupation group which is quite prevalent on a population basis, and for which the agent responsible for the excess risk has not been clearly identified. It may be reasonably speculated that aromatic amines such as benzidine and 2-nathphalymine may be responsible for some of the excess bladder cancer risk, but it is not obvious what the cause of lung cancer might be [111].

Table 1.5 shows a list of 27 occupational agents which have been classified as Group 2A (i.e., probable) causes of cancer. The table also shows five occupations and industries which have been found to be probably at risk, but for which a cause has not been identified, and another type of occupational circumstance—shift work. Some of these are agents for which there is a body of epidemiologic evidence but that body of evidence does not permit a clear-cut determination of carcinogenicity (e.g., lead compounds, creosotes); but most agents in this table are definite animal carcinogens with little or no epidemiologic evidence to confirm or contradict the animal evidence. Most agents listed in Table 1.5 have fewer workers exposed than the agents in Table 1.4.

The Evolution of Knowledge

Table 1.6 shows how current occupational carcinogens were considered in two earlier times. The lists of agents in Tables 1.4 and 1.5 were compared with lists of carcinogens noted by a WHO expert panel in 1964 [112] and also with the list accrued by the IARC Monograph Programme in 1987 [113]. One-third of today's Group 1 definite occupational carcinogens were already recognized as such by 1964. Two-thirds were considered to be definite or probable as of 1987. In contrast, none of today's Group 2A probable occupational carcinogens had even been mentioned as of 1964, and about one-third were mentioned as of 1987. While it is possible for the classification of agents to change over time in either direction, in practice there have been rather few instances of

Table 1.4 Occupational exposures, occupations, industries, and occupational circumstances classified as definite carcinogenic exposures (Group 1) by the *IARC Monographs*, Volumes 1–106

Agent, occupation, or industry	Target organ	Main industry or use
Chemical agents		
Acid mists, strong inorganic	Larynx	Chemical
4-Aminobiphenyl	Bladder	Rubber
Arsenic and inorganic arsenic compounds	Lung, skin, bladder	Glass, metals, pesticides
Asbestos (all forms)	Larynx, lung, mesothelium, ovary	Insulation, construction, renovation
Benzene	Leukemia	Starter and intermediate in chemical production, solvent
Benzidine	Bladder	Pigments
Benzo[*a*]pyrene	Lung, skin (suspected)	Coal liquefaction and gasification, coke production, coke ovens, coal tar distillation, roofing, paving, aluminum production
Beryllium and beryllium compounds	Lung	Aerospace, metals
Bis(chloromethyl)ether, chloromethyl methyl ether	Lung	Chemical
1,3-Butadiene	Leukemia and/or lymphoma	Plastics, rubber
Cadmium and cadmium compounds	Lung	Pigments, battery
Chromium (VI) compounds	Lung	Metal plating, pigments
Coal tar pitch	Lung, skin	Construction, electrodes
Engine exhaust, diesel	Lung	Transport, mining
Ethylene oxide	–	Chemical, sterilizing agent
Formaldehyde	Nasopharynx, leukemia	Plastic, textile
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
Leather dust	Nasal cavity	Shoe manufacture and repair
4,4′-Methylenebis(2-chloroaniline) (MOCA)	–	Rubber
Mineral oils, untreated or mildly treated	Skin	Lubricant
2-Naphthylamine	Bladder	Pigment
Nickel compounds	Nasal cavity, lung	Metal alloy
Shale oils	Skin	Lubricant, fuel
Silica dust, crystalline, in the form of quartz or cristobalite	Lung	Construction, mining
Solar radiation	Skin	Outdoor work
Soot	Lung, skin	Chimney sweeps, masons, firefighters
2,3,7,8-Tetrachlorodibenzo-*para* -dioxin (TCDD)	–	Chemical
Tobacco smoke, secondhand	Lung	Bars, restaurants, offices
ortho-Toluidine	Bladder	Pigments
Trichloroethylene	Kidney	Solvent, dry cleaning
Vinyl chloride	Liver	Plastics
Wood dust	Nasal cavity	Furniture
Occupation or industry without specification of the responsible agent		
Aluminum production	Lung, bladder	–
Auramine production	Bladder	–
Coal gasification	Lung	–
Coal tar distillation	Skin	–
Coke production	Lung	–
Hematite mining (underground)	Lung	–
Iron and steel founding	Lung	–
Isopropyl alcohol manufacture using strong acids	Nasal cavity	–
Magenta production	Bladder	–
Painter	Bladder, lung, mesothelium	–
Rubber manufacture	Stomach, lung, bladder, leukemia	–

Table 1.5 Occupational exposures, occupations, industries, and occupational circumstances classified as probable carcinogenic exposures (Group 2A) by the *IARC Monographs*, Volumes 1–106

Agent, occupation, or industry	Suspect target organ	Main industry or use
Chemical agents		
Acrylamide	–	Plastics
Bitumens (combustion products during roofing)	Lung	Roofing
Captafol	–	Pesticide
Alpha-Chlorinated toluenes (benzal chloride, benzotrichloride, benzyl chloride) and benzoyl chloride (combined exposures)	–	Pigments, chemicals
4-Chloro-*ortho*-toluidine	Bladder	Pigments, textiles
Cobalt metal with tungsten carbide	Lung	Hard metal production
Creosotes	Skin	Wood
Diethyl sulfate	–	Chemical
Dimethylcarbamoyl chloride	–	Chemical
1,2-Dimethylhydrazine	–	Research
Dimethyl sulfate	–	Chemical
Epichlorohydrin	–	Plastics
Ethylene dibromide	–	Fumigant
Glycidol	–	Pharmaceutical industry
Indium phosphide	–	Semiconductors
Lead compounds, inorganic	Lung, stomach	Metals, pigments
Methyl methanesulfonate	–	Chemical
2-Nitrotoluene	–	Production of dyes
Non-arsenical insecticides	–	Agriculture
PAHs (several apart from BaP)	Lung, skin	Coal liquefaction and gasification, coke production, coke ovens, coal tar distillation, roofing, paving, aluminum production
Polychlorinated biphenyls	–	Electrical components
Styrene-7,8-oxide	–	Plastics
Tetrachloroethylene (perchloroethylene)	–	Solvent
1,2,3-Trichloropropane	–	Solvent
Tris(2,3-dibromopropyl) phosphate	–	Plastics, textiles
Vinyl bromide	–	Plastics, textiles
Vinyl fluoride	–	Chemical
Occupation or industry without specification of the responsible agent		
Art glass, glass containers, and pressed ware (manufacture of)	Lung, stomach	–
Carbon electrode manufacture	Lung	–
Food frying at high temperature	–	–
Hairdressers or barbers	Bladder, lung	–
Petroleum refining	–	–
Occupation circumstance without specification of the responsible agent		
Shift work involving circadian disruption	Breast	Nursing, several others

agents being "downgraded" between successive periods. Notable counterexamples are:

- 3,3 Dichlorobenzene, which was considered a definite carcinogen in 1964 and was only considered as possible as of 1987 and as of 2002
- Acrylonitrile and propylene oxide, which were considered probable carcinogens in 1987 and only as possible in 2002.

The number of occupational agents rated by IARC as Group 1 carcinogens has tapered off since 1987, while the proportion of Group 2B evaluations increased. This reflects the fact that, when the Monograph Programme began, there was a "backlog" of agents for which strong evidence of carcinogenicity had accumulated, and, naturally, these were the agents that IARC initially selected for review. Once the agents with strong evidence had been dealt with, IARC started dealing with others.

Many of the recognized definite occupational carcinogens were already suspected or established by the 1960s. It may be that there were only a limited number of strong occupation–cancer associations, and these were sufficiently obvious that they could produce observable clusters of cases for

Table 1.6 How current IARC Group 1 ($n = 32$) and Group 2A ($n = 27$) occupational carcinogens (agents, not occupations or industries) were rated in 1964 and 1987

Past rating	Current Group 1	Current Group 2A
1964 WHO rating		
Well-documented carcinogen	9	0
Suspected carcinogen	1	0
Not mentioned	22	27
Total	32	27
1987 IARC rating		
Group 1	14	0
Group 2A	6	8
Group 2B	3	5
Group 3	1	0
Not rated	8	15
Total	32	27

astute clinicians to notice. It may be that levels of exposure to occupational chemicals were so high before the 1960s as to produce high cancer risks and cancer clusters, but that improvements in industrial hygiene in industrialized countries have indeed decreased risks to levels that are difficult to detect.

While the evaluation of the hypothesis of an agent causing human cancer depends critically on epidemiological and experimental evidence, the initial suspicion can be provoked by epidemiological surveillance, by experimental evidence, or by clinical cluster observations. Indeed, most definite occupational carcinogens were first suspected on the basis of case reports by clinicians or pathologists [114]. These discoveries were usually coincidental [115]. It is thus reasonable to suspect that there may be some, perhaps many, as yet undiscovered occupational carcinogens.

Interpreting the Lists

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. However, even such a statement requires qualification. 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.

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 nonoccupational 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 polycyclic aromatic hydrocarbons. When epidemiologic evidence accumulated on lung cancer risks among workers exposed to complex mixtures derived from 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, soots) 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. Similar considerations apply to urinary 1-OH-pyrene, the most widely used biomarker of internal PAH dose, whose excretion depends on the composition of the mixture of PAH and on metabolic pathways under the control of polymorphic genes. 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. Based in part on experimental evidence and in part on epidemiologic evidence, there has long been suspicion that emissions from diesel-powered engines may be lung carcinogens; but, until recently, the epidemiologic evidence was considered inconclusive [116–118]. The difficulty of drawing inferences regarding the effect of diesel exhaust was in part due to some methodological limitations and in part due to the indirect nature of the evidence. Namely, most of the studies had used certain job titles (most often, truck driver) as proxies for occupational exposure to diesel exhaust. Few studies were able to control for the potential confounding effect of cigarette smoking and of other occupational exposures. 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 [119, 120], 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 [121–124], and IARC classified diesel engine emissions as a human carcinogen [125].

There is less evidence, both experimental and epidemiologic, for a carcinogenic effect of exposure to gasoline engine emission than to diesel emission [126, 127].

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 that 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 the 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.

Case reports linking asbestos with lung cancer started to appear in the 1930s and 1940s [37], but the first formal investigations were published in the 1950s and 1960s [21, 128]. In the early 1960s, reports appeared linking asbestos exposure to a hitherto unrecognized tumor of the pleura and peritoneum called mesothelioma [129]. 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 have declined dramatically in most industrialized countries since 1975, public concern and controversy have not [130–136]. 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 nonoccupational 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 30–50 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 [137].

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 are 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 [63]. 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 [138, 139]. 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 [140]. 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. Control of the confounding effect of co-exposure to other metals, particularly arsenic and nickel, was limited and remains somewhat problematic.

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 [141]. 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. It has been estimated that as many as one million workers in the USA may be exposed to styrene, and the numbers worldwide would be much greater. 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 [142–144]. A number of cohort studies have been carried out since then in Europe and the USA in various industries [145–149]. 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 [150].

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 [151].

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.

1,3-Butadiene

Concern about the possible carcinogenicity of 1,3-butadiene in humans derives from the results of animal experiments, which showed an increased incidence of leukemia in mice and, to a lesser extent, rats [152]. Data on the carcinogenicity of butadiene in humans derive essentially from studies conducted among workers employed in the production of the monomer and in the production of styrene-butadiene rubber (SBR), where high exposure levels occurred in the past.

A series of analyses examined the mortality of approximately 17,000 male workers from eight SBR-manufacturing facilities in the USA and Canada. Although mortality from leukemia was only slightly elevated in the most recent updates [153–155], large excesses of mortality from leukemia were seen in workers in the most highly exposed areas of the plants and among hourly paid workers, especially those who had been hired in the early years and had been employed for more than 10 years. These excesses were seen for both chronic lymphocytic and chronic myelogenous leukemia,

with significant exposure–response relationships. The analyses showed that the exposure–response for butadiene and leukemia was independent of exposures to benzene, styrene, and dimethyldithiocarbamate [154, 155]. The inferences from these analyses are limited because of the difficulty of diagnosing and classifying lymphatic and hematopoietic malignancies. There was some evidence of an association between exposure to butadiene and non-Hodgkin lymphoma in studies in the butadiene monomer industries [156–158].

Overall, the epidemiological evidence from the styrene-butadiene and the butadiene monomer industries indicates an increased risk for hematolymphatic malignancies. Studies from the styrene-butadiene industry show an excess of leukemia and a dose–response relationship with cumulative exposure to butadiene, while studies from the monomer industry show an excess of hematolymphatic malignancies in general attributable both to leukemia and malignant lymphoma. It will be difficult to find exposed populations in which to try to replicate these findings.

Vinyl Chloride

Vinyl chloride (VC) is a large volume industrial chemical with many practical applications. In the early 1970s, clinicians observed a cluster of cases of angiosarcoma of the liver among a group of workers in a plant using VC [52]. The tumor is so rare that they were struck by the cluster. Within a very short time, other similar clusters were reported, and the association was quickly accepted as causal [159, 160]. 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 [113, 161]. However, subsequent studies have failed to demonstrate such an effect, and it is likely that the early reports were distorted by confounding or chance [162]. While there is growing evidence that lung cancer is not a target organ, it is becoming more plausible, as a result of recent meta-analyses [162], that exposure to VC may cause hepatocellular carcinoma as well as liver angiosarcoma. Detecting an association of moderate strength with a fairly rare tumor which has a long latency is difficult, and it will take more data to confirm it. A further complication is whether some of the hepatocellular carcinomas are in fact misdiagnosed angiosarcomas. An additional source of potential bias and confusion derives from the observation, in the two multicenter cohort studies [163, 164], that diagnostic misclassification may occur between liver angiosarcoma and soft tissue sarcomas, and, given the rarity of soft tissue sarcomas, this could artificially create the appearance of an association with soft tissue sarcomas. 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 is likely to be approaching, and additional cancers are increasingly likely to reflect background and risk factors other than vinyl chloride. Molecular epidemiology provides another avenue for exploring the carcinogenic effects of VC, notably studies of mutation in the p53 gene [165–167].

Radium and Radon

Radium and radon provide an interesting contrast from the point of view of prevention strategies. Both radium and radon gas induce tumors in exposed workers through ionizing radiation. Radium was used by dial painters and caused osteosarcomas. Radon gas caused lung cancer in miners. The risk due to radium was easily eliminated by, in effect, eliminating the occupation of radium dial painting. Mining cannot be eliminated, and radon gas is an inevitable exposure in mines. The best strategy here is to find a cost-effective way to reduce exposures by engineering methods, while also improving the epidemiologic database on dose–response relationships. Radon also provides one of the most successful examples of the use of high-dose occupational data for the purpose of extrapolation to lower-dose environmental exposure levels [168].

Some Methodological Considerations

The main stages in occupational cancer epidemiology are detection/discovery of hazards, which can be broken down into hypothesis generation and hypothesis testing, and characterization of risks. This categorization is simplistic. In reality, a given piece of research may serve two or three of these stages, and the operational distinctions among them are ambiguous. But it is a useful conceptual framework.

Before the 1950s, the generation of hypotheses relied primarily on astute clinicians to notice clusters of cancer among groups of workers, and the investigation of hypotheses was carried out by means of industry-based historical cohort studies. Thereafter, new approaches were introduced, including attempts to generate hypotheses from analyses of routine record sources (such as death certificates) and from case-control studies. For testing hypotheses and characterization of hazards, there was increasing use of case-control methods.

The various approaches that are used in occupational cancer epidemiology can be divided in two major families: community-based studies and industry-based studies. The following sections describe some of the salient features of these designs and their advantages and disadvantages in this area.

Industry-Based Studies

In an industry-based study, the population under investigation is defined on the basis of belonging to a union or working for a company or some other work-related institution. Because of the long latency of cancer, the study design typically used is a historical cohort design [169]. A given workforce is generally exposed to a relatively narrow range of occupational substances, and for this reason the prime role of cohort studies has been and remains to investigate specific associations (or to "test hypotheses" or characterize relationships), rather than to generate hypotheses. But this is an oversimplification; a typical cohort study produces results on possible associations between one or more exposures and many types of cancer. Since it is often difficult or costly in practice to constitute an appropriate group of unexposed subjects with whom to compare the exposed and since the cohort usually constitutes a very small fraction of the entire population, it is expedient and often acceptable to take the disease or death rates in the entire population (national or regional) as a close approximation of those in the unexposed. The latter are easily available from published statistics or databases. When the disease experience of the exposed cohort is compared with that of the entire population, it is possible to take into account such basic demographic variables as age, sex, and race. The most common statistical approach is indirect standardization, and the resulting parameter is called a standardized mortality ratio (SMR) or standardized incidence ratio (SIR).

There are two significant advantages of the cohort approach, both relating to exposures of workers. The first is the opportunity it affords to focus on a group of workers with relatively high exposure levels, thereby improving the chances of detecting a risk. Secondly, by focusing on a single industry or company, it is sometimes possible to derive detailed and valid data on the exposure histories of study subjects. It is common for companies to maintain job history records for each worker, and these are often maintained for decades. Depending on the nature of the industry, the company, and the relationship established between the investigator and the company, it may be possible to obtain detailed historic exposure measurements, and these might be linkable to the job histories of individual workers. It may also be possible to consult company hygienists or engineers or other workers who can inform the investigator about past conditions and exposure circumstances. The cooperation of employers is usually a sine qua non to conduct such studies.

It is sometimes possible to obtain quite high-quality historic exposure information and to use this in assessing and characterizing hazards [169–171]. Notable examples include studies on formaldehyde [75, 172], asphalt workers [173], acrylonitrile [174, 175], and nickel compounds [176]. In some historic examples, such as in certain cohorts of asbestos workers, there were no available quantitative data on exposure levels, but the industrial process was thought to be so "simple" that only one substance was thought to be worth considering as an explanation for the excess risk of the entire cohort [177]. Such reasoning may be acceptable in a few industries, such as the extractive industries; but most industrial processes entail diverse mixtures of exposures. The success at characterizing past exposures will depend on the skill and resources of the investigating team and the availability of adequate industrial hygiene data. Ingenious methods have been brought to bear by industrial hygienists working with epidemiologists to evaluate historic exposures to specific substances in various cohorts [178].

Community-Based Case-Control Studies

In a community-based study, the population is typically defined on the basis of living in a given geographic area or falling in the catchment area of a set of health-care providers. Questionnaire-based case-control studies provide the opportunity to collect information on lifetime occupation histories and on other relevant cofactors directly from cancer patients or close relatives and appropriate controls. From this, it is possible to estimate cancer risks in relation to various occupational circumstances.

Case-control studies provide the opportunity to conduct analyses based on job titles. Analyses using job titles are useful. Several associations with cancer have been discovered by means of analyses on job titles. Such analyses are most valid and valuable when the workers have a relatively homogeneous exposure profile. Examples might include miners, motor vehicle drivers, butchers, and cabinetmakers. Whatever attempts are made to derive specific exposures in community-based studies, it is nevertheless worthwhile to also conduct the statistical analyses to evaluate risks by job titles. However, job titles are limited as descriptors of occupational exposures [115]. On the one hand, many job titles cover workers with very diverse exposure profiles. On the other hand, many exposures are found to occur across many occupation categories. In such circumstances, epidemiologic analyses by job title may entail too much noise to allow for a signal to be detected. Several approaches have been used to ascertain exposures in community-based studies, including self-reported checklist of exposures, job-exposure matrix (JEM), and expert assessment [179].

Some Trends in Epidemiologic Research on Occupational Cancer

Since the revolution in genetic research methods, there has been a shift in research resources on occupational cancer from an attempt to assess the main effects of occupations and occupational exposures to an attempt to assess so-called gene–environment interactions. While this is an interesting and worthwhile pursuit, it has not yet led to a proportionate increase in knowledge of new carcinogens. It remains the case that almost all the knowledge that has accrued about occupational risk factors has been gained without recourse to genetic interactions. It is important to avoid the temptation to shift all the "research eggs" into the basket of gene–environment interaction studies and to keep some of the resources in research approaches that have proven their worth.

In the past, the main focus of attention was on occupational exposures associated with "dirty" industrial environments. But over the past few decades, as "dirty" environments have been cleaned up or eliminated, there has been increasing attention to nonchemical agents in the work environment. Physical agents such as radon gas and electromagnetic fields have been investigated, but behavioral and ergonomic characteristics such as physical activity (or sedentarism) and shift work have come into view as potential cancer risk factors. A majority of previous occupational cancer studies were conducted among male workers; however, given women's rising participation in the workforce, researchers start to investigate more into female occupational risk factors of cancer.

Industries and occupations are in constant evolution. Even if we knew all there was to know about the cancer risks in today's occupational environments, which we do not, it is important to continue to monitor cancer risks in the occupational environment because it is always changing and introducing new exposures and circumstances (e.g., nanoparticles, radiofrequency fields).

While the lists of occupational risk factors in Tables 1.4 and 1.5 are lengthy, they are not complete. There are likely many more occupational carcinogens that have not been discovered or properly documented. For many if not most occupational circumstances, there is no epidemiological evidence one way or the other concerning carcinogenicity. One of the foremost problems in occupational epidemiology is how to uncover the hidden part of the iceberg of occupational carcinogens.

Continued Importance of Research on Occupational Cancer

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. There was a perception that research on environmental causes of cancer was important and that it would be feasible to make breakthroughs. 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. In contrast, today we perceive a waning of interest and enthusiasm. What has happened?

The reasons are complex, but may well include the following. The political/social climate that supported work 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. These trends have been fostered by technology (e.g., computerization and robotization) and by globalization. To a certain extent, "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, as mentioned above, most large workplaces have become much cleaner, at least in some industrialized countries.

Another reason for the deflation of interest in this area is that the expectations of some for quick and dramatic discoveries of "smoking guns" like asbestos did not pan out. The expectations were unrealistic, but that was not clear at the time. There was a widespread belief that there were many cancer-causing hazards in the workplace and it would only be a matter of shining some light in the right places to find them. There was much more epidemiological research in the 1970s, 1980s, and 1990s than there had been in the preceding decades. While this research produced a large number of important findings, these were incremental in the overall scheme of things and, for some, did not seem proportional to the effort.

In the face of these social and economic changes and the ostensible diminishing returns from research in occupational cancer, is this an area of investigation that should be fostered? Our answer is an unambiguous "Yes!" for the following reasons and with the following caveats:

(a) In industrialized countries, a large fraction of the workforce still works in circumstances which bring workers into contact with chemical agents. Even if the fraction is less than it was a century ago, it is still sizeable and will remain so for the foreseeable future. While industrial design and hygiene have succeeded in lowering exposures in many industries, there remain pockets where exposure levels remain high.
(b) The story of occupational hygiene conditions in developing countries is less rosy. Enormous numbers of

people are now working in insalubrious conditions. As life expectancy in these populations rises with increasing affluence and improved living conditions and medical care, the numbers of cancer cases and most likely the numbers of occupationally related cancers are steadily increasing. There is a tremendous opportunity for epidemiologists to investigate occupation–cancer relationships in developing countries.

(c) 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 with epidemiological data.

(d) The industrial environment is constantly evolving with the introduction of new and untested chemicals. We need to maintain a monitoring capacity to detect "new" occupational carcinogens. A recent example of a suspected carcinogen is indium phosphide in the semiconductor industry [180].

(e) The occupational environment is one that lends itself to preventive intervention.

(f) 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.

(g) The discovery of occupational carcinogens is important to understanding the principles of carcinogenesis: workers represent a "natural experiment" of high exposure to a potentially carcinogenic agent.

(h) The ability to detect hazards is increasing with improvement of methods for exposure assessment and outcome assessment, as well as the tendency to use larger study sizes.

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