

SECTION I

INTRODUCTION

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THE MODERN APPROACH TO THE DIAGNOSIS OF OCCUPATIONAL DISEASE

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BACKGROUND

An understanding of the health effects that may occur from occupational exposures is critical in terms of the potential human toll and an industry's success and sustainability. The diagnosis of workplace-induced diseases is necessary if the disease in question is to be prevented. In the context of modern medicine, the diagnosis of an occupational disease is a multidisciplinary process and includes input from professionals in occupational medicine, nursing, industrial hygiene, toxicology, epidemiology, engineering, and others. Though physicians are primarily responsible for making an individual diagnosis, the remaining disciplines are critical parts of the process for establishing the nature and cause of the disease(s). It is the collective group that has become paramount to the understanding and control of occupational disease within modern societies. The diagnosis of an occupational disease may be understood in the context of a public health model, which incorporates the interplay between the agent, the host, and the disease. With this approach, the agent may be physical, chemical, or biological and has the potential to cause harm depending on its characteristics (e.g., corrosive, pathogenic, and carcinogenic), the exposure concentration and duration, and the ability to target organs in exposed individuals. The host is the individual or population exposed to the agent. The disease results from the interaction of these two factors. The host in this model includes healthy individuals as well as susceptible individuals (e.g., genetic predisposition and life stage). With acute or chronic high-level exposures, host susceptibility generally increases, due to a variety of mechanisms, including saturation of detoxification reactions and increased bioactivation. Manufacturing

facilities control exposures through engineering controls, personal protective equipment, chemical substitution, area monitoring, personal monitoring, hazard communication, and employee training and education.

Despite the vast number of professionals involved, the diagnosis of an occupational disease is complicated by important factors. First, many diseases that occur as a result of workplace exposures (e.g., asthma from isocyanates) may also occur from non-workplace exposures to the same compounds or may be caused by other agents (nonspecificity). Second, disease manifestation is often idiopathic and may be attributed to the workplace purely on the basis of the disease postceding employment. Third, the majority of chemicals in commerce either have not been tested in experimental animals or have been tested but lack data on the mode of action and human relevance of adverse effects. The absence of this type of information complicates extrapolations from animal studies to workers. Finally, many tests used in clinical medicine are not specific for identifying exposures to an agent of interest. For example, a blood test that reveals high carboxyhemoglobin (COHb) levels only confirms an internal dose of carbon monoxide. It does not confirm whether the source exposure was to carbon monoxide, methylene chloride, or some other causative agent. Similarly, chest radiograph findings that suggest interstitial lung disease do not confirm exposures to a specific causative agent (e.g., wood dust). Testing of workers is subject to each test's sensitivity, specificity, and positive and negative predictive value. To complicate matters, many tests do not have established "gold standards" to which they may be compared. All of these issues may potentially compromise the accuracy of diagnoses.

As alluded to in the above examples, a multilevel assessment is needed in the diagnosis of an occupational disease. The exposure in question must be assessed in terms of what is known about it, whether the worker's complaints are consistent with this exposure, and insights into the actual work environment are the initial necessary perspectives needed. These are followed by a detailed account of the individual's illness, the person's medical history, occupational history, physical findings, laboratory findings, and a review of the epidemiological literature involving this person's exposure-disease relationship. Finally, some type of assessment of causation is necessary to determine whether there is adequate information to suggest that an exposure could produce the disease in question. This assessment typically involves a comprehensive review of the existing epidemiological literature on the topic. All this is theoretically needed before an occupational disease can be considered. Each of these will be considered in greater detail in the subsequent paragraphs.

COMPONENTS OF THE DIAGNOSIS

The History of Illness

The worker's disease history is often the only information available to the team of professionals assigned to determine the etiology of the disease. In some cases, associations with the workplace are based entirely upon this history, hence its importance. Accordingly, the trained interviewer attempts to have as much of this as possible iterated directly in the worker's own words. A description of the worker's symptoms is the basis of this history, but there needs to also be a focus on the occupational aspects of the illness. Identification of the illness occurring temporally with the workplace is helpful since exposure-disease associations may become worse during the workday, the workweek, often with improvement after work, or on weekends away from the job. It is also important to clarify the duration of the exposure and whether coworkers with similar jobs have had health problems. Since some illnesses have long latencies, the examiner must determine the prior work history of an individual. The practitioner may also use other sources of information, including the employer, incident reports, the state or federal Occupational Safety and Health Administration (OSHA), and an industrial hygienist familiar with the workplace controls, practices, and safety data sheets (SDSs). The history should include the following:

1. *Occupational Factors.* Occupational factors must be assessed and understood. These include insights into the agent (exposure) in question as well as the involved work area. Part of this understanding is obtained through an evaluation of processes, engineering

controls, personal protective equipment, employee training and compliance, and the identification of potential causative agents (e.g., which materials or chemicals are used?) and opportunities for exposure. The chemicals used must be understood in terms of the potential routes of exposure (e.g., inhalation of volatile organics), toxicokinetics (i.e., absorption, distribution, metabolism, and elimination), and toxicity.

2. *Nonoccupational Factors.* Many diseases that may originate from exposures to a causative agent in the workplace may also occur outside of the workplace. Asthma, for example, may be triggered by occupational or consumer exposure to certain isocyanates, but it may also be triggered by exposure to cat dander. Lung cancer may be related to asbestos exposure, smoking, or both. Few diseases have only an occupational basis. In fact, estimates of 5–10% of all cancers have been attributed to exposures in the occupational setting (Doll, 1984). The vast majority of cancers are not associated with occupational exposures and are thought to be multifactorial in origin (e.g., environmental exposures, lifestyle choices/hobbies, and genetic predisposition). In particular, attention must be given to these factors in the assessment of occupational disease. Especially important are exposures that occur to individuals with preexisting diseases, since these may complicate an illness resulting from an exposure. For example, an individual with underlying chronic bronchitis may have a reduced capacity for pulmonary clearance, which may predispose this individual to an adverse outcome following exposure to specific types of agents (e.g., fibers or insoluble particles).

The Physical and Laboratory Examinations

The physical and laboratory examinations are regarded as means of verifying what is already suspected following the history of illness. A skilled examiner is able to combine these two areas with a high likelihood of an accurate diagnosis, without any additional evaluation. The occupational physical examination, such as the history of illness, needs to focus on the organ where known toxicity occurs. If the worker has breathing difficulties and has exposure to a lung irritant, the examination will need to focus on the respiratory system. Other organ systems are evaluated for the sake of being thorough and to identify additional potential areas of abnormality.

Following the physical examination, the examiner may need to verify the disease suspected with the use of specific tests. In the above case, it would be appropriate to perform a pulmonary function test (e.g., spirometry) to evaluate the worker's inhalation and exhalation during normal breathing

to assess air volume and air flow. It may also be helpful to obtain a chest radiograph. There are an infinite array of tests available, each costly and with their own inherent risks. These have to be weighed against the benefit of the information to be obtained. Most of the common laboratory tests have significant benefits, without much risk. Even so, caution must be used in subjecting workers to these tests unnecessarily, as all tests have—as a disadvantage—the possibility of false positive or negative findings. These may result in additional, more risky tests in the case of the former or missed diagnoses in the case of the latter.

Use of Toxicology, Risk Assessment, and Risk Characterization Information

All chemicals, even everyday, seemingly benign substances, can produce an adverse effect at some level and duration of exposure. The adverse effect may be an alteration of normal function or even death. For example, at a certain level and duration of exposure, carbon tetrachloride may cause reversible effects, such as drowsiness and loss of motor function; however, at higher levels of exposure, this chemical can produce irreversible liver damage and respiratory arrest.

Every chemical can produce a spectrum of toxicological effects. The effects vary and all chemicals are toxic at some dose (Table 1.1); that is, all chemicals are capable of altering some function or causing death in some biological organism. Though this may seem to be stating the obvious, it serves to emphasize the basis for risk assessment, which is identifying those circumstances and conditions under which an adverse effect can be produced. As Emil Mrak, chancellor at the University of California at Davis, stated years ago, “There are no harmless substances; there are only harmless ways of using substances.” A chemical is toxic and does harm only within prescribed conditions of usage.

Toxicology is the study of the harmful effects of chemicals on the living system. To identify and characterize chemical-induced disease or injury, the practitioner must understand both the chemical reactions and interactions with tissues and cells and the biological mechanisms of cytotoxicity. The vastness and rapid gains in this area have stimulated many new controversies over chemical-induced injury and workplace safety. However, certain

principles of toxicology apply to a large number of chemicals, and an understanding of these principles is essential to the development of insightful toxicological judgment.

Risk assessment is the process of determining whether a chemical will produce harm under specified conditions of exposure. Safety, the reciprocal of risk, is the probability that a chemical will not produce harm under specified conditions of exposure. Thus, in determining the risk or safety of a chemical, the critical factor is not necessarily the intrinsic toxicity of the chemical *per se*, but rather the likelihood that the level of exposure to the chemical is sufficient to allow the expression of its intrinsic toxicity.

Risk is determined by evaluating the exposure required to produce toxicity. The evaluation of human risk associated with chemical exposure requires an assessment of the human epidemiological and animal testing data. When available, the following data should be evaluated:

- Breadth and variety of toxic responses reported.
- Species variation or consistency in toxic responses.
- Possible proposed mode(s) of action or mechanism(s) of action.
- Validity of tests performed and their relevance for extrapolation to humans.
- Dosage used in animal tests compared with the expected level of human exposures.
- Outcomes of poisonings and long-term occupational exposures, which may serve as a guide to the expected human consequences and as validation of the human relevance of animal testing data.

Modern science, including medicine, continues to evolve as a result of the accumulation of knowledge and experience. This process of accumulation and evolution of knowledge has resulted in new principles, concepts, and treatments of disease. Discoveries have been made in medicine and toxicology that have changed medical thinking and practice in the past decade.

As a result of the evolution of regulations to protect public health, large numbers of animal tests have been conducted that have produced massive amounts of new information for the practitioner as well as the worker. A safety data sheet used for hazard communication contains the results and

TABLE 1.1 Normal and Lethal Doses of Common Substances

Substance	Normal Dose	Lethal Dose	Safety Factor
Water	1.5 qt.	15 qt.	10
Aspirin (salicylic acid)	2 tablets	90 tablets	45
Beer (ethyl alcohol)	1 beer	33 beers	33
Salt (sodium chloride)	3 tsp	60 tsp	20
Lima beans (cyanide per serving)	1.18 mg	106 mg	90

classification of animal testing data that must be appropriately interpreted and communicated to employees.

Voluntary and enforceable occupational exposure levels are considered the benchmark for determining whether a disease or injury resulted from chemical exposure. These values cannot, however, be used to determine the cause of a disease or ailment. Rather, they provide guidance for protecting workers from harmful levels of exposure. In short, occupational exposure levels protect; they do not predict. Because safety factors and other margins of safety are incorporated into these standards, exceeding the exposure level does not indicate the likelihood of harm. However, when the exposure level is exceeded, harm can occur at some point. Because all chemicals cause harm at some level of exposure, the principles of the dose–response relationship form the basis for workplace protection against chemical-induced injury.

Exposure and Dose An individual's risk of an adverse health effect is determined by evaluating exposure(s) and dose(s). Exposures must be considered based on the likely route(s) of exposure (i.e., ingestion, inhalation, and dermal/ocular). The concept of dose is different from exposure. Exposure is the opportunity to contact and absorb a chemical; this generally means that the individual and the substance are in some physical proximity. Exposure must occur to receive a dose. As used herein, the term dose refers to the actual amount of a substance absorbed by the individual, but it may also be considered in terms of the dose received at the point of contact (e.g., dermal exposure to corrosive agents). Exposure varies according to the source of the chemical, the distance from the source of contamination, and the concentration of the chemical. Even when individuals have the same or similar exposures, the actual dose received will depend on a number of variables (Table 1.2).

Duration of Exposure With some substances, even brief exposures may be harmful; with others, adverse health effects may be manifested only after chronic exposures. Exposures vary between individuals, even those working in the same areas, based on the duration of the exposure. For example, a worker exposed for 3 h in the workplace does not receive the same dose as a worker exposed for 8 h in the workplace. This necessarily varies by a number of factors, including environment. For example, a person who has lived in an area with measurable levels of specific chemicals all his or her life certainly has a different exposure duration from someone who has recently moved to the area.

Type of Contact The opportunity for contact (e.g., inhalation, ingestion, and dermal/ocular) may determine whether the exposure gives rise to adverse health effects, and if so, the nature and severity of these effects. For example, certain chemical compounds may be harmful if inhaled but are relatively harmless if swallowed.

TABLE 1.2 Variables Determining Degree of Exposure^a

Route of Exposure	Variables
Inhalation	Inhalation absorption coefficient
	Exposure period outdoors
	Vapor concentration outdoors
	Respiratory rate indoors
Dermal	Vapor concentration indoors
	Dermal absorption coefficient
	Vapor concentration outdoors
	Vapor concentration indoors
	Exposure period outdoors
	Exposure period indoors
Ingestion	Exposed body surface outdoors
	Exposed body surface indoors
	Oral absorption coefficient
	Water ingestion rate
	Soil ingestion rate
	Food ingestion rate
	Water concentration indoors and outdoors
Soil concentration outdoors and indoors	
	Food concentrations

^aTotal daily dose, micrograms/day, determined by all routes of exposure.

Level of Exposure The effect of a chemical varies with the amount of the dose. For example, even oxygen can be dangerous to human health in very high concentrations. Potential differences in exposure result from a wide range of different workplace controls and practices as well as from lifestyle choices.

Environmental Exposure Considerable attention has been focused on environmental causes of diseases in recent years, partly because of publicity and partly because of increasing concern over industrial pollution. In the eighteenth century, it was common for children of a mercury miner to develop mercury poisoning and infants in families that used leaded pottery to suffer from central nervous system damage. In Japan during the 1960s, a disease was reported that was caused by industrial methylmercury pollution of fish used for food, a disorder called Minamata disease, after the bay into which the waste was dumped (Matsumoto et al., 1965). Recently, a painful bone disease in rice field workers in Japan, a condition known as Itai-Itai disease, resulted from cadmium pollution by nearby mines that produced zinc and lead (Kobayashi, 1971).

In the United States, a dramatic example of environmentally induced disease involved 60 cases of chronic beryllium poisoning suffered by women, children, and a few men, none of whom had entered a beryllium-using plant (Hardy et al., 1967). Beryllium in nearby community air from factory stacks was one source; clothes brought from the workplace into the home proved to be a more serious source; and it is likely that soil heavily contaminated with beryllium

may be an important cause of long-delayed cases of chronic toxicity. Another example of environmentally induced disease is provided by reports of the hazards of asbestos exposure. Wagner et al. (1960) published their finding that correlated 32 cases of malignant mesothelioma with neighborhood asbestos exposure. Native women and children who lived in the South African villages close to plants that refined asbestos from nearby mines were the main victims. Newhouse and Thompson (1965) reported a series of fatal cases of mesothelioma among residents of a dwelling adjacent to a London asbestos factory. As with the beryllium industry experience in the United States, both proximity and contaminated work clothes were etiologic factors in these cases. Kiviluoto (1960) found radiographic evidence of pleural calcification in a significant number of inhabitants of a geographically limited area in Finland, with no other evidence of disease. Further study demonstrated that dust from a neighboring asbestos plant was responsible for the radiographic findings.

It cannot be overemphasized that correct diagnosis, rational treatment, and the prognosis of occupational disease rest mainly on the knowledge of workplace and/or incidental exposure. In some cases, assaying blood, urine, or tissue samples may lead to the diagnosis of industrial illness; in other cases, it may simply create confusion, because the findings reflect only exposure or levels also found in individuals who were not industrially exposed. The scientific method must be used to determine the chemical cause of a disease. Failure to use this method may result in incorrect associations and conclusions.

DETERMINING THE CAUSE OF OCCUPATIONAL DISEASE

Causal Inference

The issue of whether a particular chemical exposure causes disease in humans may be approached in different ways. Details of the exposure and the disease must be thoroughly understood. With this information, the existing scientific literature may be used to determine whether an individual's illness is related to a particular exposure. In addition to the consideration of an individual's circumstances, it is also necessary to determine if there is additional general information in the scientific literature to support a chemical-disease relationship. There are several ways of doing this. In some approaches, a more theoretical approach with causal factors described as having multiple forms (sufficient, component) and with causal inference described as a part of the more general process of scientific reasoning is used (Rothman and Greenland, 1998). In other approaches, multiple factors (biologic plausibility, strength of association, exposure response, consistency, specificity, coherence, experimental

evidence, analogy, and temporality) have received consideration (U.S. Surgeon General's Report on Smoking, 1964; Hill, 1965).

The multiple-factor approach to causation has limits, since there may be exceptions to nearly all of the factors even though an exposure-disease relationship may exist. For example, lung cancer is strongly related to cigarette smoke, but cigarette smoke is not specific to the association with lung cancer. With this approach, biologic plausibility may include an assessment of results from toxicity (animal) testing. Animal studies often exist in the absence of epidemiological data or may exist with it. In either case, the interpretation of animal data is complicated by the fact that different species process chemical and material exposures differently in terms of their absorption, distribution, metabolism, and elimination. Second, animal studies often involve the administration of high doses to elicit an effect. Once this is established, it becomes challenging to establish an exposure (dose) where no effect is present. This is often a contentious and complicated process with considerable uncertainty involved in the extrapolation of animal toxicity testing results to human beings (Green et al., 2011).

Causal inference in epidemiology relies on hypothesis testing in order for appropriate conclusions to be made between the relationship of an exposure and a disease. Because of a general lack of specific details concerning occupational/environmental epidemiological hypotheses and the subsequent difficulty in performing hypothesis testing, often the "null hypothesis" approach is used in the scientific process. The null hypothesis is used to focus on a negative association between an exposure and a disease (i.e., the exposure is not related to the disease). If an association is observed, the null hypothesis is rejected (subject to control for bias and chance) and an alternative hypothesis is considered (i.e., the exposure is related to the disease) (Rothman and Greenland, 1998). The use of the null hypothesis approach implies that studies are designed and performed where hypothesis testing is possible. In occupational epidemiology, the two designs where this is most feasible are the cohort and case-control designs (Rothman and Greenland, 1998; Elwood, 2007).

As a general rule, a causative relationship is more likely to be present if the statistical relationship is strong and if the relationship occurs in multiple hypothesis testing studies that include multiple populations where sample selection, sample size, bias, and confounding have been adequately assessed. Regardless of the approach to establishing *causation*, the practitioner must answer a series of questions satisfactorily to determine whether an *association* is present. These include the following:

1. Has the patient been exposed to the chemical?
2. Has the exposure resulted in a dose?

3. Is the dose sufficient to cause an effect?
4. Is the effect consistent with the chemical's known effects?
5. Is there objective medical evidence demonstrating a disease or illness?
6. Is the onset of the disease temporally related to the exposure?
7. Is the effect biologically plausible?
8. Have all other confounding or contributing factors been considered or eliminated?

It is apparent from these questions that the practitioner must be knowledgeable about human toxicology in combination with clinical medicine and existing epidemiological studies. The strongest and most appropriate evidence for establishing the cause of human illness comes from human epidemiological studies. In the absence of reliable human data, results from animal studies may be needed with the above caveats.

Epidemiology and Statistical Considerations

In addition to the consideration of association and possibly causation, diseases from chemicals can also be assessed based on the existing epidemiology and statistical relationships in the medical literature. Epidemiology is the study of the distribution and determinants of health-related conditions and events in specified populations along with the application of this information to the control of health problems. It uses a variety of approaches to understand diseases. Some of these approaches are common in the study of occupational groups. Occupational study types and basic statistical terminology are briefly reviewed.

There are two general measures commonly used in epidemiological investigations, incidence and prevalence. Incidence rate refers to the number of people within a specified population who become ill during a period of time (usually 1 year). This number effectively defines the "risk" of that disease within the specified population. Incidence is contrasted with prevalence or the percentage of individuals with disease in a population at a specified point in time. Prevalence is not a good estimate of risk.

There are several types of scientific investigations seen in the medical literature that involve worker populations. The most common types include cohort mortality, case-control, and cross-sectional studies. Case reports also occur in the literature. These typically involve the combination of a unique exposure and a unique disease in a person. Though they may be important in the recognition of a new disease or the exposure-disease relationship, by themselves they are unable to formally test a scientific hypothesis. The case report may occur as a series of individual reports, also known as the case series.

In the cohort mortality study, the investigator determines mortality rates within an exposed population and compares this number with the adjusted mortality rate in a non-exposed population, usually adjusted for age and gender. The ratio of the exposure-specific mortality rate in the exposed population to the standard population (usually adjusted by age, race, and gender) is referred to as the standardized mortality ratio (SMR). If the ratio is greater than 100 (also stated as 1.0), the implication is that there are more deaths in the exposed population than expected. If it is less than 100, the implication is that the death rate is less than expected. If it is equal to 100, it implies that there is no difference between the mortality rates in the exposed and the comparison populations. Cohort studies may be very helpful as they can account for the complete enumeration of all individuals within the group (cohort) along with the length of time they were exposed.

Generally, the larger the number of study participants, the better the statistical capability of determining whether there is a relationship between exposure and disease, if one truly exists. This is referred to as study "power." Power is the ability of a study to detect a true significant association between exposure and outcome. Epidemiologists can be more confident that an association does or does not exist between an exposure and an outcome when the findings are based on large studies rather than small ones.

Another type of common epidemiological investigation within occupational settings is the "case-control" study. In this type of investigation, cases include people who have the disease of interest and the other group (controls) does not have the disease but is ideally similar in all other respects. Data regarding past exposures in both groups are obtained and compared. Exposure status is unknown at the time of defining cases and controls. In this study type, the measure of risk is referred to as an "odds ratio" (OR). The OR is the comparison of odds for cases having been exposed versus the odds of controls having been exposed.

Both SMRs and ORs provide an estimate of relative risk or the risk of disease in an exposed group relative to the risk in an unexposed group. The strongest association between exposure and disease occurs when incremental exposures result in incremental disease (exposure-response). Relative risks must be interpreted within the context of bias, sample size, sample selection, and study design, as these factors may artificially increase or decrease the estimation of risk.

Cross-sectional studies evaluate the presence of diseases and exposures at one point in time. They are usually not useful in the determination of causative relationships, since it is not possible to determine which of these came first, the exposure or the disease.

If risk estimates (SMRs or ORs) are increased (>1.0), the epidemiologist (or the diagnostician) must determine if these represent true or false positive findings. Several things may affect study findings. First, due to the effect of probability on

risk estimates, it is possible that findings may be due to chance alone and not to an exposure or factor of interest. One way epidemiologists express this chance is by the p -value. The significance level is usually set to 0.05. If a statistical test has a p -value less than this, it is considered statistically significant, by convention.

Another way to consider the likelihood of a positive finding (positive risk estimate) is to determine confidence intervals around the estimate. Confidence intervals are a reflection of a study's size and express the range of possibilities for the risk estimate. Typically, confidence intervals are expressed at the 95th percentile, which provides a range in which the "true" relative risk will occur, upon repeated testing, 95% of the time. When the study's sample size is large enough, the confidence interval will be expressed as a narrower interval. This provides assurance to the epidemiologist that findings are statistically more stable. A wide interval suggests uncertainty in the estimate of relative risk. When the interval excludes 1.0, the findings are considered "statistically significant." When the interval includes 1.0, the findings are not statistically significant and may have occurred as a chance finding more than 5% of the time (Green et al., 2011).

Since SMRs and ORs (risk estimates) are calculated without taking bias into consideration, these issues must be assessed before interpretation of results. Bias refers to anything that results in nonrandom error in the design, conduct, or analysis of an investigation. There are dozens of different types of bias. Three common types are selection (how people were selected for participation), information (access to information may differ for different groups under study), and classification (groups in the study may be classified differently with an impact on relative risk). Another important term that can impact the interpretation of epidemiological findings (risk estimates) is confounding. Confounding refers to a factor that is related to both the exposure and the disease of interest, but is unaffected by the exposure. An example is that alcohol has been determined to be related to lung cancer risk. However, since people who drink are more likely to smoke, it is really the smoking that is the true risk for lung cancer. In other words, smoking confounds the relationship between alcohol and lung cancer.

The use of p -values and confidence intervals, along with the consideration of the study's size, sample selection, and an assessment of the potential for bias and confounding, are all critical considerations in the determination of whether study findings are likely to be true or false (Green et al., 2011).

REGULATORY INFORMATION

Direct extrapolation of animal data to identify human hazards is common and is done to develop voluntary and enforceable

occupational exposure levels. It is a common practice for the incorporation of uncertainty/variability factors when human data are not available for developing these levels. Thus, occupational exposure levels are not bright lines for identifying safe versus harmful levels of exposure, but rather they are levels of exposure that are intended to protect against adverse health effects.

Although it is a current regulatory practice to assume that a chemical that is carcinogenic in one or more animal studies may also be carcinogenic in humans, *this is not equivalent to saying that the chemical is in fact a human carcinogen*. The determination of whether a chemical is actually a human carcinogen is made quite differently from the regulatory procedure of assuming that humans will mimic animal responses. Therefore, although animal data are useful as a surrogate for assessing human health hazards, it is scientifically inappropriate to reach definite conclusions about the cause of human disease solely on the basis of animal studies.

In the absence of adequate human data, both qualitative and quantitative assumptions must be made to estimate human risk from animal studies. Although such assumptions are implicit in any animal-to-human extrapolation, the scientific community is well aware of contradictions for some of these assumptions. This may sound as if the process is somewhat contrary to the intended purpose (i.e., a reasonably accurate assessment of the human risk). These assumptions are, however, still accepted in most cases because, as a matter of public policy, this process protects public health. Some of these public policy assumptions are as follows:

1. When human data are not adequate, adverse effects in experimental animals are regarded as indicative of adverse effects in humans.
2. Results obtained with dose-response models can be extrapolated outside the range of experimental observation to yield estimated upper bounds on low-dose risk.
3. When an appropriate standardized dosage scale is used, observed experimental results can be extrapolated across species.
4. There may be no threshold for some carcinogens, whereas there may be one for others, depending on their mode(s) or mechanism(s) of action, and threshold effects usually apply for other toxicities.
5. When dose rates are not constant, average doses give a reasonable measure of exposure.
6. In the absence of toxicokinetic data, the effective or target tissue dose is assumed to be proportional to the administered dose.
7. Risks from many exposures and from many sources of exposure to the same chemical usually are assumed to be additive.

8. In the absence of evidence to the contrary and regardless of the route of exposure, standardized absorption efficiencies are assumed across species.
9. Results associated with a specific route of exposure are potentially relevant for other routes of exposure.

Many of these assumptions are controversial when applied to evaluation of a specific health risk. Moreover, it is important to consider that the degree of uncertainty for the final risk estimate increases in a multiplicative fashion with the uncertainty of each assumption adopted. Thus, the number of assumptions made in the final risk estimate may lead to an uncertainty so great that the final estimation of risk no longer reflects reality. The consensus of the scientific and regulatory communities is that risk estimates based on animal data represent *worst-case presumptions* rather than *best estimates* of the potential risk. The real risk of cancer is not known and, in many instances, may be zero (US EPA, 1986). For this reason, risk estimates based on animal data are suitable only for regulatory purposes, for setting an upper boundary on the potential risk posed by a chemical, or for ranking the relative risks posed by a number of animal carcinogens (OTA, 1981). The *actual* human risk associated with a particular level of exposure cannot be established with any degree of medical or scientific certainty, without a complete evaluation of the available database, including information on mode(s) of action and human relevance (OTA, 1981; US EPA, 1986). The risk estimates are, however, useful for setting upper limits of exposure that will not result in adverse health effects.

OCCUPATIONAL EXPOSURE LIMITS

Permissible exposure limit (PEL), *recommended exposure limit* (REL), and *threshold limit value* (TLV) are occupational exposure limits developed by OSHA, the U.S. National Institute for Occupational Safety and Health (NIOSH), or the American Conference of Governmental Industrial Hygienists (ACGIH), respectively. These values express the concept that there is a level below which no exposed worker will become ill. Such levels usually refer to exposures during a 40 h workweek over a working lifetime, except in a few instances when exposure restrictions are specified. An extreme position against these limits is taken by some who believe that no amount of evidence can assure that any exposure will be harmless for all workers. This position is not biologically or medically plausible.

PELs, RELs, and TLVs have been published for a large number of chemicals. PELs are the legally enforceable standards, which have been revised in some cases to adopt NIOSH RELs. Individual states also publish such lists of occupational exposure limits, which often defer to OSHA.

In the absence of formally developed values by OSHA, NIOSH, or ACGIH, manufacturers will often develop their own recommended occupational exposure limits.

The evidence that forms the basis for the PELs and TLVs, the safe-dose levels, currently in use is derived from occupational experience and animal testing. The development of a PEL for benzene (C₆H₆) has such a history. Benzene is a widely used solvent and was important in the manufacture of explosives during World War I. Unprotected workers exposed to as much as 1000 parts per million (ppm) or more died of the chemical's narcotic effect. At lower levels of exposure, benzene's unique action on the hematopoietic system caused fatal aplastic anemia. A number of workers who were exposed to benzene escaped these outcomes but at a later date developed acute myelogenous leukemia. As information on this experience with benzene toxicity was collected and publicized, the worker protective level was reduced to 25 ppm; it is now set at 1 ppm.

The experience with benzene illustrates an important point in understanding and characterizing specific chemical hazards. Toluene and xylene, which are structurally related to benzene, do not elicit the same toxic responses except for narcosis at high levels. In general, a toxic effect likely to be produced by an unknown chemical cannot always be predicted from its chemical likeness to a compound of known toxicity.

Though accidental or unanticipated human exposures provide information on toxicity, a systematic study of toxicity may require studies with animals. Whether a material is nearly inert or potentially harmful may be assessed by experimental animal studies. However, the difficulties involved in studying low-level, long-term effects and the variation in response from species to species create additional obstacles to extrapolating from animal exposure to humans.

Some of these problems are illustrated by the animal studies done to assess beryllium toxicity. Despite experience with chronic illness in 800 beryllium workers, some authorities believe that failure to reproduce the disease in animals ruled out beryllium as a cause. Rabbits exposed to beryllium compounds develop osteogenic sarcomas, whereas rats develop pulmonary tumors—a difference that illustrates the difficulty of predicting a response from one species to another.

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