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Benzene

Occupational Disease

Problems of Risk Assessment

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This article addresses, in general terms, aspects of risk assessment as an integral part of the regulation of occupational health standards. Risk—the probability, possibility, or chance that a person will suffer an adverse health effect as a consequence of exposure to a workplace hazard—has previously been defined to include all persons (family members) contaminated by workplace hazards.[19] This discussion is limited to workers and the workplace, as defined by the Occupational Safety and Health Act of 1970.[12] Events that lead to risk estimates, factors to consider in the assessment of risk, and the perceived need to separate scientific assessment from risk management are examined. Some aspects of estimating the risk of exposure to benzene are considered as an example of the process. Finally, classes of risk and the expectations and disappointments of the public are briefly addressed.

The terms risk estimation, risk evaluation, and risk assessment are frequently regarded as synonyms. However, risk estimation and risk evaluation are generic terms, whereas risk assessment has a more specific application; it is used herein to mean the *scientific assessment* of risk (unless the word appears as part of a quotation in a more general context).

EVENTS LEADING TO RISK ESTIMATES

Occupational health is concerned with the well-being of more than 110 million adult men and women who constitute the labor force in the United States. To assure "every working man and woman in the Nation safe and healthful working conditions,"[12] the possibility of hazardous working conditions must be assessed. Such assessment involves measuring the levels of toxic substances, physical hazards, or environmental dangers to which

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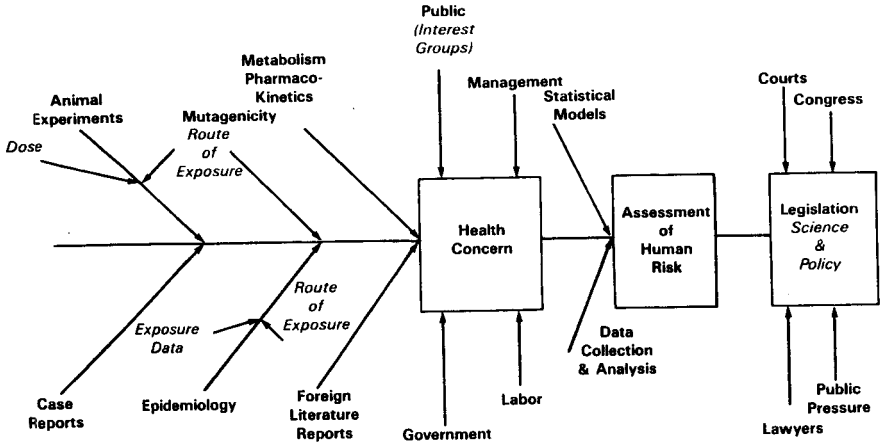

Figure 1. The process of estimating risk. (*Adapted from* Park, C. N., and Snee, R. D.: Quantitative risk assessment: State of the art for carcinogens. Fund. Applic. Toxicol., 3:320, 1983.)

workers may be exposed, and estimating the possibility or probability of contracting adverse health effects as a consequence of workplace exposure. Estimates of risk are based in part on the science that was factored into risk assessment and in part on the policy that governs the decision-making process.

The need to assess a risk to human health evolves from one or more scientific observations that give rise to a health concern. The following are representative examples:

- Hepatic angiosarcomas among workers in a vinyl chloride polymerization plant were found to be in excess of the number expected for this rare neoplasm.[3]
- An epidemiologic study of insulation workers inhaling asbestos fibers found that lung cancers among exposed workers far exceeded the number among nonexposed workers.[7]
- Increased sister chromatid exchanges and chromosome abnormalities among American workers exposed to ethylene oxide[16] reinforce a concern raised by an increased number of spontaneous abortions among Swedish health personnel similarly exposed.[8]
- In an animal experiment, rats fed acrylonitrile developed astrocytomas; supporting evidence confirmed a need to set a permissible exposure limit (PEL) for the work population of 125,000 involved in the manufacture or distribution of acrylonitrile.[11]

Other types of data used to point up the need for estimating risk appear in Figure 1.

ELEMENTS OF RISK ESTIMATES

In response to a directive from Congress in 1981, the Food and Drug Administration contracted with the National Academy of Science (NAS) to

study an institutional means for risk assessment; the NAS report was published in 1983.[2] The NAS committee identified two separate issues associated with estimating risks: assessment of the risk and management of the risk. The committee defined risk assessment as "the characterization of the potential adverse health effects of human exposure to environmental hazards."

- Both quantitative and qualitative expressions of risk are included in the assessment of risk, which is broken down into three major categories—hazard identification, dose-response assessment, and exposure assessment. All three categories are used in the characterization.
- Risk management describes the process of "evaluating alternative regulatory actions and selecting among them." The decision-making process "entails consideration of political, social, economic, and engineering information and ultimately results in the selection of appropriate regulatory response to a potential chronic health hazard."

The separation of risk assessment (performed by scientists) and decision making (performed by authorities)[14] is a subject of national and international contention. For decades, concern has existed for maintaining the intellectual content of social decisions. Oliver Wendell Holmes anticipated that the "man of the future is the man of statistics and the master of economics," while Learned Hand, understanding the value of experts, repeatedly called for scientific aids to courts hearing cases involving a technologic complexity.[18]

PROBLEMS SURROUNDING STANDARDS ESTABLISHMENT: THE EXAMPLE OF BENZENE

The standard-setting process (mandated permissible exposure limit, PEL) for the solvent benzene is an appropriate illustration of the long and arduous course of regulatory legislation. Approximately 2 billion gallons of benzene are used annually in the United States. This aromatic hydrocarbon has been shown to depress the bone marrow and produce a variety of hematologic disorders including leukemia. For many years, the carcinogenic potential of benzene was disputed, but the repeated demonstration of the link between benzene (cause) and leukemia (effect) made the association irrefutable.

Is either the dose (exposure concentration) or the duration of exposure required to produce leukemia in humans known? Although blood dyscrasias may manifest themselves in the short period of 60 days for the leukemogenic effect,[6] a longer latent period is assumed. Latency has been likened to incubation,[10] but with an unpredictable time from exposure to neoplasm. Leukemia has been reported to follow relatively high exposures (relative to the current PEL) after relatively short periods of time (expressed in years). In other cases, however, the disease manifests only itself after long exposures to smaller doses.[13]

Since the association between benzene exposure and blood dyscrasias is not inevitable, is a population of genetically susceptible or sensitive persons possible? Such a population is unlikely. Theories of carcinogenesis

include two-stage promotion and initiation, synergism, and multihit progression of the disease. Therefore, causes of disease in some victims may involve their environment (a hidden promoter in the air) or their lifestyle (smoking or eating fatty diets) rather than any genetic factor. It is significant that, among asbestos workers, cancer of the lung is nine times more frequent among those who smoke than those who do not.

Are there specific cellular markers of benzene-induced leukemia? Benzene-induced leukemia is usually, but not invariably, nonlymphocytic, although lymphocytic and even plasma cell leukemias have been reported.[5] The cause-and-effect relationship may have been missed, misdiagnosed, or misascertained for a variety of reasons, such as the attention focused on compensation and insurance. In a suicide or accident, for example, leukemia may not even be mentioned on the death certificate, or it simply may not have occurred to the examining physician to extract an occupational history. Although an estimated 270,000 persons in the workforce may be exposed to benzene, the number of potential victims of leukemia to low level (1 ppm) exposure is unknown. The PEL is merely a graphic extrapolation of what is known, and thus may understate the actual case.

In quantitative risk assessment, using suitable mathematical models, a graph is developed to show the results obtained from human epidemiology or case reports and animal experiments, comparing the risk or response to increased doses of the suspected material. Quantitative risk assessment is associated with the following scientific uncertainties concerning the methodology or technique used to provide the results:

1. Were the controls of the epidemiologic study appropriate?
2. Were the animal species appropriate?
3. Were the route of administration and dose administered scientifically acceptable?
4. Was the experiment reproducible in another species?
5. Was the correct mathematical model selected to estimate the risk of low dosage?
6. Is it possible to extrapolate to humans the animal experiments which either form the basis for the estimate or reinforce the estimate?

SUPREME COURT RULING

In July 1980, the Supreme Court gave an opinion on the proposed benzene standard, which the Occupational Safety and Health Administration (OSHA) sought to lower from 10 ppm to 1 ppm.[9] The Supreme Court upheld a previous decision by the Court of Appeals, which concluded that OSHA had exceeded its standard-setting authority insofar as the agency had not shown that 1 ppm was "reasonably necessary or appropriate to provide a safe and healthful employment."[11] Justice Stevens and his concurring colleagues determined that the burden was on OSHA to show, on the basis of substantial evidence, that long-term exposure to 10 ppm of benzene is at least more likely than not to contain a significant risk of material health impairment.

A few key sentences (with *italics* added for emphasis) demonstrate the

court's appreciation of the uncertainties of risk estimation. The court stated that, "although the Agency had *no duty to calculate the exact probability* of harm, it does have an obligation to find that a significant risk is present before it can characterize a place of employment as 'unsafe.' Second, OSHA is not required to support its findings that a significant risk exists with *anything approaching scientific certainty.*" The Agency's findings "must be supported by substantial evidence which allows the Secretary to regulate on the basis of the "*best available evidence.*" As long as it is "supported by a body of *reputable scientific thought,* the Agency is free to use conservative assumptions in interpreting the data with respect to carcinogens, risking error on the side of over protection rather than on the side of under protection."

THE CONGRESS AND RISK

The Ritter Bill, H.R. 4192, currently before Congress, contains two titles, the first dealing with risk assessment and research development, and the second with establishment of a central board of scientific risk analysis.[15] This bill epitomizes the attempt to separate policy from science and to establish a consistent approach to risk assessment. The bill states that it is "important that the public has confidence in the adequacy, consistency and independence of the scientific basis for federal regulatory decisions which assures the risk of such hazards."

The attempt to achieve consistency nevertheless raises questions about the wisdom of applying a single-risk assessment formula to every regulatory agency, each with its own specific population(s) at risk and unique types of risks. For example, benzene is found not only in the workplace, but also in the general environment (as are lead and a variety of other potentially harmful substances); however, the mode of exposure, the concentrations of gases, particulates, or radiation, and the status of the populations at risk are dissimilar.

"In a society in which democratic principles dominate, the perceptions of the public must be weighed."[16a] Our current society is a tangle of special interest groups, trade unions, management, publicly elected representatives, as well as the public at large. Since we do not have scientists who are full-time judges, an impartial board of risk manager-scientists may not be possible. An old Hindustani proverb states "The tree casts its shade upon all, even the woodcutters."

SUBJECTIVE OBJECTIVITY

In the real world, pure and objective science is a rare commodity. The simple act of selecting an experimental method is subjective, and therefore biased; this is true even for the most structured science. For example, the rationale for choosing a model for extrapolation is based on a subjective interpretation of the most logical means of extrapolating from a known result or set of results to an unknown end point. Models currently used to

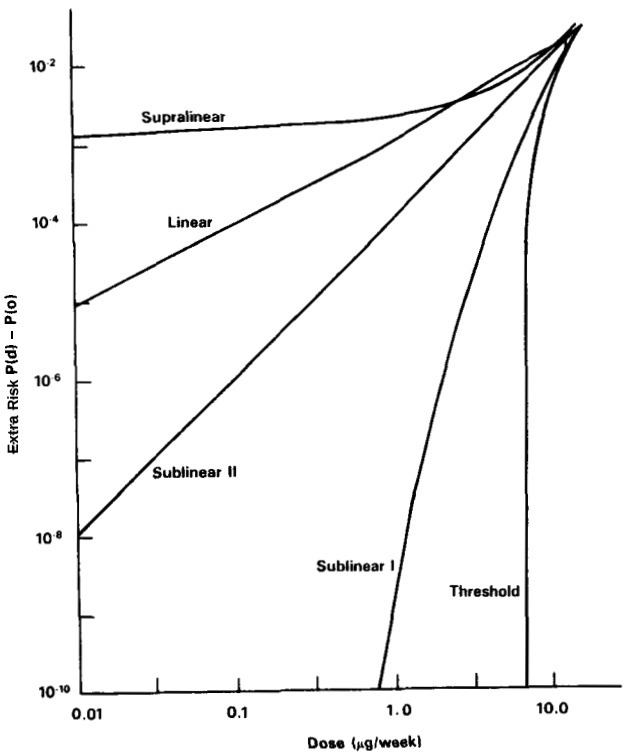

Figure 2. Results of alternative extrapolation models for the same experimental data. (*From* Committee on Institutional Means for Assessment of Risks to Public Health, Commission on Life Sciences, and National Research Council: Risk Assessment in the Federal Government: Managing the Process. Washington, D.C., National Academy Press, 1983; with permission.)

predict future toxicologic risks yield results that vary by several orders of magnitude. It follows that estimates of risk also vary by several orders of magnitude and do not reflect scientific consistency, coherence, or reproducibility[1] (Fig. 2).

These internal divergences of opinion occur across the scientific board: pathologists struggle with definitions of malignant, benign, and hyperplastic liver nodules; hematologists disagree on whether the predictability of leukemia mutagenicity is associated with a wide variety of substances other than those that cause cancer or reproductive abnormalities. The range of scientific opinion is so broad that it may be well to conclude that "no amount of data is a substitute for judgment."[16b] "Risk assessment is not a science per se. It cannot demand a certainty and completeness of science. It must produce answers because decisions will be made with or without its input."[3]

CLASSES OF RISK

Finally, a word about the risk-takers. It is pointed out, sometimes with a degree of satisfaction, that since life is never free of risks, no one can

expect to live in a risk-free world. The corollary to this is that work is a risky business, so any attempt to legislate a risk-free workplace is at best a needless expense and at worst a futile endeavor. This assumption fails to recognize *classes* of risk—whether the risk is voluntary, involuntary, or semivoluntary.

An *involuntary risk* is one over which individuals have no control and of which they are totally unaware. In a workplace setting, a risk may be inadvertently or deliberately concealed because of ignorance or avarice.

A *semivoluntary risk* is one of which the workers are aware but which they cannot avoid without taking a less pleasant or more dangerous risk. For example, the only job available to a worker may be that of a coal miner, because mining is the town's only industry. The risks surrounding coal mining are accepted because the economic or social upheaval of moving to another area is not acceptable. Moving away is too expensive or family ties cannot be broken. This choice, described as risk-risk, is well-documented, but usually in another context. An example is the preserving of bacon. The addition of sodium nitrite, to inhibit the growth of *Clostridium botulinum*, introduces a chemical capable of producing carcinogenic nitrosamines. However, the risk of a nitrosamine-induced cancer at some point in the future is preferable to the immediate risk of botulism.

Voluntary risk differs greatly from either of the other types; it is that risk, taken daily, either for pleasure (smoking, drinking) or because the chosen job (sky-diving or military career) is attractive.

SUMMARY

The variables that must be accounted for in assessing a risk make the risk assessment itself a risk. The process is time-consuming, costly, and, in a democratic society, a forum for many disparate opinions. Risk assessment encompasses many scientific disciplines, risk management, and many policy decisions. This discussion provides an overview of the problem, using benzene as an example of the process, and provides a classification of risk.

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Hepatic Injury Due to Environmental Agents

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The liver plays a central role in mediating the interaction between humans and their chemical environment. The liver is not only a target organ for toxic effects of many environmental substances, it is also the major site for the biotransformation of foreign chemicals that enter the body. There are several patterns of liver toxicity produced by noninfectious agents other than therapeutic agents (see Table 1).[12, 13, 17] Some industrial chemicals or contaminants naturally found in food products regularly produce dose-dependent hepatic necrosis. Cholestasis, when appearing as the sole manifestation of liver injury, is rare.[9] Liver injury due to environmental agents is often nonspecific and inconspicuous. This presents a challenge to the clinician or epidemiologist in establishing a cause-and-effect relationship between a contact with an environmental agent and liver toxicity. Examples include fatty metamorphosis detected only by liver biopsy, and hypertrophy of the endoplasmic reticulum (microsome induction). In the United States, veno-occlusive disease, granulomas, or hepatoportal fibrosis have been associated only with a limited number of toxic substances. Cirrhosis has been found in industrial workers exposed to chlorinated organic compounds or to plant toxins, but this, too, has been observed only infrequently.

Hepatoma, the most common form of malignancy seen worldwide, is associated with geographic regions in which both hepatitis B virus and aflatoxin are endemic.[8] In the Western world, ethanol consumption is most commonly associated with hepatocellular carcinoma, although it is uncertain whether ethanol is a carcinogen per se, or whether ethanol evokes malignancy by producing cirrhosis, a frequent precursor of hepatoma. An important unresolved question is whether some or all of the many halogenated aliphatic, aromatic, or polycyclic compounds that cause hepatocellular carcinoma in laboratory animals also are carcinogens for human liver.

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