

# Environment and health:

## 9. The science of risk assessment

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Potential hazards surround us at home, in the workplace, in our cars and even in health care facilities. Given exposure to these hazards, we may want to evaluate the risk that an adverse event will occur or that it will occur at some level of severity. In this article we introduce some concepts about risk and how it can be assessed, comment on the nature of hazards and the uncertainties inherent in the risk assessment process, and show how risk assessment affects the management of these hazards. Most of our discussion is in terms of chemical carcinogenesis, but the principles apply to the full range of threats to human health and survival.

### Scope of risk assessment

A committee of the US National Academy of Sciences proposed a model in 1983<sup>1</sup> that is now commonly used to discuss the assessment of occupational and environmental hazards. Others, such as the National Research Council,<sup>2</sup> have elaborated and refined this model. The basic model, which we use here, partitions risk assessment into 4 steps: hazard identification, dose–response modelling, exposure assessment and risk characterization. Integration of a risk assessment with a cost analysis and other matters to develop strategies for risk regulation and control is often called “risk management.”

Numerous scientific and technical disciplines are involved throughout a risk assessment. Hazard identification uses the input of biologists, chemists and others to determine whether available data indicate that some compound or exposure should be considered a possible “hazard,” and epidemiologists are needed to evaluate the strength of human studies, especially in attempts to determine whether an association between exposure and an adverse response is one of cause and effect. Dose–response modelling requires the input of statisticians, epidemiologists and people expert in developing models that predict adverse response as a function of dose. Pathologists provide additional background on the nature of the adverse response, toxicologists are especially important for understanding mechanisms of toxicity and the relevance of animal data for human exposures, and bacteriologists may be critical in elucidating the spread of an infectious disease. Exposure assessment often requires the input of engineers as well as hydrologists (for waterborne hazards), meteorologists (for airborne hazards) and analytical chemists. Industrial hygienists can be critical in providing insight into current and past occupational and environmental exposures; this insight may also be relevant to levels of exposure to the general population. The characterization of risk may involve all of these disciplines and many others.

Given the broad array of possible hazards of modern life and the complex issues raised by their assessment and possible control, it is no surprise that risk assessment, especially of chemical hazards, is difficult, plagued by uncertainty and often controversial. A major risk assessment (of lead, for example, or dioxin) can cost millions of dollars and require vast amounts of scientific talent. The need for reliable data of many kinds is enormous. Versions of the criteria of Hill<sup>3</sup> for inferring causality in epidemiology are important in this regard. These criteria include an appropriate temporal pattern, with exposure preceding response; a relation between increasing dose and increasing response; and the detection of the response across multiple studies conducted in different ways and in different populations. However, these criteria are not always appropriate. Epidemiological studies may show an increase in the frequency of a congenital abnormality as exposures rise, but a decrease in frequency at even higher doses because affected fetuses have such severe problems that most die in utero and cannot display the abnormality.

### Review

### Synthèse

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The risks associated with exposure to a hazard may be expressed by a variety of summary statistics that include individual lifetime risk, annual population risk, the percentage or proportion of increase in risk, and loss of life expectancy.<sup>4</sup> For example, individual risk might be an important feature of cigarette smoking, whereas years of potential life lost might be a relevant means of characterizing some occupational hazard such as injuries, for which younger workers may be at special risk of unintended serious or fatal mishap.

Six essential issues arise in risk assessment. First, not every person exposed to a potential hazard will exhibit an adverse response. In addition, almost every adverse response to some exposure may occur even without exposure, although the link between asbestos and mesothelioma may be a near-exception. Thus, many long-term cigarette smokers escape without lung cancer, and nonsmokers sometimes get the disease, although people who smoke are still 10 to 15 times more likely than nonsmokers to get lung cancer.

Second, the frequency or magnitude of an adverse response generally depends on the degree and extent of exposure to a hazard, possibly with a threshold below which no risk is apparent. Many toxic drug reactions fit this pattern.

Third, people vary in their responses to the same level of dose or exposure. The risk for any individual may depend on a variety of intrinsic factors such as age, sex, prior or concurrent exposures to other hazards and the level of detoxifying enzymes. Certain subgroups such as infants, the very old and those with impaired immune systems may be at unusually high risk; this is often true for infectious diseases, but reasons for special sensitivity are often unknown.

Fourth, data for the direct measurement of human risk are often absent or seriously inadequate. Thus, the carcinogenic potential of a modest intake of saccharin, for example, is still uncertain because the primary evidence of carcinogenicity was from animal studies, in which doses were very high; the mechanism of carcinogenesis may not operate at low levels of exposure in humans.<sup>5</sup> (Similar issues arise in Canada with respect to cyclamate.) Conversely, biological processes can sometimes cause low-level exposures to be almost as hazardous as high-level exposures.<sup>6</sup>

Fifth, many risks are deemed acceptable, and their acceptability depends on many, sometimes surprising, factors, including the number of people exposed, whether exposure is voluntary, the social value of the exposure, mechanisms of compensation for harm or death, and familiarity with the risk.<sup>7</sup> We accept shockingly high rates of carnage on the highways because we value the freedom and convenience of personal transportation.

Finally, criteria are often unclear about the best way to balance risks and benefits in order to establish acceptable exposure limits for a hazard. For example, tamoxifen is clearly an ovarian carcinogen, but physicians continue to use this drug because of its great benefits as a chemotherapeutic and chemoprophylactic agent for breast cancer.

## Risk in context

We cannot avoid making decisions about risk management: to ignore them is to make those decisions by default, covertly and without full appreciation of their implications. Good risk management requires good risk assessment. The list of exposures that may be considered for risk assessment is quite long. Examples include a broad range of environmental and industrial chemicals (benzene, dioxin, asbestos), physical hazards (automobile accidents, noise, medical radiation) and biological agents (*Salmonella* in hamburger, adverse reactions to vaccines). These and many other potential hazards are also closely linked to benefits we may want to retain (e.g., automotive transportation, effective and inexpensive industrial processes, vaccines). When benefits are important and perfect safety is unattainable, the acceptability of risk must be weighed with some care. Thus, estimation of the expected frequency and magnitude of outcomes under specific conditions of exposure and context, present or future, is critical when rational personal and societal choices may lead to some adverse outcomes.<sup>1,2</sup> Comparing, weighing and choosing among different interventions to respond to risks is common in medical practice. Informing a patient who is about to have a laparoscopic appendectomy that there is a 2% chance that he or she will need immediate laparotomy is an important part of the background for informed consent. One difference between medical practice and chemical risk assessment is that the 2% risk just mentioned may be based on hard data and much experience, whereas estimates of the risks of chemical exposures are often more speculative.

Two strategies are commonly used in quantitative risk assessment. One is the "margin of safety" approach, in which a scientific team looks for the highest dose that has produced no effect in animal or human studies, defined as the "no observed effect level" (NOEL), or sometimes for the lowest dose that did produce an adverse effect (LOEL). A set of "safety factors" is then applied, such as 10-fold for using animal data rather than human data, another 10-fold for the possibility that unexpected harm will arise later or in ways that have not been assessed, and still another 10-fold when safety is especially important. These 3 factors multiplied together would lead to an exposure limit of 1/1000th of the highest dose not known to cause problems in animals. The probability or size of risk at that point is not evaluated but is generally assumed to be virtually zero. A problem with this approach is that increases in knowledge about harmful effects will drive NOEL (and allowable exposures) downward, while that same greater knowledge may show that the safe limit of exposure is actually higher than had been assumed.

Margins of safety based on NOELs and safety factors have been widely used to evaluate systemic toxins and physical hazards, but quantitative regression modelling tools are more commonly used for carcinogens, and they are now the norm in risk assessments of many other adverse re-

sponses. These regression-based approaches fit a mathematical model to the data and use it to estimate the dose associated with a specified level of response. For example, in an animal tumorigenicity experiment, the proportions of animals with liver cancer at several doses (including zero dose, the control) may be used to estimate the risk added to background incidence by those and intermediate exposures. Interest often centres on exposures close to zero, and far below any of the exposures in the animal study, so that major assumptions are needed.

## Uncertainty in risk assessment

The relation of risk to dose or exposure is generally unknown and often controversial. Should linear terms be required in the model? Should threshold parameters be included? Should one use point estimates of regression-based potency end points, or lower confidence limits, which incorporate sampling variability? Although these questions may seem esoteric, different answers often lead to dramatically different conclusions about the size and nature of the risk. This is especially true in the prediction of responses to very-low-level exposures, the so-called low-dose extrapolation problem.

Unfortunately, accurate estimation of most risks is not possible. One example is the carcinogenicity of saccharin in the human diet. Very high doses of saccharin cause bladder cancer in animals; however, the biological mechanisms may have little relevance for humans, and data from human studies are limited, imprecise and uncertain because almost all saccharin users have also used other artificial sweeteners that may have their own adverse effects. Another difficult situation occurs when estimating risks in humans, for example, who have been exposed intermittently to much lower levels of a chemical that has been found to be carcinogenic at high doses over a lifetime in small rodents, and these people have been followed up for a relatively short time. This is particularly vexing in the case of carcinogenic responses, where many years must elapse before cancer is detectable.<sup>8</sup> Finally, exposure to other agents may potentiate effects associated with the hazard of concern. The extra increase in risk of oral cancer in smokers who consume alcohol is an example of such synergy.<sup>9</sup> The uncertainties in risk assessment are so great that independent and technically competent reports on the same hazard often differ by a factor of a thousand or more.<sup>10</sup>

## Using risk assessments

If risk assessments are so difficult and expensive but are still subject to great uncertainty, why should we bother with them? Arguably, what matters most is not the number(s) that one has at the end of the assessment, but the process that gets us there, although the public will ultimately want to know what level of exposure is "safe." A comprehensive risk assessment reviews, evaluates and inte-

grates the entire relevant literature to weigh the evidence for or against a hazard. A wide range of expertise will be brought to bear, and issues needing further study will be identified and refined. The needs of risk assessment provide powerful incentives for more and better science, including toxicology, pathology, epidemiology, biostatistics, industrial hygiene, exposure assessment, environmental transport studies (e.g., in air or groundwater) and many other fields of study. Risk assessment can always improve the foundation for risk management, and sometimes the best estimate of risk is so high or so low that risk management decisions are clear despite the uncertainty.<sup>10</sup>

Differences among independent risk assessments based on the same information may engender a perception that the scientific community is clueless about the true risk associated with particular hazards. This problem is often complicated by a focus of media attention on the latest in a series of studies rather than the import of the whole of the evidence — an approach that leads to the "carcinogen of the week" mentality. When there are reports today that some exposure is unexpectedly hazardous, while tomorrow's study finds no such effect, the whole process may be considered shady, and the credibility of science more generally may be damaged.

What is a prudent policy for triggering some response to a potential hazard? Some people require high levels of evidence before they will want to act (wait to see if there are bodies to count), while others require much lower levels (if a thing is at all doubtful, treat it as dangerous — the "cautionary principle"). Neither extreme seems to us to be appropriate, in part because risk management must integrate health risk assessment with such other things as economic analysis, legal mandates and constraints, level of public concern and the availability of substitutes for useful but possibly risky products. In practice, the level of risk that triggers an intervention may differ between different exposure settings. For example, a one in a million excess risk of some adverse response may be deemed acceptable for environmental exposures of the entire population, whereas a risk of one in a thousand may be deemed acceptable for some occupational exposures (we accept more than that for jockeys and steeplejacks), and one in ten may be acceptable for a medical intervention in desperate circumstances. Society accepts many risk-benefit tradeoffs, such as those implicit in driving or flying. In essence, exposure levels are set at levels that are deemed to provide an acceptable tradeoff between societal benefits and risks.<sup>11</sup>

Risk assessment reaches deep into our lives. Many members of the public may not want to learn all they would need to know to make reasoned choices about every possibly risky exposure, although some risks are well characterized and widely understood (e.g., cigarette smoking). Thus, there will be a continuing need for a cadre of strong scientist risk assessors, generally at the level of national government. In the United States, federal agencies with such interests include the Environmental Protection Agency, the National Insti-

tute of Environmental Health Sciences, the Food and Drug Administration, the Consumer Product Safety Commission, the Occupational Safety and Health Administration and the National Institute for Occupational Safety and Health. Similar agencies exist in Canada and most other developed countries. An educated citizenry should understand that there is reason for centrally recommended exposure limits, that risk is not the only important thing in the regulation of hazards, that risk assessment is inherently uncertain (even when human data are available) and that our understanding of specific risks is likely to change only slowly with the accumulation of sound research studies, each adding a bit to the evidence for or against the existence of a hazard and our ability to quantify it accurately.

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