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Risk assessment. Principles and consequences*

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Abstract: Risk assessment is an important tool in deciding how to allocate resources to controlling risks. In most cases it is based on hazard data derived from animal experiments and on exposure data from an assessment of the likely or actual exposure of the population of interest. Recent advances have improved the understanding of the use of the no adverse effect level (NOAEL) and safety factor for risk assessment by providing a scientific justification of the 100-fold safety factor. Concern about the risks of exposure by various routes simultaneously (aggregate exposure) and the risks of exposure to mixtures (cumulative risk assessment) have lead to new approaches to these issues. For many years, risk assessment of genotoxic carcinogens has relied on low-dose extrapolation using mathematical models. Recently, these methods are being reconsidered and, in some cases, replaced with the NOAEL/safety factor approach combined with all information on the mechanism of action and the magnitude of the response. It is vitally important to ensure that risk assessment provides accurate and unbiased estimates of risk of exposure so that appropriate measures can be taken to control the risks.

THE PURPOSE OF RISK ASSESSMENT

The number of different chemicals manufactured is estimated to be between 80 000 and 100 000 (medicines, food additives, cosmetics, pesticides, industrial chemicals, etc.). For the benefits of synthetic chemicals to be realized, they must be handled or used safely. In addition to synthetic chemicals, there are numerous natural chemicals with highly toxic properties—such as the mycotoxins (e.g., aflatoxin, ochratoxin, patulin, thricothecenes, etc.), plant toxins (e.g., alkaloids or cyanogenic glycosides), animal toxins (e.g., snake venoms), and chemicals that are produced naturally in the environment (such as heavy metals and ozone). We must know at what dose these chemicals are likely to cause harm. It is this task that requires risk assessment—establishing the safe dose of a chemical and the likely toxic effects that may be seen if that safe dose is exceeded.

There are so many potential hazards from human activities, including from exposure to chemicals, that we have to prioritize the risks and use our limited resources for controlling the most serious risks. In order to do so, risk assessment is used as the method of providing information on the magnitude of the risks. This is vital if we are to direct our limited resources to creating the greatest reduction in risks, for it requires that those resources are focused on reducing the largest or most serious risks first.

Definitions

There are many different definitions of risk and the processes used in risk assessment. The majority makes the clear distinction between hazard and risk**.**

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- Hazard: Set of inherent properties of a substance, or mixture of substances, that under production, usage, or disposal conditions make it capable of causing adverse effects to organisms or the environment depending on the degree of exposure; in other words it is a source of danger.
- Risk: Possibility that a harmful event arising from exposure to a chemical or physical agent may occur under specific conditions, or the expected frequency of occurrence of a harmful event arising from exposure to a chemical or physical agent under specific conditions.
- Risk assessment: The characterization of the potential adverse effects of human exposures to environmental chemicals
- Hazard identification: Qualitative evaluation of the adverse effects of a substance on humans or other organisms of concern.
- Exposure assessment: Evaluation of the types (routes and media), magnitude or doses of exposure. Where known, time and duration of actual or anticipated exposures and, when appropriate, the number of persons likely to be exposed should be included.
- Dose–response assessment: The relation between dose and incidence (or severity) of an adverse effect.
- Risk characterization: Estimation of the probable incidence of adverse health effects under various conditions of exposure, including a description of the uncertainties involved.

Thus, the distinction between the hazard (an inherent toxic property of a chemical that may or may not occur depending on whether exposure is high enough) and risk (the consequences of being exposed to a hazardous chemical at a particular dose or dose rate) is critical. An example will illustrate the importance of this distinction. Vitamin A is an essential dietary ingredient for humans, and the daily requirement for health has been well documented. However, if given in larger doses (in the region of five times the daily requirement) to pregnant women, abnormalities in the fetus may occur. Thus, at the recommended dose vitamin A is necessary for health; a dose five times higher can be severely toxic.

RISK ASSESSMENT PROCESS

Hazard Assessment

Information on the hazard of a chemical may be obtained from various sources. Initially, information about the physicochemical properties and the chemical structure may provide an indication of the toxicity of the chemical. Solubility, volatility, pH and other physicochemical properties have an important impact on the toxicity of chemicals. Similarity with other known toxic chemicals or the presence of particular structural groups in the structure of the chemical may provide more or less clear indication of the likely toxicity of a chemical. For example, chemicals with groups that are likely to be reactive with DNA are likely to be carcinogenic [1].

For the majority of chemicals, the first indication that it may have toxic properties comes from laboratory experiments. These may involve cell cultures or other *in vitro* systems, but usually the most informative data come from experiments on laboratory animals. These involve administration of the chemical to animals under controlled conditions and careful observations of the presence of toxic effects.

In vitro methods require validation to ensure that the methods provide information of value to the process of risk assessment. The process of validation has now been well described and established [2]. Even when validated, *in vitro* methods have severe limitations for providing information for risk assessment. The most serious are:

- *in vitro* methods do not provide the balanced environment of the whole body, where feedback mechanisms in different organs involving different cell types maintain the homeostasis of the organism;

- the ability of *in vitro* methods to metabolize and clear the chemical and its derivatives is usually limited and does not replicate the situation in the whole body.

Thus, the results of *in vitro* experiments are nearly always used for providing initial information on the mode of action or in classifying the toxicity of chemicals (e.g., for mutagenicity or for topical toxicity such as irritancy). Further data from animal experiments or human volunteer studies are necessary to provide the data for human risk assessment.

It should be recognized that animal experiments also have their limitations. The most frequently encountered is the use of doses that are too high, often hundreds or thousands of times higher than the human exposure, producing results that are difficult to interpret for the purpose of risk assessment.

Dose–response assessment

In the classical situation, the response observed in the animal (whether it is of a continuous variable, such as body weight, or a stochastic response, such as mortality) varies with respect to dose. Below a certain dose the effect will not be observed and hence exposure at that or a lower dose will be without effect. Establishing the no observed adverse effect level (NOAEL) provides a basis for the assessment of risk or the setting of standards to protect human health.

Exposure Assessment

The other essential component of the assessment of risk is the estimation of exposure. In some situations, the exposure is relatively easily established; for example, when considering the use of medicines, the administered dose can usually be ascertained relatively accurately. For other types of exposure, the situation is usually much more difficult.

If, for example, we consider a household product, the exposure estimate may be for an individual, the average exposed person, or the maximally exposed person. The estimate may also need to take into account the variability of exposure in individuals in the population, providing a range or estimate of the distribution of the exposure [3]. These estimates of exposure must take into consideration:

- the amount to which the individual is exposed,
- the route of exposure,
- the amount that is taken into the body via any of the media (air, water, food, or by skin contact),
- the frequency of exposure, and
- the duration of exposure and the variation of exposure among individuals who might be in contact with the chemical.

Databases are available from which the relevant data for any given exposure scenario may be extracted. The data used in such exposure assessments have a major impact on the outcome. For the United States, the Environmental Protection Agency (EPA) has developed a set of values that can be used in exposure assessment [4]. The databases may have missing data for a particular sensitive subgroup of the population [3], and default values may have to be used.

Similar variables are important in assessing the exposure to, for example, food additives or food contaminants through the food. The quantity present in each foodstuff and the amount of the foodstuff consumed by each individual will have to be known.

The models currently in use for assessing exposure of consumer products do consider all routes of potential exposure and select the most important for inclusion in the model. Similar methods and models for aggregate exposure assessment, as it is called in this context, can be used for pesticides [5].

The outcome of the exposure assessment is often in the form of a distribution of exposures allowing the mean or differing percentiles of exposure to be defined.

Exposure to mixtures

Recently, the question of exposure assessment from mixtures of pesticides has gained importance in the United States since Congress passed the Food Quality Protection Act (1996). This requires that the EPA considers exposure to all pesticides and other chemicals that act by a common mechanism of toxicity when deriving tolerances for pesticide use on crops, as part of cumulative risk assessment.

The requirement for risk assessment for mixtures, where the chemicals have a common mode of toxic action, is a difficult task. It raises the following questions:

- How similar must the mode of action of two chemicals be before considering that a cumulative risk assessment must be carried out?
- Do the chemicals cause their effects by acute or chronic exposure?
- How can the toxicity of chemicals with different potencies be "added" together?
- How does the timing of exposure to different chemicals affect the cumulative risk?
- How is the variability and uncertainty in risk presented?

These and other issues have been addressed by the International Life Sciences Institute [6]. An outline of the formulae proposed by them for cumulative risk assessment is presented in Fig. 1.

Fig. 1 Tiered framework for cumulative risk assessment. Adapted from ref. 6.

1. Hazard Index using Reference Doses (RfD)[1]

$$HI = \Sigma\,(HQ^2)_i = \Sigma(\text{Exposure metric}_i/RfD_i) \tag{1}$$

i for *n* chemicals in set

2. Hazard Index Approach Using NOAEL or Benchmark Dose[3] (BMDx)

$$HI = \Sigma\,(HQ^2)_i = \Sigma(\text{Exposure metric}_i/NOAEL_i \text{ or } BMDx_i) \tag{2}$$

i for *n* chemicals in set

3. Toxicity Equivalency[4] Factor (TEF)Approach

$$Dose_{TEQ}{}^5 = \Sigma_i\,(dose_i\ TEF) \tag{3}$$

4. Margin of Exposure[6] Approach using TEFs

$$MOE = NOAEL \div dose_{TEQ} \tag{4}$$

5. Biologically Based Cumulative Risk Assessment

Quantitative modeling using physiological, toxicological, and toxicodynamic parameters

1. A reference dose represents the daily exposure to humans that is likely to be without appreciable risk of an adverse health effect during a lifetime exposure. It is calculated by dividing the NOAEL by an uncertainty factor.
2. The hazard quotient (HQ) is the ratio of the expected exposure to a chemical compared to the RfD for that chemical.
3. Benchmark Dose (BMDx) is the dose calculated to produce a particular quantitative effect, denoted by x (for example a 10% reduction in body weight)
4. Toxic equivalency factor (TEF) represents the toxic potency of the individual chemical relative to the potency of a reference chemical.
5. Toxicity equivalency (TEQ) is derived by multiplying the TEF with the dose of each chemical in the mixture as in the equation in 3.
6. Margin of Exposure (MOE) is the margin between the RfD and the calculated or actual exposure.

Risk characterization

On the basis of data about the toxicity and about the exposure to a chemical, the risk of individuals or populations exposed can now be considered. In most cases the NOAEL is identified, and a safety factor (or uncertainty factor) is applied to produce a dose that is likely to have no toxic effects in the exposed population. The use of safety factors relies on the assumption that effects, or risks, will be insignificant below the Reference Dose. The safety factor applied is usually 100; that is, the NOAEL is divided by 100 to obtain the safe exposure. The NOAEL/safety factor approach has been used successfully for many years as the basis for risk assessment, particularly when the objective is to set standards for safe exposure.

The use of a safety factor of 100 has been the subject of much discussion. It is generally considered to be made up of a factor of 10 for interspecies extrapolation (i.e., extrapolating from the results of animal experiments to humans) and a factor of 10 for inter-individual variability within the human population. Renwick [7], and subsequently WHO [8], have analyzed the safety factors and consider that there are two components to each factor of 10—the first is related to differences in the ability to metabolize the chemical (toxicokinetics) and the second due to differences in the underlying susceptibility of the organism to toxic insults (toxicodynamics) (Table 1).

Table 1 Subdivision of safety factors according to WHO [8].

	Toxicokinetic	Toxicodynamic	Total
Inter-species	4.0	2.5	10
Inter-individual	3.2	3.2	10

The subdivision of the safety factors is valuable because, in situations where information on kinetics or dynamics is available, the default values may be replaced with values derived from the chemical under consideration. In the absence of data for a particular chemical, the toxicokinetic and toxicodynamic values collapse back to 10. A further consideration of these factors and their subdivision based on careful examination of 100 medicinal products confirmed their utility [9].

Risk characterization for carcinogens

Carcinogens produce cancer through two main mechanisms. They can be genotoxic, producing cancer by direct interaction with the DNA, or nongenotoxic, producing cancer by a variety of mechanisms [10]. For genotoxic carcinogens, it has generally been the practice to consider that there is no dose below which cancer will not develop. In particular, the methods of low-dose extrapolation rely on the paradigm that, at low incidences, the dose–response relationship will be linear or nearly so. Hence, the methods used for risk assessment include mathematical modelling of low-dose effects, often 1 000 to 1 million times lower than the doses used in experiments. Models frequently used include multistage, probit, logit and linear extrapolation. Experience of the use of these methods has revealed that the results of the modeling calculations are modified as much by the choice of the model as by the data from carcinogenicity experiments. It is also clear that it is not possible to "prove" the presence or absence of thresholds in carcinogenicity experiments [11] and that genotoxic carcinogens can produce a threshold dose response through cell cycle delay [12]. There is, therefore, a move away from the simple use of the multistage calculation of low dose effects to a more complex consideration of all the data, including that on mechanisms, in the estimation of risk from carcinogens.

The situation for nongenotoxic carcinogens is generally different. Several mechanisms of action have been identified [10]. The majority involves futile cell cycling, leading to fixation of random mutations once a growth advantage has been established for a particular cell or group of cells. Further random mutations may lead to the development of cancer. Many of these mechanisms are specific to rodents (e.g., the induction of thyroid cancer in rats following disturbance to the homeostasis between TSH and thyroxine; the induction of kidney cancer in male rats caused by an increase in the urinary α-globulin). The majority of these examples have mechanistic evidence that below critical doses, no carcinogenic effect will occur. Hence, the usual NOAEL/safety factor approach is used for risk assessment.

CONSEQUENCES OF RISK ASSESSMENT

The output from risk assessment is used in decisions about control of risks—either to avoid or replace the chemical of concern or to impose controls which reduce the exposure to levels where the risk is insignificant or acceptable, given the use of the chemical. For this reason, risk assessment should be based on logical, scientific principles. It should also strive to be accurate and to state the basis of the assumptions made in the assessment. Symmetry in risk assessment—by which is meant that the risks of all types are calculated using the same or similar assumptions, providing similar estimates of risk—is a valuable objective. It allows the risk manager to judge the appropriate allocation of resources to reduce risk in the knowledge that the estimation of risks is similar.

It has recently become apparent that the method used for assessing risk has an important impact on the perception of the risk by toxicologists or by university students [13]. When risks are presented as a probability (e.g., 10 in a million), they are perceived as larger than when the same risk is presented in terms of a safety factor (the dose you will ingest is 100 000 times lower than a dose that is without effect in experimental animals). Thus, those involved in risk assessment should recognize that the language used to explain risk has a large impact on the perception of that risk.

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