Risk assessment in the Environmental Protection Agency[☆]

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Abstract

Risk assessment is the general process used to determine the potential risk of an adverse health effect occurring from exposure to an agent. It consists of a hazard identification, a dose–response evaluation, an exposure assessment and a risk characterization. At the U.S. Environmental Protection Agency, risk assessments are used to estimate risks from environmental contaminants. Risk management uses the risk characterization along with such variables as economic, social, legal, technical, analytical and political factors to arrive at a regulatory level. The public is informed of regulatory actions prior to and after promulgation of the final rule through the process of risk communication.

1. Introduction

The US Environmental Protection Agency (EPA) has statutory requirements to regulate various contaminants to protect human health and the environment. For each chemical, it is necessary to identify whether a chemical poses a risk, to determine the potency of the chemical, and to estimate the potential risk imposed by exposure to that contaminant. The process of estimating and characterizing potential risks from various chemicals is called risk assessment. Translation of the risk assessment into a regulation involves risk management. EPA informs the public of its actions through risk communication. This review will focus on risk assessment and will only briefly consider risk management and communication.

2. Risk assessment

To perform a risk assessment, it is necessary to have a working definition of risk. Risk is considered to be the possibility of an injury, disease or death resulting from an

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[☆] The opinions expressed in this manuscript are those of the authors and do not necessarily reflect the policies of the US Environmental Protection Agency or of the Department of Defense.
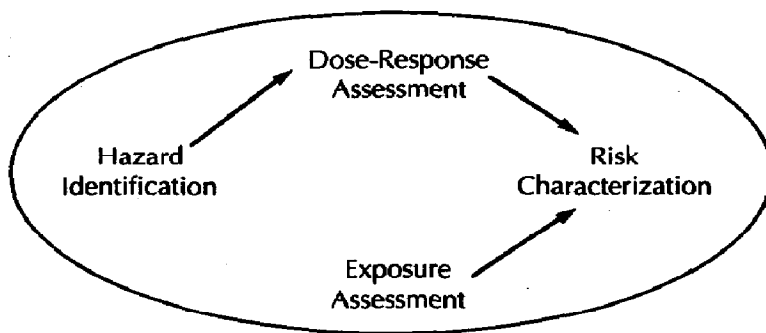[*] Corresponding author.

Fig. 1. Risk assessment paradigm demonstrates the relationships among hazard identification, dose–response assessment and exposure assessment to arrive at risk characterization. See text and Ref. [1] for details.

exposure to some agent. EPA is primarily concerned with those risks that occur after exposure to environmental compounds. Risk assessment is the effort made to estimate the risk associated with a specific set of conditions. EPA follows the risk assessment paradigm outlined by the National Academy of Sciences. They outlined risk assessment as being composed of a hazard identification, a dose–response evaluation and an exposure assessment which are integrated into a risk characterization ([1], Fig. 1). The resulting risk assessment may be quantitative and/or qualitative in nature. Some examples from the Safe Drinking Water Program will be used as illustrations.

2.1. Hazard identification

To identify a hazardous chemical, the toxicity data base of a chemical must be surveyed. The chemical in question must produce some adverse effect in humans or in experimental animals [2]. As would be expected, most of the available toxicity data base is the result of animal studies. When using animal data, it is understood that the deleterious effects observed in animals will occur, or are expected to occur, in humans. Animal toxicity data may be acute (usually 1 exposure), subacute (14 days), subchronic (90 days) or chronic (2 years) for general toxicity studies. Other toxicity tests, such as reproductive, developmental and mutagenic assays use protocols specifically designed to examine that respective endpoint [2]. Acute and subacute tests are only general indicators of toxicity and are not used to develop regulations for drinking water standards.

As previously mentioned, data on the effects of chemicals on humans are not as plentiful as those on experimental animals. Most of the human data come from case reports, correlation assessments and occupational or epidemiological cohort studies. The most desirable and informative are the epidemiological cohort studies. They examine populations that have been exposed to an agent and compare them to a matched control population. This type of study is valuable since it provides information on humans exposed to environmental concentrations [2].

2.2. Dose–response evaluation

After a potential hazard has been recognized, its potential for eliciting a response must be examined. The dose–response facet deals with the relationship between the level of exposure and the magnitude of the response. For example, increasing doses of an agent should cause greater adverse effects. If reliable data from humans are available, the quantitation of adverse effects is generally considered more reliable and more easily made. However, as with hazard identification, most dose–response studies are conducted on animals. Data from such studies must be examined critically since most toxic effects are observed after relatively high doses. In addition, animals may have different susceptibilities than humans and strains of experimental animals are less genetically diverse than the populations of humans. On the positive side, it is possible to control experimental variables for animal studies; a situation not possible in human epidemiology studies.

2.3. Exposure assessment

Exposure involves physical contact with the agent. The three primary routes are ingestion, inhalation and dermal contact. To assess exposure, data on the numbers of people exposed, the routes of exposure and the amount, duration and timing of each exposure route must be ascertained [1, 2]. For example, if exposure occurred only during recreational swimming, dermal contact would be the primary route of exposure and the assessment would incorporate this information. The total absorbed dose is a summation of the dose absorbed by each route.

2.4. Risk characterization

This facet is an integration and summation of the hazard identification, dose–response data and exposure assessment. The goal is to estimate the possibility or probability that humans, exposed to some concentration of an agent, will be affected by that agent. It is only as reliable as the information generated by each phase in the evolution of the risk characterization. Its adequacy is determined by enumeration of both the strengths and weaknesses of each part of the qualitative and quantitative assessment [3].

3. EPA risk assessment

EPA, at the present time, makes two generalizations about the effects of toxic chemicals. For noncarcinogens, it is assumed that there is a 'safe' dose or 'threshold' level, below which adverse health effects will not be observed. On the other hand, all carcinogenic agents are considered to have no 'safe' level of exposure, i.e., each increment in exposure increases the probability of producing cancer ([2], Fig. 2). Accordingly, EPA has developed separate types of risk assessment protocols for these possibilities.
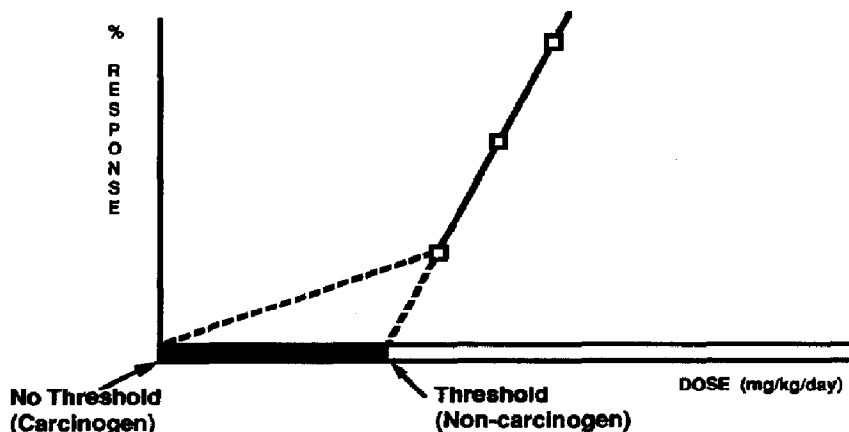
Fig. 2. Diagrammatic representation of 'threshold' and 'nonthreshold' concepts. A dose up to the threshold intercept can be tolerated by an organism without expression of adverse health effects (see text).

3.1. Threshold chemicals

As stated by Barnes and Dourson [4], this assumption is based on the theory that a "range of exposures from zero to some finite value can be tolerated by the organism with essentially no chance of expression of the toxic effect." Although this statement appears valid for most chemicals, it does not apply to one specific group of chemicals. For essential trace elements (ETEs), zero exposure would result in deleterious effects [5]. However, for ETEs, the concept of a finite upper-bound threshold for nontoxicity is supported by experimental data [6]. Therefore, the essentiality requirement does not prevent risk assessment of an ETE, it only means that the essential nature of the chemical must be considered during evaluation [5].

For noncancer effects, a Reference Dose (RfD) is derived. The RfD is defined as "an estimate (with an uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime" [7]. The RfD concept is similar to the acceptable daily intake (ADI) used by some regulatory and risk assessment groups. EPA has introduced the term 'RfD' to obviate the use of such prejudicial words as 'acceptable' and 'safety' [4]. In the RfD process, a no-observed-adverse-effect level (NOAEL) or a lowest-observed-adverse-effect level (LOAEL) is determined by evaluating the toxicity data base of a chemical. The appropriate NOAELs or LOAELs are selected, primarily, from animal studies or from human studies. Many factors such as toxicity endpoint, appropriateness of the species studied, methodology, route and length of exposure are critically reviewed. For example, in studies of similar quality, a human study would be selected over an animal study. In addition, for drinking water regulations, data from oral exposures are preferable. The most relevant study is selected and the endpoint of toxicity is considered to be the 'critical' effect. The NOAEL (or LOAEL) is divided by uncertainty factors (UFs) and, sometimes, a modifying factor MF (Table 1) to

Table 1
General description of standard uncertainty and modifying factors used in deriving Reference Doses[a]

UF[b]	General comments
Human (intraspecies)	For human studies, a 10-fold factor is normally utilized. It is used to account for variability of responses in human populations.
Animal (interspecies)	For data obtained from animal experiments, a 10-fold UF is generally used. Accounts for differences in responses between the animal species and humans.
Subchronic to chronic	When chronic data are unavailable and a ninety-day study is used for RfD derivation. Generally, a 10-fold factor is used.
LOAEL to NOAEL	A 10-fold factor is usually employed when a LOAEL, instead of a NOAEL, is used to derive the RfD. For 'minimal' LOAELs, an intermediate UF of 3 may be used.
Data gaps	'Incomplete' data bases (see Ref. [7]) are often encountered with chemicals. This factor, usually 3- to 10-fold depending on the missing studies, is meant to account for the inability of any study to consider all toxic endpoints. The intermediate factor of 3 ($\frac{1}{2}$ log unit) is often used when there is a single data gap exclusive of chronic data.
Modifying factor	Has been used for differences in absorption rates, tolerance to a chemical, or lack of sensitive endpoint. The default value is 1.

[a] Adapted from Refs. [4, 5, 7, 8]. Professional scientific judgement is used to determine the appropriateness of each UF. A value of 1, 3 or 10 may be used for each UF, although the 10-fold value is the most commonly used.
[b] Abbreviations: UF – uncertainty factor; LOAEL – lowest-observed-adverse-effect level; NOAEL – no-observed-adverse-effect level; RfD – Reference Dose.

obtain an RfD:

$$RfD = NOAEL \ (or \ LOAEL)/UFs \times MF. \tag{1}$$

The units for the RfD are in milligrams of the chemical per kilogram of body weight per day (mg/(kg day)). EPA also derives reference values for airborne chemicals. These levels are Reference Concentrations (RfCs) and the reader is referred to Jarabek et al. [8] for a discussion of this process.

3.2. Nonthreshold chemicals

Those agents that cause cancer in humans and/or animals are considered to have no threshold, i.e., there is no 'safe' exposure level unless there are data to the contrary. With these chemicals, any exposure has some risk and as exposure increases, the probability of a carcinogenic response increases [9].

EPA evaluates potential carcinogenicity from both a qualitative and a quantitative standpoint. In the qualitative evaluation, EPA uses a 'weight-of-evidence' approach to determine the potential carcinogenicity of a chemical. Factors include: occurrence (or lack of) cancers in various species, dose–response data, number(s) of tumor sites, decreases in time-to-tumor, effects on different sexes, mutagenicity and human

Table 2
EPA cancer classification categories[a]

Category	Description
A	Human carcinogen
B	Probable human carcinogen
	B_1 – Limited human data
	B_2 – Sufficient animal data and inadequate human data
C	Possible human carcinogen
D	Not classifiable
E	Evidence of noncarcinogenicity

[a] The EPA is presently revising the cancer guidelines. The draft of the revision states that a narrative section will be used to give the overall weight for carcinogenicity classification. At this time, there has been no decision on whether or not to retain an alpha-numeric system.
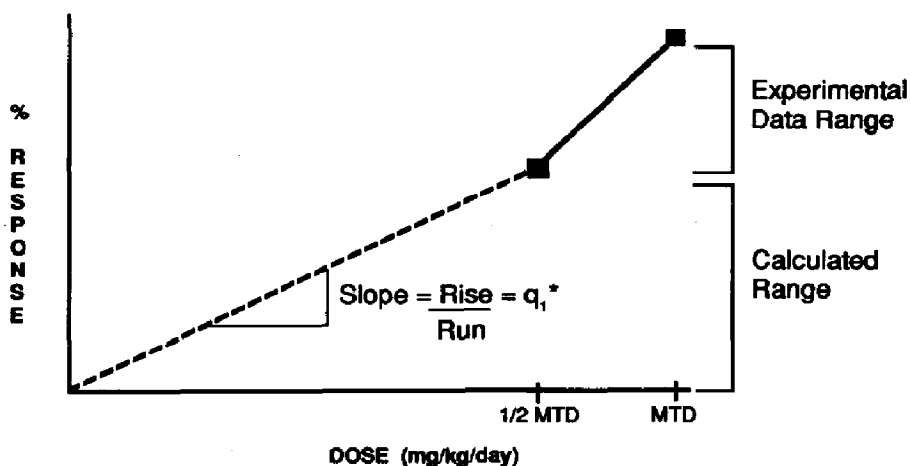

Fig. 3. Schematic presentation of calculation of slope factor (q_1^*) for a chemical that is carcinogenic after oral administration. The solid line represents actual dose levels, while the dotted line represents area of extrapolation. The upper-bound estimate of the risk response is calculated by multiplying the (q_1^*) times the daily dose. MTD – maximum tolerated dose.

case reports and epidemiology studies. Each chemical is then placed in a category (Table 2).

Quantification of carcinogenic responses is accomplished by using mathematical models. Although there are several models, EPA generally uses the linearized multistage model (LMS). It is a conservative model and the value obtained from the LMS risk model gives a plausible upper-bound estimate of the cancer risk. A chemical's carcinogenic potency after oral administration is given by a slope factor q_1^* (Fig. 3). Use of such models are generally necessary since relatively high doses are given to experimental animals and EPA needs to estimate risk at the relatively low doses that may be encountered in environmental situations.
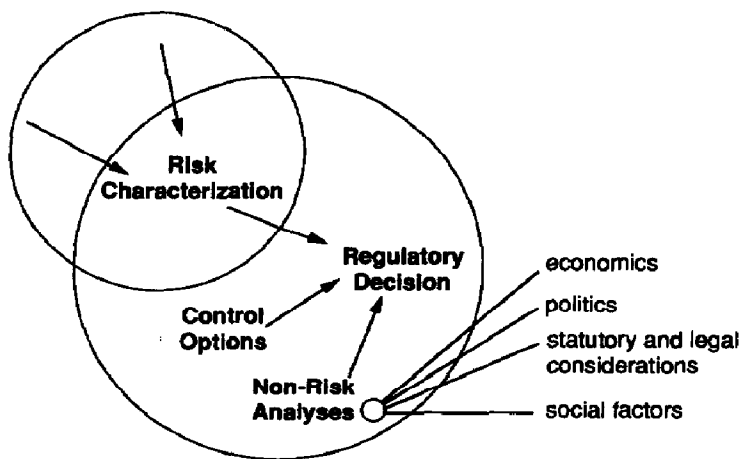
Fig. 4. Nonrisk analyses used by risk management personnel to arrive at a regulatory decision.

4. Risk management

Under the Safe Drinking Water Act (SDWA) of 1974 as amended in 1986 [10, 11], EPA is required to establish maximum contaminant level goals (MCLGs) and maximum contaminant levels (MCLs) or treatment techniques. The risk assessment process gives a scientific estimate of the magnitude of the health risk of a chemical and this information is used to set an MCLG. The MCLG reflects risk assessment (RfD and/or cancer classification) and is purely health-based; it is not enforceable.

The MCL is a risk management decision. To promulgate an MCL under the SDWA, risk managers start with the risk characterization and then factor in such considerations as economic impact, analytical and treatment techniques, political, legal and social aspects to arrive at an MCL (Fig. 4). The resulting MCL is the legally enforceable standard [10, 11].

5. Risk communication

Risk communication is the process by which the public participates in and is aware of Drinking Water Standards. Prior to, during and after promulgating a standard, EPA shares risk assessment and risk management information with the public by publishing notices of impending actions in the Federal Register.

EPA also has another mechanism for sharing chemical information with the public. It maintains an electronic data base called the Integrated Risk Information System (IRIS). All of the available data used by EPA in its risk assessments for each chemical (Table 3) is listed on this system. To obtain additional information on this system, contact IRIS User Support in Cincinnati, OH at 513-569-7254.

Table 3
General file structure for chemicals listed on the Integrated Risk Information System[a]

— Substance identification and CAS number[b]
— Chemical and physical properties
— RfD/RfC
— CRAVE
— Drinking water health advisories
— Aquatic toxicity data
— Exposure standards
— References

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[a] Certain data sets, i.e., RfC, may be missing if an RfC has not been verified for that chemical.
[b] Abbreviations: CAS number – Chemical Abstract Services registry number; RfD – Reference Dose; RfC – Reference Concentration; CRAVE – Carcinogen Risk Assessment Verification Endeavor (cancer assessments).

Acknowledgement

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