REGULATORY TOXICOLOGY AND PHARMACOLOGY 8, 471–486 (1988)

Reference Dose (RfD): Description and Use in Health Risk Assessments[1]

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Received October 8, 1987

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0273-2300/88 $3.00

For many years the concept of the "acceptable daily intake" has served the toxicological and regulatory fields quite well. However, as approaches to assessing the health significance of exposures to noncarcinogenic substances receive greater scrutiny, some difficulties with this traditional approach have become more apparent. Consequently, the concept of the "reference dose" is introduced in order to avoid use of prejudicial terms (e.g., "safety" and "acceptable"), to promote greater consistency in the assessment of noncarcinogenic chemicals, and to maintain the functional separation between risk assessment and risk management.

1. INTRODUCTION

This concept paper describes the U.S. Environmental Protection Agency's (USEPA) principal approach to and rationale for assessing risk for health effects other than cancer and gene mutations from chronic chemical exposure. By outlining principles and concepts that guide EPA risk assessment for such systemic effects, the paper complements the new risk assessment guidelines (USEPA, 1986), which describe the Agency's approach to risk assessment in other areas, specifically carcinogenicity, mutagenicity, developmental toxicity, exposure, and chemical mixtures. In this document the term "systemic toxicity" refers to an effect other than carcinogenicity or mutagenicity induced by a toxic chemical.

1.1. Background and Summary

Chemicals that give rise to toxic endpoints other than cancer and gene mutations are often referred to as "systemic toxicants" because of their effects on the function of various organ systems. In addition, chemicals that cause cancer and gene mutations also commonly evoke other toxic effects, i.e., systemic toxicity. Based on our understanding of homeostatic and adaptive mechanisms, systemic toxicity is treated as if there is an identifiable exposure threshold (both for the individual and for populations) below which there are no observable adverse effects. This characteristic distinguishes systemic endpoints from carcinogenic and mutagenic endpoints, which are often treated as nonthreshold processes.

Systemic effects have traditionally been evaluated using such terms as "acceptable daily intake (ADI)," "safety factor (SF)," and "margin of safety (MOS)," concepts that are associated with certain limitations described below. The USEPA established the Reference Dose (RfD) Work Group to address these concerns.

In preparing this report, the RfD Work Group has drawn on a seminal report on risk assessment (NRC, 1983), to more fully articulate the use of noncancer, nonmutagenic experimental data in reaching regulatory decisions about the significance of exposures to chemicals. In the process, the Work Group has coined less value-laden terminology—"reference dose (RfD)"; "uncertainty factor (UF)"; "margin of exposure (MOE)"; and "regulatory dose (RgD)"—to clarify and distinguish between aspects of risk assessment and risk management. These concepts are currently in general use in many parts of USEPA.

1.2. Overview

This document consists of four parts in addition to this Introduction. In Section 2, the traditional approach to assessing risks of systemic toxicity is presented, and issues

associated with this approach are identified and discussed. In Section 3, the modifications made to the traditional approach by the Work Group are presented. Section 4 examines how these new concepts can be applied in reaching risk management decisions, and Section 5 briefly discusses some of the additional approaches the USEPA is using and exploring to address this issue. Section 6 provides a sample RfD calculation. Section 7 consists of a glossary of terms.

2. TRADITIONAL APPROACH TO ASSESSING SYSTEMIC TOXICITY

The USEPA's approach to assessing the risks associated with systemic toxicity is different from its approach to assessing the risks associated with carcinogenicity, because of the different mechanisms of action thought to be involved in the two cases. In the case of carcinogens, the Agency assumes that a small number of molecular events can evoke changes in a single cell that can lead to uncontrolled cellular proliferation. This mechanism for carcinogenesis is referred to as "nonthreshold," since there is theoretically no level of exposure for such a chemical that does not pose a small, but finite, probability of generating a carcinogenic response. In the case of systemic toxicity, however, organic homeostatic, compensating, and adaptive mechanisms exist that must be overcome before a toxic endpoint is manifested. For example, there could be a large number of cells performing the same or similar function whose population must be significantly depleted before the effect is seen.

The threshold concept is important in the regulatory context. The individual threshold hypothesis holds 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. Further, it is often prudent to focus on the most sensitive members of the population; therefore, regulatory efforts are generally made to keep exposures below the population threshold, which is defined as the lowest of the thresholds of the individuals within a population.

2.1. Description of the Traditional Approach

In many cases, risk decisions on systemic toxicity have been made by the Agency using the concept of the "acceptable daily intake" derived from an experimentally determined "no observed adverse effect level (NOAEL)." The ADI is commonly defined as the amount of a chemical to which a person can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. The ADI concept has often been used as a tool in reaching risk management decisions (e.g., establishing allowable levels of contaminants in foodstuffs and water.)

A NOAEL is an experimentally determined dose at which there was no statistically or biologically significant indication of the toxic effect of concern. In an experiment with several NOAELs, the regulatory focus is normally on the highest one, leading to the common usage of the term NOAEL as the highest experimentally determined dose without a statistically or biologically significant effect. The NOAEL for the critical toxic effect is sometimes referred to simply as the NOEL. This usage, however, invites ambiguity in that there may be observable effects that are not of toxicological significance; i.e., they are not "adverse." For the sake of precision, this document uses the term NOAEL to mean the highest NOAEL in an experiment. In cases in

which a NOAEL has not been demonstrated experimentally, the term "lowest observed adverse effect level (LOAEL)" is used.

Once the critical study demonstrating the toxic effect of concern has been identified, the selection of the NOAEL results from an objective examination of the data available on the chemical in question. The ADI is then derived by dividing the appropriate NOAEL by a safety factor as follows:

$$\text{ADI (human dose)} = \text{NOAEL (experimental dose)}/\text{SF}. \quad (1)$$

Generally, the SF consists of multiples of 10, each factor representing a specific area of uncertainty inherent in the available data. For example, a factor of 10 may be introduced to account for the possible differences in responsiveness between humans and animals in prolonged exposure studies. A second factor of 10 may be used to account for variation in susceptibility among individuals in the human population. The resultant SF of 100 has been judged to be appropriate for many chemicals. For other chemicals, with data bases that are less complete (for example, those for which only the results of subchronic studies are available), an additional factor of 10 (leading to an SF of 1000) might be judged to be more appropriate. For certain other chemicals, based on well-characterized responses in sensitive humans (as in the effect of fluoride on human teeth), an SF as small as 1 might be selected.

While the original selection of SFs appears to have been rather arbitrary (Lehman and Fitzhugh, 1954), subsequent analysis of data (Dourson and Stara, 1983) lends theoretical (and in some instances experimental) support for their selection. Further, some scientists, but not all, within the EPA interpret the absence of widespread effects in the exposed human populations as evidence of the adequacy of the SFs traditionally employed.

2.2. Some Difficulties in Utilizing the Traditional Approach

2.2.1. Scientific Issues

While the traditional approach has performed well over the years and the Agency has sought to be consistent in its application, observers have identified scientific shortcomings of the approach. Examples include the following:

(a) Too narrow a focus on the NOAEL means that information on the shape of the dose–response curve is ignored. Such data could be important in estimating levels of concern for public safety.

(b) As scientific knowledge increases and the correlation of precursor effects (e.g., enzyme induction) with toxicity becomes known, questions about the selection of the appropriate "adverse effect" arise.

(c) Guidelines have not been developed to take into account the fact that some studies have used larger (smaller) numbers of animals and, hence, are generally more (less) reliable than other studies.

These and other "scientific issues" are not susceptible to immediate resolution, since the data base needed is not yet sufficiently developed or analyzed. USEPA work groups are presently considering these issues.

2.2.2. *Management-Related Issues*

2.2.2.1. The use of the term "safety factor." The term "safety factor" suggests, perhaps inadvertently, the notion of absolute safety, i.e., absence of risk. While there is a conceptual basis for believing in the existence of a threshold and "absolute safety" associated with certain chemicals, in the majority of cases a firm experimental basis for this notion does not exist.

2.2.2.2. The implication that any exposure in excess of the ADI is "unacceptable" and that any exposure less than the ADI is "acceptable" or "safe." In practice, the ADI is viewed by many (including risk managers) as an "acceptable" level of exposure, and, by inference, any exposure greater than the ADI is seen as "unacceptable." This strict demarcation between what is "acceptable" and what is "unacceptable" is contrary to the views of most toxicologists, who typically interpret the ADI as a relatively crude estimate of a level of chronic exposure which is not likely to result in adverse effects to humans. The ADI is generally viewed by risk assessors as a "soft" estimate, whose bounds of uncertainty can span an order of magnitude. That is, within reasonable limits, while exposures somewhat higher than the ADI are associated with increased probability of adverse effects, that probability is not a certainty. Similarly, while the ADI is seen as a level at which the probability of adverse effects is low, the absence of all risk to all people cannot be assured at this level.

2.2.2.3. Possible limitations imposed on risk management decisions. Awareness of the "softness" of the ADI estimate, as discussed above, argues for careful case-by-case consideration of the toxicological implications of an individual situation, so that ADIs are not given a degree of significance that is scientifically unwarranted. In addition, the ADI is only one factor in a risk management decision and should not be used to the exclusion of other relevant factors.

2.2.2.4. Development of different ADIs by different programs. In addition to occasionally selecting different critical toxic effects, Agency scientists have reflected their best scientific judgments in the final ADI by adopting factors different from the standard factors listed in Table 1. For example, if the toxic endpoint for a chemical in experimental animals is the same as that which has been established for a related chemical in humans at similar doses, one could argue for an SF of less than the traditional 100. On the other hand, if the total toxicologic data base is incomplete, one could argue that an additional SF should be included, both as a matter of prudent public policy and as an incentive to others to generate the appropriate data.

Such practices, as employed by a number of scientists in different programs/agencies, exercising their best scientific judgment, have in some cases resulted in different ADIs for the same chemical. The fact that different ADIs were generated (for example, by adopting different SFs) can be a source of considerable confusion when the ADIs are used exclusively in risk management decision making (see Section 2.2.2.3). The existence of different ADIs need not imply that any of them is more "wrong"—or "right"—than the rest. It is more nearly a reflection of the honest difference in scientific judgment.

However, on occasion, these differences in judgment of the scientific data can be interpreted as differences in the management of the risk. As a result, scientists may be inappropriately impugned, and/or perfectly justifiable risk management decisions may be tainted by charges of "tampering with the science." This unfortunate state of affairs arises, at least in part, from treating the ADI as an absolute measure of safety.

TABLE 1

GUIDELINES FOR THE USE OF UNCERTAINTY FACTORS AND MODIFYING FACTORS IN DERIVING REFERENCE DOSES

Standard uncertainty factors (UFs)
Use a 10-fold factor when extrapolating from valid experimental results in studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population and is referenced as "10H."
Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty involved in extrapolating from animal data to humans and is referenced as "10A."
Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there are no useful long-term human data. This factor is intended to account for the uncertainty involved in extrapolating from less than chronic NOAELs to chronic NOAELs and is referenced as "10S."
Use an additional 10-fold factor when deriving a RfD from a LOAEL, instead of a NOAEL. This factor is intended to account for the uncertainty involved in extrapolating from LOAELs to NOAELs and is referenced as "10L."
Modifying factor (MF)
Use professional judgment to determine the MF, which is an additional uncertainty factor that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study not explicitly treated above, e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

Note. Source: Adapted from Dourson and Stara (1983).

3. EPA ASSESSMENT OF RISKS ASSOCIATED WITH SYSTEMIC TOXICITY

The USEPA approach to analyzing systemic toxicity data follow the general format set forth by National Research Council in its description of the risk assessment process (NRC, 1983). The determination of the presence of risk and its potential magnitude is made during the risk assessment process, which consists of hazard identification, dose–response assessment, exposure assessment, and risk characterization. Having been apprised by the risk assessor that a potential risk exists, the risk manager considers control options available under existing statutes and other relevant nonrisk factors (e.g., benefits to be gained and costs to be incurred). All of these considerations go into the determination of the regulatory decision.

3.1. Hazard Identification

3.1.1. Evidence

3.1.1.1. Type of effect. Exposure to a given chemical, depending on the dose employed, may result in a variety of toxic effects. These may range from gross effects, such as death, to more subtle biochemical, physiologic, or pathologic changes. In

assessments of the risk posed by a chemical, the toxic endpoints from all available studies are considered, although primary attention usually is given to the effect (the "critical effect") exhibiting the lowest NOAEL. In the case of chemicals with limited data bases, additional toxicity testing may be necessary before an assessment can be made.

3.1.1.2. Principal studies. Principal studies are those that contribute most significantly to the qualitative assessment of whether or not a particular chemical is potentially a systemic toxicant in humans. In addition, they may be used in the quantitative dose–response assessment phase of the risk assessment. These studies are of two types: studies of human populations (epidemiologic investigations) and studies using laboratory animals.

3.1.1.2.1. Epidemiologic studies. Human data are often useful in qualitatively establishing the presence of an adverse effect in exposed human populations. When there is information on the exposure level associated with an appropriate endpoint, epidemiologic studies can also provide the basis for a quantitative dose–response assessment. The presence of such data obviates the necessity of extrapolating from animals to humans; therefore, human studies, when available, are given first priority, with animal toxicity studies serving to complement them.

In epidemiologic studies, confounding factors that are recognized can be controlled and measured, within limits. Case reports and acute exposures resulting in severe effects provide support for the choice of critical toxic effect, but they are often of limited utility in establishing a quantitative relationship between environmental exposures and anticipated effects. Available human studies on ingestion are usually of this nature. Cohort studies and clinical studies may contain exposure–response information that can be used in estimating effect levels, but the method of establishing exposure must be evaluated for validity and applicability.

3.1.1.2.2. Animal studies. For most chemicals, there is a lack of appropriate information on effects in humans. In such cases, the principal studies are drawn from experiments conducted on nonhuman mammals, most often the rat, mouse, rabbit, guinea pig, hamster, dog, or monkey.

3.1.1.3. Supporting studies. These studies provide supportive, rather than definitive, information and can include data from a wide variety of sources. For example, metabolic and other pharmacokinetic studies can provide insights into the mechanism of action of a particular compound. By comparing the metabolism of the chemical exhibiting the toxic effect in the animal with the metabolism found in humans, it may be possible to assess the potential for toxicity in humans or to estimate the equitoxic dose in humans.

Similarly, *in vitro* studies can provide insights into the chemical's potential for biological activity; and in certain circumstances, consideration of structure–activity relationships between a chemical and other structurally related compounds can provide clues to the test chemical's possible toxicity. More reliable *in vitro* tests are presently being developed to minimize the need for live-animal testing. There is also increased emphasis on generating mechanism-of-action and pharmacokinetic information as a means of increasing understanding of toxic processes in humans and nonhumans.

3.1.1.4. Route of exposure. The USEPA often approaches the investigation of a chemical with a route of exposure in mind (e.g., an oral exposure for a drinking water contaminant or an inhalation exposure for an air contaminant). In most cases, the toxicologic data base does not include detailed testing on all possible routes of admin-

istration, with their possibly significant differences in factors such as mechanism-of-action and bioavailability. In general, the USEPA's position is that the potential for toxicity manifested via one route of exposure is relevant to considerations of any other route of exposure, unless convincing evidence exists to the contrary. Consideration is given to potential differences in absorption or metabolism resulting from different routes of exposure, and whenever appropriate data (e.g., comparative metabolism studies) are available, the quantitative impacts of these differences on the risk assessment are delineated.

3.1.1.5. Length of exposure. The USEPA is concerned about the potential toxic effects in humans associated with all possible exposures to chemicals. The magnitude, frequency, and duration of exposure may vary considerably in different situations. Animal studies are conducted using a variety of exposure durations (e.g., acute, subchronic, and chronic) and schedules (e.g., single, intermittent, or continuous dosing). Information from all types of studies is useful in the hazard identification phase of risk assessment. For example, overt neurological problems identified in high-dose acute studies tend to reinforce the observation of subtle neurological changes seen in low-dose chronic studies. Special attention is given to studies involving low-dose chronic exposures, since such exposures can elicit effects absent in higher-dose, shorter exposures, through mechanisms such as accumulation of toxicants in the organisms.

3.1.1.6. Quality of the study. Evaluation of individual studies in humans and animals requires the consideration of several factors associated with a study's hypothesis, design, execution, and interpretation. An ideal study addresses a clearly delineated hypothesis, follows a carefully prescribed protocol, and includes sufficient subsequent analysis to support its conclusions convincingly.

In evaluating the results from such studies, consideration is given to many other factors, including chemical characterization of the compound(s) under study, the type of test species, similarities and differences between the test species and humans (e.g., chemical absorption and metabolism), the number of individuals in the study groups, the number of study groups, the spacing and choice of dose levels tested, the types of observations and methods of analysis, the nature of pathologic changes, the alteration in metabolic responses, the sex and age of test animals, and the route and duration of exposure.

3.1.2. Weight-of-Evidence Determination

As the culmination of the hazard identification step, a discussion of the weight-of-evidence summarizes the highlights of the information gleaned from the principal and supportive studies. Emphasis is given to examining the results from different studies to determine the extent to which a consistent, plausible picture of toxicity emerges. For example, the following factors add to the weight of the evidence that the chemical poses a hazard to humans: similar results in replicated animal studies by different investigators; similar effects across sex, strain, species, and route of exposure; clear evidence of a dose–response relationship; a plausible relation between data on metabolism, postulated mechanism-of-action, and the effect of concern; similar toxicity exhibited by structurally related compounds; and some link between the chemical and evidence of the effect of concern in humans.

3.2. Dose–Response Assessment

3.2.1. Concepts and Problems

Empirical observations have generally revealed that as the dosage of a toxicant is increased, the toxic response (in terms of severity and/or incidence of effect) also increases. This dose–response relationship is well-founded in the theory and practice of toxicology and pharmacology. Such behavior is observed in the following instances: in quantal responses, in which the proportion of responding individuals in a population increases with dose; in graded responses, in which the severity of the toxic response within an individual increases with dose; and in continuous responses, in which changes in a biological parameter (e.g., body or organ weight) vary with dose.

In evaluating a dose–response relationship, certain difficulties arise. For example, one must decide on the critical endpoint to measure as the "response." One must also decide on the correct measure of "dose." In addition to the interspecies extrapolation aspects of the question of the appropriate units for dose, the more fundamental question of administered dose versus absorbed dose versus target organ dose should be considered. These questions are the subject of much current research.

3.2.2. Selection of the Critical Data

3.2.2.1. Critical study. Data from experimental studies in laboratory animals are often selected as the governing information when performing quantitative risk assessments, since available human data are usually insufficient for this purpose. These animal studies typically reflect situations in which exposure to the toxicant has been carefully controlled and the problems of heterogeneity of the exposed population and concurrent exposures to other toxicants have been minimized. In evaluating animal data, a series of professional judgments is made which involve, among others, consideration of the scientific quality of the studies. Presented with data from several animal studies, the risk assessor first seeks to identify the animal model that is most relevant to humans, based on the most defensible biological rationale (for instance, using comparative pharmacokinetic data). In the absence of a clearly most relevant species, the most sensitive species (i.e., the species showing a toxic effect at the lowest administered dose) is used by risk assessors at USEPA, since there is no assurance that humans are not at least as innately sensitive as the most sensitive species tested. This selection process is more difficult when the routes of exposure in the animal tests are different from those involved in the human situation under investigation. In order to use data from controlled studies of genetically homogeneous animals, the risk assessor must also extrapolate from animals to humans and from high experimental doses to comparatively low environmental exposures, and must account for human heterogeneity and possible concurrent human exposures to other chemicals.

Although for most chemicals there is a lack of well-controlled cohort studies investigating noncancer endpoints, in some cases an epidemiologic study may be selected as the critical data (e.g., in cases of cholinesterase inhibition). Risk assessments based on human data have the advantage of avoiding the problems inherent in interspecies extrapolation. In many instances, use of such studies, as is the case with animal investigations, involves extrapolation from relatively high doses (such as those found in

occupational settings) to the low doses found in the environmental situations to which the general population is more likely to be exposed. In some cases, a well-designed and well-conducted epidemiologic study that shows no association between known exposures and toxicity can be used to directly project an RfD (as has been done in the case of fluoride).

3.2.2.2. Critical data. In the simplest terms, an experimental exposure level is selected from the critical study that represents the highest level tested in which "no adverse effect" was demonstrated. This NOAEL is the key datum gleaned from the study of the dose–response relationship and, traditionally, is the primary basis for the scientific evaluation of the risk posed to humans by systemic toxicants. This approach is based on the assumption that if the critical toxic effect is prevented, then all toxic effects are prevented.

More formally, the NOAEL is defined in this discussion as the highest experimental dose of a chemical at which there is no statistically or biologically significant increase in frequency or severity of an adverse effect in individuals in an exposed group when compared with individuals in an appropriate control group. As noted above, there may be sound professional differences of opinion in judging whether or not a particular response is adverse. In addition, the NOAEL is a function of the size of the population under study. Studies with a small number of subjects are less likely to detect low-dose effects than studies using larger numbers of subjects. Also, if the interval between doses in an experiment is large, it is possible that the experimentally determined NOAEL is lower than that which would be observed in a study using intervening doses.

3.2.2.3. Critical endpoint. As noted in Section 2, a chemical may elicit more than one toxic effect (endpoint), even in one test animal, or in tests of the same or different duration (acute, subchronic, and chronic exposure studies). In general, NOAELs for these effects will differ. The critical endpoint used in the dose–response assessment is the effect exhibiting the lowest NOAEL.

3.2.3. Reference Dose

The RfD and UF concepts have been developed by the RfD Work Group in response to many of the problems associated with ADIs and SFs, as outlined in Section 2 above. The RfD is a benchmark dose operationally derived from the NOAEL by consistent application of generally order-of-magnitude UFs that reflect various types of data sets used to estimate RfDs. For example, a valid chronic animal NOAEL is normally divided by a UF of 100. In addition, a modifying factor (MF) is sometimes used which is based on a professional judgment of the entire data base of the chemical. These factors and their rationales are presented in Table 1.

The RfD is determined by use of

$$\text{RfD} = \text{NOAEL}/(\text{UF} \times \text{MF}) \tag{2}$$

which is the functional equivalent of Eq. (1). In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is generally expressed in units of milligrams per kilogram of bodyweight per day (mg/kg-day).

The RfD is useful as a reference point from which to gauge the potential effects of the chemical at other doses. Usually, doses less than the RfD are not likely to be associated with adverse health risks, and are therefore less likely to be of regulatory concern. As the frequency and/or the magnitude of the exposures exceeding the RfD increases, the probability of adverse effects in a human population increases. However, it should not be categorically concluded that all doses below the RfD are "acceptable" (or will be risk-free) and that all doses in excess of the RfD are "unacceptable" (or will result in adverse effects).

The USEPA is attempting to standardize its approach to determining RfDs. The RfD Work Group has developed a systematic approach to summarizing its evaluations, conclusions, and reservations regarding RfDs in a "cover sheet" of a few pages in length. The cover sheet includes a statement on the confidence (high, medium, or low) the evaluators have in the stability of the RfD. High confidence indicates the judgment that the RfD is unlikely to change in the future because there is consistency among the toxic responses observed in different sexes, species, study designs, or in dose–response relationships, or that the reasons for existing differences are well understood. High confidence is often given to RfDs that are based on human data for the exposure route of concern, since in such cases the problems of interspecies extrapolation have been avoided. Low confidence indicates the judgment that the data supporting the RfD may be of limited quality and/or quantity and that additional information could result in a change in the RfD.

3.3. Exposure Assessment

The third step in the risk assessment process focuses on exposure issues. For a full discussion of exposure assessment, consult USEPA's guidelines on the subject (USEPA, 1986). In brief, the exposure assessment includes consideration of the size and nature of the populations exposed and the magnitude, frequency, duration, and routes of exposure, as well as evaluation of the nature of the exposed populations.

3.4. Risk Characterization

Risk characterization is the final step in the risk assessment process and feeds directly into the risk management (regulatory action) process. The purpose of risk characterization is to present the risk manager with a synopsis and synthesis of all the data that should contribute to a conclusion with regard to the nature and extent of the risk, including:

(a) The qualitative ("weight-of-evidence") conclusions as to the likelihood that the chemical may pose a hazard to human health.

(b) A discussion of the dose–response information considered in deriving the RfD, including the UFs and MFs used.

(c) Data on the shapes and slopes of the dose–response curves for the various toxic endpoints, toxicodynamics (absorption and metabolism), structure–activity correlations, and the nature and severity of the observed effects.

(d) Estimates of the nature and extent of the exposure and the number and types of people exposed.

(e) Discussion of the overall uncertainty in the analysis, including the major assumptions made, the scientific judgments employed, and an estimate of the degree of conservatism involved.

In the risk characterization process, a comparison is made between the RfD and the estimated (calculated or measured) exposure dose (EED). The EED should include all sources and routes of exposure involved. If the EED is less than the RfD, the need for regulatory concern is likely to be small.

An alternative measure that may be useful to some risk managers is the MOE, which is the magnitude by which the NOAEL of the critical toxic effect exceeds the EED, where both are expressed in the same units:

$$\text{MOE} = \text{NOAEL (experimental dose)/EED (human dose)}. \tag{3}$$

When the MOE is equal to or greater than UF $\times$ MF, the need for regulatory concern is likely to be small.

Section 6 contains an example of the use of the concepts of NOAEL, UF, MF, RfD, EED, and MOE.

4. APPLICATION IN RISK MANAGEMENT

Once the risk characterization is completed, the focus turns to risk management. In reaching decisions, the risk manager utilizes the results of risk assessment, other technological factors, and legal, economic, and social considerations in reaching a regulatory decision. These additional factors include efficiency, timeliness, equity, administrative simplicity, consistency, public acceptability, technological feasibility, and nature of the legislative mandate.

Because of the way these risk management factors may impact different cases, consistent—but not necessarily identical—risk management decisions must be made on a case-by-case basis. For example, the Clean Water Act calls for decisions with "an ample margin of safety"; the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) calls for "an ample margin of safety," taking benefits into account; and the Safe Drinking Water Act (SDWA) calls for standards which protect the public "to the extent feasible." Consequently, it is entirely possible and appropriate that a chemical with a specific RfD may be regulated under different statutes and situations through the use of different RgD's.

That is, after carefully considering the various risk and nonrisk factors, regulatory options, and statutory mandates in a given case (i), the risk manager selects the appropriate statutory alternative for arriving at an "ample" or "adequate" margin of exposure [MOE(i)]. As shown in Eq. (4) below, this procedure establishes the regulatory dose, RgD(i) (e.g., a tolerance under FIFRA or a maximum contaminant level under SDWA), applicable to the case in question:

$$\text{RgD}(i) = \text{NOAEL}/\text{MOE}(i) \tag{4}$$

Note that different RgD's are possible for a given chemical with a single RfD. Note

also that comparing the RfD to a particular RgD(i) is equivalent to comparing the MOE(i) with the UF × MF:

$$\text{RfD/RgD}(i) = \text{MOE}(i)/\text{UF} \times \text{MF}. \quad (5)$$

In assessing the significance of a case in which the RgD is greater (or less) than the RfD, the risk manager should carefully consider the case-specific data compiled by the risk assessors, as discussed in Section 3.4 above. In some cases, additional explanation and interpretation may be required from the risk assessors in order to arrive at a responsible and clearly articulated final decision on the RgD.

It is generally useful to the risk manager to have information regarding the contribution to the RfD from various environmental media (e.g., air, water, and food.) Such information can provide insights that are helpful in choosing among available control options. However, in cases in which site-specific criteria are being considered, local exposures through various media can often be determined more accurately than exposure estimates based upon generic approaches. In such cases, the exposure assessor's role is particularly important. For instance, at a given site, consumption of fish may clearly dominate the local exposure routes, while, on a national basis, fish consumption may play a minor role compared to ingestion of treated crops.

Work is underway in the USEPA to apportion the RfD among the various environmental media. For example, consider the case of a food-use pesticide which is a contaminant in drinking water. In selecting among risk management actions under the Safe Drinking Water Act, it might be prudent to assume an RfD for drinking water purposes which is some fraction of the total RfD. Such an apportionment would explicitly acknowledge the possible additional exposure from ingestion of treated crops. The apportionment of the RfD would, in general, provide additional guidance for risk managers of the various media-specific programs.

5. OTHER DIRECTIONS

In addition to the development of reference doses, the USEPA is pursuing other lines of investigation for systemic toxicity. For example, the Office of Air Quality Planning and Standards is using probabilistic risk assessment procedures for criteria pollutants. In this procedure, the population at risk is characterized, and the likelihood of the occurrence of various effects is predicted through the use of available scientific literature and of scientific experts' rendering their judgments concerning dose–response relationships. This dose–response information is then combined with the results of the exposure analysis to generate population risk estimates for alternative standards. Through the use of these procedures, decision makers are presented with ranges of risk estimates in which uncertainties associated with both the toxicity and the exposure information are explicitly considered. The Office of Policy, Planning, and Evaluation is investigating similar procedures in order to balance health risk and cost. In addition, scientists in the Office of Research and Development have initiated a series of studies designed to increase the reliability of risk assessments. They are investigating the use of extrapolation models as a means of estimating RfD's, taking into account the statistical variability of the NOAEL and underlying UFs. ORD is also exploring procedures for conducting health risk assessments that

TABLE 2

HYPOTHETICAL DATA TO ILLUSTRATE REFERENCE DOSE CONCEPT

Dose (mg/kg-day)	Observation	Effect level
0	Control—no adverse effects observed	—
1	No statistically or biologically significant differences between treated and control animals	NOEL
5	2% decrease* in body weight gain (not considered to be of biological significance) Increased ratio of liver weight to body weight Histopathology indistinguishable from controls Elevated liver enzyme levels	NOAEL
25	20% decrease* in body weight gain Increased* liver weight to body weight Enlarged, fatty liver with vacuole formation Increased* liver enzyme levels	LOAEL

* Statistically significant compared to controls.

involve less-than-lifetime exposures. Finally, they are working on approaches to ranking the severity of different toxic effects.

6. HYPOTHETICAL, SIMPLIFIED EXAMPLE OF DETERMINING AND USING RfD

6.1. Experimental Results

Suppose the USEPA had a sound 90-day subchronic gavage study in rats with the data found in Table 2.

6.2. Analysis

6.2.1. Determination of the Reference Dose (RfD)

6.2.2.1. Using the NOAEL. Because the study is on animals and of subchronic duration,

$$UF = 10H \times 10A \times 10S = 1000$$

(see Table 1).

In addition, there is a subjective adjustment (MF) based on the high number of animals (250) per dose group; MF = 0.8.

These factors then give UF × MF = 800, so that

$$\text{RfD} = \text{NOAEL}/(\text{UF} \times \text{MF}) = 5 \text{ mg/kg-day}/800 = 0.006 \text{ mg/kg-day}.$$

6.2.1.2. Using the LOAEL. If a NOAEL is not available and if 25 mg/kg-day had been the lowest dose tested,

$$\text{UF} = 10\text{H} \times 10\text{A} \times 10\text{S} \times 10\text{L} = 10{,}000$$

(see Table 1). Using again the subjective adjustment of MF = 0.8, one obtains

$$\text{RfD} = \text{LOAEL}/(\text{UF} \times \text{MF}) = 25 \text{ mg/kg-day}/8000 = 0.003 \text{ mg/kg-day}.$$

6.2.2. Risk Characterization Considerations

Suppose the EEDs for humans exposed to the chemical under the proposed use pattern were 0.01 mg/kg-day (i.e., the EED is greater than the RfD). Viewed alternatively, the MOE is

$$\text{MOE} = \text{NOAEL}/\text{EED} = 5 \text{ mg/kg-day}/0.01 \text{ mg/kg-day} = 500.$$

Because the EED exceeds the RfD (and the MOE is less than the UF × MF), the risk manager will need to look carefully at the data set, the assumptions for both the RfD and the exposure estimates, and the comments of the risk assessors. In addition, the risk manager will need to weigh the benefits associated with the case, and other nonrisk factors, in reaching a decision on the RgD.

7. GLOSSARY

ADI (acceptable daily intake)—The amount of a chemical to which a person can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect.

Critical endpoint—The toxic effect used as the basis of the RfD.

Critical study—The study yielding the NOAEL which is used as the basis of the RfD.

EED (estimated exposure dose)—The chemical dose anticipated to result from human exposure under a prescribed set of conditions.

LOAEL (lowest observed adverse effect level)—The lowest experimentally determined dose at which a statistically or biologically significant indication of the toxic effect of concern is observed.

MF (modifying factor)—An additional factor sometimes used in the derivation of the RfD to reflect the professional judgment of the assessor in evaluating the peculiarities of the data base for a particular chemical.

MOE (margin of exposure)—The ratio between the NOAEL and the EED; i.e., MOE = NOAEL/EED, Eq. (3).

MOS (margin of safety)—See MOE.

NOAEL (no observed adverse effect level)—An experimentally determined dose at which no statistically or biologically significant indication of the toxic effect of concern is observed.

NOEL—See NOAEL.

RfD (reference dose)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive sub-

groups) that is likely to be without appreciable risk of deleterious effects during a lifetime.

RgD (regulatory dose)—The anticipated dose resulting from human exposure to the chemical at the level at which it is regulated in the environment.

SF (safety factor)—The divisor applied to the NOAEL to calculate the ADI; i.e., ADI = NOAEL/SF, Eq. (1).

UF (uncertainty factor)—The divisor which, along with the modifying factor (MF), is applied to the NOAEL to calculate the RfD; i.e., RfD = NOAEL/(UF × MF), Eq. (2). The magnitude of the UF is generally determined by the considerations detailed in Table 1.

Systemic toxicity—Toxicity other than carcinogenicity or mutagenicity.

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