STATISTICS IN TOXICOLOGY

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Contents

Preface ix

List of Contributors xi

I. INTRODUCTION
Chapter 1 Current Challenges in Toxicity Testing
C.A. FRANKLIN 3
Chapter 2 Statistical Issues in Toxicological Research
D. KREWSKI AND M. BICKIS 11

II. ACUTE TOXICITY STUDIES
Chapter 3 Acute Toxicity Studies
S.C. GAD 45
Chapter 4 Estimation of the Typical Lethal Dose in Acute Toxicity Studies
M.A. HAMILTON 61

III. SUBCHRONIC TOXICITY STUDIES
Chapter 5 Subchronic Toxicity Testing
D.L. ARNOLD 91
Chapter 6 Statistical Analysis of Subchronic Toxicity Studies
B.D. LITT, K.E. BOYLE AND L.E. MYERS 105

IV. PHARMACOKINETICS
Chapter 7 Pharmacokinetics in Toxicological Research
D.J. JOLLOW 129
Chapter 8 Compartmental Pharmacokinetic Models
D.J. MURDOCH 143
Chapter 9 Physiological Pharmacokinetic Models
C.C. TRAVIS AND H.A. HATTEMER-FREY 161

Chapter 28

The Use of Uncertainty Factors in Establishing Safe Levels of Exposure

MICHAEL L. DOURSON AND CHRISTOPHER T. DEROSA

I. INTRODUCTION

Regulatory toxicology is a branch of the science which, in part, attempts to estimate "safe" levels of various chemicals in different environmental media such as water or air. Such estimations involve four components (NRC, 1983): hazard identification, dose-response assessment, exposure assessment and risk characterization. This chapter briefly discusses risk characterization by way of describing the estimation of standards, tolerances and criteria, and dose-response assessment by considering various uncertainties in extrapolations. Exposure assessment and hazard identification are described in part elsewhere (U.S. EPA, 1986a, 1990a).

The foundation of dose-response assessment and risk characterization for many chemicals is the assumption that a threshold exists in the dose rate (for example, mg/kg bw/day) below which adverse effects will not be evoked if the general population is exposed over lifetime. This assumption is supported by the known mechanisms of toxic action of many chemicals (for example, cyanides) and the known

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capacity of organisms to ward off adverse stimuli with a variety of physiological responses. Environmental scientists have long considered the estimation of subthreshold doses to be a reasonable goal, and several manuscripts are available that discuss this (Lu, 1983, 1985; Paynter and Schmitt, 1979; Vettorazzi, 1980). One of the terms used to describe this concept has been the acceptable daily intake (ADI), now referred to by the U.S. EPA as the Reference Dose (RfD) (U.S. EPA, 1987a; Barnes and Dourson, 1988).

By necessity most of these dose-response assessments and risk characterizations are based on toxicity studies where experimental animals are given doses of the chemical that are higher than what is expected or found in environmental media. This procedure introduces several general uncertainties in the resulting safe levels that are estimated for humans: 1) that of human variability to the chemical's toxicity irrespective of dose extrapolation, 2) uncertainties associated with the extrapolation from high experimental dose to low dose typical of human environmental exposures, and 3) the issue of whether equivalent doses of a chemical are equitoxic given the inherent variability in toxic response amongst species. However, other uncertainties exist, such as less than lifetime experimental exposure, as well as other aspects of the quality and extent of the toxicity data base.

Traditionally, for noncarcinogenic effects these scientific uncertainties are handled by the use of different factors used to divide the appropriate no-observed-effect level (NOEL) or no-observed-adverse-effect level (NOAEL) of the critical effect in the most appropriate experimental animal species or man (U.S. EPA 1990a). Each of these standard factors has theoretical and, in some cases, experimental support (Dourson and Stara, 1983). It should be well noted that chemical-specific data are preferred over the use of a 10-fold factor in each of these standard areas of uncertainty. As an example, if rats appear to be the most appropriate experimental species on which to base the RfD and pharmacokinetic data in rat and man suggest a mg/kg body weight/day dose adjustment other than the 10-fold factor, this dose adjustment should be used. However, order of magnitude values (that is, 10-fold) for different areas of scientific uncertainty in the toxicity data base are not unreasonable as default values. The resulting "safe" levels are expected to have a similar degree of imprecision.

Other authors have discussed these areas of uncertainty or uncertainty factors in general. The interested reader is referred to Zeilhuis and van der Kreek (1979) for a discussion of these factors in setting health based permissible levels for occupational exposure and Dourson and Stara (1983) for a summary of these factors regarding oral exposures. Other publications include: Gaylor (1983), who discusses the use of safety factors for controlling risk; Crump (1984), who discusses problems with the current methods that includes uncertainty factors; Krewski *et al.* (1984), who contrast safety factors and mathematical models as methods for determining "safe" levels of exposure; Calabrese (1985) and Hattis *et al.* (1987), who discuss uncertainty factors and interindividual variation; and Lu (1983, 1985), who discusses safety factors from the perspective of the World Health Organization (WHO).

For carcinogenic endpoints, such uncertainties are handled by mathematical extrapolation and dose conversion. This procedure is discussed in detail elsewhere (Anderson *et al.*, 1984; OSTP, 1985). Uncertainty factors are not commonly used in carcinogen health risk assessment.

II. HISTORY

Guidelines and recommendations on the use of acceptable intakes for unintentional exposures to systemic toxicants have been adopted by several United States governmental institutions and international bodies, such as the Food and Drug Administration (FDA) Kokoski, 1976), the U.S. EPA (1980, 1987a), the joint Food and Agricultural Organization/World Health Organization (FAO/WHO) Food Standards Programme (Codex Alimentarius Committee on Food Additives), by the FAO Committee on Pesticide Residues and the WHO Expert Committee on Pesticide Residues (Vettorazzi, 1980; Lu, 1985), and by independent groups such as the Food Safety Council (1982) and the National Academy of Sciences (NAS, 1977, 1980).

Lehman and Fitzhugh (1954) of the FDA originally suggested that safe levels of food additives or contaminants be derived from chronic animal no-effect levels (measured in mg/kg of diet) by dividing by a 100-fold safety factor. This safe level was called the Acceptable Daily Intake (ADI) by the joint FAO/WHO Expert Committee on Food Additives in 1961. This term was subsequently adopted by the joint FAO/WHO Meeting of Experts on Pesticide Residues in 1962 and

also by the food additives and pesticide residues committees of the Codex Alimentarius Committees (Lu, 1983).

The FDA expanded this initial approach in the derivation of ADIs to situations where chronic toxicity data for food additives or contaminants were unavailable. In these cases the FDA recommended estimating an ADI by division by a safety factor of 1000 when subchronic data were available for two species (Kokoski, 1976) or by a safety factor of 2000 when such data were available for only one species (Shibko 1981). The NAS (1977) recommended a similar approach when estimating safe levels of pollutants in drinking water, but also outlined the use of a 10-fold uncertainty factor when valid experimental results from studies on prolonged ingestion by man were available. NAS (1980) discussed the ADI concept in some detail; this discussion highlighted some of the problems associated with the use of ADIs as well as possible future directions in the use of mathematical models to estimates ADIs. Based on NAS reasoning, the U.S. EPA (1980) used ADIs to calculate safe levels of pollutants in ambient waters (for example, rivers, lakes), but also extended the methodology in order to estimate on ADI from a lowest-observed-adverse-effect level (if a no-observed-adverse effect level was unavailable) and in the definition and use of nonadverse and adverse effects (Stara *et al.*, 1981). U.S. EPA (1986b) has extended this concept to solid wastes. Recently, the U.S. EPA (1990a; Barnes and Dourson, 1988) has explicated this overall process in terms that are consistent with the NRC (1983) framework.

III. "SAFE" LEVELS OF EXPOSURE

As discussed in Barnes and Dourson (1988) the term "safe" suggests, perhaps inadvertently, the notion of absolute safety, i.e. the absence of risk. In practice, the ADI is viewed by many as an "acceptable" level of exposure, and, by inference, any exposure greater than the ADI is seen as "unacceptable." However, 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 not likely to result in adverse effects to humans, and whose bounds of uncertainty can span perhaps 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 risk to all people cannot be assured at this level.

In part in response to this issue, the U.S. EPA introduced the concept of the "reference dose (RfD)" and "uncertainty factor (UF)". 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 used to estimate RfDs (for example, a valid chronic human NOAEL normally is divided by a UF of 10) and an additional modifying factor (MF), which is based on a professional judgment of the entire data base of the chemical. "Uncertainty factor" is the new description applied to the term "safety factor". This new name is more descriptive in that these factors represent scientific uncertainties, and avoids the risk management connotation of "safety." The "modifying factor" can range from >0 to 10, and reflects professional judgments regarding scientific uncertainties not covered under the standard UF, such as the completeness of the overall data base and the number of animals in the study. 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 useful as a reference point for gauging the potential effects of other doses. Usually, doses that are less than the RfD are not likely to be associated with any healthy risks, and are therefore less likely to be of regulatory concern. However, as the frequency of exposures exceeding the RfD increases, and as the size of the excess increases, the probability increases that adverse effects may be observed in a human population. Nonetheless, a clear conclusion cannot be categorically drawn that all doses below the RfD are "acceptable" and that all doses in excess of the RfD are "unacceptable." This is a consequence of the inability of either the traditional or the RfD approach to completely address the question of dose-response extrapolation.

Various terms have been used to describe "safe" levels of exposure to chemicals in environmental media. In general, a "standard", measured in units of weight of chemical per volume or weight of medium (for example, mg/L of water; mg/kg of soil), represents the enforceable component of many environmental laws. A standard is often established from a criterion (defined below) after consideration of

factors such as best available technology, natural background levels, assessment of risk vs. benefits and social perceptions of risk. As an example, Maximum Contaminant Levels (MCLs) are derived for pollutants in drinking water based on Maximum Contaminant Level Goals (MCLGs) and the following considerations: analytical methods, treatment technology, regulatory impact, and economic impact. MCLGs are part of the risk assessment process. MCLs are standards (a result of the risk management process).

$$\text{Standard} = \text{Criterion} \times (\text{Risk Management Considerations}) \quad (1)$$

Tolerances represent the legal limit to control levels of pesticides on agricultural products. Tolerances are established from considerations such as good agricultural practice, pesticide usage and expected pesticide residuals on these products. As such, tolerances represent standards. Daily pesticide intakes are then estimated from these tolerances using assumptions of yearly consumption of specific agricultural products and different body weights of humans (different subgroups are routinely considered in this part of the evaluation). These daily intakes are then compared to RfDs or to toxicity data in order to estimate various margins of exposure (the new term that the U.S. EPA now uses instead of "margins of safety", U.S. EPA, 1990a).

In general, a "criterion", measured in the same units as a standard, represents the best scientific estimate of an environmental concentration of contaminant (e.g., MCLG) corresponding to a given level of hazard. Criteria are generally not enforceable. For carcinogens this estimate is the concentration associated with a specified, expected, upper-lifetime-excess-cancer risk (for example, 10^{-5}, 10^{-6}, 10^{-7}) (Anderson *et al.*, 1984). For many chemicals, however, cancer is neither observed nor expected, and a systemic effect (such as liver necrosis) becomes the endpoint of concern. These are generally referred to as threshold effects, and for these chemicals criteria represent an estimate of an environmental level that is expected to cause no additional health risk. The estimation of criteria is considered to be the risk characterization component of risk assessment, because criteria involve hazard identification, and dose-response and exposure assessments.

Criteria for noncancer toxicity are usually estimated by dividing an RfD (in units of mg of chemical per day for a person of defined body weight such as 70 kg), or another measure of acceptable intake by one or more exposure assessments or assumptions as shown below:

$$\text{CRITERION} = \frac{\text{RfD}}{\text{Exposure Assessments or Assumption(s)}} \quad (2)$$

Some exposure assumptions which have been used are 2 L of drinking water/day or 20 cubic meters of air breathed/day. These calculations often assume that the contaminant of concern is only found (or measured) in the media of interest. However, exposure assessments (that is, the qualitative or quantitative determination or estimation of the magnitude, frequency, duration, and route of exposure) can be used to refine these criteria calculations when available. Also note that a chemical may have differing criteria for a medium given differing exposure assumptions or exposure assessments; for example, daily drinking water consumption may vary from one location or country to another. U.S. EPA (1986a, 1988) gives general guidance on conducting exposure assessments.

IV. UNCERTAINTIES IN EXTRAPOLATION

Reference doses are derived by the general formula:

$$\text{RfD} = \frac{\text{NOAEL}}{\text{uncertainty factor} \times \text{modifying factor}}. \quad (3)$$

The choice of effect level as a basis for the RfD is described elsewhere (U.S. EPA, 1980, 1984, 1990a). The selection and justification of uncertainty factors is also critical.

As summarized in Table 28.1, several factors are currently recommended by the U.S. EPA to estimate RfDs for systemic toxicity (U.S. EPA 1990a). The selection of these factors in general reflects the scientific uncertainty inherent with the use of a toxicity data base that is deficient in different types of human or animal data. This quite naturally leads to the question as to what constitutes any ideal data base. If sufficient data of chronic duration are available on a chemical's critical effect in a known sensitive human population, an uncertainty factor of <10 and even as little as 1 may be used to estimate an RfD. That is to say that this "ideal" data base (deficient in no

Table 28.1
GUIDELINES FOR THE USE OF UNCERTAINTY FACTORS IN DERIVING REFERENCE DOSES (RfDs)*

	Guidelines
Standard Uncertainty Factors (UFs):	
10H	Use a 10-fold factor when extrapolating from valid experimental results from 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.
10A	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 in extrapolating animal data to the case of humans.
10S	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 in extrapolating from less than chronic NOAELs to chronic NOAELs.
10L	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 in extrapolating from LOAELs to NOAELs.
Modifying Factor (MF):	
Use professional judgment to determine another uncertainty factor (MF) 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 and data base not explicitly treated above (for example, the completeness of the overall data base and the number of species tested). The default value for the MF is 1.	

*Source: U.S. EPA 1990a.

major aspect) may be sufficiently predictive of a population subthreshold dose that uncertainty factors are not warranted. As an example, the RfD estimated by the U.S. EPA for fluoride is based on dental mottling in children. In this instance, an uncertainty factor of 1 was applied since dental mottling is the critical effect, children are the sensitive subgroup and the available data adequately cover the ranges of dose and exposure of concern (U.S. EPA, 1990b). An overall uncertainty factor of 10 might be used to estimate an RfD with chronic human toxicity data and would reflect a deficiency in toxicity data on a sensitive population of humans; alternatively, it could be said that this 10-fold uncertainty factor reflects the expected interhuman variability to the adverse effects of a chemical in the absence of chemical-specific data (that is, 10_H). An overall uncertainty factor of 100 might be used to estimate RfDs with sufficient chronic animal

toxicity data reflecting deficiencies in both human data and that of a sensitive population of humans (that is, $10_H \times 10_A$). This overall factor of 100, however, might also be used with subchronic human data and would reflect deficiencies in both information on sensitive individuals and chronic exposure (that is, $10_H \times 10_S$).

An overall uncertainty factor of 1000 is often used to estimate RfDs with satisfactory subchronic animal data (if adequate chronic data are unavailable). It incorporates the uncertainty in extrapolating toxicity data from subchronic to chronic exposures (that is, 10_S), as well as the two former uncertainty factors (that is, $10_H \times 10_A$). An uncertainty factor of 10 is usually applied to estimate RfDs using LOAELs (if (NOAELs are unavailable). This uncertainty factor defines an exposure level below the LOAEL expected to be in the range of a NOAEL.

It is important to emphasize again that uncertainty factors are imprecise. While values of 64 or 144, for example, are likely to be equally accurate (or equally inaccurate) when compared with the usual uncertainty factor of 100, the former factors are not consistent with the expected precision of these order-of-magnitude factors. The following theoretical considerations and experimental data for individual uncertainty factors show this imprecision.

A. Interhuman Adjustment

The factor of 10_H has been used to account for the expected within human variability to the toxicity of chemicals. The use of this factor can be viewed as a reduction in mg/kg body weight (b.w.) dose needed to scale-down a median response by a series of standard deviations to the general range expected for a potential sensitive subgroup of the population under study. For example, a three probit (i.e., standard deviation) reduction places a 50% (i.e. median) response into the general range of 0.1% (i.e. a potential sensitive response). What data support this consideration?

An analysis of probit, log dose slopes was done by Dourson and Stara (1983) based on the animal, lethal-dose data of Weil (1972). The most frequently occurring slopes were within the range of 6 to 8 (97 occurrences out of 490). With a 3 probit reduction this range corresponds to a dose reduction between about 3 to 2.

Approximately 92% of the slopes analyzed by Weil (1972) had values of greater than 3; for these chemicals a 10-fold decrease in dose would reduce a median response (i.e. 50%) by more than three probits, that is below the general range of 0.1% for this rather homogeneous animal population. For the remaining chemicals (that is, those with slopes of less than 3) a 10-fold reduction in dose would not achieve this concurrent reduction in expected response.

This analysis theoretically supports a 10-fold uncertainty factor to account for interhuman variability when estimating an RfD and the resulting criterion. Unfortunately, few human toxicity data are found to confirm this experimentally (Dourson and Stara, 1983), although the area is receiving increasing attention (Calabrese, 1985; U.S. EPA, 1986c; Hattis *et al.*, 1987). The basic research need in this area is to obtain additional data sets to verify this general pattern. Of course, human data would be preferred, but animal chronic toxicity data are also needed because the appropriate human data cannot be expected on a large number of chemicals. Additional statistical work could also be helpful especially if these other data sets are available.

B. Interspecies Adjustment

The factor of 10 has been used to estimate a comparable human NOAEL from animal data. It has been suggested previously that this factor of 10 approximates the mg/kg/day dose difference between experimental animals and humans based on the assumption that species are equally sensitive to the effects of the toxin on a dose/unit surface area (Dourson and Stara, 1983). If the underlying assumption of dose equivalence among species per unit of surface area is correct, the factor of 10 also incorporates a margin of safety that varies as does the size of the experimental animal species used as the basis of the risk assessment. For instance, with rats (rat to man dose per surface area difference of about 6), a 10-fold reduction in mg/kg b.w. dose would underestimate the appropriate level by a factor of about 2. With mice (mouse to man dose per surface area difference of about 13), this 10-fold dose reduction would actually predict a higher level than appropriate by about 1 to 2.

However, the validity of this assumption may depend on whether the parent compound or one of its metabolites is the toxic moiety and also on whether detoxification mechanisms varying across species. In the usual case, the metabolic rate of most experimental species is higher than that of the human. Thus, if the detoxification mechanism is similar between the experimental species and man, it would be expected that the susceptibility to a "parent" toxin would be reduced in the experimental species as compared to man due to the greater rate of detoxification. If, however, the toxin is a metabolite, this same higher metabolic rate would generally make the experimental species more sensitive than the human, again if the detoxification mechanism is similar.

The basic research need in this area of uncertainty is comparative human and animal toxicology and pharmacokinetics, with emphasis on the quantitation. Some data of this type have been developed for drugs (U.S. EPA, 1984). Moreover, Andersen and associates (Ramsey and Andersen, 1984; Clewell and Andersen, 1985; Andersen *et al.*, 1987) have published a series of experimental works on comparative pharmacokinetics for chemicals of environmental concern, emphasizing physiologically-based modeling. This work is also expected to sharpen the extrapolation of animal toxicity data to the case in humans.

C. Adjustment for Partial Lifetime Studies

Several investigators have compared toxicity data among various exposure durations, for example Weil and McCollister (1963), Weil *et al.* (1969) and McNamara (1976). These data can be used to determine ratios between subchronic and chronic effect levels, which in turn are useful as a basis for an uncertainty factor to adjust subchronic effects levels when chronic data are absent.

The dose adjustment factor of 10_S, to account for estimating an RfD from a subchronic effect level (if a chronic effect level is unavailable), is fairly well supported by these comparisons (Dourson and Stara, 1983). Approximately 96% of these ratios are below a value of 10. However, the average subchronic to chronic NOAEL or LOAEL ratio is approximately 2, which indicates that this factor of 10_S on the average also incorporates a margin of safety. Very little work exists that compares differences in effect levels between even shorter durations. (For an exception see the work of Weil *et al.*, 1969.)

From a toxicological point of view, these data indicate that unless contaminant-specific data are available, it seems reasonable to employ a 10-fold uncertainty factor to account for differences between subchronic and chronic effect levels. However, these data are only now being subjected to rigorous statistical analysis, and more experimental work is being collected to verify this general trend.

D. Lack of Optimal Data

Weil and McCollister (1963) also compared LOAELs with NOAELs for a chemical after either subchronic or chronic exposure. The term Weil and McCollister used for the LOAEL was the minimum effective dose; the term they used for the NOAEL was the maximum no ill effect dose.

These data can also be used to determine a ratio. For example, a ratio of 3 indicates that the LOAEL found after subchronic or chronic exposure is 3-fold greater than the corresponding NOAEL for a particular chemical. An analysis of these ratios indicates that all chemicals tested by Weil and McCollister (1963) had values of 10 or less. Of these ratios 96% have values of 5 or less (Dourson and Stara, 1983).

These data support the use of the adjustment factor of generally 10 to account for estimating an RfD from a LOAEL if a NOAEL is unavailable (U.S. EPA, 1986b). Other choices for this uncertainty have been made, however. For example, Weil (1972) suggested an additional 5-fold reduction in dose when estimating a corresponding NOAEL from a LOAEL.

V. SUMMARY

The assessment of health risk by way of criteria development, and ultimately the management of risk by standard setting, is composed of several steps. The appropriate use of uncertainty factors in deriving an RfD is only one of these steps. Despite the apparent arbitrary nature of uncertainty factors, such factors have theoretical and in some cases experimental support. A consideration of the precision of these factors leads one to conclude that values other than those based on order-of-magnitude (e.g., 100) such as 64 or 144 are generally inappropriate. These latter factors, while perhaps equally accurate when compared the 100-fold factor in relationship to the known variability of biological processes, are clearly not consistent with the precision associated with these 10-fold factors and resulting RfDs.

Rigorous statistical analysis is being conducted on the data that support these uncertainty factors; as important, additional data are being obtained in each area. These analyses and data should yield health risk assessments that are more credible by reducing the overall uncertainties inherent in this process.

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