

NOVEL METHODS FOR THE ESTIMATION OF ACCEPTABLE DAILY INTAKE

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This paper describes two general methods for estimating ADIs that circumvent some of the limitations inherent in current approaches. The first method is based on a graphic presentation of toxicity data and is also shown to be useful for estimating acceptable intakes for durations of toxicant exposure other than the entire lifetime. The second method uses dose-response or dose-effect data to calculate lower CLs on the dose rate associated with specified response or effect levels. These approaches should lead to firmer, better established ADIs through increased use of the entire spectrum of toxicity data.

INTRODUCTION

Toxicological data are basically of three types: quantal, continuous or graded. Quantal data specify the number of animals affected as a function of dose rate (e.g., mg/kg bw/d) and usually are given only for a single type of effect. The numbers of animals with tumors or that die from a chemical exposure are examples of quantal data. These data are often reported as an incidence (percent response) and, thus, can be used to construct a dose-response curve. Continuous data represent the change in some measured value of a biological indicator as a function of dose rate. Organ weights, triglyceride levels in the liver and serum enzyme measurements are examples of effects that are usually recorded as continuous data. Continuous data can also be used to construct a dose-effect curve. Graded data specify the form or severity of adverse effects as a function of dose rate, often without reference to the number of animals

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2. Key words: ADI, dose effect, dose response, dose severity, health risk assessment, less-than-lifetime risk assessment, NOEL.

3. Abbreviations: ADI, acceptable daily intake; AEL, adverse-effect level; bw, body weight; CL, confidence level; EPA, U.S. Environmental Protection Agency; FDA, Food and Drug Administration; FEL, frank-effect level; LOAEL, lowest-observed-adverse-effect level; LOEL, lowest-observed-effect level; NAS, National Academy of Sciences; NOAEL, no-observed-adverse-effect level; NOEL, no-observed-effect level; NOFEL, no-observed-frank-effect level; WHO, World Health Organization.

affected or to a continuous measure of one parameter. Graded data are often presented as categories (liver necrosis, lung lesions) or as judgments of severity. Fatty infiltration of the liver, single-cell liver necrosis and liver necrosis are an example of a sequence of severity judgments. These data are often considered by pathologists to be biologically important but do not lend themselves easily to statistical testing nor to the construction of dose-response or dose-effect curves.

Current methods for estimating human health risks from exposure to threshold-acting pollutants in water or food (Bigwood, 1973; Kokoski, 1976; Vettorazzi, 1976, 1980; EPA, 1980; Stara et al., 1981) are based on the types of available toxicity data as described above. These methods generally consider only chronic or lifetime exposure to individual chemicals and estimate a single, constant daily intake rate of toxicant that is low enough to be considered safe or acceptable, thus the term "Acceptable Daily Intake" or ADI.

The purpose of this text is to illustrate (1) a revised approach to estimating ADIs, using all toxicity data, that includes methods for partial-lifetime assessment and (2) novel methods for ADI estimation using quantal or continuous toxicity data. The development of these methods is described more fully in EPA (1984a,b), Stara et al. (1985a,b) and Crump (1984).

REVISED APPROACH USING ALL TOXICITY DATA

Health risk assessments generally require evaluation of several types of toxicity data (quantal, etc.) derived from studies of varied quality with varied endpoints and using several different species, different doses and different exposure durations. This variety often makes health risk assessment extremely difficult. Therefore, it is valuable to have all such toxicity data displayed simultaneously, if possible.

A graphic method is presented for this purpose. After thorough evaluation of the literature, toxicity data on a particular chemical might be summarized by four variables: (1) human-equivalent dose rate (mg/d), (2) human-equivalent exposure duration (yr), (3) ranking of effects and (4) study quality and usefulness. In this discussion, human-equivalent doses were calculated from animal doses by dividing the animal dose in mg/kg/d by the cube root of the ratio of human weight (70 kg) to animal weight in kg (w)— $(70/w)^{1/3}$ —and multiplying the resulting dose by the assumed human body weight of 70 kg. All data on exposure duration are expressed in years of equivalent human exposure. This number is found by dividing the experimental exposure duration by the species lifespan and then multiplying this fraction by the commonly assumed average human lifespan of 70 years. These simple conversions allow construction of a dose-duration graph in which all observed effects from all available studies can be compared on an approximately equal basis (Fig. 1). These conversions are presented for illustrative purposes; other approaches that allow for comparison of parameters among studies could also be applied.

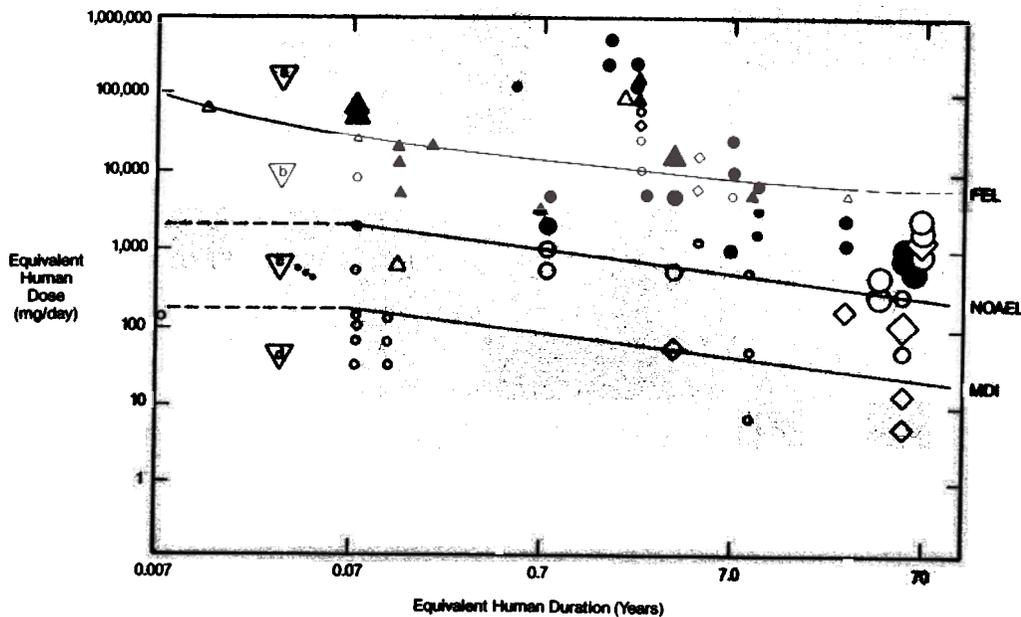


FIGURE 1. Effect-dose-duration plot of all relevant human and animal oral toxicity data for methoxychlor. Effect levels indicated by symbols are defined in Table 1. Animal doses have been converted by a body surface area factor to approximate the equivalent human dose. Dose durations are divided by the appropriate species lifespan to yield a fraction, which when multiplied by 70 yr (the assumed average human lifespan) gives the corresponding position on the x-axis. Study usefulness is denoted by symbol size (see text). The dose axis is divided into areas expected to cause either: (a) gross toxicity and death, (b) adverse effects, (c) nonadverse effects or (d) no effects.

The toxicity data from all studies (including human) are assigned to categories based on the severity of the observed effects in the case of graded data, or on the statistical significance in the case of quantal or continuous data. Note that in the latter case, the classification of quantal or continuous toxicity data into severity categories represents a loss of information. (This loss could be prevented by adding a third dimension of percent response or change in effect onto Figure 1.) These severity categories (Table 1) include NOELs, NOAELs or FELs as in a published methodology (EPA, 1980), with the addition of AELs and NOFELs to more completely describe all toxicity data. In this revised ranking, the terms LOEL and LOAEL of the EPA (1980) are replaced by the more general term AEL. Note that at any particular duration, the lowest-observed AEL is the LOAEL.

To facilitate construction of the graphic display of these data, each of the severity of effect levels described above is represented by a unique symbol (Table 1); the size of the symbol represents a scientific judgment by several toxicologists of the quality of the study and its usefulness to risk assessment (with larger size denoting better quality or usefulness).

TABLE 1
Various Effect Levels Used in Figure 1 and Their Definition

Effect Level ^a	Symbol	Definition ^b
		Frank-effect level. That exposure level which produces unmistakable adverse effects, such as irreversible functional impairment or mortality, at a statistically or biologically significant increase in frequency or severity between an exposed population and its appropriate control.
AEL	●	Adverse-effect level. That exposure level at which there are statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.
NOFEL	Δ	No-observed-frank-effect level. That exposure level at which there are no statistically or biologically significant increases in frequency or severity of frank effects between an exposed population and its appropriate control. Experimenters may or may not have looked for other adverse effects.
NOAEL	○	No-observed-adverse-effect level. That exposure level at which there are no statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control. Effects are produced at this level, but they are not considered to be adverse.
NOEL	◇	No-observed-effect level. That exposure level at which there are no statistically or biologically significant increases in frequency or severity of effects between the exposed population and its appropriate control.

^aListed in order of decreasing severity.

^bAdverse effects are considered to be functional impairment or pathological lesions that may affect the performance of the whole organism, or that reduce an organism's ability to respond to an additional challenge (EPA, 1980).

After all available toxicity data are graphically represented, a smooth boundary line is estimated (in Fig. 1, the line has been fitted by eye). This line represents, for any given time, the highest NOAEL for which no lower AEL is observed. Interpolation along this NOAEL curve can be performed to determine the NOAEL for any desired partial-lifetime exposure. To obtain a corresponding acceptable intake, the NOAEL would be divided by an uncertainty factor. Since the boundary line is hypothesized to represent the highest average human NOAEL for any given time, an uncertainty factor of 10 is suggested and accounts for the expected intraspecies variability in response to the toxicity of a chemical (in lieu of chemical-specific data). Both the choice of the highest NOAEL line (without lower AELs) and the suggested uncertainty factor of 10 are consistent with (and a logical extension of) previously established scientific principles of the EPA (1980), the FDA (Kokoski, 1976) and NAS (1977, 1980) in the use of effect levels and uncertainty factors to estimate ADIs. Using the above method, an ADI can also be derived for lifetime exposure, or an acceptable intake can be derived for any exposure that is represented within the data set. Extrapolation of the highest NOAEL line from subchronic studies to estimate an ADI might be performed if sufficient data are available to justify confidence in the line. Where potential for bioaccumulation of the toxicant, cumulative damage or decreased resistance to the toxic effect of the chemical is indicated, an additional

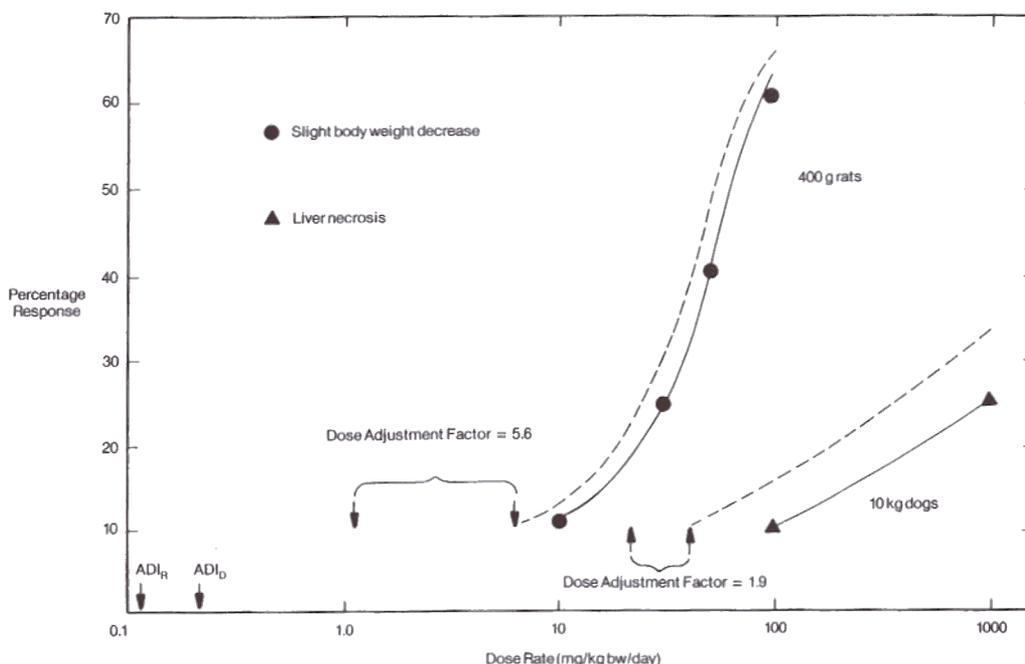


FIGURE 2. Hypothetical dose-response data for slight body weight decrease (●) or liver necrosis (▲) in rats and dogs, respectively. Solid lines indicate hypothetical data; dashed lines represent lower 95% CLs. An ADI has been estimated from the dog data (ADID) using a dose adjustment factor of 1.9 applied to the lower 95% CL and a 100-fold uncertainty factor. An ADI has been estimated from the rat data (ADIR) using a dose adjustment factor of 5.6 and a tenfold uncertainty factor. See text for additional explanation.

uncertainty factor of 10 should be considered, as suggested in the present methodologies for ADI estimation from subchronic data (Dourson and Stara, 1983). (However, in these situations, health risk assessment endpoints other than ADIs have also been considered [WHO, 1972]).

As a result of the inherent uncertainties regarding the shape of the curve, extrapolating from the observed data back to shorter durations of exposure where data are missing is usually not considered justified. Acceptable intakes for exposure durations shorter than that of the first data point might instead be set at the same level as that for the first data point. Since the duration of exposure for this data point encompasses all shorter durations, this procedure is recognized to be generally conservative. In some cases it is anticipated that data will not be of sufficient quality or quantity to construct a dose-duration graph or that the data when graphed will not yield patterns useful for estimating the NOAEL line. In these cases it is recommended that the ADI line not be estimated.

NOVEL APPROACH WITH QUANTAL OR CONTINUOUS TOXICITY DATA^{*}

Traditionally, NOAELs have been defined for quantal endpoints that have nonzero background incidences by choosing an experimental dose level that does not contribute to a statistically significant increase in the incidence of adverse effects when compared to that of a control group. In parallel, NOAELs have been defined for continuous data by choosing an experimental dose level that does not constitute a significantly different mean value for a parameter indicating an adverse effect when compared to a mean value for a control group.

Two limitations are inherent in this approach. The first limitation is that a dose-related trend in a parameter may suggest a deviation from the control incidence or mean value at an intermediate dose level that is not statistically significant. This dose would be treated as a NOAEL. Especially when experimental groups are limited to small sample sizes and, subsequently, conclusions are extrapolated to large populations, this statistically nonsignificant response could have biologically significant consequences.

The second limitation applies to the choice of dose levels. The response incidence or mean parameter measurement is expressed as the presence or absence of a statistically significant effect at discrete intervals (i.e., the experimental doses). The probability of response at a dose level between a LOAEL and a NOAEL is not addressed, possibly leading to considerable underestimation of the threshold dose, especially if doses are widely spaced.

The approach suggested here is not subject to these limitations because it uses the entire dose-response or dose-effect curve. For example, when there are studies that provide quantal (incidence) data or continuous data for effects that are considered to be adverse, this approach results in a more complete use of the available data through the construction of a dose-response or dose-effect curve, respectively. These curves allow both the evaluation of the slope and the estimation of risk above the chemical's estimated threshold level. Note that neither of these issues is addressed by the present methods.

ADIs can be calculated from dose-response curves by defining an adverse effect as a risk level of more than a certain percentage above background, such as 10%. In this paper, 10% is used in the examples because many of the mathematical models in current use agree well at estimated risks in this range and because the better studies have sufficient numbers of doses and animals per dose to measure this level directly. The lower 95% CL of the dose associated with this risk is then calculated and divided by an uncertainty factor. A similar value could be identified for continuous data and might be based on the upper limit of the normal range for the parameter being measured if this limit has been defined. When such normal ranges cannot be identi-

^{*}See also Crump, 1984.

fied, a relative percent change compared to the control group is suggested. For consistency, this percent change might also be 10%.

When quantal data are available, the dose-response relationship might be estimated by the Weibull model as outlined by Crump (1984):

$$P(d) = c + (1-c)[1 - \exp(-ad^k)]$$

where:

- P(d) is the probability of an effect at dose d,
- c is the incidence or probability of response in the control group ($0 \leq c \leq 1$),
- d is the dose, and
- a and k are nonnegative constants with $k \leq 1$.

The Weibull model is suggested because it is reasonably flexible (two free parameters) and yet is simple. However, the choice of model is expected to have little effect on the ADI value because of the expected model agreement in the risk range of 10%.

Since experience in applying dose-effect models to continuous data is limited, the suggested dose-effect relationship for such data is based on the supposition that measurements in an animal group are normally distributed. The continuous power model as outlined by Crump (1984) might be used for these calculations:

$$m(d) = c + b(d - d_0)^k$$

where:

- m(d) is the expected measured response at dose d,
- c is the average response in the control group,
- d is the dose,
- d_0 is the estimated threshold dose and
- b and k are constants.

CLs for the dose-response relationships for both quantal and continuous data might be based on the distribution of the likelihood ratio statistic as outlined by Crump and Howe (1983).

Using these models, the lower 95% CL can be calculated for the dose corresponding to a specified risk level, for example, 10% excess risk over background (for quantal data) or for the dose that corresponds to a 10% relative change in the expected value of the measured variable relative to the mean value in the control group (continuous data). To calculate an ADI, the dose associated with this lower 95% CL is adjusted by a chemical-specific, species adjustment factor or, as in the case of Figure 1, the cube root of the animal-to-human bw ratio. Uncertainty factors ranging together between 10 and 100 are then used to divide this adjusted value to yield the ADI. (These factors are based on an analysis of the areas of uncertainty remaining between the adjusted lower 95% CL and the ADI [see also EPA, 1984a]. These factors are similar in scope to the uncertainty factors currently used to estimate ADIs [Dourson and Stara, 1983].) (The first uncertainty factor of 10 is interpreted to account for the expected variability in the

general human population to the toxicity of the chemical. This uncertainty factor is consistent with previous EPA guidelines (EPA, 1980) as well as other guidelines (e.g., FDA [Kokoski, 1976], WHO [Vettorazzi, 1980] and NAS [1977, 1980]). The second uncertainty factor between 1 and 10 is thought to be necessary because the adjusted 95% CL corresponding to 10% response is considered to represent a LOAEL rather than a NOAEL. The use of this variable uncertainty factor is also consistent with previous guidelines (EPA, 1980). In practice, the choice for the value of this variable factor should depend on both the severity of the adverse effect (i.e., more severe effects yield a larger factor [EPA, 1980]; and the slope of the dose-response or dose-effect curve (i.e., flatter slopes also yield a larger factor). For example, a choice for this variable uncertainty factor of 1.0 should be associated with both a minimal adverse effect and a steep dose-response or dose-effect curve.

In estimating the ADI, when multiple studies that report multiple adverse endpoints are available, the data set providing the most appropriate estimate must be chosen. The first step in this process is to delete from consideration all studies that are considered inadequate as a result of experimental design or incomplete reporting of results, or that are not comparable to other studies on the basis of the number of animals used, parameters measured, etc. Next, the lower 95% CLs on the dose rate are calculated for each data set, and the corresponding estimated ADIs are then obtained by applying the appropriate species-dose conversions and uncertainty factors. From the estimates thus derived, the lowest one might be the most appropriate to represent the ADI, because it represents "in theory" the critical toxic effect.

An example of this procedure is given in Figure 2, which is a hypothetical plot of the percentage of rats responding with a slight bw decrease of 5% versus dose rate or the percentage of dogs with liver necrosis versus dose rate. Hypothetical responses are indicated by solid lines; lower 95% CLs on the dose rate are shown as dashed lines. The lower 95% CLs of the dose rates at a 10% response are adjusted by dividing by the cube root of the ratio of body weight between humans and rats or dogs, i.e.,

$$\left(\frac{70 \text{ kg}}{W_R \text{ OR } W_D} \right)^{1/3}$$

Note, however, that the specific adjustment factor will be based on available data. The adjustment factor chosen here is only for illustrative purposes, although it is similar in magnitude to the expected specific adjustment factors.

For rats weighing 400 g, this value is 5.6; for dogs weighing 10 kg, it is 1.9. To estimate an ADI from the rat data (shown in Figure 2 as ADI_R), the adjusted lower 95% CL is divided by a tenfold uncertainty factor to account for the expected variability in the general human population response to the toxicity of a chemical in lieu of specific data, and an additional 1.0-fold factor because the effect is both minimally severe and has a steep dose-response slope. Thus, the total uncertainty factor is 10. To estimate an ADI from the dog data (shown in Figure 2 as ADI_D), the adjusted lower 95% CL is divided by a tenfold uncertainty factor to account for the expected human variability,

as before, and an additional tenfold uncertainty factor because the effect is more severe than that of the previous study and the slope of the dose-response curve is flatter. Thus, the total uncertainty factor is 100.

DISCUSSION

The primary advantage of the graphic method is that it provides a mechanism for viewing all the data simultaneously, resulting in an integrated profile of a compound's toxicity. In addition, exposure duration-response trends, if present, are clearly delineated, providing a possible strategy for estimating acceptable intakes for partial-lifetime exposures.

The graphic method relies on a simple severity ranking system for data presentation (i.e., NOEL, NOAEL, NOFEL, AEL and FEL). Obviously with such a simple system, effects within a given category (e.g., all AELs) may not be identical, nor is it assumed that they are. Indeed, the critical toxic effect is often a function of exposure duration. In these cases, the effects within a given category will not be the same across time. However, the change in critical effect over duration (and, therefore, the change in effects within a category) is only of secondary regulatory importance. Since the NOAEL line is based on NOAELs of critical effects from all durations, the approach is consistent with the regulatory objective of guarding against any adverse effect. Moreover, although assumptions are needed in the process of extrapolating dose and duration from animal studies to their human-equivalent counterparts, this graphic method should enable regulatory scientists, at a glance, to judge (1) the overall strength of evidence of toxicity, including the change of target organ as duration of exposure changes, if desired, (2) data gaps wherever they appear and (3) the resulting regulatory options that may be derived from such data.

The proposed methods for estimating the 10% dose-effect or dose-response levels for continuous and quantal data offer a number of advantages when compared with traditional methodologies. Several of these advantages have been previously discussed (Crump, 1984). For example, with this new approach, both the slope of the dose-response curve and the number of animals used in an experiment can affect to some degree the estimation of the ADI when quantal or continuous toxicity data are available. This approach is unlike that of the present methodologies in which the slope of the dose-response curve and number of animals tested have little direct bearing on the resulting ADI. Another advantage of this novel method is that it can also estimate the health risk for suprathreshold exposure levels, which might be useful for cost-benefit analysis.

In sum, the novel methods described for estimating ADIs use more of the available toxicity data than the current methodologies and offer a consistent approach for possibly estimating health risks for less-than-lifetime toxicant exposure. They also address to some degree several of the criticisms of the current approach such as use of dose-response slopes and the number of animals tested in defining NOELs. More

work is needed, however, before either or both of these novel methods are accepted as the *status quo*. Moreover, discussions with scientists familiar with the assumptions and limitations of these concepts should result in improvements. In the interim, these methods might be considered ancillary to rather than substitutes for the present methods in establishing safety endpoints for toxic chemicals.

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