Risk Assessment for Noncarcinogenic Chemical Effects

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The fundamental assumption that thresholds exist for noncarcinogenic toxic effects of chemicals is reviewed; this assumption forms the basis for the no-observed-effect level/safety-factor (NOEL/SF) approach to risk assessment for such effects. The origin and evolution of the NOEL/SF approach are traced, and its limitations are discussed. The recently proposed use of dose–response modeling to estimate a benchmark dose as a replacement for the NOEL is explained. The possibility of expanding dose–response modeling of noncarcinogenic effects to include the estimation of assumed thresholds is discussed. A new method for conversion of quantitative toxic responses to a probability scale for risk assessment via dose–response modeling is outlined.

Introduction

Risk assessment for toxic chemicals that do not induce carcinogenic or mutagenic effects has traditionally been based on the fundamental assumption that there are levels of exposure for such agents below which adverse health effects will not occur, even if exposure is long term (Figure 1). Biological underpinnings for this "threshold" concept include the fact that the toxicity of many chemicals is manifest in exposed subjects only after the depletion of a known physiological reserve and that the biological repair capacity of many organisms can accommodate a certain degree of damage by reversible toxic processes.[1,2] The objective of risk assessment for noncarcinogenic chemical effects has thus been to establish a "threshold dose" below which adverse health effects are not expected to occur.

The NOEL/Safety Factor Approach

The classical approach to risk assessment for noncarcinogenic chemical effects is commonly believed to have originated with the setting of safe levels of food additives. Establishment of the acceptable daily intake (ADI) by the formula

$$\text{ADI} = \frac{\text{NOEL}}{\text{SF}}$$

evolved from the work of Lehman and Fitzhugh,[3] who wrote about "attempts to predict the safety of a proposed food additive to humans in terms of toxicity in animals." Here NOEL stands for no-observed-effect level, a term derived from what Lehman and Fitzhugh called "that dose just short of causing an observable effect," and SF stands for safety factor, a quantity applied in order to allow for uncertainties in extrapolating from animals to humans.

The term NOEL as used today may be defined loosely as the highest experimental dose level (or human exposure level) at which adverse effects are not observed (Figure 2). Generally, individual NOELs are established for individual toxic effects. The original SF proposed by Lehman and Fitzhugh[3] was 100, which represented a factor of 10 to allow for differences in sensitivity to the test agent in humans as compared to experimental animals (interspecies), and a factor of 10 for variation in sensitivity within the human population (intraspecies). The 100-fold safety factor gained acceptance over time.[4,5]

Modifications to the NOEL/SF Approach

In 1977, the National Research Council's Safe Drinking Water Committee[6] recommended several changes in the setting of ADIs. It proposed that the NOEL be expressed on a body weight basis (mg/kg body weight) rather than a dietary

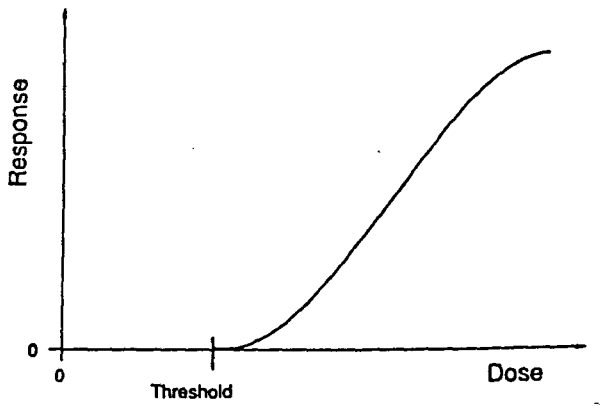

FIGURE 1. Threshold concept.

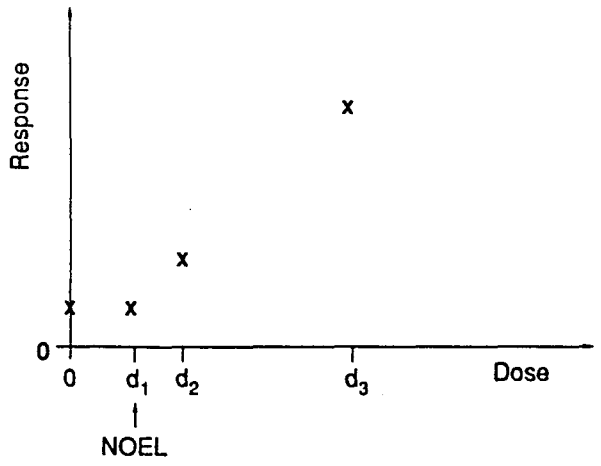

FIGURE 2. No-observed-effect level (NOEL).

percentage basis (mg/kg diet). The Committee also endorsed the reduction of the 100-fold safety factor to only 10-fold if the NOEL was based on human data but recommended that the safety factor be increased to 1000-fold if toxicity data were inadequate to establish a NOEL.

Although the NOEL/SF approach has been and still is popular in regulatory toxicology, it is subject to serious scientific limitations. Smaller, less sensitive experiments tend to yield larger NOELs and, hence, larger ADIs than larger, more sensitive experiments.[7,8] Safety factors of 10-fold for intraspecies and interspecies conversions are somewhat arbitrary and cannot be guaranteed to provide absolute assurance of safety[9] (Figure 2).

In recognition of the above limitations, the U.S. Environmental Protection Agency (EPA) recently recommended several changes in the setting of acceptable levels for toxic effects other than carcinogenicity.[10,11] Instead of calculating an ADI, the EPA[10] recommended that a "reference dose" (RfD) be established according to the expression

$$\text{RfD} = \frac{\text{NOAEL}}{\text{UF} \times \text{MF}}$$

where: NOAEL = no-observed-adverse-effect level (meaning failure to achieve statistical significance)

UF = uncertainty factor as opposed to a safety factor

MF = modifying factor to be used in cases of scientific uncertainties about the data

The UF is a composite of 10-fold factors for interspecies and intraspecies uncertainties, uncertainties in extrapolating from subchronic to chronic effects, and uncertainty associated with the use of a LOAEL (lowest-observed-adverse-effect level) in cases when a NOAEL cannot be identified.[11] In addition to these sources of uncertainty, the National Research Council's Committee on Toxicology[12] routinely considers differences in route of exposure in determining the size of appropriate safety factors; the EPA does not.

If the level of a toxic agent to which humans are already exposed or are likely to be exposed is known or can be estimated, and the degree of safety associated with such a level is desired, then the application is simply reversed. In such a case, the potential risk to humans is assessed by calculating a margin of safety (MS) defined by

$$\text{MS} = \frac{\text{NOAEL}}{\text{HEL}}$$

where: HEL = human exposure level

Explicit Risk Estimation

Although the potential for dose–response modeling of both quantal and quantitative noncarcinogenic toxic responses was illustrated by the Safe Drinking Water Committee of the National Research Council,[13] it did not recommend changing from the NOEL/SF approach for the assessment of noncarcinogenic hazards. Recently, however, efforts have been made in the area of statistical modeling of such adverse health effects in order to exploit the shape of the dose–response curve and to account for the precision of estimates of acceptable levels of chemicals.

The concept of a benchmark dose (BD) has been proposed as a replacement for the NOAEL.[8,9] The BD is defined as a statistical lower confidence limit on the dose producing some predetermined, relatively small increase in response rate (risk), such as 0.01 or 0.1 (Figure 3). The BD is promoted as representing a toxicologically relevant quantity because it is defined in the spirit of a LOAEL, although it is not usually an experimental dose level. It makes appropriate use of the sample size, as reflected in the magnitude of the confidence limit. The BD exploits the shape (steepness)

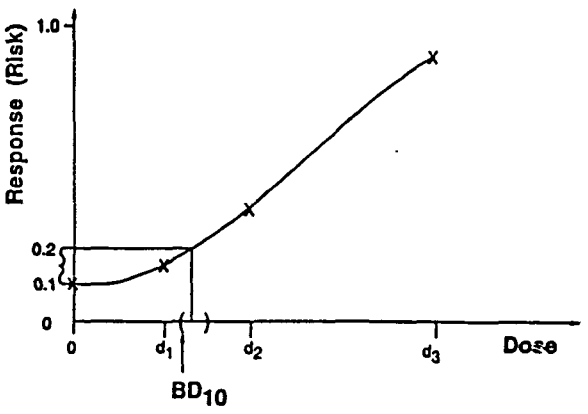

FIGURE 3. Benchmark dose (BD).

of the dose–response curve in the experimental range; however, it does not depend strongly on the particular statistical model used because the model is not followed below the 1% response level.

Crump[9] has recommended redefinition of the ADI according to

$$ADI = \frac{BD}{SF}$$

Gaylor[8] proposed that the BD could be used to determine the size of the SF needed to achieve a desired low level of risk. In this sense, Gaylor argued that setting an acceptable level of a chemical by dividing a BD by a SF was equivalent to linear, low-dose extrapolation. EPA is currently proposing the BD/SF approach for setting levels of reproductive and developmental toxicants.

Modeling Quantal Responses

The primary effort in dose–response modeling of quantal toxic responses has been for reproductive and developmental adverse effects.[14–17] By way of illustration, Chen and Kodell[16] employed a Weibull dose–response model for prediction of toxic effects and a beta-binomial probability distribution to account for intralitter correlation of fetuses. For quantitative risk assessment, they recommended linear extrapolation below the BD-LED01, i.e., the BD that corresponds to 1% excess risk above background risk. Thus, the dose–response model was proposed specifically to improve the estimation of a BD, rather than as a tool for extrapolation far below the data range.

In an effort to translate the threshold concept underlying the NOEL/SF approach to the more quantitative approach offered by statistical modeling, Kodell et al.[18] proposed a threshold model for reproductive and developmental toxicity. If a threshold is assumed to exist, it can be estimated by way of statistical dose–response modeling (Figure 4). However,

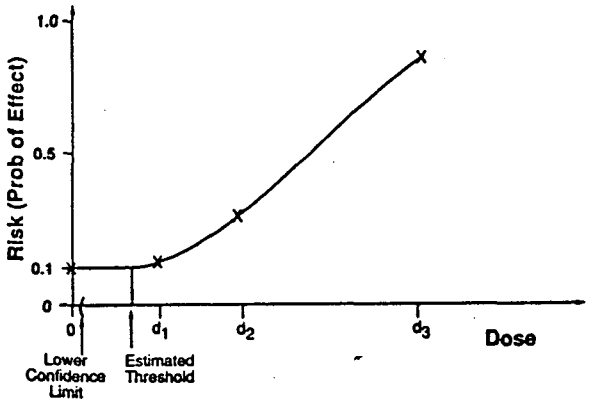

FIGURE 4. Estimation of threshold.

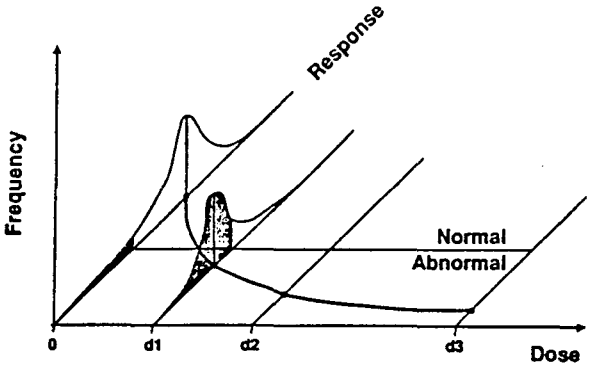

FIGURE 5. Modeling quantitative (continuous) responses.

as pointed out by Kodell et al.,[18] such modeling cannot of itself be used to establish the existence or nonexistence of true thresholds. Whereas, the lower confidence limit on an assumed threshold might often be zero even when a nonzero threshold value is estimated in the best-fitting model, simply including the possibility of a threshold in a dose–response model will tend to give higher BDs than excluding the possibility of a threshold altogether. Even with estimated thresholds, safety factors are necessary to account for uncertainties in interspecies and intraspecies differences.

Modeling Quantitative Responses

Unlike traditional, quantal, teratologic responses, many toxic responses are quantitative in nature. Some examples include organ and body weights, survival time, clinical chemistry and hematology measurements, neurological effects, and behavioral effects. For risk estimation, these response variables must be transformed to a probability scale. Then a BD can be calculated and used for risk assessment.

A fundamental approach to risk assessment for quantitative responses has been proposed by Gaylor and Slikker[19] and further developed by Chen and Gaylor.[20] In short, the process involves four basic steps. First, a dose–response relationship for the expected value of a given quantitative end point must be postulated. Next, a statistical distribution of individual measurements about the dose–response curve (e.g., normal) must be assumed. Third, an abnormal or adverse range of the distribution for the given end point must be defined, e.g., a low percentage point, perhaps 1%, of the distribution in control subjects. Finally, the previous three steps are combined to calculate the probability (risk) of an adverse effect as a function of dose (Figure 5). As with the quantal response models discussed above, the dose–response model for quantitative responses is used to improve the estimation of a BD at the lower extreme of the data range; it is not for extrapolation below that point.

Summary

Classical risk assessment for noncarcinogenic chemical effects has assumed that chemical levels associated with zero risk can be identified, i.e., it has been threshold-based. This is evidenced by the use of NOELs as representing safe levels for particular test species. Sources of uncertainty with respect to characterizing human risk based on animal data have been recognized from the beginning, as indicated by the use of safety factors in converting animal NOELs to acceptable human exposure levels. The passage of time has seen the incorporation of additional sources of uncertainty into safety factors used in the risk assessment process. In addition, a movement has begun toward explicit risk estimation for both quantal and quantitative toxic responses through the use of dose–response modeling. This modeling has had as its purpose the estimation of a BD to replace the NOEL, as opposed to low-dose extrapolation per se. Some models have included the possibility of a threshold, in the spirit of the NOEL approach, in order to exploit underlying biological theory, where justified.

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