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Dose – response models to understand toxicodynamics for pollutants in ecosystems

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ABSTRACT

The low-dose effect and non-monotonicity hypotheses challenge key concepts in eco-toxicology and risk assessment, and also the possibility to predict the effects of a chemical at low levels of exposure from its effects at higher levels of exposure. Low-dose effects and Non-Monotonic Dose-response Curves (NMDRC) provides situations to understand impacts for toxicological risk assessment paradigm. Dose response (DR) models are helpful to understand impacts of pollutants in ecosystems.

Keywords-dose; DR models; pollutants; NMDRC; ecosystem

1. INTRODUCTION

The dose–response relationship, or exposure–response relationship, describes the change in effect on an organism caused by differing levels of exposure (or doses) to a stressor (usually a chemical) after a certain exposure time [1]. The U.S. Environmental Protection Agency has developed extensive guidance and reports on dose-response modeling and assessment, as well as software [2]. Dose–response relationships generally depend on the exposure time and exposure route (e.g., inhalation, dietary intake); quantifying the response after a different exposure time or for a different route leads to a different relationship and possibly different conclusions on the effects of the stressor under consideration. A dose–response curve is a simple X–Y graph relating the magnitude of a stressor (e.g. concentration of a pollutant, amount of a drug, temperature, intensity of radiation) to the response of the receptor (e.g. organism under study). The response may be a physiological or biochemical response, or even death (mortality), and thus can be counts (or proportion, e.g., mortality rate), ordered descriptive categories (e.g., severity of a lesion), or continuous measurements (e.g., blood pressure) [3]. A number of effects (or endpoints) can be studied, often at different organizational levels (e.g., population, whole animal, tissue, cell).

Dose response relationships describe the effect on an organism caused by differing levels of exposure (or dose). Dose levels are usually expressed in mg/kg body weight of the test animal for solids and mg/m^3 or parts per million for aerosols/vapours. These levels can be plotted on a graph against the response. The dose response curve is a valuable tool to understand the levels at which substances begin to exert adverse effects and the degree of harm expected at various levels. In some cases, it is the logarithm of the dose that is plotted on the X axis, and in such cases the curve is typically sigmoidal, with the steepest portion in the middle. Biologically based models using dose are preferred over the use of log(dose) because the latter can visually imply a threshold dose when in fact there is none. Dose response curves can show a number of points including: (i) the 'no effect level' where no effect occurs or no effect is detectable; (ii) the threshold dose of the substance – the level at which the effect starts to occur; and (iii) the levels at which the effect occurs in a set percentage or all of the test animals. Particular points on dose response curves include: (i) LD_{50} (Lethal dose, 50%) the dose that kills 50% of the test population; (ii) LC_{50} (Lethal concentration, 50%) the concentration that kills 50% of the test population; (iii) TD_{50} (Toxic dose, 50%) the dose that causes a particular effect in 50% of the test population; and (iv) TC_{50} (Toxic concentration, 50%) the concentration that causes a particular effect in 50% of the test population. A commonly used dose-response curve is the EC_{50} curve, the half maximal effective concentration, where the EC_{50} point is defined as the inflection point of the curve (Fig. 1).

Statistical analysis of dose-response curves may be performed by regression methods such as the probit model or logit model, or other methods such as the Spearman-Karber method. Empirical models based on nonlinear regression are usually preferred over the use of some transformation of the data that linearizes the dose-response relationship [4]. Dose–response curves can be fit to the Hill equation (biochemistry) to determine cooperativity. The concept of linear dose-response relationship, thresholds, and all-or-nothing responses may not apply to non-linear situations. A threshold model or linear no-threshold model may be more appropriate, depending on the circumstances. A recent critique [5] of these models as they apply to endocrine disruptors argues for a substantial revision of testing and toxicological models at low doses. Dose-Response Assessment is to understand analysis of the relationship between the total amount of an agent administered to, taken up or absorbed by an organism, system or (sub)population and the changes developed in that organism, system or (sub)population in reaction to that agent, and inferences derived from

such an analysis with respect to the entire population. Dose-Response Model is mathematical relationship (function) that relates (predicts) a measure of an effect to a dose.

2. LINEAR & NON-LINEAR DOSE –RESPONSE ASSESSMENT

Risk assessment of chemicals in food is based on the paradigm of hazard identification, hazard characterization, exposure assessment and risk characterization. Hazard characterization involves evaluation of the relationship between the level of exposure and an adverse response in standardized animal toxicological studies. For threshold effects, the No-Observed-Adverse-Effect-Level (NOAEL) or the Benchmark Dose (BMD) in the study can be used to derive (by application of an uncertainty factor) a health-based guidance value (e.g. ADI or TDI). The ADI / TDI represent an exposure level at which it can be concluded with reasonable certainty that no adverse effects will occur in a human population exposed to the chemical for their lifetime. In the case of a NMDR curve the traditional NOAEL / BMDL point of departure arguably cannot be used to derive a health based guidance value. This reflects the uncertainties regarding identification of an exposure level at which it can be concluded with reasonable certainty that the risk for the exposed population is minimal / non-existent. An additional issue is the possibility that there may be critical windows of exposure for the induction of adverse health effects. It may not therefore be possible to identify a health-based guidance value that is appropriate for the lifetime of the entire population.

Non-linear dose response assessment has its origins in the threshold hypothesis, which 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, and the threshold of toxicity is where the effects (or their precursors) begin to occur. 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. If the "mode of action" information (discussed above) suggests that the toxicity has a threshold, which is defined as the dose below which no deleterious effect is expected to occur, then type of assessment is referred to by the Agency as a "non-linear" dose-response assessment. The term "nonlinear" is used here in a narrower sense than its usual meaning in the field of mathematics; a nonlinear assessment uses a dose-response relationship whose slope is zero (i.e., no response) at (and perhaps above) a dose of zero. A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no statistically or biologically significant increases are seen in the frequency or severity of adverse effect between the exposed population and its appropriate control population. The reference dose (RfD) is an oral or dermal dose derived from the NOAEL, LOAEL or BMDL by application of generally order-of-magnitude uncertainty factors (UFs). These uncertainty factors take into account the variability and uncertainty that are reflected in possible differences between test animals and humans (generally 10-fold or 10x) and variability within the human population (generally another 10x); the UFs are multiplied together: 10 x 10 = 100x. If a LOAEL is used, another uncertainty factor, generally 10x, is also used. In the absence of key toxicity data (duration or key effects), an extra uncertainty factor(s) may also be employed. Sometimes a partial UF is applied instead of the default value of 10x, and this value can be less than or greater than the default. Often the partial value is ½ log unit (the square root of 10) or 3.16 (rounded to 3-fold in risk assessment). Note, that when two UFs derived from ½ log units are multiplied together (3 x 3) the result is a 10 (equal to the full UF from which the two partial factors were derived). Thus, the RfD is determined by use of the following equation: RfD = NOAEL (or LOAEL or BMDL) / UFs.

If the "mode of action" information (discussed above) suggests that the toxicity does not have a threshold, then this type of assessment is referred to by the Agency as a "linear" dose-response assessment. In the case of carcinogens, if "mode of action" information is insufficient, then linear extrapolation is typically used as the default approach for dose-response assessment (for more detailed information. The slope of this straight line, called the slope factor or cancer slope factor, is use to estimate risk at exposure levels that fall along the line. When linear dose-response is used to assess cancer risk, EPA calculates excess lifetime cancer risk (i.e., probability that an individual will contract cancer over a lifetime) resulting from exposure to a contaminant by considering the degree to which individuals were exposed, as compared to the slope factor. Thus, Cancer Risk = Exposure x Slope Factor. Total cancer risk is calculated by adding the individual cancer risks for each pollutant in each pathway of concern (i.e., inhalation, ingestion, and dermal absorption), then summing the risk for all pathways [6-8]. A similar term, know as inhalation unit risk (IUR), is used to assess inhalation risks, where the exposure-response relationship refers to concentrations in the air.

3. DOSE-RESPONSE MODELS

Dose-Response Models (DR models) are mathematical models used to characterize the relationship between dose and response for a given set of scientific data. Mathematical models consist of three basic components; assumptions used to derive the model, a functional form for the model and parameters that are components of the functional form. For example, the simplest DR model is a linear model to describe a continuous response. For this model, the key components are assumptions: mean response is proportional to dose; functional form: $R(D)=\alpha+\beta \bullet D$ where R(D) is the mean response

as a function of dose, denoted D and parameters: α is a parameter describing the mean response in the control (unexposed) group and β is a parameter describing the mean change in response per unit dose. DR models range from very simple models, such as the linear model described above, to extremely complicated models for which the eventual functional form cannot easily be expressed as a single equation (e.g., biologically-based DR models).

Models can also be linked, meaning that one model could describe part of the DR process while another describes the remainder of the process. For example, in most cases for chemical carcinogenesis, tissue concentration is more closely linked to cancer risk than administered dose. Given data on dose, tissue concentration and tumor response, one can use a toxicokinetic model to relate dose to tissue concentration and use a multistage cancer model to relate tissue concentration to response. The two models combined are needed to describe the DR relationship. DR models may incorporate other information into the model form. Age and time-on-study are commonly used in dose-response modeling, but other factors such as species/strain/human ethnicity, gender, body weight, etc. have also been used to expand the utility of DR models. Dose-Response Models (DRM) can be described by six basic steps with a variety of options at each step (Table 1). The first four steps are aimed at the analysis of the data available for DRM, which will be referred to as DR analysis. DR analysis provides the linkage of a model to DR data for the purposes of predicting response to a given dose or predicting dose from a given response. The last two steps deal with implementation and evaluation of the analysis results.

4. RISK MANAGEMENT PERSPECTIVES

The potential use of the estimates from DRM can, from a risk management perspective, give an improved characterization for decision making by providing information about what happens above the safety level (magnitude and types of health impacts); showing risks benefits from different regulatory actions; give the decision maker a 'more-than-one-point' appreciation of the data; promoting consistency in decisions, if appropriate adjustments are made for differences in effect, effect level, species, and study design; and finally, DRM should promote an iterative interaction with risk managers on a continuous basis.

5. CONCLUSION

Ecological risk assessments can be used to predict the likelihood of future effects (prospective) or evaluate the likelihood that effects are caused by past exposure to stressors (retrospective). Integration of *in vitro* effects into a model for description of *in vivo* responses is presently not feasible, but some authors have presented examples in which the concentrations used in *in vitro* cultures are extrapolated to external exposure (doses) *in vivo*. Quality of data for studies showing NMDRC should be assessed as for any other studies. The statistical evidence and mechanistic plausibility of NMDRC should be analyzed before concluding that a dose-response is non-monotonic. DRM is a major part of the hazard characterization within the risk assessment paradigm and has been used in the past for both the characterization of DR relationships observed in animal bioassays as well as for the low dose extrapolation of incidences of adverse effects to the range of human exposure levels. DRM, as used for informing public health decisions about chemical exposures.

6. REFERENCES

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Fig. 1: The dose-response curve

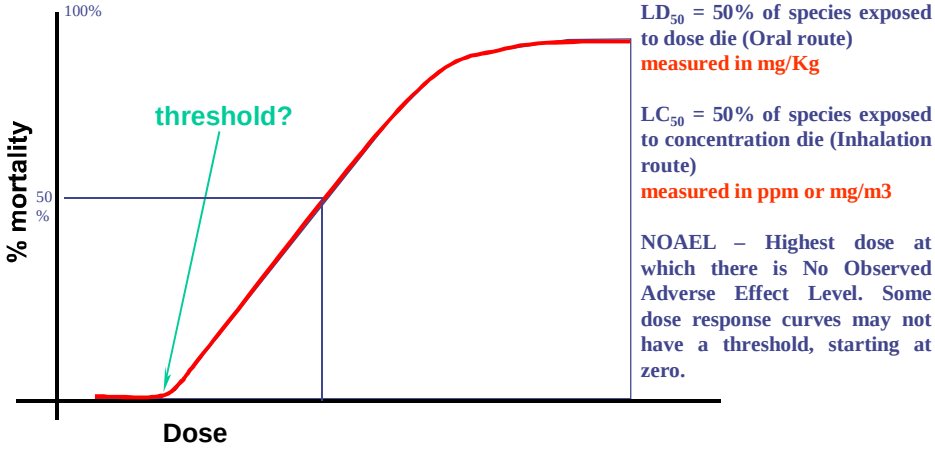

Table 1: Six basic steps with a variety of options at each step describing Dose-Response Models (DRM)

	Step	Description	Options
1	Data selection	Determine the response to be modeled and select appropriate data	Endpoint, quality, sample size, utility, availability
2	Model selection	Choose the type of model to be applied to the data	Endpoint, data availability, purpose
3	Statistical linkage	Assume what statistical distributions describe the response	Endpoint, data type, model choice, software availability
4	Parameter estimation	Combine the first three steps in an appropriate computer program to obtain estimates of the model parameters	Linkage function, Software availability, variance
5	Implementation	Use the estimated model parameters and the model formula to predict response/dose as needed	Outputs, target selection, model predictions, BMD, Direct extrapolation
6	Evaluation	Examine the sensitivity of the resulting predictions to the assumptions used in the analysis.	Model comparison, uncertainty