Title

Linear Low dose Extrapolation for Cancer Risk Assessments: Sources of Uncertainty and How They Affect the Precision of Risk Estimates

Abstract

Due to the uncertainties and variabilities surrounding input measurements, estimates of carcinogenic risk using linear low dose extrapolation should be presented in a manner that reflects the precision of the estimated risk. The precision of the risk estimate can be no better than that for the least certain input parameter into the model. Presentation of additional significant figures in risk estimates may introduce false precision, and thereby mislead risk managers as they are considering possible risk management options.

Purpose:

1)To discuss the factors affecting confidence in reporting estimates of cancer risk to risk managers and the public using the linearized multistage model (LMS) or other linear-at-low-dose extrapolations methods.

2) To propose a consistent and scientifically defensible procedure for expressing calculated risk estimates.

3) To characterize the degree of scientific confidence in the risk estimate by describing the limits of scientific knowledge and sources of uncertainty in the risk estimate.

Hypothesis:

Given the many uncertainties in the hazard, dose response and exposure measurement inputs, cancer risk estimates should reflect the precision of input parameters. Presentation of a quantitative cancer risk estimate should include qualitative information regarding the uncertainties, limitations and assumptions of the estimate.

Background:

The reliability of a risk assessment is contingent upon the validity of its components. Input values and estimates used in the risk characterization process include descriptions of hazard, dose response and exposure. The source and characteristic of each major input parameter vary in certainty from empirical, highly descriptive data (e.g., well designed, multidose studies) to assumptions, defaults and the choice of models (e.g., use of the Residential SOPs in the absence of chemical and scenario specific exposure data). This concept is presented in figure 1 below. The precision of any risk assessment can only be as good as its least precise component. For example, in figure 1, a very precise definition of the dose response for a chemical may be coupled

with the use of models or default assumptions. The resulting risk estimate reflects the precision of the default assumptions despite the very detailed understanding of dose response. Cancer risk estimates can be calculated to mathematically precise values with multiple significant figures, but those significant figures are not biologically relevant and do not reflect the actual state of knowledge concerning the cancer risk presented by the exposure scenarios of concern. Excess significant figures are misleading and are often misperceived and misused as representing the actual number of excess cancer cases that would occur in the exposed population. In other words, currently, a "stand-alone" numerical cancer risk estimate does not convey the degree of uncertainty in that estimate. Decision makers need to know about the extent of uncertainty and overestimation or underestimation of the risk estimate.

Generic Sources of Uncertainty in Input Parameters

Greater emphasis needs to be placed on communicating the quality of the available data and strengths and weaknesses of each component of the assessment (hazard, dose response, exposure). More information will convey the degree of confidence in the results of the risk assessment. In other words, when presenting the numeric risk estimate, several features of the estimate also needs to be communicated. These features include identifying and characterizing the uncertainties of each component.

Hazard Identification:

The practice of accepting the results of the rodent bioassay as presumptive evidence of a carcinogenic effect in humans at any dose introduces an uncertainty in the form of an overly conservative assumption. That is, this practice represents a choice that is more likely to result in overestimating than underestimating human risk. In most cases, the carcinogenic response(s) observed in the animal bioassay(s) occur(s) at doses in excess of those anticipated to be encountered by humans. The response in rodents is extrapolated below the observed level for application to anticipated human exposure scenarios. Further, in the absence of mode/ mechanism of action data, an assumption of linearity is made.

Interspecies Extrapolations - The major underlying assumption for all toxicity studies is that the toxicity observed in animal studies is applicable for the prediction of the likely response in to humans and that animal carcinogens will also be human carcinogens. Further site concordance is not assumed or required. These assumptions introduce further uncertainty into the assessment and the direction and magnitude of the bias that is introduced are not quantifiable.

Intraspecies Extrapolations - For estimating the carcinogenic potential of a chemical, data developed in the most sensitive strain of a species of animal or the most sensitive species are usually selected. This assumption may overestimate the actual cancer risk with some chemicals.

Dose Response Assessment:

Low Dose Linear Extrapolation Model - The cancer bioassays performed in rodents typically include two doses (to a lesser extent three or more doses) which are often several fold higher than doses expected in typical human exposure scenarios. Often, positive tumor production occurs only at the highest dose. The selection of data for estimation of carcinogenic potential from the most sensitive strain or species of animals tested and is designed to be conservative. Therefore, in some cases, the potency estimate (Q*) is often based on a few equivocal data points. These default assumptions contribute to the uncertainty in risk assessment**.** In addition, the final potency estimate (Q_1*) typically computed for cancer risk is a statistical upper bound estimate (95% upper confidence limit) on the slope of the low dose linear portion of the curve and is considered to represent an upper bound on the chemical's carcinogenic potential. These underlying assumptions, again, are designed to overstate rather than understate human risk.

Exposure Assessment:

Often, because chemical specific data are not available, specifying the population that might be exposed and estimating the magnitude, duration and timing of the doses of the chemical to which people might be exposed involves employing reasonable assumptions or modeling surrogate data. As with hazard identification and dose response assessments, exposure assessment may involve a variety of often conservative assumptions which would lead to likely overestimation of the carcinogenic risk, especially when using models or defaults. However, the magnitude of overestimation of exposure may vary from scenario to scenario and may not be quantifiable due to the lack of adequate data.

Figure 1. Sources of uncertainties in risk assessments. The input parameters can vary from well conducted human toxicity studies with definitive supporting animal studies (Certain) to an exposure scenario which employs only model assumptions (Less Certain). The precision of the risk assessment is only as good as its least precise parameter.

	CONFIRMED STUDIES	INCOMPLETE STUDIES	ASSUMPTIONS/ EXTRAPOLATIONS
TOXICITY EFFECTS	-Main studies -Mechanistic Studies -Epidemiologic Studies	-Surveys -Range-Finding -Literature Studies	-Interspecies extrapolation -Structure Activity Relationship -Route-to-Route Extrapolation
DOSE RESPONSE	-Closely spaced dosing -Multiple dosing	-Single Dose -Widely spaced dosing	-Toxicity Equivalent Factor -Benchmark Dose -Linear Low Dose -Potency Estimates
EXPOSURE	-Monitoring Studies -Biomonitoring for occupational and residential exposure	-PHED (surrogate data) -DRES	-Default Assumptions -Exposure Factors/algorithms -Models -Activity Scenarios

CERTAIN LESS CERTAIN

Changing the way OPP expresses Carcinogenic Risk Estimates

Currently, OPP expresses carcinogenic risk in scientific notation with a leading value expressed to the nearest hundredth (e.g., 2.16×10^{-x}). However, given the lack of precision in the risk estimates from the sources listed above as well as others, OPP proposes to express risk estimates as both the numeric cancer risk estimate (two significant figures) and the recommended rounded risk estimate with a discussion of the appropriateness of rounding to the nearest order of magnitude for regulatory purposes. The explanation should include the strengths and weakness of each facet of the risk assessment and their likely impact on the outcome of the assessment. Impacts should include uncertainties as well as direction and magnitude of the likely change in the estimate relative to the likely actual value. The presentation of the risk estimate in terms of relative order of magnitude with the accompanying characterization of the input parameters will simplify the risk management process by removing the focus from refining an estimated value beyond the limitations of the available data. The characterization will convey the judgments of the science to the risk manager with the information needed to evaluate the impact of the various input parameters on the outcome and also make her/him aware of how far the risk estimate is likely to deviate from the real world outcome.

Examples of Expressing Estimates of Risk

Figure 2. Presentation of an estimate such as 2.6×10^{-6} or 4.2×10^{-6} may create an inappropriate level of confidence in the risk manager with regard to the precision with which the risk can be defined. A more appropriate presentation would be to include a recommendation to round the estimate upward or downward to the nearest (integral) order of magnitude on a log scale. In the following four examples, the risk estimate would be more appropriately expressed as 10^{-6} or between 10^{-6} to10^{-5}, depending on the overall level of confidence of the estimate. In addition, qualitative information about the uncertainties of each component needs to be communicated which serves to convey the level of concern and the degree of confidence in the numeric risk estimate.

Example	Calculated Risk Estimate	Suggested Rounded Risk	Uncertainty Analysis
Chemical A	**2.6×10^{-6}**	**10^{-6}**	**The upper bound cancer risk estimate (10^{-6}) does not exceed the level of concern for this chemical as it applies to occupational exposures for a number of scenarios.** There is **high** confidence in toxicology database with well conducted long term animal studies, mechanistic studies and reliable human epidemiologic studies and dose response data. Structure-activity relationship shows that this chemical is very closely related to four other chemicals, all of which produce the same type of tumor in rats and mice. There is **high** confidence in the Q_i* (cancer potency estimate) **Medium** confidence in the exposure estimate. There were no human monitoring data, or chemical dissipation data. Default assumptions were used in all occupational exposure scenarios and most likely overestimates exposure (Pesticide Handlers Exposure Database)**.**

Chemical B	**4.6 X 10^{-6}**	**10^{-6} to 10^{-5}**	**The upper bound cancer risk estimate (10^{-5}) exceeds the level of concern for excess lifetime cancer risk to the general population including infants and children.** The toxicological database is of **medium** confidence. Although two independent, well conducted studies in two strains of mice showed tumor production, only the highest dose tested was positive, and the dose was 100-fold higher than anticipated doses to be encountered by humans. There were equivocal support for carcinogenicity in the mutagenicity studies. All rat studies were negative. The only other evidence is that Chemical A is structurally related to two other chemicals which induce the same type of tumors in mice. There is **medium to high** confidence in the dietary exposure assessment because data refinements such as percent crop treated information and anticipated residues were used to present a more realistic risk picture (Dietary Risk Evaluation System).
Chemical C	**4.6 X 10^{-6}**	**10^{-6}**	**The upper bound cancer risk estimate (10^{-6}) does not exceed the level of concern for excess lifetime cancer risk to the general population including infants and children.** **The overall cancer risk assessment is most likely to be an <u>overestimation</u> of human risk to Chemical C because the risk estimate is based on limited scientific information with high uncertainty (e.g. high to low dose and animal to human extrapolation toxicity models; unrefined dietary risk estimates representing the high end of exposure in food; and bounding estimates for occupational/residential exposure using surrogate data).** The confidence is the toxicology database is low to medium. There are no human studies but in two chronic studies in male and female mice, there were increased incidences of liver tumors only at the maximum tolerated doses. The mutagenicity data set is of low confidence because it neither supports or contradicts inferences about cancer. The acute and chronic dietary exposure analysis is considered highly conservative (health protective) because tolerance level residues with 100% crop-treated for all commodities was assumed in the estimates. There were no site and chemical specific exposure data available and occupational/residential exposure assessments were made using Pesticide Handlers Exposure Database (PHED) surrogate data for all scenarios.

Chemical D	**2.1 X 10^{-6}**	**10^{-6}**	**There is an overall confidence is the risk estimate is high based on high quality, reliable data. The upper bound cancer risk estimate (10^{-6}) does not exceed the level of concern for excess lifetime cancer risk to the general population including infants and children.** **The toxicological database is of high confidence. Epidemiological studies demonstrates evidence of cancer in humans. The bioassays (4) in rats and mice were conducted for the exposure routes of concern (dermal and oral) had positive tumor data in a dose related manner. The mutagenicity studies supported the carcinogenicity studies. Chemical D is structurally related to two other chemicals which induce the same type of tumors in rats and mice.** **There is high confidence in the dietary exposure assessment because a highly refined analysis was conducted using percent crop treated information and anticipated residues using field trial data and FDA monitoring which approximates the actual dietary exposure.** **There is high confidence in occupational/residential exposure estimates because the assessment includes quantified exposure to individuals (e.g. biomonitoring data for all scenarios as well as dermal absorption studies).**

Conclusion

Expressing risk estimates using more significant figures than would be supported by the input parameters, implies a greater precision and is misleading to decision makers. OPP proposes to express cancer risk estimates as two significant figures with a discussion of the appropriateness of rounding up or down to the nearest (integral) order of magnitude for regulatory purposes. The discussion would include characterizing the uncertainties by summarizing the limitations of scientific knowledge and the key model assumptions and indicating the potential impact on the risk estimate (e.g., do the model assumptions and/or parameter uncertainties taken as a whole overestimate or underestimate the risk?). By communicating the risk estimates to more closely approximate the level of confidence, the risk manager can focus on important features of the assessment for evaluating whether risks are acceptable or unreasonable.