Comments from Dr. Small

Value of Information
(MJS)

When human health risk assessments include an explicit representation of uncertainty, the potential value of new information (VOI) can be estimated by its ability to reduce uncertainties that matter most to the assessment target. While methods for determining VOI are most commonly associated with the decision analysis literature in the context of informing management or regulatory decisions (Raiffa, 1968; Keeney, 1982; Winkler and Murphy, 1985; Finkel and Evans, 1987; Taylor et al., 1993; Clemen, 1996; Chao and Hobbs, 1997), there are many steps in a scientific assessment well before (or even without subsequent) decision support and decision making where VOI evaluations can be of benefit in characterizing current scientific knowledge and the potential for its improvement. ORD should integrate these methods into their current and ongoing assessments of dioxin toxicity.

When uncertainty in a scientific assessment is measured by the variance of model predictions, a first measure of VOI is the extent to which this variance might be reduced by new or additional data (e.g., Patwardhan and Small, 1992; Brand and Small, 1995; Abbaspour et al., 1996; Chao and Hobbs, 1997; Sohn et al., 2000; Bosgra et al., 2005; Cooke, 2009). The relative contribution of different model assumptions and parameter uncertainties to the variance of the estimated effect (e.g., the BMD, or the cancer slope factor) provides an indication of which of these uncertainties would be most beneficial to address. In addition, a VOI assessment considers the potential for the component uncertainties to be reduced, based on the feasibility, resource requirements (time and funding), and likelihood of success of the studies that would be needed to achieve the necessary improvement in scientific knowledge.

A scientific VOI study may also target a key classification inference that results from a risk assessment, for example, whether a compound is genotoxic. Assuming the current assessment leads one to assign an inconclusive probability to this outcome (e.g., between 10% and 90%, so that neither inference can be rejected with a high degree of confidence), then potentially valuable studies are those able to shift subsequent probabilities to high values (e.g., above 90, 95, or 99%) with a positive result (e.g, providing support for genotoxicity) and/or to low values (below 10, 5, or 1%) with a negative result.

To illustrate, Small (2008) presents a simple probability tree model (a “distributional approach”) for assessing genotoxicity based on studies of DNA damage response caused by naphthalene and its metabolites. In the proposed studies a series of isogenic cell lines deficient in various DNA metabolism pathways are used to characterize the DNA damage responses caused by the targeted compounds. Following results from the cultured cells, mice deficient in the specific DNA damage responses would be exposed to naphthalene. Possible inferences are identified based on the assessed sensitivity and selectivity of study results to the genotoxicity of naphthalene. Study outcomes considered include: i) DNA damage responses in the isogenic cells; ii) increased numbers of stable DNA adducts in the DNA repair deficient mouse lung; and iii) heightened Clara cell toxicity in the DNA repair deficient mouse lung. Illustrative results are presented as follows:

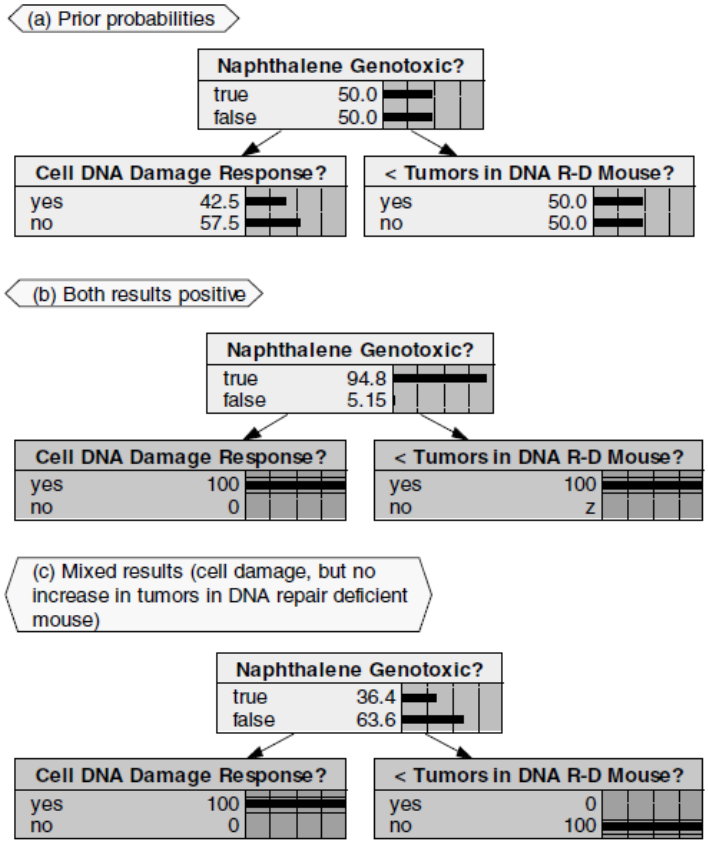

Fig. 5. Illustrative consideration of selected experimental results for naphthalene Study IV (outcomes assumed independent, prior probability of genotoxicity set to 0.5, and sensitivities and selectivities chosen by author solely for illustration of methodology): (A) Prior probability before study; (B) Positive outcomes for both study results; and (C) Positive results for cell DNA damage, but negative results for increased tumors in DNA repair-deficient mouse.

As noted, the results shown above are intended solely to demonstrate the way in which study results can be combined to support or refute targeted inferences.

Even when the event tree method is only used to delineate the set of possible outcomes and relationships among steps and assumptions in the risk assessment (i.e., mode of action; dosimetry measures for exposure; the mathematical form of the dose-response relationship; the experimental data set(s) used to fit the relationship; and the procedure used for interspecies extrapolation) *without the assignment of probabilities to the tree branches*, key assumptions and the experiments needed to support or refute them can still be identified. These will typically involve elements of the assessment that, depending on their resolution, effectively restrict the set of possible outcomes to either a positive or a negative inference regarding the endpoint of the risk assessment. Establishing a procedure of this type will allow the Agency to put in place a more formal mechanism for identifying, conducting, and integrating the results of key studies for future assessments.

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