Comments on Uncertainty Analysis

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General observations about uncertainty

- Quantitative human health risk assessment is an <u>inherently uncertain process</u>, not only because of the uncertainties in the information available
    - e.g., relevance of animal data to humans
    - exposure assessment in epidemiological studies
- but also because of uncertainties in what is necessary to achieve the stated goals
    - An ongoing exposure sufficiently protective to not result in significant adverse effects over lifetime of exposure to the most sensitive element of the population (*without being excessively or unnecessarily protective*).
    - All the more so, when the goal is a (*accurate*) quantitative expression of risk
- NRC, in part, acknowledges this: "…there will always be uncertainties surrounding the final estimates because of incomplete knowledge about the systems involved."
    - However, there are more reasons for this uncertainty:
        - because of lack of knowledge about the relationship between the systems providing the available data and the full range of the human population of interest;
            - e.g., animal - human

          and
        - because of lack of knowledge about the human population of interest – both in general and in relationship to a given endpoint and a given mode of action.
            - e.g., who will be exposed?
            - what are the relevant sensitivities in the putatively exposed population?

My perspective as a State risk assessor <u>(not merely a risk assessment user)</u>

- Several states with active environmental programs develop their own risk assessments for chemicals **from the ground-up**
    - This is independent of the IRIS process (**but obviously must be cognizant of the IRIS process)**
    - States develop their own risk assessments because:
        - States cannot necessarily wait for the IRIS process to address their immediate risk-based needs

        - State-specific chemical problems are not necessarily national problems that will engage the IRIS process
- Given this, it is critical for those States that engage in derivation of risk-based standards and guidelines - for which IRIS constitutes the gold standard – that the risk assessment process remain useable to the States and their practitioners for the development of defensible risk assessments
    - Despite the more limited resources available to the states
- This might lead to a conclusion that State-initiated risk assessments will have to operate at a different level of complexity given the apparent direction that NRC is urging for IRIS
    - **However,** the goals of IRIS and State risk assessments are essentially identical
        - At a minimum, that the bottom-line be **complete** and **transparent**
            - Complete – all relevant research included and appropriately considered
            - Transparent – all steps in the decision-making process are clearly presented so that they can be evaluated and critiqued.
        - States will be able to accomplish these goals with the addition of some, but not necessarily all of the complexity in the treatment of uncertainty called for in the NRC report
    - But at the same time, EPA should consider for its own purposes what will be gained in terms of the utility of a given risk assessment in freighting the process with overly deliberative and prescriptive requirements for the treatment of uncertainty specifically and for the overall risk assessment process in general
        - To what extent is the depth of uncertainty analysis presented in the NRC report a practical and useful use of resources, and to what extent is it an intellectually and academically interesting exercise that may add detail, but little utility to IRIS's addressing of uncertainty?
        - To what extent will such requirements actually reduce the inherent uncertainty in the metrics that EPA and States must derive?
        - To what extent will such requirements actually facilitate actions that protect public health?

How are estimates of uncertainty and variability used by users of IRIS assessments?

- Users of IRIS risk assessments (and those who develop risk assessments at the State level) use estimates of uncertainty and variability in **relatively straightforward ways**
    - Adjustments to PODs
        - These are practically limited to uncertainty factor adjustments
        - To the extent supported by data, these may not be limited to default values

- Pharmacokinetic adjustments can be estimated based on validated models and empirical inputs
    - Removing significant aspects of uncertainty
- Pharmacokinetic relationships between animals and humans
- Variability in pharmacokinetic relationships within the human population
    - Probabilistic (Monte Carlo) analyses of pharmacokinetic models
    - e.g., Stern (2005) : *A revised probabilistic estimate of the maternal methyl mercury intake dose corresponding to a measured cord blood mercury concentration*. Environ Health Perspect. 113:155-63.
- Data-based estimates of the distribution of default uncertainty factor adjustments (UFs)
    - e.g., Hattis et al. (2002). *A straw man proposal for a quantitative definition of the RfD.* Drug Chem Toxicol. 2002 Nov;25(4):403-36.
    - Martin et al. (2013*). Dispelling urban myths about default uncertainty factors in chemical risk assessment—sufficient protection against mixture effects?* Environ Health. 12:53.

- Non-quantitative assessments of study and overall confidence in the RfD/Cancer Potency
    - More useful as guidance to risk managers than as risk assessment tools *per se.*
- Presentations of inter-study variability in PODs and RfDs for a common endpoint providing information on the quantitative uncertainty in the dose-response for that endpoint
    - e.g.,

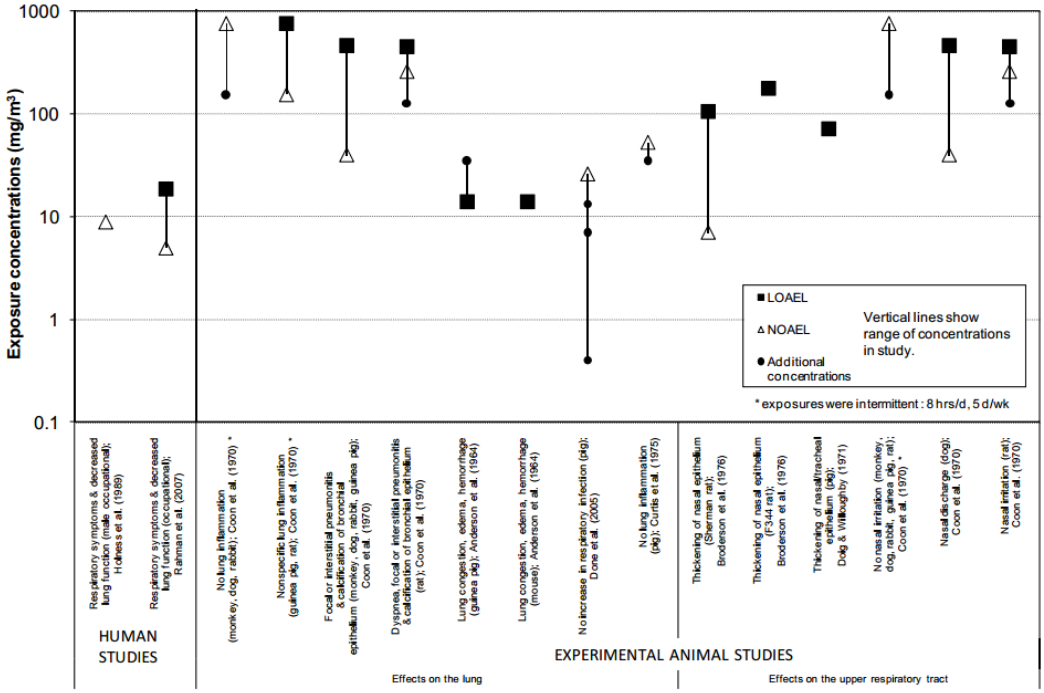
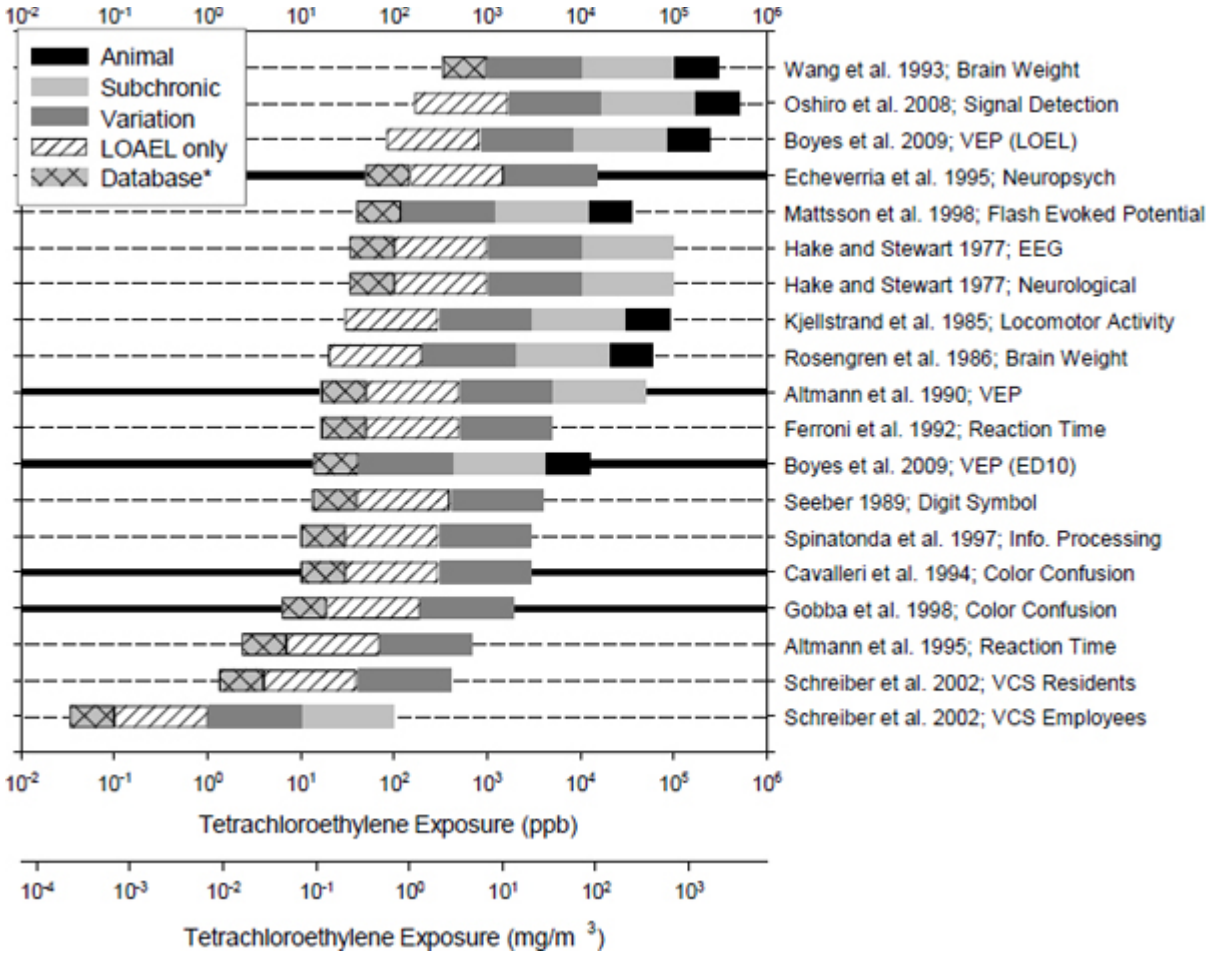


Figure 1-1. Exposure-response array of respiratory effects following inhalation exposure.



- Despite the quite detailed presentation in the NRC report, given the inherently uncertain nature of quantitative human health risk assessment, it is not clear how or to what extent more fine-grained analysis of uncertainty will make risk assessments more transparent or more useful.

Specific Comments on the treatment of uncertainty in the NRC report

- *Pg. 125 "…include a demonstration of variation in the final toxicity-value estimate under different assumptions, options models and methods."*
    - this is reasonable when these different assumption, etc. are equally plausible and/or equally useful. However, as an *a priori* requirement, it invites obfuscation and indecision.

- *Pg. 125 "…vertical integration of uncertainties over every stage of the assessment process, including*
    - ***the initial protocol design***
    - ***study identification and evaluation***
    - *dose response modeling*
    - *low-dose extrapolation*
    - *cross-species extrapolation*
    - *all other extrapolations"*
- Those stages in bold are fundamentally different in an epistemological way from the remainder - their uncertainty is conceptual rather than quantitative. Attempts to integrate their uncertainty with that of the other categories will open the process to large problems of subjective manipulation "supported" by unresolvable differences in philosophical stance.

- *Pg. 127 "Simple analyses or qualitative elucidation of various uncertainties – for example, due to plausible mechanisms – can be adequate especially when few data are available"*
    - I endorse the notion that H, M and L designations for various aspects of true uncertainty can convey adequate information without conflating different categories of knowledge/uncertainty

- *Pg. 128 "…present clearly two dose-response values in each …assessment: a central estimate…and a lower-bound estimate for a POD from which a final toxicity value is derived."*
    - There seems to be some confusion here, and elsewhere in the NRC report about the nature of the lower bound estimate from which the POD is derived. This is not a lower bound estimate of inherent risk in the sense of a judgment about the nature or relevance of the underlying toxicity data. Rather, this is simply the lower bound on the *fit* of the dose response model applied to the data in benchmark-dose modeling. It reflects only the fit of the data to the selected model (mostly in the low dose range) and has no relevance to the overall database of toxicity, or to the assessment of the relevance or nature of the endpoint.

        - Thus, defining the central tendency and upper bound risk estimates on this basis is misleading since the upper bound estimate reflects on the model fit and says nothing about the nature of the endpoint or the dose-response model chosen
        - It is not clear whether the emphasis on the central tendency in comparison to the upper bound estimate in the NRC report clearly grasps the limited nature of the differences between these two elements.

- Communicating uncertainty within the assessment document should be intuitive rather than exhaustive.
    - Good examples of such presentations are the ATSDR-type LOAEL/NOAEL figures for each potential endpoint that EPA has begun using in its IRIS documents for comparison across studies for related endpoints.
- And Fig. 7-6 in the current NRC report the displays the contribution of uncertainty factor adjustments to the relationship between LOAELs/NOAELs and RfDs across related endpoints

- *Pg. 129 "Another approach…is to conduct formal dose-response assessment only when the posterior probability that a human hazard exists exceeds a predetermined threshold, such as 50% (more likely than not likely that the hazard exists)."*
    - Even if the probability that a hazard exists is <50%, the extent of adverse outcome could still be large, and thus, the overall risk could be high. Restricting the reference value development to substances for which the probability of hazard is >50% would not address the extent of risk.