Beyond Science and Decisions: From Problem Formulation to Dose-Response Assessment
Case Study: Hypothesis-Based Weight of Evidence (Naphthalene as an Example)

May 28-30 in Northern Virginia

Abstract

Human health risk assessment consists of bringing to bear a large body of *in vitro*, animal, and epidemiologic studies on the question of whether environmental exposures to a substance are a potential risk to humans. The body of scientific information is typically less than definitive and often contains apparent contradictions. Often various possible conclusions about potential human risks may be drawn from the data and these may vary from very strong to tenuous. The task, therefore, is to communicate the uncertainties in the inferences from the data effectively, giving proper consideration to contrary data and alternative scientifically plausible interpretations. We describe an approach, Hypothesis-Based Weight of Evidence (HBWoE), to organize, evaluate, and communicate the large body of available relevant data on a given chemical, using naphthalene as an example. The goal for our use of the term "weight of evidence" (WoE) is broad in that we express the relative degrees of credence that should be placed in alternative possible interpretations of the naphthalene data and hypothesized carcinogenic modes of action, expressed in a way that shows how such credence is tied to specific scientific interpretations, considering consistencies, inconsistencies, and contradictions within the data set. Guided by the outcome of our WoE evaluation, we are conducting a dose-response evaluation of naphthalene exposure and neoplastic and non-neoplastic lesions, with the ultimate goal of deriving naphthalene toxicity values applicable to human health risk assessment that are consistent with an integrated evaluation of all realms of evidence for naphthalene (epidemiology, animal toxicology, mechanistic, and toxicokinetic). Our approach is to consider the applicability and limits on the animal responses – specifically the rat nasal tumors – to serve as a basis for estimation of potential human respiratory-tract cancer risk. We are doing this by considering the mode of action underlying the animal tumors seen in bioassays, including evaluation of the metabolic activation and detoxification of inhaled naphthalene as they depend on air concentration, as well as the nature, tissue locations, and dependence on tissue-dose of key precursor responses. Species differences in tissue dosimetry are used to evaluate whether parallel tissues in humans, or other tissues in the respiratory tract, will be subject to tissue doses that could prompt the key events of the apparent mode of action. The points of departure derived from rodent dose-response evaluations will be extrapolated to human equivalent concentrations through application of a rat/human PBPK model that describes cross-species dosimetry of the upper respiratory tract, lung, and liver.