2009 EPA Dioxin Workshop
Questions to Guide Panel Discussions

Session 1

Dose Metric
Considering all of the endpoints or target tissues, and species that EPA's dose-response modeling might evaluate, what are the best measures of dose (ingested, tissue concentrations, body burden, receptor occupancy, other surrogate) and why?

Developing Dose-Response Models from Mammalian Bioassays
How best can the point-of-departure (POD) be determined when the response range is incompletely characterized (i.e., high response at the lowes dose or low response at the highest dose; observed in several key TCDD studies)?

If considered to be biologically plausible, how can a threshold be incorporated into a dose-response function (e.g., for TCDD cancer data)?

How can non-monotonic responses be incorporated into the dose-response function?

Developing Dose Response Models from Epidemiological Studies
How can the epidemiological data be utilized best to inform the TCDD exposure-response modeling? Which epidemiological studies are most relevant?

Supporting Information
For those toxicological endpoints that are AhR-mediated, how would the receptor kinetics influence the shape of the dose-response curve? How would downstream cellular events affect the shape of the dose-response curve? How can this cascade of cellular events be incorporated into a quantitative model of dose-response?

Sessions 2, 3A, 3B, 4A and 4B

Key Study Selection
For this endpoint, what refinements should be made to the draft criteria for selection of key studies?

What are the specific effects of concern for human health for this endpoint?

Based on the draft criteria for selection of key studies, what are the key studies informing the the shape of the dose-response curve above the 'point of departure' (POD) and the choice of the POD for this endpoint?

Epidemiological Study Utility
How and to what extent do the epidemiological data inform the choice of critical effect?

How can the epidemiological data inform the quantitative dose-response modeling?

Animal Model Utility

Are there types of effects observed in animal models that are more relevant to humans than others? To what extent does information on mode of action (MOA) influence our choice of animal model (species, strain, sex)?

Supporting Information
Are there studies that establish a sufficient justification for departing from default procedures that address the shape of the dose-response curve below the POD under the cancer guidelines?

Are there studies that establish a sufficient justification for departing from EPA's default approaches for non-cancer endpoints?

To what extent can MOA information clarify the identification of endpoints of concern and dose-response metric for this endpoint? How can the cascade of cellular events for this endpoint be incorporated into a quantitative model of dose-response for either cancer or non-cancer endpoints?

Session 5

For cancer and non-cancer TCDD dose response assessments, EPA is interested in developing a quantitative uncertainty analysis addressing both parameter and model uncertainty, if feasible. Uncertainties will include, among others, choice of endpoint, underlying study uncertainties, choice of dose metric, interspecies extrapolations such as kinetic uncertainties, and choice of dose-response model, including threshold models. The EPA is currently examining techniques and tools for uncertainty analysis, including Bayesian and frequentist approaches.

Identification of Important Uncertainties

What are the major uncertainties pertaining to modeling the animal data?

Consider the dose metric (species or tissue specificity), vehicle of administration, exposure frequency, exposure duration, POD determination (e.g., BMR selection or NOAEL/LOAEL identification).

What are the major uncertainties pertaining to dose-response modeling below the POD?

Consider how receptor kinetics and downstream cellular event information might be used to bound the uncertainties associated with dose-response modeling below the POD.

What are the major uncertainties in cross-species extrapolation (e.g., half-lives, tissue distribution, toxicodynamics)?

Consider the primary species dosed with TCDD: mice, hamsters, rats, guinea pigs, and monkeys.

What are the major uncertainties pertaining to intra-human variability?

Consider what data sets would be useful to represent sensitive subpopulations.

What are other significant sources of uncertainty for the cancer and non-cancer assessments?

Considerations for Conducting Uncertainty Analysis

What data sets could be used to quantify uncertainties in cancer and non-cancer TCDD dose-response assessments?

Consider DLC dose-response data.

Consider MOA information.

What are the appropriate techniques for the TCDD dose-response uncertainty analysis?

What are the strengths and weaknesses of these approaches as applied to TCDD?