Annotated Bibliography of
Selected Recent Literature on Dioxin Related to Key Draft
Dioxin Reassessment Issues

Offered to the
Committee To
“Review EPA’s Assessment of the Health Implications of
Exposure to Dioxin”

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Introduction

Some of the important scientific issues relevant to the evaluation of the risk assessment presented in the U.S. EPA Draft Dioxin Reassessment include:

1. The use of a linear extrapolation from the point of departure for characterizing cancer risks.

2. The evidence supporting classification of TCDD as a human carcinogen and modeling of epidemiological data exhibiting SMRs less than 2.0 based on all cancer mortality.

3. The validity of the benchmark dose modeling methodology and the selection of a one percent response level (ED01) as the basis for estimating the point of departure for cancer and non-cancer risk characterization.

4. Exposure trends and the impact on the assessed “margin of exposure” (MOE).

Recent scientific literature and review papers addressing each of these topics are identified below. A few key points and questions on each topic are also presented.
Cancer Dose-Response – Mechanistic and Laboratory Animal Data

Suggested Reading


Dragan and Schrenk (2000) provide a relatively recent review of the animal carcinogenicity and mechanism data relevant to evaluating linear vs. non-linear approaches in the modeling of TCDDs (and other congeners’) cancer dose-response relationships.

The U.S. National Toxicology Program recently published four bioassays not covered in the Dragan and Schrenk (2000) review article. These consist of corn oil gavage studies in female Sprague Dawley rats: a) 2,3,7,8-TCDD, b) 2,3,4,7,8-pentachlorodibenzofuran, c) PCB-126, and d) a TEQ equipotent mixture study of all three compounds. Walker et al. (in press) provides an initial evaluation of the dose-response characteristics (on an intake dose, not body burden, basis) from these studies. All of the observed responses were highly non-linear (Hill model shape parameters >1), with clear no-effect levels for every neoplastic endpoint in each of the studies.

Other Papers For Consideration


Key Questions and Points

- Is EPA’s decision to use a linear, no-threshold extrapolation from a modeled point of
departure scientifically justified and consistent with supporting scientific data and
evaluations of that data described elsewhere within the Draft Reassessment? Examples of
statements within the Draft Reassessment on this point include:
  - “The more complex responses are more likely to assume a nonlinear shape.” [page 5-25,
    Part III],
  - “Toxic effects seen only at higher doses are presumably more likely to result from
    multiple cellular perturbations and are thus less likely to follow linear relationship.”
    [page 5-27, Part III]

- Is the series of complex, receptor-mediated events culminating in the biological expression
of dioxin’s effects consistent with a simple, linear dose-response extrapolation? These steps
include a multi-step receptor and cofactor mediated response (Ligand + AhR; Ligand-AhR +
ARNT; Ligand-AhR-ARNT + DRE [DRE I or DRE II]); binding of co-activators and co-
repressors; post-mRNA modifications and expression; protein-interactions and secondary
gene-expression events; ubiquitin deactivation of ligand-AhR-ARNT, and other steps.

- Is the knowledge of mechanism of action for carcinogenicity from TCDD including lack of
  genotoxic activity, promotional activity, interaction with hormonal factors, and lack of
tumor response in the absence of liver tissue injury, consistent with a linear, no-threshold
  approach to cancer risk assessment?

- Does the pattern of specific tumor responses observed in laboratory animals support the
  extrapolation to a human “all cancer” tumor response?
Occupational Cohort Cancer Epidemiology Review

Suggested Reading


This review provides a critical appraisal of the epidemiological studies of dioxin and cancer mortality patterns in occupationally exposed cohorts.

Key Questions and Points

• Has the EPA applied the well-known Hill Criteria in a weight-of-the-evidence assessment of the epidemiological data?

• Is EPA’s combination of all cancer mortality for the purpose of dose-response modeling a novel, unproven hypothesis or is it justified based on what is known of promoter-induced cancer? Do the animal bioassay data support this approach?

• Is quantitative modeling of “All cancer Mortality” with SMRs less than 2.0 scientifically justified? Are factors such as control for confounding and exposure reconstruction sufficiently robust to warrant quantitative modeling of weak associations?
Benchmark Dose Modeling Methodology

Suggested Reading


This paper examines the methodology used by the USEPA in the 2000 draft reassessment to estimate benchmark doses from data sets on continuous endpoints, presents an alternative approach that is more interpretable from a risk assessment point of view, and compares the results of the two approaches for key data sets.

Key Questions and Points

- Is the EPA’s use of the ED\(_{01}\) model of animal data scientifically justified in view of the types of dose-response information that is available?
Exposure Trends

Suggested Reading


These studies document the declines in exposure to and body burdens of dioxins in the U.S. Patterson et al. (2004) provide the most current available data on body burdens in the general U.S. population by age group. Their data and analyses highlight the importance of taking into account the changing historical levels of dioxin exposure when assessing dioxin risks.

Key Questions and Points

- Has the EPA based its margin of exposure conclusions on the most recent measurements of exposure and body burdens?