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, Y.P., and D. Schrenk. 2000. Animal studies addressing the carcinogenicity of TCDD (or related compounds) with an emphasis on tumour promotion. Food Addit Contam. 17(4):289-302.

Walker, N.J., P. Crockett, A. Nyska, A. Brix, M.P. Jokinen, D.M. Sells, J.R. Hailey, M. Easterling, J.K. Haseman, M. Yin, M.E. Wyde, J.R. Bucher, and C.J. Portier. In press. Dose-additive carcinogenicity of a defined mixture of "dioxin-like compounds". Environ Health Perspect.

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

Byrd, D.M., 3rd, D.O. Allen, R.L. Beamer, H.R. Besch, Jr., D.B. Bylund, J. Doull, W.W. Fleming, A. Fries, F.P. Guengerich, R. Hornbrook, L. Lasagna, B.K. Lum, E.K. Michaelis, E.T. Morgan, A. Poland, K.K. Rozman, J.B. Smith, H.I. Swanson, W. Waddell, and J.D. Wilson. 1998. The dose-response model for dioxin. Risk Anal. 18(1):1-2.

Limbird, L.E., and P. Taylor. 1998. Endocrine disruptors signal the need for receptor models and mechanisms to inform policy. Cell. 93(2):157-163.

Poland, A.D. 1996. Meeting report: receptor-acting xenobiotics and their risk assessment. Drug Metab Dispos. 24(12):1385-1388.

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

Cole, P., D. Trichopoulos, H. Pastides, T. Starr, and J.S. Mandel. 2003. Dioxin and cancer: a critical review. Regul Toxicol Pharmacol. 38(3):378-388.

> 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

Gaylor, D.W., and L.L. Aylward. 2004. An evaluation of benchmark dose methodology for non-cancer continuous-data health effects in animals due to exposures to dioxin (TCDD). Regul Toxicol Pharmacol. 40:9-17.

> 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

Aylward, L.L., and S.M. Hays. 2002. Temporal trends in human TCDD body burden: Decreases over three decades and implications for exposure levels. J Expo Anal Environ Epidemiol. 12:319-328.

Hays, S.M., and L.L. Aylward 2003. Dioxin risks in perspective: past, present, and future. Regul Toxicol Pharmacol. 37(2):202-217.

Lorber, M. 2002. A pharmacokinetic model for estimating exposure of Americans to dioxin-like compounds in the past, present, and future. Sci. Tot. Environ. 288:81-95.

Patterson, D.G., R. Canady, L.-Y. Wong, R. Lee, W. Turner, S. Caudill, L. Needham, and A. Henderson. 2004. Age specific dioxin TEQ reference range. Organohalogen Compounds. 66:2878-2883.

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?