

EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments (External Review Draft)



Presentation for the
Science Advisory Board's Dioxin Review Panel
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Acknowledgements

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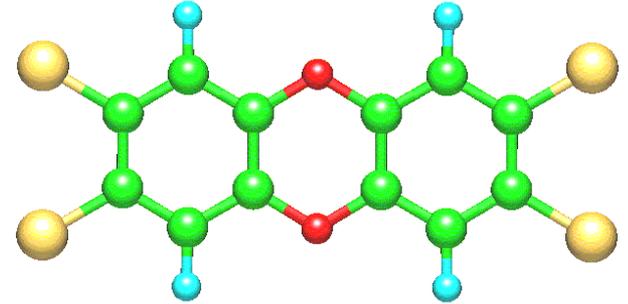
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This document has been provided for review to EPA scientists and interagency reviewers from other federal agencies and White House offices.

Overview

- History of EPA's Dioxin assessment
- Document objectives
- Procedure for screening relevant literature
- Application of pharmacokinetic modeling
- Development of the draft reference dose (RfD)
- Development of the draft cancer oral slope factor (OSF)
- Uncertainty analysis
- Scientific questions and key issues to consider

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)



- TCDD is among the most well-studied environmental contaminants and one of the most toxic dioxins
- The term “dioxins” refers to a number of chemical compounds that share certain similar chemical structures and biological characteristics
- Dioxins are comprised of three closely related families: the chlorinated dibenzo-*p*-dioxins (CDDs), chlorinated dibenzofurans (CDFs) and certain polychlorinated biphenyls (PCBs)
- Most dioxin exposure is via the diet, typically over 95% of exposure via dietary intake of animal fats

EPA's Dioxin Assessment: A Brief History

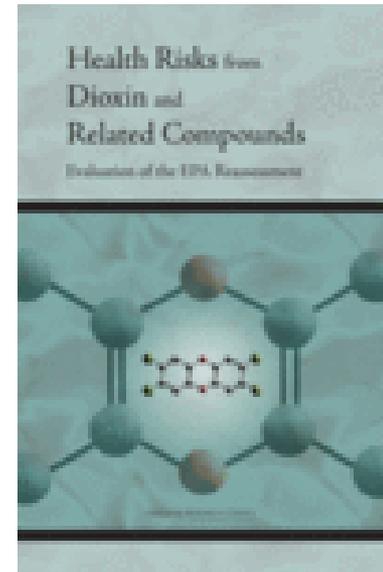
- Charge from the Administrator; May, 1991
- Science Advisory Board (SAB) review; 1995
- Peer Review and Public Comment on Draft Dose-Response Modeling (per SAB recommendation); June, 1997
- Revision, Internal and Interagency Review; 1995–2000
- External Peer Review (selected sections); 2000
- SAB re-review; 2000–2001
- Revision, Internal and Interagency Review; 2002–2004
- National Academy of Sciences (NAS) Review; 2004–2006
- Release of NAS Review Report; July, 2006
- EPA Dioxin Dose-Response and New Science Workshop; February, 2009
- Release of EPA's Science Plan for Activities Related to Dioxins in the Environment; May, 2009
- EPA Releases draft Response to Comments Document for Independent External Peer Review and Public Comment; May 21, 2010

Three Key NAS Recommendations Pertaining to Dose-response Assessment

“...to support a scientifically robust characterization of human responses to exposures to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD).

- (1) Improved transparency and clarity in the selection of key data sets for dose-response analysis,*
- (2) Further justification of approaches to dose-response modeling for cancer and noncancer endpoints, and*
- (3) Improved transparency, thoroughness, and clarity in quantitative uncertainty analysis.”*

NAS also encouraged EPA to calculate an oral Reference Dose (RfD)



Recommendations from EPA's 2009 Dioxin Workshop

- Following public release of its literature search results, in February 2009, EPA hosted a public workshop on its response to the NAS review of the 2003 Reassessment (Appendix A)
- Workshop goal: ensure that EPA's response to the NAS focuses on key NAS concerns and reflects the most meaningful science
- General recommendations/comments from expert panelists:
 - *Endorsed the idea of study selection criteria*
 - *Acknowledged that understanding of TCDD kinetics had increased significantly since EPA's released the 2003 Reassessment*
 - *Recommended the use of human data for developing cancer and noncancer reference values*

Document Overview

- Delineates a study selection process to identify TCDD epidemiology and rodent bioassay studies that could serve as a principal study for derivation of a reference value (Section 2)
- Applies physiologically-based pharmacokinetic (PBPK) modeling (Section 3 and Appendix C) to calculate human equivalent doses of TCDD
- Provides an RfD (Section 4) for noncancer effects and an oral slope factor (OSF) for carcinogenicity (Section 5) for TCDD oral exposures
- Discusses the feasibility of quantitative uncertainty analysis for TCDD dose-response assessment (Section 6)



Transparency in Selection of Key Data Sets

(Section 2)

Process to Select Datasets and Identify Points of Departure (PODs) From Human Studies for Use in Cancer and Noncancer TCDD Dose-response Analyses

All available epidemiologic studies on TCDD

Evaluate study using five considerations:

- Methods used to ascertain health outcomes are unbiased, sensitive and specific
- Confounding and other potential sources of bias are addressed
- There is an association between TCDD and adverse health effect with an exposure-response relationship
- Exposures based on individual-level estimates and uncertainties are described
- Statistical precision, power and study follow-up are sufficient

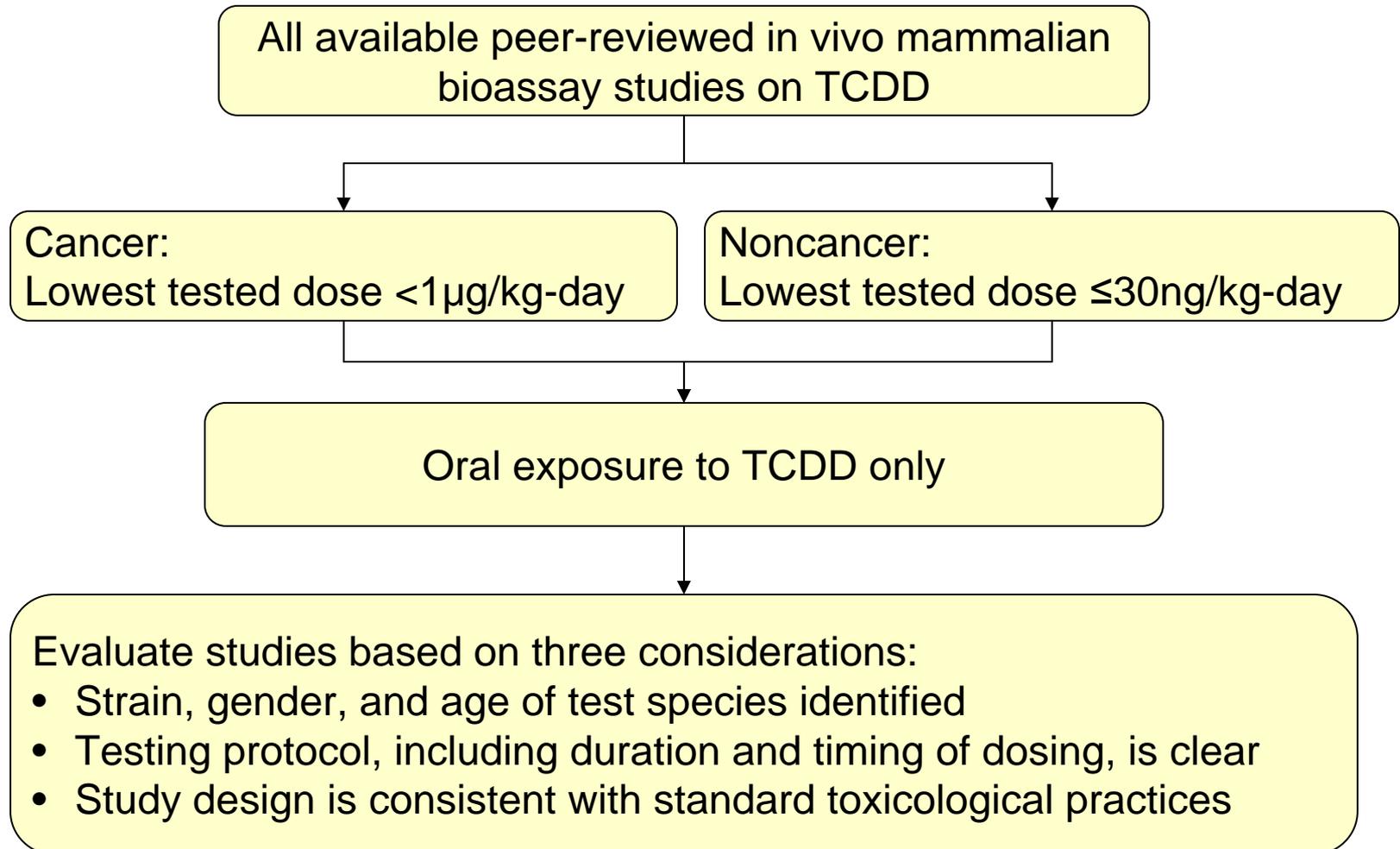
Inclusion Criteria:

- Study available in peer-reviewed literature
- Exposure primarily to TCDD and quantified
- Long-term exposures and latency information available (for cancer) or exposure windows and latency information available (noncancer)

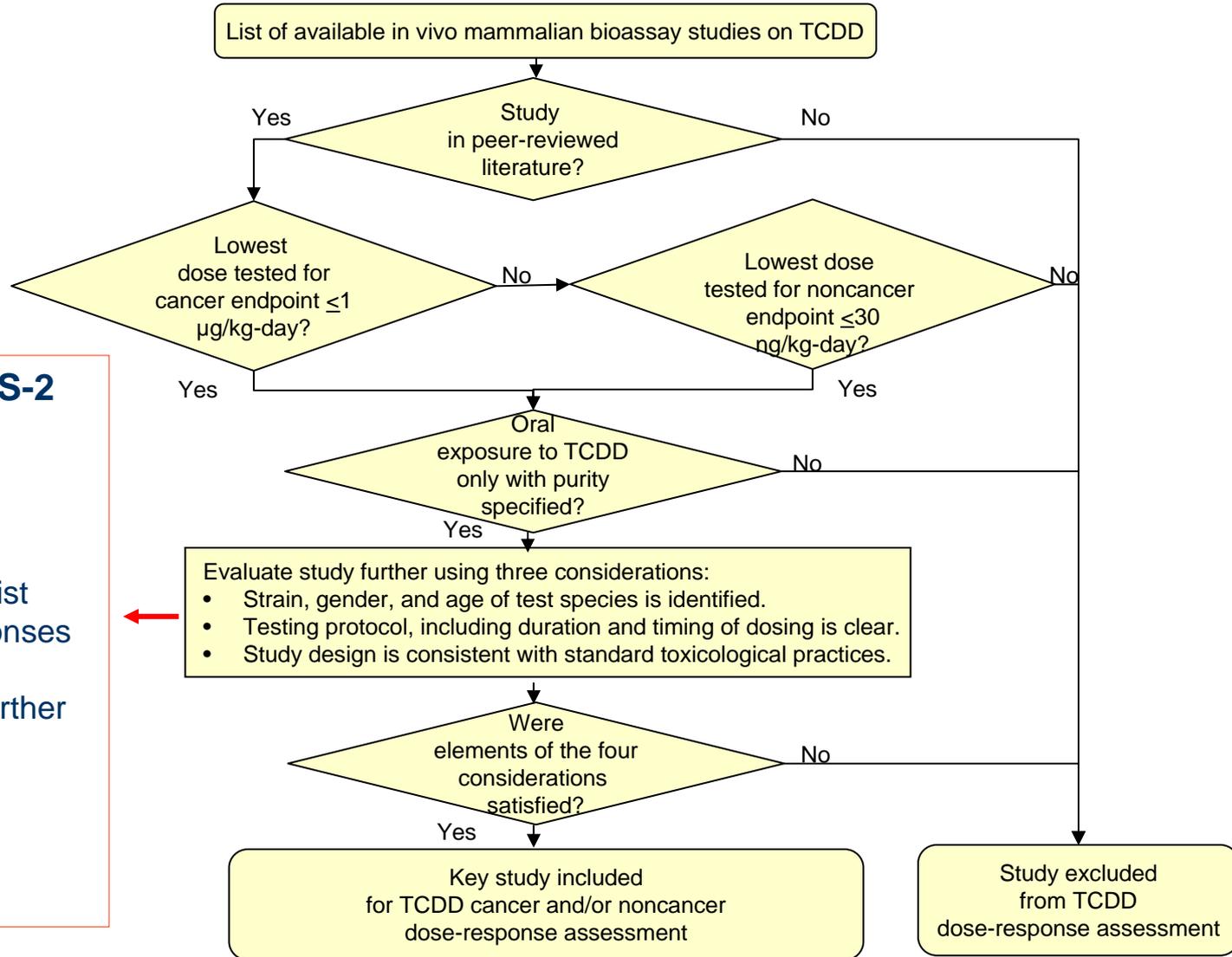
Consider for dose-response analyses

(Section 2.3)

Process to Select Datasets and Identify PODs From Animal Studies for Use in TCDD Cancer and Noncancer Dose-response Analyses



Corrected Figures ES-2 and 2-3



Erratum #1: Figures ES-2 and 2-3 in the draft document

Both these figures and the supporting text incorrectly list “Magnitude of animal responses is outside range of normal variability” as one of four further study considerations.

EPA did not use this consideration in identification of key studies



The Use of Toxicokinetics in the Dose-response Modeling for Cancer and Noncancer Endpoints

(Section 3)

TCDD Pharmacokinetic Model

Important factors influencing TCDD pharmacokinetics:

- 1. TCDD is highly lipophilic; consequently, it is preferentially stored in adipose tissue*
- 2. TCDD is slowly metabolized; consequently, TCDD has a long half-life in blood*
- 3. TCDD induces binding proteins in the liver; consequently, TCDD is sequestered in the liver, where binding induction becomes significant*
- 4. TCDD is eliminated in a dose-dependent manner*

Choice of and Use of a Pharmacokinetic Model

- NAS considered EPA's use of the body burden dose metric based on a constant elimination rate (1st order kinetics) in the 2003 Reassessment to be appropriate
- EPA's 2009 Dioxin Workshop emphasized that the understanding of TCDD kinetics had increased significantly since the Reassessment
- Consequently, EPA evaluated the published TCDD kinetic models
- EPA chose the Emond PBPK model
 - *most “physiologically-based” of the available models that considered dose-dependent elimination kinetics;*
 - *performed better than other models in simulations of serum lipid and tissue concentrations due to exposures that did not lead to onset of steady-state conditions;*
 - *rat and human model forms available; gestational and lifetime nongestational forms of the Emond PBPK model also were available.*
- EPA used the PBPK model to:
 - *estimate the lifetime average daily oral doses needed to achieve the blood TCDD concentrations that occurred during animal bioassays;*
 - *estimate the lifetime average daily doses that would correspond to the TCDD blood concentrations reported in epidemiology studies.*

(Section 3.3.4, Appendix C)

Emond PBPK Model Modifications

- To enhance the biological basis of the Emond PBPK model, three minor modifications were made prior to computing TCDD dose metrics:
 - *Recalculation of the volume of the “rest of the body” compartment after accounting for liver and fat compartment volumes;*
 - *Calculation of the rate of TCDD excreted via urine by multiplying the urinary clearance parameter by blood concentration instead of by the concentration in the rest of the body compartment;*
 - *Recalibration for the human gastric nonabsorption constant to yield observed oral bioavailability of TCDD (see Section 3.3.4.4)*
- The modified PBPK model was evaluated against all published data used to evaluate the original Emond model

Choice of TCDD Concentration in Whole Blood as Dose Metric

- Although lipid-adjusted serum concentration (LASC) is generally considered to be the most relevant metric, whole blood concentration was chosen because of the PBPK model structure
 - *Target tissue compartments connected to whole blood compartment (rather than a serum compartment)*
- LASC is related to whole blood by a scalar, so use of either is equivalent in the model
- Whole blood concentrations also reflect TCDD dose to target tissues and are biologically-relevant measures of internal dose
- EPA used the time-weighted average whole-blood concentration over the relevant exposure periods for all continuous dosing protocols, dividing the area under the time-course concentration curve (AUC) by the exposure duration

(Section 3.3.4 and Appendix C)

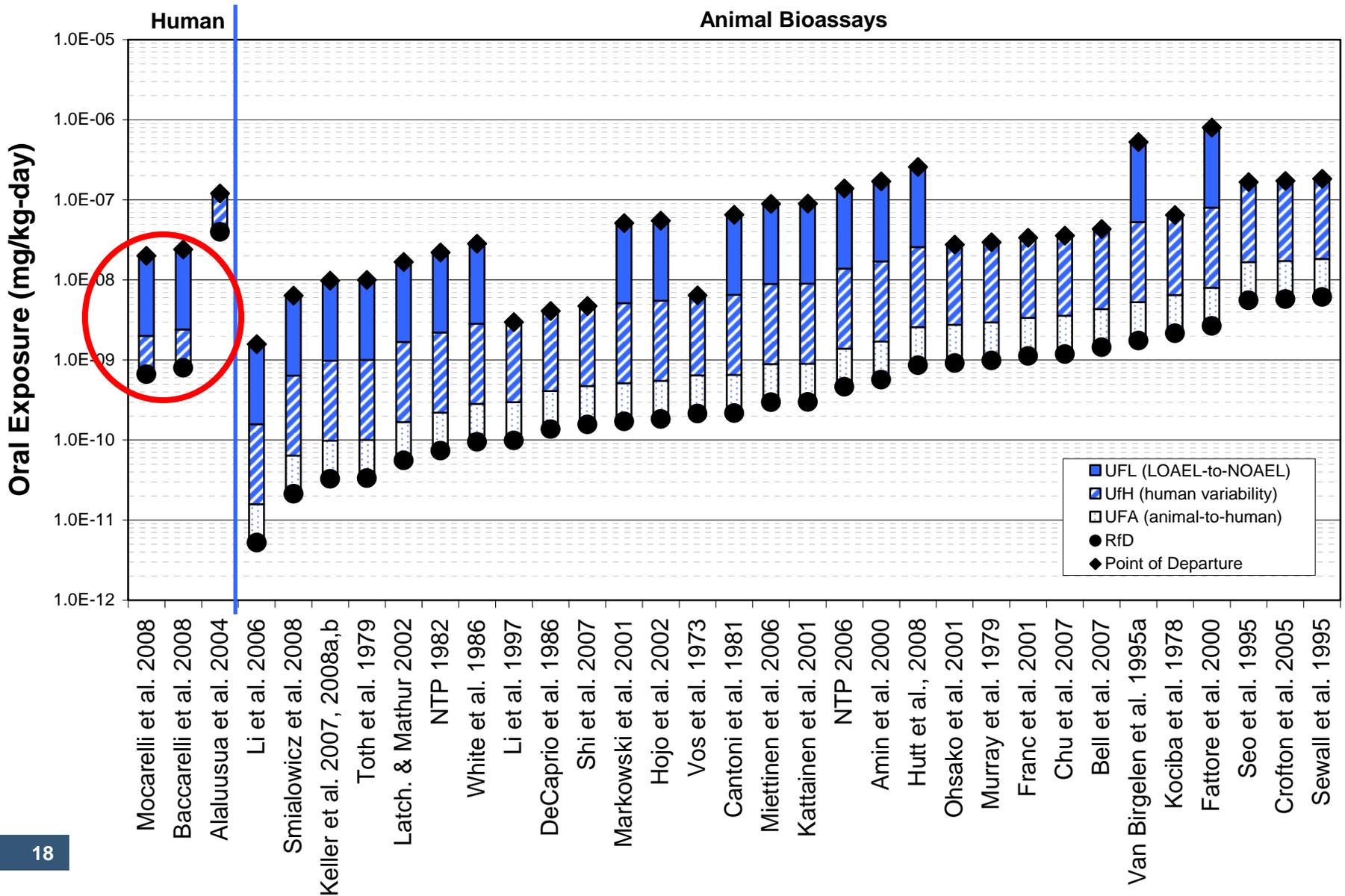


Noncancer—RfD Derivation

(Section 4)

TCDD Draft RfD Array

Section 4; Figure 4-4



Draft TCDD RfD

| RfD from 2003 Draft Dioxin Reassessment | Draft RfD from 2010 Reanalysis Document |
|---|---|
| No RfD was Derived | 7E-10 mg/kg-day (0.7 pg/kg-day) |

- Two human studies (Seveso cohort), Baccarelli et al. (2008), and Mocarelli et al. (2008), designated as coprincipal studies
- Baccarelli et al.—thyroid-stimulating hormone levels in newborns whose mothers were exposed to TCDD during the Seveso accident
- Mocarelli et al.—sperm endpoints in adult males who were exposed as children to TCDD during the Seveso accident
- Kinetic modeling used to estimate the relevant exposures for both study populations and to designate the Points of Departure (PODs)

Estimating Chronic TCDD Exposures Associated With Baccarelli Study

- EPA defined a LOAEL = 39 ppt TCDD based on a maternal serum-TCDD/TSH regression model
- Critical exposure window is nine months (duration of gestation); these developmental exposures occurred 10–15 years after the initial maternal exposure, when maternal internal TCDD concentrations were leveling off
- Emond PBPK model used to estimate the continuous daily TCDD intake that would lead to reported TCDD LASC

Estimating Chronic TCDD Exposures Associated with Mocrelli Study

- EPA defined a LOAEL = 68 ppt TCDD
- Effects were only observed in men <10 years of age at the time of accident
- TCDD LASC measured within ~1 year of the initial Seveso exposure event
- EPA could not determine if effects due to peak exposure or exposure over 10-year window; so, EPA averaged TCDD lifetime doses associated with 2 plausible exposure windows
 - *Peak exposure window associated with accident*
 - *Maximum 10-year exposure window*
- *Using Emond PBPK model, the **initial blood TCDD concentrations associated with accident** were back-calculated based on the time elapsed between the accident and serum collection; Emond PBPK model used to estimate average daily oral exposure associated with peak concentration*

Estimating Chronic TCDD Exposures Associated with Mocrelli Study (cont.)

- Starting with the peak exposure and accounting for background TCDD intake, the **average daily blood TCDD concentration experienced by a representative individual in the susceptible population** (males <10 years old) was estimated using Emond PBPK model
 - *Assuming a uniform distribution of subject ages at time of accident, the average age of exposed males = 5 years; thus, critical exposure window on average = 5 years*
 - *Using the Emond PBPK model, the average daily TCDD intake rate needed to attain the 5-year average blood TCDD concentration was calculated*
- The LOAEL POD [0.020 ng/kg-day] = average of the peak exposure (0.032 ng/kg-day) and the 5-year average exposure (0.0080 ng/kg-day)

TCDD Draft RfD Derivation

| Study | POD (mg/kg-day) | Critical Effects |
|--|--|--|
| Mocarelli et al., 2008 | 2E-8 (LOAEL) | Decreased sperm count (20%) and motility (11%) in men exposed to TCDD <10 years of age |
| Baccarelli et al., 2008 | 2E-8 (LOAEL) | Elevated TSH (> 5 µU/mL) in neonates born to mothers who were exposed to TCDD |
| RfD Derivation | | |
| POD | 2E-8 mg/kg-day | |
| UF | 30 (UF _L = 10, UF _H = 3) | |
| RfD | 7E-10 mg/kg-day (2E-8 ÷ 30) | |
| Uncertainty Factors | | |
| LOAEL-to-NOAEL (UF _L) | 10 | No NOAEL established; magnitude of effects at LOAEL sufficient to require a 10-fold factor. |
| Human interindividual variability (UF _H) | 3 | A factor of 3 (10 ^{0.5}) used because the effects were observed in sensitive populations. The sample sizes were relatively small, which, combined with uncertainty in exposure estimation, may not fully capture the range of interindividual variability. |



Cancer—OSF Derivation

(Section 5)

TCDD Weight of Evidence Cancer Descriptor: “Carcinogenic to Humans” Based on the Available Data as of 2009

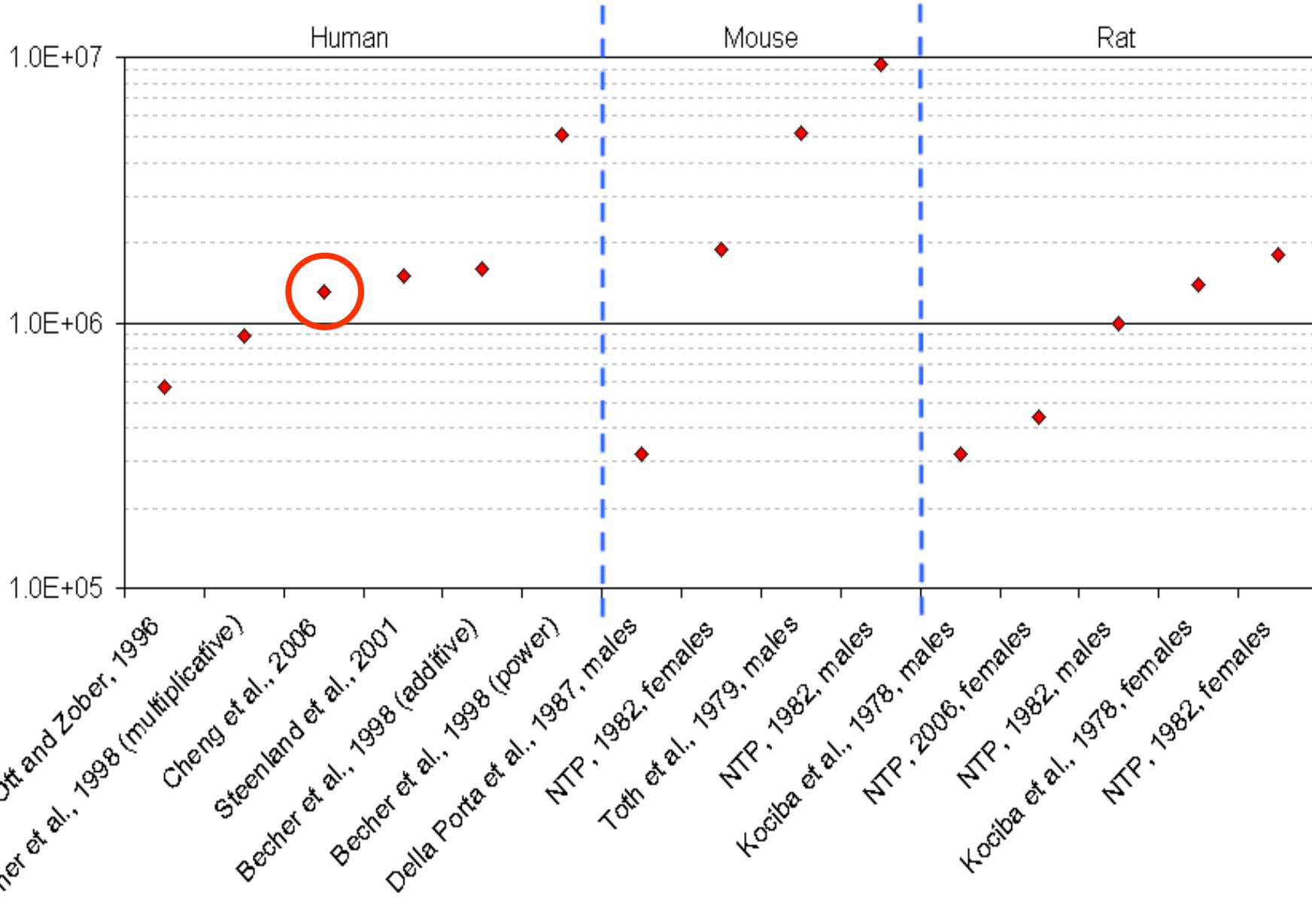
- Multiple studies of occupational and accidentally exposed epidemiologic cohorts showed an association between TCDD exposure and certain cancers or increased mortality from all cancers
- Extensive evidence of carcinogenicity at multiple tumor sites in both sexes of multiple species of experimental animals
- General scientific consensus that the mode of TCDD’s carcinogenic action in animals involves aryl hydrocarbon receptor (AhR)-dependent key precursor events and proceeds through modification of one or more of a number of cellular processes
 - *Human AhR and rodent AhR are similar in structure and function*
 - *General scientific consensus that AhR activation is anticipated to occur in humans and to progress to tumors*

Cancer Assessment

- EPA identified candidate cancer OSFs from several well-studied epidemiologic cohorts showing an association between TCDD and an increased risk of cancer or cancer mortality
- EPA identified candidate cancer OSFs for 5 animal bioassays
 - *Kociba et al. (1978), Toth et al. (1979), Della Porta et al. (1987), and NTP (1982, 2006)*
 - *Dose-response modeling conducted for each tumor type separately (individual tumor models) and composite tumor incidences (multiple tumor models)*
- EPA chose to use the human data over the animal data as recommended by panelists at 2009 Dioxin Workshop and in the 2005 Cancer Guidelines
 - *OSFs derived from both data sources fall within same range*

Candidate Cancer Slope Factors

2,3,7,8-TCDD Slope Factor
(per mg/kg-d)



Draft Cancer Oral Slope Factor (OSF)

| OSF From 2003 Draft Dioxin Reassessment | Draft OSF From 2010 Reanalysis Document |
|---|---|
| 1.0E+6 per mg/kg-day | 1.3E+6 per mg/kg-day when the target risk range is 10^{-5} to 10^{-7} |

- EPA derived the OSF from an analysis of the NIOSH occupational cohort by Cheng et al. (2006) based on total cancer mortality
- Cheng study selected from several other epidemiologic studies because longer-term TCDD exposure and kinetic modeling approach provided more biologically relevant exposure estimates when compared to other epidemiologic studies (Chapter 5; Section 5.3)
- Below POD, EPA assumed slope is linear, nonthreshold to origin
 - *Linear, nonthreshold is default in 2005 Cancer Guidelines when cancer mode-of-action is not known for all tumor types*

Comparison of Equivalent Oral Slope Factors Based on Upper 95th Percentile Estimate of Regression Coefficients of All Fatal Cancers Reported by Cheng et al. (2006) for Selected Risk Levels

| Risk level (RL) | Risk specific dose (D_{RL}) (ng/kg-day) | Equivalent oral slope factors (OSF_{RL}) per (mg/kg-day) |
|--------------------|---|--|
| 1×10^{-2} | 8.79×10^{-2} | 1.1×10^5 |
| 1×10^{-3} | 2.88×10^{-3} | 3.5×10^5 |
| 1×10^{-4} | 1.29×10^{-4} | 7.8×10^5 |
| 1×10^{-5} | 8.94×10^{-6} | 1.1×10^6 |
| 1×10^{-6} | 8.08×10^{-7} | 1.2×10^6 |
| 1×10^{-7} | 7.92×10^{-8} | 1.3×10^6 |

Due to nonlinearities in the PBPK model and Cheng's modeling of log response (Cheng analyzed the NIOSH Cohort using Cox Regression models), there is a nonlinear relationship of OSF across doses.

Consideration of Nonlinear Dose-response Approaches for Cancer

- NAS commented extensively on extrapolation of cancer dose-response modeling below the POD
 - *Questioned reassessment's choice of a linear, nonthreshold model*
 - *Concluded that current scientific evidence sufficient to justify nonlinear methods*
- Based on the NAS review, EPA presents two illustrative RfDs for TCDD-induced carcinogenesis (Section 5.2.3.4)
- EPA identifies limitations that preclude making strong conclusions based on the nonlinear dose-response modeling exercises

Erratum #2: Executive Summary in the draft document

The Executive Summary incorrectly states, “EPA presents a hypothetical sublinear dose-response modeling example of rodent carcinogenicity.”

EPA does not report such an analysis.



Feasibility of Quantitative Uncertainty Analysis

(Section 6)

Feasibility of Conducting Quantitative Uncertainty Analysis for Different Types of Uncertainty (Section 6)

- *Cognitive uncertainty* (uncertainty that can be expressed as probabilities) can be operationalized using frequentist or Bayesian approaches
 - *E.g., BMDL estimation, epidemiologic dose reconstruction (such as, biological half-life, body fat, and background levels)*
- *Volitional uncertainty* (uncertainty regarding choices on the best course of action) cannot be analyzed by sampling from a probability distribution and is not amenable to complete quantitative uncertainty analyses
 - *Choice of occupational cohort data set or bioassay data set for setting reference value*
 - *Choice of PODs (e.g., ED_{01} , ED_{05} , and ED_{10})*

Limited Quantitative Comparisons Provided in Document

- Although EPA determined that a comprehensive data driven, quantitative uncertainty analysis was not feasible, selected limited quantitative comparisons are provided
 - *EPA compares BMDs, BMDLs, and OSFs from animal cancer bioassay BMD modeling assuming 1, 5, and 10% extra risk (Tables 5-18 and 5-19)*
 - *EPA compares central tendency slope estimates and upper bound slope factor estimates based on Cheng et al. (2006)(Tables 5-3 and 5-4)*
 - *For noncancer effects, EPA compares key animal study PODs for different dose metrics: administered dose, first-order body burden HED, and blood concentration (Tables 4-3 and 4-4)*
 - *EPA presents a sensitivity analysis for the kinetic modeling*
 - *EPA compares TCDD kinetic dose estimates from Emond and Aylward models*

Next Steps

- EPA's Science Advisory Board (SAB) will convene an expert panel to review this draft report; the SAB is expected to hold it's first public meeting on July 13-15, 2010
- EPA has extended public comment period to September 20, 2010

Charge Questions

- EPA has provided charge questions for the SAB review
 - *Original charge questions were modified based on comments received during intra- and interagency review of the document*
- These questions address the document's major conclusions:
 - *Process used to select key studies for further analyses*
 - *Pharmacokinetic modeling*
 - Choice of and modifications to Emond model
 - Choice of whole blood TCDD concentration as dose-metric
 - *Noncancer assessment*
 - Selection of co-critical human studies from Seveso Cohort
 - Derivation of the RfD including POD and choice of uncertainty factors
 - *Cancer assessment*
 - Weight of evidence—cancer classification
 - Key quantitative issues:
 - *Derivation of OSF from NIOSH Cohort data*
 - *Decision to use a linear, nonthreshold extrapolation*
 - *Background DLC exposures*
 - *EPA's determination that it could not produce a comprehensive data driven, uncertainty analysis*