United States Environmental Protection Agency

The U.S. EPA's Draft Oral Reference Dose (RfD) for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)

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Laboratory-Animal Dose-Response Data Available for Dose-Response Assessment

- Species
  - Mouse, hamster, rat, guinea pig, mink, monkey
- Range of effects
  - Developmental, reproductive, immunological, neurological, hormonal, cytotoxic
- Exposure level cut
  - 64 studies with low dose <= 30 ng/kg-day
- Internal DLC Exposure cut
  - Monkey studies showing high serum DLC levels
- Toxicological relevance cut
  - Adverse effect: "…a biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge."
  - Discounted sensitive endpoints lacking toxicological significance (adaptive, biochemical, not immediate precursor to functional/pathological alteration)
    - CYP induction, protein phoshorylation, TBARS, Cx32 plaque number, UDP glucuronyl transferase, TNF-alpha

Dose-Response Modeling for Animal Bioassays

- Dose-response modeling protocol
  - Dose metric = TCDD concentration in whole blood (Emond PBPK model)
  - Benchmark Dose (BMD) modeling to determine POD
    - Dichotomous BMR = 10%
    - Continuous BMR = 10% or 1 Std Dev
  - NOAELs and LOAELs assigned to rest
- Dose-response modeling results
  - 4 BMDL PODs
  - 9 NOAEL PODs
  - 17 LOAEL PODs (including 7 most sensitive endpoints)
- Most data sets poorly fit or “unanchored”
  - Response near BMR lacking
  - Unconstrained fits mostly supralinear

Human Dose-Response Data Available for Dose-Response Assessment

- TCDD Cohorts
  - NIOSH, Hamburg, BASF
    - Occupational, mortality endpoints only
  - Seveso
    - General population, single pulse exposure, non-fatal endpoints (developmental, reproductive)
- Primary issue for Seveso cohort is exposure profile
  - High initial pulse followed by low-level background exposure
  - Determination of effective dose
    - Internal dose metric (whole blood TCDD concentration from Emond PBPK model)
    - Identification of critical exposure windows
    - Consideration of peak exposure
- 4 Seveso studies identified
  - Baccarelli et al., 2008 (increased neonatal TSH)
  - Mocarelli et al., 2008 (decreased sperm counts)
  - Alaluusua et al., 2004 (developmental dental defects)
  - Eskenazi et al., 2002 (increased length of menstrual period)

Baccarelli et al., 2008 Overview

- Increased levels of TSH in newborns exposed to TCDD in utero, 10 to 20 years following initial peak maternal exposure
  - Gestational exposure levels relatively constant
- TSH levels greater than 5 µU/mL considered to be indicative of potential thyroid or neurological functional impairment
  - WHO trigger for follow-up
- Regression model of maternal serum TCDD levels and neonatal TSH links exposure and effect
  - Maternal serum TCDD of 270 ppt associated with neonatal TSH levels greater than 5 µU/mL defined as the LOAEL
- A corresponding continuous 30-year daily oral TCDD intake of 0.024 ng/kg-day was determined using the Emond human gestational PBPK model

Mocarelli et al., 2008 Overview: Study Description

- Decreased sperm counts in men who were exposed to TCDD as boys aged 1–9 years
  - Mean total sperm concentration and motile sperm concentration reduced 20% and 11%, respectively, in the 1st-quartile exposure group (68 ppt in serum; *n* = 71) compared to reference group (15 ppt TCDD in serum)
  - No dose-related effect of TCDD on sperm counts for men aged 10-17 years when exposed
  - Critical exposure window of 1st 10 years of life identified
  - Exposed boys averaged 6.2 years of age
    - Average time in critical window = 3.8 years
- No TCDD-free control group
  - Reference group response probably not influenced by TCDD (same response as all men exposed as 10-17 year-olds)
- LOAEL defined by the 1st-quartile exposure group
  - 20% decrease in exposed population deemed to be biologically significant

Mocarelli et al., 2008 Overview: Exposure Modeling

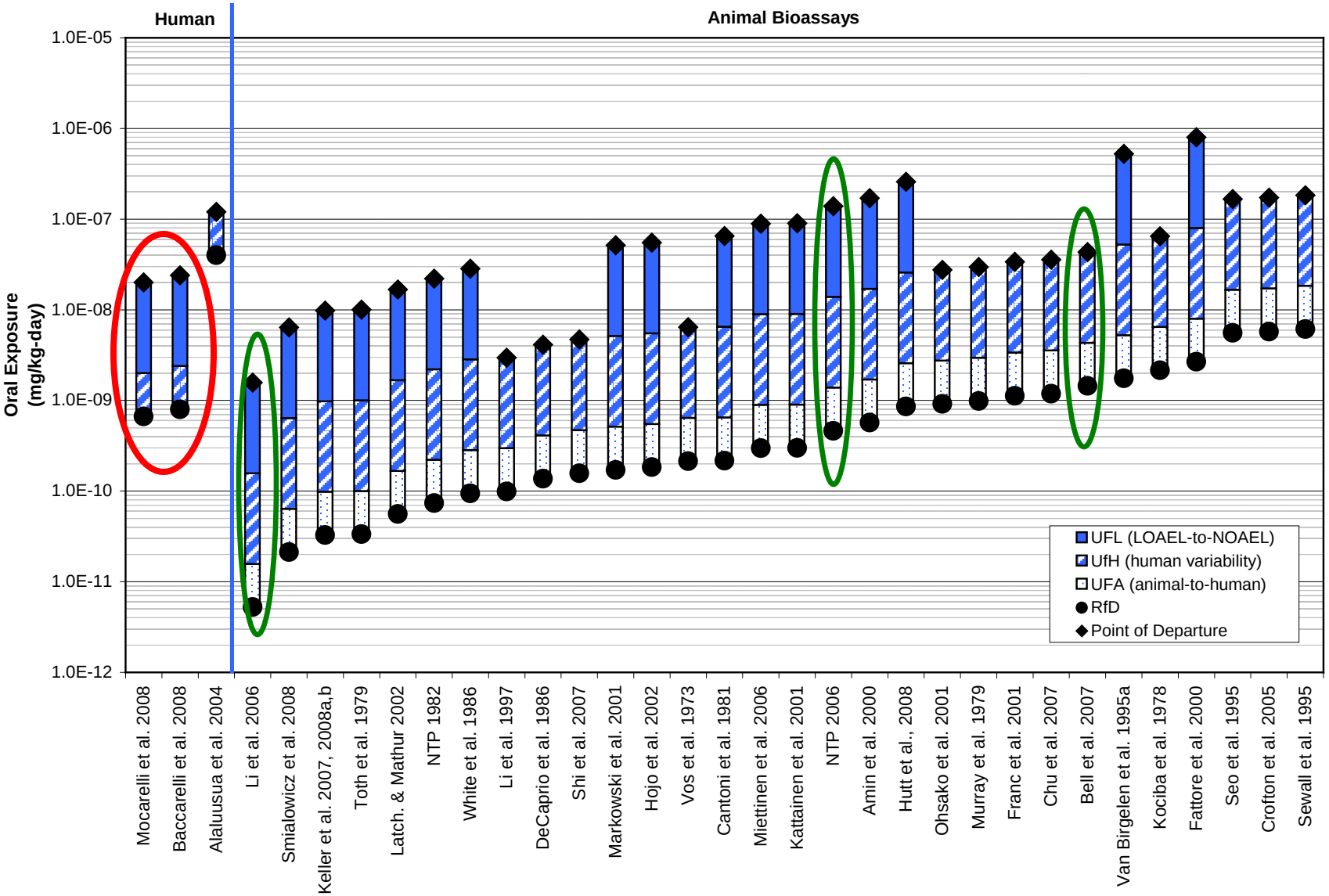
- LASC at LOAEL for peak exposure and 3.8-year critical-window average estimated using Emond human PBPK model
  - Peak LASC = 248 ppt; critical window average LASC = 58 ppt
- Corresponding continuous10-year intake for peak and 10-yr window average LASC modeled (Emond)
  - Intake for peak LASC = 0.032 ng/kg-day; intake for critical-window average LASC = 0.008 ng/kg-day
  - LOAEL of 0.020 ng/kg-day is the average of the peak exposure and window average

Basis and Derivation of the Draft TCDD RfD

Principal study detail		
Study	**POD (ng/kg-day)**	**Critical effects**
Mocarelli et al. (2008)	0.020 (LOAEL)	Decreased sperm count (20%) and motility (11%) in men exposed to TCDD during childhood
Baccarelli et al. (2008)	0.024 (LOAEL)	Elevated TSH (>5 µU/mL) in neonates

RfD derivation	
POD	0.020 ng/kg-day (2.0E-8 mg/kg-day)
UF	30 (UF_L = 10, UFH = 3)
RfD	7×10^{-10} (7.0E-10) mg/kg-day

Candidate RfD Array



Uncertainties in the Draft TCDD RfD

- Seveso exposure profile
- Impact of background DLC exposures
  - Greater for human studies than for rodent bioassays
- Chronic effect levels not well-defined for humans
- No-effect levels hard to pin down
- Effects in rodents more overtly toxic than in humans
- No true controls
  - Humans and rodents

Draft TCDD RfD Summary

- RfD = 7×10^{-10} mg/kg-day
  - Human LOAEL = 0.02 ng/kg-day
    - Increased neonatal TSH (Baccarelli et al., 2008)
    - Decreased sperm counts (Mocarelli et al., 2008)
  - Uncertainty factors
    - UFL = 10
    - UFH = 3
- Human epidemiologic data selected over rodent bioassay data
  - Direct relevance
  - Uncertainty in human exposure profile vs. uncertainty in rodent-human extrapolation
    - 75 to 3,000 for kinetic extrapolation factor