

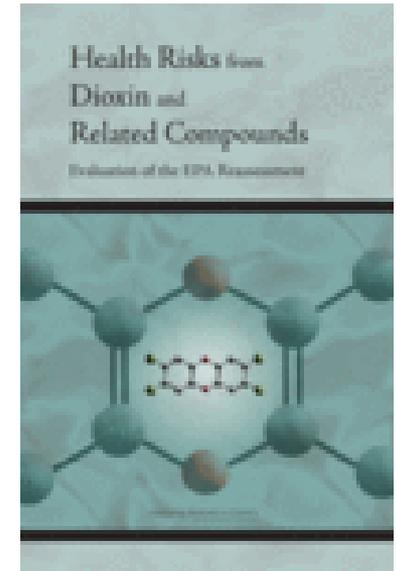
The Application of Study Selection Criteria to TCDD Epidemiologic Studies and Animal Bioassays for Development of a Reference Dose and Cancer Oral Slope Factor

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NAS (2006) Charge to Improve Transparency and Clarity in the Selection of Key Data Sets for Dose-Response Analysis

- “EPA should *specify inclusion criteria for the studies (animal and human) used* for derivation of the benchmark dose (BMD) for different noncancer effects and potentially for the development of RfD values and discuss the strengths and limitations of those key studies.”
- “...in its *[EPA’s] evaluation of the epidemiological literature of carcinogenicity, it did not outline eligibility requirements or otherwise provide the criteria used* to assess the methodological quality of other included studies.”
- “With regard to EPA’s review of the animal bioassay data, the *committee recommends that EPA establish clear criteria for the inclusion of different data sets.*”



Overview of EPA's Draft Study Selection Process

- Goal is to identify a group of studies for TCDD dose-response evaluation that spans
 - The types of adverse health effects associated with TCDD exposures
 - The range of doses in the lower end of the dose-response region that are most relevant to human health protection
- EPA developed detailed study selection criteria that
 - Consider TCDD-specific issues
 - Reflect EPA methods for
 - Point of departure (POD) identification
 - Noncancer Reference Dose (RfD) derivation
 - Cancer Oral Slope Factor (OSF) derivation
 - Contrast with EPA's 2003 Reassessment where focus was on individual endpoints and goal was to compare dose-response across studies

Overview of EPA's Draft Study Selection Process (cont.)

- Different approaches for animal and human studies
 - Significant differences in nature of health effects and exposure data and their use in EPA risk assessment
- Applied to ~500 potentially relevant studies
 - Identified most relevant studies for TCDD quantitative human health risk analyses
 - Screened out those studies that did not qualify
- Studies not screened, but used as supporting information were on
 - Dioxin-like compounds (DLCs)
 - Mixtures toxicity
 - Mode of action
 - In vitro toxicity
 - Nonmammalian toxicology
 - Risk assessment

TCDD-Specific Draft Study Selection Process for Animal Bioassays

All available peer-reviewed in vivo mammalian bioassay studies on TCDD through Oct 2009

Cancer:
Lowest tested dose ≤ 1 $\mu\text{g}/\text{kg}\text{-day}$

Noncancer:
Lowest tested dose ≤ 30 $\text{ng}/\text{kg}\text{-day}$

Oral exposure to TCDD only

Evaluate studies based on three considerations:

- Strain, gender, and age of test species identified
- Testing protocol, including duration and timing of dosing, is clear
- Study design is consistent with standard toxicological practices

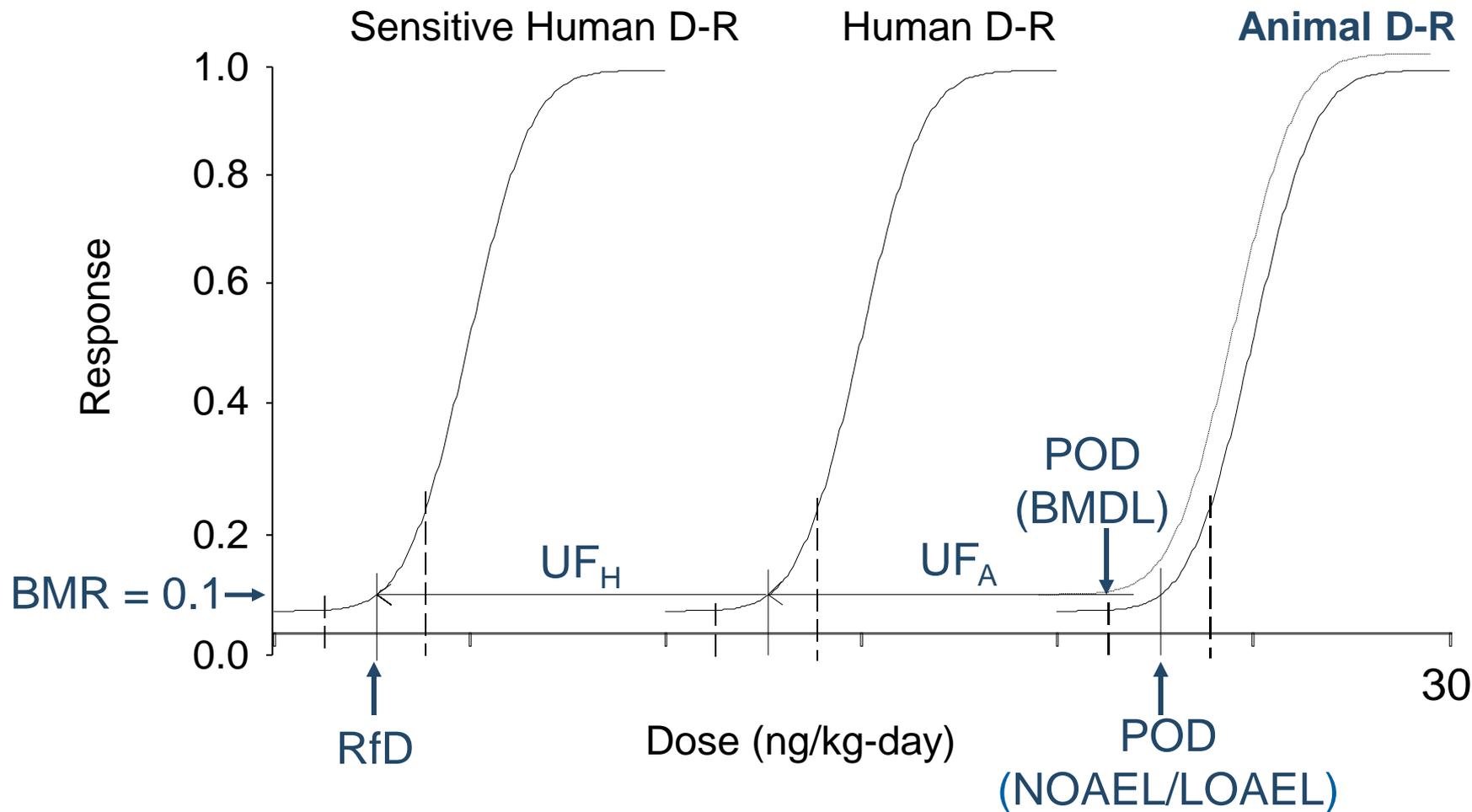
Rationale for Dose Cut-Offs in Draft Study Selection Criteria

- RfD and OSF derived to be protective of human health, including sensitive populations
- Data sets used demonstrate adverse effects, or their precursors, in the low-dose range
- Low-dose requirements do not imply that higher dose studies are of poor quality
 - Studies with doses too high to impact the numeric derivations of the RfD or OSF used as supporting evidence
- Studies with the lowest exposures showing effects drive RfD and OSF derivations, all other considerations being equal

Examples of Animal Noncancer Studies Meeting Draft Study Selection Criteria; Lowest Dose ≤ 30 ng/kg-day

Study	Endpoint	Administered dose	
		NOAEL	LOAEL
Bell et al. (2007)	Delay in onset of puberty in pups	–	2.4
DeCaprio et al. (1986)	Decreased body weight	0.61	4.9
Fattore et al. (2000)	Decreased hepatic retinol	–	20
Franc et al. (2001)	Organ weight changes	10	30
Hutt et al. (2008)	Embyrotoxicity	–	7.14
Latchoumycandane and Mathur (2002)	Decreased sperm production	–	1
Li et al. (1997)	Increased serum FSH	3	10
Li et al. (2006)	Hormone levels in pregnant dams (increased serum estradiol)	–	2
Markowski et al. (2001)	Neurobehavioral effects in pups	–	20
NTP (1982)	Liver lesions	–	1.39
NTP (2006)	Liver and lung lesions	–	2.14
White et al. (1986)	Decreased serum complement	–	10

Conceptual RfD Derivation

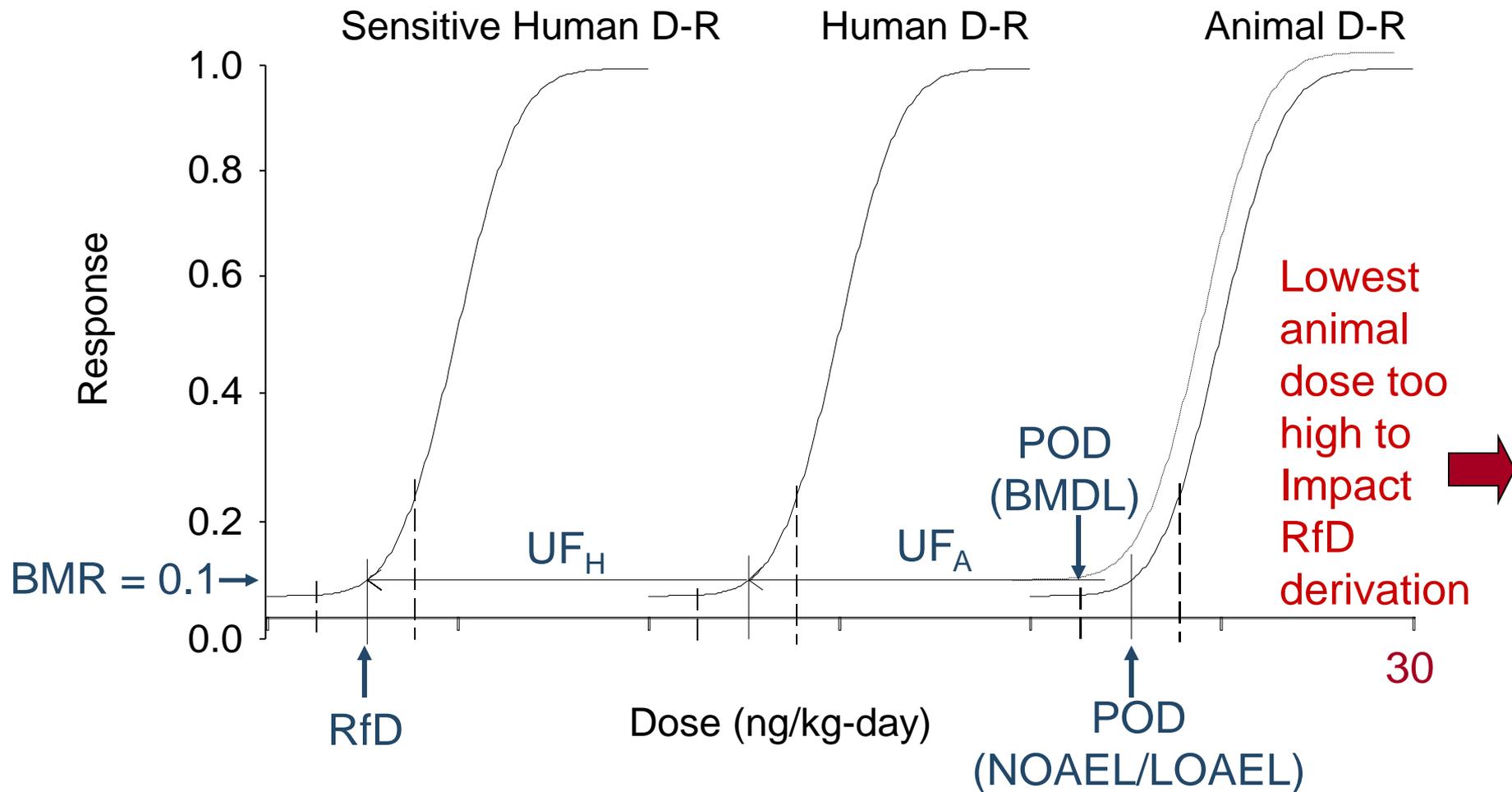


POD = Lower Bound on 5 or 10% Response (BMDL), LOAEL, or NOAEL

Uncertainty Factors: UF_A = Animal to Human; UF_H = Human to Sensitive Human;

UF_S = Subchronic to Chronic; **UF_L = LOAEL to NOAEL**; UF_D = Database

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UF_S = Subchronic to Chronic; UF_L = LOAEL to NOAEL; UF_D = Database

Animal Cancer Studies Meeting Draft Study Selection Criteria; Lowest Dose $\leq 1 \mu\text{g}/\text{kg}\text{-day}$

Study	Sex/Species/Tumor Sites	Average Daily Doses (ng/kg-day)
Della Porta et al. (1987)	Male mice: liver	0, 351, 714
Kociba et al. (1978)	Female rats: liver, oral cavity, lung	0, 1, 10, 100
Kociba et al. (1978)	Male rats: adrenal cortex, tongue, nasal/palate	0, 1, 10, 100
NTP (1982)	Female mice: liver, thyroid, subcutaneous fibrosarcoma, hematopoietic system	0, 5.7, 28.6, 286
NTP (1982)	Female rats: liver, adrenal cortex, thyroid	0, 1.4, 7.1, 71
NTP (1982)	Male mice: liver, lung	0, 1.4, 7.1, 71
NTP (1982)	Male rats: thyroid, adrenal cortex	0, 1.4, 7.1, 71
NTP (2006)	Female rats: liver, oral mucosa, lung, pancreas	0, 2.14, 7.14, 15.7, 32.9, 71.4
Toth et al. (1979)	Male mice: liver	0, 1, 100, 1,000

Summary of Applying Draft Study Selection Criteria to Oral *in vivo* Mammalian Animal Bioassays

- Process results
 - Once a study failed one criterion, it was not evaluated for the other criteria, so exact statistics on all failed criteria not known
 - Majority of excluded studies failed the dose cuts-offs
 - Some TCDD exposures were confounded with DLCs
 - Study design also important
 - Knock out mice excluded because relevance to humans of genetically altered strain unknown
- Selected studies
 - 6 cancer bioassays
 - 64 noncancer bioassays—developmental (16), reproductive (11), acute toxicity (10), subchronic toxicity (16), chronic toxicity (11)

TCDD-Specific Draft Study Selection Process for Epidemiologic Studies

All available peer-reviewed epidemiologic studies on TCDD through Oct 2009

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:

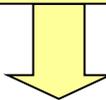
- Study available in peer-reviewed literature
- Exposure primarily to TCDD and quantified
- Long-term exposures and latency information available (for cancer) or exposure windows and latency information available (noncancer)

Consider for dose-response analyses

Examples of Epi Draft Study Selection Criteria Applied to Peer-Reviewed Cancer Mortality Studies

Study (NIOSH Cohort)	Exposure primarily to TCDD and quantified?	Effective dose and oral exposure estimable? Latency and exposure window(s) examined?	Pass for D-R analyses?
Fingerhut et al. 1991.	Exposure duration surrogate for TCDD exposure	√	No
Steenland et al. 1999.	√	√	No - Study superseded by Steenland et al. (2001)
Steenland et al. 2001.	√	√	Yes – combined cancer sites
Cheng et al. 2006.	√	√	Yes – combined cancer sites
Collins et al. 2009.	√	√	Yes – soft tissue sarcoma

Examples of Epi Draft Study Selection Criteria Applied to Peer-Reviewed Cancer Mortality Studies

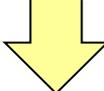
Study (NIOSH Cohort)	Exposure primarily to TCDD and quantified?	Effective dose and oral exposure estimable? Latency and exposure window(s) examined?	Pass for D-R analyses?
Fingerhut et al. 1991.	Newer studies used measured TCDD serum lipid levels and kinetic models to estimate individual-level human exposures 		No
Steenland et al. 1999.			No - Study superseded by Steenland et al. (2001)
Steenland et al. 2001.	✓	✓	Yes – combined cancer sites
Cheng et al. 2006.	✓	✓	Yes – combined cancer sites
Collins et al. 2009.	✓	✓	Yes – soft tissue sarcoma

Examples of Epi Draft Study Criteria Applied to Peer-Reviewed Noncancer Studies

Study;	Exposure primarily to TCDD and quantified?	Effective dose and oral exposure estimable? Latency and exposure window(s) examined?	Pass for D-R analyses ?
Cohort: Seveso (S), Ranch Hand (R); Nonfatal Endpoint			
Michalek and Pavuk. 2008. (R) Diabetes	Co-exposures to DLCs*	√	No
Baccarelli et al. 2002; 2004. (S) Immune effects	√	Difficult to identify endpoint-relevant time interval for TCDD dose estimation	No
Baccarelli et al. 2008. (S) Neonatal thyroid function	√	√	Yes
Mocarelli et al. 2008. (S) Semen quality	√	√	Yes

*Mean TCDD (pg/g lipid) comprised only 7% and 24% of Total TEQ for Comparison Group and Ranch Hands, respectively, using WHO 2005 TEFs (Pavuk et al., 2007).

Examples of Epi Draft Study Criteria Applied to Peer-Reviewed Noncancer Studies

Study;	Exposure primarily to TCDD and quantified?	Effective dose and oral exposure estimable? Latency and exposure window(s) examined?	Pass for D-R analyses ?
Cohort: Seveso (S), Ranch Hand (R); Nonfatal Endpoint			
Michalek and Pavuk. 2008. (R) Diabetes	<p>Endpoint-relevant critical windows were identified for exposure estimation; Exposures primarily to TCDD</p> 		No
Baccarelli et al. 2002; 2004. (S) Immune effects			No
Baccarelli et al. 2008. (S) Neonatal thyroid function	√	√	Yes
Mocarelli et al. 2008. (S) Semen quality	√	√	Yes

*Mean TCDD (pg/g lipid) comprised only 7% and 24% of Total TEQ for Comparison Group and Ranch Hands, respectively, using WHO 2005 TEFs (Pavuk et al., 2007).

Summary of Applying Draft Study Selection Criteria to Epidemiologic Studies

- Process results
 - Criteria most frequently failed for studies not selected:
 - TCDD exposures confounded by co-exposures to DLCs
 - TCDD exposures not quantified, so dose-response could not be analyzed
 - Studies did not have individual human TCDD exposure estimates
 - Information not provided on critical window of exposure to allow for human TCDD exposure estimates
- Selected studies
 - 4 noncancer studies from the Seveso cohort
 - 6 cancer studies from the NIOSH (3), Boehringer (1), BASF (1), and Seveso (1) cohorts

Conclusions

- EPA's draft TCDD-specific study selection criteria developed to be responsive to NAS (2006) call for transparency
 - All references in document available in EPA's HERO database
- Identified relevant group of studies, each with its own limitations and uncertainties, to span the possible risk analytic choices for human health protection
- Greatly reduced scope of dose-response modeling/analyses to a manageable size, from ~500 to 80 studies
- Exposure information was key
 - Primarily to TCDD and quantifiable for dose-response
 - Dose cut-offs in animal studies generated low dose toxicity data for RfD and OSF derivation
 - Critical exposure windows in epi studies provided vital data to develop human exposure estimates
- Criteria reflect data needed for RfD and OSF derivation based on current EPA methods