

ToxStrategies Comments on EPA's Draft Dioxin Assessment and Response to NAS Recommendations

Summary Page

ToxStrategies reviewed the draft document titled "EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments" (Draft Report). The massive 1,850-page draft report serves as a response to recommendations made the NAS related to the dose-response assessment for TCDD. Our comments are focused on developing robust, meaningful, toxicological factors based on the best science available and using guidelines and procedures set forth by the EPA.

We commend EPA for their major efforts to conduct additional analyses and respond to the NAS committee. However, there are a number of issues that should be carefully evaluated by the SAB and revisited by the EPA prior to finalizing the Draft Report.

Given the voluminous nature of the Draft Report and the brief timetable established by the Agency for the public to provide the SAB with feedback, these comments should be regarded as initial comments; ToxStrategies will provide the EPA and SAB with more extensive comments by September 20, 2010.

1 The EPA should evaluate the mode of action (MOA) when determining the extrapolation approach (nonlinear or linear) for carcinogenic effects of TCDD.

Action: EPA denied sufficient evidence for an MOA for TCDD. The Agency then relied on the supposed lack of knowledge regarding the MOA to support a linear approach for deriving a CSF.

Limitations: EPA clearly acknowledged key events in the MOA for TCDD-induced carcinogenesis, and particularly the role of AhR activation. Despite these robust data available, the Agency did not fully develop an MOA, nor was adequate support regarding the lack of data on an MOA for TCDD provided. Further, the Agency appeared to misinterpret and/or ignore their own technical guidelines and frameworks regarding analysis of such.

Suggested Improvements: Given the abundance of available data, EPA should consider a thorough evaluation of TCDD MOA — including application of such to the Agency's MOA framework and incorporation of key concepts from the Agency's cancer guidelines.

2 The EPA should reconsider their selection of a linear extrapolation approach to evaluate cancer risk given that three previous scientific panels have recommended nonlinear approaches.

Action: The EPA chose to evaluate cancer risk using a linear model rather than nonlinear model.

Limitations: Three prestigious scientific advisory panels asked to review the EPA's dioxin reassessment all identified the linear modeling assumption as a specific point of concern and recommended that nonlinear approaches be incorporated into the assessment. This recommendation was founded on data demonstrating clear nonlinear dose-response relationships.

Suggested Improvements: Given the Agency's lack of rationale for selecting a linear model, and clear recommendations from multiple scientific panels that have reviewed the assessment, the EPA should reconsider their selection of a linear model.

3 The EPA should evaluate the impact of the qualitative exposure estimates used in the derivation of the OSF.

Action: The EPA derived an OSF using the Cheng et al. (2006) analysis of the NIOSH cohort based on their exposures to TCDD. These exposures were estimates derived using a job exposure matrix (JEM) rather than actual measured serum TCDD values for the majority of workers in the cohort. The resulting estimates of exposure were used in highly quantitative mathematical models by the EPA to derive the OSF.

Limitations: The JEM relies upon qualitative parameters that incorporate subjective judgment. The resulting exposure estimates were not quantitative and thus have limited application in the mathematical models used by the EPA to derive an OSF. This major limitation is acknowledged by original authors in the peer review literature but was not recognized by the EPA.

Suggested Improvements: EPA should acknowledge the subjective nature of the exposure estimates and, at a minimum, conduct an analysis to address the uncertainty in the underlying data and the potential impact of such on the resulting OSF.

4 The EPA should address the role of confounding exposures in the cohort from the epidemiological study used to derive the OSF.

Action: The EPA derived an OSF using the Cheng et al. (2006) analysis of the NIOSH cohort based on their exposures to TCDD (without considerations for other exposures).

Limitations: In addition to the TCDD-contaminated products to which the NIOSH cohort was exposed, workers were clearly exposed to other carcinogenic compounds (e.g., benzene, ethylene oxide, acetaldehyde, etc.).

Suggested Improvements: Given the fact that the EPA's OSF is based on a cancer mortality analyses of the NIOSH cohort in which all cancer sites have been combined, an evaluation of how exposures to these carcinogens could have impacted such analyses is essential to the validity of the updated OSF.

5 Additional rationale is needed to support the decision to use linear extrapolation to derive an OSF — the rationale provided in the Draft Report was insufficient.

Action: The EPA supported their decision to use linear extrapolation to derive an oral cancer slope factor (OSF) with several lines of reasoning, including linear responses on a population basis, linear responses involving ROS, and the theory of additivity with other AhR agonists.

Limitations: The draft rationale is not sufficient to support the decision to use a linear approach. Collectively, the reasoning is not biologically plausible and is not supported by the wealth of data available (on the contrary, it suggests the use of nonlinear extrapolation).

Suggested Improvements: It is suggested that the EPA revisit this topic. Additional discussion regarding biological plausibility is required in addition to the current statistical arguments, which are not in line with EPA guidelines. EPA should not use a linear model given that TCDD acts via a receptor mediated process.

6 Given the high level of variability and lack of clinical significance of the selected endpoint for the development of noncancer toxicity criteria (Reference Dose), additional discussion and evaluation are warranted.

Action: The EPA's noncancer RfD is based on Mocarelli et al. (2008), which reports significantly lower total and motile sperm counts in residents of Seveso, Italy relative to a comparison population

Limitations: There are many significant limitations both with the underlying study data (or lack thereof) as well as with the interpretation and application of such by the Agency. These limitations include:

1. The EPA selected Mocarelli et al 2008 as a key study for noncancer evaluation based on a critical effect (decreased sperm concentration) from data that wasn't actually reported by the original authors, but rather was assumed (though not confirmed) by the EPA. Further, the EPA had no information about the TCDD levels in the people that were supposedly associated with the critical effect
2. The EPA selected a critical effect based on endpoint data unadjusted for confounders, but then used adjusted endpoint data for the RfD calculations (importantly, the adjusted endpoint data would not have classified as a critical effect by the Agency)

3. The study data did not demonstrate a dose response relationship between sperm concentration and TCDD serum levels

4. The actual sperm counts in the exposed persons (and controls) were not clinically significant (i.e., were well within normal ranges)

5. The study results were inconsistent within and among endpoints

6. The EPA did not address how the clear differences in demographics between the control and exposure groups impacted the findings related to sperm concentrations

7. The study authors did not measure TCDD serum concentrations in the control group (thus is it difficult to understand how the authors, and the EPA, can determine the supposed effects are TCDD-related)

Suggested Improvements: The Agency should provide additional rationale and discussion on the many shortcomings related to the study and the underlying data. Given that the primary author is an SAB member, the EPA should obtain the original study data and conduct more robust quantitative analyses (e.g., BMD). Further, the Agency should consider other scientific studies available that provide more appropriate datasets for derivation of an RfD.

7 The implications of the draft toxicological benchmarks should be considered by the EPA.

Action: The EPA has proposed toxicological benchmarks, when used in typical risk assessment calculations, that indicate current levels of TCDD in breast milk, foodstuffs, and soil may pose unacceptable health risks.

Limitations: The EPA failed to determine the impact of the proposed toxicological benchmarks (cancer slope factor and RfD), and failed to address the potential downstream events associated with such. For example, using the proposed toxicological benchmarks we calculated "safe" concentrations of TCDD in foods and soil. Comparison of these "safe" TCDD concentrations to current TCDD concentrations in foods and soil indicates that "background" levels of TCDD exceed the "safe" levels generated using the proposed toxicological benchmarks. Additionally, the dose of dioxin an infant receives from nursing is many times greater than the proposed RfD.

Suggested Improvements: The draft toxicological benchmarks will have significant impacts on public health policy and various regulatory actions (e.g. Superfund, RCRA, state environmental programs etc.). The EPA needs to explain to the public the significance of the proposed toxicological benchmarks and the significant cost to the United States if these toxicological benchmarks are utilized by the EPA. For example, will use of these toxicological benchmarks lead to the US Government discouraging mothers from breast feeding an infant and/or how will the EPA and other US government agencies deal with concerns about the safety of the US food supply? Finally, the EPA should provide a detailed uncertainty analysis of the proposed toxicological benchmarks.

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Limitations: EPA clearly acknowledged key events in the MOA for TCDD-induced carcinogenesis, and particularly the role of AhR activation. Despite these robust data available, the Agency did not fully develop an MOA, nor was adequate support regarding the lack of data on an MOA for TCDD provided. Further, the Agency appeared to misinterpret and/or ignore their own technical guidelines and frameworks regarding analysis of such.

Suggested Improvements: Given the abundance of available data, EPA should consider a thorough evaluation of TCDD MOA — including application of such to the Agency's MOA framework and incorporation of key concepts from the Agency's cancer guidelines.

Sufficient data are available to develop an MOA

Although the EPA denied sufficient evidence for an MOA for TCDD, events in the MOA were clearly discussed throughout the draft document.

In this regard, the EPA has demonstrated a generalized MOA for multiple tumor types that share some common key events and themes in their carcinogenic processes (see Figures 5-1 and 5-2 in the draft document; Figure 5-2 copied here (See **Figure 1**)). The Agency further stated "a picture is emerging wherein TCDD is considered a "receptor-mediated carcinogen" in laboratory animals...acting in a manner similar to peroxisome proliferators, phorbol esters, or estrogen," (p. 5–11). For liver, lung, and thyroid tumors, the first key event involves interaction between TCDD and AhR. In both the liver and lung hypothesized MOAs, the next key event is changes in gene expression. The penultimate key event in the three tumor types appears to be cell proliferation ultimately leading to adenomas and carcinomas. This suggests the Agency recognized a generalized MOA for three tumor types associated with TCDD in laboratory animals.

Despite the voluminous data available characterizing key events in MOA (and particularly the role of the AhR), the EPA attempts to inject uncertainty in the TCDD MOA by citing that "non-AhR mediated carcinogenic effects are possible." The Agency only provides one reference in support of this conclusion, and in doing so, did not accurately convey the authors' findings. Fernandez-Salguero et al. (1996) used AhR-null mice to demonstrate that toxicity of TCDD was in fact AhR mediated. At an incredibly high dose (2000 µg/kg), some of the AhR-null mice demonstrated occasional scattered hepatocellular necrosis or pulmonary vacuolitis, an observation that was not evaluated statistically nor confirmed in later studies. Yet the EPA characterize these same observations as "several minor lesions including scattered necrosis and vacuolitis in the liver and

lungs," later claiming that these observations were "consistent." The authors concluded "these results conclusively demonstrate that essentially the *in vivo* effects of TCDD are AhR-mediated;" in stark contrast to these author findings, the EPA concluded that AhR-independent carcinogenic effects of TCDD were possible. The more logical conclusion is that the occasional yet minimal toxicities observed in AhR-null mice administered a very high TCDD dose represent non-specific, high-dose effects and are irrelevant to any discussion of TCDD's MOA.

It is of particular interest to note that the EPA has a rather inconsistent approach in their discussions related to AhR-mediated events in TCDD MOA; though the EPA considers the TCDD AhR MOA to be insufficient to support the nonlinear modeling of TCDD cancer risk, it relies on this MOA in several areas in its Draft Response, most notably using the TCDD AhR MOA as evidence in support of the biological plausibility of tumor causality in humans.

The document also cites evidence that constitutively activated AhR can also induce cancer; however, it is not made clear how this refutes the MOA that TCDD activation of the AhR can cause cancer at certain doses. Moreover, it has recently been reported that low levels of AhR activation may act as a tumor suppressor (Fan et al., 2010); thus if EPA's intent is to suggest that all AhR activation is pro-carcinogenic, there is evidence to the contrary.

Data suitable for the EPA framework on developing an MOA are readily available

Given the amount of literature on TCDD (over 7,000 citations in PubMed), there would appear to be sufficient data to suggest that the MOA for at least some TCDD-induced tumors can be plausibly hypothesized and their relevance to humans evaluated. The EPA should have identified tumors from animal studies, applied their own MOA framework, and examined human relevance through consideration of available epidemiological data. It is not clear why EPA did not consider these data as supporting a general MOA for TCDD-induced tumors. It would seem that understanding exact events between AhR activation and cell proliferation would constitute a level of mechanistic detail that rarely exists for chemicals. At the very least, examining these tumors through the MOA Framework would allow for a more transparent assessment of these tumors and their potential relevance to humans.

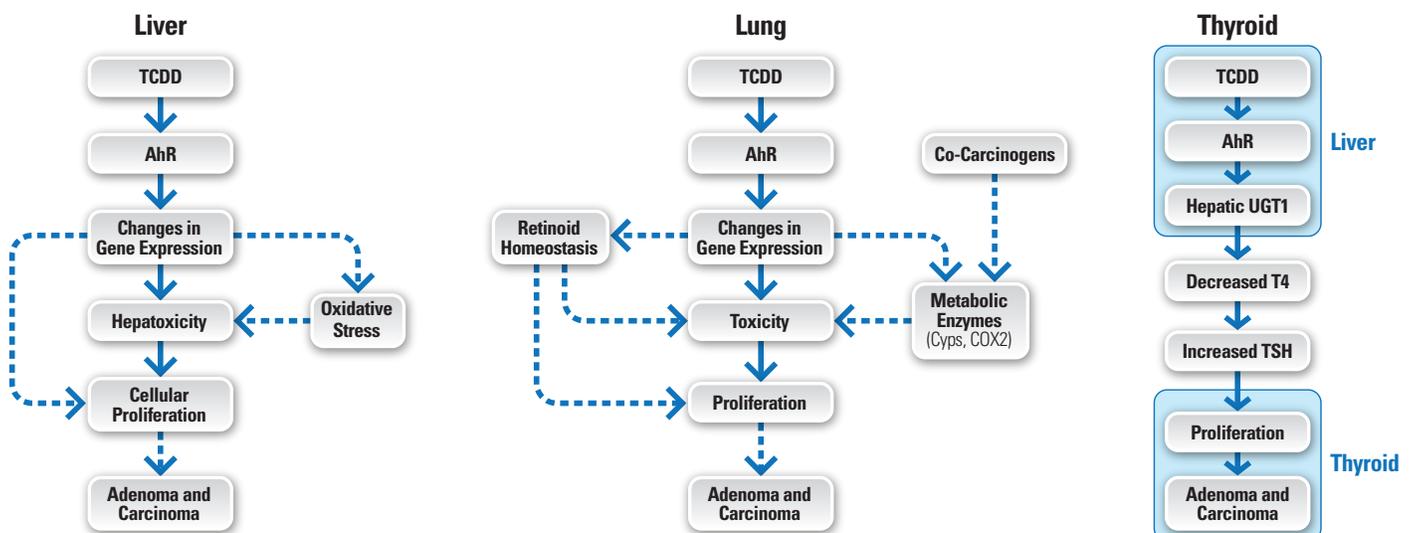
For EPA to suggest that the available data equate to an unknown MOA, places TCDD together with numerous less- or unstudied chemicals for which there may truly be limited or no data beyond evidence for carcinogenicity. In this regard, a full MOA evaluation and the identification of data gaps would allow for a more appropriate evaluation.

References:

Fan Y, Boivin GP, Knudsen ES, Nebert DW, Xia Y, Puga A (2010). The Aryl Hydrocarbon Receptor Functions as a Tumor Suppressor of Liver Carcinogenesis. *Cancer Research* 70: 212–220.

Fernandez-Salguero PM, Hilbert DM, Rudikoff S, Ward JM, Gonzalez FJ (1996). Aryl-hydrocarbon receptor deficient mice are resistant to 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced toxicity. *Toxicol Appl Pharmacol.* 140: 173–v179.

Figure 1. Adapted from Figure 5-2. TCDD's hypothesized modes of action in site-specific carcinogenesis. See text for details. In each instance, the solid arrows depict pathways that are well-established and are associated with low uncertainty. The dashed arrows represent connections that are less established and are associated with higher uncertainty.



2 The EPA should reconsider their selection of a linear extrapolation approach to evaluate cancer risk given that three previous scientific panels have recommended nonlinear approaches.

Action: The EPA chose to evaluate cancer risk using a linear model rather than nonlinear model.

Limitations: Three prestigious scientific advisory panels asked to review the EPA's dioxin reassessment all identified the linear modeling assumption as a specific point of concern and recommended that nonlinear approaches be incorporated into the assessment. This recommendation was founded on data demonstrating clear nonlinear dose-response relationships.

Suggested Improvements: Given the Agency's lack of rationale for selecting a linear model, and clear recommendations from multiple scientific panels that have reviewed the assessment, the EPA should reconsider their selection of a linear model.

During the EPA's ongoing dioxin reassessment process, three scientific panels have identified the linear modeling assumption as a specific point of concern and clearly stated that alternate, non-linear approaches should at the very least be identified and discussed in the context of the available epidemiological, pharmacokinetic modeling, and bioassay data.

The 1995 SAB identified EPA's reliance on a linear model a major deficiency

In the review report issued in 1995, the SAB stated that the major deficiency of the EPA's dioxin reassessment draft was "its reliance on the standard EPA default assumption of a linear non-threshold model for carcinogenic risk," and suggested using available data to construct an alternate model that would better fit minimal responses to low levels of environmental exposure (SAB, 1995). The report also urged the EPA to further examine fundamental principals of receptor theory, saying that dioxin is a cancer promoter, not initiator, that acts via the AhR which exhibits a U-shaped dose response curve. The report included that all other agencies that have evaluated the same toxicological and epidemiologic dioxin data have incorporated some type of threshold approach in their risk evaluations.

The 2001 SAB stated that non-linearity better describes the receptor mediated response

The report issued by the 2001 SAB review panel further addressed the importance of identifying and evaluating possible alternatives to linear modeling, again bringing to attention that non-linearity better describes a receptor mediated response that could potentially follow very strict thresholds. Additionally, this panel pointed out that some of the epidemiological carcinogenicity data appears to be non-linear and fitting this data with a linear model results in much higher risk estimates. The report stated, that, "given the current questions about how much more regulatory action is appropriate for dioxin, there is a legitimate need to also include "best estimates" of the cancer risk, and even a "lower" risk estimate that is not solely reliant on a linear model." Consistent with the 1995 review, the 2001 panel concluded that at the very minimum other modeling approaches should be addressed and that there appears to be sufficient data that would support the use of a non-linear modeling approach, especially given what we know about the receptor-mediated mode of action of dioxin.

The 2006 NAS thought that the decision to rely on a linear model lacked scientific support

The final review report submitted by the NAS in 2006 again highlighted the need to explore non-linear dose-response models, stating that, "EPA's decision to rely solely on a default linear model lacked adequate scientific support," and, "the committee unanimously agrees that the current weight of evidence on TCDD, other dioxins, and DLCs carcinogenicity favors the use of nonlinear methods for extrapolation below the point of departure (POD) of mathematically modeled human or animal data." The committee summarized four major areas where the scientific evidence supports the use of a nonlinear over a linear model: (1) TCDD, other dioxins, and DLCs are not directly genotoxic, and act as tumor promoters, which exhibit nonlinear dose-response relationships; (2) adverse effects of dioxin exposure are receptor mediated, which have been shown to exhibit more complex dose-response curves, and the EPA has concluded in previous assessments of receptor-mediated agents that a nonlinear model at low doses is appropriate; (3) liver tumors, which the EPA used in the reassessment to evaluate response, are secondary to hepatotoxicity, which raises concern for using tumor data to extrapolate at low doses; and (4) there is clear evidence of a nonlinearity, sigmoidal dose-response relationship in recent bioassay data. As discussed in previous review reports, this committee also recommended that the EPA include risk estimates based on nonlinear models in addition to linear approaches for comparison purposes, and discuss the strengths and weaknesses of each method.

References:

SAB (1995). A Second Look at Dioxin: Science Advisory Board's Review of the Draft Dioxin Exposure and Health Effects Reassessment Documents. EPA-SAB-EC-95-021, September 29, 1995.

SAB (2001). Dioxin Reassessment — An SAB Review of the Revised Sections (Dose Response Modeling, Integrated Summary and Risk Characterization, and Toxicity Equivalency Factors) of the EPA's Reassessment of Dioxin by the Dioxin Reassessment Review Subcommittee of the EPA Science Advisory Board (SAB). EPA-SAB-EC-01-006, May 2001.

NAS (2006). Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment by the Committee on EPA's Exposure and Human Health. The National Academies Press, Washington D.C.

3 The EPA should evaluate the impact of the qualitative exposure estimates used in the derivation of the OSF.

Action: The EPA derived an OSF using the Cheng et al. (2006) analysis of the NIOSH cohort based on their exposures to TCDD. These exposures were estimates derived using a job exposure matrix (JEM) rather than actual measured serum TCDD values for the majority of workers in the cohort. The resulting estimates of exposure were used in highly quantitative mathematical models by the EPA to derive the OSF.

Limitations: The JEM relies upon qualitative parameters that incorporate subjective judgment. The resulting exposure estimates were not quantitative and thus have limited application in the mathematical models used by the EPA to derive an OSF. This major limitation is acknowledged by original authors in the peer review literature but was not recognized by the EPA.

Suggested Improvements: EPA should acknowledge the subjective nature of the exposure estimates and, at a minimum, conduct an analysis to address the uncertainty in the underlying data and the potential impact of such on the resulting OSF.

“...the job-exposure matrix constructed by NIOSH researchers necessarily relied on limited sampling data over time, and on subjective judgments on contact time, contact factor, and relative exposure potential for jobs at 12 different manufacturing facilities over a period of decades (including numerous process changes) (Piacitelli et al., 2000). The parameter for contact factor assigned by Piacitelli et al. (2000) varied among jobs by 150-fold (from 0.01 to 1.5), and the total exposure score assigned to individual jobs varied by a factor of more than 1,000,000. Furthermore, the dose-rate regressions presented here and in Steenland et al. (2001) for this cohort are based solely on data for a small subcohort of individuals with measured serum lipid TCDD concentrations sampled in 1987–1988. These individuals were drawn from a single plant out of the 12 originally included in the NIOSH cohort (only eight plants were included in the exposure reconstruction effort by NIOSH). Thus, the results of the dose-rate regression for these individuals may or may not be representative of the exposures of cohort members from other plants.” — Aylward et al. (2005).

The study relied upon by the EPA utilized a job exposure matrix that is inherently dependent on subjective, qualitative values (that are even recognized as such by study authors)

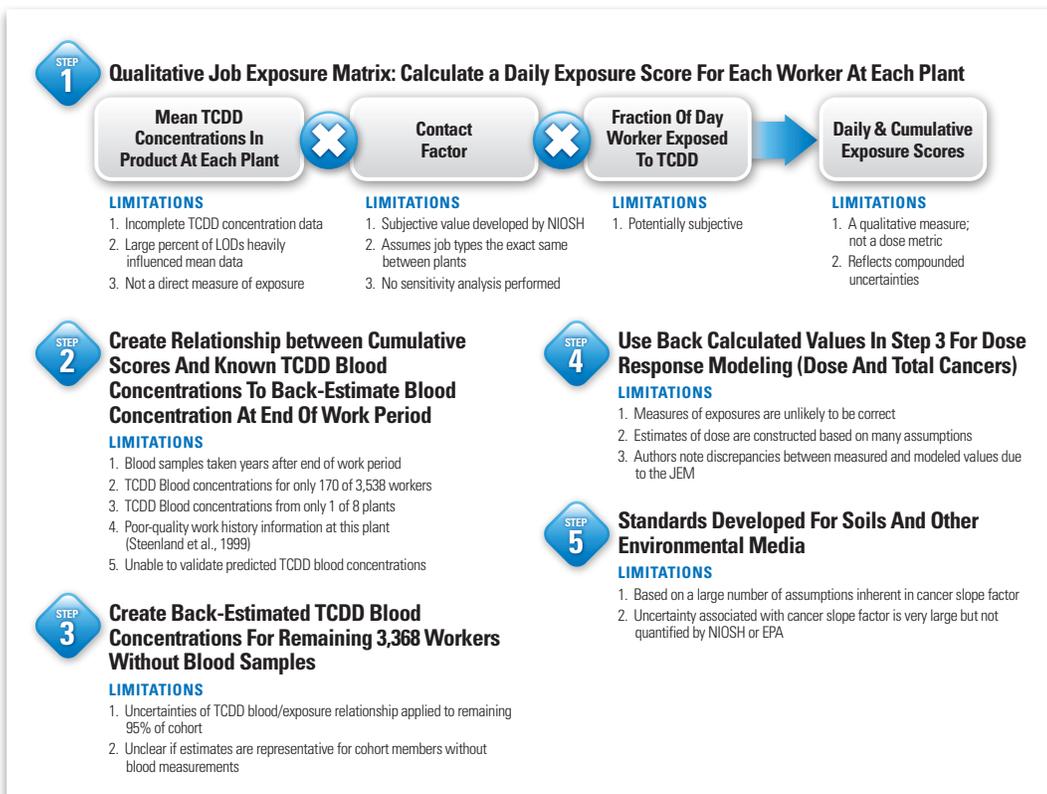
The EPA derived an oral cancer slope factor (OSF) using the analyses of the NIOSH occupational exposure subcohort reported by Cheng et al. (2006). The NIOSH subcohort consisted of 3,538 workers from eight U.S. chemical plants, and of these only 170 workers from one plant provided blood samples in 1987–1988, more than two decades after initial TCDD exposures. In an effort to estimate TCDD exposures, the NIOSH investigators developed a job exposure matrix (JEM) that assigned a relative TCDD exposure score to each of the workers (Piacitelli et al., 2000) (Figure XX). However, the job exposure matrix incorporates qualitative and subjective factors that, in turn, render subsequent exposure calculations, such as those presented by Cheng et al. (2006), qualitative estimates. Further shortcomings include: (1) NIOSH assumed each job description involved the same degree of worker contact with the process materials regardless of the plant site NIOSH investigated, and (2) little to no explanation of how NIOSH derived the fractions of daily exposure it applied to each exposure score algorithm. The authors of Cheng et al. (2006) specifically noted a number of these limitations in an earlier publication (Aylward et al., 2005):

Additionally, the creators of the JEM lacked key information about the TCDD concentration in various products. For example, the TCDD concentrations for 2,4,5-T operators at Plant 1 from Feb 1951–Aug 1967 was assumed to be 18.6 mg/g based on samples collected in 1965 and 1966; whether those samples are reflective of the entire time period is not known.

The qualitative nature of the estimates is associated with a great deal of uncertainty

Given the qualitative nature of important elements of the exposure matrix upon which the Cheng et al. (2006) analyses relies, the EPA’s updated OSF is, by extension, itself a qualitative estimate that contains a great deal of uncertainty derived from the subjective judgments applied to the exposure scores. **Figure 2** overviews how these limitations clearly impact the resulting OSF. The EPA does not address these important limitations, nor does the Agency account for such in their quantitative analysis, despite their significant potential for impacting the resulting OSF. Thus it is suggested that quantitative sensitivity analyses be conducted to determine the impact of the underlying subjective, qualitative parameters on their assessment.

Figure 2. Dose Estimation from Epi Studies for EPA CSF derivation: Process and Limitations



References:

- Aylward LL, Brunet RC, Starr TB, Carrier G, Delzell E, Cheng H, Beall C (2005). Exposure reconstruction for the TCDD-exposed NIOSH cohort using a concentration- and age-dependent model of elimination. *Risk Anal* 25(4):945–56.
- Cheng H, Aylward L, Beall C, Starr TB, Brunet RC, Carrier G, Delzell E (2006). TCDD exposure-response analysis and risk assessment. *Risk Anal* 26(4):1059–71.
- Piacitelli L, Marlow D, Fingerhut M, Steenland K, Sweeney MH (2000). A retrospective job exposure matrix for estimating exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Am J Ind Med* 38(1):28–39.
- Steenland K, Deddens J, Piacitelli L (2001). Risk assessment for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) based on an epidemiologic study. *Am J Epidemiol* 2001 154(5):451–8.

4 The EPA should address the role of confounding exposures in the cohort from the epidemiological study used to derive the OSF.

Action: The EPA derived an OSF using the Cheng et al. (2006) analysis of the NIOSH cohort based on their exposures to TCDD (without considerations for other exposures).

Limitations: In addition to the TCDD-contaminated products to which the NIOSH cohort was exposed, workers were clearly exposed to other carcinogenic compounds (e.g., benzene, ethylene oxide, acetaldehyde, etc.).

Suggested Improvements: Given the fact that the EPA's OSF is based on a cancer mortality analyses of the NIOSH cohort in which all cancer sites have been combined, an evaluation of how exposures to these carcinogens could have impacted such analyses is essential to the validity of the updated OSF.

Figure 3.

Workers at the eight plants had the opportunity to be exposed to more than 20 carcinogens

benzene	para-aminobiphenyl
aniline	trichloroethylene
hexachlorobenzene	petroleum polymer resins
dichlorodiphenyltrichloroethane	dichlorobenzene
acetaldehyde	polychlorinated biphenyls
2,4-dichlorophenol	n-butyl benzyl phthalate
2,4,5-trichlorophenol	hexachlorobutadiene
2,4,6-trichlorophenol	parathion
tetrachlorophenol	ethylene oxide
pentachlorophenol	ethylene dichloride
N-nitrosodimethylamine	methylene chloride
N-nitrosomorpholine	sulfuric acid

The EPA derived an updated oral cancer slope factor (OSF) using the analyses of the NIOSH occupational exposure subcohort reported by Cheng et al. (2006). Initially the NIOSH study identified 12 U.S. chemical plants where workers were potentially exposed to process materials contaminated with TCDD. NIOSH prepared a Dioxin Registry Report for each of the 12 plants, which provided information on the chemical processes involved at each plant. These reports clearly demonstrate that workers at the eight plants identified by NIOSH to have the most TCDD exposure data also had the opportunity to be exposed to more than 20 carcinogens (See **Figure 3**). This is of particular concern given that the endpoint used to derive the OSF was "all cancers." Fingerhut et al. (1991) noted the following:

"Two observations argue against a carcinogenic effect of TCDD. First, there was not a significant linear trend of increasing mortality with increasing duration of exposure to products contaminated with TCDD (Table 4). However, our use of duration of exposure may have misclassified the cumulative dose of some workers. In addition, a dose-response relation is generally viewed as strong evidence for an association when it is present, but as fairly weak evidence against an association when it is absent. Second, our study did not directly assess the effect of exposure to TCDD alone. The workers were exposed concurrently to the chlorophenols and phenoxy herbicides that were contaminated with TCDD. In addition, they may have exposed to numerous other chemicals while employed at the plants."

Thus, it seems essential that the EPA address the potential confounding nature of exposures to these many other carcinogenic compounds.

References:

Cheng H, Aylward L, Beall C, Starr TB, Brunet RC, Carrier G, Delzell E (2006). TCDD exposure-response analysis and risk assessment. *Risk Anal* 26(4):1059–71.

Fingerhut MA, Halperin WE, Marlow DA, Piacitelli LA, Honchar PA, Sweeney MH, Greife AL, Dill PA, Steentland K, Suruda AJ (1991). Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *N Engl J Med* 324(4):212–8.

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Limitations: The draft rationale is not sufficient to support the decision to use a linear approach. Collectively, the reasoning is not biologically plausible and is not supported by the wealth of data available (on the contrary, it suggests the use of nonlinear extrapolation).

Suggested Improvements: It is suggested that the EPA revisit this topic. Additional discussion regarding biological plausibility is required in addition to the current statistical arguments, which are not in line with EPA guidelines. EPA should not use a linear model given that TCDD acts via a receptor mediated process.

EPA provides a discussion of “biological data” on TCDD that support the “appropriateness” of low-dose linear extrapolations. However, there are a number of limitations to these arguments.

The EPA suggests that a linear response in ROS may support the use of linear extrapolation, but does not provide actual evidence of such.

The EPA has suggested that if TCDD generated reactive oxygen species (ROS) at low doses, it would support their application of a low-dose linear cancer model similar to what would be used for directly DNA reactive agents (note: the EPA clearly documents that TCDD is a nongenotoxic compound). It is unclear why this would be the case as this assertion is made without citation or the support of any evidence. The mere induction of oxidative markers does not in itself support the use of a low-dose, one-hit dose response model since background and low dose ROS induce adaptive cellular responses capable of preventing and removing potential DNA damage (Feinendegen, 2002). Thus, the induction of such adaptive response activities supports the application of a low dose, nonlinear dose response model (Trosko, 1998).

The EPA suggests that statistical modeling for other compounds supports linear extrapolation on a population basis but does not provide sufficient evidence of such for receptor-mediated compounds such as TCDD

The Agency relies greatly on White et al. (2009) for supporting the mathematical basis of the low-dose linearity for TCDD. These authors reported the general consensus (though there were exceptions) of a workshop held in 2007 on low-dose extrapolation in which participants felt that low-dose linear extrapolation was the most appropriate extrapolation method for both cancer and noncancer endpoints. This approach was based on the notion that the dose-response for a population will be linear due to interindividual variability, background disease, and background exposure. The authors cite examples of particulate matter, ozone, lead, environmental tobacco smoke (ETS), and radon as supporting low-dose linearity at the population level. However, the applicability of the MOAs for these chemicals to those that act through receptor-mediated mechanism (e.g. TCDD) was not addressed in White et al. (2009) or the Draft Report. A thorough consideration of a) the validity of low-dose linearity for the aforementioned chemicals, and b) the relevance of the examples discussed in the workshop to chemicals with receptor-mediated MOAs is needed in order for the EPA to rely on the concepts presented at a workshop (rather than on their own guidance and/or the many other publications on this topic in the peer review literature).

It is of interest to note that White and colleagues cite Lutz et al. (2005) as a key publication for supporting low-dose linear approaches. Yet White et al. do not appear to consider statements by Lutz such as,

“Strongly sublinear (up-bent) curves and apparent thresholds may allow for a rejection of the linear-no threshold (LNT) default assumption and for a discussion of threshold doses and safety factors to derive tolerable exposure levels. This appears to be appropriate if mechanistic considerations can explain the threshold-like shape of the dose-response curve” (emphasis added).

In an earlier publication, Lutz (1998) specifically cited TCDD as an example of a compound that exhibited J-shaped tendencies in liver tumor formation in rodents as well as in initiation/promotion studies with phenobarbital (and thus was non-linear).

Based on the rationale expressed in White et al. (2009), the “linearization” of population dose-response curves would be a universal phenomenon for all toxicants. This theory is not supported by the scientific community (Rhomberg et al. 2009). These issues need to be further considered by the Agency.

The EPA provides an incomplete rationale for suggesting that additivity impacts receptor mediation involved in carcinogenic responses

The Dioxin Assessment also cites Crump et al. (1976) in support of a linear low-dose extrapolation based on the concept of “additivity.” EPA argues that since AhR activity exists at some background level (due to endogenous, natural, and dioxin-like AhR ligands), the additional stimulation by TCDD adds to background responses and thus supports a linear model. But here the EPA contradicts itself: it assumes the AhR-mediated process for carcinogenicity is equivalent for induction by TCDD and endogenous/natural AhR agonists, while also recognizing that AhR can be selectively activated. The existence of AhR ligands that can activate certain — but not all — aspects of AhR-mediated pathways associated with TCDD argues against the EPA’s assertion of background additivity in this case. A review of the literature indicates there is much more evidence that the AhR can be selectively modulated than EPA suggests. In addition to Fretland et al. (2004), several studies have demonstrated selective AhR modulation in both in vitro and in vivo model systems (Chen et al., 1995; Fritz et al., 2009; McDougal et al., 2001; Murray et al., 2010a,b). Thus, it is suggested that the Agency review the additional studies cited here, as well as others available in the literature, and revisit the theory of additivity in their support of a linear model.

The EPA did not address commonly-accepted principles regarding thresholds for receptor-mediated responses

Given that receptor-mediated responses are generally regarded as having a threshold, the EPA failed to adequately address the non-linear nature of receptor-mediated dose response. Basic receptor theory dictates that most receptor-based effectors are not activated in a linear fashion. As indicated by EPA, this concept was originally put forth by Stephenson et al. (1956), who was the first to formulate a receptor binding model (based on the availability of spare receptors) that accounted for the observed discordance between ligand binding affinities and activating doses. The issue of non-linear receptor-based thresholds regarding TCDD has been put forth to the Agency on several prior occasions (e.g., in a letter to the editor of Risk Analysis signed by 20 pharmacologists, Byrd et al., (1998) identify the need for EPA to focus its TCDD risk assessment on the nonlinear consequences of AhR activation). These issues were not adequately addressed by the EPA, particularly considering many previous comments on such from previous SAB panels.

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6 Given the high level of variability and lack of clinical significance of the selected endpoint for the development of noncancer toxicity criteria (Reference Dose), additional discussion and evaluation are warranted.

Action: The EPA's noncancer RfD is based on Mocarelli et al. (2008), which reports significantly lower total and motile sperm counts in residents of Seveso, Italy relative to a comparison population

Limitations: There are many significant limitations both with the underlying study data (or lack thereof) as well as with the interpretation and application of such by the Agency. These limitations include:

1. The EPA selected Mocarelli et al 2008 as a key study for noncancer evaluation based on a critical effect (decreased sperm concentration) from data that wasn't actually reported by the original authors, but rather was assumed (though not confirmed) by the EPA. Further, the EPA had no information about the TCDD levels in the people that were supposedly associated with the critical effect
2. The EPA selected a critical effect based on endpoint data unadjusted for confounders, but then used adjusted endpoint data for the RfD calculations (importantly, the adjusted endpoint data would not have classified as a critical effect by the Agency)
3. The study data did not demonstrate a dose response relationship between sperm concentration and TCDD serum levels
4. The actual sperm counts in the exposed persons (and controls) were not clinically significant (i.e., were well within normal ranges)
5. The study results were inconsistent within and among endpoints
6. The EPA did not address how the clear differences in demographics between the control and exposure groups impacted the findings related to sperm concentrations
7. The study authors did not measure TCDD serum concentrations in the control group (thus is it difficult to understand how the authors, and the EPA, can determine the supposed effects are TCDD-related)

Suggested Improvements: The Agency should provide additional rationale and discussion on the many shortcomings related to the study and the underlying data. Given that the primary author is an SAB member, the EPA should obtain the original study data and conduct more robust quantitative analyses (e.g., BMD). Further, the Agency should consider other scientific studies available that provide more appropriate datasets for derivation of an RfD.

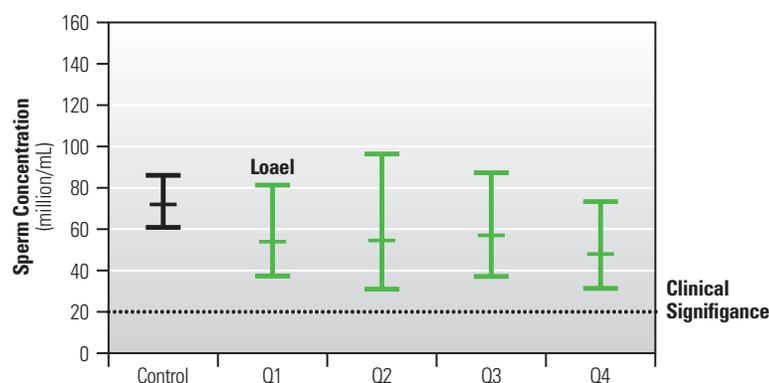
The EPA determined a critical effect based on data that was not actually reported by the study authors

The EPA relied on decreased sperm concentrations measured in Seveso males who were ages 1-9 years of age at the time of the Seveso incident as a critical effect. The Agency correctly noted that the actual values used to make this determination (unadjusted mean: 53.6 million/ml, SD: 21.8–131.8 million/ml) do not fall below the clinical level of concern (20 million/ml). However, the EPA rationalizes selecting this as an endpoint of concern by claiming that there must be individuals within this group whose sperm concentrations fall below the low-end standard deviation value of 21.8 million (and therefore may have sperm concentrations that would be of clinical concern). Not only was the EPA unable to verify this (the Agency was unable to obtain the original data even though the primary author is an SAB member), but the Agency also had no information regarding the actual TCDD concentrations in the persons that may have had sperm concentrations below the low end of the standard deviation (e.g., these persons could have had high or low serum concentrations of TCDD). Thus, in determining the critical effect, the EPA had no information to verify that the persons with the potentially low values were associated with higher exposures to TCDD. In addition, the Agency fails to comment on the low-end standard deviation value for the control group (31.7 million/ml), which is also near the level of clinical significance. Using their reasoning, this would also suggest that a fraction of the control population also has sperm concentrations of clinical concern (and therefore may not be different than the exposure group). The Agency needs to address these issues and provide a more scientifically robust rationale, as well as a statistical evaluation, to support their decision in selecting this endpoint and dataset.

The EPA used data that were not clinically significant and did not demonstrate a dose-response relationship to derive an RfD

Separately, the Agency used data adjusted for confounders (rather than the unadjusted data used to rationalize the selection of the endpoint as critical) provided by the study authors to calculate an RfD. The original study authors conducted an analysis based on adjusted data and compared sperm concentrations by TCDD serum concentration quartile (see **Figure 4**) to the control group (note: the study did not evaluate TCDD serum concentrations in the control group). The EPA then selected the median serum TCDD concentration (68 ppt) in first quartile as the LOAEL, which was further evaluated in a PBPK model to determine the point of departure for the RfD derivation. It is important to note the lack of dose response for this effect (and for most other effects evaluated), as well as the lack of clinical significance for all groups (including control).

Figure 4. (Adapted from Figure 3A from Mocarelli et al. 2008). Sperm concentration (adjusted mean and 95% confidence interval) for exposed men 1-9 years old in 1976 and sampled for sperm endpoints in 1998.



Insufficient data were available to determine exposure-related effects

Mocarelli et al. (2008) determined statistical significance by comparing to the control group. However, it seems there is a significant amount of uncertainty given that the reported demographics of the control population were different than the exposure groups, and because the study authors had no information on the TCDD levels in the control group. It is very difficult to understand how the EPA can derive an RfD using a dataset in which neither the study authors nor the Agency can confirm that the findings were exposure-related. It should also be noted that Mocarelli et al. (2008) do not present information on the geographic origins of the control group. Several studies to date have demonstrated that sperm counts can vary dramatically from city to city and among different geographic regions (Fisch et al., 1996a; Swan et al., 2003; reviewed in Safe et al., 2000). For example, Fisch et al. (1996b) conducted a literature review of geographical sperm concentration data and reported a high degree of variability within the United States, with mean values ranging from 52.9 million/ml in Iowa to 134 million/ml in New York. Thus, this is an important factor that could have clearly impacted the analysis, yet was not considered by the study authors or the EPA.

The EPA appeared to have selectively chosen a dataset to derive an RfD given the inconsistent findings of the study

From a more general perspective, the Mocarelli et al. (2008) study reports very inconsistent results on which the EPA fails to comment. Although sperm concentration and motility counts are significantly reduced for the youngest of the Seveso age group relative to control, there is no significant reduction in total sperm count or testosterone levels. More interestingly, study reports significantly elevated sperm concentrations and motility counts for the Seveso pubescent males (10-17 years old) present at the time of the incident relative to controls. The lack of consistent findings and dose response relationships are concerning and need to be addressed by the Agency.

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7 The implications of the draft toxicological benchmarks should be considered by the EPA.

Action: The EPA has proposed toxicological benchmarks, when used in typical risk assessment calculations, that indicate current levels of TCDD in breast milk, foodstuffs, and soil may pose unacceptable health risks.

Limitations: The EPA failed to determine the impact of the proposed toxicological benchmarks (cancer slope factor and RfD), and failed to address the potential downstream events associated with such. For example, using the proposed toxicological benchmarks we calculated “safe” concentrations of TCDD in foods and soil. Comparison of these “safe” TCDD concentrations to current TCDD concentrations in foods and soil indicates that “background” levels of TCDD exceed the “safe” levels generated using the proposed toxicological benchmarks. Additionally, the dose of dioxin an infant receives from nursing is many times greater than the proposed RfD.

Suggested Improvements: The draft toxicological benchmarks will have significant impacts on public health policy and various regulatory actions (e.g. Superfund, RCRA, state environmental programs etc.). The EPA needs to explain to the public the significance of the proposed toxicological benchmarks and the significant cost to the United States if these toxicological benchmarks are utilized by the EPA. For example, will use of these toxicological benchmarks lead to the US Government discouraging mothers from breast feeding an infant and/or how will the EPA and other US government agencies deal with concerns about the safety of the US food supply? Finally, the EPA should provide a detailed uncertainty analysis of the proposed toxicological benchmarks.

Table 1. Comparison of Dioxin Risk-Based Concentrations (RBCs) in Food to Average Concentrations

Media	RBC Based on OSF ^c			RBC Based on RfD ^d	Average Media Concentration ^e
	Risk Level: 1E-06 (pg/g)	Risk Level: 1E-05 (pg/g)	Risk Level: 1E-04 (pg/g)		
Beef	0.003	0.03	0.34	1.03	0.142
Milk	0.001	0.01	0.10	0.29	0.017
Fish	0.011	0.11	1.10	3.30	0.94

Notes:

- a All scenarios are based on adult exposures.
- b Bolded, shaded cells indicate calculated RBCs below the respective average media concentrations
- c EPA (2010)-recommended OSF of 1 x 10⁻⁶ mg/kg-day⁻¹ [based on Cheng et al. (2006)]
- d EPA (2010)-recommended RfD of 7 x 10⁻¹⁰ mg/kg-day [based on Mocarelli et al. (2008)]
- e As reported by Lorber et al. (2009)

Definitions:

- OSF = oral slope factor
- pg/g = picogram per gram
- RBSC = risk-based screening concentration
- RfD = oral reference dose
- TEQ = toxicity equivalent
- TR = target risk

Several comparisons and/or calculations were completed in an effort to understand the potential impact of the draft toxicological benchmarks on exposures to TCDD in breast milk, foodstuffs, and soil. The results collectively indicate that the conservative nature of the values suggest that current exposures to TCDD in breast milk, food stuffs, and soils will be unacceptable by EPA and/or state standards (e.g., pose an unacceptable health risk). However, the implications of such were not addressed by the Agency. These issues clearly have great impact on public perception of health and may result in unwarranted and/or unnecessary concerns or actions.

EPA does not address the major issue that the current intake of TCDD from breast milk far exceeds the RfD proposed in the draft report

Dioxin intake for a breastfeeding infant was compared to the draft RfD. EPA scientists reported high-end, typical background concentrations in human breast milk of 242 pg TEQ/kg-day (Lorber and Phillips, 2002). The draft RfD, a daily intake that the Agency suggests is likely to be without an appreciable risk of deleterious effects during a lifetime, is 0.7 pg/kg-day. Thus, use of the draft RfD yields an unacceptable hazard for nursing infants when compared to typical background concentrations of dioxins in breast milk. This is particularly concerning, as mothers may opt to not breastfeed their infants and forgo the nutritional benefits to the baby if they believe there are dangerously high dioxin levels present in human breast milk. The EPA clearly needs to address the public significance of this issue.

The draft toxicological values suggest that the U.S. food supply is unsafe for human consumption, though the EPA does not address how the public should deal with such.

Using generic equations, risk-based concentrations (RBC) (“safe” levels based on the proposed toxicological values) for foodstuffs which contain dioxin (i.e., beef, milk, and fish) were determined and compared to average dioxin concentrations reported in these media by EPA scientists (Lorber et al., 2009). Exposure scenarios, ingestion rates, and other parameters were based on those applied by the EPA when reporting intakes associated with these foodstuffs (Lorber et al., 2009). As shown in **Table 1**, the results indicate that risk based concentrations for beef, milk, and fish, derived using the OSF were all below their respective average background concentrations at cancer risk levels of 1 x 10⁻⁶ and 1 x 10⁻⁵. This yields the conclusion that average beef, milk, and fish available in the U.S. for human consumption contain unacceptable levels of dioxin, which may lead to widespread, unnecessary concern regarding the safety of the U.S. food supply. However, because of the large and unquantified uncertainty surrounding the proposed toxicological benchmarks, the real human health risk associated with TCDD in the food supply and environmental media may actually be below levels of concern.

Use of the draft toxicological values indicates that soils in typical urban areas are contaminated with unacceptable levels; the EPA needs to address the potential concern and unnecessary soil cleanup efforts that would result

Using the same equations and exposure assumptions employed by the EPA in calculating soil risk-based screening concentrations (RBSC) for dioxin in EPA (2009), we calculated soil-based RBSCs using both the OSF (at three different risk levels: 1 x 10⁻⁶, 1 x 10⁻⁵, and 1 x 10⁻⁴) and the RfD. The results were then compared to maximum soil concentrations in the U.S. (EPA, 2007 and UM, 2009). **Figure 5** clearly demonstrates that the RBSCs based on the EPA’s draft toxicological benchmarks – both cancer and non-cancer – result in levels that are below maximum concentrations measured in rural areas of the U.S. Therefore, use of these toxicity benchmarks yields the conclusion that soils in typical urban areas of the U.S. are contaminated with dioxin at unacceptable levels; such a conclusion could lead to unwarranted alarm and costly, unnecessary soil cleanup efforts.

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Figure 5. Comparison of Dioxin Risk-Based Soil Concentrations Calculated Using EPA 2010 — Recommended Toxicity Factors with Background Concentrations

