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VIA EMAIL
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Dr. Thomas Armitage
Designated Federal Officer
EPA Scientific Advisory Board
Office of Environmental Information (OEI) Docket
(Mail Code: 2822T), U.S. Environmental Protection Agency, 1200
Pennsylvania Ave., NW. Washington, DC 20460

Subject: **Docket ID No. EPA-HQ-ORD-2010-0395**
Comments on EPA's external review draft entitled, ``EPA's Reanalysis of Key Issues
Related to Dioxin Toxicity and Response to NAS Comments'' (EPA/600/R-10/038A).

Dear Dr. Armitage:

Attached please find Georgia Pacific's comments on the EPA External Review Draft entitled *Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments*, which are submitted today to be considered by the EPA Science Advisory Board (SAB) as indicated in the *Federal Register* Volume 75, Number 98 (Friday, May 21, 2010[Pages 28610-28612]). We appreciate the opportunity to comment, but regret that the designated comment period was so short to review such a complex document. The EPA and affected parties have already committed tremendous resources and time to this issue. The draft toxicity values, if implemented would result in cleanup levels well below background in many contexts, requiring tremendous commitment of resources and time for both responsible parties and regulators managing state or federal sites. Given the lack of consensus on the toxicity of TCDD, we urge the Science Advisory Board to carefully consider the comments provided herein and other submitters, to direct EPA in preparing a document that will be based on the best available science.

If you require further information regarding these comments please contact Stewart Holm at SEHOLM@gapac.com.

Sincerely,

Traylor Champion
Vice President, Environmental Affairs

Attachment

Exponent[®]

Draft

**Comments on EPA's "Draft
Reanalysis of Key Issues
Related to Dioxin Toxicity and
Response to NAS Comments"**

Draft



Draft

**Comments on EPA's Draft
Reanalysis of Key Issues Related to
Dioxin Toxicity and Response to
NAS Comments**

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Acronyms and Abbreviations

AUC	area under the curve
b-TSH	thyroid-stimulating hormone levels in the blood
CSF	cancer slope factor
EPA	U.S. Environmental Protection Agency
IRIS	EPA's Integrated Risk Information System
JECFA	World Health Organization's Joint Exposure Committee on Food Additives
NAS	National Academy of Science
NIOSH	National Institute for Occupational Safety and Health
PBPK	physiologically based pharmacokinetic (model)
PCB	polychlorinated biphenyl
PCDD/Fs	2,3,7,8-substituted polychlorinated dibenzodioxins and furans
POD	point of departure
RfD	reference dose
TCDD	2,3,7,8-tetrachlorodibenzo- <i>p</i> -dioxin (TCDD)
TEQ	Toxic equivalence
TSH	thyroid-stimulating hormone
UCL	upper confidence level

Executive Summary

This document provides comments on the recently released draft of the U.S. Environmental Protection Agency's *EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments*. The draft EPA report identified and sought to address the following three key recommendations that the National Academy of Science (NAS) indicated required "substantial improvement to support a scientifically robust characterization of human responses to exposures to 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
3. Improved transparency, thoroughness, and clarity in quantitative uncertainty analysis.

Within the document, EPA proposes and attempts to document the derivation of a new cancer slope factor (CSF) and of a reference dose (RfD), where previously, no RfD had been established. The voluminous document released represents considerable time and effort spent by EPA to respond to the NAS recommendations; however, there remain significant technical flaws in the derivation of the proposed toxicity factors. Below is a brief summary of some key technical issues identified by Exponent, followed by more detailed technical discussion of the limitations of EPA's analysis.

Non-Cancer Endpoints

The draft EPA report provides documentation and substantiation of an oral RfD for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) of 7×10^{-10} mg/kg-day. To date, the National Center for Environmental Assessment has not provided RfD values for TCDD or other dioxins, so this is a departure from historical EPA precedent. The proposed RfD is based on two epidemiologic studies of a population exposed in childhood to high concentrations of TCDD and other 2,3,7,8-substituted polychlorinated dibenzodioxins and furans (PCDD/Fs) following an accident at a 2,4,5-trichlorophenol plant in Seveso, Italy. As a basis for the RfD, EPA used studies describing decreased sperm concentration and motility in men who were exposed during childhood (Mocarelli et al. 2008) and increased thyroid-stimulating hormone levels in newborn infants (Baccarelli et al. 2008).

The draft RfD of 7×10^{-10} mg/kg-day can be compared with the World Health Organization's Joint Exposure Committee on Food Additives' (JECFA 2001) value of 2.3×10^{-9} mg/kg-day, which is used widely throughout the world and is derived from decreased sperm counts in an animal model, based on studies in rats by Gray et al. (1997). Comments regarding the technical approach applied to derive an RfD from these studies of the Seveso population are provided here regarding the following:

- **Study selection:** The Seveso population experienced extreme acute exposures that are likely not representative of risks posed by low environmental exposures in the U.S.
- **Exposure analysis:** EPA focused only on TCDD exposures. Although the Seveso population may have been exposed predominantly to TCDD, they also experienced substantial exposures to additional PCDD/Fs that contribute to the overall TEQ, which were not accounted for in the exposure analysis. Underestimating the TEQ exposure overestimates risk and results in an RfD that is lower than necessary to protect human health.
- **Biological plausibility:** EPA relied on a paper that attempted to link decreased sperm quality measures from a single semen sample taken from fertile men who had been exposed 22 years earlier as children (1-9 years old) in Seveso.
- **Clinical significance:** EPA relied on a study that found increased TSH levels in a small sample of 3-day old newborns whose mothers had been exposed in Seveso; the newborns developed no manifestations of thyroid deficiency and were not evaluated for TSH levels at other times in the newborn period, which limits the usefulness of this observation.

Weight of Evidence

The selection of epidemiological studies does not follow a comprehensive and unbiased evaluation of the weight of evidence, including consideration and implementation of the many studies that found no excess. Nor does the EPA review consider the Hill Criteria, that requires consistency in the cancer endpoint, a dose-response gradient for effects, and biological plausibility.

Cancer Endpoints

The draft EPA document classifies TCDD as carcinogenic to humans, based on epidemiologic studies of occupationally and accidentally exposed cohorts that show an association between TCDD exposures and certain cancers or increased mortality from all cancers combined, and on evidence of carcinogenicity at multiple tumor sites in both sexes of multiple species of experimental animals. Drawing from these data sources, EPA derives oral cancer slope factors that are dose dependent, and the slope factor varies at different exposure levels. In the risk range of 10^{-6} , EPA proposes a CSF of 1×10^6 (mg/kg-day)⁻¹ based on all cancers combined from the NIOSH cohort, as investigated by Cheng et al. (2006). This value represents a large increase over the current value of 156,000 (mg/kg-d)⁻¹. As discussed further in these comments, several concerns arise regarding this approach:

- **Biological plausibility of combining all cancer endpoints:** EPA has not identified a plausible mode of action in which TCDD would cause increases in every type of cancer. The finding of an excess of all cancers combined

ignores the significant differences in disease processes among various cancers.

- **Study interpretation:** The EPA derivation is at odds with what was reported by the study authors.

Animal studies are considered, but ultimately are not selected as the basis for derivation of a CSF. While it is recognized that epidemiological data are preferred as a basis for deriving toxicity values, there are also significant limitations in the approach selected by EPA, as elucidated below.

Issues Related to EPA's Derivation of an RfD

The draft EPA report provides documentation and substantiation of an oral reference dose (RfD) for TCDD of 7×10^{-10} mg/kg-day, which is based on acute exposures to PCDD/Fs following an accident at a plant manufacturing 2,4,5-trichlorophenol in Seveso, Italy. As a basis for the RfD, EPA used studies describing decreased sperm concentration and motility in men who were exposed during childhood (Mocarelli et al. 2008) and increased thyroid-stimulating hormone levels in newborn infants (Baccarelli et al. 2008). Concerns regarding the selection of these studies, the actual exposure concentrations, and the lack of biological plausibility concerning the reproductive toxicity reported are described below.

Acute exposures to high PCDD/F concentrations are likely not the most representative data set for derivation of an RfD for application in U.S. populations. The dose received by this population is very likely not representative of typical exposures in the U.S., because their exposure was the result of an industrial accident and, as such, was a high initial exposure that constituted a peak exposure much higher than exposures experienced in environmental exposure settings in the U.S., followed by lower level exposures over many years. There are many other available data sets from chronic or subchronic dosing regimens that would be more representative of chronic environmental exposures such as those typically experienced by U.S. populations and that are more likely consistent with the mode of action relevant to dioxin and dioxin-like chemicals. The selection of the Seveso cohorts as a basis for the RfD is in direct contrast with the approach used by EPA to derive the CSF. EPA notes that chronic continuous exposures are likely more representative for the purpose of assessing cancer risks, and that acute exposures may result in high disease rates that are associated with the high peak exposure levels, rather than the subsequent long-term exposure levels that are calculated or measured after the acute exposure incident] This assertion led the EPA to select the National Institute for Occupational Safety and Health (NIOSH) (Steenland et al. 2001; Cheng et al. 2006) and Hamburg cohorts (Becher et al. 1998) as more representative of environmental health risk, stating:

Among the human studies, the occupational TCDD exposures in the NIOSH and Hamburg cohorts are assumed to be reasonably constant over the duration of occupational exposure. In contrast, the TCDD exposure pattern for the Seveso and BASF accidents is acute, high dose, followed by low-level background exposure. *Such exposure patterns similar to those experienced by the BASF and Seveso cohorts have been shown to yield higher estimates of risk when compared to constant exposure scenarios with similar total exposure magnitudes* (Kim et al., 2003, [199146](#); Murdoch and Krewski, 1988, [548718](#); Murdoch et al., 1992, [548719](#)). Thus, EPA has judged that the NIOSH and Hamburg cohort response data are more relevant than the BASF and Seveso data for assessing cancer risks from continuous ambient TCDD exposure in the general population. (Executive Summary, page xlvi, lines 25–31, and xlviii, lines 1–3)

While it is recognized that the use of chronic studies may be even more important for evaluation of cancer, the exposure level in the Seveso accident was much higher than what is typical from

exposure to dioxin in environmental media in the U.S. As such, effects from this dose experience are not readily extrapolated to lower dose exposures.

Exposure in Seveso, while predominantly to TCDD, also included substantial exposure to other PCDD/Fs, which may underestimate exposure and the resulting RfD. The estimated dose selected as a point of departure (POD) from the Mocarelli et al. and Baccarelli et al. studies are likely to underestimate the total dose of dioxin-like compounds, because they disregard background and contributions from PCDD/F compounds other than TCDD. Specifically, Baccarelli et al. (2008) reported a mean maternal serum 2,3,7,8-TCDD concentration of 18.9 ppt (n of 51, range 1.4–309.5) and also indicated that mean plasma toxicity equivalence (TEQs) were 44.8 ppt (n of 51, range 11.6–330.4) for PCDD/Fs and coplanar polychlorinated biphenyls (PCBs). Given that the same exposure setting occurred for the population studied by Mocarelli et al., it is reasonable to accept that additional PCDD/F exposure occurred there as well. To the extent that PCDD/Fs contributed to any observed effect, if these were not accounted for in deriving the POD and the resulting RfD, the calculated dose would be underestimated, resulting in an overestimation of toxicity and an RfD that is lower than needed to protect public health.

Additionally, data are available that allow for comparison of the Seveso-based studies against U.S. populations, to allow an understanding of whether the dose levels from the Seveso populations are relevant to assessing risks from exposure to environmental contaminants in the U.S. As discussed above, the Seveso population data support total TEQ values that range as high as 50 to 100 ppt. In combination with the TCDD exposures, studies that form the basis for the RfD total TEQ estimate that value to range from 18 ppt to over 210 ppt. In contrast, Patterson et al. (2009) indicate that the *upper bound* of current average serum TEQ concentrations in persons of reproductive age in the U.S. range between approximately 6 and 12 ppt. Candidate papers selected by EPA for noncancer dose-response assessment of epidemiological data to be used in the determination of a POD were based on changes in human sperm parameters (Mocarelli et al. [2008] *Environ Health Persp* 116:70–77) or on changes in levels of thyroid-stimulating hormone (TSH) in the blood of the mothers and their infants (Baccarelli et al [2008] *PLoS Med* 5:1133–1142). The following paragraphs provide comments on the usefulness of these two papers for use in derivation of an RfD for TCDD.

Human Sperm Parameters

Approximately 22 years after the 1976 industrial accident in Seveso, Italy, Mocarelli et al. (2008) measured reproductive hormone levels and a variety of semen quality parameters in 135 males who had been exposed to TCDD. The subjects were divided into three age categories at the time of exposure: pre-puberty (1–9 years; mean age 6.2 years), puberty (10–17 years; mean age 13.2 years), and young adults (18–26 years; mean age 21.5 years). Serum samples had been collected from each of the subjects during the year following the accident; these had been frozen and stored and were available for measurement of TCDD concentrations. The authors conclude that pre-puberty exposure to TCDD caused a decrement in sperm quality, especially decreased sperm concentration and diminished sperm motility. These endpoints and their associated serum TCDD concentrations are used in the draft EPA Integrated Risk Information System (IRIS) document to determine a candidate POD for derivation of a reference dose (RfD).

The authors' interpretation of their results is poorly substantiated. Findings of decrement in sperm quality can be a meaningful endpoint of concern; however, the findings in this paper are based on a single sample per subject, and there is no clinical evidence of impaired fertility. Thus, there is no objective, clinically adverse finding. The authors suggest that the decrement in sperm quality may be due to impacts on the Sertoli (nurse) cells in the seminiferous epithelium. While a reduction in the number or efficiency of Sertoli cells in the seminiferous epithelium would adversely affect spermatogenesis, it is important to demonstrate that Sertoli cells are indeed the target cells. In the case presented by Mocarelli et al. (2008), this is not plausible, for the following reasons.

- As recounted in Mocarelli et al. (2008), human Sertoli cells are formed during the late gestational period and early postnatal period (to ~8 months of age). The seminiferous epithelium then remains dormant until the period just preceding spermatogenesis (beginning around 11 years of age). The pre-puberty group of boys in Seveso was exposed when they were at an average age of 6.2 years. This is at least 5 years after the Sertoli cells have been formed and about 5 years before they will become active at spermatogenesis. The Sertoli cells are quiescent at this time and are unlikely targets for toxicants.
- Furthermore, the pattern of exposure (a high bolus exposure in children at ages 1–9, with an average age of 6 years of age, followed by 5 years of declining circulating TCDD) does not correlate well with the developmental schedule of the Sertoli cell population, which does not become active until the end of the period of declining circulating TCDD.

While the preceding scenario suggests that the Sertoli cells would not be exposed during their active phase, it is not possible to assess their status in the human subjects. Nevertheless, it is noted that sperm quality was not reported to be diminished in the two older age groups (who had active Sertoli cells). Interestingly, data from animal studies contradict the hypothesis that TCDD toxicity in Sertoli cells will result in decreased sperm production: when the ratio of Sertoli cells to spermatocytes was determined in Holtzman rats that had been exposed to TCDD during the maximally sensitive period (gestational day 15), no changes in the ratio compared to controls were seen at any age, from 49, 63, or 120 days (Mabry et al. 1992). This indicates that the Sertoli cells are an unlikely target for TCDD.

Taken together with the fact that the judgment of decreased sperm quality was based on a single measurement for each patient, the above information suggests that there is little biological plausibility for the putative toxic endpoint of concern selected for assessing the reference dose for dioxins. This is because: the target cell types would not have been active at the time of the reported exposure of young boys in Seveso; the single measurement point is likely unreliable for this endpoint of concern; the dose received by this exposed population was a single large dose that is not relevant to assessing toxicity from long-term exposures to TCDD in environmental media; and animal studies conducted to evaluate exactly this mechanism of toxicity indicate no linkage between effects on Sertoli cells and subsequent spermatogenesis.

Thyroid-Stimulating Hormone Levels

TCDD contamination of the area surrounding Seveso, Italy, occurred as the result of an industrial accident in July 1976. Because exposure to TCDD and related compounds causes hypothyroidism in animals, Baccarelli et al. (2008) investigated the effects on thyroid function of TCDD exposure in women of reproductive age living nearby at the time of the accident (and residing nearby thereafter), and in their children born between 1994 and 2005. Thyroid function of the neonates was inferred from thyroid-stimulating hormone levels in the blood (b-TSH) of the neonates at three days of age. Exposure to high or low amounts of TCDD was inferred from residence locations relative to the site of the accident (determined by soil concentrations measured shortly after the accident), measurements of dioxin in the blood of the exposed women were made on blood samples collected in 1992–1998, and TCDD blood levels at the time of birth were estimated in a subset of mother/infant pairs (N=51) by linear extrapolation. Pregnancy status of the women at the time of blood collection was not reported. The reference population included women and their babies living nearby but not located within the contamination zones.

This is a creative and provocative study, but one that should not be used as a primary basis for risk assessment, for the following reasons.

- First, the population of interest is small, especially for the high-exposure group, which leads to questions about the overall representativeness of the sample.
- Second, the infants involved showed no signs or clinical manifestations of hypothyroidism. The authors cite the World Health Organization (WHO) as declaring that the b-TSH level in iodine-sufficient populations should not exceed 5 $\mu\text{U}/\text{mL}$ in more than 3% of infants. In the current study, the mean b-TSH measured on the third day after birth was $<1.7 \mu\text{U}/\text{mL}$ for all exposure groups, although the percentage of infants that exhibited $>5 \mu\text{U}/\text{mL}$ exceeded 3% in the TCDD exposure areas. It should be noted, however, that the clinical criterion associated with hypothyroidism in adults is 10 $\mu\text{U}/\text{mL}$. It should be noted that b-TSH levels in newborns are very high ($\sim 30 \mu\text{U}/\text{mL}$) but they fall dramatically over the first 48–72 hours of life (Galway and Burrow 1992) to levels that are generally 5 $\mu\text{U}/\text{L}$ or lower. Given the small total number of infants in this aspect of the study, differences of a few hours in the exact timing of blood collection from the infants could possibly contribute to perceived elevations in measurements of b-TSH levels. In the absence of additional measurements taken a few hours later and the lack of any manifestation of hypothyroidism, it is likely that this finding is of no clinical significance.
- Third, as described above, the exposure pattern for these individuals is unique, because the subject received a massive exposure over a very brief period, followed by many years with greatly reduced exposure. The pharmacokinetics of these types of exposures differ from exposures in the population of interest in the U.S. that might receive a low daily dose over many years.

Conclusions

The hard work put into the construction of this document is obvious. Given the large database of epidemiological and animal studies on the potential for non-cancer health effects to be associated with exposure to TCDD, it is disappointing that the studies selected for this aspect of the risk assessment are unremarkable with respect to identifying clear-cut adverse effects. EPA should use a meaningful weight-of-evidence approach that includes results from studies that report both positive and negative findings, incorporates an appropriate dose range, and evaluates a biologically plausible endpoint for assessment of non-cancer toxicity endpoints from TCDD exposure.

Weight of Evidence

The weight of evidence in evaluating whether an observed exposure is associated with a given outcome is often evaluated through consideration of the Bradford Hill Criteria, which include the following: 1. strength of association, 2. consistency, 3. specificity, 4. temporality, 5. dose response gradient, 6. biological plausibility, 7. coherence (consistency with present scientific knowledge), 8. appropriate experimental design, 9. analogy (similar outcomes have been seen in similar exposures) (Hill 1965; Goodman 2005). While these criteria are most often considered relative to interpretation of epidemiological studies, these criteria have also been applied to the interpretation of studies conducted in experimental animals (Pastoor et al. 2005), and bear consideration here in evaluating the adequacy of study selection for dose-response analysis within the draft EPA document.

Comparison of these criteria to study selection methods within the document (as described in Section 2.1.3 of EPA's report), and review of the studies that EPA did select from this extraordinarily extensive data set for TCDD, suggests that some of the Bradford Hill Criteria have been met, but many have not. Considering first the strength of the association, studies with weak associations were included as part of the basis, including most notably the Cheng et al. 2006) study, which was selected as basis for the CSF and included a 17% increase of all cancers combined in the study population evaluated. EPA has also overlooked the lack of consistency in the cancer endpoint between studies by selecting the "all cancers" endpoint.

EPA notes (Section 2.1.3) the importance of high specificity of health outcomes (within EPA's point 1), and the lack of potential biases (point 2) in selecting studies to serve as the basis for the dose-response assessment. Both of these points can be considered part of the specificity of the association, and they are critical to identification of studies that are appropriate for use in risk assessment. However, in selecting "all cancers" as the endpoint of concern, neither of these criteria can be readily met, because each cancer endpoint is a separate disease with unique causes, etiology, and prognosis, as described further in the next section.

A lack of biological plausibility and issues regarding the timing of exposure were discussed relative to the use of the Mocarelli data to derive an RfD and will be discussed further, below, relative to the selection of all cancers as the basis for the CSF. In the selection criteria for animal studies, EPA noted that only those studies in which, "The lowest dose level tested is ≤ 1 $\mu\text{g}/\text{kg}\text{-day}$ for cancer studies and ≤ 30 $\text{ng}/\text{kg}\text{-day}$ for noncancer studies." While it is recognized that selecting the most sensitive endpoint is an important public health consideration in deriving conservative, health-protective toxicity values for use in risk assessment, this criterion focused the evaluation on studies in which exposures were exceedingly low, and the observed effects, in many cases, were not repeated in other investigations, lacked biological plausibility, or were not biologically relevant. EPA should re-evaluate this basis for exclusion of studies.

A few examples of a larger problem in the study selection are noted, which suggest that, although EPA improved the transparency of the study selection process, consistent with the NAS request, EPA did not apply an appropriate weight of evidence in identifying studies for use

in deriving the CSF. Most fundamentally, EPA indicates that to be selected for inclusion, a study must “demonstrate[s] an association between TCDD and an adverse health effect (assuming minimal misclassification of exposure and absence of important biases) with some suggestion of an exposure-response relationship.” This appears to have been applied literally with inclusion only of those studies that show an adverse effect. Exclusion of all data that did not result in an adverse effect removes a tremendous amount of information that could inform the dose-response analysis.

Issues Related to Derivation of a Cancer Slope Factor (CSF)

The draft EPA document classifies TCDD as carcinogenic to humans, based on epidemiologic studies of occupationally and accidentally exposed cohorts showing an association between TCDD exposures and certain cancers or increased mortality from all cancers combined, and on evidence of carcinogenicity at multiple tumor sites in both sexes of multiple species of experimental animals. Drawing from these data sources, EPA derives oral cancer slope factors that are dose dependent, and the slope factor varies at different exposure levels. In the risk range of 10^{-6} , EPA proposes a CSF of 1×10^6 per (mg/kg-day), based on all cancers combined from the NIOSH cohort as investigated by (Cheng et al. 2006). This value represents a large increase over the current value of $156,000 \text{ (mg/kg-d)}^{-1}$. As discussed further in these comments, there are several concerns regarding the approach used in deriving this value:

- **Biological plausibility of all combining all cancer endpoints:** EPA has not identified a plausible mode of action in which TCDD would cause increases in every type of cancer. The finding of an excess of all cancers combined ignores the significant differences in disease processes among various cancers, and while some co-factors are considered, use of all cancers as a grouped endpoint limits the evaluation of co-factors.
- **Study interpretation:** The EPA derivation is at odds with what was reported by the study authors.

Animal studies are considered, but ultimately are not selected as the basis for derivation of a CSF. While it is recognized that epidemiological data are preferred as a basis for deriving toxicity values, there are also significant limitations in the approach selected by EPA, as elucidated below.

Biological Plausibility of the All Cancers Endpoint

EPA identified “all cancers” as the endpoint for analysis in the epidemiological analyses. In their analysis, EPA did not provide a summary of the endpoint by endpoint findings in the various studies, and consequently, it is not possible to fully evaluate consistency in the studies evaluated. EPA does not provide a plausible mode of action supporting the finding that TCDD could have a role in combined cancer incidence. Such a mode of action seems unlikely, given that cancer across a diversity of tissue types is not a single disease and is instead a group of distinct diseases each with unique etiology and prognosis (American Cancer Society 2010). Different cancers have unique risk factors linked to very specific disease processes (NCI 2010). Even for cancers within a single tissue type, new research indicates that it is probably not a single disease, but a set of diseases “each with a distinct underlying molecular disease process” (UNC 2010). The selection of “all cancers” as a toxic endpoint upon which to base the cancer potency assessment is not consistent with the use of the best available science.

Study Interpretation for Selection of an Oral Cancer Slope Factor

Following a detailed analysis, EPA selects the results published by Cheng et al (2006) as the basis for derivation of the oral CSF for TCDD based on total cancer mortality. Based on these data, EPA derives a series of “equivalent oral slope factors” at different risk levels. The EPA’s analysis, however, appears to be flawed. Below are comments on two particular areas of concern in the methods, approaches, or conclusions drawn by EPA from this study.

EPA’s use of Cheng et al. (2006) appears to be in contrast with study authors’ analysis

In EPA’s draft report, the Cheng study is reported (Table ES-1 and Section 5.2.3.1.2.1.) to support oral slope factors ranging from 1.1×10^5 to 1.3×10^6 over the target risk levels ranging from 1×10^{-2} to 1×10^{-7} . Based on these calculations, EPA “recommends use of an OSF [oral CSF] of 1×10^6 (per mg/kg-d) when the target risk range is 10^{-5} to 10^{-7} . First, there is no documentation for this target risk range, which is not consistent with the National Contingency Plan, and more fundamentally, the values calculated and recommended by EPA raise concern, because they are not consistent with the conclusions that Cheng et al. drew from their own analysis. Specifically, EPA states a preference for the modeling approach presented by Cheng et al. over approaches used by Steenland et al. (2001) and Becher et al. (1998), because the physiological process provided in the Cheng et al. model is “more realistic” than is allowed by the approaches used by other authors.

In apparent contrast with the approach used by EPA, Cheng et al. specifically state that EPA’s use of first-order elimination kinetics, such as proposed by Steenland (2001), supported an estimated oral CSF of 1.5×10^6 (per mg/kg-d), but that appropriate incorporation of the approach proposed by Cheng et al. resulted in estimated cancer slope factors that were 6- to 150-fold lower. Cheng et al. specifically state what cancer potency estimates are supported by the NIOSH database and their pharmacokinetics, listing values ranging from 1×10^4 to 2.4×10^5 (per mg/kg-d). For this reason, this apparent discrepancy has been evaluated. Specifically, Equations 5-1 and 5-2 in the draft EPA document were used to re-create the derived estimates. The following are findings from that attempt to better understand this apparent discrepancy:

1. It appears that Cheng et al. derived the central estimate of the Cox Regression Coefficient (β value), and EPA used Cheng’s results to derive a 95% UCL (upper confidence level) of the β (β_{95}). The effect of using β_{95} increases the slope factor by roughly two- to three-fold and does not appear to be consistent with the study authors’ approach to deriving the estimate, which already included considerable potential for overestimation.
2. EPA miss-applied the Cheng β value by using 70 years in the area under the curve (AUC) calculation. Cheng’s β value is derived based on 60 years (75 years – 15-year lag). The effect of using 70 years increases the slope factor by ~35%–45% and is an inappropriate application of the data and methods specified in Cheng et al.
3. EPA’s re-arrangement of the equations is confusing and difficult to verify. It is unclear where Eq. 5-1 was obtained (no cited reference), and there is

uncertainty as to how the mathematical terms are defined in the text. For example, “ER” in Eq. 5-1 is not defined in the text, and if ER represents “extra risk,” then it should have been shown as “RL” (as defined in the text as the extra risk). But if RL is extra risk, then it becomes inconsistent with the follow-up equation 5-2, in which the extra risk is shown as “RD.” For this reason, it appears that there may be an error in the EPA equations when they tried to apply Cheng’s relative risk (RR) equations. Conversely, we are able to understand and re-arrange Cheng’s equations and replicate Cheng’s risk calculations shown in Table IV of Cheng et al. (2006). If equations from Cheng et al. are used but adjusted to incorporate EPA’s input values of 70 years and β_{95} , the slope factor derived is still 15%–20% lower than EPA-derived slope factors, suggesting that there is an error in EPA’s application (or rearrangement) of the equations from Cheng.

Taken together, these three factors (use of β_{95} , a 70-year input, and an apparent numerical error in use of the equations from Cheng) result in a significant difference between the oral CSF values derived by Cheng et al., and the oral CSF values derived by EPA based on Cheng et al. Cheng et al. specifically list a range of cancer potency estimates yielded from their evaluation of 10,000 to 240,000 (per mg/kg-d), which are 4- to 100-fold lower than the 1,000,000 (per mg/kg-d) recommended by EPA for use in the target risk range of 10^{-7} to 10^{-5} .

4. Finally, an additional reason that EPA has higher oral CSF values, but which is difficult to verify, may be associated with the use of the Emond physiologically based pharmacokinetic (PBPK) modeling results to convert serum lipid (ng/kg) to intake (ng/kg-d) values. EPA uses a table in Appendix C.4.1 to look up values, but it is not possible to verify the accuracy of that table. EPA specifically states an intent to have transparency in the full analysis that they conduct, but they have not achieved this goal in deriving the oral CSF.

Conclusions

The EPA draft document clearly represents a tremendous amount of effort and careful analysis. Unfortunately however, the document appears to have significant flaws that can be identified even in the short time frame allowed for this review prior to the SAB meeting. Among these problems is derivation of an RfD through use of data from the Seveso population, which experienced extreme acute exposures that may not be representative of risks for environmental exposure settings in the U.S.. The Seveso data also likely underestimate exposure to additional PCDD/Fs, which could result in an overestimate of risks and an RfD that was lower than necessary to protect public health. Another issue is that EPA should better consider the weight of evidence in deriving toxicity values. Perhaps the most significant problem is that the current draft lacks clear consideration of biological plausibility in both (1) derivation of the RfD through ascribing a causal relationship, with reproductive decrements resulting from exposures prior to the sensitive time period in childhood; and (2) derivation of the oral cancer slope factor by basing the evaluation on all cancers combined.

Exposure analysis: EPA focused only on TCDD exposures. Although the Seveso population exposure may have been predominantly to TCDD, there were also substantial exposures to additional PCDD/Fs that contribute to the overall TEQ, and these other exposures were not accounted for in the exposure analysis. Underestimating the total TEQ exposure may have led to overestimation of risk and resulted in an RfD that was lower than necessary for adequate protection of human health.

In addition, review of the derivation of the oral CSF indicated that EPA's interpretation of the findings differed from that of the study authors and contained aspects that were not readily reproduced in independent calculations.

The draft toxicity values, as provided, would result in cleanup levels well below background in many contexts, requiring tremendous commitment of resources and time for both responsible parties and regulators managing state or federal sites. Given the lack of consensus on the toxicity of TCDD, we urge the Science Advisory Board to carefully consider the comments provided by this and other submitters, to direct EPA in preparing a document that will be based instead on the best available science.

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