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Dr. Armitage,

On February 8, 2011, the U.S. Environmental Protection Agency (EPA) released a draft document titled *SAB Review of EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* (hereafter referred to as the Draft SAB Review Document). This Draft SAB Review Document contains comments and recommendations from the U.S. EPA's Dioxin SAB Review Panel on the Agency's Response to the NAS. As part of the review process (FRL-9263-7), we have prepared comments on the Draft SAB Review Document on behalf of Tierra Solutions, Inc. These comments are attached for the benefit of the SAB Panel as they work to finalize their review of the EPA's Response to the NAS.

We recognize that this review represents no small undertaking and commend the SAB Panel members for the time, energy and thought that they have put into their assessment of the EPA Response to the NAS. We agree with many of the comments and recommendations offered by the SAB. Most notably, we agree with the SAB regarding the three major deficiencies that were identified:

- 1) the failure by EPA to assess cancer risk using a nonlinear approach
- 2) the shortcomings regarding EPA's characterization of the mode of action, and
- 3) the failure to complete a quantitative uncertainty analysis.

It is essential that these issues be addressed in a scientifically sound manner. We also urge the SAB to provide corrections, clarification and/or additional guidance for a number of their recommendations, and particularly for those related to selection of key datasets and the "allowance" for the EPA to not conduct good science in the interest of completing the dioxin assessment expeditiously.

We appreciate the opportunity to comment on this important component of the EPA's Dioxin Science Initiative and believe that the peer-review process is essential for ensuring that the EPA provide to the public a risk assessment for dioxin that truly reflects the best available science.

Sincerely,

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**Comments on “SAB
Review of EPA’s
Reanalysis of Key
Issues Related to Dioxin
Toxicity and Response
to NAS”**

FEBRUARY 23, 2011

ToxStrategies

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Comments on “SAB Review of EPA’s Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS”

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1.0 Introduction

On February 8, 2011, the U.S. Environmental Protection Agency (EPA) released a draft document titled *SAB Review of EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments EPA's* (hereafter referred to as the Draft SAB Review Document). The Draft SAB Review Document contains comments and recommendations from the U.S. EPA's Dioxin SAB Review Panel on the Agency's Response to the NAS. We are in agreement with many of the comments and recommendations offered by the SAB Panel. In particular, we would like to emphasize the concerns expressed by the SAB regarding the major deficiencies identified by the Panel - that the EPA (a) address the serious shortcomings in their characterization and assessment of the mode of action for TCDD, (b) evaluate cancer risk using a nonlinear dose-response modeling approach, and (c) conduct a quantitative uncertainty analysis using an approach recommended by the Panel.

However, there are also a number of issues that require attention and/or clarification from the SAB. Most importantly, Panel recommendations should focus on science and avoid policy matters such as feasibility, timeliness, and practicality. In the draft SAB report, the Panel has presented a strong scientific basis for each of the three major deficiencies identified. It is essential that each of these three major deficiencies be addressed to ensure that EPA's assessment truly reflects the best available science. However, for each of the three major deficiencies, despite the strong evidence provided by the Panel regarding the deficiency, the Panel ultimately qualifies their recommendations on a path forward based on policy rather than science. For example, with respect to mode of action (MOA), the Panel recommended that EPA characterize the MOA as "reasonably well known" rather than as "largely unknown." Given the overwhelming body of data concerning the MOA underlying the toxicity of TCDD, such a change in the classification is clearly warranted. It stands to reason that if the MOA is "reasonably well known," then the overall weight of evidence regarding the MOA is sufficient. The EPA Cancer Risk Assessment Guidelines do not require that every step of the MOA be definitively known, nor do the Guidelines require, as the panel has indicated, that "the exact mechanism of action [be] fully delineated for any distinct TCDD toxicity endpoint." Rather, the Guidelines require that the overall weight of evidence be sufficient to support the MOA. In accordance with the Guidelines, there is no default MOA and the bar for the default approach is as high as the bar for alternative MOAs. Knowledge regarding the MOA, in turn, dictates the dose-response modeling approach (linear vs non-linear). To this end, the Panel concluded that EPA was not responsive to the NAS and ultimately recommended that the EPA "present both linear and non-linear risk assessment approaches." However, the Panel qualified this recommendation stating "*.....that EPA might still conclude that, in the absence of a definitive nonlinear mode of action, policy dictates that the linear option is preferred to assure protection of public health.*" Such a qualifier is perplexing and is contrary to a policy committed to good science. While the Panel states that the MOA is reasonably well known [i.e., the overall weight of the evidence is sufficient] and the

science clearly supports a non-linear approach [as other EPA SAB panels and the NAS have all concluded] it then concludes that EPA is free to ignore all of the available data and advice from numerous scientific peer-review panels and use a precautionary approach if they so desire.

As another example, with respect to the need for a quantitative uncertainty analysis, the SAB Panel stated [with emphasis added]: *“The Panel found that it would be possible to conduct a QUA [quantitative uncertainty analysis] for dioxin toxicity without using expert elicitation, and has recommended a number of methods that could be used. The Panel notes, however, that **EPA’s decision to not conduct an integrated QUA might have been justified on grounds of practicality or timeliness. Therefore, the Panel recommends that EPA consider omitting Section 6 or revising its argument that QUA for dioxin toxicity is unfeasible.**”* In their final recommendation on this matter, the Panel stated [with emphasis added]: *“Most members of the Panel concur that a quantitative uncertainty assessment is **essential, although not everyone on the Panel believes that one is necessary** if it will delay finalization of the dioxin reassessment even more.”* How can the conclusion be that a quantitative uncertainty analysis is not necessary if it is “**essential**”? Further, how can a scientific peer-review panel recommend omitting an entire section from a report when the analysis has been deemed “essential” merely to meet some arbitrary deadline? Is the SAB saying that the Agency does not have to use good science if they are in a hurry; that the Agency can delete this section from the report so as not to call attention to the fact that they failed to complete this essential component of their analysis? We do not believe this to be a prudent recommendation from a scientific peer-review panel.

These recommendations by the SAB Panel reflect policy and, as such, are clearly not consistent with guidelines for scientific peer-review laid out in the EPA’s Peer Review Handbook (EPA/100/B-06/002) which states [with emphasis added]: *“The specific and general comments should focus on the scientific and technical merits of the work product and, where germane, whether the scientific/technical studies have been applied in a sound manner. Remember, the peer review is not for the decision or action itself, but for the underlying scientific and/or technical work product; **reviewers should not be asked to provide advice on policy.**”* The EPA should be required to use good science in all that they do and the Panel’s recommendations should be based solely on the science and not on what is practical, timely, or feasible for the Agency.

In addition to the concern regarding the intermingling of science and policy in the recommendations suggested by the Panel, there are a number of additional comments/recommendations that warrant further discussion. Given the limited amount of time provided to review the SAB Panel Report and to prepare comments, we have focused, in particular, on the following topics: 1) Cancer Assessment, 2) Noncancer Assessment, 3) Modeling, and 4) Quantitative Uncertainty Analysis. We believe that it is essential that the SAB consider, and that the EPA ultimately address, the issues that we have identified to ensure development of a scientifically robust assessment for TCDD. Our specific comments are outlined in the sections that follow.

2.0 Cancer Assessment

2.1 The Panel should carefully consider the dissenting opinion offered by Dr. Rozman

The dissenting opinion offered by Dr. Rozman reflects sound science and states the obvious – that is, there is no scientific basis for concluding that TCDD would be carcinogenic to humans at background levels when there is, at best, equivocal evidence (statistically NOT significant) of carcinogenicity in occupational settings where the body burdens were at least 100 to 1000 times higher than current or previous background levels. If TCDD truly was as potent as the Agency believes, then there would be clear evidence of carcinogenicity in the numerous occupational cohorts where workers were exposed to very high levels for long periods of time. The fact that there is no such evidence further supports the idea that there is, in fact, a practical threshold in the population and the cancer risk at current background levels is negligible despite extremely high exposures. Only when the EPA transforms the data and combines all tumor types together is evidence of carcinogenicity seen, and even then only a marginal increase is observed - which is not even statistically significant. As stated so eloquently and accurately by Dr. Rozman, “*Any other conclusion is incompatible with sound science...*”

2.2 The Panel’s recommendation regarding what is known about the MOA underlying dioxin toxicity and the need to develop an OSF based on a non-linear approach is consistent with recommendations made by several prior expert panels including the NAS. Clearly there is strong support for the use of a non-linear approach and this Panel’s recommendation should not be compromised based on “policy.”

This current SAB Panel is the fourth scientific peer-review panel to recommend that the EPA use a nonlinear approach to evaluate cancer risk. Specifically, the 1995 Dioxin SAB Panel identified the EPA’s reliance on a linear model as a major deficiency 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 2001 SAB Panel stated that non-linearity better described the receptor-mediated response and 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*” (SAB, 2001). The 2006 NAS stated that “*EPA’s decision to rely solely on a default linear model lacked adequate scientific support,*” and that “...*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*” (NAS, 2006). And now again in 2011, this current SAB Panel has concluded that the mode of action underlying dioxin toxicity is “largely known” and that EPA’s failure to develop an OSF

based on a nonlinear dose-response modeling approach is a “major deficiency” and represents a failure to respond adequately to the NAS recommendation on this topic. It is perplexing how the Agency can continue to ignore this recommendation made by multiple expert panels. What is the purpose of having a peer-review if the Agency can ultimately ignore panel recommendations and “good science?”

2.3 We encourage the SAB to recommend that the EPA adhere to their own Cancer Risk Assessment Guidelines and develop a mode of action framework and evaluate all of the available data in this framework prior to drawing conclusions about the MOA.

Although the SAB identified EPA’s assessment of the MOA as a major deficiency, the Panel did not address the Agency’s failure to develop a mode of action framework and to evaluate all of the available data in this framework prior to determining whether or not there is, in fact, sufficient data. It is unclear how the cancer assessment can be considered anything short of flawed until the EPA develops a mode of action framework using all of the available data for dioxin in accordance with the Agency’s Cancer Risk Assessment Guidelines. This is an essential component of completing an assessment based on sound science – and specifically for determining the appropriate dose-response modeling approach in the cancer evaluation

It is suggested that the EPA identify tumors from animal studies, apply their own MOA framework, and then examine the human relevance through consideration of available epidemiological data. Given the amount of literature on TCDD (over 7,000 citations in PubMed), there would appear to be sufficient data for the EPA framework. It is well known that there are a multitude of publications on key and associative events essential to a MOA assessment (as defined by the EPA’s cancer Guidelines), such as cell cycle, cytotoxicity, and receptor-ligand changes. Thus, we very strongly agree with the Panel’s conclusion that the MOA is reasonably well known, although the exact mechanism of action is unknown. In fact, 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. A suggested MOA for TCDD was included in comments previously submitted to the docket by ToxStrategies, Inc., on behalf of Tierra Solutions, for consideration by the SAB panel.

2.4 We echo the Panel’s concern that EPA ignored the NAS recommendation to evaluate cancer risk using a non-linear approach.

The SAB expressed concern that the EPA did not adequately respond to the NAS recommendation to adopt both linear and nonlinear methods when evaluating cancer risk. This topic was discussed many times throughout the report, surfacing in discussions on MOA, evaluation of data, and uncertainty in risk estimates. The failure to adopt a nonlinear approach was even identified as a major deficiency. The toxicology of dioxin,

especially with respect to its carcinogenicity and tumor promotion capabilities, involves some of the most studied endpoints in science. Scientists in general and other regulatory agencies, such as the World Health Organization's Joint Exposure Committee on Food Additives, have concluded that dioxin is a threshold carcinogen. Conversely, "... *linearity is intended for agents that are DNA-reactive and have direct mutagenic activity, or, agents for which human exposure or body burdens are high and near doses associated with key precursor events in the carcinogenic process, so that background exposures to this and other agents operating through a common mode of action are in the increasing, approximately linear portion of the dose-response curve*" (p 3-21, USEPA, 2005). The fact that dioxin is not genotoxic and the fact that background dioxin blood levels of around 20 parts per trillion are orders of magnitude below those required to simply induce CYP1A activity, the preponderance of the evidence justifies the threshold approach as the best science. As such, we strongly agree with the SAB recommendation to provide a more balanced assessment, including non-linear approaches, for evaluating carcinogenic risk.

2.5 The SAB overlooked the potential impact of confounding exposures in the cohort studied for the cancer assessment.

The SAB panel endorsed EPA's use of the Cheng et al (2006) study for quantitative cancer risk assessment without mentioning concerns about the potential for co-exposures to other carcinogenic chemicals. This is particularly perplexing given that there is, in fact, a substantial amount of environmental data that have been collected on plant sites that were included in the NIOSH study indicating the presence of numerous non-dioxin carcinogenic compounds in soil and groundwater (e.g., benzene, ethylene oxide, acetaldehyde, etc). If these chemicals are present in the soil and groundwater at the plants, then there had to have been releases and the workers had to have been exposed. This information was included in comments submitted to the docket by ToxStrategies, Inc., on behalf of Tierra Solutions, for consideration by the SAB panel. It should be noted that in his statements before the SAB panel, one of the NIOSH cohort investigators, Dr. Kyle Steenland, summarily dismissed co-exposures in the NIOSH cohort (the basis of the Cheng et al (2006) study used by the EPA) by stating that these chemicals merely represented inventories of chemicals at the plants. This is not at all accurate as demonstrated by the extensive environmental data. Site environmental data are available for Plant 1 and likely available for Plants 3, 4, 7, 8 and 11 that were evaluated by NIOSH.

EPA excluded data from the Ranch Hand study due to confounding exposures to 2,4-D, yet failed to address the confounding exposures in the NIOSH cohort. Given the marginal, at best, increase in cancer in the NIOSH cohort, we request that the SAB instruct EPA to more closely examine this issue of potential co-exposures in the NIOSH cohort.

2.6 The SAB should provide rationale for their support of EPA’s use of “all cancer mortality data” in the cancer assessment.

The SAB panel endorsed EPA’s use of all-cancer mortality data from the Cheng et al (2006) study “...*because of the extensive dose-response information.*” This endorsement is not supported by sound scientific data or reasoning. In particular, the SAB needs to address the extensive uncertainties associated with both the “dose” and the “response.” The exposure (dose) information is based on serum measurements from only 170 workers at a single plant that were then extrapolated to all of the other individuals in the subcohort (a total of 3,538 in the subcohort), including those at other plants, using a job exposure matrix (JEM) that is based on qualitative parameters that incorporate subjective judgment. As such, the resulting exposure estimates are 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 the original authors in the peer-reviewed literature but was not recognized by the EPA. With respect to the “response,” the SAB has not addressed the lack of biological plausibility that would link exposure with a mode of action that results in all cancers. EPA has taken the position that one must know the mode of action for each specific cancer endpoint, when in fact no single cancer endpoint is elevated relative to that seen in non-exposed individuals. In fact, as already mentioned, the increase is marginal at best (and not statistically significant) even when all cancers are combined.

2.7 It is essential that the EPA consider null epidemiological studies when evaluating data used for derivation of cancer potency values.

We support the Panel’s recommendation that it is important for EPA to provide a more balanced assessment of negative studies – and specifically to provide more discussion and clarity regarding the exclusion of the many null epidemiological studies that evaluated cancer. We further support the Panel’s recommendation to discuss these studies, along with others, in a weight of the evidence assessment. The SAB’s concern for the Agency’s lack of consideration of the wealth of negative epidemiological data are well justified; currently, it appears that the EPA arbitrarily selected studies that support agenda desired outcome when deriving cancer potency values.

3.0 Noncancer Comments

3.1 The SAB should provide justification for their support of a non-clinically significant endpoint used in the derivation of the draft RfD.

The EPA derived an RfD from a critical effect (change from normal sperm counts and sperm motility) based on data that (a) were not actually reported by the study authors, (b) were not clinically significant, (c) did not demonstrate a dose-response relationship, and (d) were not supported by a discussion on biological plausibility. It is therefore very difficult to understand how the SAB can support the use of this endpoint by simply stating [with emphasis added]: “...while the shifts observed in sperm counts may or may not pose a significant health effect in a single individual, such shifts on a population basis could *presumably* lead to potential adverse health outcomes.” This statement is difficult to understand given the findings of ecological studies that have examined reproductive effects and the impact on populations. Such studies are important as they are the only studies in the published literature that have examined population-level effects associated with exposures to dioxin-like compounds (see our next comment). As such, the SAB should provide scientific justification for suggesting that such shifts in a population may occur (particularly in the absence of effects in individuals in the study). Additionally, the SAB should also comment on why it is appropriate to use a study that evaluates individual responses for application to the entire U.S. population. Finally, the SAB should request that the study authors make the underlying raw data available for closer examination and peer-review by others.

3.2 The SAB should consider the findings of ecological studies when drawing conclusions about the potential for population level reproductive effects associated with exposures to dioxins

Reproductive effects and the potential for population level impacts have been evaluated in several ecological studies conducted in a variety of species along the Tittabawassee River area, as well as at upstream and downstream locations (Zwiernick et al 2008; Seston et al 2010; Coefeld et al 2010)¹. These studies were designed to examine the potential for adverse effects associated with exposures to dioxin-like compounds at a population-level in mink, Great Blue Herons, and Great Horned Owls. Collectively, these studies indicate a lack of population level reproductive effects despite elevated exposures to dioxins. For example, Zwiernick et al (2008) specifically noted,

¹ Zwiernick MJ, Kay DP, Moore J, Beckett KJ, Khim JS, Newsted JL, Roark SA, Giesy JP.

2008 Exposure and effects assessment of resident mink (*Mustela vison*) exposed to polychlorinated dibenzofurans and other dioxin-like compounds in the Tittabawassee River basin, Midland, Michigan, USA. *Environ Toxicol Chem.* 27(10):2076-87.

Seston RM, Fredricks TB, Tazelaar DL, Coefield SJ, Bradley PW, Newsted JL, Kay DP, Fitzgerald SD, Giesy JP, Zwiernick MJ. 2010. Tissue-based risk assessment of great blue heron (*Ardea Herodias*) exposed to PCDD/DF in the Tittabawassee River floodplain, Michigan, USA. *Environ Toxicol Chem.* 29(11):2544-58.

Coefield SJ, Fredricks TB, Seston RM, Nadeau MW, Tazelaar DL, Kay DP, Newsted J, Giesy JP, Zwiernick MJ. 2010. Ecological risk assessment of great horned owls (*Bubo virginianus*) exposed to PCDD/DF in the Tittabawassee River floodplain in Midland, Michigan, USA. *Environ Toxicol Chem.* 29(10):2341-9.

“reproductive potential was deemed to be normal, because no statistical difference was found in the number of fetus implant points between sites (placental scarring is indicative of the most recent reproductive cycle).” Similar findings were noted by Seston et al (2010), which included an assessment of clutch size and the number of nestlings per successful nest. Importantly, the concentrations of dioxins in eggs, plasma, adipose, liver or muscle did not correlate with the number of nestlings per nest in this study. Coefeld et al (2010) found that the Great Horned Owl population and productivity were greater in the study area than reference area, and were consistent with what was expected for the area.

If the SAB Panel desires to draw conclusions about the potential for reproductive effects at a population level, then they should rely upon data for population level effects that have been explicitly examined rather than speculating that although [with emphasis added] *“...shifts observed in sperm counts may or may not pose a significant health effect in a single individual, such shifts on a population basis could **presumably** lead to potential adverse health outcomes.”* The ecological literature provides a rich source of valuable information concerning the potential for dioxin-like compounds to cause population level reproductive effects and the SAB should recommend that this literature be carefully reviewed by EPA to determine the likelihood that the effects observed in both Mocarelli et al (2008) and Baccarelli et al (2008), which are not clinically significant and hence not adverse, could result in population level effects.

3.3 We strongly agree with the SAB that it is essential for the EPA to discuss weaknesses with the studies used in the noncancer assessment.

The Panel recommended that the weaknesses of both the Mocarelli et al (2008) and Baccarelli et al (2008) studies (the studies used to derive an RfD) be delineated. We are in agreement that this is essential. Just considering the Mocarelli et al (2008) study, some of the shortcomings of both the study itself, as well as the EPA’s application of the data, include:

1. the critical effect was based on data that were not actually reported by the study authors
2. the critical effect was not clinically significant
3. the critical effect did not demonstrate a dose-response relationship
4. RfD calculations were based on data that were insufficient to determine that effects were related to TCDD exposure
5. the appropriateness of using a high-level dioxin exposure event (that is considerably atypical relative to the experience of the general population) was not addressed sufficiently
6. the likely over-estimate of risk due to exposures to other dioxin-like chemicals was not accounted for in the quantitative exercises
7. the increased elimination rate of TCDD in children was not factored in to the assessment

8. the study reported significantly elevated sperm concentrations and motility counts in males 10-17 years old, but suppressed sperm concentrations for males 1-9 years old - how does the AhR know to suppress sperm concentrations for males 1-9 years old and then to elevate them in males 10-17? These results call into doubt the validity of the entire study.
9. the study does 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,b; Swan et al., 2003; reviewed in Safe et al., 2000)

Clearly these weaknesses, as well as others associated with study design and interpretation, need to be addressed for each study. Further, the SAB should request that the study authors make the raw data available for independent review and verification.

3.4 The SAB's recommendation for the EPA to use WHO reference values to validate the endpoint selected for the RfD derivation actually provides even more evidence that the effects observed in Mocarelli et al (2008) are not clinically significant and hence not adverse.

The SAB “*strongly suggests that further discussion of WHO reference values for male reproductive parameters be included in the Report.*” However, while we are clearly in agreement regarding the importance of looking at levels of clinical significance as defined by esteemed public health agencies such as the WHO, this recommendation by the SAB is perplexing as the newest WHO reference values for sperm concentrations (the critical endpoint used in the derivation of the RfD) actually indicate a lower level of clinical concern (15 million/ml) than was originally considered by the EPA (20 million/ml). Even the lowest sperm concentration presented by Mocarelli et al (2008) (i.e., one standard deviation below the mean) was above the EPA reference value and thus the lack of effect is even more pronounced if one uses the WHO reference value recommended by the Panel. Thus, it remains very difficult to understand how the SAB Panel can support the use of this endpoint as the basis for the RfD given that the lack of effect (lack of clinical significance) is even more pronounced using the WHO reference value. Finally, it should be noted that while the SAB Panel recommends that EPA incorporate the WHO reference value in their assessment, the document that the Panel cites (Skakkebaek, 2010) is actually a critique of the WHO guidelines.

3.5 We agree that the EPA should discuss the biological plausibility of noncancer endpoints

Of particular importance, the SAB emphasized the “*...need to think of [Mocarelli et al (2008) and Baccarelli et al (2008)] within the context of the weight of the dioxin and DLC database. The strength of the RfD should not be based solely on these two human epidemiology studies, but rather should be supported by integration with other similar supporting dioxin and DLC studies.*” The comments go on to recommend that the

selected endpoints should be supported by both animal and human studies, and should demonstrate a consistent and integrated signal of toxicity across species and endpoints.

Two recent reviews provide excellent resources for noncancer effects of dioxin. One of these reviews, Bell et al. (2010), was already recommended for consideration by the SAB. This comprehensive review provides information on rodent studies that address potential impacts of in utero and lactational exposures to dioxins on sperm parameters. Regarding the other critical endpoint changes in thyroid hormone levels, it is recommended the EPA consider Goodman et al. (2010), a comprehensive review of the available human data including a dose-response assessment for alterations in thyroid hormone levels.

3.6 The SAB 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 SAB needs to direct EPA to address this issue – does the proposed RfD lead to the conclusion that it is not safe for mothers to breastfeed their children?

4.0 PBPK Modeling Comments

4.1 We agree that the Emond PBPK mouse model should be subject to external peer review

When addressing the charge question related to the development of EPA's mouse model, the SAB Panel not only suggested validating the model with human data, but also recommended that the model undergo external peer review. This is not only a typical requirement for models used by the Agency, as the SAB noted, but also for most data used by the Agency. We strongly support this recommendation

4.2 It is essential that the EPA conduct additional modeling using biologically plausible values for the Hill coefficient in the PBPK model

The SAB expressed concern regarding a key parameter in the PBPK model used in the dose-response modeling for both cancer and noncancer endpoints. As part of their recommendation regarding the need to conduct a quantitative uncertainty analysis, the Panel noted that the Hill coefficient used by the EPA was well outside the confidence interval that is appropriate for chronic exposures to dioxins. The Panel further stated *“The use of a Hill coefficient value well below unity would lead to a nonlinear model behavior that is biologically implausible (hypersensitivity to induction at doses near zero)”* and provided several examples of how this single parameter leads to overly conservative estimates of exposure. We strongly support the Panel's suggestion that the calculations be repeated with multiple values to characterize the resulting uncertainty. This is an essential action going forward given that the Hill coefficient is one of the most important parameters in the PBPK model used for low-dose extrapolation.

5.0 Miscellaneous Comments

5.1 We strongly support the SAB's recommendation to conduct an uncertainty analysis

The SAB expressed a number of critical concerns regarding the need for a quantitative uncertainty analysis. Some of the Panel's key conclusions on this topic include the following:

1. It is in fact feasible to conduct a quantitative uncertainty analysis and, moreover, that doing so is *“essential”*
2. *“The current decision, in effect, to “punt” on quantitative uncertainty analysis is not adequate for informing responsible risk management decision and policy-making, and is not justified.”*
3. *“Without such quantitative analysis, risk management decisions for TCDD will not be adequately informed, and principles other than those of rational decision making may dominate risk management decisions for TCDD.”*

We strongly support the SAB's recommendation to conduct an uncertainty analysis. This will not only increase the technical defensibility of the assessment, but also help regulators to make informed policy decisions. A quantitative uncertainty analysis will help characterize the uncertainties pointed out by the SAB – specifically,

- how likely is it that TCDD is not a human carcinogen at current exposure levels;
- what is the probability that reducing TCDD exposures would not reduce cancer risk at all;
- what is the probability that reducing TCDD exposures would reduce cancer risk by less than 1 excess cancer risk per decade in the whole U.S. population;
- what is the probability that reducing TCDD exposures would increase cancer risk;
- etc.

5.2 It is unclear how the Panel can support the selection of key studies given their concerns that other studies (or study weaknesses from the key studies) have not been adequately described in the EPA report.

It is unclear how the SAB Panel can support EPA's selection of key studies for noncancer and cancer assessment given that they also recommend that the EPA (a) provide more information about study weaknesses from key studies, (b) provide greater clarity and transparency in indicating which studies did not satisfy inclusion criteria, and (c) further justify the rationale for excluding studies of dioxin-like compounds (which should be instead used in a weight of the evidence discussion). Without reviewing and

understanding other scientific data, it is difficult to understand how the SAB can support the key studies used by the EPA in the derivation of an RfD or OSF.