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Subject:
Comments on the Science Advisory Board (SAB) February 2011 Draft Report: Review of EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to National Academy of Sciences (NAS) Comments

Dear Dr. Armitage:

We appreciate the opportunity to provide comments to the SAB on their Draft Review of the U.S.EPA Office of Research and Development (ORD) Dioxin Reanalysis. We agree with the overall conclusion of the SAB that the Reanalysis contains significant deficiencies and falls short of addressing the comments made by the National Academy of Sciences (NAS) in their 2003 review of the Draft Reassessment. Specifically, we share the opinion that ORD must do more to incorporate a nonlinear (or threshold) based model into the approach to low-dose extrapolation, and we would further comment that the current, generally accepted understanding of the mode of action for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, hereafter dioxin) favors a threshold model. Policy should not dictate the methods used to derive toxicity criteria.

Further, we also believe that some form of a quantitative uncertainty analysis is imperative if the objective of the Reanalysis is truly to address the NAS comments. ORD should not dispense with the call for an uncertainty analysis by NAS only because the uncertainty analysis that ORD envisions is not feasible. It would be preferable, and relatively easy to at least present a range of toxicity criteria that are possible, based on the divergent, yet equally valid, approaches to their derivation.

There are numerous instances in the Reanalysis where equally valid choices were available to ORD, in many cases provided by qualified scientists outside the Agency, as a means for achieving the goals of the Reanalysis. Merely choosing the most conservative value at every decision-point and dismissing the other valid options is not in the spirit of U.S.EPA guidance, which emphasizes transparency, balance (weight of evidence assessments), and reasonableness.[1]

Our detailed comments to the SAB are as follows:

Issue: The SAB is requesting additional clarification and transparency with regards to the choice of uncertainty factors applied towards the development of RfDs using human data. Specifically, the SAB report recommends that ORD provide "a short discussion of the decision not to include a data base uncertainty factor" (p. 5), and again later in the report, to include "a short discussion for the basis of the decision not to include an UF for data quality." (p. 29)

Comment: We believe that it is important to emphasize that "[t]he Panel agrees that EPA has used the appropriate uncertainty factors for the derivation of the RfD" (p. 5), and that the SAB is merely requesting an additional discussion for the approach, as "…it might benefit the overall document with respect to transparency."

Of potential concern is the possibility that this recommendation might be interpreted as a recommendation to reconsider the uncertainty factors in the development of the RfD, when this is not its intention. We therefore recommend that the SAB be even more clear and explicitly state that *the Panel is not suggesting that a UF for data quality or database inadequacies is necessary*.

Despite the data quality and database adequacy characterizing the effects of TCDD on thyroid hormone levels in neonates and sperm count/quality in men, the need for an additional uncertainty factor to account for these factors is obviated by the fact that there is an abundance of related data in humans and animals that present mixed

[1] U.S.EPA. 2005. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. EPA/630/P-03/001F; U.S.EPA. 1995. Memorandum from Administrator Carol Browner on EPA Risk Characterization Program. April 21.

findings. Thus, the true uncertainty in the application of these data is in the opposite direction with a high likelihood that the reported effects are not caused by TCDD.

In our previous comments to ORD on the Dioxin Reanalysis we made the simple observation that the dramatic declines in the environmental concentrations and human intakes of dioxins are not being paralleled by similar declines in some of the human health effects attributed to dioxin; in addition there is no evidence that historic exposures, well in excess of the Draft RfD (and Draft OSF risk-specific dose) caused any higher incidence of these health effects. These observations are consistent with the opinion shared by many scientists that the Draft criteria are overly conservative.

It is also important to acknowledge that the nature of the RfDs and the derivation of these values preclude the need for a substantial safety factor. For example, in the derivation of the RfD based on thyroid hormone changes in neonates, the point of departure (POD) is chosen at a level that is intended for the screening of TSH levels which *may be indicative* of hypothyroidism (actually it is a benchmark intended to screen for iodine deficiency). Therefore, the choice of the POD is not an effect level, and thus, this choice already builds in a substantial margin of safety into the subsequent RfD.

It might also be noted that the Mocarrelli et al. (2008) and Bacarelli et al. (2008)[2] studies on decreased sperm counts and decreased neonatal TSH levels, respectively, are two studies in a long series of studies that have examined numerous potential health effects in the Seveso populations. The effects so far investigated (not necessarily found) have included total cancer mortality, several specific cancers (e.g., breast cancer), endometriosis, dental aberrations, hepatoxicity (biochemical measures), cardiovascular disease, changes in menstrual cycle duration, onset of menarche, diabetes, and the sex ratio among newborn children. Thus, the fact that ORD is focusing on only two endpoints for which a statistically significant correlation with dioxin exposure was reported lends considerable confidence to the conclusion that EPA was not likely to be overlooking a lower-dose effect.

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[2] Mocarrelli et al. 2008. Environ Health Perspect. 116:70-77; Bacarelli et al. 2008. PLoS Med. 5:e161.

With respect to the neonatal TSH levels, Bacarelli et al. (2008) provides a review of the other studies examining the effects of TCDD on TSH levels in animals and humans. They cite several studies in both categories and candidly point out that their study is the only human study reporting a positive correlation between TCDD serum levels and decreased neonatal TSH levels. Thus, the most significant uncertainty in using the Bacarelli et al. data is, in fact, in the potential for overstating the role of dioxin. A recent weight of evidence review of these data by Goodman et al.[3] summarizes the body of literature on TCDD-induced changes in thyroid hormones. The data give us confidence in stating the thyroid changes are very unlikely to occur at lower exposure levels.

With regards to Mocarrelli et al. (2008) and the reported changes in sperm quality, we are dealing with an endpoint that is notoriously difficult to measure, and it behooves ORD to consider the underlying mode of action that could plausibly be responsible for the reported effects. ORD acknowledges that these effects are likely to be caused by the very well-documented antiestrogenic effects of TCDD. The antiestrogenic effects of dioxins are, in general, high dose effects, as compared to other 'hallmark' biochemical and toxicological effects of TCDD, general requiring a dose of >1000 ng/kg in the whole animal, as compared to <100 ng/kg (required to see, for example induction of CYP1A1). While this may raise questions about the (exclusive) role of TCDD in the effects observed by Mocarelli et al. (2008), it certainly also provides great confidence that we are not likely to see these effects at even lower doses.

Issue: On p. 5, the SAB report states: "The Panel supports EPA's decision to use the Baccarelli et al. (2008) estimates of the relevant effective doses. The Panel also suggests that since the bulk of the calculations were based on zonal averages of exposed individuals in Baccarelli et al. (2008), EPA should clarify how these measurements relate to ranges and variations in exposure in utero."

Comment: We believe that ORD should not have simply relied on the regressions performed by Bacarelli et al. (2008), but should have obtained the data and conducted the regression analysis of the data themselves, in order to derive a POD. Compelling cases for an alternative use of these data and POD selection have been

[3] Goodman, et al. 2010. Regul Toxicol Pharmacol. 58(1):79-99.

presented, which should be considered by ORD.[4] Regarding SAB's second suggestion, we agree that greater clarity is warranted in the discussion of residential zone- vs. serum dioxin-based comparisons presented in by Bacarrelli et al. (2008) and how the two are connected. ORD should also address how the connection (or potential discordance) between these data could affect the overall results of this study. We would encourage the SAB to be more specific in their recommendations to ORD for addressing this issue.

The Bacarelli et al. (2008) study contains two distinct analyses of the data: the first that examines the relationship between neonatal TSH levels and the residence location (by zone) of the mother, and a second that examines the correlation between neonatal TSH levels and maternal serum dioxin concentrations. The authors and ORD rely on the findings from the zonal comparisons to bolster the confidence in the conclusions of the study as a whole. However, if one examines the serum concentration data from the second part of the study, it is easy to speculate that TSH changes due to maternal serum levels of dioxin that are barely discernible (Fig. 2 regressions, where $\beta = 0.45$ and 0.47) could be insufficient to explain the relatively strong reported differences from the zonal comparisons.

The connection between the two parts of the study would likely be elucidated by presenting the distribution of the dioxin serum data across the zones of residence. However, this analysis was not provided. In the early 1980s the relationship between maternal serum dioxin concentrations and zone of residence might have been obvious; however, in the 1990s, it is not obvious, and it should be examined. The question is important because if the maternal serum levels no longer correlate well with zone of residence, this may suggest that there is another influence (e.g., iodine deficiency) that is somehow correlated with zone of residence, and this factor is actually responsible for the observed effects on neonatal TSH.

Issue: The SAB report recommends that ORD elaborate further on the clinical manifestations of congenital hypothyroidism as it pertains to the TSH levels observed by Bacarelli et al. (2008).

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[4] Aylward, L. 2010. Review and recalculation of the U.S.EPA Draft Proposed Reference Dose (RfD) for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) based on weight of evidence methods. Organohalogen Compounds, 72:1142-1145. (Accessible at: http://www.dioxin20xx.org/pdfs/2010/10-1433.pdf)

Comment: We support this recommendation to the extent that the latter part of the recommendation, "…as it pertains to the TSH levels observed…," is emphasized. The Reanalysis currently describes some clinical manifestations of congenital hypothyroidism, although the relevance of subtle changes in neonatal TSH (as observed by Bacarelli et al. 2008) remains unclear. The problem is that a connection between these two distinct endpoints is inferred and, in fact, ORD seems to suggest that congenital hypothyroidism can be a consequence of altered TSH levels. Of course, by its very name congenital hypothyroidism is a developmental anomaly, and therefore, while congenital hypothyroidism is associated with, and can be diagnosed by high TSH levels, it is not the consequence of high TSH levels (or changes in thyroid hormones).

Congenital hypothyroidism almost always stems from a malformed or profoundly impaired thyroid gland, and if it even did have a chemical cause, it would be classified as a **developmental** effect. Bacarelli et al. (2008) did not examine the question, nor provided any finding relevant to the question of whether dioxin plays a role in congenital hypothyroidism. The subtle changes in neonatal TSH observed by Bacarelli et al. (2008) is an effect best classified as a hormone modulating (or endocrine) effect, which could be transient and of unknown clinical relevance. If the developmental toxicity of dioxin were the endpoint of interest, then it might be worth mentioning that the maternal serum dioxin levels may have been examined at an inappropriate time point. As a scientific review body, it would be quite heartening to see the SAB demand that these two endpoints (developmental and hormonal/biochemical) be treated separately within the categories they belong for the purposes of risk assessment.

Sincerely,

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