

Group comments summary for section 4 -- Faustman

First meeting summary comments—Section 4 Reference dose (Initial Draft)

General comments—A strong voice from the committee was given for looking at the comprehensive data base of both animal and human epi studies together due to a consistent and integrative signal of toxicity across species and endpoints for TCDD. This “collective” impact of the studies needs to be made stronger in the document and represents the contextual framing for understanding dioxin health impacts. The comparisons presented in Figure 4-4 were very important and useful.

4.1-Choice of the Mocarelli et al (2008) and Baccarelli et al (2008)

The EPA asks the committee to determine if the scientific rationale for these two studies to inform the RfD is clearly and scientifically presented in the document. They have also asked the committee to determine the appropriateness in using these studies as co-critical effects.

Choice of epidemiology studies—In general there was support for the use of the Mocarelli et al 2008 and Baccarelli et al 2008 studies as identifying “co-critical” effects for the RfD calculation.

These are extremely interesting and well thought out studies. The endpoints of changes in sperm count and TSH levels are of public health relevance and therefore of interest for determining an RfD. Collectively, there was support for these endpoints within the context of the broader dioxin literature.

The committee discussed that they studies have several very strong features including use of a well characterized human cohort and assessment by dioxin epidemiology experts however in isolation from each other or from the consistent signal from the supportive animal studies they are less useful for setting RfD. The committee emphasized to EPA the need to think of these within context of the weight of the database on TCDD.

Note – Need to add details on the types of studies ie population based, size etc. Also need to mention weaknesses such as sample size for sperm number and also add in comments regarding known variability in these biological endpoints. However, the committee noted that these factors would have made it more difficult to identify a TCDD relationship and could have made detection of significance more difficult.

Numerous times the committee referred to Figures 4.4 and 4.3 that showed quantitative comparisons across the RfDs calculated from the animal and epi studies as being useful in understanding the quantitative similarities in these calculations. The committee also noted that since this figure did not have an indication of endpoints the consistency in signal was not as readily apparent as it could be. The committee encourages EPA to make this more explicit in the figure and supportive text.

The strength of section 4 is that there is integration of these studies and in fact encouragement should be given to EPA to do further integration by even looking more integratively across the animal and human studies. For example the type and dose-response relationships for dioxin would strengthen if EPA would include more studies – especially the studies that had DLCs in their test mixtures. The strength of both the human epidemiology studies and the animal studies is the signal on these pathways across the studies not in any study in isolation.

4.2 – The committee discussed extensively both as part of the deliberations on Section 4 but also as part of the discussion on section 3 that the pattern of exposure from Seveso poses some extrapolation issues for the EPA. Issues raised include the question whether the same endpoints and or dose response would be expected from such exposure scenarios with high acute exposures when extrapolating to low-dose chronic exposures. In general the committee understood EPA's rationale that in order to identify studies with largely TCDD contaminants use of the Seveso cohort was justified however again the committee felt that discussion of the broader literature on dioxin and DLCs could be supportive if included (see comments for 4.5 below).

The group discussed and generally supported the EPA's decision to use the Baccarelli et al estimates of the relevant effective doses however additional discussion from the reviewers for the kinetics section is needed in order to respond to this part of the question. Support for EPA's approach to use the WHO reference value for determining TSH levels of concern is also evident. (Add further discussion on WHO reference values for male reproductive parameters). Group also referred to EPA guidance documents on repro and developmental endpoints and encouraged EPA to use and refer to their own documents for justifications on biological significance.

4.3 – These factors need to be reviewed after group decides on appropriate endpoints.

4.4 – This omission is of great concern to this reviewer as these early responses have been the hallmark of TCDD exposures. The committee was very surprised to learn that these responses were not used in supporting the continuum of effects that follow TCDD exposure and strongly expressed that the committee should provide significant advice and discussion on this approach.

4.5 Baccarelli et al (2008) – There was extensive discussion regarding the use of the exposure average time for the TCDD concentrations. This is of biological significance as several papers have indicated that the unique aspects of high peak exposure of TCDD as occurred in Seveso and in several of the animal studies. The endpoints affected as a result from these peaks does not always translate to impacts from lower chronic exposures. These potential differences are of concern and must be examined by the committee as the RfDs are reviewed.

Two considerations are offered – first, conduct a series of sensitivity analyses to evaluate the impact of averaging time on the RfDs and second, return to the broader animal

literature with DLCs to see if biological support for the endpoints could be added. Time and dose-response studies from the broader DLC literature could be informative

4.6 – In general the committee’s limited discussion would suggest agreement with the BMD modeling approaches used in this section for these two endpoints. As stated on the first day of discussion, the authors of this report need to more specifically cite the endpoint guidance that is present within EPA documents for defending their approaches for the two choices and application of BMD models for the critical effects. Expanded discussion on known human variability and WHO guidance would also be important in this section.

4.7 – The approach of EPA to apply the kinetics on the actual data present at the POD is preferred in this assessment.

4.8 – Committee needs to re-visit this issue. Please see earlier comments on need for sensitivity analysis and inclusion of other studies.