EPA's Response to Major Interagency Comments on the Interagency Science Discussion Draft IRIS Toxicological Review of Tetrachloroethylene

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Purpose: The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (Step 3 and 6) where White House offices and other federal agencies can comment on draft assessments. The following are EPA's responses to major interagency review comments received during the Interagency Science Discussion step (Step 6b) for the draft IRIS *Toxicological Review of Tetrachloroethylene* (U.S. EPA, 2011). All interagency comments provided were taken into consideration in revising the draft assessment prior to posting the final Toxicological Review. The complete set of interagency comments is available on the IRIS website (www.epa.gov/iris) and includes comments from the Office of Management and Budget (OMB), the National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP), the National Institute for Occupational Safety and Health (NIOSH), the Small Business Administration (SBA), the Agency for Toxic Substances and Disease Registry (ATSDR), and the Department of Defense (DoD).

For a complete description of the IRIS process, including Interagency Science Discussion, visit the IRIS website at www.epa.gov/iris.

Topic #1: Selection of principal studies for the derivation of non-cancer toxicity values– *NRC (2010) recommended five studies for consideration in deriving non-cancer toxicity values (Cavalleri et al., 1994; Echeverria et al., 1995; Gobba et al., 1998; Altmann et al., 1990; and Boyes et al., 2009). The three principal studies selected by EPA in its interagency science discussion draft included two of the chronic studies recommended by NRC—Cavalleri et al. (1994) and Echeverria et al. (1995)— as well as a third chronic study (Seeber, 1989). OMB and SBA questioned the adequacy of EPA's explanation for including Seeber (1989) as one of three principal studies in the interagency science discussion draft. They noted that NRC did not include Seeber (1989) among studies recommended for consideration for non-cancer toxicity value derivation, and that NRC discussed specific concerns regarding Seeber (1989) that EPA had not addressed.*

> **EPA Response:** Based on further consideration of the NRC recommendations and interagency comments, EPA revisited its selection of principal studies for derivation of the noncancer reference values. In its final Toxicological Review, EPA no longer selects Seeber (1989) as a third principal study. EPA relies on the two chronic principal studies recommended by the NRC peer review panel—Cavalleri et al. (1994) and Echeverria et al. (1995)—for reference value derivation. Compared with previous drafts, exclusion of Seeber (1989) as a principal study did not change the derived RfC and RfD values.

Topic #2: Benchmark Dose (BMD) modeling of principal non-cancer studies–*DoD commented that EPA did not adequately explain the lack of BMD modeling of the dose-response data from the principal*

non-cancer studies (i.e., Cavalleri et al., 1994; Echeverria et al., 1995). Specific recommendations were for EPA to discuss dose metrics that might have provided better fits, consider modeling approaches outside BMDS (Benchmark Dose Software; U.S. EPA, 2009), and include modeling attempts in the assessment for documentation.

EPA Response: EPA examined the feasibility of dose-response modeling for the selected principal non-cancer studies. EPA concludes that the available data were inadequate to support BMD modeling for the principal non-cancer studies, independently of whether refinements of the dose metrics were relevant; thus, no dose-response modeling was performed. Specific issues include the following:

- Cavalleri et al. (1994) reported the results of statistical significance testing based on logistic regression that controlled for age and other potential confounders, but did not report details that could have facilitated modeling (i.e., model parameters that might have permitted BMD/BMDL estimation, or raw data including the ages that might have permitted repeating the analysis), nor were any summary results that had been adjusted for these confounders reported. Models outside BMDS would have been considered had the relevant data been available.

- Echeverria et al. (1995) lacked an unexposed control group. Had individual exposure and response data been available, responses corresponding to no exposure might be inferred. However, this data set had only summary values (means and standard deviations) for exposures and responses in the three groups, with substantial uncertainty regarding whether or not extrapolation toward an inferred control response would be linear.

These rationales are discussed in Section 5.1.2 of the Toxicological Review.

Topic #3: Selection of a Database Uncertainty Factor (UF_D) of 10 for derivation of noncancer reference values—*OMB, NTP and DoD recommended reducing the database uncertainty factor from 10 to 3 (NTP, OMB) or 1 (DoD). OMB commented that EPA did not provide a scientific justification for choosing a factor of 10, recommending that EPA evaluate the points of departure from new animal studies (Boyes et al., 2009; Oshiro et al., 2008) cited by NRC (2010). DoD commented that if the residential studies involving lower exposures than the occupational studies were insufficient to support a point of departure, they were also insufficient to suggest that the point of departure should be lower than those derived from occupational studies. NTP commented that because EPA used some of the most sensitive neurotoxicity endpoints, additional animal studies were unlikely to augment the existing database.*

EPA Response: In the External Peer Review Draft (2008), EPA had applied an UF_D of 3. Based on concerns raised by NRC in the external peer review, EPA re-examined the adequacy of the database and increased the UF_D from 3 to 10 in the interagency science discussion draft (2011).

EPA's application of an UF_D of 10 to address the lack of data to adequately characterize the hazard and dose response in the human population is consistent with EPA's *A Review of the Reference Dose and Reference Concentration* (U.S. EPA, 2002), and is in accord with NRC recommendations. Specifically, the committee stated,

> "Notable gaps in the animal literature still include the paucity of studies of developmental or chronic exposures. Another consideration is that the committee found the human study of exposed children (Schreiber et al., 2002) to be methodologically flawed. The committee judged these to be serious gaps in the database, which suggests that a factor of 3 may be inadequate to account for database deficiencies."

EPA's scientific justification is based on a number of data gaps identified from both the human and animal literature. Regarding neurotoxicity, animal studies of chronic exposures (including in developing animals) examining sensitive neurotoxic endpoints are lacking. Additionally, the most sensitive neurotoxic endpoint associated with tetrachloroethylene exposure in humans—decrement in visual contrast sensitivity—was identified in residential studies that were judged to be limited for developing an RfC (Storm et al., 2011 [previously reported in NYSDOH, 2010]; Schreiber et al., 2002; Altmann et al., 1995). This specific endpoint was not evaluated in any of the occupational studies used for developing the RfC. Regarding sensitive endpoints other than neurotoxicity, the available human and animal studies of immunologic and hematologic toxicity [e.g., Emara et al. (2010); Marth (1987)] are limited. In sum, uncertainties associated with database deficiencies on neurological, developmental, and immunological effects provide scientific support for a database uncertainty factor of 10.

EPA evaluated the points of departure from the available database of studies as part of its considerations in choosing a UF_D. Specifically, EPA presents in the Toxicological Review a tabular summary of points of departure from the inhalation (refer to Table 4-49) and oral (refer to Table 4-50) studies suitable for dose-response analysis, considering all studies across toxicity endpoints. New animal studies (Boyes et al., 2009; Oshiro et al., 2008) cited by NRC (2010) are presented therein, and also quantitatively evaluated in Section 5.1.1 (refer to Table 5-1 and Figure 5-1). EPA's quantitative characterization of the relative sensitivity of different organs/systems to tetrachloroethylene (refer to Sections 5.1.4 and 5.2.4, Figures 5-3 and 5-5) considers studies identifying sensitive endpoints other than neurotoxicity, including hematologic toxicity studies also identified by NRC (2010). These analyses provide support for the view that critical data gaps remain for the most sensitive endpoints in neurotoxicity and other types of toxicity.

EPA's scientific justification for choosing this UF_D is presented in Section 5 of the Toxicological Review, specifically where the reference concentration (Section 5.1.3) and dose (Section 5.2.3) are derived.

Topic #4: Selection of tumor type for quantitative cancer risk estimation– *EPA's interagency science discussion draft relied on male and female rat mononuclear cell leukemia data for the derivation of the oral slope factor and inhalation unit risk. OMB commented that it was not clear that EPA adequately justified its choice of rat mononuclear cell leukemia for cancer risk estimation, recommending that EPA reconsider the chosen cancer endpoint. OMB recommended that EPA respond directly to the scientific concerns raised by the majority of the NRC panel regarding use of mononuclear cell leukemia, particularly regarding the high background incidence, uncertainty about the dose response relationship and poor understanding of mode of action. OMB also stated that EPA had not performed the recommended life-table analysis of the mononuclear cell leukemia data recommended by NRC.*

> **EPA Response:** EPA revisited its choice of tumor type for derivation of the oral slope factor and inhalation unit risk, based on further consideration of the NRC recommendations. EPA no longer selects mononuclear cell leukemia as the basis for cancer risk estimation. EPA's final Toxicological Review relies on the male mouse hepatocellular tumor data from the JISA (1993) bioassay, as recommended by the majority of the NRC peer review panel (refer to Sections 5.3.4.2 and 5.3.4.3). EPA also presents the cancer risk estimates based on the mononuclear cell leukemia data, as supported by the minority of the NRC peer review panel. In its final Toxicological Review, EPA addresses the scientific issues concerning the mononuclear cell leukemia data raised by NRC (poor understanding of mode of action, high background incidence, and uncertainty about the dose response relationship) (refer to Section 4.6 and 5.3.2.3). Regarding the life-table analysis recommended by NRC, the final Toxicological Review presents statistical analyses of the bioassay findings, including an analysis of the JISA mononuclear cell leukemia data that appropriately considered time of death.

Topic #5: BMD modeling of cancer studies–*DoD stated that EPA did not use its normal model selection procedures, including the evaluation of multiple BMD models for deriving cancer risk values, and was not transparent in summarizing the procedures used.*

> **EPA Response:** For the cancer risk estimation, EPA followed its normal model selection procedure. In brief, it is EPA's general practice to use the multistage model as its baseline choice for dose-response modeling of cancer incidence data. This practice is supported by the parallel between the multistage model and the multistage carcinogenic process and the flexibility of the multistage model in fitting a broad array of dose-response patterns. When the multistage model does not fit the available data, alternative models and approaches are considered. This procedure is consistent with EPA's Guidelines for Carcinogen Risk Assessment [refer to Section 3.2.3, U.S. EPA (2005)], and its use has contributed to greater consistency among cancer risk assessments.
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> The model selection process as implemented for tetrachloroethylene followed this procedure with some augmentation based on concerns raised by the NRC (2010). First, as recommended

by the NRC (2010), EPA analyzed all the tumor sites from the JISA (1993) bioassay using the full suite of BMDS models to characterize model uncertainty at the point of departure for each site. Second, while the external peer review draft concluded that the multistage model fits to all the tumor sites were adequate, the NRC (2010) concluded that several data sets, such as male mouse hepatic tumors and both male and female rat mononuclear cell leukemias, were not adequately represented by the multistage fit, and could underestimate low-dose risk due to these datasets' supralinear dose-response shape. In the final Toxicological Review, EPA agrees that these were essentially "borderline" cases regarding model fit that should be re-evaluated. Following EPA's normal procedure, a number of options were considered:

- All other dichotomous BMDS models were considered first. Among these, there were insufficient degrees of freedom to fit the full dichotomous Hill model. As the Hill model is a generalization of the simpler Michaelis-Menten model (which is the dichotomous Hill model with the slope set to 1), this model was among those considered. Note that this is an empirical form of the model in which the modeling process determines the parameter values, not the more classical version which uses experimentally determined V_{max} and K_m values to describe enzyme kinetics.
- Other options, such as including historical control responses, combining male and female data, and dropping higher doses, were considered next.

For the mouse hepatic tumors, none of the alternative approaches was clearly superior to the standard multistage model for addressing this dataset's supralinearity at the lower doses. Therefore, the multistage model results were carried forward as candidate cancer risk estimates. For the male rat mononuclear cell leukemias, a number of models fit adequately and led to better visual fits in the low-dose region than the multistage model, with the Michaelis-Menten model capturing the supralinear dose-response shape of the data most closely. Therefore, the Michaelis-Menten model results were carried forward as candidate cancer risk estimates. In the female rat mononuclear cell leukemias, the Michaelis-Menten model also better captured the supralinear dose-response shape of the data, but the statistical uncertainty was too great to support BMD estimates. The only remaining options that led to better fits than the multistage model were dropping all but the lowest dose group and combining the male and female datasets. Results from both these analyses were also carried forward as candidate cancer risk estimates.

Finally, concerning transparency of the rationales for the dose-response analyses, EPA has provided additional details in Section 5.3 (starting on p. 5-66) and in Appendix D, and noted where the NRC recommendations augmented EPA's usual procedures. EPA has added cross-referencing to the document to indicate more clearly where the procedures are described.

Topic #6: Use of the multistage model in cancer dose-response analyses: *DoD disagreed with EPA's statement that "The multistage model has been used by EPA in the vast majority of quantitative cancer assessments." DoD noted that prior to EPA's 2005 cancer guidelines, EPA used the linearized multistage model, and asserted that the two models have significant differences. DoD concluded that*

most of EPA's cancer potencies have been estimated using the linearized multistage model and recommended correction of the statement.

> **EPA Response**: The quoted statement is correct. As implemented by EPA for cancer dose-response modeling, the multistage and linearized multistage models are very similar. For both models, parameters are restricted to be non-negative, in order to describe monotonically increasing dose-response patterns. The only difference between the two models involves restricting the upper bound in the low-dose region to be linear for the linearized multistage model. A comparison of these two model forms has shown them to provide virtually identical BMD_{10}s and $BMDL_{10}$s (when rounded to 2 significant digits), using 102 data sets (Subramaniam et al., 2006).

Topic #7: EPA's application and external peer review of the Chiu and Ginsberg (2011) physiologically based pharmacokinetic (PBPK) model— *The Toxicological Review utilizes a harmonized PBPK model that EPA developed in response to NRC recommendations. This harmonized PBPK model was peer-reviewed and published (Chiu and Ginsberg, 2011). Additionally, EPA conducted a focused peer review on the application of the published harmonized model in the Toxicological Review. While welcoming EPA's initiative in seeking peer review comments on this aspect of the assessment, OMB and SBA questioned whether EPA fully responded to the peer review, particularly with respect to recommendations for improving model documentation. DoD stated that conclusions regarding the model's validity were incompletely summarized in the assessment. NTP recommended including more information in the assessment about the model's validity for predicting oral exposures.*

> **EPA Response:** EPA's focused peer review on the application of the published harmonized PBPK model in the Toxicological Review sought input on whether the model 1) was clearly and transparently described, and adequately responsive to the NRC recommendations; and 2) was used appropriately in the dose-response assessment. The peer reviewers commented that the PBPK model developed by EPA is adequately responsive to the NRC recommendations, and supported both the technical soundness of the application of the PBPK model and the numerical results. No changes to the model were requested by the peer reviewers. However, EPA fully implemented peer review recommendations to improve the clarity and transparency of the description of the model and its use, either by adding documentation to the text (refer to Section 3) or by making model documentation publicly available on EPA's HERO database (Chiu and Ginsberg, 2011; U.S. EPA, 2011). EPA also provided additional detail regarding these changes in Appendix A.
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> With respect to NTP's comments on the validity of the model for predicting oral exposure, EPA notes that kinetic data from oral exposures in rats and mice were used to calibrate and evaluate the new harmonized model. Only inhalation data were available in humans, but those data were adequate to predict with confidence that first pass metabolism (which strongly affects predictions

from oral dosing) is minimal. These findings therefore support the reliability of predictions of tetrachloroethylene blood levels following human oral exposures.

References:

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