

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

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Purpose: The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (i.e., Step 3 and 6b) 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 (i.e., Step 6b) for the draft IRIS Toxicological Review of Tetrahydrofuran (dated July 2011). All interagency comments provided were taken into consideration in revising the draft assessment prior to posting to the IRIS database. The Interagency Science Discussion draft assessment and the complete set of interagency comments are available on the IRIS website (www.epa.gov/iris). Comments were received from the Office of Management and Budget (OMB), National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP), and Center for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry (CDC/ATSDR).

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 the critical effect for the derivation of the reference dose (RfD) – *The oral database for tetrahydrofuran (THF) contains a two-generation reproductive toxicity study in rats (BASF, 1996; subsequently published as Hellwig et al., 2002) and a range-finding, one-generation reproductive study in rats (BASF, 1994). EPA selected the two-generation reproductive study in rats as the principal study on which to base the derivation of the RfD. Several reported effects (e.g., decreased body weight gain, delayed eye opening, and increased incidence of sloped incisors) in offspring of female rats exposed to THF were evaluated, with decreased body weight gain selected as the critical effect for the derivation of the RfD. Although the external peer reviewers agreed with the selection of this study as the principal study, their response to the selection of the critical effect and the implication that THF could be a developmental toxicant was mixed -- four out of six reviewers agreed with the selection of decreased pup body weight gain as the critical effect; and one of these reviewers noted that this effect represented a marginally adverse effect. The other two peer reviewers stated that the observed effects were minimal, and indicated a low potential for developmental toxicity of THF*

by the oral route of exposure. One of these reviewers also commented that while the selection of the critical effect was transparently and objectively described in the Toxicological Review, the critical effect was only observable during a small period of time, may have been impacted by decreased water consumption in the dams, and did not lead to more pronounced changes in growth or reproductive ability in the F1 generation. This reviewer concluded, however, that there did not appear to be a better endpoint from these studies that could be used to derive the RfD. The other reviewer commented that classifying the decreased pup body weight gain as a developmental effect was tenuous due in part to the overall, low magnitude of the effect and the decreased water intake in dams. This reviewer stated that while the Hellwig et al. (2002) study may remain the most appropriate study to serve as the principal study due to the absence of more high quality data sets, the interpretation of this study as direct evidence of THF-induced developmental toxicity was questionable.

During the Interagency Science Discussion step of the IRIS process, NTP reiterated the concerns of the two peer reviewers who had questioned the critical effect, stating that none of the oral toxicity studies in the literature clearly identified target organ toxicity for THF and that the critical effects selected for derivation of the RfD were marginal at best. In addition, OMB stated that EPA's response in the Interagency Science Discussion draft to peer reviewers' comments on the critical effect for the RfD did not seem to capture their concerns regarding the lack of adversity of the critical effects. ATSDR agreed with the derivation of the RfD.

EPA Response: In response to the interagency comments and after further consideration of the two external peer reviewers' comments regarding the adversity of the critical effect, additional text has been added to augment the interpretation and characterization of the adversity of these endpoints in Section 5.1.1 (*Choice of Principal Study and Candidate Critical Effects—with Rationale and Justification*) and Appendix A (*Summary of External Peer Review and Public Comments and Disposition*) of the Toxicological Review of Tetrahydrofuran. Clarifying text has been added to indicate that the decreased pup body weight gain findings were consistent in males and females across both generations (i.e., in both F1 and F2 pups) within the study, with all four datasets showing statistically significant trends and approximately 10% decreases in body weight gain at the highest dose tested as compared to controls. In addition, a significant number of F2 pups/litter had delayed eye opening and an increased number of sloped incisors at the high dose. Text has also been added to indicate that these endpoints in pups are considered common markers of an adverse effect on development, consistent with the principles and practices of EPA's *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991). For these reasons EPA considers the decreased pup body weight gain to be an adverse effect, and in

agreement with the majority of the external peer reviewers used this effect as the basis for the RfD.

In addition, the inhalation database also provides support for the selected critical effect for the RfD. Specifically, developmental toxicity studies of THF via inhalation show decreased fetal body weight gain (Mast et al., 1992; DuPont Haskell Laboratory, 1980). The potential for developmental effects associated with THF exposure is also indicated by delayed growth in the F2 generation and effects on reproductive capacity in the F1 generation. Specifically, the mean number of delivered F2 pups/litter was decreased 16% in the high-dose group compared with control and was outside the range of historical control values. The study authors considered this finding to be consistent with a slight developmental delay (Hellwig et al., 2002).

With regard to comments related to maternal water intake, data on the possible relationship between decreased water intake in dams and decreased production of milk were not provided in this study. As detailed in Section 4.3 (*Reproductive/Developmental Toxicity Studies—Oral and Inhalation*) of the Toxicological Review of Tetrahydrofuran, the decreased pup body weight gain is supported by the statistically significant correlation between F2 pup body weight gain and maternal THF intake after multivariable regression analyses were conducted to control for the other possible confounding factors, namely, average water intake and number of pups in each litter. Thus, the observed responses in the pups appear to be associated with THF exposure.

Topic #2: Selection of the benchmark response (BMR) for the derivation of the RfD – *In deriving the RfD in the External Peer Review draft assessment, EPA selected a BMR of a 5% decrease in fetal body weight gain from the control mean in rat pups to identify the point of departure (POD), based on the assumption that a 5% decrease in pup body weight is a minimal, biologically significant change. Most of the peer reviewers recommended using a BMR of 1 standard deviation (SD) decrease in the mean body weight gain of controls instead of a 5% decrease, on the basis that a percentage reduction in body weight gain is an arbitrary choice compared with a measure of effect that considers the variation among animals. In the Interagency Science Discussion draft assessment, EPA continued to present a BMR of 5%, but described the rationale for this selection over 1 SD in response to the peer reviewers in Appendix A (Summary of External Peer Review and Public Comments and Disposition) of the Toxicological Review. At that time, EPA had only been able to locate the data from Hellwig et al. (2002) and BASF (1996) that would characterize the variability in pup body weight gain between litters and not among pups. Variability among pups is considered to be the relevant*

measure for calculating a 1 SD BMR. Thus, the analysis recommended by the peer reviewers was not considered to be feasible using the available data. OMB commented that EPA's response to the peer reviewers' comments on this topic was not clear and suggested that EPA reconsider the comments they received from the majority of reviewers.

EPA Response: Following the Interagency Science Discussion step in the IRIS process, EPA again attempted to obtain the individual pup data and was successful, allowing for the determination of the variability among pups and the derivation of an RfD based on a 1 SD BMR as recommended by the peer reviewers. Analyses utilizing both a BMR of 1SD from the control mean and a 5% change in fetal body weight gain are presented in the assessment. A 5% change in fetal body weight is included for comparison purposes and is assumed to be relevant for pups by analogy to body weight in adult animals, for which a 10% change is generally recognized to support identification of maximum tolerated doses, and based on the assumption that developing animals represent a sensitive lifestage that is a period of vulnerability involving active development of functional systems, and would be more sensitive to a decrease in body weight change than an adult lifestage. EPA has revised Section 5.1.2 (*Methods of Analysis*) and Appendix A (*Summary of External Peer Review and Public Comments and Disposition*) of the Toxicological Review to reflect this change in the BMR calculation.

Topic # 3: Quantitative cancer assessment – *EPA's Interagency Science Discussion draft assessment characterized THF as having suggestive evidence of carcinogenic potential and presented an inhalation cancer risk estimate (i.e., an inhalation unit risk). The inhalation unit risk was derived from tumor data in rats utilizing a linear low-dose extrapolation, an approach that is recommended in cases where the mode of action of carcinogenicity is not well understood. OMB commented that EPA's rationale for providing a quantitative cancer risk estimate was unclear given that the EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005) state that EPA generally would not attempt a dose-response assessment in cases in which the evidence of carcinogenicity is suggestive in nature. OMB also cited some of the peer reviewers' comments regarding the linear low-dose extrapolation approach. The peer reviewers agreed with EPA's conclusion that based on the available data, the mode of carcinogenic action for THF is not well understood. They also stated that this conclusion is consistent with the application of a linear low-dose extrapolation; however, most reviewers commented that THF is a weak, nongenotoxic carcinogen which would have a threshold response (i.e., a nonlinear response at low-dose), and further stated that use of a linear low-dose extrapolation would result in an overestimation of cancer risk.*

EPA Response: In cases in which there is suggestive evidence of carcinogenic potential, EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) state: "When there is suggestive evidence, the Agency generally would not attempt a dose-response assessment, as the nature of the data generally would not support one; however, when the evidence includes a well-conducted study, quantitative analyses may be useful for some purposes, for example, providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities. In each case, the rationale for the quantitative analysis is explained, considering the uncertainty in the data and the suggestive nature of the weight of evidence. These analyses generally would not be considered Agency consensus estimates." For THF, evidence of carcinogenicity in animals was reported in a well-conducted study (NTP, 1998) showing liver tumors in female mice that were increased in a dose-related manner. The data from this study are amenable to modeling; EPA would generally derive a cancer risk estimate from such data.

Because very little data are available to inform the mode of action for THF and no data are available to indicate the shape of the dose-response curve at low doses, a linear low-dose extrapolation approach was utilized in the derivation of the inhalation unit risk in the External Peer Review and Interagency Science Discussion draft assessments. In response to peer reviewer comments, EPA considered the application of a nonlinear analysis; however, because the mode of carcinogenic action is not well understood and there are no noncancer effects reported that could serve as a precursor endpoint upon which to base a nonlinear analysis, the nonlinear low-dose extrapolation approach recommended by the peer reviewers could not be readily implemented. Based on the peer reviewers' concern for the potential overestimation of risk in deriving an inhalation unit risk for THF using a linear low-dose extrapolation approach combined with the uncertainty associated with the carcinogenic potential of THF, EPA's final assessment for THF does not derive an inhalation unit risk. The text in Section 5.3 (*Cancer Assessment*) and Appendix A (*Summary of External Peer Review and Public Comments and Disposition*) of the Toxicological Review was revised to reflect this change.

Because there may be some circumstances for which a cancer risk estimate for THF would be useful, EPA has presented what the inhalation cancer risk estimate would be if it were derived using a linear low-dose approach. This derivation can be found in Appendix B of the Toxicological Review. The accompanying text indicates that risk assessors should use caution when considering the use of this value due to the uncertainty associated with this value.

References:

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