

## **NTP Comments on Draft IRIS Toxicological Review of Tetrachloroethylene**

The draft IRIS Toxicological Review on tetrachloroethylene is a very comprehensive document prepared by EPA. The data is well organized and clearly presented. The selection of the principal studies and toxicity endpoints in the derivation of guidance values is well justified. While preparing this document EPA has taken into consideration and responded to all the comments received from the NRC review. We agree with the approach of using multiple human studies to derive the inhalation RfC based on the neurotoxicity endpoints. In the earlier draft, EPA used inhalation data to derive the oral RfD by using three PBPK models in support of route-to-route extrapolation. Based on the concern raised by the NRC for lack of any oral parameter in the models, EPA in the current draft has used a new harmonized model developed by Chiu and Ginsberg for route to route extrapolation. We are not sure about the strengths and appropriateness of this model in predicting oral exposures. If there is some information available on validity of this model, EPA should consider including that in the text.

We agree with all the uncertainty factors EPA has used in derivation of inhalation RfC and oral RfD. However, in our opinion, application of uncertainty factor of 10 for gaps in the database is excessive considering a vast amount of data in humans and laboratory animals is available. Furthermore, the neurotoxicity endpoints used are some of the most sensitive biomarkers in chemical toxicity in general and it is unlikely that additional animal studies would add any valuable information to the existing database. In our opinion, the uncertainty factor of 3 is more appropriate for derivation of RfD.

Overall, we find the document as one of the best we have recently reviewed.

Submitted by:

Rajendra S. Chhabra, BVSc. PhD. DABT