



## Memorandum

**Date:** November 28, 2011

**From:** Center for Disease Control and Prevention / Agency for Toxic Substances and Disease Registry

**Subject:** Comments on EPA's Toxicological Review of Dioxin (non-cancer)

**To:** Environmental Protection Agency

We appreciate the opportunity to review the draft Toxicological Review of Dioxin (non-cancer). Overall, we found the review to be well-written and clear. Although a different method was used to develop EPA's non-cancer health guidance value, the resulting RfD of 0.7 pg/kg/day is relatively close to ATSDR's chronic oral MRL of 1.0 pg/kg/day.

We have two specific comments on the document and peer reviewer comments:

1. **EPA's Comment No. 8 from Peer Reviewers:** Plasma lipoprotein profile varies among groups in the population for several reasons, such as age, certain diseases and disorders, and fasting state. Among mammals, humans have higher plasma lipid concentrations than other species (Marinovich et al. 1983). Also, the lipoprotein profile can vary among mammalian species. For example, LDL is higher in humans than in rats (Gallenberg and Vodcnik, 1989), and the major lipoprotein carriers for lipids in plasma are VLDL and LDL in humans and HDL in canines (McIntosh et al., 1999). These differences among mammalian species can lead to variations in the distribution of chemicals among the lipoprotein species in plasma.

Marinovich and colleagues (1983) demonstrated a greater proportion of TCDD in LDL than in VLDL and HDL in a mixing study using human plasma. The distribution of TCDD among the lipoprotein fractions was similar when rat plasma was used. Although the distribution of TCDD in rat plasma was similar among the lipoproteins, it was different than the distribution of TCDD among the lipoproteins in human plasma.

For certain chemicals, the correlation coefficient between the chemical and an individual apolar lipid, such as triglyceride, can be less than that between the chemical and the sum of apolar lipids. Thus, the manner by which serum total lipids is determined can be relevant when interpreting the concentration of chemicals, such as TCDD. Biological conditions associated with changes in the lipoprotein profile can alter the distribution of chemicals, such as TCDD, in the body.

2. **IASD IRIS Summary Document – p. 4, line 33:** TCDD LASC might not change during the physiologic hyperlipidemia of human gestation. Longitudinal human or rat data is desired.

Reference: Marinovich M, Sirtori CR, Galli CL, Paoletti R. The binding of 2,3,7,8-tetrachlorodibenzodioxin to plasma lipoproteins may delay toxicity in experimental hyperlipidemia. *Chem Biol Interact.* 1983 Aug 1;45(3):393-9.