Agency for Toxic Substances and Disease Registry (ATSDR) Comments on the final Agency/Interagency Science Discussion Draft IRIS Toxicological Review of Hexachloroethane (dated April 2011)

Memo to: Environmental Protection Agency

From: NCEH/ATSDR, Centers for Disease Control and Prevention

Regarding: Interagency review of EPA's Draft Toxicological Review, IRIS Summary and Fact Sheet for Hexachloroethane

Date: May 17, 2011

General Comments

Submitted for ATSDR/DTEM review are EPA draft documents Toxicological Review of Hexachloroethane (HCE), IRIS Summary on HCE, and the HCE Fact Sheet. This information presents the scientific basis supporting the human health assessment of HCE that will appear on the EPA online database, the Integrated Risk Information System (IRIS). The draft health assessment being reviewed here includes a chronic reference dose (RfD), reference concentration (RfC), and a carcinogenicity assessment.

Overall, this toxicological review and assessment is well written. EPA has clearly synthesized the scientific evidence and presents a non cancer and cancer hazard assessment of HCE that is logical, transparent, and concise.

Non Cancer Toxicity of Hexachloroethane

A chronic RfD of 7×10^{-4} mg/kg/day has been proposed for HCE. This value is based on a 16-week oral (via diet), subchronic study in rats (Gorzinski et al., 1985). Atrophy and degeneration of renal tubules in male rats was selected as the critical effect for RfD derivation.

A major concern of this reviewer was the relevance of this male rat renal end point to human risk assessment. Chronic progressive nephropathy (CPN) in the aging male rat typically complicates the assessment of chemically induced renal changes in chronic rat studies. However, lesions of CPN in exposed male rats may be utilized as potential

endpoints for estimating non carcinogenic risk if exposed male and female rats have CPN lesions that exhibit a clearly defined dose response.

The question that had to be answered here by EPA is whether the exacerbation of CPN lesions in male rats was HCE- induced (with dose response), or was the exacerbation of these kidney lesions brought about by nephropathy associated with accumulation of α_{2u}-globulin.

If accumulation of α_{2u}- globulin played a role in the exacerbation of CPN lesions in male rats exposed to HCE—these end points would not be suitable or relevant for extrapolation to human risk assessment.

In the data and conclusions that are presented by EPA there is insufficient evidence to attribute the kidney effects of HCE- exposure to an α_{2u}- globulin mode of action. With this being the case, ATSDR concurs with the selection of "atrophy and degeneration of renal tubules in male rats" as an appropriate point of departure (POD) for RfD derivation.

The RfD of 7×10^{-4} mg/kg/day was derived by applying a total uncertainty factor (UF) of 1000 to a $BMDL_{10}$ of 0.728 mg/kg/day . The UF of 1000 was composed of the following components: UF of 10 for interspecies extrapolation; UF of 10 for intraspecies variation; UF of 3 for subchronic-to-chronic exposure duration extrapolation; and UF of 3 for database deficiencies.

This reviewer suggests that the total uncertainty factor should be 3000 (rather than 1000). The individual component UF that I disagree with, is the UF of 3 that was used to account for extrapolation from subchronic-to-chronic exposure duration. I recommend that the most appropriate UF here would be 10.

Part of the rationale that EPA gives for using the UF of 3 in this situation is that evidence suggests that an increase in duration of HCE exposure may not increase the incidence of nephropathy. Generally, in regards to chemical exposure one would expect that increased duration of exposure to a nephrotoxin would increase the incidence/severity of nephropathy. Furthermore, chronic progressive renal disease is a common senescent change that begins fairly early in the life of a male rat—and making an accurate judgment of how increased duration of exposure relates to increased incidence of nephropathy is difficult because of the "normal" baseline of nephropathy in male rats as they age. Nephropathy effects involving the male rat kidney is a far from optimal endpoint to use

as the basis for using an UF of 3 (rather than the typical default of 10) to account for subchronic-to-chronic duration extrapolation.

If the UF used for subchronic-to-chronic exposure duration was 10 (rather than the proposed 3) the resulting RfD would be 2×10^{-4} mg/kg/day.

A chronic RfC of 3×10^{-2} mg/m^3 has been proposed for HCE. This value is based on a 6 week subchronic inhalation study in rats (Weeks et al., 1979). Neurobehavioral effects in male and female Sprague-Dawley rats were selected as the critical effect. Based upon this study EPA considered 465 mg/m^3 the NOAEL and 2,517 mg/m^3 the LOAEL. The NOAEL of 465 mg/m^3 was selected as the POD and there was an UF of 3000.

In regards to the proposed RfC of 3×10^{-2} mg/m^3 that is being proposed : ATSDR concurs with the appropriateness of the study from which it is derived, the end point selection, the use of NOAEL/LOAEL methodology and assumptions, and the uncertainty factors applied in the derivation of this RfC.

Carcinogenicity of Hexachloroethane

In reviewing these documents, critical evaluation of the RfD and RfC values, and detailed assessment of non cancer hazard has been the primary focus of the review. However, the sections pertaining to the carcinogenicity of HCE are well written and scientifically sound.