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**Chemical Name: Tetrachloroethylene (Perchloroethylene)**

**Interim Chronic Risk Assessment Advice**

**CAS: 127-18-4**

**Synonyms: PERC; Perchloroethylene; Ethylene tetrachloride**

**Chronic Value(s): 20 ug/m<sup>3</sup> (cancer); 100 ug/m<sup>3</sup> (non-cancer)**

**Endpoints: Cancer, Nervous System**

**Source: MDH**

**Review History:**

In 2006, in response to requests from the Minnesota Pollution Control Agency (MPCA) and the Minnesota Department of Health (MDH) Site Assessment and Consultation (SAC) unit, the Health Risk Assessment (HRA) unit conducted a thorough literature review of tetrachloroethylene (perchloroethylene) and developed interim chronic Risk Assessment Advice (RAA). The MDH recommended using a value of 20  $\mu\text{g}/\text{m}^3$  for assessment of cancer risks associated with exposure to tetrachloroethylene, and a value of 100  $\mu\text{g}/\text{m}^3$  to protect against the chronic noncancer effects of tetrachloroethylene (<http://www.health.state.mn.us/divs/eh/hazardous/topics/perc.pdf>). Generally, RAA may contain greater uncertainty than Health Risk Values (HRVs) and Health-Based Values (HBVs) because the available information is more limited, and MDH determined that there was insufficient information to develop HBV values. MDH communicated this new advice to MPCA in a memo (<http://www.health.state.mn.us/divs/eh/risk/guidance/air/tfmemo.pdf>).

In June, 2009, SAC requested a review of new information on the health risks of tetrachloroethylene. In October 2010, HRA completed a review of the available information on the health risks of tetrachloroethylene and, based on this review, MDH reaffirms that RAA first developed in 2006 is protective of public health.

**Summary of the 2010 review:**

In June, 2008 the U.S. EPA released a draft *IRIS Toxicological Review of tetrachloroethylene (CAS No.127-18-4)* for external peer review (U.S. EPA, 2008). In this document the U.S. EPA proposed a reference concentration (RfC) of 0.016  $\text{mg}/\text{m}^3$  based on neurotoxicity reported in an epidemiological study of area residents living around dry cleaning establishments (Altmann et al 1995). This number is about six times lower than the chronic RAA previously developed by the MDH. The U.S. EPA classified tetrachloroethylene as likely to be carcinogenic to humans and calculated an inhalation cancer unit risk range of  $2 \times 10^{-6}$  to  $2 \times 10^{-5}$  per  $\mu\text{g}/\text{m}^3$  (0.5 – 5.0  $\mu\text{g}/\text{m}^3$  at a  $10^{-5}$  increased risk level). The range was provided to reflect the uncertainty associated with the choice of a pharmacokinetic model. This value is based on the development of mononuclear cell leukemia (MCL) in rats and provides a value 40 to 4 times lower than the MDH recommended cancer RAA.

The U.S. EPA subsequently requested that the National Research Council (NRC) of the National Academy of Sciences review the draft IRIS assessment from toxicologic, epidemiologic, and human clinical perspectives. The NRC committee was asked to evaluate the adequacy of the U.S. EPA assessment, the data and methods used for deriving cancer values for inhalation and oral exposures and the oral and inhalation cancer unit risks posed by tetrachloroethylene; to evaluate whether the key studies underlying the draft IRIS assessment are of requisite quality, reliability, and relevance to support the derivation of the reference values and cancer risks; to evaluate whether the uncertainties in the U.S. EPA's risk assessment were adequately described and, where possible, quantified; and to identify research that could reduce the uncertainty in the current understanding of human health risks associated with tetrachloroethylene exposure.

The NRC, while praising the amount of work that the U.S. EPA did in producing the draft assessment, was very critical of a number of aspects of the review (NRC, 2010).

“The committee has identified concerns about some of the approaches that EPA used to evaluate the data on tetrachloroethylene and subjects about which inadequate information or rationales are used to support its risk assessment – factors that call into question the soundness and reliability of EPA's proposed reference values and cancer risk assessments for tetrachloroethylene.”

The committee was especially concerned with the U.S. EPA's apparent lack of critical analysis of methodologic strengths and weaknesses of the data the agency used in its evaluation of the toxicity of tetrachloroethylene – particularly with epidemiologic and genotoxic data. The committee expressed concern that the draft sometimes failed to consider weaknesses in the study methods and inconsistencies in the results.

For noncancer reference values the committee agreed with the selection of neurotoxicity as the critical endpoint, but the NRC committee criticized the U.S. EPA's selection of the Altmann et al (1995) study for calculating the RfC. The committee concluded that the validity of this study was seriously compromised by methodologic deficiencies and suggested that it appeared that the study had been selected because it produced the largest estimate of risk. On the basis of study selection criteria (emphasizing validity, methodology and consistency with the literature) the committee felt that five of the studies evaluated by the U.S. EPA were stronger and would be more appropriate for use as points of departure determination for the RfC. RfCs developed from the strongest studies ranged from 40-340  $\mu\text{g}/\text{m}^3$  (mean of 190  $\mu\text{g}/\text{m}^3$ ) and bracket the RAA of 100  $\mu\text{g}/\text{m}^3$  previously developed by the MDH.

The committee agreed with the U.S. EPA's classification of tetrachloroethylene as likely to be carcinogenic in humans, but disagreed with the selection of the MCL data for the calculation of a unit risk. The committee felt that “the use of MCL data can only be justified if it is EPA's policy to choose the most conservative unit risk when considering a range of options, but that such a justification should be distinguished as a policy decision and not a scientific one.”

The committee suggested that the rodent hepatic cancer data reviewed by the U.S. EPA would have the least uncertainty associated with it followed by kidney and then by MCL.

The modeled unit risk for hepatic cancer would be eight fold less than the estimate for MCL –  $2.5 \times 10^{-7}$  to  $2.5 \times 10^{-6}$  – resulting in an increased risk of  $10^{-5}$  with exposures ranging from 4-40  $\mu\text{g}/\text{m}^3$ .

The modeled unit risk for renal cancer would be five fold less than for MCL –  $4 \times 10^{-7}$  to  $4 \times 10^{-6}$  – resulting in an increased risk of  $10^{-5}$  with exposures ranging from 2.5-25  $\mu\text{g}/\text{m}^3$ .

Each of these values brackets MDH's previously developed tetrachloroethylene cancer RAA of 20  $\mu\text{g}/\text{m}^3$ .

Because of the NRC committee's significant concerns about the U.S. EPA's assessment of the toxicity of tetrachloroethylene, and because MDH's previously developed RAA values for tetrachloroethylene are within the range of health protective values proposed by the NRC, MDH recommends the continued use of 20  $\mu\text{g}/\text{m}^3$  for cancer risk assessment and 100  $\mu\text{g}/\text{m}^3$  for assessment of the potential for noncancer effects.

Although MDH is confident that the current RAA values are protective of public health, MDH will revisit this decision when the U.S. EPA issues a formal response to the NRC review.

### **References:**

Altmann, L; et al. (1995) Neurobehavioral and neurophysiological out come of chronic low-level tetrachloroethylene exposure measured in neighborhoods of dry cleaning shops. Environ. Res.**69**:83-89.

NRC (National Research Council). (2010) Review of the Environmental Protection Agency's Draft Iris Assessment of Tetrachloroethylene. Washington D.C.; ISBN: 0-309-15095-7, 174 pg.

[http://books.nap.edu/openbook.php?record\\_id=12863&page=R1](http://books.nap.edu/openbook.php?record_id=12863&page=R1)

U.S. EPA (Environmental Protection Agency). (2008) Draft Toxicological Review of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4). Washington D.C.; EPA/635/R-08/011A.

<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=192423#Download>