MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY
WATER BUREAU

TOXICOLOGICAL ASSESSMENT FOR 1,2-*trans*-Dichloroethylene (CASRN 156-60-5) HUMAN NONCANCER VALUE

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A review of the literature indicates that the best available data for HNV derivation for *trans*-1, 2-dichloroethylene (*trans*-DCE) are subchronic in duration, as there is a lack of chronic oral studies. Two studies have evaluated the toxicity of *trans*-DCE in drinking water to CD-1 mice for 90 days. The study by Barnes et al., (1985) involves a broad toxicological evaluation, while the study by Shopp et al., (1985) evaluates primarily the effects of *trans*-DCE on immune status.

In the Barnes et al., (1985) study, *trans*-DCE was administered *ad libitum* in the drinking water to groups of male and female CD-1 mice for 90 days. Groups received 0.1, 1.0, or 2.0 milligrams per milliliter (mg/ml). The authors calculated the equivalent doses to be 17, 175, and 387 milligrams per kilogram per day (mg/kg/d) for males, and 23, 224, and 452 mg/kg/d for females. Each of these groups consisted of 140 mice, while 260 mice per sex served as controls. A decrease in female mice thymus weight occurred at 224 mg/kg/d (18 percent decrease) and at 452 mg/kg/d (33 percent decrease), and an increase in serum alkaline phosphatase in male mice occurred at 175 mg/kg/d (62 percent increase) and at 387 mg/kg/d (33 percent increase). Some other statistically significant changes appeared to be spurious and without a clear dose/response relationship, and therefore may not be attributable to *trans*-DCE exposure. Other effects are considered to be of questionable biological significance or to be effects that are not necessarily adverse. These included a 20 to 28 percent increase in serum glucose in all dose groups of both sexes, reduction of SGOT and SGPT in mid- and high-dose females, and possible effects on the functional integrity of microsomal mixed function oxidase processes. The latter effect was indicated by a 21 percent reduction in glutathione levels among the high-dose males, and a 21 to 32 percent reduction in aniline hydroxylase activity among female mice in all dose groups.

In the Shopp et al., (1985) study, groups of male or female CD-1 mice received *trans*-DCE in their drinking water for 90 days. The concentrations of 0.1, 1.0, or 2.0 mg/ml equated to doses of 17, 175, and 387 mg/kg/d for males, and 23, 224, and 452 mg/kg for females. These are the same concentrations and doses used in the Barnes et al., (1985) study because the same team of researchers conducted the study. Various assays were employed to evaluate the competency of the immune system, including humoral immune status, cellular immunity, and the functional ability of the fixed macrophages of the reticuloendothelial system. Depending on the assay, dose group, and sex, the number of animals involved in the assays ranged from 2 to 20. Effects upon the immune system that were statistically significant included many that were not dose dependent or did not coincide with other assay results measuring similar parameters. Male mice at all dose levels experienced suppression of humoral immune status, indicated by a decreased ability of spleen cells to produce IgM antibody against sheep erythrocytes. The authors considered this effect to be not severe, as assays of the functional ability of the immune system did not reveal any clear effect. The authors concluded that the immune system "does not appear to be overly sensitive to the effects of *trans*-DCE. The few effects that were seen were probably the result of general toxicity as opposed to specific target organ toxicity."

In a study by Ress (2002), F344/N rats and B6C3F1 mice (10 animals/sex/group) were fed diets containing microcapsules of *trans*-DCE. Dietary concentrations of 3,125; 6,250; 12,500; 25,000; and 50,000 parts per million (ppm) microencapsulated *trans*-DCE resulted in average daily doses of 190, 380, 770, 1,540, and 3,210 mg/kg for male rats; 190, 395, 780, 1,580, and 3,245 mg/kg for females rats; 400, 920, 1,900, 3,850, and 8,065 mg/kg for male mice; and 450, 915, 1,830, 3760, and 7,925 mg/kg for female mice. Mean body weights of male rats and male mice in the 50,000 ppm groups were significantly less than controls. The mean body weight gains of female mice in the 12,500 and 25,000 ppm groups were also significantly decreased. At the end of the study, mild decreases in hematocrit values, hemoglobin concentrations, and erythrocyte counts occurred in groups of male and female rats in the 25,000 and 50,000 ppm groups. These effects also occurred in male rats exposed to 6,250 ppm or greater. The liver weights in female rats exposed to 6,250 ppm or more were significantly greater than the controls. The absolute kidney weights of male rats exposed to 25,000 or 50,000 ppm were significantly decreased. No alterations occurred in clinical chemistry parameters in rats or mice and no gross or microscopic lesions were observed in rats or mice that could be attributed to *trans*-DCE exposure. The no-observed-adverse-effect levels (NOAELS) for this study are 380, 395, 915, and 3,850 mg/kg/d for male rats, female rats, female mice, and male mice, respectively.

The NOAELs found in the Ress (2002) and Barnes et al., (1985) studies differed substantially. The most important difference in the design of the two studies was that the Ress (2002) study exposed the animals to a microencapsulated form of *trans*-DCE, whereas, the study by Barnes et al., (1985) exposed the animals to the compound via their drinking water. The results of the Barnes et al., (2002) study will be used for criteria development since it used an exposure pathway that is more appropriate for the development of surface water criteria. The NOAEL of 17 mg/kg/d found in the Barnes study with an uncertainty factor of 10 times for each intraspecies approach is consistent with the approach used by the United States Environmental Protection Agency (USEPA) to derive a reference dose in the Integrated Risk Information System (IRIS) database.

References:

Barnes, D., et al., 1985. Toxicology of *trans*-DCE in the mouse. Drug Chem. Toxicol. 8(5): 373-392.

Ress, N.B. 2002. NTP Technical Report on the Toxicity Studies of *trans*-DCE (CAS #156-60-5) Administered in Microcapsules in Feed to F344/N Rats and B6C3F1 Mice. NIH Publication No. 02-4410.

Shopp, G., et al., 1985. Humoral and cell-mediated immune status of mice exposed to *trans*-DCE. Drug Chem. Toxicol. 8(5): 393-407.

USEPA. 2008. IRIS Database. Chemical File for *trans*-DCE (CAS #156-60-5). Verification Date April 20, 1988. Last revised January 1, 1989.

HUMAN NONCANCER VALUE WORKSHEET

Chemical Name: 1,2-*trans*-dichloroethylene CAS No. 156-60-5
Developed By: S. Briggs
Reviewed By: D. Bush Verification Date: 10/2/08

Key Study: Barnes et al. (1985) exposed male and female CD-1 mice to 1,2-*trans*-dichloroethylene in drinking water for 90 days. The HNV is based on the male mouse NOAEL of 17 mg/kg/d.

ADE = 0.017 mg/kg/d

$$ADE = \frac{(17\ mg/kg/d)}{1000}$$

UF = 10x for each interspecies, intraspecies and subchronic-to-chronic extrapolation.

drinking water

$$HNV = \frac{(0.017\ mg/kg/d)\quad (70\ kg)\quad (0.8)}{(2\ L/d) + (0.0036\ kg/d * 2.1\ L/kg) + (0.0114\ kg/d * 2.8\ L/kg)} = 0.47\ mg/L$$

Human Noncancer Value for drinking water = 470 ug/L

non-drinking water

$$HNV = \frac{(0.017\ mg/kg/d)\quad (70\ kg)\quad (0.8)}{(0.01\ L/d) + (0.0036\ kg/d * 2.1\ L/kg) + (0.0114\ kg/d * 2.8\ L/kg)} = 19\ mg/L$$

Human Noncancer Value for non-drinking water = 19,000 ug/L