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SNARL For Trichloroethylene

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In the absence of a formal drinking water standard for trichloroethylene, the Office of Drinking Water has estimated a suggested no adverse response level (SNARL) following the state-of-the-art concepts in toxicology for non-carcinogenic risk for short and long term exposures. For carcinogenic risk a range of risk estimates are provided for life-time exposures using a model and computations from the National Academy of Sciences Report: Drinking Water and Health (1977). However, SNARLS are given on a case-by-case basis in emergency situations such as spills and accidents. The SNARL calculations for short-term and chronic exposures ignore the possible carcinogenic risk that may result from those exposures. In addition SNARLS usually do not consider the health risk resulting from possible synergistic effect of other chemicals in drinking water, food and air.

I. General information and health effects

Trichloroethylene is used primarily as a metal degreasing agent. It is also used, however, in dry-cleaning as a solvent, and in refrigerants and fumigants. Trichloroethylene is slightly soluble in water.

Trichloroethylene, like other halogenated hydrocarbons at high dose levels, has been reported to produce liver and kidney damage and central nervous system disturbances in ... mammals, including humans. These effects have been observed as a result of short-term exposures and the intensity of the response was dependent upon the dosage levels. Salvini et al. (Brit. J. Med. 1971. 28:293) observed psychophysiological changes in human volunteers in a controlled inhalation study using trichloroethylene at as low a level as 110 ppm for two four-hour periods.

Long-term exposures of mice to trichloroethylene produced carcinogenic effects in both male and female animals (National Cancer Institute, 1976). In addition to the carcinogenic effect, trichloroethylene has been reported to be mutagenic in microorganisms, transforms cultured mammalian cells to carcinogenic cells, and binds with tissue macromolecules, thus supporting the carcinogenic potential of trichloroethylene.

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There has been some controversy over the current evidence linking trichloroethylene and carcinogenicity in animal studies. Although the NCI bioassay was positive, others have argued that the effects may have been due to contaminants (epichlorohydrin and epoxybutane) in the tested trichloroethylene. NCI has agreed to retest. The NAS in its 1979 report, however, recognizing the issue, accepted the NCI result and computed a risk value based upon carcinogenic potential.

Recent studies on the metabolism and elimination of trichloroethylene in rats and human volunteers reveal that the metabolites of trichloroethylene, namely trichloroethanol and trichloroacetic acid, are not immediately eliminated from the body. Trichloroethanol was found to have a half-life of 12 hours in human volunteers. This would mean that repeated daily exposure to trichloroethylene via drinking water would result in some accumulation of trichloroethanol in the body. Moreover, the metabolite trichloroacetic acid has been reported to bind to plasma proteins. This property of trichloroacetic acid may result in interaction with drugs and chemicals having similar properties, thereby resulting in toxic effects. (Ertle et al. Arch. Toxicol. 29, 171-188, 1972.)

II. SNARL Development

Trichloroethylene is a carcinogen in mice, and also causes non-carcinogenic bioeffects. One-day, 10-day and chronic SNARL values based on non-carcinogenic bioeffects are computed incorporating appropriate factors of safety. Estimates of concentrations projected to increase the lifetime cancer risk by one in 100,000 and one in a 1,000,000 are also provided using the NAS model. The non-carcinogenic SNARL recommendations are made considering the child and other possibly sensitive members of the population.

Using a study where human volunteers were exposed via inhalation to 110 ppm (590 mg/m^3) of trichloroethylene for an 8-hour period where psychophysiological symptoms were observed, a one-day SNARL value of 2 mg/l could be calculated for the child.

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$$\frac{(590\ mg/m^3)(3\ m^3/day)(0.30)}{(1\ l/day)(100\ \text{uncertainty factor})} \times \frac{1}{7} = 2.02\ mg/l$$

where: 1/7 = child/adult body weight ratio
0.30 = absorption factor
1 l/day = child daily water consumption
100 = uncertainty factor via 10 factor because a human experiment was used and 10 factor because data did not specify the no observed adverse effect level

To calculate a SNARL for 10 days metabolic and pharmacokinetics data are required. Since that data is not available a conservative method would be to divide the one-day SNARL of 2 mg/l by 10 whereby the 10-day SNARL value would become approximatley 200 ug/l.

Since the one-day and 10-day SNARL values are determined for emergencies and spills for a short period of time, it should be assumed that drinking water would be the primary or sole source of human intake of trichloroethylene. This is in opposition to that for a chronic SNARL where a lesser contribution from drinking water may be appropriate. Therefore, a relative source contribution factor has not been incorporated into the suggested one-day and 10-day SNARL values of 2 mg/l and 0.2 mg/l, respectively.

The NAS (1979) has computed a one-day SNARL of 105 mg/l and 15 mg/l for the seven-day SNARL. Their calculations were based upon the observation of intoxication of adults and the application of uncertainty factors. Our calculations, however, were based upon psychophysiological parameters and extrapolated to the child with the appropriate uncertainty factors.

The NAS chose to work with uncontrolled case histories where trichloroethylene was accidentally ingested. The study which the Office of Drinking Water chose to evaluate and extrapolate, while being an inhalation study, was conducted under controlled conditions.

A longer exposure SNARL for trichloroethylene, can be calculated using a study by Kimmerle and Eben entitled "Metabolism, Excretion and Toxicology of Trichloroethylene after Inhalation." This study evaluated the subacute exposure to trichloroethylene via inhalation in adult rats for so

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14 weeks following exposure to 55 ppm (300 mg/m^3), five days a week. Indicies of toxicity include hematological investigation, liver and renal function tests, blood glucose and organ/body weight ratios. Liver weights were shown to be elevated while the other test values were not different from controls. The elevated liver weights could be interpreted to be the result of hydropic changes or fatty accumulation. The no-observed-effect level was not identified.

Using the method of Olsen and Gehring (1976) whereby the lung-whole body ratios for humans (adults) and rats (adults) are assumed to be roughly equivalent, the total dose of trichloroethylene to the child can be determined and a longer term SNARL can be calculated to be approximately 75 ug/l when the principal source of trichloroethylene is assumed to be from drinking water.

$$\frac{(300\ mg/m^3)\quad 8\ m^3/day\ (5)(1)(0.30)}{(1\ l/day)\qquad\qquad (7)(7)\ (1000)} = 73.5\ ug/l$$

Where:

55 ppm (5.46) = 300 mg/m^3 minimum effect level
8 m^3 = according to Olsen/Gehring
5/7 = fraction converting from 5 to 7-day exposure
1/7 = child/adult body weight ratio
0.30 = absorption rate
1 l/day = child consumption per day
1000 = uncertainty factor due to animal study where minimal effect was reported

In cases where other sources of exposure are prevalent and, for example, drinking water is assumed to account for a portion of the total exposure, say 20%, of the trichloroethylene intake, then the SNARL value would become 15 ug/l. By-and-large, however, the 75 ug/l SNARL would be assumed to be appropriate under normal circumstances in the absence of other major sources of TCE.

A chronic SNARL approximately equivalent to the SNARL of 75 ug/l can be justified on the basis that (1) long-term exposure to low doses of trichloroethylene probably does not

bioaccumulate much more over a lifetime than in 3-6 months, and (2) the SNARL was calculated for the child and not the adult thus providing a somewhat larger safety margin.

Since trichloroethylene is considered a carcinogen, at least for mice, and using the risk estimates generated by the National Academy of Sciences (NAS), it is possible to identify that range of trichloroethylene concentrations that would increase the risk of one excess cancer per 10^6 or 10^5 people exposed over a lifetime. From the NAS model it is estimated that consuming 2 l/day over a lifetime having a trichloroethylene concentration of 4.5 ug/l or 45 ug/l would increase the risk by one excess cancer/million exposed or one excess cancer/100,000 exposed, respectively. This is the range of risks where many EPA regulatory values for other carcinogens have been.

These risk extrapolations were based on an assumption that there is no threshold level for carcinogens. The state-of-the-art at the present time is such that no experimental tools can accurately define the absolute numbers of excess cancer deaths attributable to trichloroethylene in drinking water. Due to the biological variability and a number of assumptions required, each of the risk estimating procedures lead to a different value. There is wide variation among these estimates and also in their interpretation. For this reason we report the results of the NAS risk computations, which is a conservative approach, as a range of values in the one in one hundred thousand to one in one million incremental risk (risk above background) for a carcinogen. The NAS risk estimates are based on the multistage model concept. "At low dose the multistage model is often mathematically equivalent to the linear or single hit model. Therefore, its use for extrapolation is consistent with the conservative linear risk estimation. If the precise mechanism of carcinogenesis is represented by a threshold or log-normal dose response relationship, the multistage model may considerably over estimate the risk at low dose levels. However, this possibility cannot be reasonably quantified." (NAS-1979)