Advisory Opinion for Dichloromethane (Methylene Chloride)
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, D.C. 20460
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AN OFFICE OF DRINKING WATER HEALTH EFFECTS ADVISORY

The Office of Drinking Water provides advice on health effects upon request, concerning unregulated contaminants found in drinking water supplies. This information suggests the level of a contaminant in drinking water at which adverse health effects would not be anticipated. A margin of safety is factored in so as to protect the most sensitive members of the general population. The advisories are called Suggested No Adverse Response Levels (SNARLs). SNARLs have been calculated by EPA and by the National Academy of Sciences (NAS) for selected contaminants in drinking water. An EPA-SNARL and a NAS-SNARL may well differ due to the possible selection of different experimental studies for use as the basis for the calculations. Furthermore, NAS-SNARLs are calculated for adults while the EPA-SNARLs are established for a 10 kg body weight child. Normally EPA-SNARLs are provided for one-day, ten-day and longer-term exposure periods where available data exist. A SNARL does not condone the presence of a contaminant in drinking water, but rather provides useful information to assist in the setting of control priorities in cases where contamination occurs. EPA-SNARLs are provided on a case-by-case basis in emergency situations such as spills and accidents.

In the absence of a formal drinking water standard for an identified drinking water contaminant, the Office of Drinking Water develops EPA-SNARLs following the state-of-the-art concepts in toxicology for non-carcinogenic risk for short and longer term exposures. In cases where a substance has been identified as having carcinogenic potential, a range of estimates for carcinogenic risk based upon lifetime exposure as developed by the NAS (1977 or 1980) and/or EPA's Carcinogen Assessment Group (EPA, 1980a) is presented. However, the EPA-SNARL calculations for all exposures ignore the possible carcinogenic risk that may result from these exposures. In addition, EPA-SNARLs usually do not consider the health risk resulting from possible synergistic effects of other chemicals in drinking water, food and air.

EPA-SNARLs are not legally enforceable standards; they are not issued as an official regulation, and they may or may not lead ultimately to the issuance of national standards or Maximum Contaminant Levels (MCLs). The latter must take into account occurrence, relative source contribution factors, treatment technology, monitoring capability, and costs, in addition to health effects. It is quite conceivable that the concentration

set for EPA-SNARLs may also change as additional information becomes available. In short, EPA-SNARLs are offered as advice to assist those such as Regional and State environmental and health officials, local public officials, and water treatment facility personnel who are responsible for the protection of public health when dealing with specific contamination situations.

General Information

Dichloromethane, commonly known as methylene chloride (CH_2Cl_2) is a colorless, non-flammable solvent, soluble in water (2 gm in 100 ml), with a boiling point of 40.1˘ C and specific gravity of 1.325. One part per million in air is equivalent to 3.5 mg/m^3.

Inhalation exposure level recommendations for dichloromethane are: OSHA - 500 ppm, ACGIE - 200 ppm, NIOSH - 75 ppm (to be lowered in the presence of carbon monoxide). Dichloromethane at concentrations of 7.5 mg/l in drinking water can be detected by taste and odor (Tugarinova et al. 1965). Dichloromethane has miscellaneous uses as a solvent in certain pharmaceutical applications, for degreasing engine parts in the motor transportation, railway and aircraft industries, in the extraction of natural products, such as edible fats, cocoa butter, decaffeinated coffee and the beer flavoring in hops.

Sources of Exposure:

Humans are exposed to methylene chloride from air, food and water. Urban air in Japan has been reported to contain 0.035 - 32.9 ug/m^3 methylene chloride (Okuno et al. 1974). Concentrations as high as 1.6 ug/l have been detected in U.S. drinking water (U.S. EPA, 1975). Higher levels might be encountered in drinking water as a result of spills or seepage from land fills. Since methylene chloride is being used for extraction of some food material, it has been detected in the oleoresins of several spices: the highest concentrations of 83 mg/kg was detected in Cassia, followed by all-spice, nutmeg and others (Page and Kennedy, 1975). Dichloromethane was detected in the expired air of human subjects at levels of 0.12 - 340 ug/hr (Conkle et al. 1975).

Metabolism:

There is a paucity of data concerning the absorption of ingested dichloromethane, however it is expected to be absorbed

completely considering the physico-chemical properties of this compound. Absorbed dichloromethane vapor is biotransformed to carbon monoxide resulting in the formation of carboxyhemoglobin in human as well as experimental animals (Kubic et al. 1974, Stewart et al. 1972). Dichloromethane and related dihalomethanes are also metabolized to formaldehyde and halide ions in *in vitro* experiments (Ahmed and Anders, 1976; Kubic and Anders, 1975).

Health Effects:

Experiments in animals, as well as in humans, suggest that exposure to dichloromethane at high dose levels results in central nervous system depression; it also affects the liver and the blood. Carboxyhemoglobin formed as a result of dichloromethane exposure interferes with work performance capability and adversely affects patients with ischemic heart disease.

Acute Exposure:

On ingestion, the lowest recorded lethal dose for humans is 500 mg/kg (NIOSH, 1978). Tugarinova et al. (1965) compared acute toxicity of dichloromethane in mice, rats and guinea pigs. They administered single doses of dichloromethane in oil to the animals and established that guinea pigs were not as sensitive as mice and rats. Toxic symptoms included central nervous system effects characterized by initial excitation leading to convulsions and respiratory disorders and death. Histopathological examination revealed no overt changes in the internal organs with the exception of cerebral hyperemia. The animals that died in the later periods showed signs of liver toxicity. A daily dose of 750 mg/kg for 10 days given to mice resulted in no deaths. At the end of the experiment, the autopsied animals revealed signs and symptoms of liver toxicity.

In another study, Kimura et al. (1971) suggested a maximum permissible single oral dose 0.001 ml/kg, based on their experiments with rats, utilizing a single oral dose of one ml/kg dichloromethane. They observed gross signs of toxicity. Signs and symptoms of toxicity were not described.

Chronic Exposure Including Reproductive Effects:

Information on the long-term exposure of humans to dichloromethane is not available. For a longer-term experiment, the rats and guinea pigs were given dosages of 0.4 and 377 mg/kg 6 days a week for 5-6 months (Tugarinova et al. 1965). Six

animals were used for each dose level. No treatment related toxic symptoms were observed at the low dose level; however, at the high dose level, the ascorbic acid content of the adrenals decreased. The significnace of this effect is not clear.

In another longer-term study, dichloromethane was administered to rats in drinking water at a concentration of 0.125 g/l (15 mg/kg/ day) for 3 months. The animals were examined for changes in behavior, weight, blood and urin chemistries, reproductive function, organ weight/body weight ratio and histology. No significant treatment related effects were observed; however, the urine-albumin test was frequently positive. The authors did not attach any biological significance to this finding (Bornmann and Loeser, 1967).

Mutagenicity and Carcinogenicity:

Dichloromethane was mutagenic in Salmonella typhimurium TA 100 and TA 98 both in the presence and absence of a liver microsomal activation system (Jongen et al. 1978). The carcinogenic potential of dichloromethane was studied by Theiss et al. 1977. Six to eight week old Strain A/St male mice were injected intraperitoneally three times a week (total of 24 injections) at dose levels of 160, 400 and 800 mg/kg body weight. Twenty-four weeks after the first injection the animals were sacrificed and examined for lung adenomas. The observed adenomas in the treated animals were not statistically significant from those of the control.

Other Observations:

Since dichloromethane is metabolized to carbon monoxide in experimental animals as well as in humans, it is appropriate to consider the toxic effects of carbon monoxide. Astrup et al. 1972 studied the effect of carbon monoxide on fetal development in rabbits. Exposure to 180 ppm CO for 30 days (resulting in 16-18 percent carboxyhemoglobin) during pregnancy resulted in a 20 percent decrease of birth weight and a neonatal mortality of 35 percent as against 1 percent in the control group. Exposure to 90 ppm carbon monoxide (8-9 percent carboxyhemoglobin) had a less pronounced effect.

Several reports indicate the adverse health impact of carboxyhemoglobin on the heart, work performance capability and fetal development. In a well conducted study, Anderson and co-workers (1973) exposed human subjects with ischemic heart disease to 50 and 100 ppm carbon monoxide for four hours on five successive days. After each exposure subjects were asked to go through

standard treadmill exercises ECG test. Blood carboxyhemoglobin levels were determined before and after the exposure and the time of onset and duration of angina pain were recorded. The mean duration of exercise before onset of pain was significantly shortened after 50 and 100 ppm CO exposure. Exposure to CO at 50 and 100 ppm for four hours resulted in mean carboxyhemoglobin concentrations of 2.9 and 4.5 percent, respectively. In another study, Putz et al. 1978 studied the effects of carbon monoxide and methylene chloride on human task performance. The effects were assessed by the performance of human subjects on a visual-manual, dual task and an auditory vigilance task. The experimental procedure involved exposing the subjects to about 200 ppm dichloromethane for 4 hours and to 70 ppm CO to achieve desired carboxyhemoglobin concentrations of 5 percent. The authors suggest that 5 percent carboxyhemoglobin significantly impaired human performance under difficult or demanding task conditions.

EPA-SNARL Development:

Dichloromethane at higher dose levels produces central nervous system and liver effects. It is mutagenic in bacterial test systems and evidence of its carcinogenic potential is inconclusive. The available data suggest that the dichloromethane EPA-SNARL should be developed based on its potential to produce carboxyhemoglobin in humans.

Dichloromethane is metabolized to carbon monoxide as indicated by the formation of carboxyhemoglobin. At 5 percent carboxyhemoglobin level in humans, it is reported to interfere with the work performance as well as adversely affect the subjects with ischemic heart disease (Anderson et al. 1973). At slightly higher carboxyhemoglobin concentrations, it lowers the birth weight of the newborn rabbits, if their mothers are exposed during gestation. Therefore, the dichloromethane EPA-SNARL should be set below the dichloromethane concentration in drinking water that would not maintain 5 percent carboxyhemoglobin for an extended period of time. In fact, it should be at much lower concentrations in order to accommodate exposure to carbon monoxide from other sources.

An experiment to delineate the carcinogenic potential of dichloromethane is in progress at the National Cancer Institute. The results from this experiment or any other would be assessed to update the EPA-SNARL, if necessary.

One-Day EPA-SNARL:

The lowest lethal oral dose of 500 mg/kg (0.38 ml/kg) for

humans has been recorded. This dose cannot be used for the calculation of an EPA-SNARL, since this might have been an isolated incidence and certainly was not a well-controlled study. In addition, the cause of death and other adverse health effects need to be recognized before any degree of confidence is placed on this value. Using the same data base as chosen by the National Academy of Sciences, a one-day EPA-SNARL has been determined. This involves a study by Kimura et al. (1971) where the minimal effective dose of 1 ml/kg (1.3 g/kg) was established. Using a safety factor of 1,000, calculations of an EPA-SNARL for a 10 kg child, consuming one liter of water, are given below:

Calculations

$$\frac{1.3 \text{ g/kg} \times 10}{1000 \times 1 \text{ liter}} = 0.013 \text{ g/liter}$$

where: 10 = 10 kg body weight of a child
1 liter = assumed consumption of drinking water by 10 kg body weight child
1000 = safety factor

Ten-Day EPA-SNARL:

A study by Bornmann and Loeser (1967) appears to be most appropriate to use to determine the 10-day EPA-SNARL. In this study, adult rats were fed dichloromethane (15 mg/kg/day) for three months whereby no observed adverse health effects were identified. Applying a safety factor of 100 instead of 1000 used for longer-term SNARL calculations, to a no observed effect level of 15 mg/kg/day, the ten-day EPA-SNARL is calculated as 1.5 mg/l. This assumes 10 kg body weight of a child consuming one liter of water a day. Another method of calculating the ten-day EPA-SNARL would have been to merely divide the one-day EPA-SNARL by ten indicating a value of 1.3 mg/l.

It is expected that consumption of 13 mg/l and 1.5 mg/l dichloromethane for one and ten days, respectively, would not increase carboxyhemoglobin levels significantly.

The National Academy of Sciences (1980) calculated a one-day and a seven-day NAS-SNARL for dichloromethane in drinking water. They used the study by Kimura et al. (1971) where the minimal effective dose of 1 ml/kg (1.3 g/kg) was established. Using a safety factor of 1000 and a consumption volume of 2 liters of water by an adult the one-day adult NAS-SNARL should be 45 mg/l and consequently a seven day adult NAS-SNARL of 6.4 mg/l. However, the Academy values are 35 mg/l and 5 mg/l for

one-day and seven-day, respectively. There appears to have been a typographical error which was perpetuated in the seven-day NAS-SNARL.

Longer-term EPA-SNARL:

A longer-term EPA-SNARL cannot be estimated with confidence with the present available data; however, in case drinking water containing dichloromethane has to be consumed during an interim period before treatment, a study by Bornmann and Loeser (1967) could be used for determining longer-term dichloromethane EPA-SNARL. In this study, dichloromethane was administered to rats in drinking water at concentrations of 0.125 g/l (15 mg/kg/day) for three months. The animals were examined for changes in behavior, weight gain, blood and urine chemistry, reproductive functions, organ weight/body weight ratio and histology. No significant treatment related effects were observed. Another study by Tugarinova et al. (1965) where dosages of 0.4 and 377 mg/kg six days a week for 5-6 months were used, was not acceptable for these calculations because of inherent problems of statistical significance of the results.

Using a no-observed-effect dose level of 15 mg/kg/day for three months, the following calculations for determining a longer-term EPA-SNARL are made:

Calculations:

$$\frac{15\text{ mg} \times 10}{1\text{ l} \times 1000} = 0.150\text{ mg/l}$$

where: 15 mg = no observed effect dose level
10 = assumed average body weight of a child
1 l = assumed consumption of drinking water by 10 kg body weight child
1000 = a safety factor for a three month study

Note: This may be an overly conservative estimate, but this is based on the data available at the present time. Ideally, the study should have three to four dose levels to establish a no adverse effect dose level.

The U.S. EPA's Ambient Water Quality Criteria for Halomethanes (1980) recommended a criterion of 12.4 mg/l dichloromethane. It was calculated from American Conference of Govermental Industrial Hygienists recommended threshold limit value of 200 ppm (694 mg/m^3) for occupational exposure. This criterion applies to ambient water, not drinking water. It is noteworthy that NIOSH recommended a level of 75 ppm dichloromethane

for work-room exposure and suggested that the exposure to dichloromethane should be lowered further if the workers are exposed to carbon monoxide.

Analysis

Dichloromethane can be analyzed by the purge and trap method used for the halogenated hydrocarbons - chloromethanes, chloroethanes, chloroethylenes. The method involves trapping the purgeable halogenated solvents onto a suitable sorbant. The trapped compounds are thermally desorbed from the trap, passed through a programmed gas chromatograph for analysis. Detection is by the use of a microcoulometric or an electrolytic conductivity detector. By using this method, dichloromethane can be detected at 1 ug/l (Bellar & Lichtenberg, 1974, AWWA 66:739).

Treatment

Limited information is available concerning the removal of methylene chloride from drinking water. Studies were conducted to evaluate the capability of granular activated carbon to remove actual mixtures of contaminants, including methylene chloride in drinking water. In one of the studies, an untreated ground water containing low levels of halogenated hydrocarbons (methylene chloride concentration 0.08 ug/l) was passed through granular activated column (1 inch diameter and 30 inches of activated carbon). Empty bed contact time was 6.2 minutes. The water source had a color of approximately 50 color units, a TOC concentration of about 10 mg/l and pH of about 7.1. Methylene chloride was not detected in the effluent (EPA, 1978).

Conclusions and Recommendations

Based on the available data and the state-of-the-art concept in toxicology, the EPA-SNARL for one day is 13 mg/l, for ten-days 1.3 mg/l and the longer-term EPA-SNARL of 0.15 mg/l has been determined. These EPA-SNARLs are based on the acute and sub-acute toxicity data. Furthermore, these EPA-SNARLs would result in a carboxyhemoglobin level much below 5 percent at which level adverse health effects have been observed.

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