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SNARL for 1,1,1-Trichloroethane

Office of Drinking Water
U.S. Environmental Protection Agency
Washington, D.C. 20460

THE OFFICE OF DRINKING WATER "SNARLS" PROGRAM

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 with a margin of safety; it is called a SNARL (suggested no adverse response level). Normally values are provided for one-day, 10-day and longer-term exposure periods where available data exists. 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 when they have been found.

In the absence of a formal drinking water standard for 1,1,1-trichloroethane 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 is provided for life-time exposures using a model and computations from the NAS Report (1979) entitled "Toxicity of selected drinking water contaminants." 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.

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 a national standard or Maximum Contamination Level (MCL). 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 SNARL purposes might differ from an eventual MCL. The SNARLs may also change as additional information becomes available. In short SNARLs are offered as advice to assist those that are dealing with specific contamination situations to protect public health.

General Information and Health Effects

The organic chemical 1,1,1-trichloroethane (methyl chloroform) is used as a cleaner and degreaser of metals and is considered a solvent of lipophilic substances. This substance is found in drinking water supplies in the United States of America.

According to the National Academy of Sciences, 1,1,1-trichloroethane is probably readily absorbed from the gastrointestinal tract, however, there is insufficient data on the uptake, distribution, metabolic and excretion patterns of this compound or its metabolites. Fortunately, some toxicological data does exist following ingestion and/or inhalation of animals and/or man. Compared to other alkyl halocarbons, 1,1,1-trichloroethane is considered less toxic perhaps due to its relative metabolism and excretion.

The health effects from 1,1,1-trichloroethane exposure at high doses include:

1. depression of the central nervous system and psychophysiological changes as demonstrated by the loss of manual dexterity, coordination and perception;
2. some fatty vacuolation and weight gain of the liver;
3. transient eye irritation and dizziness especially following an inhalation exposure;
4. some cardiovascular changes including diminished systolic pressure and premature ventricular contractions; and
5. weakly mutagenic activity.

1,1,1-Trichloroethane SNARL

Since 1,1,1-trichloroethane is not considered to be a carcinogen, is relatively low in toxicity compared to some of the other alkyl halocarbons and has a taste and odor threshold range of 300-500 ug/l, it would appear reasonable to establish a chronic SNARL.

In the absence of definitive information on the chronic toxicity of ingested 1,1,1-trichloroethane, the NAS chose to identify a dose of 750 mg/kg given to mice and rats in a NCI study as the observed adverse effect level. At this dose a depression in body weight gain was observed in males while diminished survival times were noted for both male and female rats. Consequently, the NAS calculated the chronic SNARL value to be 3.8 mg/l as follows:

$$\frac{(750\ \text{mg/kg})(5\ \text{days})(20\%\ \text{D.W.})(70\ \text{kg man})}{(7\ \text{days})(2\ \text{l/day})(1{,}000)} = 3.8\ \text{mg/l}$$

where:
- 750 mg/kg = observed adverse effect dose
- 5/7 = fraction converting from 5 to 7-day exposure
- 20% D.W. = relative source contribution from drinking water
- 70 kg = average weight of an adult
- 1000 = uncertainty factor via 100 factor for an animal study and 10 factor because data did not specify the no observed adverse effect level
- 2 l/day = adult consumption per day

Extrapolation of an inhalation threshold limit value (TLV) of the National Institute of Occupational Safety and Health to an equivalent chronic ingestion limit for drinking water for the general population could be made which supports the NAS lifetime SNARL for the adult. This can be obtained by assuming a TLV of 200 ppm or 1092 mg/m^3 where 10 m^3 are inhaled/day, a 30% absorption factor and 20% contribution from drinking water, 2 l/day consumption by adults, and a 100 safety factor for extrapolating an adult occupational exposure to the general population. Numerically a supporting lifetime SNARL for the adult could be determined to be 3.3 mg/l:

$$\frac{(1092\ \text{mg/m}^3)(10\ \text{m}^3\text{/day})(0.30)(0.20)}{(2\ \text{l/day})(100\ \text{safety factor})} = 3.27\ \text{mg/l}$$

In order to protect the child and most sensitive members of the population, the Health Effects Branch feels that the 10 kg child should be considered with the assumption that a child drinks water 1 liter/day. Applying this concept to the NAS data, the chronic SNARL value becomes approximately 1 mg/l. This value is obtained as follows:

$$\frac{(750\ \text{mg/kg})\ (5)(.20)(10\ \text{kg})}{(7)(1\ \text{l/day})(1000)} = 1.07\ \text{mg/l}$$

where:
- 750 mg/kg = observed adverse effect dose
- 5/7 = fraction converting from 5 to 7-day exposure
- .20 = relative source contribution (20%) via drinking water
- 10 kg = average weight of a child
- 1000 = uncertainity factor via 100 factor for an animal study and 10 factor because data did not specify the no observed adverse effect level
- 1 l/day = child consumption of drinking water each day

It should be concluded that based on health a 1 mg/l chronic SNARL should protect the public especially since 1,1,1-trichloroethane was negative in the NCI cancer bioassay. It should also be remembered that the taste and odor concentration for 1,1,1-trichloroethane ranges from 300-500 ug/l. Consequently, the limiting concentration to protect the aesthetic value of drinking water should also protect public health.

1,1,1-TRICHLOROETHANE

1,1,1-Trichloroethane (TCE), or methyl chloroform, is used widely as an industrial chemical for such purposes as a cleaner and degreaser of metals, a spot remover, and a solvent of lipophilic substances. It is a clear, colorless liquid at room temperature; its solubility in water is 4,400 mg/l at 20°C (Verschuerer, 1977); its boiling point is 74°C; and its vapor is heavier than air and nonflammable. Dioxane is commonly added to promote its stability. TCE has been identified in drinking water supplies in the United States (USEPA, 1978).

METABOLISM

There have been extensive studies on the uptake and distribution of TCE in humans and laboratory animals that have been exposed to the chemical by inhalation. Unfortunately, there is little information on the pharmacokinetics of ingested TCE. One would expect that this compound would be readily absorbed from the gastrointestinal tract in light of the report by Stewart and

Dodd (1964) who found that it penetrated intact human skin. Astrand et al. (1973) reported rapid absorption of inhaled TCE and measurable levels of the chemical in the arterial blood of human subjects after inhaling 250 ppm TCE for 10 seconds. The arterial blood contained substantially higher TCE levels than the venous blood throughout a 2-hour exposure, indicating ready uptake of the compound from blood into tissues. Blood concentrations of 3-5 ppm have been measured in humans breathing 350 ppm TCE (Astrand et al., 1973; Gamberale and Hultengren, 1973; Stewart et al., 1961), the current threshold limit value for occupational exposure in the United States. Apparently, there are no data on blood levels of the compound following oral exposures.

The majority of systemically absorbed TCE is eliminated via the lungs. Hake et al. (1960) reported that about 98.7% of a 700 mg/kg dose of radio-labeled TCE, which was injected intraperitoneally into rats, was exhaled unchanged within 25 hours. They also observed small amounts of radio-labeled carbon dioxide in expired air and of the glucuronide conjugate of 2,2,2-trichloroethanol in urine. Later studies revealed trichloroacetic acid to be a second metabolite, although the amounts that were formed in the urine of both rats (Eben and Kimmerle, 1974; Ikeda and Ohtsuji, 1972) and humans (Stewart et al., 1969) were substantially less than those for trichloroethanol. No chloral hydrate was detected in the blood or tissues of the rat by Eben and Kimmerle

(1974). In studies by Van Dyke and Wineman (1971) and Ikeda and Ohtsuji (1972) on the metabolism of a series of alkyl halocarbons, TCE was one of the least extensively metabolized compounds. Nevertheless, it is known to exhibit Type I binding characteristics with cytochrome P-450 (Pelkonen and Vainio, 1975) and to be capable of inducing microsomal enzyme and P-450 activity (Fuller et al., 1970). A progressive increase in urinary output of trichloroethanol was observed in humans that had been subjected to five daily inhalation exposures to TCE. This indicates that TCE induces its own metabolism (Stewart et al., 1969).

Upon termination of TCE exposure, the chemical is rather quickly eliminated in exhaled air. Levels in the blood and alveolar air decrease exponentially, showing an initial rapid fall, followed after several hours by a somewhat slower decline (Astrand et al., 1973; Stewart et al., 1969). This latter stage probably reflects slow mobilization of the agent from lipoidal tissues. Stewart et al. (1969) reported that a slight amount accumulated in humans who inhaled TCE at 500 ppm, 6.5-7 hours/day, for 5 days, despite the relatively rapid loss of TCE from the body. These investigators also found TCE in breath samples from one subject 1 month after exposure. Thus, it appears that TCE can accumulate in the body if intake is frequent enough and/or of sufficient magnitude.

TCE's relative lack of toxicity, in comparison to certain other alkyl halocarbons, can be attributed to TCE's relatively rapid elimination and stability. This compound is much more volatile (Ikeda and Ohtsuji, 1972) and, therefore, more readily excreted via the lungs (Morgan et al., 1970) than the more toxic congener 1,1,2-trichlorethane. Although neither halocarbon is metabolized to a significant degree, Carlson (1973) observed that microsomal enzyme induction with phenobarbital potentiates hepatotoxicity of both TCE and 1,1,2-trichloroethane. Thus, it appears that metabolite(s) of each compound are responsible for cytotoxicity, although the identity and mechanism of the actual toxicant(s) remain unknown.

HEALTH ASPECTS

Observations in Humans

The primary toxic effects in humans that have been subjected to short-term, high-level exposure to TCE are manifestations of depression of the central nervous system. In the majority of reports of human fatalities resulting from TCE inhalation, death is attributed to a functional depression of the central nervous system. Levels of TCE in the victim's blood vary considerably, generally ranging from 60 (Hatfield and Maykoski, 1970; Stahl et al., 1969) to 720

ppm (Hall and Hine, 1966). As might be predicted, the highest concentrations of TCE are found in the brains of victims (Caplan et al., 1976; Stahl et al., 1969). Due to problems that are inherent in analyses of volatile toxicants in autopsies, it is difficult to establish lethal TCE concentrations in blood or tissue.

Inhalation of high concentrations of TCE can cause irritation of the respiratory tract and minimal organ damage, as well as depression of the central nervous system. Acute pulmonary congestion and edema typically found in fatalities result from inhalation of TCE (Bonventre et al., 1977; Caplan et al., 1976). There are also scattered reports of modest fatty vacuolation in the liver (Caplan et al., 1976; Hall and Hine, 1966; Stahl et al., 1969). In most such instances there probably would have been insufficient time between exposure and death for hepatotoxicity to be fully expressed. Stewart (1971) reported the case histories of four individuals who were monitored clinically after being overcome by TCE vapors. In each case, recovery from depression of the central nervous system was quite rapid and largely uneventful. However, one of the four patients exhibited elevated urinary urobilinogen but no alteration of other indices of hepatotoxicity. These studies indicate that TCE possesses a limited capacity to exert hepatic injury in cases of acute, high-level inhalation exposure.

Clinical experience and scientific investigations suggest that acute high-level inhalation of TCE can adversely affect the cardiovascular system of humans. Dornette and Jones (1960) used concentrations of 10,000-26,000 ppm TCE to anesthetize surgery patients. They noted that both induction of and recovery from anesthesia were quite rapid. No evidence of respiratory depression or hepatotoxicity was seen. However, there were disturbing cardiovascular effects including diminished systolic pressure, premature ventricular contractions, and, in one patient, even cardiac arrest.

Bass (1970) reported a syndrome termed "sudden sniffing death" in persons dying abruptly while inhaling volatile solvents for self-intoxication. TCE was one of the most frequently implicated solvents in such incidents. The fatalities were tentatively attributed to cardiac arrhythmias that resulted from a combined action of the solvent and endogenous biogenic amines. Recent investigations of the phenomenon with laboratory animals are discussed below.

A single account of ingestion of TCE by a human has appeared in the literature (Stewart and Andrews, 1966). A 47-year-old male mistakenly consumed 1 oz of TCE (approximately 0.6 g/kg). He became nauseated within 30 minutes and developed progressively severe vomiting and diarrhea over the next few hours. Clinical evaluation

following gastric lavage revealed neither drowsiness nor difficulty with coordination. Urinalysis and clinical chemistry tests revealed evidence of only minimal hepatorenal injury early in the course of hospitalization. After resolution of the vomiting and diarrhea, the patient was asymptomatic during a 2-week observation period.

Since depression of the central nervous system is the predominant effect of TCE on humans, certain manifestations of the depression should be the most sensitive indices of the physiological action of small quantities of the solvent. Early studies with volunteers indicate that inhalation of 500 ppm TCE for several hours has no significant effect other than transient, mild eye irritation (Stewart et al., 1961a, b; Torkelson et al., 1958). Stewart and his coworkers (1969) concluded in a later study that 500 ppm may be excessive for persons who are particularly susceptible to the chemical's depressant effects on the central nervous system. In an even more recent investigation, inhalation of 350 ppm TCE for 4 hours was not effective, but 450 ppm elicited subjective complaints of transient eye irritation and dizziness (Salvini et al., 1971a, b). Although a battery of psychophysiological tests did not reveal a statistically significant degree of functional inhibition, lower scores resulted when tests were conducted during TCE exposure than when under control conditions. Results of an investigation by Gamberale and Hultengren (1973) indicated

that inhalation of 350 ppm TCE can significantly inhibit psychophysiological functions of humans. Blood levels in these "inhibited" subjects averaged approximately 3-4 ppm, although the investigators noted wide intersubject differences in blood and alveolar air concentrations. Gamberale and Hultengren concluded that it would be difficult, with any degree of accuracy, to set a threshold for the vapor concentration of TCE that would not alter function of the central nervous system. Their tests of psychophysiological function are certainly more sensitive and objective than the indices used in the earlier studies of Torkelson et al. (1958) and Stewart et al. (1961, 1969). Nevertheless, the current U.S. threshold limit value for occupational exposure to TCE remains at 350 ppm. This standard is designed to protect the majority of workers from mucous membrane irritation and performance inhibition. One interesting facet of the studies by Torkelson et al. (1958) and Stewart et al. (1969) is their failure to find any evidence of organ damage in humans that were subjected to acute TCE inhalation regimens.

Short-term exposure to TCE appears to be no more harmful to humans or laboratory animals than does acute exposure. Stewart et al. (1969) exposed humans via inhalation to 500 ppm TCE for 6.5 hours daily for five consecutive days. They observed some objective and subjective signs of depression of the central nervous system, but no evidence of toxicity

upon examination for neurological, respiratorty, and hepatorenal function. There were also a small accumulation of TCE and an increase in urinary trichloroethanol levels.

Observations in Other Species

Acute Effects. Overall results of animal experimentation confirm the previously described findings in humans--namely, that TCE is relatively nontoxic upon short-term exposure. The acute oral LD_{50} for TCE, as determined in several species of animals, is reported by Torkelson et al. (1958) to range from 5.7 to 14.3 g/kg. Unfortunately, little other toxicological data involving oral dosing are available. LD_{50} values that were derived upon administration of TCE by routes of administration other than oral illustrate the difficulty in using such data to predict consequences of ingestion of the chemical. In contrast with an oral LD_{50} value of 11 g/kg in the mouse (Torkelson et al., 1958), the LD_{50} is approximately 16 g/kg for subcutaneous injection (Plaa et al., 1958) and approximately 4.9 g/kg for intraperitoneal injection (Klaassen and Plaa, 1966). By administering equivalent intraperitoneal and oral doses of carbon tetrachloride to rats, Nadeau and Marchand (1973) demonstrated that significantly higher hepatic concentrations of carbon tetrachloride and more

extensive hepatotoxicity are manifested in the intraperitoneally-dosed animals.

Despite the problems that are inherent in extrapolating data from one route of chemical exposure to another, we may gain qualitative insight into the toxicity of TCE by examining information from studies in which the oral route was not used. Plaa and his colleagues found TCE to be the least hepatotoxic of a series of alkyl halocarbons that were given subcutaneously (Plaa et al., 1958) and intraperitoneally (Klaassen and Plaa, 1966) to mice and intraperitoneally to dogs (Klaassen and Plaa, 1967) and rats (Klaassen and Plaa, 1969). Near-lethal quantities of TCE were generally required to produce hepatotoxicity. They observed little to no evidence of nephrototoxicity. In contrast to TCE (ED_{50}=2.5 ml/kg for SGPT elevation in mice), its congener 1,1,2-trichloroethane was much more toxic (ED_{50} = 0.1 ml/kg), and tetrachloroethylene was of equivalent potency (ED_{50} = 2.9 ml/kg).

In laboratory animals, as well as humans, the primary hazard of inhalation of high concentrations of TCE is excessive depression of the central nervous system. Adams et al. (1950) reported the 3-hour LC_{50} in rats to be 18,000 ppm. They observed that recovery of several test species of animals from marked depression of the central nervous system was rapid and uneventful. The lowest and shortest exposure that elicited histologic change in tissues of the rat was

8,000 ppm for 7 hours. This produced an increase in liver weight and fatty vacuolation of hepatocytes. Disturbance of vestibular function in rabbits that had been infused intravenously with TCE was observed by Larsby et al. (1978) when blood levels in the rabbits exceeded 75 ppm TCE. Levels of TCE in the cerebrospinal fluid were approximately one-third of that in the blood. Although this vestibular disturbance is physiologically significant, it should be recalled that Gamberale and Hultengren (1973) observed inhibition of psychophysiological function in humans with blood levels of only 3-5 ppm TCE.

A second hazard that is associated with acute exposure to vapor containing high concentrations of TCE is cardiovascular toxicity. The aforementioned accounts of cardiotoxic effects of TCE in humans (Bass, 1970; Dornette and Jones, 1960) have been confirmed in studies of dogs. Reinhardt et al. (1973) found TCE to be more potent than trichloroethylene in inducing arrhythmias in dogs concomitantly dosed with epinephrine. The lowest effective concentration of TCE was 5,000 ppm. However, Egle et al. (1976) did not detect adverse cardiovascular effects in freely moving dogs that had been exposed to 5,000 and 10,000 ppm TCE in a Freon propellant. They attributed the disparity between their own findings and those of Reinhardt et al. (1973) to differences in experimental design. Herd et al. (1974) found TCE to exert a biphasic action on the

cardiovascular system of anesthetized dogs, which was characterized by an initial decrease in blood pressure that was associated with peripheral vasodilation as well as reflex chronotropic and inotropic effects on cardiac function, and subsequent depression of cardiac function. In a study of the biochemical mechanism of TCE's cardiotoxicity, Herd and Martin (1975) observed inhibition of respiratory function and alteration of permeability characteristics in mitochondria that were isolated from rats. Herd et al. (1974) emphasized that studies are needed to determine whether low-level exposure to TCE may be injurious to the cardiovascular system.

In contrast to previous findings of microsomal enzyme induction in mice (Lal and Shah, 1970) and rats (Fuller et al., 1970) that inhaled 3,000 ppm TCE for 24 hours, inhibition of microsomal drug metabolism was observed in rats that had been given approximately 1.4 g/kg orally (Vainio et al., 1976) and in mice that had been given 1.0 ml/kg of undiluted TCE intraperitoneally (Shah and Lal, 1976). Shah and Lal (1976) further demonstrated that dilution of the TCE with olive oil reduced the inhibitory effect, while TCE that was diluted with dimethyl sulfoxide (DMSO) potentiated the effect. These investigators suggested that the olive oil inhibited the systemic absorption of TCE and that the DMSO potentiated TCE's hepatotoxicity.

Chronic Effects. McNutt et al. (1975) exposed mice continuously to 250 and 1,000 ppm TCE for up to 14 weeks. Serial sacrifices were performed at weekly intervals to ascertain the development of any histopathologic abnormalities. Hepatocytic vacuolations and significant increases in liver weight and triglyceride content were observed throughout the study in the 1,000 ppm animals. After 4 weeks of exposure to 1,000 ppm TCE a number of ultrastructural alterations were observed in centrilobular hepatocytes, including proliferation of smooth endoplasmic reticulum. Such a structural alteration would be expected in light of the reports of microsomal enzyme induction by Fuller et al. (1970) and Shah and Lal (1976). McNutt et al. (1975) saw a return to normal of each of the indices at 2 and 4 weeks after exposure. Quite modest ultrastructural alterations and increases in liver weight and triglyceride were occasionally observed in the animals that were exposed to 250 ppm during the 14-week study. Thus, this exposure level might be considered a threshold for a biological effect of TCE in the mouse. Platt and Cockrill (1969) studied biochemical changes in rat livers in response to a series of aliphatic halocarbons. They found seven daily oral doses of 1.65 g/kg to enhance cytoplasmic and microsomal protein content and to exert no hepatotoxicity. Savolainen et al. (1977) recently reported slight decreases in brain RNA and liver microsomal P-450 in rats inhaling 500

ppm TCE 6 hours daily for 4 or 5 days. The significance of these latter findings is uncertain.

The only lifetime feeding study that has been reported was conducted as a part of the National Cancer Institute Bioassay Program (NCI, 1977). In an initial range-finding study, oral doses ranging from 1,000 to 10,000 mg/kg TCE in corn oil were given to male and female mice and rats 5 days weekly for 6 weeks. The highest "no-effect" dose for rats was 3,160 mg/kg while that for mice was 5,620 mg/kg. Indices of toxicity that were evaluated included body weight and gross evidence of organ damage. A chronic dosing study was then initiated but had to be discontinued because of undefined intoxication in rats receiving 3,000 mg/kg. In the final chronic dosing study, male and female rats received 750 or 1,500 mg/kg TCE in corn oil by gavage five times weekly for 78 weeks. Similarly, male and female mice were given TCE doses that were increased during the study when it became apparent that larger quantities of the chemical could be tolerated. The time-weighted averages for the two dose levels in mice for the 78-week regimen were approximately 2,800 and 5,600 mg/kg. Diminished body weight gain and decreased survival time were manifest in both mice and rats. Surprisingly, the incidence of histopathologic change was no greater for TCE-dosed than for control animals of either species. No other indices of toxicity were evaluated.

A number of long-term animal studies of the toxic potential of inhaled TCE have been conducted over the last 20 years. These studies have been directed largely towards assessing potential hazards of TCE in occupational exposure situations. Daily exposure of a variety of species to 500 ppm of TCE over a 6-month period elicited no recognizable adverse effect, but 1,000 ppm produced fatty changes and increased weight of livers of guinea pigs (Torkelson et al., 1958). Rowe et al. (1963) reported similar findings when testing a solvent mixture consisting of approximately 75% TCE and 25% tetrachloroethylene. However, guinea pigs in the latter study did show some decrease in body weight gain, which was attributed to reduced food consumption, as well as an increase in liver weight. In studies of responses to even lower concentrations, Prendergast et al. (1967) exposed rats, guinea pigs, dogs, rabbits, and monkeys to TCE vapor continuously for 90 days. They observed depressed body weight in rabbits and dogs inhaling 370 ppm, but no adverse effects in any species inhaling 135 ppm. Eben and Kimmerle (1974) detected no evidence of hepatorenal injury, hematologic change, or histopathologic alteration in rats that received 200 ppm TCE 8 hours daily, 5 days weekly for 14 weeks.

Mutagenicity. Simmon et al. (1977), when conducting a mutagenesis screen of 71 chemicals that had been identified

in U.S. drinking water, found TCE to be very weakly mutagenic *in vitro* for *Salmonella typhimurium*. Microsomal activation appears to have little effect on its potency.

Carcinogenicity. The only study of the carcinogenic potential of TCE that has been conducted to date failed to reveal any evidence of carcinogenicity (NCI, 1977).

Teratogenicity. No available data.

CONCLUSIONS AND RECOMMENDATIONS

Suggested No Adverse Response Level (SNARL)

24-hour Exposure

The literature indicates that TCE is one of the least toxic of the commonly used alkyl halocarbons. Since depression of the central nervous systems is its predominant effect when inhaled, it appears that loss of manual dexterity, coordination, perception, etc., may be the most sensitive indices of exposure. Unfortunately, it is unclear whether significant inhibition of psychophysiological functions will occur in humans who ingest the chemical. The 0.6 g/kg of TCE reportedly ingested by the patient of Stewart and Andrews (1966) might be considered to be a minimum oral hepatorenal toxic dose. However, the nausea,

vomiting, and diarrhea that were experienced by the patient are toxicologically significant manifestations that must be avoided, although the gastrointestinal upset may have resulted from consumption of undiluted TCE. Moreover, the vomiting, diarrhea, and gastric lavage may have prevented systemic absorption of a portion of the TCE.

A single case history is obviously not sufficient to serve as a basis for setting an exposure level for acute ingestion of TCE. However, a similar quantity of TCE in laboratory animals appears to be what might be termed a "minimum effect level." Vainio et al. (1976) found that a single oral dose of approximately 1.4 g/kg depresses some hepatic microsomal metabolic indices in rats. In light of reports of hepatic microsomal enzyme induction in mice and rats following inhalation of TCE, it is possible that oral doses lower than 1.4 g/kg might also stimulate xenobiotic metabolism. Nevertheless, it seems appropriate that calculations for a suggested 24-hour SNARL for contamination of drinking water by TCE be based upon a minimum (oral) effect level that is derived from actual experimentation, namely 1.4 g/kg. This SNARL is based upon the assumption that the sole source of TCE during this time will be drinking water and that a 70-kg human consumes 2 l/day. An uncertainty factor of 100 is applied.

$$\frac{1.4 \text{ g/kg} \times 70 \text{ kg}}{100 \times 2 \text{l}} = 490 \text{ mg/l}$$

1-week Exposure

TCE appears to be no more hazardous upon short-term exposure than it does upon acute exposure. A study in which humans were subjected to 500 ppm of TCE vapor on 5 consecutive days, revealed no evidence of toxicity (Stewart et al., 1969). Platt and Cockrill (1969) reported seven daily oral doses of 1.65 g/kg not to be hepatotoxic in rats, but to enhance hepatic microsomal and cytoplasmic protein content. However, their use of liquid paraffin as a vehicle may have markedly retarded systemic absorption of the TCE. Thus, because of the lack of more definitive information regarding short-term minimum- or no-effect levels, the suggested 7-day SNARL for drinking water contamination is obtained by dividing the 24-hour SNARL by 7. Assuming that the sole source of TCE during this period will be drinking water:

$$\frac{490 \text{ mg/l}}{7} = 70 \text{ mg/l}$$

Definitive studies in several species of animals should be undertaken using a range of oral doses of TCE to characterize dose-effect and dose-response relationships for both single and multiple ingestions over a 1-week period. A variety of tests, which are valid indices of injury to potential target organs (e.g., heart, liver, kidneys), should be monitored. As no data pertaining to the uptake, distribution, metabolism, and excretion of TCE upon

ingestion are available, pharmacokinetic studies should be undertaken using a range of oral doses in several animal species. Vehicles for administration should be carefully selected to avoid discrepancy from actual exposures via drinking water or foods.

Limited studies of ingestion of small quantities of TCE might be undertaken in humans. These studies appear warranted since the toxic end points that might serve as a basis for setting standards include subjective (e.g., nausea) as well as subtle objective (e.g., performance) indices. It would be valuable to determine the quantity of TCE that must be consumed to produce a blood level of 3-4 ppm TCE, the level that Gamberale and Hultengren (1973) associated with inhibition of psychophysiological function. Other indices that might be evaluated include cardiovascular function and microsomal xenobiotic metabolism.

Chronic Exposure

TCE seems to be no more toxic upon long-term exposure than it is upon acute or short-term exposure. Quite large quantities of the chemical given orally to mice and rats five times weekly for 78 weeks elicited little apparent histopathologic change of any organ in either species (NCI, 1977). However, decreased body weight gain, obvious ill health, and diminished survival time in certain of these

animals suggest that more sensitive and/or appropriate tests may reveal adverse effects by comparable ingestion regimens. Indeed, McNutt et al. (1975) reported increased liver weight, liver lipid content, and ultrastructural alterations in hepatocytes of mice that had been subjected for weeks to a vapor concentrations as low as 250 ppm. Unfortunately, since no information on TCE blood or tissue levels was presented by these investigators, it is difficult to extrapolate their data to oral exposure.

In the absence of more definitive information regarding the chronic toxicity of ingested TCE, the lowest dosage level that was administered to either species in the NCI (1977) study (i.e., 750 mg/kg to rats) will be used as a basis for calculating a chronic SNARL. Depression in body weight gain in males and diminished survival time in both males and females have been observed in rats that were maintained on the 750 mg/kg oral dose. The following calculation assumes that a 70-kg human consumes 2 l of water per day and that 20% of the total TCE intake is provided by water. An uncertainty factor of 1,000 is used and the dose is multiplied by 5/7 to convert from the 5- to 7-day exposure.

$$\frac{750\ \text{mg/kg} \times 5\ \text{days} \times 0.1\ \text{l} \times 70\ \text{kg}}{7\ \text{days} \times 1{,}000} = 3.8\ \text{mg/l}$$

The study from which this value was calculated did not provide a no observed adverse effect level. The large

uncertainty factor is used for this reason. Because of the expected high use of this compound, the subcommittee considered it important to provide some provisional guidelines.

Appropriately designed oral, long-term dosing studies using several species of animals and a range of doses of TCE should be conducted in order to establish minimum toxic dose levels with accuracy. Vehicles for administration should be selected to assure that artificial exposure conditions are not created, e.g., use of large quantities of corn oil, as in the NCI (1977) study. Sensitive indices of aliphatic halocarbon exposure should also be selected carefully. Since only one investigation of the carcinogenic potential of TCE has been reported to date, additional research should be conducted with doses of TCE that do not shorten the life-span of the subjects. Vehicles for TCE dilution/administration should not create highly artificial exposure conditions. Appropriate studies to investigate the mutagenic and teratogenic potential of TCE should also be conducted.