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Health Risk Assessment of Environmental Exposure to 1,1,1-Trichloroethane[1]

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In 1986 a survey was published by CEFIC on the occurrence of chlorinated solvents in ambient air, in surface water, and in ground water. The present article concentrates on 1,1,1-trichloroethane (1,1,1-T), and puts into perspective the environmental occurrence and the toxicity. Critical toxicological data are briefly discussed. As no evidence of a carcinogenic effect of 1,1,1-T is apparent, the no-adverse-effect levels in chronic inhalation exposure in rats (875 ppm) and mice (1500 ppm) form the basis for the estimation of potential risk to human health. Environmental exposure to 1,1,1-T is mainly via the atmosphere (120 μg/day); the contributions of drinking water (2 μg/day) and food (3 μg/kg) are negligible. Safety margins are calculated by comparing the no-adverse-effect levels in rat and mouse studies with the total body burden. Safety margins are also calculated after converting no-adverse-effect levels into estimated internal dose levels by physiologically based pharmacokinetic modeling. Safety margins vary with the starting point, but are of the order of 10^5 for the general population and more than 10^4 for the population close to industrial activities. It may be concluded that the risk of a potential health effect resulting from environmental exposure to 1,1,1-trichloroethane is negligible.

INTRODUCTION

Comprehensive review documents on the toxicology of 1,1,1-trichloroethane (1,1,1-T) have been published, e.g. UK Health and Safety Executive (UK-HSE, 1984). A survey of the environmental occurrence of 1,1,1-T in ambient air and, in ground and surface water has been published by CEFIC (1986). The data show that the possibility exists that members of the general population can be exposed to small, yet measurable quantities of the chlorinated solvent in their drinking water, in food,

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and in ambient air. Enough data are available from animal experiments and from workplace and experimental exposure of volunteers to compare the no-observable-effect level (NOEL) for health effects with the level of environmental exposure. This comparison has been done in the traditional way and by calculating the internal dose using physiologically based pharmacokinetics (PBPK), incorporating specific information about the physiology of different animal species, the appropriate physicochemical properties, and dose dependency of biochemical processes involved in metabolism and elimination.

The present article reviews briefly the choice of the toxicological bases for the risk assessment, selects the relevant figures for environmental exposure, and provides an assessment of the potential risk for human health resulting from the environmental exposure using the traditional method as well as physiologically based pharmacokinetics.

SELECTION OF THE TOXICOLOGICAL BASIS FOR RISK ASSESSMENT

Acute and Subchronic Toxicity

In view of the low toxicity after acute exposure, other criteria are more suitable as a basis for risk assessment. A number of subchronic studies with inhalation exposure are reported in the literature, the most relevant of which are summarized here.

In a 6-month inhalation study with primates, guinea pigs, rabbits, and rats, 500 ppm had no toxic effects (Torkelson *et al.*, 1958).

Prendergast *et al.* (1967) worked with rats, rabbits, dogs, and squirrel monkeys at 135, 370, and 2200 ppm for 6 weeks or 3 months. Reduced weight gain was noted in dogs at 2200 ppm. In all four species, 370 ppm had no toxic effect. The NOEL for subchronic studies is therefore at least 500 ppm.

The studies of McNutt *et al.* (1975) did not qualify for this review because of the exposure regimen.

Effects on Reproduction and Developmental Toxicity

No evidence of any teratogenic effect was noted when pregnant rats and mice were exposed to 875 ppm 1,1,1-T by inhalation (Leong *et al.*, 1975). Fetotoxic effects, indicative of delayed development, were seen when pregnant rats were exposed to 2100 ppm 1,1,1-T (York *et al.*, 1982).

In another study, exposure to 1000, 3000, and 6000 ppm 1,1,1-T by vapor inhalation in rats and rabbits resulted in no embryotoxicity or teratogenicity (HSIA, 1987).

No adverse effects were noted in a two-generation fertility study in mice exposed to 1,1,1-T in drinking water at dose levels equivalent to 100–1000 mg/kg body wt/day (Lane *et al.*, 1982).

It may be concluded that adequate testing of 1,1,1-T does not show reproductive or developmental effects.

Mutagenicity

A number of short-term mutagenicity tests have been carried out with 1,1,1-T. Tested as a liquid for its capacity to produce point mutations in bacteria and yeasts,

the results were consistently negative (UK-HSE, 1984). When the compound was tested in the vapor phase, positive results were obtained. As the mutagenic activity was obtained in the absence of a metabolic activation system, it is suggested that this is related to the presence of an epoxide stabilizer in the 1,1,1-T rather than the compound itself (Gocke *et al.*, 1981).

Negative results were obtained when the compound was investigated for DNA damage *in vitro* (Althaus *et al.*, 1982). In cell transformation assays conflicting results were obtained (Daniel *et al.*, 1981). These results are discounted here because the significance of the results is unclear, and in a similar test the same results could not consistently be reproduced (Styles, 1981).

In a micronucleus test in mice, 1,1,1-T was negative, suggesting that the compound does not produce chromosome abnormalities (Salamone *et al.*, 1981). Likewise, negative results were obtained in a dominant lethal assay using mice (Lane *et al.*, 1982). In summary, 1,1,1-T has been extensively investigated for mutagenicity in prokaryotic and eukaryotic systems and to a limited extent in mammalian systems. There is no evidence that the compound itself has mutagenic potential.

Carcinogenicity and Chronic Toxicity

1,1,1-T was given to Osborne Mendel rats by gavage as a 75% solution in corn oil at doses of 1500 and 750 mg/kg 5 days a week for 78 weeks: both dose levels caused reduced weight gain. No significant compound-related nonneoplastic lesions were noted at autopsy and no significant increase in any type of tumor was observed. There was a poor survival rate in all groups in both sexes, including controls (NCI, 1977).

1,1,1-T was given by gavage as a 40–60% solution in corn oil at two dose levels, 5 days a week for 78 weeks to B6C3F1 mice. The top dose was increased from 4000 via 5000 to 6000 mg/kg as from week 20, the lower dose from 2000 via 2500 to 3000 mg/kg. A moderate reduction in weight gain occurred in treated groups and the survival was decreased. No significant increase in tumors was seen. No other compound-related toxicity was noted at autopsy (NCI, 1977).

Sprague–Dawley rats were exposed for 12 months to 0, 875, and 1750 ppm 1,1,1-trichloroethane. After 30 months no treatment-related increases in tumors were observed. The top exposure level caused an increased incidence of focal hepatocellular alterations. The NOEL was 875 ppm (Rampy *et al.*, 1978).

B6C3F1 mice were exposed to 0, 150, 500, and 1500 ppm 1,1,1-trichloroethane for 2 years. No tumorigenic effect nor any other toxic effect attributable to the exposure was observed (Quast *et al.*, 1988). The highest NOEL is therefore 1500 ppm.

Fisher 344 rats were equally exposed to these dose levels for 2 years. At 1500 ppm minor microscopic effects in the liver were observed. A small decrease in body weight was observed at 1500 ppm in the females. The exposure did not result in an oncogenic effect. In this study 500 ppm was a NOEL also for other parameters (Quast *et al.*, 1988).

An oral gavage study with 500 mg/kg body wt in Sprague–Dawley rats suggested an increase in immunoblastic lymphosarcomas. The author found his results inconclusive (Maltoni *et al.*, 1986).

Oral gavage studies in rats and mice have been carried out under the auspices of the NTP program. Due to apparent deficiencies in the laboratory procedures, these studies will not be published.

In summary, six studies have shown no evidence for carcinogenic effects of 1,1,1-trichloroethane. The NOEL for chronic inhalation exposure in rats is 875 ppm and for mice, 1500 ppm.

Human Data

Male volunteers were exposed to 500 ppm 1,1,1-T for 7 hr per day for 5 consecutive days. Drowsiness was consistently reported. Slight impairment in the behavioral tests was observed in two volunteers but not consistently. There was no evidence of liver or kidney dysfunction (Stewart *et al.*, 1969).

Male volunteers were exposed for 30 min to increasing concentrations via breathing tubes. Some impairment in performance was observed at 350 ppm, but this was not significant for the group of 12 individuals (Gamberale and Hultengren, 1973). Very few studies have been carried out to investigate the health of workers occupationally exposed to 1,1,1-T. There was no evidence of any impairment in liver or kidney function, nor of any cardiovascular disturbances in workers exposed to average levels of 1,1,1-T up to 250 ppm (Kramer *et al.*, 1978). The duration of exposure of these workers, however, was relatively short (1–3 years).

A study to investigate neurotoxic effects in a small group of female workers exposed up to 6 years to average levels of 1,1,1-T up to 350 ppm provided no evidence of any adverse effects on the central or peripheral nervous system. No effects other than neurotoxicity were investigated in this study (Maroni *et al.*, 1978).

The epidemiological studies available have concentrated on central nervous system (CNS) effects and morbidity, including liver and kidney disorder. These studies do not provide a valid measurement of carcinogenic potential (UK-HSE, 1984).

Selection of the Biological Basis for Risk Assessment

Acute toxicity studies on 1,1,1-T do not provide a basis for risk assessment. The absence of convincing mutagenic effects and the negative results of long-term studies both by oral gavage and in the more relevant inhalation studies exclude carcinogenic effects as the basis for the risk assessment.

Two different types of studies are available to evaluate the toxic potential of 1,1,1-T: (1) chronic and subchronic studies in animals and (2) subchronic studies in humans. Because environmental exposure is chronic, the NOELs in long-term studies in rats (875 ppm for 1 year) and in mice (1500 ppm) have been chosen as the basis for risk assessment for potential liver effects. In addition the available data on humans with a NOEL at 350 ppm have been chosen as the basis for risk assessment for CNS effects. The NOEL in humans is obtained in people at rest. In the risk assessment the situation of people at work is taken into account.

ENVIRONMENTAL EXPOSURE

Exposure of the general population to 1,1,1-T occurs as a result of its presence in ambient air, drinking water, and food. In this study, exposure levels are given which

cover a large proportion of the population (over 95%), and also worst-case circumstances.

Air

Because of the physicochemical properties of 1,1,1-T and the way it is used, most of it will ultimately diffuse into the air. Ambient air levels are highest in areas of concentrated industry and population, while the lowest levels occur in rural and remote areas.

In the 1970s, in urban centers, average values in ambient air up to several parts per billion were frequently reported (CEFIC, 1984; EPA, 1984). Due to emission reductions, ambient concentrations have now decreased. Surveys of ambient air concentrations in cities both in the United States and the Federal Republic of Germany during 1980–1982 show average values between 0.2 and 0.7 ppb (EPA, 1984; Battelle, 1982).

Emissions from industrial activities involving either production or use of 1,1,1-T may locally cause higher ambient air concentrations. Estimates of air concentrations near an industrial degreasing operation (source category with the highest emissions), based on dispersion modeling, indicate that population exposures are not expected to exceed 4.6 to 9.2 ppb as an average over a 12-month period (EPA, 1984).

Thus, in general, people in cities are exposed to levels less than 1 ppb 1,1,1-T in air. In exceptional cases (mainly close to an industrial activity) levels up to 4.6–9.2 ppb may occur.

Drinking Water

Background concentrations of 1,1,1-T in ground water are about 0.2 ppb (μg/liter). However, in industrialized areas where the solvent is used, background levels of about 5 ppb are measured (Pearson, 1982).

Surveys in the United States of drinking water have found that 97% of all public water supplies derived from well water contain less than 0.5 ppb 1,1,1-T, whereas a small number (0.1%) are reported to have levels higher than 100 ppb. Public water supplies derived from surface water also have been found to contain 1,1,1-T but at lower levels (EPA, 1985).

A survey in Western Europe carried out in the 1970s showed a range of 0.04–1.0 ppb (CEFIC, 1984). In a more recent survey in 100 cities in the Federal Republic of Germany drinking water levels were on the average 0.04 ppb (ranging from not detectable to 1.7 ppb) (Bauer, 1981).

The available data indicate that, in general, the population is not exposed to levels higher than 1 ppb 1,1,1-T in drinking water.

Foodstuffs

Analyses of foodstuffs for 1,1,1-T contamination failed to demonstrate its presence in milk, beer, and coffee (less than 0.1 ppb) (BGA, 1983). Concentrations ranging

from 1 to 7 ppb were detected in vegetables, bread, fruit, and meat; fatty substances contained 5 to 10 ppb (McConnell *et al.*, 1975).

Somewhat higher levels (up to 30 ppb) may occur in fish and other seafood (Pearson, 1982; Pearson and McConnell, 1975).

Because complete food-basket analyses are not available, it is difficult to estimate the exposure to 1,1,1-T via foodstuffs. Therefore the assumption is made that the average concentration of 1,1,1-T in foodstuffs is 2 ppb.

RISK ASSESSMENT

Body Burden

Using the above estimates of environmental exposure, the various contributions to the body burden can be calculated. When considering ambient air, assuming 20 m^3 of air is inhaled by a 70-kg person per day, the contribution to the total exposure is calculated as follows: For the general population exposed to 1 ppb (=6 $\mu g/m^3$), the body burden is 6 $\mu g/m^3 \times 20$ m^3/day = 120 μg/day. For a small fraction of the population, close to industrial activity (<10 ppb), the body burden is less than 1200 μg/day. Assuming that a person drinks 2 liters of water per day, a contribution of 2 μg/day to the body burden can be calculated.

Foodstuff consumption is assumed to be 1500 g per person per day. The average concentration of 1,1,1-trichloroethane is assumed to be 2 ppb, resulting in a calculated maximum uptake of 3 μg/person/day.

Drinking water and foodstuffs contribute only a small fraction to the total daily exposure to 1,1,1-T. The daily cumulative exposure for the general population is calculated as follows:

Air	120 μg/day
Drinking water	2 μg/day
Food	3 μg/day
Total body burden	125 μg/day

This calculated total body burden is not inconsistent with the average body burden of 35.8 μg/day estimated by others (von Düszeln *et al.*, 1982).

Evaluation

The no-observed-effect level for CNS effects of 1,1,1-trichloroethane in humans at rest has been estimated to be 350 ppm (equivalent to 2100 mg/m^3). For humans at work the internal dose resulting from 350 ppm is not significantly different compared with humans at rest (Reitz, 1989, personal communication). The corresponding body burden by inhalation of 10 m^3 during the 8-hr working day is 21,000 mg per day.

The *safety margins* resulting from a comparison of the body burden associated with the NOEL for CNS effects in humans and that anticipated to occur as a result of environmental exposure are, therefore,

TABLE I

	NOEL	Body burden		Safety margin
Rat	875 ppm	345 mg/kg body wt	1	
Mouse	1500 ppm	1700 mg/kg body wt	2	
	Ambient air concentration			
Human	0.001 ppm	0.00179 mg/kg body wt	3	$1/3 = 1.9 \times 10^5$ $2/3 = 9.8 \times 10^5$

for air

$$\frac{21{,}000 \text{ mg}}{0.12 \text{ mg}} = 1.75 \times 10^5$$

for drinking water

$$\frac{21{,}000 \text{ mg}}{0.002 \text{ mg}} = 1.05 \times 10^7$$

for food

$$\frac{21{,}000 \text{ mg}}{0.003} = 7 \times 10^6$$

total body burden

$$\frac{21{,}000 \text{ mg}}{0.125} = 1.6 \times 10^5.$$

The second endpoint upon which a health risk assessment can be based is the potential occurrence of nonneoplastic changes in the liver. The dose–response relationship for this effect in humans is poorly understood. As such, it is necessary to turn to data from animal studies.

The NOELs for nonneoplastic changes in the liver following chronic exposure to 1,1,1-trichloroethane by inhalation have been estimated to be 875 ppm for the rat (12-month exposure) and 1500 ppm for the mouse (2-year exposure). Comparing the body burden in animals with the body burden in humans from environmental exposure, it leads to the calculation of safety margins in the same order of magnitude as those described above (Table 1).

Assuming the minute volumes in mice and rats are 0.021 and 0.073 liters/min, respectively, the body burden relating to the NOELs in mice and rats can be calculated:

Body burden for *rats* of 400 g: 5.25 mg/liter (=875 ppm) × 6 (hr/day) × 60 min × 0.073 (liters/min) = 138 mg/day/rat or (138 × 1000)/400 = 345 mg/kg/day.

Body burden for a *mouse* of 40 g: 9.0 mg/liter (=1500 ppm) × 6 (hr/day) × 60 min × 0.021 (liter/min) = 68 mg/mouse/day or 68 mg × (1000/40) = 1700 mg/kg/day. The safety margins are now obtained by comparing the body burden for rats and mice at the NOELs with the body burden for humans at the environmental exposure concentration.

TABLE 2

INTERNAL DOSES CALCULATED BY THE PB-PK OF REITZ *et al.* (1988)[a]

	NOEL (ppm)	Internal dose ACL (mg/liter liver tissue)		Safety margin
Rat inhalation	875	0.151	1	
Mouse inhalation	1500	0.520	2	
	Ambient air concentration (ppm)			
Human at rest	0.001	1.97×10^{-6}	3	$1/3 = 7.7 \times 10^4$ $2/3 = 2.6 \times 10^5$
Human at work	0.001	2.04×10^{-6}	4	$1/4 = 7.4 \times 10^4$ $2/4 = 2.6 \times 10^5$

[a] In rat and mouse reference studies, the internal dose is the average concentration of 1,1,1-T in the liver (ACL) in mg eq/liter of tissue averaged over the entire lifetime of the animal. In the calculations for environmental exposure, internal doses are reported for humans at rest or engaged in moderate work (50 W) (Johanson and Naslung, 1988).

An alternative approach to interspecies comparison of dose–response relationships for 1,1,1-T has recently been proposed by Reitz *et al.* (1988). This approach applies the concept of physiologically based pharmacokinetics modeling for extrapolating between species, taking into account differences in the physiology between the species, the physicochemical properties of the chemical in question, and the dose dependency of the biochemical processes involved in the metabolism and/or excretion of the chemical concerned. Applying this approach to the observed NOEL for nonneoplastic changes in the liver in animal studies leads to an estimate of the body burden in humans that might be associated with such a NOEL. The estimates of the internal doses in humans are also summarized in Table 2. For details of the principles and background figure, reference is made to Reitz *et al.* (1988).

DISCUSSION AND CONCLUSION

For CNS effects a NOEL in humans could be used, allowing direct comparison of the body burden at 350 ppm exposure with the body burden at environmental exposure. A safety margin of 1.6×10^5 was calculated. For the effect in the liver, marginal in animals and not well documented in humans, the traditional approach has been used alongside the method involving physiologically based pharmacokinetics. Comparing the safety margins in Tables 1 and 2 shows how remarkably close the calculated margins of safety are.

This provides more confidence in those risk assessments where the basic data necessary to follow the more sophisticated PBPK approach are not available.

The magnitude of the safety margins allows the conclusion that the risk of a potential health effect resulting from environmental exposure to 1,1,1-T is negligible. For

the general population the safety margin is around 10^5. For the population close to industrial activities the safety margin is more than 10^4.

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