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Avoidable Deaths Due to Acute Exposure to 1,1,1-Trichloroethane*

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Summary

Two deaths occurred as a result of exposure to 1,1,1-trichloroethane in factories in Surrey within a period of 18 months. Both workers were in their mid-teens and had started their first jobs only a few weeks previously. One death can be attributed to sniffing. In the second case, the worker is thought to have been washing his hands in the few inches of cold solvent at the base of an open tank used for metal degreasing. The operator was found slumped over the side of the tank and could not be revived when eventually discovered. The concentration of solvent in the general atmosphere of the workroom was well below the Threshold Limit Value (TLV) of 350 parts per million (ppm). The concentration immediately below the rim of the tank was 6000 ppm when the tank was not in use, and rose to over 70 000 ppm when the liquid solvent was disturbed.

The reputation which 1,1,1-trichloroethane has achieved for low chronic toxicity at or below the TLV does not justify a belief in total absence of risk in its use. The solvent is readily volatile even at room temperature, and the vapour is heavier than air. Therefore, concentrations sufficient to rapidly induce general anaesthesia can be present locally above cold liquid solvent in open tanks or vessels in workrooms where the concentration in the general atmosphere is well below the TLV.

Introduction

The main use of 1,1,1-trichloroethane in industry is as a cleaning and degreasing agent. Absorption of its vapour occurs rapidly through the lungs. Absorption of the liquid can take place through the gastrointestinal tract and, less readily, through the skin. Absorption of toxic amounts through the skin is unlikely in the course of normal industrial operations. Almost all the dose absorbed is excreted unchanged in expired air but traces are metabolized to trichloroethanol (Stewart, 1968). As a result of animal and human experiments, 1,1,1-trichloroethane has earned the reputation of being one of the less toxic chlorinated aliphatic hydrocarbon solvents. It has a current TLV, 8-hour time weighted average, of 350 ppm. Its relative safety has resulted in its use in many industrial processes in preference to more toxic solvents such as trichloroethylene, which has a current TLV of 100 ppm and is under consideration by the American Conference of Governmental Industrial Hygienists following a proposal that its TLV should be reduced to 50 ppm, 8-hour time weighted average. However, 1,1,1-trichloroethane is about twice as volatile as trichloroethylene at room temperature and in certain situations this would offset the advantage of the higher TLV.

A study was recently conducted in the USA in 2 adjacent textile plants, only one of which used 1,1,1-trichloroethane. One hundred and fifty-one matched pairs of employees were studied. Those in the exposed group had used the solvent for up to 6 years under well-controlled conditions in which the TLV was seldom exceeded. The unexposed controls were from the adjacent plant where no solvent was in use. A comparison of health questionnaire responses, physical findings, haematological, biochemical and electrocardiographic investigations did not reveal any clinically significant findings in the exposed group (Kramer et al., 1978).

The 2 deaths reported here suggest that the popular reputation of 1,1,1-trichloroethane as a safe solvent may not be justified for all circumstances of use.

Case Reports

Case 1

Mr R, aged 16 years, died in March 1979, 6 weeks after starting his first job. His duties involved using the solvent in a centrifuge to degrease small metal parts. During the fortnight before his death, he was twice found by colleagues in a stuporose condition at work, but is said to have recovered

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quickly on both occasions. He was subsequently found dead in a lavatory 9 m from his place of work. An older woman employee (from whom Mr R took over) had carried out the same work without incident for some years previously under identical conditions.

HM Factory Inspectorate (HMFI) investigated 2 contrasting sets of working conditions. Under Mr R's usual working conditions, with normal ventilation in the area, the concentration of 1,1,1-trichloroethane did not exceed 65 ppm. Monitoring was repeated with all doors shut and the extract fan turned off; a concentration of 735 ppm of 1,1,1-trichloroethane was then reached.

Samples taken at Mr R's post mortem examination showed levels of 1,1,1-trichloroethane of 27 mg/100 ml in the blood and 118 mg/100 g in lung tissue. The skin around his mouth showed a reaction which suggested that he had indulged in sniffing. The cause of death was certified as asphyxia due to the inhalation of 1,1,1-trichloroethane. There was no relevant medical history.

Case 2

Mr A, aged 15 years, died in July 1980, 6 weeks after starting his first job. He also was required to degrease small metal parts. The process involved supporting the parts on perforated trays which rested across the top of a tank containing cold 1,1,1-trichloroethane to a depth of a few inches, and running the solvent, scooped up in cans, over the parts. The open top of the tank measured approximately 0·9 m × 0·6 m. It stood 0·75 m above floor level by an open doorway and was not fitted with extract ventilation. After a lunch interval one day, Mr A's body was found slumped over the edge of the tank, his head touching the solvent at the base of the tank.

Environmental monitoring was carried out by HMFI. Under static conditions, when no degreasing work was being carried out, the concentration of 1,1,1-trichloroethane vapour in the general atmosphere of the room was less than 5 ppm. Fifteen cm above the top of the tank, the level was 200 ppm, well below the TLV of 350 ppm. However, 8–15 cm below the rim of the tank the level was 6000 ppm, and at the base of the tank 8–15 cm above the surface of the solvent, the concentration exceeded 70 000 ppm. At a subsequent visit, HMFI repeated the monitoring during normal degreasing operations. General atmospheric concentrations were again well below the current TLV, as was the concentration in the operator's breathing zone (163 ppm). Monitoring within the tank demonstrated the effect of disturbing the liquid solvent and the vapour equilibrium above it. Concentrations rose to 73 000 ppm 8 cm below the rim of the tank, and to 94 000 ppm 15 cm below the rim of the tank.

No quantitative measurements were carried out at Mr A's post mortem examination. Death was certified as being due to cardiorespiratory failure due to trichloroethane vapour. Mr A had no relevant medical history and is said to have behaved responsibly. It is thought he may have decided to wash his hands in the solvent before going to lunch, and been overcome by the vapour while bending over the edge of the tank, or possibly stooping into it.

Management at this factory was unaware of the very serious hazards involved in using a volatile solvent in this manner. A data sheet from the suppliers, which had been filed in the factory office, mentioned in relatively small print that the substance was 'harmful by inhalation' and advised adequate ventilation and the avoidance of prolonged or repeated breathing of the vapour. Detailed information was given about the precautions which should be taken when entering a degreasing tank; but an uninformed reader would not have gained the impression that the solvent had anaesthetic properties which could prove fatal even when relatively small quantities of cold solvent were used for simple degreasing operations, in circumstances where very high concentrations of vapour can accumulate, and where the method of work permits operator exposure to them, even intermittently.

Discussion

The 2 deaths reported here have certain features in common. They both resulted from severe, acute exposure to the vapour of 1,1,1-trichloroethane. The 2 young men were employed in small factories in Surrey. They were in their mid-teens and were within a few weeks of starting their first jobs. They are unlikely to have been aware as a result of previous experience or training of the dangers of the substance to which they were exposed. Neither was supervised by a more experienced colleague with adequate knowledge of the dangers of his work.

The cases differ in this respect; in the first case, exposure to high concentrations of the solvent was deliberate, and in the second case, it was unforeseen. The first case is an example of sniffing, which was probably carried out to induce the symptoms of mild narcosis. It is difficult to estimate the extent of the practice of sniffing of solvents inside and outside the workplace. In addition to the incidents reported at work, it is possible that industrial solvents such as 1,1,1-trichloroethane may be illegally taken home for some particular practical purpose where they become available for further misuse. Bass reported 110 sudden deaths from sniffing volatile hydrocarbons in the USA during the 10-year period up to 1970. All those affected were young people aged between 11 and 23 years. Twenty-nine cases were attributed to the inhalation of 1,1,1-trichloroethane vapour derived from liquid solvent or from aerosol sprays. It was suggested that some of these deaths may have been caused by cardiac arrhythmias (Bass, 1970). There is evidence from electrocardiographic monitoring, during 32 surgical operations, that the use of 1,1,1-trichloroethane as an anaesthetic agent has a tendency to

cause ventricular arrhythmias especially during periods of hypoxia (Dornette and Jones, 1960).

In the second case, the young worker is thought to have died as a result of washing his hands in the solvent. This might have seemed to him an entirely reasonable procedure, but it was one for which neither the solvent nor the system of work was designed. This action would have resulted in his breathing vapour concentrations in excess of 6000 ppm. The Toxicology Committee of the American Industrial Hygiene Association has reported, from human data, the probable results of single exposures to 1,1,1-trichloroethane vapour at differing concentrations and for differing periods of time. They stated that a concentration of 2000 ppm would be expected to cause definite disturbances of equilibrium within 5 minutes (Stewart, 1968). It is easy to understand how, in the case described, the operator's loss of balance would have resulted in his breathing vapour concentrations in excess of 70 000 ppm and sufficient to prove rapidly fatal.

The high risk to a worker who enters a solvent tank without adequate respiratory protection is well known. A recent EEC publication reported 13 deaths amongst workers exposed in solvent tanks to concentrations of 50 000 to 70 000 ppm of 1,1,1-trichloroethane. Post mortem findings showed only pulmonary oedema (Mercier, 1977). It may not be generally realized, however, that comparable concentrations can be present during simple degreasing operations just below the rim of a relatively small open top tank, as in the second case reported here. Under these conditions, environmental monitoring carried out only in the general atmosphere of the room and in the operator's breathing zone would not reflect the much higher exposure which an operator would be subjected to if required to stoop inside the tank as part of his working practice, and would be likely to give a false sense of security. Information about the circumstances of the case has been circulated internally in the Health & Safety Executive and implications of the findings continue to be considered.

In spite of its reputation for low toxicity, 1,1,1-trichloroethane should be treated with respect. Manufacturers' and suppliers' printed data sheets should explain that because of its volatility and high vapour density (vapour density = 4·62: air = 1), very high concentrations of solvent can be present above liquid surfaces especially in enclosed or partially enclosed containers. Warnings should make it clear that at high concentrations, the solvent has potent anaesthetic properties which can be fatal. New workers in industry should receive instructions from experienced staff well aware of the dangers, and be closely supervised in the early months of their employment.

Acknowledgements

I would like to thank Mr K. A. Dobson, Principal Inspector, and Mr P. E. Lovering, Senior Chemical Inspector, HM Factory Inspectorate, for their data and comments on environmental monitoring.

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Two Case Reports of Deaths on Industrial Premises Attributed to 1,1,1-Trichloroethane

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ABSTRACT. Two fatal poisonings resulting from exposure to 1,1,1-trichloroethane are described. Each case occurred at a separate workplace where the solvent was used as a degreasing agent. These cases are considered in light of other 1,1,1-trichloroethane poisonings reported to Her Majesty's Factory Inspectorate. Factors common to these and other incidents are discussed.

CHLORINATED HYDROCARBONS have been used as industrial solvents and anesthetic agents. One such compound, 1,1,1-trichloroethane (methyl chloroform), is a nonflammable, colorless, volatile liquid now widely used as an industrial degreasing solvent. This solvent has gained considerable popularity during the past 20 yr, partly due to its apparently less toxic nature when compared with other solvents. Unlike many chlorinated hydrocarbons, it has not been implicated as a hepatotoxin. Toxic effects of the compound in man include depression of the central nervous system resulting at high concentrations in anesthesia and death from respiratory depression. Cardiac dysrhythmias have been described.[1] Fatal cases of 1,1,1-trichloroethane poisoning have been reported elsewhere,[2,3] but prior to 1978 no fatal case was reported in the United Kingdom. It was not until 1966 that Her Majesty's Factory Inspectorate (HMFI) received its first notification of an industrial gassing due to this compound. Since the beginning of 1978, however, six of the 1,1,1-trichloroethane poisoning cases reported to HMFI have been fatal. Two such cases are described elsewhere,[4] and we report two further cases here.

Case 1

A 20-yr-old apprentice electrician was found dead in a workroom at his factory, where he had been using 1,1,1-trichloroethane earlier as a degreasing solvent from an open bowl. The exact circumstances of the solvent's use leading to the incident are not known. The man was found on the floor of a fume-filled room with the window and door closed. An upright half-full can of 1,1,1-trichloroethane was on the workbench, together with an empty bowl and funnel. There was evidence of spillage of solvent on the floor. The man had been seen in the room approximately 2 hr previously by a workmate who indicated he had appeared well. At that time the bowl was noted to be full of solvent and there had been a strong smell of vapor. At post-mortem there was evidence of blistering and second degree chemical burns on his face and neck. Skin changes on the trunk were in line with the folds of the clothing. These findings were consistent with prolonged contact of the solvent with the body. There was edema and congestion of the brain and lung, and small serous effusions in both pleural cavities. Petechial hemorrhages were noted on the pleural and pericardial surfaces. The stomach showed mucosal congestion and a few scattered petechial hemorrhages. The blood concentration of 1,1,1-trichloroethane was 4.2 mg/100 ml. The brain concentration of the solvent was 123 mg/100 g, and 1,1,1-trichloroethane was present in the liver. At inquest it was concluded that death resulted from suppression of the respiratory center secondary to severe central nervous system depression.

Case 2

A 17-yr-old garage employee was found collapsed in a motor car. He had been cleaning the upholstery with 1,1,1-trichloroethane. The employee applied the compound with a small handsprayer and wiped the upholstery with a muslin cloth. The volume of solvent used was estimated to be between 100 and 200 ml. The car was parked in a large work bay and he had worked alone for 0.5 to 1 hr. The back of each of the front seats was pushed into the forward position and he was found slumped on the floor at the back of the car with his head in the floor well immediately behind the driver's seat. The door on the passenger's side was open. He had vomited and was thought to be unconscious. He was transferred to a hospital by ambulance but was dead on arrival.

At post-mortem the upper air passages contained vomit and the main bronchi were almost completely blocked. The lungs showed patchy over aeration and there was a small hemorrhage low in the right upper lobe. Forensic evidence demonstrated the presence of 1,1,1-trichloroethane in brain, liver, lungs, and blood. A blood level of 1.8 mg 1,1,1-trichloroethane/100 ml blood was found. Brain and liver both contained 8 mg of solvent/100 g of tissue. Death was certified as being due to 1,1,1-trichloroethane intoxication with inhalation of vomit.

Simulation exercise. Using a car of the same model in the same work bay with doors and windows positioned as found when the victim was discovered, a simulation exercise was conducted. When an operator carried out the process in the usual way, a concentration of 36 ppm of 1,1,1-trichloroethane was found at his breathing zone. The sampling time was 27 min. Deliberately using excessive amounts of solvent, 440 ppm was recorded in the breathing zone sampled during 6 min. In both instances, however, approximately three times these concentrations were recorded at a sampling point just 15 cm above the floor. Sampling for 9 min following a spillage of 100 ml solvent onto a cloth placed on the floor behind the driver's seat resulted in a concentration of 6410 ppm obtained 2.5 cm above the floor. This figure rapidly fell as distance from the floor increased and at a height of 15 cm, 515 ppm was recorded, sampled during 15 min.

DISCUSSION

The short-term exposure limit recommended by both the American Conference of Governmental Industrial Hygienists and the Health and Safety Executive for 1,1,1-trichloroethane is 450 ppm.[5] Stewart et al.[6,7] reported that impairment of coordination is minimal at 900 to 1,000 ppm, but marked disturbance of equilibrium can occur above 1700 ppm. A concentration of 10,000 to 26,000 ppm is probably necessary to produce anesthesia.[1] The data obtained from the simulation exercise following the occurrence of Case 2 suggested that where a small amount of solvent is used and reasonable general ventilation exists, anesthetic concentrations are unlikely to occur except at points very close to the solvent source or where conditions favor collection of the heavy vapor at low level. Even in this situation levels just exceeded the minimal concentration of trichloroethane found necessary to maintain light anesthesia.[1] The circumstances in Case 1 suggest that dermal absorption of the solvent might have also occurred. From the work of Stewart and Dodd[8] it seems unlikely that absorption via this route would have been sufficient to significantly alter the toxic effects produced.

All commercially available 1,1,1-trichloroethane contains a very small percentage of an inhibitor which is added to the solvent to prevent its decomposition. Given the nature and quantity of these substances, it is not thought that the inhibitors have any toxicological relevance in these cases. In both cases the solvent used was commercially available 1,1,1-trichloroethane containing approximately 95% 1,1,1-trichloroethane and 5% inhibitor.

Notification of any industrial accident occurring in the United Kingdom must, by law, be made to Her Majesty's Inspectorate if the incident results in death or an absence from work for more than 3 days. The 6 fatalities reported to date have all occurred within the past 5 yr and all victims have been males who were 20 yr of age or under. The fact that all 6 were young men may be coincidental, but the observation causes concern and a possible explanation for increased vulnerability in this age group should be sought. There have been instances where deliberate sniffing of these substances has occurred and addiction to chlorinated hydrocarbons has been reported.[4,9,10]

Blood levels found in these two cases were not as high as have been reported elsewhere.[3] In Case 2 it is probable that inhalation of vomit was the most significant event—a known hazard of anesthesia.[11] The blood level found in Case 1, however, is the same order of magnitude as that found in a fatal industrial 1,1,1-trichloroethane poisoning reported by Hatfield and Maykoski.[2]

The occurrence of fatalities in recent years and in younger age groups might be indicative of the increased prevalence of solvent abuse among young people and might be a possible explanation for this recent trend. In the two cases reported here, however, the possibility of sniffing was specifically investigated at inquest. Neither victim had a history of solvent or drug abuse and it was considered in both cases that sniffing would not have been consistent with the usual behavior of the particular individual.

It is, of course, necessary for persons working with this, as with other solvents, to be made aware of the hazards of inhaling vapor in appreciable concentrations. Whether such fatalities occur as a result of sniffing or as a result of inexperience to some extent may be irrelevant. The essential point is that the unaccompanied young worker may be particularly at risk from the hazard of this solvent. It would seem extremely important, therefore, that more publicity be given to these incidents so that persons with the responsibility for the education and supervision of workers are made fully aware of the potential problems that may arise in

persons with occupational access to 1,1,1-trichloroethane.

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ERRATUM

The editors regret that the captions to Tables 1 and 2 were incorrectly printed in Baden et al.'s article entitled "Smoking Status and the Electrocardiogram: A Cross-Sectional and Longitudinal Study" (*AEH*, Vol. 37, No. 6, pp. 365–69). The corrected Tables appear below.

Table 1.—Examination 1 Mean Values of Electrocardiographic Variables for Smoking-Status Groups, Adjusted for Age and Body Mass Index

Variable	Cigarette-Smoking Status			
	Current (*N* = 291)	Former (*N* = 203)	Never (*N* = 208)	*P*
R amplitude A* (mm)	9.461	9.781	9.467	0.440
R amplitude B† (mm)	14.958	15.364	15.781	0.181
S amplitude A‡ (mm)	1.925	2.184	2.224	0.221
S amplitude B§ (mm)	13.219	13.055	13.025	0.860
Frontal plane axis (°)	44.379	40.388	40.144	0.185
P-R duration (1/100 sec)	15.880	16.103	16.395	0.038
QRS duration (1/100 sec)	7.212	7.444	7.323	0.328
Q-T duration (1/100 sec)	38.160	37.998	38.023	0.804
T amplitude (mm)	4.662	4.495	4.418	0.401

* R amplitude A = the largest R wave amplitude from leads I, II, and III
† R amplitude B = the largest R wave apiitude from leads V_4, V_5, and V_6
‡ S amplitude A = the largest S wave amplitude from leads I, II, and III
§ S amplitude B = the largest S wave amplitude from leads V_1, V_2, and V_3

Table 2.—Mean Annual Change in Electrocardiographic Variables for Smoking-Status Groups, Adjusted for Baseline Electrocardiographic Measurement, Age, and Body Mass Index

Variable	Cigarette-Smoking Status			
	Current (*N* = 291)	Former (*N* = 203)	Never (*N* = 208)	*P*
R amplitude A* (mm)	−0.231	−0.146	−0.177	0.020
R amplitude B† (mm)	−0.106	−0.049	−0.080	0.672
S amplitude A‡ (mm)	−0.007	0.027	−0.020	0.270
S amplitude B§ (mm)	−0.345	−0.268	−0.191	0.022
Frontal plane axis (°)	−1.869	−1.775	−1.504	0.570
P-R duration (1/100 sec)	0.019	0.050	0.032	0.717
QRS duration (1/100 sec)	−0.024	0.034	0.045	0.098
Q-T duration (1/100 sec)	0.244	0.321	0.223	0.178
T amplitude (mm)	−0.186	−0.172	−0.065	<0.001

* R amplitude A = the largest R wave amplitude from leads I, II, and III.
† R amplitude B = the largest R wave amplitude from leads V_4, V_5, and V_6
‡ S amplitude A = the largest S wave amplitude from leads I, II, and III
§ S amplitude B = the largest S wave amplitude from leads V_1, V_2, and V_3

STUDIES ON 1,1,1-TRICHLOROETHANE

Re. Carcinogenicity and Related Studies, Teratology, and Mutagenicity

Published/"Public" Knowledge

Study	Conducted By	Results/Observations
2-Year gavage study in rats and mice exposed over entire period.	NCI	Poor survival, apparent anti-carcinogenic effect on tumors of breast in treated animals.
2-Year inhalation study in rats exposed 1 year and held 1 year before sacrifice.	Dow	Tumor incidence of treated animals comparable to control.
2-Year gavage study in rats and and mice.	NCI	Completion (exposure) May 1981. Report 1982-83.
2-Year gavage study in rats exposed 1 year and held 1 year before sacrifice.	Maltoni	Completion 1981; report 1982.
Microbial mutagenicity (Ames) test.	Simons et al., 1977	Weakly positive.
	Litton Bionetics (Dow) 1975	Negative; one bacterial strain at toxic doses positive.
	NIOSH, 1977	Negative.
	Henschler et al., 1977	Negative.
	Snow et al., 1979	Weakly positive.
Mutagenicity assays (29-test battery).	National Tox. Program	Overwhelmingly negative.
Yeast mutagenicity (Ames) tests	Litton Bionetics (Dow) 1975	Negative.

SL 036476

STUDIES ON 1,1,1-TRICHLOROETHANE

Re. Carcinogenicity and Related Studies, Teratology, and Mutagenicity

Published/"Public" Knowledge

Study	Conducted By	Results/Observations
Host mediated assay.	Loprieno et al., 1979	Negative.
	Loprieno et al., 1979.	Negative.
Cell transformation	Price et al., 1978	Positive, unvalidated test.
Cytogenetics	Dow	Negative.
Epidemiology	Dow	Negative.
Teratology study in rats.	Dow	Negative.
Metabolism study in rats.	Van Dyke and Wineman, 1971	Chloroethanes metabolized by microsomal enzymes.
	Ikeda and Ohtsuji, 1972	Urinary metabolites trichloroethanol and trichloroacetic acid.
Human pharmacokinetics elimination.	Monster et al., 1979	Urinary metabolites trichloroethanol and trichloroacetic acid.

Methyl Chloroform

ACGIH Doc (1984)

(1) beginning anesthetic effect @ ~500 ppm
(2) deaths @ 14 - 15,500 ppm
(3) no teat. effect
(4) 2 concentrations - negative (1 inhalation, 1 oral gavage)

Rothy's

(1) 3 repr. studies
(inhalation) • @ 875 ppm - 2 hr/day, 6 day 6-15 of gestation - neg. teat
(inhalation) • @ 2100 ppm 2 weeks prior to 20 days post - neg teat + neg neurotox + offspring
(ingestion) • @ 0, 55.4, 2640 + 8520 mg/kg (drinking water) neg dom. lethality + neg dominant lethal "no dose dependent effects"
(2) 2 lifetime studies - neg carcinogenicity

Lit file

(1) 2 weakly pos. Ames assays, 3 neg Ames assays
(2) NTP Mut. assays (25 tested) overwhelmingly neg.
(3) Anesthesia: "exposures greater than 800-1000 ppm" (Dow Summary)

RTECS Reproductive: (specific reprod. effect reported at admin. dose

→ TY6 - musculoskeletal (2100 ppm/24H (14D pre/1-20D preg))
→ TS3-TS7 - urogenital system, other developmental abnormalities (2100 ppm/6H (10D pre/1-20D preg))
→ TY4 - fetotoxicity (except death, e.g. stunted fetus) (2100 ppm/6H (1-20D preg))

SL 036478

Peripheral Vasodilatation following 1,1,1-Trichloroethane Inhalation: Peripheral Vessels as a Site of Action

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ABSTRACT. The effects of 1,1,1-trichloroethane (1,1,1-TCE) inhalation on total peripheral vascular resistance and the possibility of the peripheral vessels being a site of action for 1,1,1-TCE were investigated in anesthetized dogs. In acute inhalation experiments, a decrease in total peripheral vascular resistance was observed following inhalation of 1,1,1-TCE concentrations sufficient to induce systemic hypotension. The threshold concentration of 1,1,1-TCE required to produce a decrease in perfusion pressure of the isolated hindlimb was approximately 0.4–0.5% in inspired air. A dose-response relationship between the decrease in perfusion pressure and 1,1,1-TCE concentration, which exceeded the threshold level, was observed. It is suggested that the decrease in total peripheral vascular resistance is related to systemic hypotension following 1,1,1-TCE inhalation; further, this vasodilator effect may be induced in the peripheral vessels, which is one of the sites where 1,1,1-TCE acts.

IN PREVIOUS PAPERS it was reported that respiratory arrest and peripheral vascular collapse[1-3] may be related to the cause of death following inhalation of a high concentration of 1,1,1-trichloroethane (1,1,1-TCE). In addition, it has been reported that these effects may originate with a functional depression of the central nervous system. For example, Stewart[2,3] has reported that the absorption of a toxic quantity of 1,1,1-TCE results in a functional depression of the central nervous system which may result in death from respiratory arrest or peripheral vascular collapse. Stahl et al.[4] have also expressed similar opinions about the function of the central nervous system following 1,1,1-TCE inhalation. Moreover, because 1,1,1-TCE has a potent anesthetic effect,[5,6] it has been suggested that systemic hypotension or shock following inhalation may be related to the functional depression of the central nervous system.[1,7] We have reported,[8] however, that an increase in efferent sympathetic nerve activity and a decrease in systemic blood pressure were observed following inhalation of relatively low concentrations. It is doubtful whether this decrease in systemic blood pressure following inhalation of relatively low 1,1,1-TCE concentrations is related to the functional depression of the central nervous system as a site of action.

The purpose of this study is to clarify the reaction of the peripheral vessels as a site of action in systemic hypotension following acute inhalation of 1,1,1-TCE vapor.

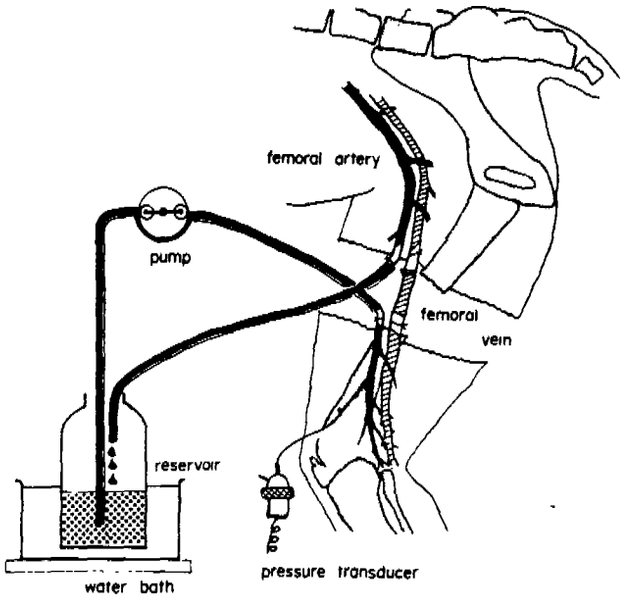

Fig. 1. Schematic diagram of the hindlimb perfusion experiment.

METHOD

Adult male and female mongrel dogs (10–13 kg body weight) were used in this study. Each dog was anesthetized with 25–30 mg/kg sodium pentobarbital injected intravenously and ventilated with a volume type respirator through a tracheal tube. The respiratory rate was 20 cycles/min, and tidal volume was adjusted to yield a peak inspiratory pressure of 10 cm H_2O. Techniques of 1,1,1-TCE inhalation and measurement of concentration in inspired air have been described previously.[8] The 1,1,1-TCE vapor was inhaled during a period of approximately 2 min. As a control condition, respiration with fresh air (without 1,1,1-TCE) preceded and then followed each 1,1,1-TCE administration.

Measurement of total peripheral vascular resistance. Twenty-five dogs were used in this study. A thoracotomy was conducted through the third and fourth intercostal space on the animal's left side. A catheter tip was placed in the ascending aorta through the right femoral artery, and aortic blood pressure was measured with a pressure transducer (Nihon Kohden, MPU-0.5). Aortic blood pressure was presented as mean aortic blood pressure, which was calculated by pulse pressure divided by 3, plus diastolic aortic blood pressure. To measure aortic blood flow, an electromagnetic flow transducer (Nihon Kohden, MFV-1100) was placed around the ascending aorta. Mean aortic blood flow, which was obtained by an electronic integration circuit (time constant = 1 sec), and aortic blood pressure was recorded simultaneously with a pen oscillograph. Before and after inhalation the total peripheral vascular resistance was obtained by dividing the mean aortic blood pressure (mm Hg) by the mean aortic blood flow (ml/min . kg).[9,10]

Hindlimb perfusion experiment. Twenty mongrel dogs anesthetized with sodium pentobarbital were used in a perfusion experiment. To prevent blood coagulation, sodium heparin was injected intravenously before the operation. The right hindlimb of the anesthetized dog was amputated at the central level of the thigh bone (Fig. 1). The hindlimb was placed on a heated panel on which the temperature was maintained at 37°C. As shown in Figure 1, a catheter was inserted into the right femoral artery, and arterial blood was led to a reservoir which was placed in a water bath where the temperature was maintained at 37°C. The hindlimb was perfused with blood led from the reservoir using a pump at a constant flow rate. The amputated femoral vein was reconnected by a tube so that blood pumped into the leg returned to the body. Lost blood was complemented by transfusion of physiological saline with intravenous drip. To measure perfusion pressure of the hindlimb, a small catheter was inserted into the branch of the artery in the hindlimb, and was connected to a pressure transducer (Nihon Kohden, MPU-0.5). In this perfusion experiment, alteration of perfusion pressure following 1,1,1-TCE inhalation shows the response of the denervated peripheral vessels as a site of action of 1,1,1-TCE.

RESULTS

Changes of total peripheral vascular resistance. The effects of 1,1,1-TCE inhalation on aortic blood pressure and aortic blood flow were studied. Figure 2 shows a typical record of aortic blood flow and pressure before, during, and after termination of an inhalation at a concentration of 1.6%. As shown in Figure 2, aortic blood flow increased immediately after inhalation, and was followed by a return to the pre-exposure baseline. Aortic blood pressure decreased immediately after inhalation began. Aortic blood flow returned to a pre-exposure level during inhalation, and aortic blood pressure gradually returned to pre-inhalation level within approximately 5–10 min after termination of inhalation.

It has been stated that systemic blood pressure is mainly determined by changes of total peripheral vascular resistance.[11] We therefore studied the alteration of total peripheral vascular resistance as a factor in the decrease in systemic blood pressure following 1,1,1-TCE inhalation. Total peripheral vascular resistance was found to decrease following inhalation of 1,1,1-TCE concentrations sufficient to elicit sytemic hypotension. The decrease in total peripheral vascular resistance returned to pre-inhalation levels within 5–10 min after termination of inhalation. The relationship between the decrease in total peripheral vascular resis-

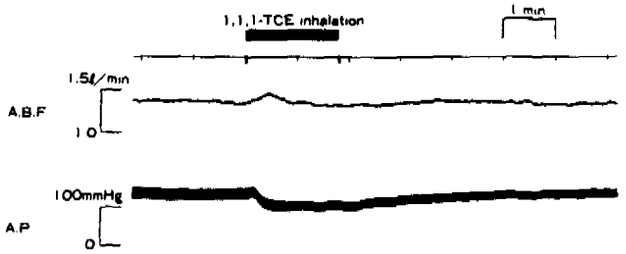

Fig. 2. Effects of 1,1,1-TCE inhalation at a concentration of 1.6% on aortic blood flow (*top trace*) and aortic blood pressure (*bottom trace*).

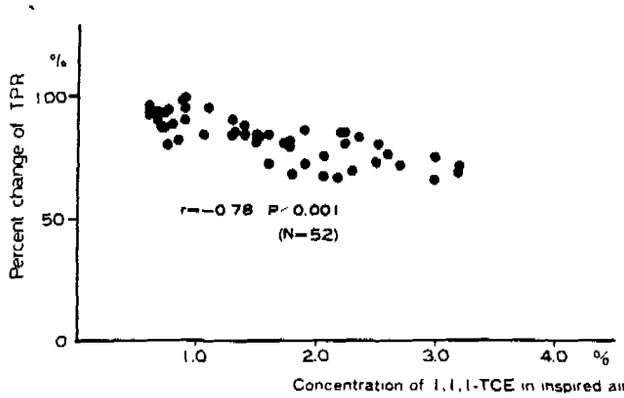

Fig. 3. Correlations between decreases in total peripheral vascular resistance (T.P.R.) and concentrations of 1,1,1-TCE in inspired air.

tance and 1,1,1-TCE concentration in inspired air is shown in Figure 3. A significant linear regression between the decrease in total peripheral vascular resistance and 1,1,1-TCE concentration was observed ($Y = -0.91x + 97.03$, $r = -0.78$, $P < .001$). Therefore, a dose-response relationship between the decrease in total peripheral vascular resistance and 1,1,1-TCE concentration was observed.

Hindlimb perfusion experiment. As a decrease in total peripheral vascular resistance (i.e., vasodilatation) was observed following 1,1,1-TCE inhalation, possibilities of peripheral vessels as a site of action where 1,1,1-TCE acts were studied in the hindlimb perfusion experiment. Typical traces of perfusion pressure following various concentrations of 1,1,1-TCE inhalation are shown in Figure 4. During a period of approximately 2 min inhalation, perfusion pressure remained unchanged at a 1,1,1-TCE concentration of 0.12% in inspired air. A very slight decrease in perfusion pressure was observed for a concentration of 0.48%. For concentrations of 1.0 and 2.8%, perfusion pressure further decreased. The decrease in perfusion pressure resulting from 1,1,1-TCE inhalation gradually returned to each pre-inhalation level within 7–10 min after termination of inhalation. Accordingly, a decrease in perfusion pressure following 1,1,1-TCE inhalation shows that vasodilatation appears at the level of peripheral vessels as a site of action.

The relationship between the decrease in perfusion pressure and the concentration of 1,1,1-TCE in inspired air is shown in Figure 5. The decrease in perfusion pressure following inhalation is presented as delta p in mm Hg. As shown in Figure 5, 0.4–0.5% concentrations of 1,1,1-TCE induced no decrease in perfusion pressure. Inhalation of higher concentrations effected marked decreases in perfusion pressure. However, a decrease of more than 30 mm Hg in perfusion pressure was not observed even at the highest concentration of 3.8% in inspired air. A significant linear regression was obtained between the decrease in perfusion pressure and those 1,1,1-TCE concentrations which exceeded the threshold level in inspired air ($Y = -6.36x - 3.48$, $r = -0.88$, $P < .001$). Thus, a dose-response relationship between the decrease in perfusion pressure and 1,1,1-TCE concentration was observed.

It is still uncertain whether systemic hypotension in the intact dog was induced only by a decrease in perfusion pressure following inhalation. Therefore, the extent of the decrease in perfusion pressure in the present study and the decrease in systemic blood pressure that was reported previously[8] were compared (Fig. 6). As shown in this Figure, concentrations of 1,1,1-TCE required to produce the decrease in systemic blood pressure and a decrease in perfusion pressure showed identical threshold concentrations of 0.4–0.5% in inspired air. At relatively low concentrations both systemic blood pressure and perfusion pressure decreased to roughly the same level; however, at higher concentrations, systemic blood pressure decreased more than perfusion pressure. To examine in more detail the decrease in pressure, 1,1,1-TCE concentrations were separated into the following three groups: (1) each threshold level up to 1.0%, (2) 1.0 to 2.0%, and (3) more than 2.0% in inspired air. The degree of the decrease in both pressures was compared in each group by the t test (Fig. 7). For 1,1,1-TCE concentrations up to 1.0%, no significant difference was found between the decrease in systemic blood pressure (-8.17 ± 1.46 mm Hg, mean $\pm$ *SE*) and perfusion pressure (-6.90 ± 1.22 mm Hg). However, at concentrations of 1.0 to 2.0%, the decreases in systemic blood pressure and perfusion pressure were -31.0 ± 3.13 mm Hg and -14.10 ± 1.41 mm Hg, respectively. In addition, at inhalation concentrations above 2%, further decreases in systemic blood pressure (-42.4 ± 5.87 mm Hg) and perfusion pressure (-22.63 ± 1.21

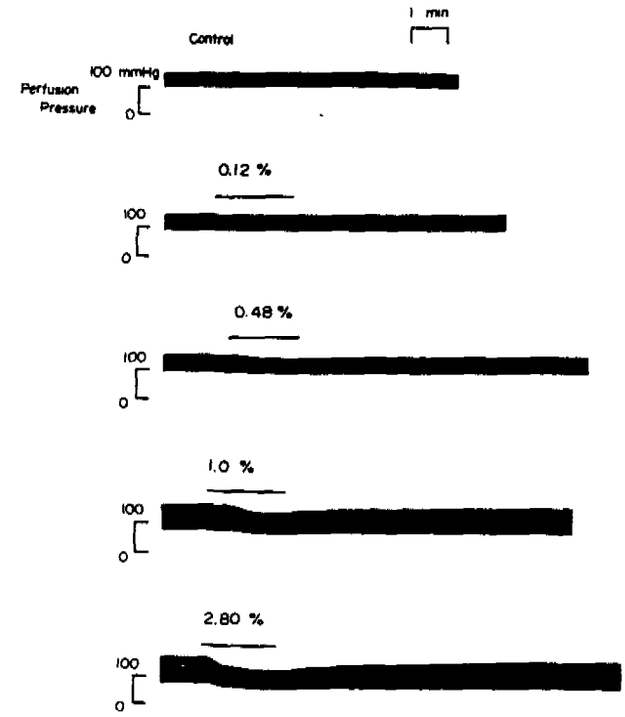

Fig. 4. Typical records of perfusion pressure in the hindlimb following 1,1,1-TCE inhalation. Each *horizontal bar* shows the duration of inhalation.

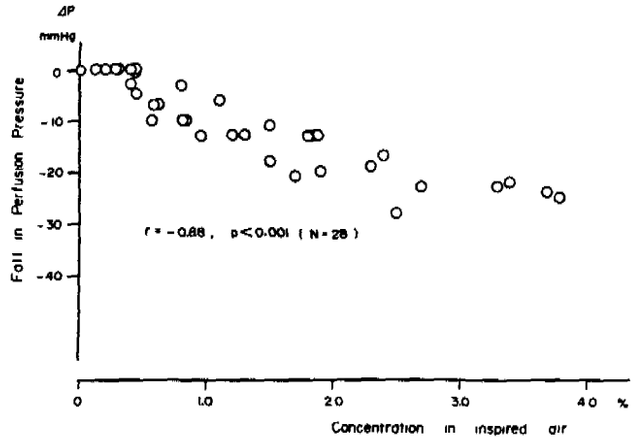

Fig. 5. Correlations between various concentrations of 1,1,1-TCE in inspired air and decreases in perfusion pressure. The degree of fall in perfusion pressure is shown as ΔP in mm Hg.

mm Hg) were observed. Both groups (1.0–2.0% and more than 2.0% inhalation) showed a significant difference between the decrease in systemic blood pressure and perfusion pressure (for both, $P < .01$).

DISCUSSION

It has been reported that peripheral vascular collapse[1,2] or shock[3] resulting from inhalation of 1,1,1-TCE at high concentrations may be one of the important cause of death. Systemic hypotension, which was induced by unknown factors, was addressed hemodynamically in our first experiment. It is known that blood pressure is hemodynamically controlled by the change of total peripheral vascular resistance and aortic blood flow (cardiac output) and that of the two mechanisms, changes in total peripheral resistance are considered far more powerful than changes in cardiac output.[11,12] Accordingly, changes in total peripheral vascular resistance were measured following administration of various concentrations of 1,1,1-TCE. As was shown in Figure 3, total peripheral vascular resistance decreased following 1,1,1-TCE inhalation. This decrease in total peripheral vascular resistance shows that peripheral vasodilatation was induced following 1,1,1-TCE inhalation. A similar decrease in total peripheral vascular resistance was obtained by Herd et al.[13] It is suggested that the decrease in total peripheral vascular resistance may be related to systemic hypotension following 1,1,1-TCE inhalation.

So far, it has been presumed that systemic hypotension may be related to the effects originated from depression of the central nervous system following 1,1,1-TCE inhalation.[1-4] However, evidence[14] has been presented that the toxic properties of compounds which act on the circulatory system, particularly during acute inhalation, cannot be adequately explained as a manifestation of generalized central nervous system depression. We therefore studied the possibility that vasodilatation is induced by the effects of 1,1,1-TCE on peripheral vessels as a site of action. To remove the effects of the central nervous system, we performed a perfusion experiment on the hindlimb (Fig. 1). Our data showed that a decrease in perfusion pressure in the

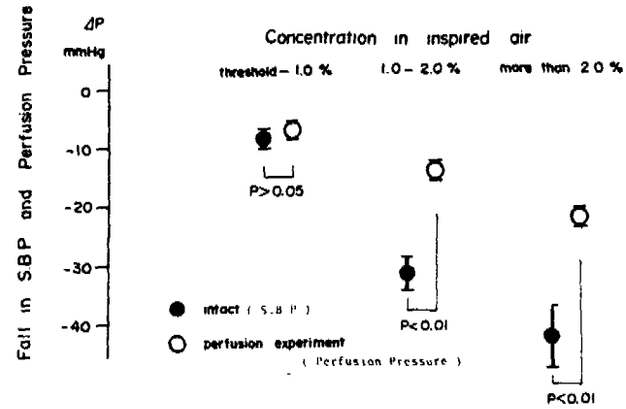

Fig. 7. Decreases in systemic blood pressure (intact animals) and perfusion pressure (perfusion experiment) were compared by *t* test between groups according to 1,1,1-TCE concentrations shown.

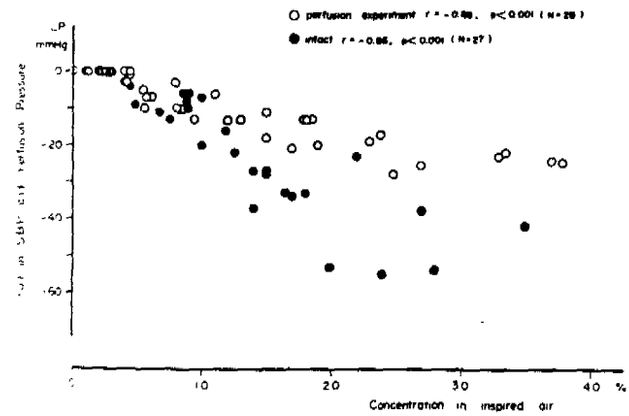

Fig. 6. **Comparison between decreases in systemic blood pressure (intact animals) and perfusion pressure (perfusion experiment). *Open circles* show systemic blood pressure, and *closed circles* show perfusion pressure. (Changes in systemic blood pressure following 1,1,1-TCE have been reported previously.[8]).**

hindlimb (i.e., peripheral vasodilatation) was induced at the level of peripheral vessels as a site of action when 1,1,1-TCE concentrations exceeded 0.4–0.5% in inspired air. And we found that inhalation of 1,1,1-TCE concentrations which exceeded the threshold level resulted in a dose-dependent decrease in perfusion pressure in the hindlimb. Therefore, it is suggested that one site of action whereby 1,1,1-TCE decreases systemic blood pressure may exist in peripheral vessels.

It could not be clarified in this perfusion experiment whether systemic hypotension following 1,1,1-TCE inhalation is induced by vasodilatation only at the level of peripheral vessels as a site of action. Other sites of action involved in systemic hypotension may exist. To explore this possibility, the degree of the decrease in systemic blood pressure[8] and perfusion pressure were compaired following inhalation of various 1,1,1-TCE concentrations (Figs. 6 and 7). Relatively low concentrations (threshold to 1.0%) showed no significant dif-

ference between the decrease in systemic blood pressure and perfusion pressure. We suggest that the decrease in systemic blood pressure for relatively low 1,1,1-TCE concentration may be almost totally induced by vasodilatation at the level of peripheral vessels as a site of action. At higher concentrations (more than 1.0%), however, systemic blood pressure decreases more than perfusion pressure. It is presumed that this additional decrease in systemic blood pressure may be related to some other hypotensive mechanism besides vasodilatation at the level of peripheral vessels as a site of action. It has been reported that 1,1,1-TCE depresses the central nervous system;[1-4,7] however, a concentration of 1,1,1-TCE that induces peripheral vascular collapse originating from depression of the central nervous system has not been reported. Moreover, vasodilator effects at the level of peripheral vessels as a site of action may account for the decrease in blood pressure that was reported by Krantz et al.[7] Therefore, a comparison between the concentration of 1,1,1-TCE which induces vasodilatation directly, as indicated by our data, and that induces vasodilatation via depression of the central nervous system[1-4,7] could not be discussed. It is still uncertain, however, if this decrease in systemic blood pressure at a high 1,1,1-TCE concentration originates from an action of the central nervous system. Further investigations are needed to evaluate the effects of 1,1,1-TCE on central nervous system properties.

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TOXICOLOGY AND APPLIED PHARMACOLOGY 63, 409–421 (1982)

Effects of 1,2-Dichloroethane and 1,1,1-Trichloroethane in Drinking Water on Reproduction and Development in Mice[1]

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Effects of 1,2-Dichloroethane and 1,1,1-Trichloroethane in Drinking Water on Reproduction and Development in Mice. LANE, R. W., RIDDLE, B. L., AND BORZELLECA, J. F. (1982). *Toxicol. Appl. Pharmacol.* 63, 409–421. A multigeneration reproduction study was modified to include screening for dominant lethal and teratogenic effects of 1,2-dichloroethane (1,2-DCE) and 1,1,1-trichloroethane (1,1,1-TCE) in drinking solution (Emulphor:deionized water, 1:99, v/v). Male and female ICR Swiss mice received either 1,2-DCE at concentrations of 0, 0.03, 0.09, or 0.29 mg/ml or 1,1,1-TCE at concentrations of 0, 0.58, 1.75, or 5.83 mg/ml. These concentrations were designed to yield daily 1,2-DCE doses of 0, 5, 15, or 50 mg/kg and 1,1,1-TCE doses of 0, 100, 300, or 1,000 mg/kg. No taste aversion was evident for either of the chemicals at any concentration. There appeared to be no dose-dependent effects on fertility, gestation, viability, or lactation indices. Pup survival and weight gain were not adversely affected. 1,2-DCE and 1,1,1-TCE failed to produce significant dominant lethal mutations or terata in either of the two generations tested.

1,2-Dichloroethane (ethylene dichloride; 1,2-DCE) is used industrially as a solvent, chemical intermediate, and gasoline additive; it is used agriculturally as a fumigant of stored grains (IARC, 1979a). 1,1,1-Trichloroethane (methyl chloroform; 1,1,1-TCE) is used as a degreaser and chemical intermediate (IARC, 1979b). Both chemicals are found in drinking water (U.S. EPA, 1975). Because these chlorinated hydrocarbons are ubiquitous in the environment, men and women may be exposed to them during their reproductive years. A review of the literature revealed a paucity of data concerning the effects of these chemicals on reproduction.

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[2] Supported by NIEHS Training Grant IT32E507087.

[3] To whom requests for reprints should be addressed.

Human exposure to 1,2-DCE may result in central nervous system depression, anorexia, nausea, abdominal pain, and dysfunction of the hepatic, renal, and hematic systems (IARC, 1979a). 1,2-DCE is mutagenic in *Salmonella typhimurium* strains TA100, TA1530, and TA1535 and causes sex-linked recessive lethality in *Drosophila melanogaster* (IARC, 1979a; Rannung, 1980). No genetic effects were observed in *Aspergillus nidulans*, in various strains of *Escherichia coli*, or in the mouse micronucleus test (IARC, 1979a; Rannung, 1980). Metabolically activated 1,2-DCE binds to protein and to DNA (Banerjee *et al.*, 1980). 1,2-DCE administered by gavage to B6C3F1 mice (195 mg/kg/day for high-dose males and 299 mg/kg/day for high-dose females) for 78 weeks was tumorigenic (National Cancer Institute, 1978). Male and female Osborne Mendel rats receiving a high dose

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TABLE 1

PREPARATION OF DOSING SOLUTIONS

Compound	Group	Concentration (mg/ml)	Nominal dose[a] (mg/kg/day)
1,2-Dichloroethane[b] (1,2-DCE)	Naive control	DW[d]	0
	Emulphor vehicle control	0.00 in EDW[e]	0
	Low concentration	0.03 in EDW	5
	Mid concentration	0.09 in EDW	15
	High concentration	0.29 in EDW	50
1,1,1-Trichloroethane[c] (1,1,1-TCE)	Naive control	DW	0
	p-dioxane-Emulphor vehicle control	0.00 in 0.17 mg/ml *p*-dioxane in EDW	0
	Low concentration	0.58 in EDW	100
	Mid concentration	1.75 in EDW	300
	High concentration	5.83 in EDW	1,000

[a] Calculated on the basis of a 6 ml/mouse/day average fluid consumption for a 35-g mouse.
[b] Aldrich Chemical Co., Milwaukee, Wisc.; 99 + % pure.
[c] Aldrich Chemical Co., Milwaukee, Wisc.; 97% pure, inhibited with 3% *p*-dioxane.
[d] Deionized water.
[e] 1% Emulphor in DW.

of 95 mg/kg/day by gavage for 78 weeks also developed an increased incidence of squamous cell carcinomas in males, mammary gland adenocarcinomas and fibroadenomas in females, and hemangiosarcomas in both sexes (National Cancer Institute, 1978). The tumorigenic effects were not seen following lifetime inhalation exposure to 1,2-DCE (Maltoni, 1980, cited in Guengerich *et al.*, 1980). There is no indication of carcinogenicity in humans (IARC, 1979a). One reproduction study (Alumot *et al.*, 1976) concluded that there were no adverse effects on male or female rats that received 12.2 and 24.5 mg 1,2-DCE/kg/day in fumigated food from 6 weeks to 2 years. Another reproduction study (Rao *et al.*, 1980) found that 60 days of exposure (both males and females) to 15, 75, or 150 ppm of 1,2-DCE vapor produced no adverse effects in rats. The same group (Rao *et al.*, 1980) found that 100 and 300 ppm of 1,2-DCE vapor caused no teratogenic effects, even at maternally toxic doses, in rats and rabbits.

1,1,1-TCE causes central nervous system depression; hepatotoxicity has been reported only at doses near the LD_{50} (IARC, 1979b). 1,1,1-TCE is weakly mutagenic in *Salmonella typhimurium* TA100 with and without microsomal activation (Simmon *et al.*, 1977). There is no indication that 1,1,1-TCE is carcinogenic to mice, rats (National Cancer Institute, 1977), or humans (IARC, 1979b). No data on the reproductive effects of 1,1,1-TCE were found in the literature. Fetal development in mice and rats was not affected by 7 hr of exposure to 875 ppm 1,1,1-TCE on Days 6 to 15 or gestation (Schwetz *et al.*, 1975). Abnormal fetal development and fetal death were exhibited by chicks exposed to 5 to 100 μmol 1,1,1-TCE injected into the air space of the egg (Elovaara *et al.*, 1979).

No studies with either compound have been reported in which the drinking water was the method of exposure. The following studies were therefore performed to determine whether 1,2-DCE or 1,1,1-TCE would affect male or female reproductive function or fetal development when administered subchronically in the drinking water.

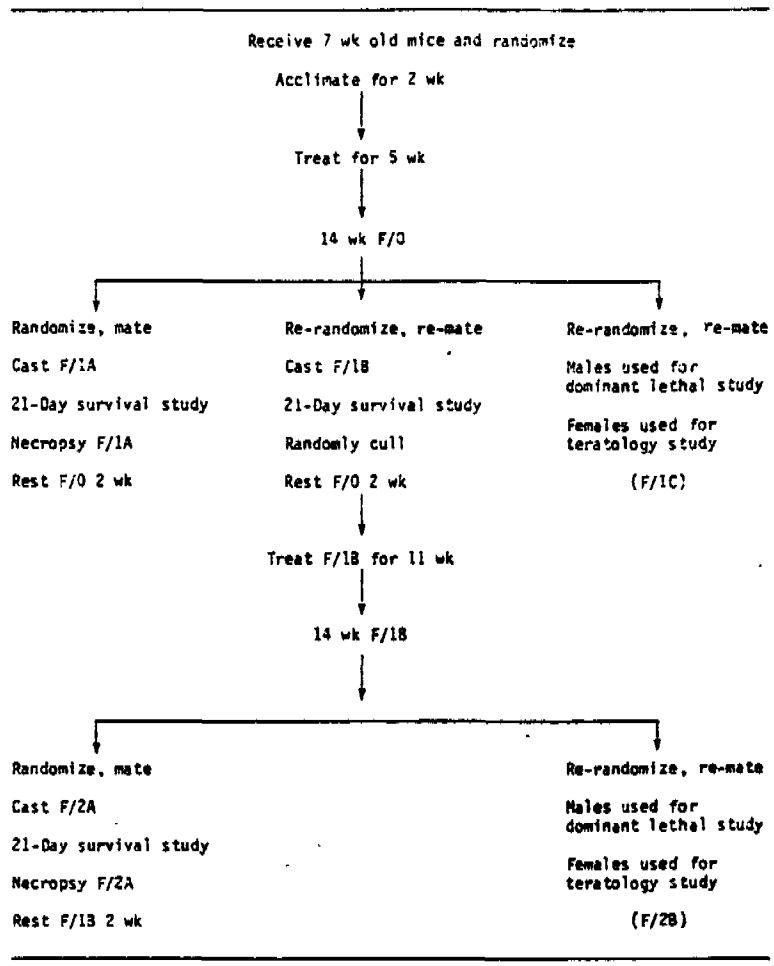

FIG. 1. Flowchart of the modified multigeneration/reproduction protocol used in this study.

METHODS

Animal husbandry. Seven-week-old ICR Swiss mice (Flow Laboratories, Dublin, Va.) were acclimated for 2 weeks, randomly assigned to groups, and marked by toe clipping. The mice were housed on sawdust bedding in polycarbonate cages. The environment was maintained at 22 to 23°C with 40 to 60% relative humidity and 12 hr of light per day. The mice were allowed food (Purina Rodent Laboratory Chow 5001) and drinking solution (see below) *ad libitum*. Males were housed singly; females were kept three per cage, except during parturition and lactation, when they were housed one per cage. Males and females were co-housed (1:3, respectively) for 7 days at each mating. Litters were weaned at 21 days of age.

Preparation of drinking solutions. 1,2-DCE (Aldrich Chemical Co., Milwaukee, Wisc.; 99+% pure) and 1,1,1-TCE (Aldrich Chemical Co., 97% pure, inhibited with 3% *p*-dioxane) were dissolved in a 1% solution of Emulphor EL-620 (GAF Corp., Linden, N.J.) in deionized water. This vehicle was necessary due to the limited solubility of the test materials in water. No aversion (decreased fluid consumption) to the vehicle or either haloalkane was observed. Fresh drinking solutions were prepared twice weekly, according to the specifications in Table 1, and were placed in 225-ml amber glass bottles with cork stoppers and stainless steel drinking tubes. Levels of 1,2-DCE and 1,1,1-TCE were based on acute male oral LD_{50} data (unpublished data). The highest concentration was chosen to provide a nominal daily dose (based on a 35-g adult mouse consuming 6 ml

TABLE 2

REPRODUCTIVE PERFORMANCE OF ADULT MICE INGESTING 1,2-DICHLOROETHANE OR 1,1,1-TRICHLOROETHANE

Compound	Concentration (mg/ml)	Litter					
		F/1A		F/1B		F/2A	
		FI[a]	GI[b]	FI	GI	FI	GI
1,2-Dichloroethane	0.00[c]	90.0	92.6	70.0	71.4	76.2	100.0
(1,2-DCE)	0.00[d]	93.3	82.1	76.7	78.2	86.2	96.0
	0.03	89.3	92.0	89.3	84.0	93.1	81.5
	0.09	82.8	83.3	62.1	94.4	82.8	100.0
	0.29	90.0	85.2	70.0	90.5	85.2	78.3
1,1,1-Trichloroethane	0.00[c]	90.0	92.6	73.3	90.9	85.2	82.6
(1,1,1-TCE)	0.00[e]	96.7	92.6	90.0	66.7	70.0	100.0
	0.58	96.7	89.7	82.7	87.5	84.6	90.9
	1.75	90.0	85.2	85.7	83.3	76.7	95.7
	5.83	82.8	75.0	85.2	78.3	94.4	100.0

[a] FI (Fertility Index) = (No. females pregnant/no. females mated) × 100.
[b] GI (Gestation Index) = (No. females with live litters/no. females pregnant) × 100.
[c] Naive control.
[d] 1% Emulphor vehicle control.
[e] 0.17 mg/ml *p*-dioxane in 1% Emulphor.

solution per day) approximately equal to 1/10th the LD_{50}. Mid and low doses, respectively, were one-half and one log unit lower than the high dose.

Experimental design. Figure 1 depicts the multigeneration reproduction study modified to include screening of dominant lethal and teratogenic effects. Test animals were continuously maintained on drinking solutions containing specified concentrations of 1,2-DCE and 1,1,1-TCE or on appropriate naive and vehicle control solutions (see Table 1). The F/0 mice were randomized by computer into test groups of 10 males and 30 females, acclimated for 2 weeks, and then placed on the appropriate test regimen. After 35 days on the test solutions, the 14-week old F/0 mice were randomly mated to produce the F/1A litters. Two weeks postweaning of the F/1A litters, the F/0 adults were rerandomized and remated to produce the F/1B litters. Parental stock for the second generation was drawn randomly from the F/1B litters. F/0 females were rested for 2 weeks, following weaning of the F/1B pups. The F/1C mating was for dominant lethal and teratology screening as described below.

At weaning, the F/1B litters were culled to 30 females and 10 males per group. Matings between siblings were avoided. The F/1B weanling mice were placed on appropriate test solutions, and at 14 weeks of age, were randomly mated to produce the F/2A litters. Two weeks postweaning of the F/2A pups, the F/1B adults were randomly remated (F/2B mating) for dominant lethal and teratology screening.

Adult observations. Weekly body weight and twice-weekly fluid consumption data were collected for the F/0 and F/1B adult mice throughout the study. Using the Statistical Analysis System (Raleigh, N.C.), mean daily fluid consumption per mouse was calculated and analyzed for significant ($p \leq 0.05$) group differences with Duncan's multiple range test. Mean body weights were analyzed similarly.

Adult reproductive performance was evaluated by calculation of fertility and gestation indices (FI and GI, respectively; Collins, 1977).

Adult percentage mortality was calculated at the termination of each generation (25 weeks of dosing for the F/0; 24 for the F/1B). Mice found moribund or sacrificed at the end of the study were necropsied.

Litter observation. Twenty-one-day survival studies were performed on litters from the F/1A, F/1B, and F/2A matings. Litter size was recorded on Days 0, 4, 7, 14, and 21. Litters were randomly culled to 10 pups each on Day 4 (Collins, 1977). Offspring were weighed collectively on Days 7 and 14 and individually on Day 21. Viability and lactation indices (VI and LI, respectively; Collins, 1977; Fitzhugh, 1968) were calculated. The statistical sampling unit for litter survival studies was the litter (Gaylor, 1977). Litter size and viability and lactation indices were tested for group effects by

TABLE 3

MORTALITY AMONG ADULT MALES AND FEMALES INGESTING 1,2-DICHLOROETHANE OR 1,1,1-TRICHLOROETHANE

Compound	Concentration (mg/ml)	F/0 percentage mortality[a]		F/1B percentage mortality[b]	
		Males	Females	Males	Females
1,2-Dichloroethane (1,2-DCE)	0.00[c]	0.0	3.3	20.0	7.4
	0.00[d]	0.0	3.3	0.0	0.0
	0.03	20.0	13.3	0.0	3.3
	0.09	0.0	6.7	0.0	3.3
	0.29	0.0	0.0	0.0	0.0
1,1,1-Trichloroethane (1,1,1-TCE)	0.00[c]	20.0	20.0	0.0	0.0
	0.00[e]	10.0	3.3	0.0	0.0
	0.58	0.0	10.0	0.0	7.4
	1.75	10.0	6.7	0.0	0.0
	5.83	20.0	13.3	0.0	0.0

[a] After 25 weeks of dosing.
[b] After 24 weeks of dosing.
[c] Naive control.
[d] 1% Emulphor vehicle control.
[e] 0.17 mg/ml *p*-dioxane in 1% Emulphor.

the Kruskal–Wallis χ^2 approximation; effects were localized by Dunn's approximation to a distribution-free multiple comparison (Hollander and Wolfe, 1973). Mean pup weights were analyzed in the same manner as the adult body weights.

All pups from each litter were sacrificed and necropsied at the conclusion of each 21-day survival study.

Dominant lethal screening. In the F/1C and F/1B matings, treated males were co-housed 1:3 with 9-week-old naive, nulliparous females for 7 days (Green *et al.*,

TABLE 4

MEAN LITTER SIZE AT BIRTH[a] FOR LITTERS OF MICE INGESTING 1,2-DICHLOROETHANE OR 1,1,1-TRICHLOROETHANE

Compound	Concentration (mg/ml)	Litter		
		F/1A	F/1B	F/2A
1,2-Dichloroethane (1,2-DCE)	0.00[b]	13.1 ± 3.2	13.1 ± 4.5	11.8 ± 2.4
	0.00[c]	12.0 ± 2.3	12.1 ± 3.0	12.2 ± 2.1
	0.03	13.2 ± 3.2	12.5 ± 4.1	11.3 ± 3.8
	0.09	12.9 ± 2.7	10.5 ± 4.4	12.3 ± 2.7
	0.29	11.4 ± 2.7	10.4 ± 4.8	12.6 ± 1.9
1,1,1-Trichloroethane (1,1,1-TCE)	0.00[b]	12.7 ± 2.4	11.4 ± 4.1	12.8 ± 2.3
	0.00[d]	12.1 ± 3.5	13.3 ± 4.3	11.3 ± 3.4
	0.58	11.8 ± 2.4	11.2 ± 4.8	12.2 ± 2.5
	1.75	12.0 ± 3.1	10.3 ± 5.2	12.9 ± 2.2
	5.83	11.8 ± 3.1	10.6 ± 4.1	12.1 ± 2.2

[a] Mean pups per litter ± SD.
[b] Naive control.
[c] 1% Emulphor vehicle control.
[d] 0.17 mg/ml *p*-dioxane in 1% Emulphor.

TABLE 5

MEAN POSTNATAL BODY WEIGHTS[a] OF OFFSPRING OF MICE INGESTING 1,2-DICHLOROETHANE OR 1,1,1-TRICHLOROETHANE

	Litter								
	F/1A			F/1B			F/2A		
	Day 7	Day 14	Day 21	Day 7	Day 14	Day 21	Day 7	Day 14	Day 21
1,2-DCE concentration (mg/ml)									
0.00[b]	4.8 ± 1.0	7.1 ± 1.3	11.0 ± 2.4	4.8 ± 0.8	7.7 ± 1.5	12.0 ± 1.5	3.7 ± 1.2	5.2 ± 2.2	7.1 ± 3.3
0.00[c]	4.8 ± 0.5	7.5 ± 0.7	11.5 ± 1.5	5.0 ± 0.5	8.0 ± 0.7	12.7 ± 4.1	4.0 ± 0.6	5.7 ± 1.5	7.6 ± 2.9
0.03	4.8 ± 0.5	7.1 ± 0.8	10.5 ± 1.8	5.0 ± 0.4	7.9 ± 0.7	12.2 ± 1.3	4.7 ± 0.9	7.0 ± 1.6	9.7 ± 2.9
0.09	4.7 ± 0.7	7.4 ± 1.1	10.9 ± 1.8	5.0 ± 0.8	7.6 ± 1.0	11.0 ± 2.2	3.7 ± 1.1	5.3 ± 2.0	7.1 ± 2.7
0.29	5.1 ± 0.6	7.1 ± 0.9	10.7 ± 1.7	4.9 ± 0.7	7.8 ± 1.4	11.0 ± 2.3	4.4 ± 0.5	6.6 ± 0.9	8.9 ± 1.1
1,1,1-TCE concentration (mg/ml)									
0.00[b]	4.8 ± 1.0	7.5 ± 1.3	10.9 ± 2.4	5.2 ± 1.9	8.7 ± 2.1	13.1 ± 3.6	3.8 ± 0.7	5.5 ± 1.7	7.5 ± 2.9
0.00[d]	4.8 ± 0.5	7.5 ± 0.7	11.5 ± 1.5	4.8 ± 0.4	7.1 ± 0.8	10.4 ± 1.3	3.6 ± 0.5	5.7 ± 1.1	7.1 ± 2.1
0.58	4.8 ± 0.5	7.1 ± 0.8	10.5 ± 1.8	4.8 ± 1.0	7.8 ± 1.5	11.5 ± 2.7	3.9 ± 0.7	5.5 ± 0.9	7.5 ± 1.4
1.75	4.7 ± 0.7	7.4 ± 1.1	10.9 ± 1.8	5.0 ± 0.8	8.1 ± 1.1	11.6 ± 2.1	3.9 ± 1.1	6.0 ± 1.7	8.0 ± 2.6
5.83	5.1 ± 0.6	7.1 ± 0.9	10.7 ± 1.7	4.7 ± 0.6	7.0 ± 0.6	10.3 ± 1.5	3.9 ± 1.2	5.9 ± 2.0	7.9 ± 3.0

[a] Mean pup body weight (g) ± SD.
[b] Naive control.
[c] 1% Emulphor vehicle control.
[d] 0.17 mg/ml p-dioxane in 1% Emulphor.

1977). Females were sacrificed 14 days from the mid-week of co-housing, their uteri were exposed, and the number of fetal implants, early and late resorptions, and viable fetuses were counted. Females without implantations were disregarded except for calculation of the fertility index (FI; Collins, 1977). These data were used to calculate a number of reproductive indices (see Tables 7a and b), as well as the frequency of dominant lethal factors (Ehling *et al.*, 1978). Statistical analyses of the dominant lethal reproductive indices were performed using two by two contingency tables, with a correction for continuity.

Teratology screening. Also in the F/1C and F/1B matings, the treated females were co-housed 3:1 with 9-week-old naive males for 7 days. Females were examined each morning for copulation plugs. The discovery of a vaginal plug marked Day 0 of gestation. Failure to find a vaginal plug during the week of mating disqualified the female from the teratology screening. Females were sacrificed on the 18th day of gestation, their uteri were exposed, and the number of implants, resorptions, and viable and nonviable males and females were counted. Fetuses were individually weighed and examined for gross defects. In the event that no gross malformations were found, every third fetus was fixed in Bouin's fluid for subsequent serial sectioning and examination for visceral anomalies. The remainder of the fetuses were prepared for skeletal visualization by evisceration, removal of soft tissue in 1% KOH, and staining with aqueous alizarin red S (Barrow and Taylor, 1969; Wilson, 1965). The number of visceral and skeletal malformations were tabulated. Appropriate statistical tests were performed (Gaylor, 1977).

RESULTS

Adult Findings

Statistical analysis indicated no significant treatment-related reduction in mean daily fluid consumption by the test animals receiving either haloalkane. Body weights of F/0 male and female animals treated with 1,2-DCE and 1,1,1-TCE were not affected by either compound (data not shown). F/1B body weights for 1,2-DCE- and 1,1,1-TCE-treated mice (data not shown) also demonstrated no compound or dose-related effects. The difference between F/0 high concentration 1,1,1-TCE-treated and control female mean body weights following the F/1A mating appeared to be due to a fluctuation in the fertility index of the high-dose group

TABLE 6

SURVIVAL INDICES FOR LITTERS OF MICE INGESTING 1,2-DICHLOROETHANE OR 1,1,1-TRICHLOROETHANE[a]

Compound	Concentration (mg/ml)	Litter F/1A VI[b]	F/1A LI[c]	F/1B VI	F/1B LI	F/2A VI	F/2A LI
1,2-Dichloroethane	0.00[d]	97.2	94.8	96.9	90.4	88.5	86.3
(1,2-DCE)	0.00[e]	97.5	98.2	94.0	94.4	89.6	81.3
	0.03	98.1	97.8	96.7	96.4	91.8	95.0
	0.09	94.3	97.5	97.0	99.0	89.6	86.8
	0.29	93.0	97.2	93.1	97.7	92.3	89.6
1,1,1-Trichloroethane	0.00[d]	92.3	97.0	96.4	97.2	92.3	76.4
(1,1,1-TCE)	0.00[f]	94.1	97.4	90.2	94.0	92.3	87.5
	0.58	97.4	97.5	91.8	85.5	88.0	88.0
	1.75	85.9	93.2	94.1	94.0	89.6	83.0
	5.83	91.3	95.7	89.6	92.1	83.0	80.0

[a] The F/1C and F/2B pregnancies were interrupted for dominant lethal and teratology studies.

[b] VI (viability index) = $\sum_{i=1}^{N}\left[\frac{(\text{Day 4 litter size})i}{(\text{Day 0 litter size})i}\right]/N$; N = No. litters

[c] LI (lactation index) = $\sum_{i=1}^{N}\left[\frac{(\text{Day 21 litter size})i}{(\text{pups kept at Day 4})i}\right]/N$; N = No. litters. Pups kept at Day 4 ≤ 10.

[d] Naive control.

[e] 1% Emulphor vehicle control.

[f] 0.17 mg/ml *p*-dioxane in 1% Emulphor.

(Table 2). That is, the smaller percentage of pregnant females in the high concentration group skewed their mean body weight. This gap in mean body weights was narrowed in subsequent weeks. Fertility and gestation indices are presented in Table 2. Adult mortality is summarized in Table 3. The reason for the sporadic incidences of increased mortality could not be discerned at necropsy. At scheduled necropsy (after Week 24 or 25 of dosing), neither chemical- nor dose-related gross pathology was observed in either generation.

Litter Findings

Data from the three 21-day litter survival studies (F/1A, F/1B, and F/2A) are shown in Tables 4 to 6. 1,2-DCE and 1,1,1-TCE appeared to produce no significantly adverse intragenerational or transgenerational effects on mean litter size at birth (Table 4), mean postnatal body weights (Table 5), or birth to Day 4 survival and Days 4 to 21 survival (Table 6). Values of the F/2A postnatal body weights (Table 5) and survival indices (Table 6) were decreased from the F/1A and F/1B values with few exceptions. The reason for this decrease is not known. The decrease occurred among all groups, so it is not believed to be treatment related. Necropsies of weanling male and female pups from each litter yielded no evidence of dose-dependent gross pathology or congenital malformations for either haloalkane.

Dominant Lethal Screening

Findings from the dominant lethal screenings of both chemicals are listed in Tables

TABLE 7a

RESULTS OF DOMINANT LETHAL SCREENING IN FEMALES MATED TO MALES INGESTING 1,2-DICHLOROETHANE

	Concentration (mg/ml)	Number pregnant	Fertility index[a]	Implants[b]	Resorptions[b]	Live fetuses[b]	DF/LF	DF ≥ 1	DF ≥ 2	FL%
F/1C	0.00[c]	17	56.7	14.1	1.4	12.7	23/216	9/8	6/11	
Mating	0.00[d]	19	63.3	14.0	0.7	13.3	13/252*	11/8	2/17	−1.89
	0.03	16	66.6	14.0	1.6	12.4	26/198*	8/8	1/15	2.60
	0.09	23	76.7	14.5	0.9	13.6	21/312	16/7	5/18	−6.77
	0.29	17	56.7	13.2	0.6	12.5	11/213	7/10	2/15	1.42
F/2B	0.00[c]	15	62.5	12.2	1.0	11.2	15/168	3/12	1/14	
Mating	0.00[d]	25	83.3	11.6	0.8	10.8	19/271	9/16	3/22	3.21
	0.03	27	90.0	12.3	0.9	11.4	23/309	14/13	5/22	−2.14
	0.09	24	80.0	12.0	1.7	10.3	40/247*	12/12	5/19	8.13
	0.29	16	63.3	10.9	0.1	10.8	2/172*	2/14	0/16	4.02

TABLE 7b

RESULTS OF DOMINANT LETHAL SCREENING IN FEMALES MATED TO MALES INGESTING 1,1,1-TRICHLOROETHANE

	Concentration (mg/ml)	Number pregnant	Fertility index[a]	Implants[b]	Resorptions[b]	Live fetuses[b]	DF/LF	DF ≥ 1	DF ≥ 2	FL%
F/1C	0.00[c]	14	58.3	13.9	1.0	12.9	14/181	7/7	4/10	
Mating	0.00[e]	22	81.5	13.2	1.9	11.3	41/248*	14/8	8/14	12.77
	0.58	19	63.3	13.2	0.7	12.5	13/238*	9/10	2/17	3.02
	1.75	21	77.8	12.8	0.7	12.1	15/254*	8/13	5/16	6.35
	5.83	15	50.0	13.7	0.9	12.8	13/192*	8/7	5/10	0.93
F/2B	0.00[c]	17	56.7	12.6	1.1	11.5	19/196	11/6	5/12	
Mating	0.00[e]	19	63.3	11.8	0.6	11.3	11/214	10/9	1/18	2.34
	0.58	27	90.0	12.1	1.3	10.8	35/292*	10/17	6/21	6.24
	1.75	28	93.3	11.9	0.8	11.2	21/313	12/16	4/24	3.04
	5.83	25	83.3	12.0	0.7	11.3	17/283	12/13	4/21	1.82

[a] Indices defined:

$$\text{Fertility index} = \frac{\text{number of females pregnant}}{\text{number of females available}} \times 100;$$

$$\text{DF/LF} = \frac{\text{total number of dead fetuses}}{\text{total number of live fetuses}};$$

$$\text{DF} \geq 1 = \frac{\text{total number of females with one or more dead fetuses}}{\text{total number of females with zero dead fetuses}};$$

$$\text{DF} \geq 2 = \frac{\text{total number of females with two or more dead fetuses:}}{\text{total number of females with less than two dead fetuses}};$$

$$\text{FL\% (frequency of dominant lethal factors)} = \left[1 - \left(\frac{\text{mean live fetuses, treatment}}{\text{mean live fetuses, naive}}\right)\right] \times 100 \text{ (Ehling } et\ al.\text{, 1978).}$$

[b] Mean value per dam.

[c] Naive control.

[d] 1% Emulphor vehicle control.

[e] 0.17 mg/ml *p*-dioxane in 1% Emulphor.

* Significantly different from control at $p \leq 0.05$. Vehicle controls were compared to naive controls; treatment groups were compared with their vehicle controls.

TABLE 8a

RESULTS OF TERATOLOGY SCREENING IN FEMALES INGESTING 1,2-DICHLOROETHANE

	Concentration (mg/ml)	No. of litters	Fecundity index[a]	Implants[b]	Resorptions[b]	Live fetuses[b]	DF/LF[a]	DF ≥ 1[a]	DF ≥ 2[a]	M:F[a]
F1/C mating	0.00[c]	9	90.0	12.0	1.8	10.2	16/92	4/5	1/8	49:51
	0.00[d]	8	100.0	12.1	5.6	6.5	47/51*	6/2	6/2*	59:41
	0.03	10	100.0	14.9	2.5	12.4	25/121*	6/4	5/5	48:52
	0.09	6	100.0	13.8	5.3	8.5	32/51	5/1	3/3	48:52
	0.29	8	80.0	13.4	1.0	12.4	8/99*	3/5	2/6	43:57
F/2B mating	0.00[c]	9	100.0	14.1	1.0	13.1	9/118	7/2	2/7	47:53
	0.00[d]	6	100.0	14.5	2.7	11.8	17/71*	3/3	2/4	39:61
	0.03	4	100.0	16.0	0.8	15.2	3/61*	2/2	1/3	57:43
	0.09	9	100.0	13.1	2.7	10.5	24/94	5/4	2/7	46:54
	0.29	6	85.7	13.0	0.7	12.3	5/74*	5/1	0/6	49:51

TABLE 8b

RESULTS OF TERATOLOGY SCREENING IN FEMALES INGESTING 1,1,1-TRICHLOROETHANE

	Concentration (mg/ml)	No. of litters	Fecundity index[a]	Implants[b]	Resorptions[b]	Live fetuses[b]	DF/LF[a]	DF ≥ 1[a]	DF ≥ 2[a]	M:F[a]
F/1C mating	0.00[c]	5	100.0	13.8	0.8	13.0	4/65	2/3	2/3	52:48
	0.00[e]	4	100.0	16.3	0.5	15.8	2/63	1/3	1/3	46:54
	0.58	0	—	—	—	—	—	—	—	—
	1.75	9	100.0	14.3	4.9	9.4	44/85*	7/2	5/4	49:51
	5.83	5	71.4	12.2	2.2	10.0	11/50*	4/1	4/1	62:38
F/2B mating	0.00[c]	4	100.0	14.5	1.5	13.0	6/53	3/1	1/3	46:54
	0.00[e]	5	83.3	15.0	1.0	14.0	5/70	4/1	1/4	54:46
	0.58	11	100.0	14.1	1.5	12.6	16/140	7/4	1/10	41:59
	1.75	6	75.0	15.7	3.0	12.7	18/77*	2/4	1/5	43:57
	5.83	5	100.0	15.2	1.8	13.4	9/67	5/0	2/3	34:66

[a] Indices defined: *Fecundity index* = percentage of copulation plug-positive females bearing live fetus(es) at sacrifice. For definitions of DF/LF, DF ≥ 1, and DF ≥ 2 see footnotes to Table 7. M:F = ratio of live male to female fetuses expressed as a percentage of the total number of live fetuses.

[b] Mean value per dam.

[c] Naive control.

[d] 1% Emulphor vehicle control.

[e] 0.17 mg/ml *p*-dioxane in 1% Emulphor.

* Significantly different from control at $p \leq 0.05$. Vehicle controls were compared to naive controls; treatment groups were compared with their vehicle controls.

7a and b. Statistically significant effects in the ratio of dead to live fetuses (DF/LF) were observed in both generations for both compounds. However, these effects, which were both increases and decreases compared to controls, do not appear to be dose related. In two cases, greater effects were seen among the vehicle control groups than among the treated groups. The frequency of dominant lethal factors (F_L%; Ehling *et al.*, 1978) for both chloroalkanes in both generations was minimal (−7 to +12) when compared to the results in females mated to males receiving 0.05 mg/ml cyclophosphamide in drinking water for 14 weeks (F_L%, cyclophosphamide = 62, data not shown).

TABLE 9a

DISTRIBUTION OF VISCERAL AND SKELETAL MALFORMATIONS AMONG FETUSES/LITTERS OF FEMALES INGESTING 1,2-DCE

	F/1C litters					F/2B litters				
Conc. (mg/ml):	0.00[a]	0.00[b]	0.03	0.09	0.29	0.00[a]	0.00[b]	0.03	0.09	0.29
Total No. fetuses/total No. litters:	92/9	51/8	121/10	51/6	99/8	118/9	71/6	61/9	94/9	74/6
Visceral malformations										
Total number examined	33/8	19/7	46/9	18/4	29/7	38/9	24/5	20/4	29/8	24/6
Hydrocephalus	0/0	0/0	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Cleft palate	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Atrial, ventricular, or cardiac hypertrophy	0/0	0/0	1/1	0/0	0/0	0/0	1/1	0/0	1/1	0/0
Malrotation of the heart	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Hydronephrosis	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Dilated renal pelvis	0/0	1/1	0/0	2/1	1/1	1/1	0/0	0/0	0/0	0/0
Dilated bladder	0/0	0/0	0/0	0/0	0/0	0/0	0/0	1/1	0/0	0/0
Cryptorchidism/malpositioned testis	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Skeletal malformations										
Total number examined			(c)			80/9	47/5	41/4	65/8	50/6
Dysplastic skull						0/0	0/0	0/0	0/0	1/1
Dysplastic supraoccipital region						3/2	3/2	0/0	2/2	1/1
Microagnathia						0/0	0/0	0/0	0/0	0/0
Asymetric sternebrae						24/6	9/4	2/2	9/5	16/6
Bifid sternebrae						8/3	1/1	7/2	4/3	5/3
Hypoplastic sternebrae						3/1	0/0	0/0	0/0	1/1
Extra ribs						2/2	1/1	0/0	2/2	2/2
Wavy ribs						0/0	0/0	0/0	1/1	0/0

[a] Naive control.
[b] 1% Emulphor vehicle control.
[c] F/1C skeletal specimens were lost due to a preparation error.

Teratology Screening

Maternal ingestion of 1,2-DCE or 1,1,1-TCE produced no apparent adverse reproductive effects (Tables 8a and b) or increased incidence of fetal visceral or skeletal anomalies (Tables 9a and b). No F/1C females consuming the lowest dose of 1,1,1-TCE were found with copulation plugs. Although some females did become pregnant, it was impossible to ascertain when pregnancy began and, hence, no teratological examinations were performed on this group.

DISCUSSION

1,2-DCE and 1,1,1-TCE are industrially important chemicals which also are found in the drinking water. Since people of reproductive age may be exposed to these materials, an evaluation of the effects of 1,2-DCE and 1,1,1-TCE on reproduction and development was indicated. Mice were exposed for a minimum of 6 weeks prior to the initiation of mating. The total duration of exposure for the F/O and F/1B adults, respectively, was 25 and 24 weeks. Adult re-

TABLE 9b

DISTRIBUTION OF VISCERAL AND SKELETAL MALFORMATIONS AMONG FETUSES/LITTERS OF FEMALES INGESTING 1,1,1-TCE

	F/1C litters					F/2B litters				
Conc. (mg/ml):	0.00[a]	0.00[b]	0.58	1.75	5.83	0.00[a]	0.00[b]	0.58	1.75	5.83
Total No. fetuses/total No. litters:	65/5	63/4	0/0[c]	85/9	50/5	53/4	70/5	140/11	77/6	67/5
Visceral malformations										
Total number examined	23/5	22/4	—	29/7	18/5	18/4	23/5	49/10	27/5	23/5
Hydrocephalus	0/0	0/0	—	1/1	0/0	0/0	0/0	0/0	0/0	0/0
Cleft palate	0/0	0/0	—	0/0	1/1	0/0	0/0	0/0	0/0	0/0
Atrial, ventricular, or cardiac hypertrophy	0/0	0/0	—	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Malrotation of the heart	0/0	0/0	—	0/0	0/0	0/0	0/0	1/1	0/0	0/0
Hydronephrosis	0/0	0/0	—	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Dilated renal pelvis	1/1	0/0	—	1/1	0/0	1/1	0/0	1/1	0/0	0/0
Dilated bladder	0/0	0/0	—	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Cryptorchidism/malpositioned testis	0/0	0/0	—	2/2	0/0	0/0	0/0	1/1	0/0	0/0
Skeletal malformations										
Total number examined			(d)			35/4	47/5	91/10	50/5	44/5
Dysplastic skull						1/1	0/0	1/1	0/0	0/0
Dysplastic supraoccipital region						1/1	0/0	0/0	0/0	4/1
Micrognathia						0/0	1/1	1/1	0/0	0/0
Asymetric sternebrae						16/4	13/3	16/9	15/5	8/3
Bifid sternebrae						1/1	2/1	10/5	4/3	2/1
Hypoplastic sternebrae						2/1	1/1	1/1	0/0	1/1
Extra ribs						0/0	0/0	0/0	1/1	0/0
Wavy ribs						0/0	0/0	0/0	1/1	0/0

[a] Naive control.
[b] 0.17 mg/ml *p*-dioxane in 1% Emulphor.
[c] There were no plug-positive females in this group.
[d] F/1C skeletal specimens were lost due to a preparation error.

productive performance, litter survival and growth, dominant lethal effects, teratogenesis, and general pathology were evaluated.

No dose of 1,2-DCE produced deleterious effects on male or female reproductive function or on offspring development. These negative findings contrast with the genetic toxicity demonstrated by 1,2-DCE (see Introduction) and with the severe reproductive toxicity demonstrated by a close structural analog, 1,2-dibromoethane (Rannung, 1980). The results presented for 1,2-DCE support the findings of Alumot *et al.* (1976) and Rao *et al.* (1980) for different routes of administration.

The results for 1,1,1-TCE were also uniformly negative at the concentrations tested. The 1,1,1-TCE teratological findings of this study agree with those obtained by Schwetz *et al.* (1975) in both mice and rats exposed to 875 ppm 1,1,1-TCE for 7 hr per day on Days 6 to 15 of gestation. Calculations indicate that the inhalation dose (mg/kg/day) was in the range of the low to the middle

doses used in the present drinking water study.

EPA-reported mean concentration drinking water levels for 1,2-DCE and 1,1,1-TCE are 4.3 and 1.5 ppb, respectively (U.S. EPA, 1975). For a 70-kg man consuming 2 liters of water per day, these concentrations represent doses of 1×10^{-4} mg 1,2-DCE/kg/day and 4×10^{-5} mg 1,1,1-TCE/kg/day. Using the highest concentration of each haloalkane available to a 35-g mouse consuming 6 ml/day, a mouse would receive 50 mg 1,2-DCE/kg/day or 1000 mg 1,1,1-TCE/kg/day. The highest doses of 1,2-DCE and 1,1,1-TCE administered to mice in the present study are approximately five and seven orders of magnitude, respectively, greater than the potential average human dose (assuming exposure by the drinking water only). These differences between average animal and human exposures are well above the "safety factor" of two orders of magnitude generally used when extrapolating from a highest no-observed-effect level in animals to man.

On the basis of these results and other published reports, it is concluded that the concentrations of 1,2-dichloroethane and 1,1,1-trichloroethane in the drinking water pose little hazard to human reproduction and development.

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