TOXICITY INFORMATION: METHYL CHLOROFORM Ch_3CCl_3

Acute Toxicity:

1,1,1-Trichloroethane, (methyl chloroform), has been reported to produce a functional (narcotic) depression of the C.N.S., possibly resulting in fatal respiratory depression. Ventricular arrhythmia may be induced with sensitization to epinephrine. Permanent liver and kidney damage is unknown.

Eye contact can result in discomfort, pain and mild conjunctivitis. While 1,1,1-Trichloroethane has been reported to be poorly absorbed through the skin, it does have skin defatting properties.

Lethal doses have been calculated to be:

Oral LD_{50} (rabbit, Guinea pig)-- 5.6 - 9.5 gm/kg
LD_{50} (Rat)-- 10 - 12 gm/kg
Inhalation LC_{50} (Rat)-- 8,000 ppm/7 hr.

In man, incoordination, as well as other effects, has been reported at 800 to 1,000 ppm. Concentrations around 30,000 ppm may be lethal in five to six minutes. Eye irritation has be reported at 500 ppm in man.

Chronic Toxicity:

Torkelson, et. al. (1959) has reported that female guinea pigs had slight inflammation of lungs and fatty changes in liver at chronic exposure concentrations of 2,000 ppm. Other information on chronic toxicity is sketchy if not nonexistent.

Properties:

Volatile, colorless liquid with aromatic chloroform-like odor. Odor threshold reported to be between 20--100 ppm.

Molecular weight is 133.42, vapor pressure 125 mm Hg at 25°C.

Except for inhibited methyl chloroform, no flash point has been reported.

Thermal decomposition may product toxic concentrations of chlorine, HCl and phosgene.

Noninhibited methyl chloroform should not be used with aluminum due to its reactivity.

This information has been prepared from informations in the following publications:

Industrial Toxicology, Hamilton/Hardy, 1974
Toxicity and Metabolism of Industrial Solvents, Browning, 1965
Toxicology, the Basic Science of Poisons, Casarett/Doull, 1975
Registry of Toxic Effects of Chemical Substances, NIOSH, 1975

Copy To RLF

KI94500. ETHANETHIOIC ACID
CAS 000507095 MW: 76.12 MOLFM O S-C2-H4
WLN SHV1
SYN: ACETIC ACID, THIO- * ETHANETHIOLIC ACID * METHANECARBOTHIOLIC ACID * THIACETIC ACID * THIOACETIC ACID * THIOLACETIC ACID *
TXDS ipr-mus LDLo:750 mg/kg NTIS** AD691-490

ETHANETHIOIC S-ACID, 2-FLUOROETHYL ESTER see AJ75250 ACETIC ACID, THIO-, S-(2-FLUOROETHYL) ESTER

ETHANETHIOIC S-ACID, 4-FLUOROBUTYL ESTER see AJ69000 ACETIC ACID, THIO-, S-(4-FLUOROBUTYL) ESTER

KI96250. ETHANETHIOL
CAS 000075081 MW 62.14 MOLFM: S-C2-H6
WLN: SH2
SYN AETHANETHIOL (German) * AETHYLMERCAPTAN (German) * ETANTIOLO (Italian) * ETHAANTHIOL (Dutch) * ETHYL HYDROSULFIDE * ETHYLMERCAPTAAN (Dutch) * ETHYL MERCAPTAN * ETHYL SULFHYDRATE * ETHYL THIOALCOHOL * ETILMERCAPTANO (Italian) * THIOETHANOL * THIOETHYL ALCOHOL *
TXDS: ihl-hmn TCLo 4 ppm TFX CNS DTLVS*
orl-rat LD50 682 mg/kg AIHAAP 19,171,58
ihl-rat LC50 4420 ppm/4H AIHAAP 19,171,58
ipr-rat LD50 450 mg/kg AIHAAP 19,171,58
ihl-mus LC50 2770 mg/kg AIHAAP 19,171,58
U S OCCUPATIONAL STANDARD USOS- FEREAC 37,22139,72
air CL10 ppm

ETHANETHIOL, 2-(ACETYLAMINO)- see: AC46200 ACETAMIDE, N-(beta-MERCAPTOETHYL)-

KJ01750. ETHANETHIOL, 2-AMINO-
CAS 000060231 MW: 77.16 MOLFM N-S-C2-H7
WLN: Z2SH
SYN 2-AMINOETHANETHIOL * 2-AMINOETHYL MERCAPTAN * BECAPTAN * CYSTEAMINE * CYSTEINAMINE * DECARBOXYCYSTEINE * LAMBRATEN * MERCAMINE * MERCAPTAMINE * beta-MERCAPTOETHYLAMINE * (2-MERCAPTOETHYL)AMINE * THIOETHANOLAMINE *
TXDS: ipr-mus LD50 305 mg/kg BCPCA6 14,289,65
scu-mus LD50:247 mg/kg AIPTAK 109,108,57

KJ03500. ETHANETHIOL, 2-CHLORO-
CAS: 004325977 MW: 96.58 MOLFM S-Cl-C2-H5
WLN SH2G
TXDS: ivn-cat LD50 25 mg/kg NDRC** -,118,43

KJ04300. ETHANETHIOL, 2-CYANO-
MW 87.15 MOLFM N-S-C3-H5
SYN: beta-CYANOETHYLMERCAPTAN * ETHANE, 1-CYANO-2-MERCAPTO *
TXDS ipr-mus LD50:100 mg/kg NTIS** AD691-490

KJ05250. ETHANETHIOL, 2-(DIETHYLAMINO)-
CAS 000100389 MW 133.28 MOLFM N-S-C6-H15
WLN SH2N2&2
SYN: N-DIATHYL CYSTEAMIN (German) * N-DIETHYL CYSTEAMINE * N,N-DIETHYL-CYSTEAMINE *
TXDS ipr-mus LD50:96 mg/kg BCPCA6 14,289,65
scu-mus LD50 120 mg/kg AIPTAK 109,108,57

KJ07000. ETHANETHIOL, 2-(DIETHYLAMINO)-, HYDROCHLORIDE
CAS 001942525 MW 169.74 MOLFM N-S-C6-H15 .Cl-H
WLN: SH2N2&2 &GH
TXDS ipr-mus LDLo 100 mg/kg CURL** -,9,62

KJ08750 ETHANETHIOL, DIISOPROPYLAMINO
TXDS ipr-mus LDLo 5 mg/kg CURL** -,9,62

KJ10500. ETHANETHIOL, 2-(DIMETHYLAMINO)-
CAS 000108021 MW: 105.22 MOLFM N-S-C4-H11
WLN SH2N1&1
SYN N-DIMETHYL CYSTEAMIN (German) * N-DIMETHYL CYSTEAMINE *
TXDS scu-mus LD50:214 mg/kg AEPPAE 225,428,55

ETHANETHIOL, 2-(ETHYLSULFINYL)-, S-ESTER with O,O-DIETHYL PHOSPHORODITHIOATE see TD85750PHOSPHORODITHIOIC ACID, O,O-DIETHYL S-(2-(ETHYLSULFINYL)ETHYL)ESTER

ETHANETHIOL, 2-(ETHYLSULFINYL)-, S-ESTER with O,O-DIMETHYL PHOSPHOROTHIOATE see TG14200PHOSPHOROTHIOIC ACID, S-(2-(ETHYLSULFINYL)ETHYL) O,O-DIMETHYL ESTER

ETHANETHIOL, 2-(ETHYLSULFONYL)-, S-ESTER with O,O-DIETHYL PHOSPHORODITHIOATE see: TD89250PHOSPHORODITHIOIC ACID, O,O-DIETHYL S-(2-(ETHYLSULFONYL)ETHYL)ESTER

ETHANETHIOL, 2-(ETHYLTHIO)-, S-ESTER with O,O-DIETHYL PHOSPHORODITHIOATE see TF31250PHOSPHOROTHIOIC ACID, O,O-DIETHYL O-(2-(ETHYLTHIO)ETHYL) ESTER

KJ21000. ETHANETHIOL, 2-(METHYLAMINO)-
CAS 010061402 MW 91.19 MOLFM N S C3-H9
WLN SH2M1
SYN: N-MONOMETHYLCYSTEAMIN (German) * N-MONOMETHYLCYSTEAMINE *
TXDS: scu-mus LD50 262 mg/kg AEPPAE 225,428,5

ETHANETHIOL, 2-(METHYLTHIO)-, O,O-DIMETHYL PHOSPHOROTHIOAT TF94500 PHOSPHOROTHIOICACID, O,O-DIMETHYL S-(2-(METHYLTHIO)ETHYL) ESTER

ETHANETHIOL, 2-(METHYLTHIO)-, S-ESTER with O,O-DIMETHYL PHOSPHOROTHIOATE see: TF94500PHOSPHOROTHIOIC ACID, O DIMETHYL S-(2-METHYLTHIO)ETHYL) ESTER

KJ26250. ETHANETHIOL, 2-(TRIMETHOXYSILYL)-
CAS 007538456 MW: 182.34 MOLFM O3-S-Si-C5-H14
WLN: SH2-SI-/O1 3
SYN 2-MERCAPTOETHYL TRIMETHOXY SILANE *
TXDS: orl-rat LD50:2460 mg/kg AIHAAP 30,470,69

ETHANE TRICHLORIDE see: KJ31500 ETHANE, 1,1,2-TRICHLORO

KJ29750. ETHANE, 1,1,1-TRICHLORO-
CAS: 000071556 MW: 133.37 MOLFM Cl3 C2 H3
WLN: GXGG
SYN AEROTHENE TT * CHLOROFORM, METHYL * CHLOROTHENE(Inhibited) * CHLORTEN * METHYLCHLOROFORM * 1,1,1-TRICHLOORETHAAN (Dutch) * 1,1,1-TRICHLORAETHAN (German) * alpha-TRICHLOROETHANE * 1,1,1-TRICHLOROETHA * 1,1,1-TRICLOROETANO (Italian) *
TXDS ihl-man TCLo:350 ppm TFX:PSY WEHI** 10,82,73
ihl-hmn TCLo:920 ppm/70M TFX CNS AIHAAP 19,353,58
orl-rbt LD50:5660 mg/kg AIHAAP 19,353,58
orl-gpg LD50:9470 mg/kg AIHAAP 19,353,58
AQTX:
U.S OCCUPATIONAL STANDARD USOS-air FEREAC 37,22139
TWA 350ppm

KJ31500. ETHANE, 1,1,2-TRICHLORO-
CAS: 000079005 MW: 133.40 MOLFM Cl3-C2-H3
WLN: GYG1G
SYN: ETHANE TRICHLORIDE * beta-TRICHLOROETHANE * 1,1,2-TRICHLORETHANE * 1,1,2 TRICHLOROETHAN * TROJCHLOROETAN(1,1,2) (Polish) * VINYL TRICHL *
TXDS: orl-rat LD50: 580 mg/kg AIHAAP 30,470,69
ihl-rat LCLo:500 ppm/8H AIHAAP 30,470,69
scu-mus LD50:227 mg/kg JPETAB 123,224,5
orl-dog LDLo 750 mg/kg QJPPAL 7,205,34
ivn-dog LDLo:95 mg/kg QJPPAL 7,205,34
scu-rbt LDLo:500 mg/kg QJPPAL 7,205,34
AQTX:
U.S OCCUPATIONAL STANDARD USOS- FEREAC 37,22139
air:TWA 10 ppm(skin)

SL 036382

AMERICAN Industrial ASSOCIATION

HYGIENIC GUIDE SERIES

1,1,1-Trichloroethane
(Methyl Chloroform)
(Revised 1961)

I. Hygienic Standards

A. RECOMMENDED MAXIMUM ATMOSPHERIC CONCENTRATION (8 hours): 500 parts of vapor per million parts of air, by volume (ppm)[1]

1. *Basis for Recommendation:* Repeated administration to animals and human experience.[2, 5]

B. SEVERITY OF HAZARDS:

1. *Health:* Moderate for acute exposure, but chronic exposure to concentrations that are without acute effects are unlikely to produce injury. 1,1,1-Trichloroethane is readily absorbed and excreted through the lungs.[3] In acute exposure the most important toxic action is a functional depression of the central nervous system leading ultimately to respiratory failure. Experiments with dogs have indicated that this material can induce ventricular arrhythmia similar to that produced by other chlorinated solvents.[4] Animals exposed repeatedly to high concentrations exhibited some reversible changes in liver histology, but they were not the severe effects associated with carbon tetrachloride. Chronic exposures to 1000 ppm resulted in moderate fatty degeneration of the liver but no liver necrosis or kidney injury. Growth depression occurred at 650 ppm. No effects were seen from repeated 7-hour daily exposures to 500 ppm. In controlled human exposures to 500 ppm no effects other than slight, transient eye irritation were noted, but at 1000 ppm and above, mild eye irritation was experienced by all subjects, and some became dizzy.[2, 5] As with most solvents, dermatitis might result from repeated skin contact, but 1,1,1-trichloroethane is only poorly absorbed through the skin. Eye contact may result in pain and discomfort, but no impairment of vision is likely.

2. *Fire:* 1,1,1-Trichloroethane has no flash point when tested by standard ASTM procedures for the TAG Closed or Cleveland Open Cup tests. Some *inhibited* 1,1,1-trichloroethanes have been found to have explosive limits of 10% to 15.5% in air, but a high energy source is required to cause ignition and, if the ignition source is removed, the vapor will not continue to burn.[2] When inhibited products are evaporated to a small volume the residue may flash. Thermal decomposition products are very irritating and may be quite toxic, but voluntary overexposure to such materials (largely hydrogen chloride)[6] is not likely.

C. SHORT EXPOSURE TOLERANCE: Beginning anesthetic effects, including incoordination, appear in some human subjects exposed to concentrations of 800 to 1000 ppm. They occur quickly in humans at concentrations of 2000 ppm or higher.[2] Exposures to concentrations in excess of 30,000 (3% by volume) may be lethal in 5–6 minutes.[7]

D. ATMOSPHERIC CONCENTRATION IMMEDIATELY HAZARDOUS TO LIFE: 30,000 ppm (3% by volume) based on animal experiments.[5, 7]

II. Significant Properties

Methyl chloroform is a volatile, colorless liquid with an aromatic "chloroform-like" odor. The odor threshold may range from 20–100 ppm.[8]

Chemical formula:	CH_3CCl_3
Molecular weight:	133.42
Specific gravity:	1.3366 (25°/4°C)
Boiling point:	74.07°C at 760 mm Hg
Vapor pressure at 25°C:	125 mm Hg
Solubility:	Insoluble in water, but miscible with alcohol, ether and most organic solvents.

At 25°C and 760 mm Hg:	
1 ppm of vapor:	0.00545 mg/liter
1 mg/liter of vapor:	183 ppm
Saturated air concentration:	16.5%
Relative density of vapor:	4.6 (air = 1.0)
Relative density of saturated air:	1.6 (air = 1.0)

III. Industrial Hygiene Practice

A. RECOGNITION: Methyl chloroform is used as a solvent and as a degreasing and cold-cleaning agent. In many instances it has been substituted for the more toxic carbon tetrachloride.

B. EVALUATION OF EXPOSURE:

1. *Instrumentation:* Instruments based on the Beilstein test such as the Davis Halide Meter[9] and halide leak detectors may be calibrated for 1,1,1-trichloroethane. Instruments employing measurement of the conductivity of water which has absorbed the combustion products of this material are available, and those using hydrogen flame ionization, while almost completely non-specific, can probably be used. Gas chromatographic, infrared, and mass spectrographic methods can be used, especially when absolute identification is necessary.

2. *Chemical Analysis:* Direct combustion followed by absorption in a basic, reducing solution and determination of the halide ion has been used successfully,[10] as has adsorption on silica gel followed by thermal desorption and combustion.[11] The method of Fahy[12] using isopropyl alcohol to desorb from silica gel, followed by alkaline hydrolysis, is said to be applicable.[14] A modified Fujiwara reaction may be used.[13] Detector tubes by various manufacturers can probably be used, but each batch should be separately calibrated before use.

C. RECOMMENDED CONTROL PROCEDURES: Concentrations to which men are repeatedly exposed should not exceed 500 ppm. General ventilation is usually sufficient to maintain such control at room temperature unless large surfaces are wet with the solvent. Halogenated solvents should not be used where their vapors (in concentrations of a few ppm or more) will come into contact with very hot surfaces (such as near a welding operation) because toxic decomposition products such as chlorine and hydrogen chloride may be formed. In such cases local exhaust ventilation will be necessary.

Non-inhibited methyl chloroform should not be used in contact with aluminum because of its reactivity with this metal.

Gross skin contact should be prevented; spectacles will usually offer adequate eye protection.

IV. Specific Procedures

A. FIRST AID: Remove victim to an uncontaminated atmosphere and apply artificial respiration if breathing has stopped. Remove wet clothing and do not allow it to be re-worn until it is thoroughly dry. If eyes are contaminated they should be flushed with large amounts of water.

B. SPECIFIC MEDICAL PROCEDURES: Treat symptomatically, watch the cardiac rhythm in any case of anesthesia produced by 1,1,1-trichloroethane Oxygen therapy may be used, but epinephrine is contraindicated. Some indication of the extent of exposure may be obtained from an analysis of exhaled air.[5] Urinary urobilinogen may be of interest as a liver function test following acute excessive exposures.[5] Recovery from a non-fatal acute episode can be expected to be complete and prompt.

V. References

1. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for 1961. *Amer. Ind. Hyg. Assoc. J. 22:* 325 (1961).
2. Torkelson, T. R., *et al.: Amer. Ind. Hyg. Assoc. J. 19:* 353 (1958).
3. Hake, C. L., *et al.: AMA Arch. of Env. Health 1:* 101 (1960)
4. Rennick, B. R., *et al.: Federation Proc. 8:* 327 (1949).
5. Stewart, R. D., *et al.: Amer. Ind. Hyg. Assoc. J. 22:* 252 (1961).
6. Crummett, W. D., and V. A. Stenger: *Ind. Eng Chem. 48:* 434 (1956).
7. Adams, E. M., *et al.: AMA Arch. of Ind. Hyg. and Occup. Med. 1:* 225 (1950).
8. The Dow Chemical Company, unpublished data.
9. Schaffer, A. W., and H. R. Hoyle: *Amer. Ind. Hyg. Assoc. J. 22:* 93 (1961).
10. Jacobs, M. B.: *Analytical Chemistry of Poisons, Hazards and Solvents,* 2nd Edition. Interscience Publishers, Inc., New York (1949).
11. Peterson, J. E., *et al.: Amer. Ind. Hyg. Assoc. Quart. 17:* 429 (1956).
12. Fahy, J. P.: *J. Ind. Hyg. and Toxicol. 30:* 205 (1948).
13. Rogers, G. W., and K. K. Kay: *J. Ind. Hyg. and Toxicol. 29:* 229 (1947).
14. Elkins, H. B., Personal Communication.

HAMILTON HARDY INDUS. TOXICOLOGY

bon tetrachloride intoxication has also been reported (Tracey and Sherlock, 1968), and this compound is a potent hepatocarcinogen in animals. It is of course possible that regeneration itself in these cases is the precancerous lesion and that carbon tetrachloride is not a specific carcinogenic material.

A bleeding tendency has been observed in many cases of actue carbon tetrachloride poisoning. In some cases it may reflect visceral damage. In others bleeding may be a consequence of aplastic anemia. The evidence that carbon tetrachloride is a direct bone marrow poison is not indisputable, but cases have been presented in which the nature of the exposure and the sequence of events are reasonably convincing (Straus, 1954).

ETHYL CHLORIDE

Ethyl chloride is a gas at room temperature; however, it is easily liquefied and is familiar to physicians as a local anesthetic agent which freezes the skin when the agent is applied as a spray from a glass cylinder. Ethyl chloride is found in industry almost entirely as a chemical intermediate used in the synthesis of tetraethyl lead and other ethyl compounds. The physiological properties of ethyl chloride are related to its anesthetic effect and perhaps to its cardiotoxic properties as a sensitizer of the myocardium to endogenous epinephrine. As far as is known, this compound is excreted via the lungs without significant metabolic degradation in the body.

ETHYLENE DICHLORIDE

The ethylene dichloride, or ethylene chloride, of industry is 1,2-dichloroethane. 1,1-Dichloroethane is commonly known as ethylidene dichloride or ethylidene chloride. These are saturated compounds, chlorinated ethanes, and the "ene" endings should not lead to confusion of those compounds with dichloroethylene. Much of this terminology is quite unfortunate, but is so well established among the various industrial traditions that change is unlikely.

Both chlorinated ethanes are used as solvents and as chemical intermediates. They are irritating to the eyes and the respiratory tract, producing salivation, sneezing, and coughing. In those few cases of intoxication which have been reported, the anticipated anesthetic effects have been observed with associated dizziness, nausea and vomiting. In severe and fatal cases hepatic and renal injury have been observed.

METHYL CHLOROFORM

Methyl chloroform (1,1,1-trichloroethane) is a chlorohydrocarbon solvent which, because of its very low toxicity (Stewart, 1971), is being utilized at an accelerated rate. It is widely applied as a

vapor degreaser, dry cleaning agent, aerosol vehicle, and cold cleaner. Like many chlorohydrocarbons, methyl chloroform is somewhat unstable, and small amounts of stabilizing compounds are added to the solvent material sold in commerce. Such stabilizers or inhibitors may be various ketones, alcohols, esters, nitrogen compounds, etc., which do not change the toxicity of the commercial product sold under trade names such as Chlorothene or Triethane.

harmful effects

Methyl chloroform is a narcotic and skin defatting solvent as are the chlorohydrocarbons in general. Exposures to high air concentrations of methyl chloroform may lead to narcosis and even fatal respiratory depression under conditions of grossly negligent overexposure. There is no evidence that this solvent causes hepatic or renal injury such as is characteristic of carbon tetrachloride. Experimental work (Reinhardt et al., 1971; Aviado and Belej, 1973) and clinical experience with anti-tussive preparations containing trichloroethane identifies serious cardiotoxic properties of this compound, and deaths have been attributed to cardiac arrhythmias, probably mediated through epinephrine sensitization.

1,1,2-Trichloroethane, vinyl trichloride, an isomer of methyl chloroform, is a more potent anesthetic agent, an irritant to mucous membranes, and a significant hepato- and nephrotoxin. It does not have major industrial uses.

TETRACHLOROETHANE

Industrial references to acetylene tetrachloride or tetrachloroethane are invariably to the symmetrical isomer of 1,1,2,2-tetrachloroethane. Clinical evidence indicates that this compound is by far the most poisonous of the chlorohydrocarbons used as industrial solvents. Unfortunately from the health point of view, it is an excellent solvent, often the best available for many applications. Early utilization of tetrachloroethane as a vehicle for the so-called dope to cover airplane fabrics led to numerous severe and fatal cases of toxic hepatitis and atrophy of the liver. The compound is the best solvent for cellulose acetate, which for many years was the best available coating material for fabrics to be used in aviation and products requiring a thin, light, impervious surface.

The recognized toxicity of tetrachloroethane has caused it to be eliminated from most industrial uses unless its specific solvent properties are necessary. The use of this compound is rarely justified. Toxic manifestations resemble those associated with carbon tetrachloride; however, the hepatotoxicity of tetrachloroethane is much more prominent.

Toxicology, BASIC Science of Poisons

microsomal enzyme system all support the hypothesis that metabolism is a prerequisite to carbon tetrachloride hepatotoxicity.

Methyl Chloroform (1,1,1-Trichloroethane, Cl_3CCH_3)

Methyl chloroform has received widespread acceptance as an industrial solvent since it has many of the solvent and volatility characteristics of carbon tetrachloride. Like the other halogenated hydrocarbons solvents, methyl chloroform has a depressant action on the central nervous system. Irish (1963) reports that humans exposed to 2000 ppm exhibited drunkenness and incoordination. Exposures at 1000 ppm showed no significant response in individuals exposed for as long as 70 minutes. Irish also reports that only two fatal cases are known and they occurred in a tank where the concentration may well have been close to saturation. Acute vapor exposures in animals, as reported by Adams and coworkers (1950), indicated that rats could survive a seven-hour exposure at 8000 ppm. At 3000 ppm, rabbits and monkeys showed no abnormal response over a two-month period. The acute LD50 in male rats is approximately 12 g/kg and in female rats approximately 10 g/kg. Experimental human exposures to 500 ppm of methyl chloroform for 6.5 to 7 hours per day for five days gave no evidence of abnormal organ function as measured by a variety of clinical laboratory tests. Ability to perceive the odor decreased during the exposure period. The subjective responses obtained during the exposure were mild and inconsistent except for the complaint of drowsiness (Stewart *et al.*, 1969).

Studies of the comparative toxicity of a series of halogenated hydrocarbons (Klaassen and Plaa, 1969; Watrous and Plaa, 1972) have demonstrated that in experimental animals, near-lethal doses of 1,1,1-trichloroethane are required to produce a measurable hepatotoxic response to a single dose. As shown in these same reports, 1,1,2-trichloroethane is considerably more toxic than 1,1,1-trichloroethane; thus it is apparent that one must be certain of the correct identification of chemical compounds in order to prevent confusion and error in defining their toxicity. The present TLV for methyl chloroform is 350 ppm.

The metabolism of 1,1,1-trichloroethane is also somewhat different from that of 1,1,2-trichloroethane in that it is partially metabolized to trichloroethanol and to a lesser extent to trichloroacetic acid (Ikeda and Ohtsuji, 1972). The overall metabolism of 1,1,1-trichloroethane was considerably less than that of trichloroethylene. Although some metabolism of 1,1,2-trichloroethane was apparent, the low levels made identification of the products uncertain.

Trichloroethylene $Cl_2C{=}CHCl$

Trichloroethylene is widely used as an industrial solvent in degreasing and extraction processes as well as in the dry-cleaning industry. The toxicity of trichloroethylene has been included in a number of reviews (Browning, 1965; Smith, 1966).

Overexposure to trichloroethylene produces central nervous system depression resulting in mental confusion, incoordination, and insomnia. The acute response of experimental animals to trichloroethylene vapor has been reported by Adams and coworkers (1951). At 3000 ppm, a six-month daily exposure resulted in increased liver and kidney weights. Rats and rabbits exposed for a six-month period to 200 ppm showed no effect. Baker (1958) reported severe changes in the cerebellum, particularly in the Purkinje cell layers in dogs chronically exposed to trichloroethylene. Fatal cases of trichloroethylene exposure reported by Kleinfeld and Tabershaw (1954), showed no tissue abnormalities at autopsy. Death was evidently due to cardiac arrhythmia resulting from the potentiation of endogenous epinephrine by trichloroethylene. Comparative studies on the hepatotoxicity of chlorinated hydrocarbons demonstrated that large, near-fatal acute doses were required to produce mild hepatic dysfunction. In this respect, the acutely toxic response was comparable to that seen with 1,1,1-trichloroethane.

Butler (1949) indicated that trichloroacetic acid, trichloroethanol, and small amounts of chloroform and monochloroacteic acid were the metabolic products of trichloroethylene. Several early reports had attempted to relate the concentration of trichloroacetate in urine to the inhalation exposure to trichloroethylene in man (Ahlmark and Forssman, 1951). Additional studies on the metabolism of trichloroethylene (Bartoníček, 1962; Stewart *et al.*, 1970a) confirm the major metabolites of trichloroethylene as trichloroacetic (TCA) acid and trichloroethanol (TCE). In general, considerably more TCE is excreted than TCA. For example, in animal studies (Ikeda and Ohtsuji, 1972) rats excreted five to seven times more TCE than TCA after being exposed to trichloroethylene. With respect to the toxicity of these metabolites, Mikiskova and Mikiska (1966) demonstrated that trichloroethanol had a pronounced depressant effect upon the central nervous system and suggested that the rate of metabolism of trichloroethylene appeared sufficient for trichloroethanol to play a role in its depressant action.

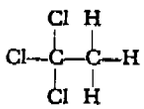
BROWNING; TOXICITY AND METABOLISM OF INDS. SOLVENTS

25. Trichloroethane

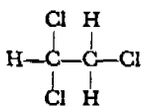
Trichloeroethane exists in two isomers; 1,1,1 – the α isomer and 1,1,2 – the β isomer. Until recently it has been stated that the α-isomer is more toxic than the β. The error apparently arose from a misconception of the results of experiments published by Lazarew in 1929 on its minimal anaesthetic concentration, though this was given at the time as 45 mg/l compared with 15 mg/l for the β-isomer and the respective lethal doses as 65 mg/l and 60 mg/l. Boehring (1958, personal communication) and Stewart (1963) both agree that the α-isomer is the less toxic of the two.

Synonyms: methylchloroform, vinyl trichloride

Structural formula: 1,1,1-trichloroethane



1,1,2-trichloroethane



Molecular formula: $C_2H_3Cl_3$ $C_2H_3Cl_3$

Molecular weight: 133.42 133.42

25a. 1,1,1-Trichloroethane

Properties: a volatile colourless liquid with chloroform-like odour

boiling point: 74.1 °C

melting point: none? (Stewart, 1963)

vapour pressure: 127 mm Hg at 25 °C

vapour density (air = 1): 4.6

specific gravity (liquid density): 1.336 at 25 °C

flash point: none (Irish, 1963)

conversion factors: 1 p.p.m. = 5.46 mg/m³
1 mg/l = 183 p.p.m.

solubility: soluble in many organic solvents, but only slightly in water (Van Arkel and Vles, 1936).

maximum allowable concentration: 500 p.p.m. (Threshold Limit Values, 1962)

Bibliography on p. 263

ECONOMY, SOURCES AND USES

Production

Reacts with aluminium and aluminium alloys, but inhibited formulae are now marketed under trade names (Stewart, 1963) such as Chlorothene, a compound which contains 94–97% of 1,1,1-trichloroethane, 2.4–3% of dioxane, 0.12–0,3% of butanol and small amounts of ethylene dichloride, water and other materials (Torkelson *et al.*, 1958). It is not flammable, nor will it support combustion, but it will decompose if sufficient heat is applied. At 500 °F large amounts of HCl and trace amounts of phosgene are formed (Crummett and Stenger, 1956).

Industrial uses

The volatility and solvent power of 1,1,1-trichloroethane closely resemble those of CCl_4 and it has come into wider use as a substitute for CCl_4 in recent years:
(1) as a solvent for natural and synthetic resins, oils, waxes, tar and alkaloids,
(2) as a degreaser,
(3) in organic synthesis.

BIOCHEMISTRY

Estimation

(1) In the atmosphere

Like many other halogenated hydrocarbons, 1,1,1-trichloroethane can be determined by hydrolysis with alkali in isopropyl alcohol.

The method advised by Elkins (1959) is based on absorption of the vapour in *sec.*-butyl or isopropyl alcohol. The vapour is collected on a silica-gel absorber, followed by reduction with metallic sodium. The silica gel is then extracted with the alcohol and refluxed with metallic sodium; ethylalcohol (95%) is then added and the refluxing continued until all the sodium has reacted. After cooling and addition of water through the condenser, phenolphthalein and dilute nitric acid are added until the solution is acid. After addition of 0.1 N $AgNO_3$, filtration and washing of the precipitate with water, ferric sulphate solution is added and titration with 0.05 N KCNS solution carried out until a permanent yellow colour is obtained.

The amount of hydrolysis of 1,1,1-trichloroethane is 59% compared with 84% for CCl_4.

(2) In blood and tissues

A rapid infra-red technique for the analysis of certain organic compounds in the blood has been described by Stewart *et al.* (1959). They state that it has been satisfactory for 1,1,1-trichloroethane. In this method the suitable extracting solvent is added to the oxalated blood and, after centrifuging, the solvent layer is transferred to a standard infra-red sample cell of any standard infra-red spectrometer and the spectrum scanned from 2–16 mμ.

(3) In urine

The aforementioned method has also been applied successfully to urine.

Metabolism

Williams (1959) stated that the metabolic fate of 1.1.1-trichloroethane was unknown, but according to Hake *et al.* (1960) it is very stable in the body, and while a large part of an intravenous dose is excreted unchanged by the lungs, a very small amount is metabolised to chloroethanol and excreted in the urine as the glucuronate. Irish (1963) remarks that the high stability and rapid excretion may well account for the low toxicity and quick recovery from anaesthetic concentrations.

TOXICOLOGY

There is no doubt that methylchloroform is much less toxic than carbon tetrachloride. Its main toxic effect is exerted on the central nervous system, in a manner similar to that of any anaesthetic agent. In animals lethal dosage causes central nervous depression culminating in respiratory paralysis (Adams *et al.*, 1950) and at anaesthetic level it has the property of sensitising the heart to epinephrine, with induction of idioventricular rhythms (Rennick *et al.*, 1949). For this reason it is advisable that epinephrine should never be given to a person overcome by its vapour.

It can also cause a mild conjunctivitis if in contact with the eyes, but is not highly irritant to the skin except for the irritation caused by its defatting action with repeated contact.

With chronic exposure, the only animal species showing significant organic injury were, in the experiments of Torkelson *et al.* (1959), female guinea pigs: these showed slight inflammation of the lungs and fatty changes in the liver.

In industry 3 deaths have been reported from high exposure, all from open tanks; in one case to a concentration of more than several thousand p.p.m.

Bibliography on p. 263

Toxicity to animals

(1) Acute

(a) Lethal dose. – *(i) By oral administration* – for rats 10.3–12.3 g/kg, for rabbits 5.6 g/kg, for guinea pigs, 9.47 g/kg (Torkelson *et al.*, 1958). – *(ii) By inhalation,* – for rats, 30,000 p.p.m. for 6 min; 15,000 p.p.m. for 1½ h; 8000 p.p.m. for 7 h (Adams *et al.*, 1950).

(b) Narcotic dose. – 18,000 p.p.m. in 18 min, 8000 p.p.m. in 5 h (Irish, 1963).

(2) Chronic

The effects of repeated administration, either oral or by inhalation, do not suggest a high potential chronic toxicity. Rats, rabbits, guinea pigs and monkeys exposed to 500 p.p.m. 7 h a day, 5 days a week for 6 months showed no evidence of impairment of growth or health, and when the concentration was increased to 10,000 p.p.m. male rats showed as the only sign of organic injury a slight increase in the weight of the liver. A separate group of guinea pigs (female) however, exposed to 2000 p.p.m. for periods of up to half an hour a day, 69 times in 98 days, did show some irritation of the lungs and fatty infiltration of the liver, and some, at the shorter periods of exposure, an increased incidence of interstitial nephritis; since this did not occur at the higher intensities of exposure, Torkelson *et al.* believed that it was probably not related to the exposure. Adams *et al.* (1950) also carried out experiments with repeated exposure over long periods. Rats which succumbed to 10,000 p.p.m. appeared to have died from either cardiac or respiratory failure, but they survived 31 exposures to 5000 p.p.m. without apparent injury, while rabbits showed slight retardation of growth.

Inhalation of concentrations of 1000 p.p.m. 7 h a day for 5 days a week were lethal to guinea pigs after two exposures, to rats after 3 to 14, to rabbits, after 2 to 64. Dogs, cats and monkeys were less susceptible, surviving for 23 to 55 days (Heppel *et al.*, 1944). Some variation in species susceptibility was noted by Spencer *et al.* (1951), rats and guinea pigs showing a high mortality at 400 p.p.m.

SYMPTOMS OF INTOXICATION

Lethal doses cause anaesthesia followed by respiratory arrest. Concentrations somewhat below the lethal level (about 10,000 p.p.m.) cause irregular respiration and a semicomatose state.

Some central nervous depression; the eyes of dogs showed reversible clouding of the cornea, with repeated exposure they became resistant to this effect (Heppel *et al.*, 1944).

(1) The skin

Some irritation of the shaven skin of a rabbit following application of a pad saturated with methyl chloroform, and when applied under a cuff in a dosage of 15.8 g/kg killed less than half of the rabbits treated.

(2) Respiratory disturbances

Effect on the circulation. – Depression of the blood pressure of dogs and monkeys anaesthetised by 1,1,1-trichloroethane was observed by Krantz *et al.* (1959) the level reaching about half its normal value at the point of respiratory arrest. Administration of epinephrine during anaesthesia produces ventricular fibrillation in animals (Rennick *et al.*, 1949).

CHANGES IN THE ORGANISM

(1) The lungs

Only mild congestion even after 125 exposures to 200 p.p.m. (Heppel, 1944).

(2) Liver and kidneys

Only slight pathological changes, most marked in guinea pigs with repeated exposure to 200 p.p.m., none in rats.

Toxicity to human beings

Human beings were exposed to concentrations ranging from 506–1900 p.p.m. for periods of 5–45 min (Stewart *et al.*, 1961). At 1000 p.p.m. a strong unpleasant odour was noted after 30 min, and at 920 p.p.m. three of the individuals exposed showed a slight loss of co-ordination and equilibrium, and complained of lightheadedness.

These signs of intoxication became very obvious, with a positive Romberg test, at 1900 p.p.m. for 5 min (Stewart, 1963). No evidence of systemic injury, as judged by tests of urine and liver function, was observed.

Industrial poisoning. – In industry three fatal cases due to high exposure have been reported. In the two recorded by Torkelson *et al.* (1958) the exposure occurred in an open tank where the concentration was believed to be close to saturation, and in one case for a period of about 30 min. The third case, recorded by Stewart (1963), was also due to entry into an open tank, and the concentration was stated to be "more than several thousand p.p.m.". The symptoms resembled those of drunkenness, with disturbance of equilibrium and incoordination.

Prevention of poisoning. – The measures of prevention advised by Stewart (1963) include protection of the eyes by safety glasses, and of the skin by removing contaminated clothing in case of spillage; keeping the workroom atmosphere to a level not higher than 500 p.p.m.; if higher levels should be present owing to accident or unavoidable circumstances, no workman should be allowed to remain in contact for more than a few minutes.

Treatment. – Removal to fresh air; if breathing has stopped artificial respiration should be tried, but epinephrine should never be given in case ventricular fibrillation should supervene. Oxygen may be necessary if there is severe hypotension.

Bibliography on p. 263

mation, loss of
depression of
distress was most
nea pig. Rabbits
excess of 10 ppm
d cyanosis. Signs
stimulation were
2-nitro-2-butene
tological changes
rat consisted of
ll count, hemo-
s, and moderate
A significant de-
hocytes to poly-
curred following
Immature forms
after exposure to
-butene.
s included con-
id, occasionally,
in the nasal pas-
onchi; and con-
nage, consolida-
abscess forma-
. The processes
abscess forma-
animals which
osure.

al Physiology of Los
1342 (1952).
GADWICK: Industrial
Power Plants (Gas
l Conference on Air
(Nov. 1958)
on the Practicability
Olefin Content of
Pollution Control
1-3 (April, 1959).
Air Pollution Confe
ence on Air Pollu-
1958).
dings Second Air
p. 27, Cincinnati,

V. ORCUTT, L. A.
rim Report No. 1,
Control District, p.

Report No. 24,

INGER, and G. E.
ts upon Experimental
312 (1958).
DEICHMANN, M. G.
ion of Conjugated
Air Pollution. *Ind.*

dings Air Pollution
Cincinnati, Ohio

s Air Pollution Re-
cinnati Ohio (Dec.

IREON: The Physio-
nd to a Mixture of
l Hyg. & Toxicol

Toxicity of a Solvent Mixture of 1,1,1-Trichloroethane and Tetrachloroethylene as Determined by Experiments on Laboratory Animals and Human Subjects

V. K. ROWE, T. WUJKOWSKI, M.A. WOLF, S. E. SADEK, D.V.M., Ph.D., and R. D. STEWART, M.D.*

Biochemical Research Laboratory and Medical Research Laboratory, The Dow Chemical Company, Midland, Michigan

The toxicological properties of a solvent mixture (Dowclene† EC cleaner) consisting by weight of 75% inhibited 1,1,1-trichloroethane (Chlorothene NU solvent) and 25% tetrachloroethylene were studied on rats, mice, guinea pigs, rabbits, dogs and human subjects. The material was low in oral toxicity, not appreciably irritating to the eyes or skin, not absorbed through the skin to an appreciable extent, and was low in toxicity when inhaled. The animals given seven-hour exposures five days a week for six months to a vapor concentration of 1,000 ppm of the mixture suffered slight changes of a reversible character in the liver and kidney. Rats exposed four hours a day for six months to 1,000 ppm and the animals (4 species) exposed seven hours a day for six months to 500 ppm exhibited no evidence of adverse effects. Human subjects were exposed seven hours a day for up to five days to 500 ppm and subjected to intensive medical study. No adverse effects were detected. The rate of excretion of the solvent via the lungs was studied in both dogs and humans.

Introduction

A NEED was established for a solvent which would be more effective than the solvent systems presently available for the cleaning of sizeable pieces of equipment. An example of such a need is in the cleaning of large electrical generators where the flushing off of dissolved soil is necessary, but without slow drying of the cleaned equipment. It was agreed that such a solvent should possess the following characteristics: (a) good solubility for greases, oils, tars, and other common soils; (b) negligible effects on insulating materials during a normal cleaning cycle; (c) essentially no electrical conductivity; (d) no flash or fire point; (e) an evaporation rate slow enough to permit efficient cleaning and yet fast enough to permit prompt reuse of the equipment; (f) low cost; and (g) favorable toxicological properties. The solvent combination considered in this paper was found to possess the desired physical and chemical attributes.

Although toxicological data on the individual constituents of the combination have been reported,[1,2] none was available on the system as a whole. These studies were undertaken to provide data upon which the hazards of handling and using the material could be evaluated and upon which an industrial hygiene standard could be based.

The following report summarizes the results of acute oral, eye and skin irritation, and acute and repeated exposures of laboratory animals and human subjects to controlled vapor concentrations of the mixture.

Material

Chemical

The solvent system studied was a colorless, pleasant smelling liquid having a specific gravity of 1.373 at 25°/25°C, a boiling range (5-95%) of 77 to 122°C at 760 mm Hg, and a freezing point of −56.6°C. Like many

*Dr. Stewart is with the Medical Research Laboratory.
†Trademark of the Dow Chemical Company.

chlorinated hydrocarbons, this material reacts readily with aluminum and aluminum alloys, therefore it must be inhibited if corrosion is to be prevented.

The mixture studied was shown by infrared analysis to contain on a molecular basis, 74% 1,1,1-trichloroethane, 22% tetrachloroethylene, 3.3% dioxane, 0.31% butylene oxide and 0.16% of unidentified impurities. It has no flash point or fire point using standard ASTM procedures for the Tag closed cup and Cleveland open cup tests.

Animals

The rats, rabbits, and guinea pigs were from the stock colony of this laboratory[3] except that the guinea pigs used in the paired-feeding study as well as the mice, and the dogs were obtained from commercial suppliers. The mice were Webster-Swiss whites obtained from Buckberg Laboratory Animals of Croton Falls, New York; the guinea pigs from Milton Erard of Decker, Michigan; and the dogs from Heric Fahrenbach of Essexville, Michigan. The rats, mice and dogs were maintained on Famo Laboratory Ration, the rabbits on Famo Rabbit Ration, and the guinea pigs on Famo Guinea Pig Ration. All of these rations are products of the Harris Milling Company of Mt. Pleasant, Michigan.

In all cases, neither food nor water was available to the animals while they were in any exposure chamber but both were available immediately after each exposure.

Human Subjects

All subjects were healthy male volunteers, ranging in age from 32 to 62 years from the Medical Department, the Biochemical Research Laboratory, and the Chemical Physics Laboratory of The Dow Chemical Company.

Procedures

Oral Administration, Eye Contact, and Skin Contact

The animals and methods used for determining the toxicity from single oral doses, eye contact and skin contact have been described previously.[3] Skin absorption studies were conducted by employing the "sleeve" technique described by Draize *et al.*[4] with slight modifications.

Inhalation

Single exposure—rats. The animals, equipment, and procedures used to determine the single-dose vapor toxicity of the solvent mixture were essentially the same as described previously.[2]

Repeated exposures—animals. Large metal chambers (3700 liter capacity) were used for the repeated exposures to 1000 and 500 ppm and for the air-exposed control animals. The desired concentrations were obtained by metering the liquid and vaporizing it into the airflow entering the chamber. Metering of the liquid was done by Dual Syringe Pumps (Modern Metalcraft, Midland, Michigan). Total air flow through all three chambers was measured by means of calibrated flow meters and maintained at 450 liters per minute.

All exposures were continuously monitored by a calibrated conductivity combustion analyzer.[5] In addition, spot samples were analyzed frequently by pyrolyzing a known volume of solvent-laden air, trapping the resulting chloride in a 1% sodium formate—1% sodium carbonate solution, and then determining the liberated chloride using a micro-Volhard technique. The mean concentrations found were 1005.9 (range 954 to 1092) and 496.1 (range 470 to 559) ppm, respectively.

All of the animals used in these experiments were carefully selected on the basis of general appearance, body weight, and growth during a preliminary period of observation.

Groups, each consisting of 24 male and 24 female rats, nine male and eight female guinea pigs, three male and three female rabbits and one male and one female dog, were exposed seven hours a day to either 1000 or 500 ppm of the mixture. Actually the rats were divided into two groups of 12 males and 12 females each, one group (A) to be sacrificed at the end of the six-month exposure period and the other group (B) to

be sacrificed six weeks later. In addition, separate groups of 10 male rats each were exposed to either 1000 or 500 ppm for four, two, or one hour per day for a period of six months.

The control groups were well-matched with the experimental animals in respect to number, age, sex, and body weight. The "unexposed controls" were simply maintained in the animal quarters, while the "air-exposed controls" were exposed repeatedly to a flow of room air in a manner similar to that followed with the solvent-exposed animals.

The animals exposed repeatedly for seven hours a day were placed in the chamber before any of the solvent was introduced. The rats exposed repeatedly for short daily periods were introduced into the chamber during the seven-hour exposures without opening the doors by dropping the rats through chutes made of 3¼ inch stainless steel tubing. These chutes were closed with a rubber stopper except during the brief time it took to insert the rats. The chutes, which were sloped at a 45° angle, ended in covered, screened cages inside the chamber. The additional groups were started three, five and six hours after the seven-hour exposures started. Since all the animals were removed when the seven-hour exposure was completed, this routine resulted in daily exposures lasting, seven, four, two or one hour.

During the course of the experiment, each animal was weighed twice a week until the growth pattern was established, after which they were weighed once a week. They were observed frequently for general appearance and behavior.

Hematological examinations consisting of erythrocyte, leukocyte, and differential counts and hematocrit and hemoglobin determinations were made on all the dogs and rabbits and representative groups of rats prior to any exposure, after about eight weeks of exposure, and about a week before the exposures ended.

Urinalyses consisted of routine evaluations of appearance, color, reducing sugar, albumen, pH, and specific gravity and microscopic checks for erythrocytes, leukocytes, casts, bacteria, crystalline material, and mucous. They were done on samples of urine from representative groups of rats and on samples from each rabbit and each dog about a week before exposure ended.

Alkaline phosphatase and serum-urea-nitrogen (SUN) determinations were made on blood taken at autopsy from representative rats, each of the rabbits, and each of the dogs. At the same time serum-glutamic-pyruvic-transaminase (SGPT) determinations were made on the blood from each of the dogs. Bromsulfalein (BSP) retention was determined before exposures began and about a week before they ended. The dose of the dye was 10 mg/kg and the blood sample for analysis was drawn 15 minutes later. Liver biopsies were performed on each dog prior to any exposure and about midway during the study.

Expired air samples were collected from the dogs at frequent intervals during the first two weeks of exposure and were collected occasionally during the rest of the experiment. Collection was accomplished by having them breath through a mask fitted with a 2-way Collins plastic "J" valve. (Warren E. Collins, Incorporated, Boston, Massachusetts). This allowed them to inhale fresh air and to exhale into a collapsed 10-liter saran bag. The exhaled air in the bag was analyzed by infrared spectrometry using a 10-meter gas cell.[6,7] The 1,1,1-trichloroethane was determined by absorbance at 9.2μ and the tetrachloroethylene at 10.9μ. The method of analysis was highly accurate and reliable, the lower limit of detection being 0.5$\pm$ 0.1 ppm for the 1,1,1-trichloroethane and 0.25$\pm$ 0.2 ppm for the tetrachloroethylene.

Failing animals were sacrificed for examination when moribund, or nearly so. At the termination of the experiment, part of the rats were starved overnight and then these and all the guinea pigs, and rabbits were decapitated and examined for evidence of organic injury on the day following the exposure. The dogs were sacrificed by exsanguination after anesthesia with thiamylal sodium (Surital sodium, Parke-Davis).

The weights of the principal organs (lung, heart, liver, kidney, spleen and testes) were

obtained routinely from all animals of each species. These weights were compared to the corresponding weights of the air-exposed control group on both an absolute and relative basis.

Portions of numerous tissues were taken and fixed for histopathological examination. Routinely, histologic examinations were made on hematoxylin-eosin stained sections of the lung, heart, thyroid, liver, spleen, adrenal, kidney, pancreas, and testes. In addition, sections of the brain, sciatic nerve, lymph nodes, stomach, small and large intestine, urinary bladder, gall bladder, and skeletal muscle from the dogs were also examined. The rats that were not killed the day after exposures were stopped, were maintained without exposure for six weeks and then sacrificed and studied in the manner described above.

A paired-feeding study was conducted using 24 male guinea pigs. Prior to beginning the critical portion of the study all the guinea pigs were exposed to air seven hours a day, five days a week in a control chamber. It was necessary to continue this routine for 34 days before all of the animals were gaining weight normally. At this time, six animals were selected for exposure to 500 ppm and six for exposure to 1000 ppm of the solvent vapor. Each of these animals was paired to one of the remaining twelve which were to continue exposure to room air in a control chamber. Each exposed guinea pig was offered 60 grams of feed daily, more than their normal daily consumption. The controls which were exposed in the air-exposed chamber were fed the exact amount of food their paired, exposed-mate had eaten the day before. Records of growth and daily food consumption were kept. At the termination of the experiment, all animals were autopsied, final organ weights were obtained, and tissues were saved for microscopic examination. Food efficiency data were calculated for the 5-week period.

The t-test was used in comparing mean values of body weights and of organ weights; probability values (P) of 0.05 or less were interpreted to indicate a significant difference.

Repeated inhalation studies—humans. Exposures were conducted in a room measuring 32 x 13 x 8 feet in size and provided with a continuous, positive air supply. The vapor concentration was generated by atomizing the solvent mixture into the faces of two large circulating fans. The vapor concentration was automatically controlled and continuously monitored by an infrared spectrophotometer equipped with a recorder. Vapor concentrations were also measured continuously with a Davis Halide Meter[9] and spot samples were taken from various portions of the room either in saran bags for measurement by another infrared analyzer or on silica gel for analysis by combustion and chloride determination.[10] The time-weighted concentration was 520 ppm with a range of 476 to 590; the duration of the extreme concentrations being but a few minutes.

All of the persons participating in this study were given a complete history and physical examination the week preceding the exposure. The criteria employed in an effort to detect any adverse effect of the exposure were as follows:

Immediately before each exposure: oral temperature; blood pressure; pulse rate; expirogram; venous blood for complete blood count, serum-glutamic-oxalacetic-transaminase (SGOT), serum electrophoresis, and total eosinophile count; and urine for complete analysis.

During the exposures: complete neurological examination after six hours of vapor exposure; evaluation of vestibular, cerebellar, and proprioceptive function every 75 minutes; questioning as to odor perception, eye, nose, or throat irritation, headache, dizziness, or speech difficulty every 45 minutes; Crawford Manual Dexterity Test every three hours; Flanagan Aptitude Classification Tests; expirograms; expired air for solvent concentration after three hours of exposure; two-hour postprandial blood sugar; blood for eosinophile count after six hours of exposure; urine collection begun for 24-hour urobil-

TABLE I
Single-Dose Oral Toxicity of a Solvent Mixture (Dowclene EC Cleaner)

Species	Sex	No. of Animals Used	LD_{50} Value gm/kg	Range gm/kg
Rats	Male	20	14.8	10.6—20.7
Rats	Female	26	14.8	9.6—22.8
Mice	Female	25	10.3	8.4—12.8
Guinea Pigs	Male	16	5.7	3.5— 9.2
Rabbits	Mixed	16	12.6	6.2—25.6

inogen determination; and electrocardiogram after Master's double two-step exercise after three hours of exposure.

Following the exposures: serial expired air analyses for solvent concentration; 24-hour urinary urobilinogen determinations for ten days; complete blood count 72 hours after exposure; serial SGOT determinations; and serum protein electrophoresis.

The expired air samples were obtained by having the subject take a deep breath, hold it for five seconds, then forcibly expel all of the breath possible into a saran bag. This was repeated until a sample of about 15 liters was obtained.

Results

Oral Administration: Rats, Mice, Guinea Pigs, and Rabbits

Groups of five male and five female rats, five female mice, five male guinea pigs and four male or female rabbits were given graded doses of the undiluted solvent mixture by intubation. The LD_{50} values and their ranges are given in Table I. The typical signs in the treated animals were various stages of anesthesia, diarrhea, and sometimes death. Deaths occurred from a few hours to a few days after feeding. The cause of death appeared to be respiratory failure. Gross examination of rats sacrificed 24 hours after treatment with various sized doses revealed only mild liver and kidney effects.

Eye Contact: Rabbit

When the undiluted solvent mixture was introduced directly into the eye of a rabbit, it caused immediate pain and a slight conjunctival irritation which cleared within 48 hours.

Skin Contact: Rabbits

Repeated applications (nine applications in 11 days) to the uncovered ear of a rabbit caused only a very slight erythema and exfoliation. When cotton pads wet with the solvent mixture were bandaged onto shaven intact abdominal skin nine times in 11 days, slight to moderate erythema, slight edema and slight exfoliation resulted. No necrosis occurred. When the material was bandaged onto abraded skin three times in three days, moderate erythema, edema, and exfoliation occurred. Healing was complete within a week without scar information.

Studies to evaluate the capacity of the material to penetrate the skin showed that doses as large as 30 gm/kg were not lethal to rabbits. Some weight loss did occur during the first few days post exposure, but recovery was complete within two weeks. The skin of these animals was burned superficially but healed promptly without scarring.

Inhalation

Single exposure—rats. Thirty groups of ten female rats each were exposed for either 0.5, 1.0, 2.0, 4.0, or 7.0 hours to various concentrations of the solvent vapor. The LD_{50} values were calculated and the results are shown in Figure 1. For comparison, similar data were obtained on the two major constituents, 1,1,1-trichloroethane and tetrachloroethylene, of the solvent mixture and these results are shown also in Figure 1.

The only important effect of excessive acute exposure was depression of the central nervous system (anesthetic effect). The degree of depression varied with the intensity of the exposure and deaths generally were attributable to cardiac or respiratory failure.

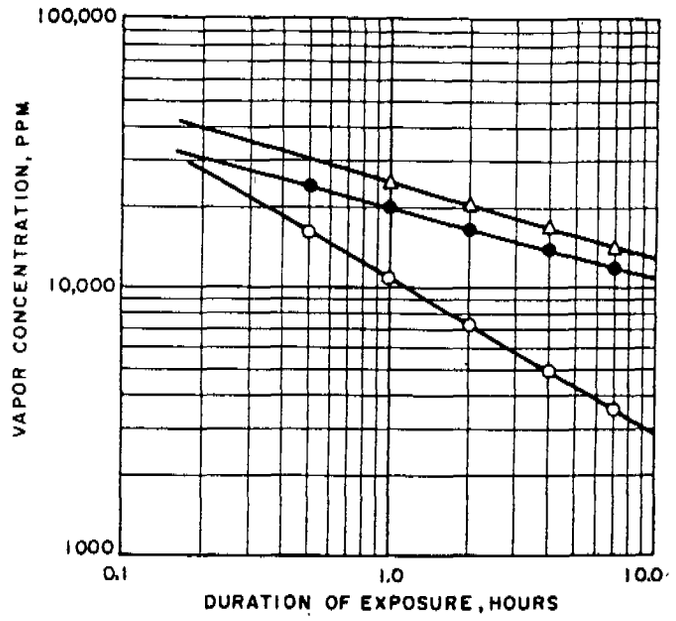


FIGURE 1. Comparison of the single-dose inhalation toxicity for rats of a solvent mixture (Dowclene EC Cleaner) with that of its major constituents, 1,1,1-trichloroethane and tetrachloroethylene. The middle line (solid dots) represents the LC_{50} values for the solvent mixture: the top line (triangles), the same for 1,1,1-trichloroethane; and the bottom line (circles), the same for tetrachloroethylene.

A few delayed deaths occurred but when examinations were possible evidence of respiratory infection was always found.

Repeated exposure—rats. Rats tolerated as many as 130 seven-hour exposures in 186 days to either 1000 or 500 ppm of the solvent vapor without evidence of adverse effects as judged by mortality, general appearance, behavior, hematologic examination, urinalysis, alkaline phophatase and urea nitrogen levels in the serum, and organ and organ-to-body-weight ratios. The most pertinent of these data are given in Table II. Detailed data for those animals maintained as controls for six weeks after the exposures ceased (group B) and those that received repeated exposures over a six-month period for four, two, or one hour per day are not tabulated because they were all within normal limits when compared to the control groups. This would be expected in view of the data presented.

Microscopic examination of the sections prepared from the various organs taken at autopsy from the rats exposed seven hours a day over a period of six months to 1000 ppm of the solvent vapor revealed only the following abnormalities. Changes in the liver were characterized by moderate diffuse cloudy swelling, occasional vacuolization, scattered foci of focal necrosis in the central portion of the lobule, and some enlarged liver cells having a hyperchromatic nucleus and a prominent nucleolus. In the kidney, the only abnormality observed was a moderate degenerative change in the epithelial lining of the convoluted tubules.

These or other deviations from normal were not observed in those rats exposed in a similar way to 500 ppm of the solvent vapor.

Repeated exposure—guinea pigs. Groups each consisting of nine males and eight female guinea pigs were started on the experiment at both the 500 and 1000 ppm

TABLE II

Final Average Body, Liver, and Kidney Weights and Biochemical Values from Rats that Received Repeated Seven-hour Exposures to a Solvent Mixture (Dowclene EC Cleaner) Five Days a Week for Six Months

Vapor Conc. ppm	Sex	No. of each group surviving		Final** Avg. Body Wt., gm	Organ Weights* gm/100gm Body Wt.		Alk. Phosphatase* King-Armstrong Units	Serum Urea Nitrogen*
		group A	group B		Liver	Kidney		mg/100 ml.
Unexposed control	M	11	9	333	2.63	0.73	32.6	21.6
Air-exposed control	M	9	10	346	2.70	0.79	22.4	18.2
1000	M	8	8	341	2.67	0.77	28.6	18.7
500	M	10	10	343	2.67	0.78	23.7	19.6
Unexposed control	F	10	11	190	2.99	0.83	20.4	26.5
Air-exposed control	F	11	11	198	3.12	0.81	14.6	24.8
1000	F	11	8	193	3.19	0.85	14.6	26.6
500	F	12	10	207	3.03	0.82	16.1	26.9

* Based on animal of group A, autopsied the day after the last exposure.
** Animals starved for 24 hours.

levels. After a few weeks it became apparent that growth of the males in both concentrations and of the females at the 1000 ppm level was being depressed. Measurement of food consumption revealed that the exposed animals were consuming only about one half as much food as the controls. Before the cause of this effect could be determined, an epidemic of respiratory infection occurred in the control as well as in the experimental groups and this made it necessary to terminate this portion of the study by sacrificing the few remaining animals. Gross and microscopic examinations of sections of the few remaining animals in the control and exposed groups revealed severe infection in the lungs with pronounced liver and kidney involvement in all groups.

Since it was believed important to determine whether the growth depression noted above was due to simple anorexia or to injury to some organ, a paired-feeding study was initiated. Males were used in this study because it appeared from the previous study that they were more sensitive than the females.

At the beginning of the experiment it was apparent promptly that the exposure to the solvent caused a marked reduction in food intake during the week when exposures were given. On the weekends, when no exposures were given, food consumption was essentially normal. Also, the magnitude of the reduction in food intake was markedly smaller for those animals exposed to 500 ppm than for those exposed to 1000 ppm of the solvent. The magnitude of the reduction in both experimental groups decreased each succeeding week so that after four weeks, food consumption was essentially normal for both experimental groups.

The growth of the animals exposed to the

TABLE III

Final Average Body, Liver, and Kidney Weights and Food Efficiency Values from Male Guinea Pigs that Received Repeated Seven-hour Exposures to a Solvent Mixture (Dowclene EC Cleaner) Five days a Week for Seven Weeks in a Paired-feeding Study

Vapor Conc. ppm	No. of Animals	Final Avg. Body Wt., gm	Avg. Body Wt. gain, gm	Organ Weights gm/100gm Body Wt.		Food Efficiency
				Liver	Kidney	gm of food eaten / gm of wt. gained
Air-exposed control	6	740	106	3.15	0.67	12.3
500	6	762	129	4.00(a)	0.71	10.6
Air-exposed control	6	706	73	3.37	0.67	16.0
1000	6	706	74	3.75(b)	0.68	16.0

(a) $P = 0.027$
(b) $P = 0.25$

TABLE IV

Final Average Body, Liver, and Kidney Weights and Biochemical Values from Rabbits that Received Repeated Seven-hour Exposures to a Solvent Mixture (Dowclene EC Cleaner) Five Days a Week for Six Months

Vapor Conc. ppm	Sex	No. Surviving / No. Started	Final Avg. Body Wt., kg.	Organ Weights gm/100gm Body Wt.		Alk. Phosphatase	Serum Urea Nitrogen
				Liver	Kidney	King-Armstrong Units	mg/100 ml
Unexposed control	M	3/3	3.57	2.29	0.48	9.1	24.5
Exposed control	M	2/3	3.42	2.66	0.54	5.8	28.2
1000	M	3/3	3.88	2.63	0.51	6.8	21.5
500	M	2/3	3.38	2.66	0.47	14.2	24.0
Unexposed control	F	3/3	4.01	2.42	0.40	10.4	28.8
Exposed control	F	3/3	3.45	2.48	0.44	7.5	23.4
1000	F	3/3	3.69	2.53	0.47	11.2	26.1
500	F	3/3	3.86	2.79	0.45	9.1	28.2

solvent vapors was not significantly different from that of their controls eating the same amount of food. The animals exposed to 1000 ppm of vapor ate less and hence gained less than those exposed to 500 ppm. Also, the food efficiency (grams of food required per gram of weight gained) of those exposed to 1000 ppm of vapor was poorer than that of those exposed at 500 ppm, but it was essentially the same as that of their controls.

The pertinent data obtained from the paired-feeding study is given in Table III. Organ weight studies show that the livers of those animals that received 500 ppm of solvent vapor were elevated slightly above those of their controls. Although the difference is statistically significant, it is not consistent with the findings for those animals exposed to 1000 ppm. Furthermore, histopathologic examination of sections from the livers and other organs from those animals exposed to 500 ppm revealed no changes when compared to the controls whereas sections from the guinea pigs exposed to 1000 ppm did reveal changes in the liver and kidney. In the liver, moderate hydropic degenerative changes in the central areas of the lobule and a few foci of focal necrosis were observed. The effect on the kidneys was characterized by degenerative changes in the epithelial lining of the convoluted tubules and round cell infiltration in the interstitial tissues, particularly around the glomeruli.

Repeated exposure—rabbits. Rabbits tolerated 126 seven-hour exposures in 182 days to 1000 ppm of the solvent vapor without any evidence of adverse effects except mild changes in the liver and kidneys observed microscopically. The changes were of the same character, but milder in intensity than those described for the rats.

The rabbits exposed to 500 ppm of solvent vapor did not show these changes and were normal in all respects when compared to control animals. The pertinent data are given in Table IV.

Repeated exposure—dogs. Dogs tolerated 131 seven-hour exposures in 189 days to 1000 ppm of the solvent vapor without any adverse effects as judged by appearance, behavior, mortality, growth, hematologic studies, urinalyses, organ weights, and the results of the various biochemical studies shown in Tables V and VI. Microscopic examination of sections of liver taken from each dog prior to any exposure, after about three months of exposure, and at autopsy revealed that definite changes had occurred in the liver of the female dog exposed to 1000 ppm of the solvent vapor. There was little difference between the effects noted in the sections from the midterm biopsy and those prepared from the liver taken at autopsy. The liver cells were large and distended and their nuclei were hyperchromatic. There was a

n Rabbits that Received
C Cleaner) Five

osphatase	Serum Urea Nitrogen
Armstrong nits	mg/100 ml
9.1	24.5
5.8	28.2
6.8	21.5
1.2	24.0
0.4	28.8
7.5	23.4
1.2	26.1
9.1	28.2

abbits. Rabbits toler-posures in 182 days to nt vapor without any effects except mild and kidneys observed changes were of the ilder in intensity than rats.

to 500 ppm of solvent changes and were n compared to con-ment data are given in

dogs. Dogs tolerated rs in 189 days to 1000 apor without any ad-l by appearance, be-o w t h, hematologic n weights, and the re-biochemical studies VI. Microscopic ex-liver taken from each ure, after about three d at autopsy revealed had occurred in the exposed to 1000 ppm There was little dif-ects noted in the sec-liopsy and those pre-ken at autopsy. The d distended and their natic. There was a

TABLE V
Final Average Body and Organ Weights from Dogs that Received Repeated Seven-hour Exposures to a Solvent Mixture (Dowclene EC Cleaner) Five Days a Week for Six Months

Vapor Conc. ppm	Sex	No. of Animals	Final Avg. Body Wt., kg	Organs Weights gm 100gm Body Weight					
				Lung	Heart	Liver	Kidney	Spleen	Testes
Unexposed control	M	1	10.4	0.99	0.85	3.52	0.52	0.24	0.16
Air-exposed control	M	1	12.5	0.72	0.57	2.85	0.41	0.21	0.10
1000	M	1	11.7	0.85	0.78	2.95	0.49	0.27	0.13
500	M	1	14.1	0.56	0.66	2.11	0.35	0.18	0.09
Unexposed control	F	1	7.9	0.90	0.66	3.40	0.40	0.19	
Air-exposed control	F	1	12.3	0.69	0.72	2.50	0.34	0.25	
1000	F	1	6.4	1.05	0.94	2.74	0.55	0.29	
500	F	1	9.6	0.86	0.84	3.71	0.52	0.40	

TABLE VI
Summary of Biochemical Values from Dogs that Received Repeated Seven-hour Exposures to a Solvent Mixture (Dowclene EC Cleaner) Five Days a Week for Six Months

Vapor Conc. ppm	Sex	No. of Dogs	Alkaline Phosphatase King-Armstrong Units			Serum Urea Nitrogen mg 100 ml			Bromsulfalein Percent Retention in Serum		SGP-T Sigma-Frankel Units
			Pre-exposure	Midterm	Terminal	Pre-exposure	Midterm	Terminal	Pre-exposure	Terminal	Terminal
Unexposed control	M	1	12.4	11.8	7.0	27.3	15.8	30.0	0.8	3.0	lost
Air-exposed control	M	1	12.2	6.8	3.8	17.0	20.0	15.1	3.4	3.9	20
1000	M	1	20.2	11.8	5.6	20.4	16.0	21.4	4.2	5.6	20
500	M	1	13.3	11.1	5.2	28.8	26.6	24.2	5.7	6.2	19
Unexposed control	F	1	14.2	10.4	6.1	19.8	30.9	16.1	2.9	3.9	20
Air-exposed control	F	1	15.4	12.9	5.0	23.6	25.0	25.4	lost	lost	27
1000	F	1	5.8	4.5	3.4	20.4	16.0	11.9	lost	4.0	26
500	F	1	13.7	13.1	8.6	31.2	18.8	18.6	7.6	5.0	23

TABLE VII

Average Concentration of Vapors in Expired Air of Dogs‡ that Received Repeated Seven-hour Exposures to a Solvent Mixture (Dowclene EC Cleaner) Five Days a Week for up to Six Months

Species	Sex	Exposure Conc. ppm	No. of Exposures	Time Sample Taken from Dogs After Last Exposure (Hours)									
				0.2 ± 0.05		1.2 ± 0.2		3.5 ± 0.1		17 ± 0.5		65 ± 1	
Dog No.				A* ppm	B * ppm	A ppm	B ppm	A ppm	B ppm	A ppm	B ppm	A ppm	B ppm
272	F	500		66	15	40	10	19	7.5	4.7	3.4	1.2	1.4
270	M	500	Up	50	11	27	7.1	15	4.6	7.1	3.5	2.4	1.8
274	F	1000	to	119	24	85	21	44	16	7.7	7.7	1.8	1.8
235	M	1000	115	94	22	55	16	25	7.8	11.3	6.8	1.9	1.5
276-279	M-F	None		None detected									

*A = 1,1,1—trichloroethane
**B = tetrachloroethylene
‡ values include an undetermined dilution factor inherent in the sampling procedure employed and hence they are not directly comparable with the values given in Table VIII.

slight increa
tissue in the
ceiving the
changes whi
normal limi
other tissue
tributable t

The dog
exposures t
were norma
of the criter

Single an
jects. The
one, four, o
ppm of the
hibited no
deviations
merous chr
jected. Th
tom obser
that his th

Observ
vapor of
The conse
initially th
tionable, a
not strong
perceptibl
days were
odor after
then only

human v
the sample
dogs and I
VII and V
from the
the conce
ethane or
air of the
posure w
posures. I
trations f
number 2
29, and 1
41, and 4
10.1, 9.7,
tetrachlor

slight increase in the amount of connective tissue in the portal spaces. The male dog receiving the same exposure showed minimal changes which were considered to be within normal limits. Sections from the numerous other tissues taken revealed no changes attributable to the exposure.

The dogs that received 131 seven-hour exposures to 500 ppm of the solvent vapor were normal in all respects as judged by all of the criteria employed.

Single and repeated exposure—human subjects. The human beings that received either one, four, or five seven-hour exposures to 520 ppm of the vapor of the solvent mixture exhibited no evidence of any adverse effect nor deviations outside normal limits in the numerous clinical tests to which they were subjected. The only untoward subjective symptom observed was the assertion by one subject that his throat felt dry during exposures.

Observations in regard to the odor of the vapor of the mixture are worthy of note. The consensus of the group was as follows: initially the odor was strong but not objectionable, after an hour it was perceptible but not strong, and after five hours it was barely perceptible. Persons exposed on consecutive days were barely able to detect the solvent odor after two or three hours of exposure, and then only upon deep inspiration.

Analysis of expired air from dogs and human subjects. The results of analyses of the samples of expired air taken from the dogs and human subjects are given in Tables VII and VIII. Although it is not apparent from the summary data given in Table VII, the concentration of either 1,1,1-trichloroethane or tetrachloroethylene in the expired air of the dogs at any given time after an exposure was not related to the number of exposures. For example, the range of concentrations found in samples taken from dog number 272 about 1.2 hours after 1, 2, 5, 10, 29, and 113 exposures were 49, 43, 32, 35, 41, and 41 ppm of 1,1,1-trichloroethane and 10.1, 9.7, 10.8, 9.4, 12.9, and 9.1 ppm of tetrachloroethylene. The same type of data were obtained at the other sampling times. The ranges were always narrow for any one dog but varied from one dog to another. It is interesting to note also that 65 hours after the last exposure, the levels of each constituent material in the exhaled air of the dogs do not appear to be dependent upon the concentration inhaled, at least within the range of 500 to 1000 ppm.

The data in Table VIII indicate that the concentration of either 1,1,1-trichloroethane or tetrachloroethylene in the expired air of humans becomes stabilized after two or three seven-hour exposures, rather than after one exposure as in a dog. It also indicates that although the levels of solvent in the expired air one-half hour after a single exposure are similar to the levels one-half hour after several exposures, the levels an hour or more postexposure are distinctly lower. The rate of excretion after the first few hours appears to be independent of the number of exposures. This suggests that there is some deposition of both constituent solvents within the body as a result of a single exposure, and that the level of deposition is only slightly greater after repeated exposures than after one.

Discussion

The results of the studies described in this report show that the solvent mixture does not possess toxic properties above and beyond those which would be expected from a knowledge of the toxicity of its constituents. Exposure to 500 ppm of the vapors of the mixture amounts to simultaneous exposure to 400 ppm of inhibited 1,1,1-trichloroethane (Chlorothene NU Solvent) and 100 ppm of tetrachloroethylene. Under the conditions described, neither material alone in these concentrations would be expected to cause any adverse effect and in the absence of potentiation, none would be expected from the mixture; the data obtained substantiate this expectation. Likewise, exposure to 1000 ppm of the vapors of the mixture amounts to simultaneous exposure to 800 ppm of inhibited 1,1,1-trichloroethane and 200 ppm of tetrachloroethylene. Although 800 ppm of

TABLE VIII

Concentration of Vapors in Expired Air of Male Human Subjects that Received Seven-hour Exposures to 520 ppm of a Solvent Mixture (Dowclene EC Cleaner)

Individual	No. of Exposures	Time After Exposure Sample Was Taken (Hours)											
		0.5		1.0		3.0		16		24		64	
		A* ppm	B** ppm	A ppm	B ppm	A ppm	B ppm	A ppm	B ppm	A ppm	B ppm	A ppm	B ppm
R.S.	1	82	20	73	17	33	9	11	4				
	2	90	22	75	20	40	11	—	—				
	3	91	26	81	22	34	15	17	8				
	4	—	—	68	20	43	17	16	8				
	5	81	27	66	23	46	16	—	—	11	5	10	4
D.E.	1	83	22	62	19	32	10	10	4				
	2	92	28	54	20	40	15	—	—				
	3	114	27	66	21	44	16	21	10				
	4	—	—	57	21	44	18	18	10				
	5	93	32	76	28	44	17	—	—	—	—	7	4
H.O.	1	83	20	54	14	30	8	9	3				
	2	66	20	53	15	38	10	12	5				
	3	81	22	52	16	33	12	—	—				
	4	—	—	49	17	40	13	12	6				
	5	67	21	57	19	40	12	—	—	12	4	9	4
V.R.	1	—	—	—	—	39	10	10	3				
	2	—	—	64	18	39	12	16	5				
	3	75	20	64	20	42	13	16	6				
	4	—	—	66	10	43	14	14	7	11	4	—	—
T.T.	1	83	20	45	13	20	6	10	3	—	—	6.5	2.4

*A = 1,1,1—trichloroethane
**B = tetrachloroethylene

the inhibi
would not
jury, some
ppm of te
is no poten
injury woul
tained subs
support for
single-dose
1. The fac
ture lies h
1,1,1-triehl
lack of pot
calculating
mixture fo
stituent; t
superimpos

The dat
pired air s
subjects gi
nificance
at the pre
similar dat

The stu
dogs exp
tained fro
up to 5 d
equilibriu
further, t
which oc
absence o
interpreta
study inv
but also s
tissues an

Summary

A solve
consisting
1-trichlor
ylene by
using mu
and hum
single-do
ing from
of small
the eyes
absorbed
for 24-h
gm/kg.

the inhibited 1,1,1-trichloroethane alone would not be expected to cause organic injury, some injury would be expected from 200 ppm of tetrachloroethylene. Again, if there is no potentiation, some, but not substantial injury would be expected and the data obtained substantiate this expectation. Further support for this is found in the results of the single-dose inhalation studies shown in Figure 1. The fact that the LC_{50} curve for the mixture lies below, but close to the curve for 1,1,1-trichloroethane alone, is evidence of the lack of potentiation. This was confirmed by calculating an "expected LC_{50} curve" for the mixture from the LC_{50} data for each constituent; this resulted in a line essentially superimposed on the observed line.

The data obtained from the analysis of expired air samples from both dogs and human subjects gives valuable information, the significance of which may not be entirely clear at the present time because of the lack of similar data on other substances.

The similarity in data obtained from the dogs exposed for six months and that obtained from the human subjects exposed for up to 5 days, strongly suggests that a state of equilibrium must be readily attained; and further, the major portion of any deposits which occur must be readily depleted in the absence of exposure. Confirmation of these interpretations will have to await further study involving not only expired-air samples but also serial sampling and analysis of body tissues and possibly material balance studies.

Summary

A solvent mixture (Dowclene EC Cleaner) consisting essentially of 75% of inhibited 1,1,-1-trichloroethane and 25% of tetrachloroethylene by weight has been studied extensively using mice, rats, guinea pigs, rabbits, dogs, and human subjects. The solvent is low in single-dose oral toxicity, the LD_{50} doses ranging from 5.7 to 14.8 gm/kg for the four species of small animals. It is but mildly irritating to the eyes and skin of rabbits. It is not readily absorbed through the skin of rabbits; the LD_{50} for 24-hour exposures being greater than 30 gm/kg. The single-dose inhalation toxicity is low for rats, the LC_{50} concentration being approximately 24,000, 20,000, 16,500, 14,000, and 12,000 ppm for exposures of 0.5, 1.0, 2.0, 4.0, and 7.0 hours.

The repeated-dose inhalation toxicity of the solvent also is low. Rats, guinea pigs, rabbits, and one of two dogs that received repeated seven-hour exposures to 1000 ppm of the vapor exhibited mild and reversible liver and kidney changes. Rats exposed to 1000 ppm for four hours a day or less and those maintained under control conditions for six weeks after six months of daily exposure were normal. The growth of guinea pigs was depressed; a paired-feeding study showed this to be due to a decreased intake of food.

Rats, guinea pigs, rabbits, and dogs that received repeated seven-hour exposures to 500 ppm of the vapor suffered no adverse effects other than a slight depression of growth in the guinea pigs; again, this was due to decreased intake of food.

Human subjects that received from one to five seven-hour exposures to 520 ppm of the solvent vapor experienced no adverse effects when judged by a battery of subjective observations and clinical and laboratory studies.

Excretion of both major constituents of the mixture via the lungs occurs in both dogs and human subjects at a substantial rate, particularly during the first 18 to 24 hours postexposure. This fact may well be one of the main reasons why the toxicity, both acute and chronic, is so low.

As a result of the extensive studies conducted, it is concluded that there is no appreciable hazard from repeated seven-hour exposures to 500 ppm of the solvent mixture (Dowclene EC Cleaner). Therefore, it is recommended for normal operation that the concentrations of vapor to which persons are exposed repeatedly, seven to eight hours a day, be below 500 ppm. Occasional exposure of short duration to slightly higher concentrations would not be expected to cause organic injury, but from a subjective viewpoint, might well be objectionable to some people. It is further recommended that any exposures to concentrations exceeding 800 ppm be avoided and that the time-

*A = 1,1,1-trichloroethane
**B = tetrachloroethylene

weighted average concentration not exceed 400 ppm.

Acknowledgment

The authors wish to thank H. H. Gay, M.D., D. S. Erley, C. F. Licht, H. Ode, G. J. Wright, T. R. Torkelson for participating in the studies on human subjects, A. W. Schaffer and Lorna Stolpe for their help in monitoring the vapor concentrations to which persons were exposed, and the many other persons who assisted in the biochemical and analytical work.

References

1. Torkelson, T. R., F. Oyen, D. D. McCollister, and V. K. Rowe: Toxicity of 1,1,1-Trichloroethane as Determined on Laboratory Animals and Human Subjects. *Amer. Ind. Hyg. Assoc. J. 19:* 353 (1958).
2. Rowe, V. K., D. D. McCollister, H. C. Spencer, E. M. Adams, and D. D. Irish: Vapor Toxicity of Tetrachloroethylene for Laboratory Animals and Human Subjects. *AMA Arch. Ind. Hyg. and Occup. Med. 5:* 566 (1925).
3. Wolf, M. A., V. K. Rowe, D. D. McCollister, R. L. Hollingsworth, and F. Oyen: Toxicological Studies on Certain Alkylated Benzenes and Benzene. *AMA Arch. Ind. Health 14:* 387 (1956).
4. Draize, J. H., G. Woodard, and H. O Calvery: Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes. *J. Pharmacol. Exptl. Therap. 82:* 377 (1944).
5. Yaffe, C. D., D. H. Byers, and A. D. Hosey, Technical Editors: *Encyclopedia of Instrumentation for Industrial Hygiene.* p. 95, University of Michigan Institute of Industrial Health, Ann Arbor, Michigan (1956).
6. Stewart, R. D., H. H. Gay, D. S. Erley, C. L. Hake, and A. W. Schaffer: Human Exposure to 1,1,1-Trichloroethane Vapor: Relationship of Expired Air and Blood Concentrations to Exposure and Toxicity. *Amer. Ind. Hyg. Assoc. J. 22:* 252 (1961).
7. Stewart, R. D., H. H. Gay, D. S. Erley, C. L. Hake, and A. W. Schaffer: Human Exposure to Tetrachloroethylene Vapor: Relationship of Expired Air and Blood Concentrations to Exposure and Toxicity. *AMA Arch. Environ. Health 2:* 516 (1961).
8. Fisher, R. A.: Statistical Methods for Research Workers, Ed. 7, London, Oliver and Boyd Ltd., (1938).
9. Schaffer, A. W., and H. R. Hoyle: Nine Years' Experience with the Davis Halide Meter. *Amer. Ind. Hyg. Assoc. J. 22:* 93 (1961).
10. Peterson, J. E., H. R. Hoyle, and E. J. Schneider: The Analysis of Air for Halogenated Hydrocarbon Contaminants by Means of Adsorption on Silica Gel. *Amer. Ind. Hyg. Assoc. J. 17:* 429 (1956).

Obituary

Dr. Charles W. LaBelle, Assistant Professor of Environmental Hygiene at Jefferson Medical College of Philadelphia, died on November 7, 1963, after an illness of only two days' duration. He received his bachelor degree from the University of Rochester in 1945. He became a Research Assistant in the Department of Pharmacology of the Medical School of this University and participated in its Atomic Energy Project. From 1950 to 1954, he worked as toxicologist at the Army Chemical Center. Since then, he had been with the Department of Preventive Medicine, Jefferson Medical College, and obtained the doctoral degree in pharmacology and toxicology in 1959. Dr. LaBelle is widely known for his work in the field of behavior and biological effects of particulate air contaminants. This Journal was privileged to publish one of his most recent publications in the preceding issue. He joined the American Industrial Hygiene Association in 1948 and had been an active member of the Association since that time. We join Dr. LaBelle's friends and co-workers in expressing our deep sense of loss, both personal and professional.

A Continuously
Air-

ALFRED L.

U. S. Publ

A vacuum tube el
ble, shortened con
ion concentrations in
which produce a cons
stant of approximatel
levels of concentration

Introduction

INTEREST in the biologi
borne ions dates from t
F. Dessauer in 1921, and l
ject of many investigations
An attempt to make a q
of the effects of ions on ani
able instruments for gen
measuring their concentra
describes an instrument f
concentrations in air.

A review of the literatu
struments and techniques o
us to adopt many of the
ion collectors and to de
inexpensive, continuously
trometer. The advantag
recording over intermitte
apparent; one important
any change in the ion l
the ion generators is quick
effects of adjustments are d
ly that it is relatively simpl
best ways to generate the
of ions desired.

The ions found in the
to be formed by the actio
other circumstances whic
electron from an otherwi
gas. The immediate prod
event is an ion pair; the
atom or molecule with
and an electron which q

*Present address: The Univer
School of Public Health, Chapel H

Ann. Occup. Hyg. Vol. 11, pp. 71–79. Pergamon Press 1968. Printed in Great Britain

THE TOXICOLOGY OF 1,1,1-TRICHLOROETHANE

RICHARD D. STEWART

Department of Environmental Medicine, Marquette University School of Medicine, Milwaukee, Wisconsin, U.S.A.

(*Received* 23 *September* 1967)

Abstract—Judging from the human toxiological data reported, 1,1,1-trichloroethane appears to be one of the least toxic members of the group of chlorinated aliphatic hydrocarbon solvents. This compound is rapidly absorbed through the lungs and the gastrointestinal tract. Most of it is excreted unchanged via the lungs. The absorption of a toxic quantity results in a functional depression of the central nervous system which may result in death from respiratory arrest or peripheral vascular collapse. Acute over-exposure to anesthetic concentrations of the vapour can result in transcient kidney or liver dysfunction. Permanent organic injury has not been observed following recovery from the anesthetic effects of this solvent.

The diagnosis of exposure to this compound can be made by specifically identifying 1,1,1-trichloroethane in the expired breath of the exposed person. Comparison of the results of serial breath analyses with available human data affords a means with which to estimate the magnitude of the chemical exposure.

SINCE the commercial introduction of 1,1,1-trichloroethane (methyl chloroform) in 1954, this solvent (in its inhibited form available under the trademark Chlorothene NU) has become increasingly popular, primarily because of its low toxicity. Its use now exceeds 40 million pounds per year in the United States, where it has been used principally for cold-cleaning, dip-cleaning, and bucket-cleaning of metal for the removal of greases, oils, and waxes. It has also proved useful in dry-cleaning, in vapour degreasing, and in aerosol applications. Because of the solvent's increasing use in Europe and since it is being promoted as one of the safest of the chlorinated aliphatic hydrocarbon solvents, it is appropriate for the physician to examine the existing toxicological information.

Physical and chemical properties

1,1,1-trichloroethane, CH_3CCl_3, is a colourless liquid possessing a distinctive, chloroform-like odour. It has a specific gravity of 1·336 at 25°C, a vapour pressure of 127 mm Hg at 25°C, and a boiling point of 74·1°C. This compound is very soluble in organic solvents such as carbon bisulfide and carbon tetrachloride, but it is only slightly soluble in water (VAN ARKEL and VLES, 1936). Like many chlorinated hydrocarbons it reacts with aluminium and aluminium alloys and must be inhibited if corrosion is to be prevented. Inhibited formulations are marketed under various trade names.

1,1,1-trichloroethane is not flammable, nor will it support combustion in air at standard temperature and pressure. The limits of flammability of the vapours of the

inhibited compound are 10 15·5 per cent in air with hot wire ignition only when considerable energy is used for ignition. It has no flash point or fire point using the standard ASTM procedures for the Tag closed-cup and Cleveland open-cup tests.

At temperatures below 260°C, only minimal thermal decomposition occurs. At 260°C, large amounts of hydrogen chloride and trace amounts of phosgene are formed (CRUMMET and STENGER, 1956). Sufficient hydrogen chloride is formed to provide adequate warning.

Absorption, metabolism, and excretion

1,1,1-trichloroethane is rapidly absorbed through the lungs and the gastro-intestinal tract. Following absorption, most of the compound is eliminated unchanged via the lungs. Nearly 98 per cent was excreted unchanged in the expired air of the rat following an intraperitoneal injection of C^{14}-labeled compound (HAKE *et al.*, 1960). One-half per cent of the dose was metabolized to carbon dioxide while the remainder appeared in the urine as the glucuronide of 2,2,2-trichloroethanol.

Man, like the rat, is able to metabolize a small percentage of this solvent to trichloroethanol (STEWART *et al.*). Five male volunteers were exposed to 500 ppm of inhibited* 1,1,1-trichloroethane, 7 hours per day for five consecutive days. Nine months later the same subjects were exposed to trichloroethylene vapour, 200 ppm, 7 hours per day for five days. Twenty-four hour urine collections obtained before, during, and following these vapour exposures were analyzed for trichloroethanol and trichloroacetic acid. These data are presented in Table 1. The difference in the metabolism of these two compounds in man is striking.

TABLE 1.† URINARY EXCRETION OF TRICHLOROACETIC ACID (TAC) AND TRICHLOROETHANOL (TCE) IN FIVE SUBJECTS DURING AND FOLLOWING VAPOR EXPOSURES TO 1,1,1-TRICHLOROETHANE AND TRICHLOROETHYLENE

	1,1,1-Trichloroethane, 500 ppm 7 hr/day for 5 days		Trichloroethylene, 200 ppm 7 hr/day for 5 days	
	TCA (mg/24 hr)	TCE (mg/24 hr)	TCA (mg/24 hr)	TCE (mg/24 hr)
Control value (mean and range)	14,2 (8–22,8)	< 1 (<1–1)	2 (1–4)	<1 (<1–3)
1st Exposure day	7,5 (2,6–10,5)	20,1 (7,9–49)	51 (34–84)	308 (179–430)
2nd Exposure day	10,9 (8,2–19,3)	30,1 (14,8–66,5	175 (113–238)	359 (294–480)
3rd Exposure day	12,3 (5,6–27)	29,3 (19,1–51)	229 (148–416)	399 (296–546)
4th Exposure day	14,1 (7,8–19,2)	46,6 (23,4–93,6)	306 (231–439)	538 (249–822)
5th Day following last exposure	18 (13–26)	7 (1–14,9)	50 (35–61)	15 (10–18)
12th Day following last exposure	17,5 (8–22)	<1 (<1,)	8 (2–22)	14 (1–37)

†Stewart *et al.*, to be published.

The absorption of 1,1,1-trichloroethane through the skin of the hand has been measured in six human subjects (STEWART and DODD, 1964). Continuous immersion of the thumb for 30 minutes demonstrated that this solvent was able to penetrate the skin, enter the blood stream, and be excreted in part through the lungs. The total

*Chlorothene–NU.

amount absorbed through the skin, however, was very small (Fig. 1). Continuous topical application of this solvent to the entire hand for 30 minutes resulted in even less absorption. These skin absorption studies showed that unless the solvent is confined to the skin beneath an impermeable barrier, absorption of toxic amounts through the skin in the course of normal industrial operations is highly unlikely.

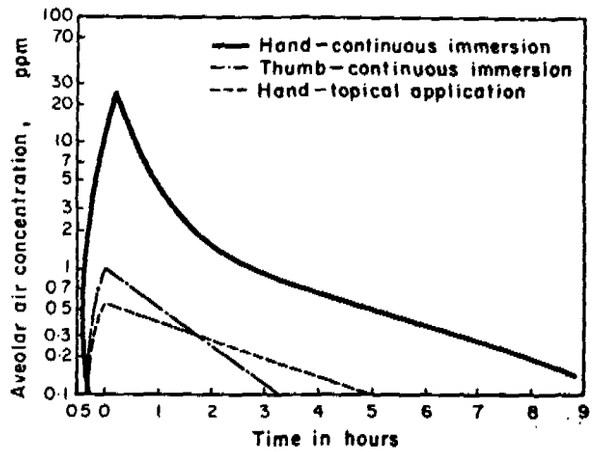


FIG. 1. The alveolar air concentrations for 1,1,1-trichloroethane during and following 30 minutes of skin exposure are plotted vs. time. Topical application of the solvent to the skin of the hand resulted in far less absorption than when the hand was continuously immersed for a similar period of time.

Toxicity

Acute vapour exposure. The principal toxic action of a single vapour exposure is a functional depression of the central nervous system, proportional to the magnitude of exposure, and typical of an anesthetic agent.

Humans exposed to 900–1000 ppm experienced transient, mild eye irritation and prompt, though minimal, impairment of coordination (STEWART *et al.*, 1961; TORKELSON *et al.*, 1958). Above 1700 ppm obvious disturbances of equilibrium in humans have been observed (STEWART *et al.*, 1961). Exposures of this magnitude also may induce headache and lassitude. Nausea has not been reported.

Below the current Threshold Limit Value* of 350 ppm no physiological effects have been observed. The studies on man which have been conducted have demonstrated that there is a variation in human response to a given concentration of 1,1,1-trichloroethane vapour (STEWART *et al.*, 1961 and unpublished work). Of the test procedures investigated, the modified Romberg test† has proved to be the most sensitive, objective, neurological sign of over-exposure (STEWART *et al.*, 1961 and

*The Threshold Limit Value of the American Conference of Governmental Industrial Hygienists is a limiting concentration which should not be exceeded by the *average* of the time-weighted concentrations throughout the 8-hr day.

†Modified Romberg test: subject with eyes closed and with his arms at his sides, balances on one foot.

unpublished work). In the past 15 years, two individuals have been studied who normally had difficulty in performing the modified Romberg test and who demonstrated increased difficulty in performing the test at a vapour concentration of 400 ppm. Another individual has demonstrated a normal modified Romberg test at a vapour concentration of 2650 ppm (STEWART *et al.*, 1961). Thirty healthy volunteer subjects exposed to a vapour concentration of 500 ppm for periods from one hour to one work week, were able to repeatedly perform normal modified Romberg tests (STEWART *et al.*, 1961 and unpublished work; TORKELSON *et al.*, 1958).

General anesthesia in 51 humans, male and female, ranging in age from 9 to 70 years, has been reported (KRANTZ *et al.*, 1959; DORNETTE and JONES, 1960). Recovery from anesthesia and regaining of reflexes was quite rapid, usually within 3 to 5 minutes after discontinuance of the anesthetic agent if the patient had been in a light plane. Recovery from deeper planes was slightly more prolonged. Twenty patients were conscious and responsive before being taken into the recovery room and the majority of the others recovered soon after arriving. These patients had a very low incidence of post-operative nausea and vomiting and the normal serum glutamic oxaloactic transaminase values measured on the second, fourth, and sixth post-operative days suggested that anesthesia with this compound up to two hours duration would not produce hepatotoxicity (DORNETTE and JONES, 1960).

Six human deaths as a result of over-exposure to 1,1,1-trichloroethane have been reported. Four deaths occurred following exposure to very high concentrations in unventilated tanks (STEWART *et al.*, 1961; KLEINFELD and FEINER, 1966) In one of these tanks the concentration of 1,1,1-trichloroethane at the time of the accident was "well in excess of 5000 ppm" (KLEINFELD and FEINER, 1966). One death occurred in an open tank in which vapour concentrations exceeded several thousand ppm (ROWE, personal communication). Two suicide deaths by inhalation have been reported (HALL and HINE, 1966). One of these deaths was attributed to respiratory arrest while the second death was caused by aspiration pneumonitis.

In 1964 the Toxicology Committee of the American Industrial Hygiene Association presented a new series of guides to Emergency Exposure Limits which were intended to give guidance to industrial hygienists in the management of single, brief exposures to airborne contaminants in the working environment. Table 2 lists the recommendations for 1,1,1-trichloroethane (Toxicology Committee, Am. Ind. Hyg. Ass., 1964).

Vapour exposures in experimental animals have been the basis for most of our understanding of the effects of 1,1,1-trichloroethane on man. Acute deaths in experimental animals presumably have been due to central nervous system depression culminating in respiratory arrest (ADAMS *et al.*, 1950). A vapour concentration of 18,000 ppm for three hours was lethal for 50 per cent of exposed white rats; a 3-hr exposure to 10,000 ppm produced irregular respiration and a semicomatose state, but no deaths resulted.

A disturbing property of this compound, as is the case with most solvents, is that at anesthetic concentrations, idioventricular rhythms may be induced in animals with epinephrine (RENNICK *et al.*, 1949). Therefore, it is possible that ventricular fibrillation leading to sudden death could occur in humans exposed to anesthetic concentrations.

TABLE 2.* PROBABLE RESULT OF SINGLE EXPOSURE TO THE VAPORS OF 1,1,1-TRICHLOROETHANE

Exposure time (min)	Concentration in air (ppm)	Expected effect in humans
5	20,000	Complete incoordination and helplessness (R)
	10,000	Pronounced loss of coordination (R)
	5000	Definite incoordination (R, M)
	2000	Disturbance of equilibrium. Odor is unpleasant but tolerable (H)
15	10,000	Pronounced loss of coordination (R)
	2000	Loss of equilibrium (H)
	1000	Possible beginning loss of equilibrium (H)
30	10,000	Pronounced loss of coordination (R)
	5000	Incoordination (R, M)
	2000	Loss of equilibrium (H)
	1000	Mild eye and nasal discomfort; possible slight loss of equilibrium (H)
60	20,000	Surgical anesthesia, possible death (R)
	10,000	Pronounced loss of coordination (R)
	5000	Obvious loss of coordination (R, M)
	2000	Loss of coordination (H)
	1000	Very slight loss of equilibrium (H)
	500	No detectable effect, but odor is obvious (R, H)
	100	Apparent odor threshold (H)

*Toxicology Committee, Am. Ind. Hyg. Ass., 1964.
(H) Expected effects are based on human data.
(M) Expected effects are based on monkey data.
(R) Expected effects are based on rat data.

Studies conducted on dogs and monkeys anesthetized with 1,1,1-trichloroethane by a closed technique revealed no significant change in electrocardiograms during 60 minutes of deep surgical anesthesia; however, a depressor response upon the blood pressure was observed (KRANTZ *et al.*, 1959). At the point of respiratory arrest, the blood pressure was reduced to approximately one-half of its normal value. This is in contrast to the minimal blood pressure depression produced by ethyl ether-indiced respiratory arrest.

Rats deeply anesthetized with 1,1,1-trichloroethane for one hour showed a 33·3 per cent diminution in oxygen uptake of the myocardium, very similar to that observed with chloroform anesthesia (KRANTZ *et al.*, 1959).

The failure of 1,1,1-trichloroethane to significantly impair liver function in mice, as measured by the prolongation of pentobarbital sleeping time, has been reported by PLAA *et al.* (1958). The hepatotoxic potency of the chlorinated hydrocarbons studied, arranged in order of increasing toxicity was: 1,1,1-trichloroethane, tetrachloroethylene, trichloroethylene, tetrachloroethane, 1,1,2-trichloroethane, chloroform, and carbon tetrachloride. Following intraperitoneal injections of near-lethal dosages of 1,1,1-trichloroethane into mice, only mild hepatic dysfunction and no renal dysfunction was noted (KLAASSEN *et al.*, 1966).

To produce histological evidence of liver injury in white rats, vapour concentrations of 8000 ppm for 7 hours were required (ADAMS *et al.*, 1950). A 5-hr exposure at the same concentration did not result in histological evidence of liver injury.

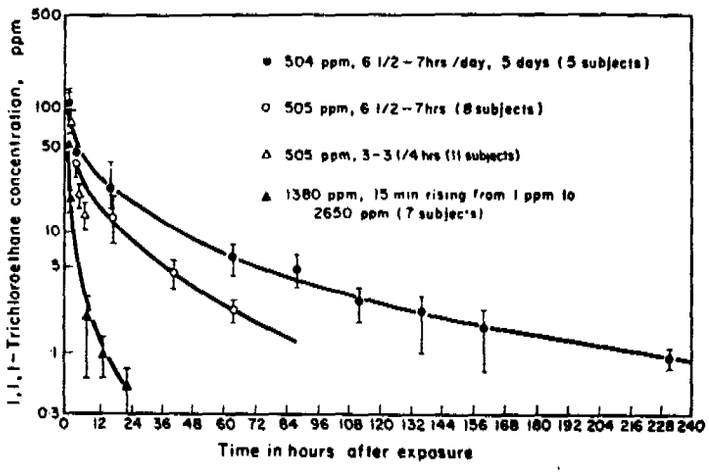


FIG. 2. 1,1,1-Trichloroethane alveolar air concentrations following exposures to different vapor concentrations and for varying periods of time are shown. Mean and range breath concentrations are plotted.

Repeated vapour exposure

It is unlikely that significant organic injury resulting from repeated vapour exposure will occur in the absence of acute effects. No injury to man following repeated exposures to vapour concentrations of less than 500 ppm has been observed (STEWART *et al.*, 1961 and unpublished work; DOW CHEMICAL COMPANY, Medical Records). Rats, guinea-pigs, rabbits, and monkeys were unaffected after 6 months repeated 7-hr exposures, 5 days per week to 500 ppm (TORKELSON *et al.*, 1958; ADAMS *et al.*, 1950). Female guinea pigs which were found to be the most sensitive in previous experiments were able to tolerate 1000 ppm for 0·6 hr per day for three months. Male rats tolerated exposure of 0·5 hr per day to 10,000 ppm with no organic injury (TORKELSON *et al*, 1958). Rabbits and dogs exposed to 2200 ppm for 8 hr per day for 6 weeks showed no visible signs of toxicity, although body weight loss occurred (PRENDERGAST *et al.*, 1967).

Ingestion

Absorption of a substantial amount of 1,1,1-trichloroethane from the gastrointestinal tract will produce the same functional depression of the central nervous system as described following vapour inhalation. If the amount ingested is sufficient to produce loss of consciousness, impairment of liver function may result.

The case of a 47 year old male, who accidentally ingested one ounce of inhibited 1,1,1-trichloroethane, has been reported (STEWART and ANDREWS, 1966). Thirty minutes after solvent ingestion the patient became nauseated. One hour after ingestion he began vomiting and experienced the onset of diarrhea. Two and one-half hours after ingestion, the vomiting and diarrhea became incapacitating. Six hours after ingestion the diarrhea and vomiting subsided at which time the patient's only complaint was fatigue. The physical examination was completely within normal limits. Two and one-half hours after ingestion, the patient had a leukocytosis and 1+ proteinuria. A slight elevation in the serum bilirubin concentration was noted 48 hours following admission. No deviation from normal was noted in serial complete blood cell counts, urinalyses, tests for serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, blood urea nitrogen and electrocardiograms performed throughout the hospital stay and again six months following the incident.

The median lethal oral dose of inhibited 1,1,1-trichloroethane in four species of experimental animals is reported to range from 8·6 to 14·3 gm/kg (CARPENTER *et al.*, 1949).

Eye contact

Several drops of 1,1,1-trichloroethane splashed directly on the cornea may produce a mild conjunctivitis which will subside within a few days (DOW CHEMICAL COMPANY, Medical Records).

Skin contact

Prolonged or repeated contact with the skin results in transient erythema and slight irritation, secondary to the solvent's defatting action. Significant skin absorption is unlikely in industrial applications unless the compound is confined to the skin surface beneath an impermeable barrier.

Diagnosis of exposure to 1,1,1-trichloroethane

The presumptive diagnosis of 1,1,1-trichloroethane exposure is usually suggested by the history. In the cases of acute intoxication, the chloroform-like odour of the compound can be detected on the patient's breath for several hours after exposure. When excessive absorption of the compound has occurred, a clinical complex is observed which features depression of the central nervous system, occasionally followed by transient hepatic and renal dysfunction.

Diagnosis of excessive absorption of 1,1,1-trichloroethane can be established unequivocally upon quantitative determination of the compound in the patient's blood, tissue, or expired breath. At the present time, breath analysis is the most practical and most sensitive detection method to employ. The analytical techniques have been described in detail (STEWART and DODD, 1964; STEWART and ERLEY, 1965; STEWART *et al.*, 1965).

If a significant exposure has occurred, the compound will be present in the expired breath in sufficient concentrations to allow specific identification by simple infrared

spectrographic techniques for at least 24 hours into the post-exposure period (STEWART *et al.*, 1961 and unpublished work). Gas chromatographic techniques offer exquisite sensitivity and can be used to detect compound in the breath for days following vapour exposure.

Expired air (alveolar) for analysis is conveniently collected in 6 l. plastic (Saran) bags when infrared techniques are to be employed (STEWART and ERLEY, 1965). When the gas chromatographic techniques are used, 50 ml aliquots of breath are collected in small glass pipettes (STEWART and DODD, 1964). Breath samples can be stored for long periods of time in the pipettes, which can be conveniently mailed to analytical laboratories.

The concentration of 1,1,1-trichloroethane in the post-exposure expired air is directly related to several factors: (1) the atmospheric concentration of the solvent, (2) the duration of exposure, (3) the time elapsed following exposure, (4) the respiratory characteristics of the individual during and following the exposure, and (5) the total body-lipid repository.

Serial breath analyses establish the rate of excretion through the lungs. Comparison of the patient's peak breath concentration and rate of excretion with those human data available (Fig. 2) affords the physician a means with which to estimate the magnitude of the chemical exposure (STEWART *et al.*, 1964 and unpublished work; TORKELSON, 1958).

Treatment

There is no specific treatment for 1,1,1-trichloroethane intoxication. Prompt supportive measures should be utilized to combat the effects of central nervous system depression. Because this compound is primarily excreted via the lungs, oxygen with carbon dioxide can be administered to facilitate its elimination. Breathing should be assisted if the respiratory centre has been overly depressed.

Severe hypotension may be induced by a combination of central nervous system depression and myocardial anoxia, secondary to poor oxygen uptake. Epinephrine-like drugs must not be used to combat this hypotension because of the danger of inducing ventricular fibrillation. This danger is not unique to 1,1,1-trichloroethane, but is common to many solvents.

Acknowledgement—This work was performed while the author was employed by THE DOW CHEMICAL COMPANY and is published with their permission.

REFERENCES

ADAMS, E. M., SPENCER, H. C., ROWE, V. K. and IRISH, D. C. (1950) Vapor toxicity of 1,1,1-trichloroethane (methyl chloroform) determined by experiments on laboratory animals. *A.M.A. Archs. ind. Hyg.* 1, 225.

CARPENTER, C. P., SMYTH, H. F., JR. and POZZANI, U. C. (1949) The assay of acute vapor toxicity and the grading and interpretation of results on 96 chemical compounds. *J. ind. Hyg. Toxicol.* 31, 343.

CRUMMETT, W. B. and STENGER, V. A. (1956) Thermal stability of methyl chloroform and carbon tetrachloride. *Ind. Engng Chem. analyt. Edn* 48, 434.

DORNETTE, W. H. L. and JONES, J. P. (1960) Clinical experiences with 1,1,1-trichloroethane (a preliminary report of 50 anesthetic administrations). *Anesth. Analg.* 39, 249–253.

THE DOW CHEMICAL COMPANY, Midland, Michigan. Medical Records.
HAKE, C. L., WAGGONER, T. B., ROBERTSON, D. N. and ROWE, V. K. (1960) The metabolism of 1,1,1-trichloroethane by the rat. *Archs. envir. Hlth.* **1**, 101.
HALL, F. B. and HINE, C. H. (1966) *Trichloroethane Intoxication*, a report of two cases presented before the American Academy of Forensic Sciences, Chicago, Illinois.
KLAASSEN, C. D. and PLAA, G. L. (1966) Relative effects of various chlorinated hydrocarbons on liver and kidney function in mice. *Toxic. appl. Pharmac.* **9**, 139
KLEINFELD, M. and FEINER, B. (1966) Health hazards associated with work in confined spaces. *J. occup. Med.* **8**, 358–364.
KRANTZ, J. C. JR., PARK, C. S. and LING, J. S. L. (1959) Anesthesia LX: the anesthesic properties of 1,1,1-trichloroethane. *Anesthesiology* **20**, 635.
PLAA, G. L., EVANS, E. A. and HINE, C. H. (1958) Relative hepatotoxicity of seven halogenated hydrocarbons. *J. Pharmac. exp. Ther.* **123**, 224.
PRENDERGAST, J. A., JONES, R. A., JENKINS, L. J. and SIEGEL, J. (1967) Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane, and 1,1-dichloroethylene. *Toxic. appl. Pharmac.* **10**, 270.
RENNICK, B. R., MALTON, S. D., MOE, G. K. and SEEVERS, M. H. (1949) Induction of idioventricular rhythms by 1,1,1-trichloroethane and epinephrine. *J. Pharmac. exp. Ther.* **8**, 327.
ROWE, V. K. The Dow Chemical Company, Midland, Michigan. Personal communication.
STEWART, R. D. and ANDREWS, J. T. (1966) Acute intoxication with methylchloroform. *J. Am. med. Ass.* **195**, No. 11.
STEWART, R. D. and DODD, H. C. (1964) Absorption of carbon tetrachloride, trichloroethane, tetrachloroethylene, methylene chloride, and 1,1,1-trichloroethane through the human skin. *Am. ind. Hyg. Ass. J.* **25**, 439–446.
STEWART, R. D. and ERLEY, D. S. (1965) Detection of Volatile Organic Compounds and Toxic Cases in Humans by Rapid Infrared Techniques, in *Progress in Chemical Toxicology* (Edited by STOLMAN, A.) Vol. 2, Academic Press, Inc., pp. 183–220. New York.
STEWART, R. D. *et al.* (1965) Diagnosis of solvent poisoning. *J. Am. med. Ass.* **193**, 1097–1100.
STEWART, R. D., GAY, H. H., ERLEY, D. S., HAKE, C. L. and SCHAFFER, A. W. (1961) Human exposure to 1,1,1-trichloroethane vapor: relationship of expired air and blood concentrations to exposure and toxicity. *Am. ind. Hyg. Ass. J.* **22**, 252.
STEWART, R. D., GAY, H. H., DODD, H. C., SCHAFFER, A. W., ROWE, V. K. and ERLEY, D. S. Experimental human exposure to 1,1,1-trichloroethane vapor. *Archs. envir. Hlth.* to be published.
TORKELSON, T. R., OYEN, F., MCCOLLISTER, D. D. and ROWE, V. K. (1958) Toxicity of 1,1,1-trichloroethane as determined on laboratory animals and human subjects. *Am. ind. Hyg. Ass. J.* **19**, 353.
TOXICOLOGY COMMITTEE, AMERICAN INDUSTRIAL HYGIENE ASSOCIATION. (1964) Emergency exposure limits. *Am. ind. Hyg. Ass. J.* **25**, 578–586.
VAN ARKEL, A. E. and VLES, S. E. (1936) Solubility of organic compounds in water. *Revue Trav. Chim.* **55**, 407.