Topical Review

The Toxicology of Methyl Chloroform

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METHYL CHLOROFORM, 1,1,1-trichloroethane, has become an increasingly popular solvent in recent years because of its low toxicity. It has been used primarily for cold-cleaning, dip-cleaning, and bucket-cleaning of metal for the removal of greases, oils, and waxes. Its use as a solvent in several other applications is being investigated, e.g., agricultural chemicals, dry-cleaning, and vapor degreasing. Because of its increasing use and since it has been promoted as a carbon tetrachloride substitute, it is appropriate for the physician to examine the existing toxicological information.

The 1,1,2-isomer, a more toxic compound,[1-3] has had only limited use in the laboratory and will not be included in the discussion to follow.

Physical and Chemical Properties

1,1,1-Trichloroethane, CH_3CCl_3, is a colorless liquid possessing a distinctive, chloroform-like odor. It has a specific gravity of 1.336 at 25°C., a vapor pressure of 127 mm. Hg at 25°C., and a boiling point of 74.1°C. This compound is readily soluble in organic solvents such as carbon bisulfide and carbon tetrachloride, but it is only slightly soluble in water.[4] Like many chlorinated hydrocarbons it reacts with aluminum and aluminum 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. The limits of flammability of the vapors of the inhibited compound are 10–15.5% 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.

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Only minimal thermal decomposition may be induced at temperatures below 500°F.; at 500°F. large amounts of hydrogen chloride and trace amounts of phosgene are formed.[5] 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 gastrointestinal tract. It may be absorbed in toxic quantities through the intact skin if trapped against the skin beneath an impermeable barrier. Following absorption, most of the compound is eliminated unchanged via the lungs. Nearly 98% was excreted unchanged in the expired air of the rat following an intraperitoneal injection of C^{14}-labeled compound.[6] 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.

Toxicity

Acute Vapor Exposure

The principal toxic action of a single vapor 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 experience transient, mild eye irritation and prompt, though minimal, impairment of coordination.[7,8] Below the current Threshold Limit Value of 500 ppm no physiological effects have been observed. Above 1700 ppm obvious disturbances of equilibrium in humans have been observed.[7] Exposures of this magnitude also may induce headache and lassitude. Nausea has not been reported.

Anesthesia in a human volunteer was maintained uneventfully for 30 min.[9] No significant electrocardiographic changes occurred during anesthesia; the blood pressure stabilized at 70%

Diagnosis of Exposure to 1,1,1-Trichloroethane

The diagnosis of exposure to 1,1,1-trichloroethane may be confirmed by detection of the compound in the expired air, blood, or tissue of the individual. If the exposure has been significant, the compound will be present in the expired breath in sufficient concentration to allow specific identification by simple infrared spectrographic techniques in the immediate postexposure period.[7, 13]

The concentration in the expired air and in the blood is directly related to several factors: (1) the concentration of the vapor inhaled; (2) the duration of exposure; (3) the time elapsed following exposure; (4) the breathing rate of the individual during the exposure; and (5) the whole-blood lipid concentration. The latter two factors account for most of the individual variation noted among persons who have experienced identical exposures. For example, a vapor exposure of 500 ppm for 1 hr. resulted in expired air concentrations of 22 ± 5 ppm in a group of individuals 1 hr. following exposure.[7] This decreased to 1.5 ± 0.5 ppm, 20 hr. following exposure. When the vapor exposure was extended to 3 hr., the expired air concentration was in the range of 38 ± 1 ppm 1 hr. after exposure and 3 ± 1 ppm 20 hr. after exposure. Limited expired air data have been published.[7]

Expired air for infrared analysis may be collected in 6-L.-volume Saran bags. The bagged air is introduced into a long path-length gas cell and the absorbance at 9.2 μ is measured to determine the concentration. The exponential elimination of the compound in the expired air may be followed for a prolonged period of time with the use of the electron capture detector.[16] While this device possesses exquisite sensitivity, it does lack the specificity of the infrared spectrographic method.

Following a vapor exposure, the blood concentration decreases exponentially and may not be detected by infrared methods[7] unless the vapor concentration has approached anesthetic levels.

Clinical Laboratory Tests

Very limited human data have been published regarding laboratory test findings following exposure to this compound. From the information available, it appears that the urinary urobilinogen excretion may be the most sensitive index of liver insult following exposure. An increase in urinary urobilinogen has been observed on the seventh day following vapor exposures ranging from 900 to 2650 ppm.[7] Other liver function studies, including the serum transaminases, remained normal. The significance of such a finding remains obscure, but this delayed elevation of the urinary urobilinogen following exposure to other chlorinated hydrocarbons has been observed.[16, 17]

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. Oxygen with carbon dioxide should be administered. Breathing should be assisted if the respiratory center fails to respond to the carbon dioxide stimulation.

Severe hypotension may be induced by a combination of central nervous system depression and myocardial anoxia secondary to poor oxygen uptake. Unless the situation is desperate, epinephrine *must not* be used to combat this hypotension because of the danger of inducing ventricular fibrillation.

It is not anticipated that permanent organic injury will result following recovery from the anesthetic effects of the compound.

Summary

1,1,1-Trichloroethane (methyl chloroform), a popular solvent and carbon tetrachloride substitute, is rapidly absorbed through the lungs and the gastrointestinal tract. Most of the compound is eliminated 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.

The diagnosis of exposure to this compound may be confirmed by specifically identifying it in the expired breath of the exposed person. Using the expired-air data, it may be possible to make a crude estimate of the magnitude of the exposure.

No detrimental effect upon man has been observed when vapor exposures have not exceeded 500 ppm.

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of the preanesthetic value. Recovery was slow, but uneventful. The subject complained of being tired for several hours after anesthesia.

Three human deaths as a result of over-exposure to 1,1,1-trichloroethane have been reported. One death occurred in an open tank in which vapor concentrations exceeded several thousand ppm,[10] and in 2 cases, death followed exposure to very high concentrations in unventilated tanks.[5]

Vapor 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.[3] A vapor concentration of 18,000 ppm for 3 hr. was lethal for 50% of exposed white rats; a 3-hr. exposure to 10,000 ppm produced irregular respiration and a semicomatose state, but no deaths resulted.

There is a modest safety factor present in that the ratio between the concentration of the vapor causing the loss of reflexes and that producing death in mice is 20, as compared to 15 for chloroform.[1]

A disturbing property of this compound is that, at anesthetic concentrations, idioventricular rhythms may be induced in animals with epinephrine.[11] Therefore, it is possible that ventricular fibrillation leading to sudden death could occur in humans exposed to anesthetic concentrations. This is not a unique property of 1,1,1-trichloroethane, but one common to most of the chlorinated aliphatic hydrocarbon solvents.

Studies conducted on dogs and monkeys anesthetized with 1,1,1-trichloroethane by a closed technique revealed no significant change in electrocardiograms during 60 min. of deep surgical anesthesia; however, a depressor response upon the blood pressure was observed.[9] 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-induced respiratory arrest.

Rats deeply anesthetized with 1,1,1-trichloroethane for one hour showed a 33.3% diminution in oxygen uptake of the myocardium, very similar to that observed with chloroform anesthesia.[9]

The failure of 1,1,1-trichloroethane to impair significantly liver function in mice, as measured by the prolongation of pentobarbital sleeping time, has been reported by Plaa *et al.*[12] The hepatotoxic potency of the chlorinated hyd[illegible] studied, arranged in order of increasing toxicity was: 1,1,1-trichloroethane, tetrachloroethylene, trichloroethylene, tetrachloroethane, 1,1,2-trichloroethane, chloroform, and carbon tetrachloride.

To produce histological evidence of liver injury in white rats, vapor concentrations of 8000 ppm for 7 hr. were required.[3] A 5-hr. exposure at the same concentration did not result in histological evidence of liver injury.

Repeated Vapor Exposure

It is unlikely that significant organic injury resulting from repeated vapor exposure will occur in the absence of acute effects. No injury to man following repeated exposures to vapor concentrations of less than 500 ppm has been observed.[13] Rats, guinea pigs, rabbits, and monkeys were unaffected after 6 months of repeated 7-hr. exposures, 5 days per week to 500 ppm.[3, 8]

Of the laboratory animals investigated, the guinea pig appears most prone to liver injury. While an earlier study[3] reported no organic injury after 3 months of repeated daily exposure to 1500 ppm, 7 hr. per day, a later study[8] reported the presence of slight lung and liver pathology in guinea pigs exposed repeatedly to 1000 ppm for 1.2 hr. per day, or 2000 ppm for 0.5 hr. per day. This inconsistency merits further investigation.

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 vapor inhalation. If the amount ingested is sufficient to produce loss of consciousness, impairment of liver function may result.

Eye Contact

Several drops of 1,1,1-trichloroethane placed directly on the cornea may produce a mild conjunctivitis which will subside within a few days.[18]

Skin Contact

Prolonged or repeated contact with the skin results in 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

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