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I hereby recommend that the thesis prepared under my supervision by Arthur M. Edwards, M. D.
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Approved by:

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CHLORINATED ALIPHATIC HYDROCARBON SOLVENTS
A Review of the Literature and a Summary of the Experimental
Results with Specific Reference to Their Application to
Industrial Hygiene

A dissertation submitted to the
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by

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CHAPTER I

INTRODUCTION

For many years the hydrocarbon solvents have furnished a fertile field for toxicological discussion, but information concerning them is widely scattered, and not readily available. These solvents have been widely used in industry, despite inadequacies in current knowledge concerning their toxic properties, and, while many investigations have been carried out, their objectives and results have varied considerably. Some compounds have been investigated precisely and comprehensively, others, in a cursory manner, and others, not at all.

Without considering the aromatic hydrocarbons, or those combined with halogens other than chlorine, it is difficult to name an industry in which the hydrocarbon solvents are not used. They are used in the paint and lacquer industries, in those concerned with the artificial silks and plastics, in rubber mills, in chemical plants, metal trades, and all those industries in which degreasing is a problem. They are used as dry-cleaners, fire-extinguishers, insecticides, oil and fat extractors, fumigants, gas purifiers, refrigerants and perfume extractors. Often they are constituents of soaps, adhesives, cleaners, and sterilizing solutions. Lenses, films, printing rolls and type, safety glass, furs and artificial pearls are among the varied products cleaned with these solvents. Agriculture finds use for them as accelerators of the growth of potatoes, as treaters of tobacco,

seeds and grains. Every day, carloads of one solvent or another are sent to industrial establishments for varied uses.

These varied and widespread uses have led to many casualties and, unfortunately, many fatalities. This casualty rate has resulted directly from the intrinsic and unavoidable dangers associated with the characteristics of the compounds themselves. It has been the result of ignorance, poor dissemination of information, and carelessness, or combinations of these factors. Considering carbon tetrachloride, this solvent has been widely used for many years. For these same years, efforts have been made to impress upon industry the danger attending its use. Despite these efforts, 325 cases of poisoning by carbon tetrachloride, with 17 deaths, have been reported in the literature over the past 17 years. Undoubtedly, many more have been unreported and, perhaps, unrecognized. Recently, a New Jersey physician had to request an explanation as to why a patient, a dry-cleaner, seemed to become quite ill from the fumes of carbon tetrachloride. The early experiences during World War I with tetrachloroethane as a solvent for aeroplane "dope" demonstrate well the effects of using such materials without proper investigation of toxic properties. The number of casualties became so great that the use of tetrachloroethane for this purpose was forbidden.

It is not safe, nor wise, to estimate the toxic properties and limits of a solvent by the knowledge one has of other members of the same group, or of similar groups.

Dichloromethane, for example, when inhaled as a vapor, is harmless within limits of concentration which in the case of carbon tetrachloride would yield disastrous effects. Similarly, if one considers a solvent similar to carbon tetrachloride in its chlorine content, but having two carbon atoms, we again see the dangers of improper assumptions, for tetrachloroethane is considerably more toxic than carbon tetrachloride for animals and man.

Comparative data of this type are not readily available, in toxicological or clinical reports, and there is an even greater dearth of summarized information on the practical hazards associated with the use of these materials for a variety of purposes and under varied conditions. It is the purpose of this paper to attempt to bring material together, as it relates to the chlorinated straight-chain hydrocarbons, with emphasis on the correlation between their chemical structure and their toxicity. In combining the reports on these compounds, one should be able to see at once what is, or is not, known about solvents in current use.

In preparing a summary of the investigative work, it has been difficult to adopt uniform standards for the comparison of the compounds. The individual reports vary considerably in the quality and completeness of their data. Many investigators have limited their observations to one species of animal, though variation in the susceptibility of species is a well known phenomenon. Also, the information in many reports has little or no industrial application.

The results of the intravenous administration of chemicals, while interesting, obviously have no relationship to industrial hazards. The effects of the exposure of animals to high concentrations of vapor in the atmosphere on one occasion merely provide the starting point for further investigation, and act as indicators of industrial hazards. The investigation of the effect of the inhalation of low concentrations, repeatedly or over prolonged periods of time, provides the information most readily used in commercial applications. The results of one application of a material upon the skin of an animal, while revealing, perhaps, are not as informative as the consequences of repeated applications over a period of time. These points have not been considered in much of the work now reported in the literature. Such is the scarcity of controlled work on the solvents that most of the presently accepted "maximum allowable concentrations" of these materials in industrial air are either reasonable estimates, or somewhat informal guesses.

The most serious liver damage caused by solvents is that of a fatty degeneration. This damage is often reversible and, under the conditions of repetitious exposure, it may be encountered in all of its stages. Kidneys usually show fatty degeneration, with some tubular damage. In some instances discrete and conglomerate hemorrhages are seen. Glomerular destruction is rare. In a few cases there is an irritation of the central nervous system, with rare residual sequelae. Changes in irritability of the cardiac muscle

are sometimes seen. Practically all the solvents have a narcotic action, with the signs and symptoms of narcosis in general. Deaths that follow narcosis from heavy concentrations are not peculiar to solvents. They show the cardinal signs of liver and kidney degeneration that Boyce demonstrated in deaths from anesthesia during, and following, surgery; the so-called liver-kidney syndrome. The skin is affected mostly through ordinary irritation, though some of these compounds have the ability to sensitize the skin. Generalized dermatoses, toxic changes in organs following percutaneous absorption of the solvent, and frank destruction of the skin can be seen. In most cases, the cutaneous damage is a result of the de-fatting property of the solvent.

For purposes of comparison, the compounds under consideration are dealt with by chemical groups, or series. The simplest, based on the number of carbon atoms, the methane (CH_4) series, is considered first, followed by the ethane (C_2H_6) series. The unsaturated ethylene (C_2H_4) series is then discussed, with the higher-carbon saturated chains following in order. Various compounds of the groups are not considered if no industrial uses as solvents have been reported. Moreover, the last two compounds dealt with do not fit into the pattern adopted for the presentation of the others. Information becomes scanty as the chemical complexity of the compounds increases, little or none being available beyond a certain point. The two compounds referred to have been subjected to some investigation because of their

practical usefulness, and one of them, hexachlorobutadiene, only recently came to our attention for investigation and provided part of the stimulus for assembling of the facts on the more common chlorinated hydrocarbons, for purposes of comparison.

The basic chemistry of the compounds has been omitted, since it is readily available in standard texts. The treatment of the toxic effects of absorption is not discussed.

CHAPTER II

THE METHANE SERIES

Methyl chloride, CH_3Cl , the first member of this series of four, is a gas. It is not considered here because it has no use as a solvent.

Dichloromethane CH_2Cl_2

Dichloromethane is a colorless liquid with a boiling point of $40 - 41^\circ\text{C}$. Like many of these compounds, dichloromethane decomposes in contact with flame to produce chlorine, hydrochloric acid, and some quantity of phosgene (59). Its principal uses are in the manufacture of silk, and in paint removers.

All experimental work has indicated that dichloromethane is a narcotic of fairly low order. In mice, light narcosis results after exposure to air containing 8,700 p.p.m. of the solvent. Loss of reflexes occurs at 10,000 p.p.m. The LD for mice has been found to be 14,500 p.p.m. (73); the LD_{50} , 16,186 p.p.m. (113). Heppel (61) exposed rats, rabbits and dogs to atmospheres containing 5,000 p.p.m. for 7 hours per day on 5 days per week, over the period of six months, with no discernible signs of abnormality of any kind, except a decrease in the activity of the rats. Mice, rabbits and rats exposed to 10,000 p.p.m. were mildly narcotized in four hours. Similar exposure on 5 days per week, for 7-1/2 weeks, caused no organ damage or sequelae. Dogs became wild under such a regimen, and showed mild to slight fatty degeneration of the liver after the 6th exposure. Guinea pigs showed liver damage, four out of six dying. Static exposure of guinea pigs, rats, and mice to 10% dichloromethane, combined with Freon 11 and 12 and 2% insecticide (Chlorton), produced no signs of any pathological changes. The animals were exposed for 45 minutes on each of 38 days over a total period of 54 days, the air in the cage containing (by

calculation) 9.6 mg. of dichloromethane per liter. A single exposure of mice to 105 mg/L caused only signs of asphyxia, with no after effects (59).

Barsoum and Saad (9) demonstrated fatty degeneration in the organs of dogs and rabbits, but limited their experiments to administration by the intravenous and subcutaneous routes.

Applied upon the skin of rabbits, dichloromethane acted only as an irritant, probably through its action as a fat solvent.

Toxic effects upon man have not been described in the literature. Browning (17) summarizes certain early reported cases, and concludes, rightly, that they are not definitely proved cases of poisoning by dichloromethane per se. Von Oettingen (118), on the other hand, accepted these cases as of the toxic effects exerted by this compound. Johnston (68) does not even consider this solvent in his discussion of industrial hazards.

In California the preferred upper limit in the industrial atmosphere is set at 200 p.p.m., while New York allows 500 p.p.m. (27). Lehmann and Flury (74) favor 279 p.p.m.; Heppel and co-workers (61) suggest 500 p.p.m., and offer their well controlled animal experiments in support of such a standard.

In summary, dichloromethane is a mild narcotic which causes no damage to the organs of animals exposed to high concentrations (5,000 p.p.m.). The effects on the skin are limited to irritation. No definite cases of human poisoning have been reported.

Chloroform CHCl_3

Chloroform has a boiling point of 61 - 62°C. Its industrial use as a solvent is somewhat limited. Many investigators have used this compound as a reference point in expressing the toxicity of new compounds.

There has been little or no reported work on prolonged exposure, or on human experience with known concentrations in industrial air. Chloroform has been studied in connection with its use as an anesthetic, rather than as an industrial solvent.

The concentration in the air lethal for mice was found to be 8,700 - 11,600 p.p.m. The reflexes of mice were lost during exposure to concentrations of 4,100 p.p.m., and narcosis was deep when inhalation continued for half an hour (73). Fatty changes were seen in the livers of dogs and rats after anesthesia induced by chloroform (43). Damage to organs varied directly with the age of the dogs (81). The inhalation of 1,800 p.p.m. of chloroform for 7 hours per day, at intervals of 2 - 4 days, caused delayed deaths of rabbits and cats (76).

Fatty degeneration of the liver and kidneys of dogs and rabbits is found after intravenous and subcutaneous administration (9, 77). The repetitious administration of oral doses to C3H mice produces hepatomas (42).

Studies on men have indicated that the margin between narcotic and toxic doses is very small. Atmospheres containing more than 2,000 p.p.m. are considered dangerous, while concentrations of 30,000 p.p.m. cause immediate deep narcosis (69). Concentrations of 25,000 p.p.m. are lethal in 5 - 10 minutes; 15,000 p.p.m. are dangerous in 1/2 - 1 hour, while 5,000 p.p.m. are tolerated for 1/2 - 1 hour (46). Prolonged exposure to small quantities of chloroform causes symptoms in man suggestive of chronic alcoholism.

On contact with the skin, chloroform induces burns, and is also readily absorbed (109).

Industrial use has caused few casualties, and no fatalities have been reported. Complaints have been limited

to drowsiness and headaches (17).

The preferred atmospheric concentration for industry has been set at 100 p.p.m. by most regulating bodies (27).

Lehmann and Flury suggest 40 p.p.m. (74).

Chloroform limited in its industrial uses, has escaped causing serious damage because of its narcotic properties. Exposure may cause degeneration of the liver. Absorption occurs through the intact skin.

Carbon Tetrachloride CCl₄

Carbon tetrachloride is a colorless liquid that boils at 76.74°C. Its thermal decomposition products are chlorine and HCl, together with small amounts of phosgene, which may reach significant concentrations under suitable conditions. It is, perhaps, the most widely used of the industrial solvents because it has been readily obtainable. Efforts are being made to replace it where possible.

The nature of the effects in the animal are agreed on by all workers. Besides narcotic properties, carbon tetrachloride is toxic to the kidney and liver. The epithelium of the nephrons is destroyed, and both secretory and filtering functions are interfered with on initial poisoning. An acute type of hemorrhagic nephritis occurs in fatal cases of poisoning (28). Cirrhosis of the liver developed in rats following their exposure to concentrations in air of 400 p.p.m. per day for 54 days (109). Similar liver damage was seen after administration of 1,000 p.p.m., seven hours per day, for 20 days (113). The solvent causes hepatomas in C3H mice, a condition not dependent on repetitious dosage (41). It has been shown, recently that high carbohydrate, low protein diets have a protective action on the livers of animals exposed to carbon tetrachloride. Rats were exposed to the

vapors of the solvent in the concentration of 20 mg/L, 8 hours per day, three times per week. Those given diets composed of 6 per cent of protein, 75 per cent of carbohydrate and 13 per cent of fat lived longer than any of the group fed on other diets. Other rats were injected with CCl_4 and fed on diets containing no protein, 18 per cent of protein (as casein) or 54 per cent of protein. The least damage was observed in the rats that were fed the highest carbohydrate (protein-free) diet (14, 21, 34). Not to minimize or ignore the experiments carried out by many investigators on animals, it seems unnecessary to refer to them all here. Browning and Von Oettingen have capably recorded them elsewhere (17, 118).

To record here the effects of carbon tetrachloride on man would be redundant. Its toxic effects on animals have been duplicated disastrously many times in man. Unfortunately, the medical literature is full of reports from all sections of the world confirming what has been known for years; this is a toxic material. Each new report adds nothing but proof of the folly and carelessness of men. Even the Navy, long users of "carbon tet", continues to report fatalities due to carelessness. In the last seventeen years there have been 325 cases of CCl_4 poisoning reported in the literature; 17 of these cases died (97).

This material is a cutaneous irritant and sensitizer (105), but men continue to use it promiscuously on their skins.

The recommended limit in industrial atmospheres ranges from 50 p.p.m. in Massachusetts and Oregon, 75 p.p.m. in New York, to 100 p.p.m. in California, Connecticut and Utah (27).

There is, at present, considerable discussion urging the lowering of the limit to 50 p.p.m. in all states. Smyth and co-workers (109), in 1936, furnished animal studies as the basis for the safety of 100 p.p.m. for continuous exposure during the working day. Subsequent reports indicate that this limit is too high. Lehmann and Flury (74) suggest 30 p.p.m. Elkins (38) and Bowditch (15) recommend 50 p.p.m. as the maximum, and present industrial observations as evidence. Men complained of nausea, vomiting and headache in atmospheres containing 35 - 70 p.p.m. of carbon tetrachloride. The question, here, is that of comfort and freedom from minor symptoms, as against significant damage to tissues. Something less than 100 p.p.m. is desirable, but it is unlikely that 75 p.p.m. causes injury to tissues.

CCl_4 is hepato- and nephrotoxic in low concentrations, and is readily absorbed through the skin.

The methane series thus increases its toxicity as the chlorine atoms are increased. Liver damage is questionable in the case of dichloromethane intoxication, present in that of chloroform, severe in that of carbon tetrachloride. Percutaneous absorption of the latter two occurs to an appreciable extent.

CHAPTER III

THE ETHANE SERIES

Monochloroethane, C_2H_5Cl , the first of this series, is a gas. It is not considered here because it has no use as a solvent.

1,2-Dichloroethane $C_2H_4Cl_2$

1,2-Dichloroethane is a colorless liquid, with an odor like chloroform, which boils at $53.5^\circ C$. It has extensive use in industry as a solvent, as an insecticide, and as one of the halogen carriers in antiknock compounds in which the active agent is tetraethyl lead. Its isomer, 1,1-dichloroethane, has less extensive use.

Indications are that only a short exposure is necessary for the induction of toxic signs and symptoms in animals. Concentrations of 2,717 p.p.m. killed mice after two hours of exposure, while 8,892 p.p.m. killed after 30 minutes (94, 73). 5,928 p.p.m. in air are classed as being dangerous to guinea pigs on short exposure (104). Experiments on chronic toxicity have been reported by Lehmann (74), who found that rabbits died regularly within seven days, under conditions of daily exposure to air containing 4,940 p.p.m. Heppel et. al. (61) studied the toxicity of dichloroethane in well controlled experiments on the inhalation of the compound. Exposure of rabbits, mice, rats, and guinea pigs to air containing 3,000 p.p.m., for 7 hours, resulted in the death of most of the animals. Air bearing 1,500 p.p.m. was toxic after six seven-hour periods of exposure. Animals exposed to 100 p.p.m. showed no effects after 74 periods of exposure of seven hours each. Concentrations of 200, 400 and 1,000 p.p.m. caused death and/or organ damage on repeated exposure. Concentrations of 400, 1,000, and 1,500 p.p.m. caused cloudiness of the corneas of dogs and foxes but not of nine other species.

Anesthesia was not necessary to produce this change. The cloudiness disappeared, generally in less than two days, though there were a few cases in which only one eye cleared. It was noticed that dogs eventually became tolerant to dichloroethane, and that their corneas no longer became cloudy. The lesion is considered to be a loss of the normal turgescence state of the posterior layer of the cornea. Apparently, the injury was not caused directly by dichloroethane. Pathology in affected animals was marked in the lungs, kidneys and livers.

Oral administration to rabbits of 1,2-dichloroethane indicated that the minimum lethal dose lay between 0.6 and 0.8 gm./kg. Application to the skin of rabbits indicated that there is no appreciable cutaneous absorption (58).

Hulst (63) reported fatal poisoning in man with dichloroethane, resulting in multiple organ hemorrhages in addition to the changes typical of exposure to CCl_4 . Carter (23) reported irritation of mucous membranes, plus toxic action on the heart. Undue exposure is indicated by anorexia, fatigue, and a feeling of heaviness in the epigastrium. Urine shows increased urobilinogen (121).

Irritation or sensitization of the skin has not been reported (105).

With one exception, the states which have taken action in relation to this compound have set 100 p.p.m. as the allowable concentration. Massachusetts prefers 75 p.p.m. (27). Lehmann and Flury (74) suggested 500 p.p.m.

1,2-Dichloroethane appears to be one of the more toxic solvents. Liver and kidney damage is caused in animals by exposure to atmospheres containing 200 p.p.m. There is no significant absorption through the skin.

1,1,2-Trichloroethane $C_2H_3Cl_3$

Trichloroethane exists as two isomers, the beta-, or 1,1,2-trichloroethane being industrially important. It boils at $114^{\circ}C$.

The effect of this compound on animals has been studied principally by Lehmann and Schmidt-Kehl (75). Their reports are mainly concerned with comparative effects. Compared with carbon tetrachloride taken as 1.0, its narcotic effect is 2.5. Delayed deaths occurred in 40 per cent of the animals exposed to carbon tetrachloride; 58 per cent of those exposed to trichloroethane.

Exposure to a concentration of 2,745 p.p.m. in air was necessary to induce complete narcosis of mice, while 10,980 p.p.m. were found to be the MLD (73).

The effects of this compound on man have not been reported.

No limits for industrial atmospheres have been established. Lehmann and Flury (74) suggested a concentration of about 200 p.p.m.

1,1,2-Trichloroethane not only is a less toxic narcotic than others of this series, but is also has the advantage of a relatively high boiling point. Damage to organs is questionable. There is no absorption through the skin.

Tetrachloroethane $C_2H_2Cl_4$

Tetrachloroethane boils at $146.3^{\circ}C$. In the presence of moisture it liberates HCl, and on thermal decomposition, chlorine and hydrochloric acid. It is possible that phosgene appears under suitable conditions of combustion. The compound had extensive industrial use during World War I, but other compounds have now taken its place, to a large extent, in informed industrial circles. Because of its high toxicity, it should not be used except under carefully controlled conditions.

There were no toxic symptoms, other than drowsiness, in cats exposed to air containing 8,200 p.p.m., 4 to 7 hours per day, for 18 days. One animal that died had fatty degeneration of the liver (76). Concentrations of 5,000 - 5,800 p.p.m. have been considered as lethal for mice (73, 97). Cats showed only loss of weight following repetitious exposure to 160 - 480 p.p.m. for 6 to 7 hours per day, over the period of 4 weeks. Repetitious inhalation of the vapor of this material caused increased susceptibility (118).

Intravenously, Barsoum and Saad (9) found 60 mg./kg. to be fatal, as compared with 90 mg./kg. for chloroform.

The results of human exposure to tetrachloroethane in air are well known. During World War I, many cases of poisoning resulted from its use as an aeroplane "dope" solvent. Marked liver damage was noted. Willcox (124) reported in detail the four stages of so-called chronic poisoning. The first, or early pre-jaundice, stage is difficult to diagnose since the symptoms are those of a typical gastro-enteritis.

The second stage, one of jaundice without toxemia, is marked by an increase in the severity of the gastroenteric symptoms and the appearance of a slight jaundice, increasing fatigue and clay colored stools. The jaundice increases, the liver becomes enlarged and tender, and toxic symptoms appear to indicate the third stage, that of jaundice with toxemia.

The toxemia, with its convulsions and coma, may lead to death without passing through the fourth stage, which is marked by the appearance of ascites. Cases of acute, non-fatal poisoning have been reported recently. Women are considered more susceptible than men, workers over 30 years of age being more so than younger ones (55). Coyer (29) reported seven cases, one fatal, from industrial use. A number of cases occurred during World War II as a result of the use of this solvent in the weather-proofing, and also cleaning, of clothing. Symptoms of damage to the liver predominated. Unfortunately, no one has reported air concentrations involved in any of the cases.

Tetrachloroethane is readily absorbed through the skin (105).

Early toxic effects are manifested by severe malaise. Later symptoms are those of the nervous system and of the gastroenteric tract, or both. Minot and Smith (91) believe an incidence of large mononuclears in the peripheral blood over 12 per cent to be an early sign of poisoning.

Massachusetts has established 5 p.p.m. as an acceptable limit in industrial atmosphere. All other states

and agencies have set 10 p.p.m. as the limit (27). Lehmann and Flury (74) suggested 1.5 p.p.m. Kohn-Abrest (69) reported that 145 p.p.m. are detectable by odor, while Gurney (55) reported 25 p.p.m. as being easily recognized.

Tetrachloroethane is a very toxic solvent. Fortunately, it is falling into disuse. Organ damage is severe following exposure to low concentrations of the material. It is readily absorbed through the skin.

Pentachloroethane C_2HCl_5

Pentachloroethane boils at 161.9°C. Its uses are those of tetrachloroethane, and it is considered as toxic, but not as dangerous, because of its low volatility.

It is believed to be a powerful narcotic, possessed of a considerable degree of persistent irritating effect (75). Air concentrations of 900 p.p.m. caused light narcosis in mice, 3,000 p.p.m. caused deep narcosis, while 4,200 p.p.m. killed the animals. At autopsy, a number of the animals showed liver degeneration (73). Cats exposed to 121 p.p.m., for 8 hours per day, on 23 days, showed few changes clinically. At autopsy, fatty degeneration of the livers was found.

Similar damage was found in dogs, after they were exposed to the vapors for 3 weeks (66).

No cases of poisoning in man have been reported.

No states have established maximum levels for industry. Lehmann (74) suggested 2.4 p.p.m.

Equally as toxic as tetrachloroethane, pentachloroethane can be considered safer because it is less volatile. Following

exposure to low concentrations, liver damage is severe. It is probable that this compound is capable of absorption through the intact skin, but no evidence is available on this point.

Thus the members of the ethane series are increasingly toxic to the liver as the chlorine atoms increase, with one exception. Dichloroethane is severely hepatotoxic, trichloroethane is questionably so, while tetra- and pentachloroethane are both highly toxic to the liver. Percutaneous absorption is known to occur to a significant, or dangerous, extent only in the case of tetrachloroethane.

CHAPTER IV

THE ETHYLENE SERIES

Four unsaturated compounds comprise this group, but only three have industrial use as solvents. Monochloroethylene, $\text{CH}_2:\text{CHCl}$, is a gas, so is not considered in this discussion.

Dichloroethylene $\text{CH}_2:\text{CCl}_2$

Dichloroethylene is a colorless liquid consisting of a mixture of two isomers, cis- and trans-, with boiling points of 61°C . and 48.4°C , respectively. When stored in the presence of oxygen, without a polymerization inhibitor, formaldehyde, phosgene, and hydrochloric acid are produced (3). It is used as a solvent for cellulose acetate, rubber, oils, shellac, waxes and resins.

All workers agree on the narcotizing effect of the material upon animals. Exposure of mice and guinea pigs to air containing 9,770 p.p.m. and 17,380 p.p.m., respectively, resulted in narcosis (125). The concentration of 10,000 p.p.m. was the least capable of inducing narcosis in mice in 1/2 to 3/4 hour (90, 94). Exposure of cats to 18,000 - 19,500 p.p.m. for 1-1/2 to 3 hours, and for 2-3/4 to 6-1/4 hours, induced light and deep narcosis, respectively (76, 107). Lehmann (76) reported one cat as having been killed after exposure to 12,500 p.p.m.; another survived at 55,000 p.p.m. Only after repetitious inhalation of air containing dichloroethylene on successive days were dogs affected (66, 78). For mice and guinea pigs, lethal doses were found to be 19,000 and 39,000 p.p.m., respectively (125).

No degenerative lesions have been found in the tissues of acutely poisoned animals. Prolonged exposure, accomplished by repetitious inhalations on successive days, resulted in fatty degeneration of the liver and kidneys, congestion of all organs,

and marked dilatation of the blood vessels (66).

The intravenous lethal dose has been found to be 225 mg./kg. (9).

Acute or chronic poisoning in industry is practically unreported. Hamilton (56) reported the death of a man trapped over night in a vat containing dichloroethylene. All other reported illnesses have derived from its use in inducing anesthesia.

Concentrations of 280 p.p.m. in air are perceptible to man by odor. There is no unpleasantness associated with breathing air containing 830 p.p.m. for 30 minutes, but dizziness, sleepiness, and increased intracranial pressure follow exposure to 1,700 - 2,200 p.p.m. for five minutes (74).

The compound is a primary cutaneous irritant, but it has no sensitizing properties (105).

The limit of concentration of the vapor for industrial atmospheres has been set at 200 p.p.m. in California and at 100 p.p.m. in Utah (27).

The primary danger associated with the industrial use of this solvent is that its narcotic action may cause delayed reaction in workers and thus lead to accidents. Prolonged or repetitious exposure to the vapors of dichloroethylene causes liver damage. The material also acts as a cutaneous irritant.

Trichloroethylene $\text{CHCl}_2\text{CCl}_2$

Trichloroethylene is a colorless liquid which boils at 87°C. Used in the presence of open flame, bright light, aluminum dust, alkalies, or hot metals, decomposition products, notably hydrochloric acid and phosgene, are formed (117). Its industrial uses are many and varied, it being very popular as a degreaser. It has also extensive use as an anesthetic and as a medication.

Animal experimentation on toxicity has been fairly extensive, but its results have been confusing, probably because of impurities in the samples tested. The bulk of the evidence indicates that trichloroethylene acts principally on the central nervous system. In cats, trichloroethylene stimulates and then paralyzes the pulmonary inflation receptors. There is also prolonged stimulation of the deflation endings. This occurs whether the cats are decerebrated or not (122). Dogs and rabbits, on inhaling the vapor exhibit a slowing of the heart rate, alteration in the P and T waves, and irregular ectopic systole (86). The arterial divisions of the capillary loops are constricted in frogs and rabbits. There is no permanent damage unless the trichloroethylene is given in extremely large doses to the frog, or in multiple doses to the rabbit (87).

Exposure of dogs to concentrations of 175 - 200 p.p.m. for 6 hours per day on 5 days per week produced no injury of any kind. Concentrations of 500 - 700 p.p.m. for 4-6 hours per day on 5 days per week caused liver damage after 8 weeks of exposure. Dogs exposed to 750 p.p.m. for 7-8 hours per day on 6 days per week showed liver damage after 3 weeks of exposure. The liver pathology was that of fatty degeneration in each case (106). McCord (82), working with rabbits, reported deaths in 2 hours after exposure of the animals to 20,000 p.p.m.; in 28 to 41 days after a single exposure to 1,000 p.p.m. Exposure of guinea pigs to air containing 1,200 p.p.m. of trichloroethylene, for 1,100 hours, resulted in no pathology (7). Cats exposed to atmospheres containing 700 p.p.m. for 6 hours per day on 10-17 days showed loss of weight, but no liver degeneration. Two dogs, one male and one female, exposed to 200 p.p.m. for 6 hours per day on 119-129 days, showed no pathology in any of the tissues, including the bone marrow. Of

9 rats exposed to 300 p.p.m. for 6 hours per day on 5 days per week over the period of 6 weeks, 4 died. Rats exposed to 200 p.p.m. or less, on 116-122 days, were not affected in any way. Females in this group bore normal litters during the period of intermittent exposure, and the males normally took the females during oestrus. Further observations on rats showed that exposure to 300 - 500 p.p.m. for 6 hours per day on 8-10 days caused narcosis in every case but no deaths or liver damage. Rats exposed similarly to concentrations of less than 300 p.p.m. showed no narcosis, and there were no deaths or pathologic alterations (114).

Dervillée (31) administered trichloroethylene by stomach tube to guinea pigs in doses of 0.15 - 4.0 cc./kg. Those that were given 0.15 - 1.0 cc./kg. showed no disturbances or only slight somnolence. Those given doses of 1.0 - 3.0 cc./kg. showed somnolence and paralysis of the posterior extremities, while those given 3.0 - 4.0 cc./kg. died. Little microscopic evidence of kidney or liver damage was found in these animals beyond a moderate centrolobular cellular degeneration in the livers and tubular degeneration in the kidneys. Five to 12 cc. of trichloroethylene given orally to dogs caused marked hyperemia of the intestinal mucosa. Repeatedly induced narcosis was not followed by evidence of degeneration of any of the internal organs (66). Jackson (118) found no injury to the organs of dogs following anesthesia. Only three investigators have reported the occurrence of damage to the livers and kidneys of animals following respiratory exposure to trichloroethylene (2, 79, 103).

A number of human fatalities have been reported in European literature. These can be accounted for by their exposure to phosgene, rather than to trichloroethylene per se (45). Trichloroethylene is excreted in the urine of man as trichloroacetic acid, and the Fujiwara test has been observed to remain positive for two weeks following exposure (8). The level of trichloroacetic acid in the urine parallels that of trichloroethylene in the blood. No further elimination of trichloroethylene from the lungs occurs after 48 hours (96). There are no changes in the blood pressure or in the pattern of the EKG of man following 4-6 deep inhalations of the vapors (86, 119). Following the use of trichloroethylene as an anesthetic in 105 cases of neuro-surgery, there were no harmful effects to patients, and no persistent bradycardia. Six per cent of the cases showed temporary cardiac irregularities. Cardiac lesions were present prior to anesthesia in three instances. None of the irregularities were permanent (67). There are, at times, cardiac irregularities in men and dogs while under trichloroethylene anesthesia, but they do not persist after the administration of the anesthetic has been terminated (120). Various changes in the electrocardiogram that appear during the induction of anesthesia with trichloroethylene disappear either during or after the period of anesthesia (6, 39, 49). Cranial nerve palsies and herpes, which have occurred in association with the use of this compound as an anesthetic in England, have been shown to have been caused by inhalation of soda-lime used in the induction apparatus (64).

Following clinical use of this compound as a therapeutic agent in trigeminal neuralgia and angina pectoris, psychoses and sporadic neurological disturbances have occurred (37, 80, 101, 126). Glaser (50) considers the compound non-toxic, while others regard it as mildly toxic (70, 79, 101). It is believed to have a depressant effect on the basal ganglia (70).

Browning (18) has reported one fatal case of aplastic anemia, and one case of serious hypoplastic anemia in association with heavy industrial exposure. Five women involved in the same exposure showed no changes.

The symptoms in man reported by many investigators of trichloroethylene have been so many and varied as to justify the conclusion that they were largely irrelevant. It seems evident that true trichloroethylene intoxication expresses itself in the form of a narcosis, in which restlessness, vertigo, headache, "drunkenness", nausea, and vomiting are the predominant symptoms (31, 32, 48, 49). The danger to the worker exposed to high concentrations lies principally in the diminished cortical perception and the retarded reactivity which contribute to accident proneness (7, 45). The symptoms referable to the eyes, lungs and liver, and the chronic conditions reported by a number of workers, can be traced to the effects of impurities, rather than to the compound itself (54, 92, 98, 110).

Trichloroethylene is a primary irritant and sensitizer of the skin. Systemic poisoning from percutaneous absorption has been reported (105). Baker (5) has reported

an unusual case of generalized dermatitis following the inhalation of low concentrations of trichloroethylene fumes, the recurrence of which was prevented by the use of an effective respirator.

The accidental drinking of 1/2 - 1 ounce of trichloroethylene, by two persons, resulted in narcosis, followed by vomiting and headache. No permanent sequelae were noted (111).

Trichloroethylene appears to be a narcotic. The occurrence of damage to the organs of man is doubtful, even after severe repetitious exposure over prolonged periods of time. No sequelae of acute industrial intoxications induced by trichloroethylene per se have been reported. Sequelae, including fatalities, can be traced to the decomposition products or impurities in the material. No chronic type of intoxication has been described in connection with prolonged exposure to this material.

Suggestive of the "jags" and parties seen in the early history of ether, many reports on trichloroethylene addiction are in the literature. Numbers of men are known to develop a fondness for the odor of the compound, and a distinct "chronic liking" for the resulting state of drunken euphoria.

The concentration of the vapors of this material in the industrial atmosphere considered to be compatible with the safety of men who may be exposed regularly has been set at 200 p.p.m. in a number of the states (27). Morse (93) suggested 100 p.p.m. as a standard, since this level can be

maintained efficiently in actual practice. He feels that this lower level is necessary because of the anesthetic properties of trichloroethylene. Gasq (48) suggested 900 p.p.m.

Used in chemically stabilized form, as are most of the commercial grades, and under proper conditions with respect to ambient temperature and associated measures of control of atmospheric contamination, trichloroethylene appears to be possessed of the potentialities of a simple narcotic, somewhat less potent than chloroform, from the standpoint of potential hazard. The concentration of 200 p.p.m. seems to be safe for industrial atmospheres. The occurrence of liver damage, following heavy exposure, is dubious. Percutaneous absorption occurs only to a slight extent, but irritation and sensitization of the skin are to be regarded as definite hazards.

Tetrachloroethylene $\text{CCl}_2:\text{CCl}_2$

Tetrachloroethylene is a colorless liquid which boils at 120.8°C . Exposure to light and air results in decomposition, the products being hydrochloric acid and questionable amounts of phosgene (54). Its industrial uses are not so extensive as those of trichloroethylene, but it has considerable use as a degreaser and as a solvent.

Most of the experimental observations on tetrachloroethylene have been concerned with its toxicity when used as an anthelmintic, and are inadequate in relation to occupational hazards. Cats were unaffected when exposed to concentrations as high as 16,509 p.p.m. (76). The minimum

lethal dose for mice, by inhalation, has been found to be 6,000 p.p.m. (17). Rats are killed by exposure to 5,000 p.p.m. for 6 hours (114). Carpenter (22) exposed rats to concentrations of 70, 230, 470, and 7,000 p.p.m. for 8 hours per day, on 5 days per week, until the total period of exposure reached 1,200 hours, with no signs of injury. Concentrations of 19,000 - 31,000 p.p.m. induced fatal poisoning, which resembled that associated with an overdose of a narcotic. Rats survived exposure to the lower concentrations, and displayed normal growth, normal blood and organs, and stimulated fertility. The narcotic concentration in the air breathed by dogs was found to be 9,114 p.p.m. No pathologic changes were induced by such exposure (71).

Oral doses of 2 cc./kg., administered repeatedly for several months, caused no demonstrable pathology in dogs (14).

Reported cases of industrial poisoning have been very few; no fatalities nor organ pathology has been seen. Several inconclusive acute episodes are described in the literature but no chronic cases have been reported. The toxicity of tetrachloroethylene, when used as an anthelmintic, is well known, being demonstrated by stupor, dizziness, nausea, vomiting and sweating (103). One fatality is reported from such therapeutic use in the case of a malnourished beggar (24). One writer states that lesions of the central nervous system, kidney, and liver occur, following severe exposure to tetrachloroethylene in the air. He also assumes that the

material is absorbed through the skin, but no references or data are given (98). Large mononuclears are thought to increase in number in the peripheral blood after poisoning by this compound, and a rise in the count of these cells above 12 per cent is considered to be the first sign of poisoning. Values as high as 40 per cent have been seen in some cases (91). Carpenter (22) exposed himself and co-workers to various concentrations in the air. The concentration of 2,000 p.p.m. caused faintness in 7-1/2 minutes; 1,000 p.p.m. caused inebriation after 1 hour and 35 minutes; 500 p.p.m. caused very slight discomfort after 2 hours. The material could be identified by its odor in the air in concentrations as low as 50 p.p.m. In these experiments and in those conducted with rats, the mononuclears in the peripheral blood never exceeded 10 per cent of the leucocytes.

All states that have established standards accept 200 p.p.m. as a concentration compatible with the safety of the worker in industry (27, 12). The American Conference of Government Hygienists in 1947 set 100 p.p.m. as their acceptable standard (30). Gasq (48) believes 147 p.p.m. to be the upper limit of safety. Unfortunately, these limits have been based on sketchy toxicological investigation. Crowley and others (30), in 1945 reported the concentrations found in association with degreasing operations in an unvented kettle without a condenser system; during loading of the kettle the air contained 180 p.p.m., during unloading, 484 p.p.m. and, when idle and uncovered, 151 p.p.m. In 1946,

Morse and Goldberg (93) found 96 p.p.m. in the air at a kettle that was equipped with both vent and condenser, 135 p.p.m. when the condenser only was operated, and 221 p.p.m. when neither vent nor condenser were in operation.

Apparently, tetrachloroethylene acts as a simple narcotic, which exerts no remarkably injurious effect upon the internal organs. There seems to have been too little direct work on this compound to warrant the popular beliefs concerning other toxic effects. Its action to the skin is that of an irritant.

The unsaturated ethylene compounds appear to lack the capacity for causing serious injury to organs. Narcosis and cutaneous irritation are the principal hazards of their use as solvents.

CHAPTER V

THE PROPANE SERIES

Monochloropropane C_3H_7Cl

Monochloropropane boils at $46.4^{\circ}C$. Its industrial use is not extensive.

Its toxic and narcotic effects are believed to be slight. Muller (94) regards its narcotic action as one-seventh of that of chloroform, while he finds it one-tenth as toxic. No degenerative changes in the tissues of animals have been reported in experimental studies.

Toxic effects are unreported in man.

No limits of safety have been established for industrial atmospheres.

Monochloropropane appears to have little toxic effect. Considering its low boiling point, little more than this can be said on the basis of available experimental evidence.

1,2-Dichloropropane $C_3H_5Cl_2$

1,2-Dichloropropane is a colorless liquid having a boiling point of $96.8^{\circ}C$. It has use as a solvent and as an insecticide.

The only investigation of the toxicity of this material on record is the work of Heppel and his associates (62). A single exposure of 6 guinea pigs, 2 rabbits and 3 rats to air containing 1,600 p.p.m. of the vapors of dichloropropane caused the death of only the 3 rats. Of 45 rats exposed to 1,000 p.p.m. for 7 hours daily on 5 days per week, 25 died, some after as few as 7 days of exposure. Deaths occurred among dogs after 24 days of such exposure and, among guinea pigs, after 22. Animals that died after 7-12 periods of exposure showed marked fatty degeneration of the liver kidney and heart. Those that were killed after 12-35 periods of exposure to the same concentration showed little or no damage in the organs.

Exposure to 2,200 ppm. on fewer than 8 days caused many deaths among experimental animals, but after 35 days of exposure when the concentration did not exceed 1,500 p.p.m., most of the animals survived. Animals that survived repetitious exposure failed to develop degenerative changes in the liver, but examination of the tissues indicated that there had been some damage that apparently had regressed.

Rats, guinea pigs, and dogs showed no ill effects after 128-140 days of exposure to 400 p.p.m. Many mice of the C3H strain died, and several developed hepatomas. Low protein-choline diets increased the susceptibility of the animals to the vapor.

No safe limit for industrial atmospheres has been established, though it should be of the order of that of dichloroethane. The absorption of 1,2-dichloropropane in sufficient concentration causes liver damage that tends to disappear under conditions of repetitious exposure to equivalent concentrations. Effects on the skin have not been reported.

Trichloropropane $C_3H_5Cl_3$

Trichloropropane boils at $140^{\circ}C$. Its industrial use is slight at the present time. Exposure of animals to its vapors causes paralysis of the respiratory center and residual cardiac damage, but no experiments have been carried out in such manner as to define the toxic levels in air.

In man, oral doses of 2 gm. caused sleepiness, headache, lumbar pain, and an unsteady gait (118). No evidence is available with respect to the occurrence or extent of percutaneous absorption.

No cases of industrial poisoning have been reported. There is no established permissible concentration in the air in relation to prolonged exposure in industry.

Of the propane series, only 1,2-dichloropropane has been studied to any important extent. The absorption of the compound in adequate dosage causes definite liver and kidney damage. ✓ Only fragmentary knowledge is available concerning the other members of this series.

CHAPTER VI

ADDITIONAL COMPOUNDS RECENTLY INVESTIGATED

2-Chlorobutadiene $C_4H_4Cl_2$

2-Chlorobutadiene boils at $59.4^\circ C$. Its industrial use is not extensive.

Von Oettingen has supplied certain toxicological data relative to animals. The inhalation of air containing 276 p.p.m. is considered dangerous. Exposure to 83 p.p.m. or lesser concentrations may cause toxic effects. Pulmonary irritation in all degrees and lowering of the blood pressure were the principal effects. If absorption (exposure) occurred in sufficient degree, damage to the liver and kidney was seen. Mice and rats are said to have given microscopic evidence of degenerative changes in the testicles after exposure for 8 hours to 140 or more p.p.m. The compound is readily absorbed through the skin of animals.

No reports are available of the toxic manifestation on the part of men in respect to exposure to, or absorption of this compound. Utah has set 83 p.p.m. as the concentration in air compatible with the safety of the exposed worker (27), this being the threshold level found by Von Oettingen and co-workers (118). Cook has recommended 25 p.p.m. as a safer level (27), as has the Conference of Governmental Hygienists.

2-Chlorobutadiene is a strong hepatotoxin in low concentrations. Percutaneous absorption occurs readily.

Hexachlorobutadiene C_4Cl_6

Hexachlorobutadiene boils at $210 - 221^\circ C$. Its industrial use is slight at the present time.

Cats are killed by exposure for $3\frac{1}{2}$ hours to the concentration of 34 p.p.m. of the vapors of this compound. Exposure to the concentration of 27.5 p.p.m. for 7 hours killed the guinea pigs while that of 132.9 p.p.m. killed the rats (116). such exposure re-

sulted in severe damage to the liver and kidneys, in association with marked pulmonary edema and hemorrhage.

The minimum lethal dose of hexachlorobutadiene administered orally to rabbits lies between 0.024 and 0.037 gram per kilogram of body weight. Fatally poisoned animals were found to have severe damage to their liver and kidneys. Rabbits given a series of sub-lethal oral doses of 0.0046 gram per kilogram of body weight, on successive days excepting Sundays and holidays, survived as many as 100 doses. All animals, including those that died and those that were killed for examination, suffered marked renal damage. The livers appeared to be unaffected (116).

Repetitious application of undiluted hexachlorobutadiene in quantities of 1.0 ml. or greater upon the skin of rabbits caused marked fissuring of the skin and subsequent death of the animals(116).

The effects on man of the absorption of this compound have not been reported. No state or other agency has established safe limits for its industrial use.

This highly toxic compound appears to be absorbed readily from the alimentary tract, by way of the lungs and through the skin. Severe toxic changes in the organs of poisoned animals occurred regularly.

The butadienes, after only preliminary investigation, appear to be the most toxic of the aliphatic chlorinated solvents. Damage to the organs is extensive, following absorption of small quantities by way of the lungs, skin or alimentary tract.

CHAPTER VII

DISCUSSION

The toxicologic data on many of these compounds are too incomplete to provide bases for sound standards and preventive measures. The experiments, in many instances, have been limited to brief exposure of animals to relatively high concentrations and, therefore, they are inadequate sources of information as to cumulative action or chronic intoxication.

It is apparent that different species of animals react differently to specific compounds, while only rarely does an animal of any species respond to the administration of a specific dose in a manner that reveals all, or almost all, of the potential toxic effects of a range of individual or repetitious dosages. Broad conclusions, therefore, must rest first, upon extensive observations, under a variety of experimental conditions, upon animals of varied species, and finally, upon systematic clinical observations on exposed persons.

Difficulties arise in trying to interpret data from experiments in which several species of animals were subjected to short and long periods of exposure. Few men employ the same criteria in defining the stages or degrees of narcosis, nor are such criteria given in the reported work. Moreover, lesions and functional abnormalities are graded as positive or negative, or as one-plus or multiples thereof, without any recorded or reproducible basis for these gradations. The data, therefore, can be interpreted and compared only roughly.

Since these solvents are of interest chiefly because of their industrial applications, the data assembled herein for examination are limited to those that appear to have industrial significance.

The observed concentrations expressed in p.p.m. necessary for deep narcosis and lethal action in animals exposed to vapors in air are presented in Table 1. The same data are presented again in Table 2, expressed in millimols.

Table 1

The Comparative Effects of Various Solvents with Respect to the Narcotic and Lethal Concentrations of Their Vapor in Air, When Inhaled by Animals of Various Species, as Reported in Toxicologic Literature.

	Deep Narcosis in 30 Minutes (b) (p.p.m.)	Lethal Dose (p.p.m.)		
		Cats	Mice	Guinea Pigs
ichloromethane	20,000		14,500 (d)	
hloroform	13,000	25,000 (a) 53,000 (b)	6,150 (d)	16,400 (e)
arbon tetrachloride	22,000	63,000 (a) 65,000 (b)	10,400 (d)	
ichloroethane	12,000	150,000 (b)	8,700 (d)	10,000 (g)
richloroethane	8,000		10,000 (d)	
etrachloroethane	3,200	7,300 (a) 7,300 (b)	5,800 (d) 4,200 (f)	
entachloroethane	3,200	9,600 (a) 9,600 (b)	4,260 (d)	
ichloroethylene	5,000 (i)	44,000 (a) 12,500 (c)	19,000 (e)	39,000 (e)
richloroethylene	13,500	37,000 (a) 37,000 (b)	7,400 (d)	27,000 (h)
etrachloroethylene	8,000	31,000 (a)	6,000 (d)	
-Chlorobutadiene		276 (k)	140 (k)	
exachlorobutadiene		34 (j)		

(a) Mellan (89)

(b) Henderson and Haggard (59)

(c) Lehmann (76)

(d) Lazarew (73)

(e) Wittgenstein (132)

(f) Pantelitsch (17)

(g) Sayers (104)

(h) Carrieu (17)

(i) Müller (94)

(j) Treon (116)

(k) von Oettingen (118)

Table 2

Data of Table 1 Expressed as Millimols Instead of p.p.m.

	Deep Narcosis in 30 Minutes	Lethal Dose		
		Cats	Mice	Guinea Pigs
Dichloromethane	0.81		0.65	
Chloroform	0.53	1.02	0.25	0.60
Carbon tetrachloride	0.89	2.57	0.43	
Dichloroethane	0.49	6.13	0.36	0.41
Trichloroethane	0.33		0.41	
Tetrachloroethane	0.13	0.29	0.17	
Pentachloroethane	0.13	0.39	0.17	
Dichloroethylene	0.20	0.51	0.77	1.59
Trichloroethylene	0.55	1.51	0.30	1.10
Tetrachloroethylene	0.32	1.27	0.25	
2-Chlorobutadiene		0.01	0.005	
Hexachlorobutadiene		0.001		

With but few exceptions, the results relating to a given species of animal exposed to a single material seem to be in general agreement. It is readily apparent that the dosage necessary to achieve the specific effect varies with the species, sometimes very markedly.

As to concentrations that cause deep narcosis, tetrachloroethane and pentachloroethane are at the top of the list in point of efficacy. Carbon tetrachloride, its toxicity to man so well known, takes last place in such

a grading. It is also low in the list with respect to its ability to induce primary lethal effects.

The data of Tables 1 and 2 are better compared if the various concentrations of the solvents are rated against one of their number (Table 3). Chloroform has been taken arbitrarily as the base value, and is rated as 1.0.

Table 3

Comparative Toxicity of the Solvents, Based on the Narcotic and Lethal Doses for Cats and Mice

Chloroform = 1.0

	Deep Narcosis	Lethal Doses	
		Cats	Mice
Dichloromethane	0.7		0.4
Chloroform	1.0	1.0	1.0
Carbon tetrachloride	0.6	0.4	0.6
Dichloroethane	1.8	0.2	0.7
Trichloroethane	1.6		0.6
Tetrachloroethane	4.1	3.4	1.4
Pentachloroethane	4.1	2.6	1.4
Dichloroethylene	2.6	0.6	0.3
Trichloroethylene	1.0	0.7	0.8
Tetrachloroethylene	1.6	0.8	1.0
2-Chlorobutadiene		90.6	43.9
Hexachlorobutadiene		735.6	

In Table 4 the hepatotoxic effects of the solvents are listed. The grading of +++ indicates that severe liver damage results from small dosage. Those graded as ++ cause definite liver damage although very large doses are required. The grade of ± indicates that liver damage in animals is slight, questionable, or undetermined. No finer gradations are possible in view of the crudity of some of the data.

Table 4

The Comparative Action of Solvents on the Livers of Animals Subjected to the Inhalation of Vapor

	Rating	Boiling Point °C.
Dichloromethane	±	40.0 - 41.0
Chloroform	++	61.0 - 62.0
Carbon tetrachloride	+++	76.7
Dichloroethane	+++	53.5
Trichloroethane	±	114.0
Tetrachloroethane	+++	146.3
Pentachloroethane	+++	161.9
Dichloroethylene	++	48.0 - 61.0
Trichloroethylene	±	87.0
Tetrachloroethylene	±	120.8
Monochloropropane		46.4
Dichloropropane	++	96.8
Trichloropropane		140.0
2-Chlorobutadiene	+++	59.4
Hexachlorobutadiene	+++	210.0 - 221.0

± questionable damage +++ severe damage, small doses
 ++ definite damage, large doses

Based on these gradings, carbon tetrachloride is as toxic as any of the others, regardless of its position in the series as determined by other criteria.

In considering certain physical properties of the solvents, the boiling point of a compound was thought to have obvious bearing upon its potentialities for exerting a toxic effect. It can be assumed generally that increased volatility increases the practical hazards associated with the use of a material. This assumption is not borne out by the available data, either within various series, or between them. Using hepatotoxicity as a basis of comparison in the methane series, the hazard varies with the boiling point. In the other series, there appears to be no definite relationship.

Chemical structure seems to have no simple or well-defined bearing on toxicity. In the methane series, as chlorine atoms are added, the toxicity increases. The ethane series is inconsistent in this respect, since trichloroethane appears to be less toxic than dichloroethane. Among the unsaturated compounds, toxicity, in terms of damage to the liver decreases as chlorine atoms are added. It is noticeable, however, that, as the carbon atoms increase, the corresponding groups or series of compounds, on the average, tend to increase in toxicity. The olefins seem not to cause any damage in the livers of animals.

Another factor to be considered in the study of the solvents is that of chemical stability. Recent scanty data from studies of the highly stable fluoride substitution

compounds indicates that stability must be considered in relation to the toxicity and the hazards of an industrial solvent. For example, CF_4 , CF_3Cl , CF_2Cl_2 and $CFCl_3$ are all less toxic than CCl_4 , and they decrease in toxicity with increase in the number of fluoride radicals. CF_2Cl_2 ("Freon 12") has an almost negligible toxicity, animals surviving, with no demonstrable injury to tissues, during and after prolonged intermittent inhalation of concentrations of 20 per cent by volume in air or oxygen.

There is need of greater uniformity in viewpoint and approach, and also of greater thoroughness, in the investigation of industrial solvents and other industrial chemicals.

Basic values should be established as reference points to facilitate the reporting on the hazards of a new compound. It is inaccurate and often misleading, to report a new compound to be as hazardous as a well known material when only the lethal dosages are considered. Of more value and accuracy is a standard of comparison that considers volatility and stability, in addition to toxic dosage, when the potential hazards of a material are referred to. Routes of administration must be considered also. If absorption through the intact skin is readily accomplished by one compound and not by another, the former is certainly the more hazardous even though their "vapor" thresholds are the same.

The animals used in investigative work should be selected carefully for each type of procedure, and, for comparative purposes, one species at least should be common

to all of the experiments. As has been pointed out, studies should be directed toward feasible industrial interpretations. The mode of administration, time element and size and frequency of dosage should be so governed. Whenever it is feasible and safe, certain observations should be carried out on human subjects under careful conditions of physiologic and clinical control, since, in the final analysis, the indirect determination of effects of the material upon man is the object of the experimental work upon animals. Safety, in terms of freedom from undesirable effects upon man, can be established only by observations on man. This is true with especial emphasis, in relation to the effects of materials upon the nervous system, whether obvious as in the case of narcosis, or obscure and insidious, as in the case of impairment of coordination and judgment.

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