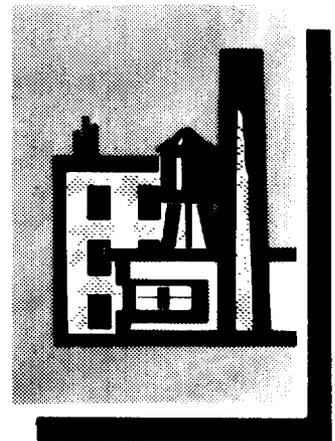# NIOSH

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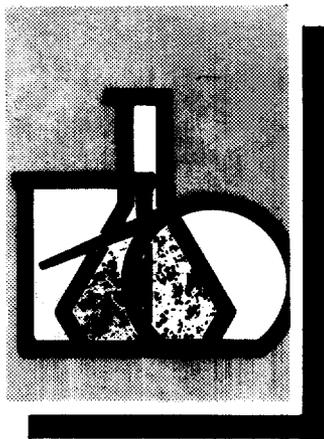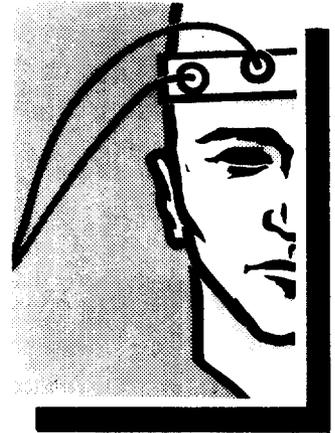
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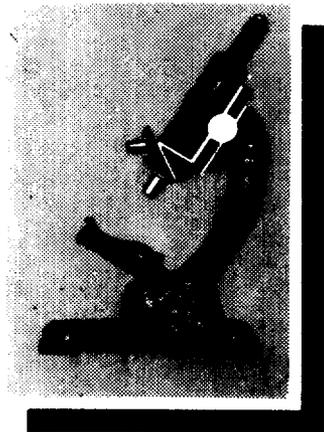
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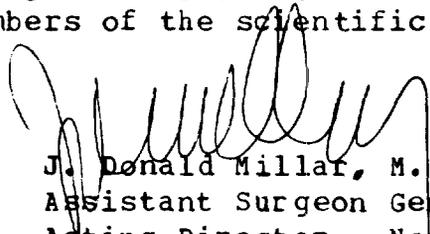TRICHLOROETHYLENE

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and

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Disclaimer

Mention of company names or products does not constitute endorsement by the National Institute for Occupational Safety and Health.

Foreword

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards in their workplace. Pursuant to the fulfillment of this need, the National Institute for Occupational Safety and Health (NIOSH) has developed a strategy of disseminating information about adverse effects of widely used chemical or physical agents intended to assist employers in providing protection for employees from exposure to substances considered to possess carcinogenic, mutagenic, or teratogenic potential. This strategy includes the development of Special Occupational Hazard Reviews which serve to support and complement the other major standards development or hazards documentation activities of the Institute. The purpose of Special Occupational Hazard Reviews is to analyze and document, from a health standpoint, the problems associated with a given industrial chemical, process, or physical agent, and to recommend the implementation of engineering controls and work practices to ameliorate these problems. While Special Occupational Hazard Reviews are not intended to supplant the more comprehensive NIOSH Criteria Documents, nor the brief NIOSH Current Intelligence Bulletins, they are nevertheless prepared in such a way as to assist in the formulation of regulations. Special Occupational Hazard Reviews are disseminated to the occupational health community at large, e.g., trade associations, industries, unions, and members of the scientific community.

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ABSTRACT

Trichloroethylene (TCE) has been an important industrial chemical for the past 40 years, primarily because of its utility as a highly effective solvent. While the great majority of TCE has been used for vapor degreasing of metal parts, it also has had many other applications, including use as a cold solvent, a solvent in food processing, in drycleaning, as an anesthetic, and as a heat-transfer medium. U.S. production in 1977 is estimated to be in excess of 115-million kilograms (253-million pounds). NIOSH estimates that over 100,000 workers are exposed full time to TCE, with up to 3-1/2-million more workers subjected to continuous low levels or to brief exposures of various levels.

This hazard review provides a brief description of the production, uses, toxicity, and metabolism of TCE and a more detailed assessment of TCE's potential as a workplace carcinogen. In addition, the results of a recent survey of industrial vapor degreasing operations, the primary source of occupational exposures to TCE, are presented along with data from other surveys or reviews to document the extent and nature of occupational exposures to TCE and existing control methods.

TCE's acute toxicity is well known and is related mainly to central nervous system depression, cardiac arrhythmias, and dermal effects. In contrast, chronic effects are not as well documented under usual occupational exposure conditions. There is evidence, however, for latent effects, including those of the liver, kidneys, and nervous system. Toxic effects have been reported in animal studies as well as in workers chronically exposed to TCE levels around 100 ppm, the current OSHA permissible limit.

The earliest concern for TCE's carcinogenic potential was based upon its structural and metabolic similarities to vinyl chloride. Subsequently, an animal bioassay conducted by the National Cancer Institute documented carcinogenicity in mice but not in rats after exposure to TCE by gavage. Several positive mutagenic tests and malignant transformation of cultured cells have also been reported. Overall, however, the results do not indicate a strong response.

There is strong presumptive evidence that a highly reactive metabolite, trichloroethylene epoxide, is produced during the metabolism of TCE and is likely responsible for the carcinogenic and mutagenic activity of TCE. This metabolite has been synthesized and confirmation of its formation during in vitro metabolism has been obtained and it has been demonstrated capable

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of covalent binding with cellular macromolecules, including DNA. Spectral evidence for the formation of trichloroethylene epoxide in vivo has also been obtained; however, the extent and nature of biochemical interactions in the intact animal, including the formation, inactivation, and possible activity of intermediate metabolites, has not been resolved as yet. Nevertheless, the evidence for such potential reactivity, associated with carcinogenicity, is strong.

No evidence is known which associates TCE with an increased risk of cancer in humans. However, epidemiology studies to test for such an association have only recently been initiated. The first reports provide preliminary results of studies underway in Finland and Sweden. No association of TCE with cancer has been found. The investigators cautioned against ruling out carcinogenicity, however, as the sensitivity of the studies is low and the period of observation short.

Based upon this special review of all these data, NIOSH concludes that TCE has a carcinogenic potential in the workplace; however, it is not considered to be a potent carcinogen. The results of NIOSH surveys indicated that substantial exposures are occurring in vapor degreasing operations that could be largely abated by proper maintenance, modification, and operation of existing equipment, and by the education of employees and supervisors as to the potential hazards of TCE.

Based on the toxic effects at the current OSHA limit and the carcinogenic potential of TCE, several control recommendations are made to provide for an improved degree of worker protection. Among these are: reduction in permissible exposure limit, use of existing engineering technology, and improved work practices.

Many current degreasing operations, including open top tanks, are maintaining a time-weighted average (TWA) of considerably less than 50 ppm. NIOSH considers that a level of 25 ppm, as a TWA, can be uniformly achieved by use of existing engineering control technology. However, this should not serve as a final goal; rather, industry should exert a concerted effort to develop methodology which would enable an even further reduction in worker exposure. It is considered unwise at this time for industry to substitute other organochlorine solvents for TCE, as these also exhibit health and environmental hazards. Hazard reviews or updates of existing NIOSH criteria documents for two possible substitutes, tetrachloroethylene and methyl chloroform, are planned.

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CONTENTS

Acknowledgments

I. INTRODUCTION

Trichloroethylene (TCE), CAS No. 79-01-6, a volatile liquid at room temperature, has been an important industrial chemical for the past 40 years. Its main use has been as an industrial solvent for liquid or vapor degreasing of metal parts. It has also been used for a variety of other applications including: (1) an extractant for substances of natural origin (e.g., waxes and greases from cotton or wool) and in food processing (e.g., manufacture of spices and caffeine-free coffee, (2) a drycleaning solvent, (3) cold degreasing solvent, (4) a component in rust prevention formulations, (5) an analgesic or anesthetic, and (6) a heat-transfer medium (Hardie, 1971).

While such varied applications of TCE have promoted its wide usage, it has also been well recognized that it produces both acute and chronic health effects. Some of the toxic properties of TCE have been known since 1911, when Lehmann discovered its narcotic effect. Several comprehensive toxicology reviews have been published, including those of von Oettingen (1937, 1955), Browning (1953), NIOSH (1973), Aviado et al. (1975), Fuller (1976), International Agency for Research on Cancer (1976), and Waters et al. (1977). The major concerns have been with CNS depression, cardiac arrhythmias, dermal irritation, and liver-kidney toxicity. In 1972 the Occupational Safety and Health Administration (OSHA) adopted, as a workplace standard, the standard of the American National Standards Institute (ANSI, 1967) for workplace exposure to TCE of 100 ppm (525 mg/m^3) as an 8-hour time-weighted average (TWA) concentration, 200 ppm as an acceptable ceiling limit, and 300 ppm as a peak exposure limit during not more than 5 minutes in any 2-hour period.

In 1973, the National Institute for Occupational Safety and Health (NIOSH) issued Criteria for a Recommended Standard for Occupational Exposure to Trichloroethylene. This document provided a comprehensive review of the uses, exposures, and known biological effects of TCE. Based upon that review, NIOSH recommended that occupational exposures to TCE be controlled so that no worker shall be exposed to a peak concentration in excess of 150 parts of TCE per million parts of air (ppm) as measured over a maximum sampling time of 10 minutes or to a concentration in excess of 100 ppm determined as a time-weighted average exposure for an 8-hour workday. Various control measures, medical surveillance, and methods of chemical analysis were recommended. The OSHA standard and the NIOSH recommended standard and control measures were based upon TCE's known toxic properties at that time, but did not include an assessment of its carcinogenic potential.

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Occupational health standards for TCE vary greatly throughout the world with respect to the maximum allowable exposure levels. While a few countries other than the United States have set 100 ppm as the environmental limit, many others have set much lower limits, as shown in Table 1. The lowest limits are those of several Eastern European countries at less than 2 ppm (10 mg/m^3).

Table 1. Occupational standards for trichloroethylene

Country	mg/m^3	ppm
Australia	535	100
Spain	535	100
United Kingdom	535	100
United States of America	535	100
Austria	267	50
Egypt	267	50
Federal Republic of Germany	267	50
Finland	267*	50
Japan	267*	50
Switzerland	267	50
Yugoslavia	267*	50
German Democratic Republic	250	47
Czeckoslovakia CSSR	250	47
Sweden	160	30
Hungary	53	10
Rumania	53	10
Bulgaria	10**	2
Poland	10**	2
Soviet Union USSR	10	2

* Recent changes from 535 to 267 mg/m^3
** Recent changes from 50 to 10 mg/m^3

Following the confirmation in 1974 that vinyl chloride was carcinogenic in animals and man, the similarity in chemical structure and metabolism of TCE to vinyl chloride (Van Duuren, 1975; Corbett, 1975), led to speculation that TCE might also have a potential for carcinogenesis. On March 21, 1975, the National Cancer Institute (NCI) released a preliminary report of an animal bioassay indicating carcinogenicity of TCE in mice (Saffiotti, 1975). Based upon those results, NIOSH issued (June 6, 1975) a brief announcement alerting the occupational community to the potential carcinogenicity of TCE. OSHA followed this action on October 20, 1975, by proposing a modification of its occupational exposure standard. While OSHA expressed concern as to the

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possible carcinogenicity of TCE, it nevertheless believed that treating TCE as a human carcinogen solely on the preliminary NCI data and the NIOSH alert was inappropriate. Based on concern for other toxic effects, OSHA proposed to modify the occupational standard so as to retain the 8-hour TWA limit of 100 ppm based on a 40-hour work week, but to reduce the 200 ppm ceiling limit to 150 ppm, as averaged over a 15-minute period, and to eliminate the concept of an allowable peak concentration limit above the ceiling limit (OSHA, 1975). Although the final results of the NCI tests were published in February 1976 (NCI, 1976), OSHA has not as yet taken further action.

A more recent review of the use of anesthetic gases and vapors, including TCE, has been conducted by NIOSH (NIOSH, 1977b). In view of well-established toxic effects found among occupationally exposed medical and dental personnel, including maternal and fetal effects and possible carcinogenicity, NIOSH recommended that exposure to halogenated anesthetic gases, including TCE, be controlled so as not to exceed 2 ppm, sampled over a period not to exceed 1 hour. A similar review made in 1974 by the Hospital Engineering Cooperative Groups of Denmark (see NIOSH, 1977b), resulted in their recommendation of 3 ppm as the highest permissible average concentration of TCE in the breathing zone of anesthesiology personnel.

In response to the NCI announcement, and the controversial nature of the results, a number of studies were initiated or planned to further explore the carcinogenic potential of TCE. Among these was an attempt by NIOSH to establish a retrospective epidemiologic study to assess the carcinogenic risk to workers under the usual occupational conditions. At the time of this writing, an appropriate worker population exposed to TCE has not been identified for study. Other research, however, was initiated in several laboratories, including animal and in vitro studies. Some of these studies are of a long-term nature and will not be completed for another 1-2 years. A NIOSH survey of degreasing operations which use TCE and other industrial solvents indicates little change in operations or intensity of exposures since the NCI announcement. NIOSH believes that sufficient experimental evidence has now accrued to demonstrate a possible carcinogenic potential of TCE in the occupational environment. It is the intent of this document to present the results of the .'IOSH survey, to review the toxicity of TCE, to conduct a carcinogenic hazard appraisal, and to recommend appropriate controls based upon the assessment of hazard from occupational exposure to TCE.

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II. CHEMICAL AND PHYSICAL PROPERTIES

At room temperature, TCE is a clear, colorless, noncorrosive, heavy liquid with a sweet odor characterized as ethereal or chloroform-like, and a reported odor threshold ranging from 21 to 400 ppm. Its important physical properties are listed in Table 2.

Table 2.   Physical properties of trichloroethylene

Molecular Formula:	C_2HCl_3, $ClHC = CCl_2$
Molecular Weight:	131.4
Percentage Composition:	C=18.24%; H=0.77%; Cl=80.95%
Physical State:	Colorless liquid
Specific Gravity:	1.46 ($20^{\circ}/4^{\circ}C$)
Melting Point:	$-73^{\circ}C$
Boiling Point:	$87.1^{\circ}C$ (760 mm Hg.)
Vapor Pressure:	57.8 mm Hg, $20^{\circ}C$
	146.8 mm Hg, $40^{\circ}C$
Vapor Density (1 atm. B.P.):	4.5 g/liter (air = 1.2 g/l)
Autoignition Temperature:	$410^{\circ}C$
Decomposition Temperature:	$700^{\circ}C$
Flash Point:	None by standard methods
Odor Threshold:	21.4 ppm
Solubility in Water:	0.11 g/10 μg H_2, $20^{\circ}C$
Soluble in:	Ethanol, chloroform, ethyl ether
Conversions:	1 mg/liter = 186.1 ppm
	1 ppm = 5.38 mg/m^3 at $25^{\circ}C$

Volatility/Flammability - Trichloroethylene is volatile, but neither flammable nor explosive at room temperature. It is only moderately flammable at higher temperatures, with an ignition temperature of $410^{\circ}C$ (Patty, 1962). However, mixtures of TCE and oxygen will ignite at temperatures above $25.5^{\circ}C$ when the TCE concentration is between 10.3 and 64.5% (Jones and Scott, 1942). While such mixtures are not normally encountered in degreasing operations, they could constitute a hazard during the use of TCE as an anesthetic agent.

Solubility - Trichloroethylene is practically insoluble in water and is not readily hydrolyzed by water. It is readily miscible in a variety of organic solvents including ether, chloroform, acetone, benzene, and various alcohols.

Stability/Degradability - Trichloroethylene decomposes under a number of environmental conditions and may degrade to more hazardous compounds. Among these are phosgene, carbon monoxide, dichloroacetylene, TCE ozonides, hydrochloric acid, and TCE epoxide. In the presence of oxygen and light, especially ultraviolet radiation, TCE undergoes autooxidation, decomposing to such acidic products as hydrogen chloride. High temperatures, especially above 125°C, further promote the degradation process, with the production of phosgene and hydrogen chloride. These same compounds are readily produced when TCE in either liquid or vapor form comes into contact with hot metals, such as magnesium and aluminum, at 300-600°C. Such conditions may be found in the vicinity of arc welding and degreasing operations (Smith, 1966). Of the metals, aluminum is the most reactive and can initiate violent reactions with unstabilized TCE. Storage of TCE for prolonged periods should be in steel or plastic cans or dark glass bottles (Noweir et al., 1973). Stowell (1943) cautioned that dangerous amounts of phosgene might be generated within an operating room during use of TCE as an anesthetic simultaneously with the use of a high-frequency cautery. This hazard is particularly likely to be present during surgical procedures within the oral cavity.

In the presence of strong alkali, e.g., sodium hydroxide, dichloroacetylene (C_2Cl_2), an explosive, flammable, and highly toxic agent may be formed. In 1944 Humphrey and McClelland reported two human fatalities and several nonfatal cases of severe toxicity resulting from trichloroethylene anesthesia. In all cases, the toxicity was attributed to dichloroacetylene, formed as the TCE passed through a soda-lime canister used as a CO_2 absorbent in closed circuit anesthesia systems. During the first MESA (Manned Environmental Systems Assessment) test run, the mission was aborted because of the formation of dichloroacetylene (DCA) from TCE used to clean the equipment in the chamber. In this case, the DCA was produced as the TCE passed through the sodium superoxide used to remove CO_2, adsorb acid gases and regenerate O_2. Although the test subjects became extremely sick, there were no fatalities. Dichloroacetylene can decompose further to phosgene and carbon monoxide, also highly toxic chemicals (Lehmann, 1911).

Chloroacetyl chloride and chloral (Cl_3CCHO) may be formed in the presence of anhydrous aluminum chloride. Impurities, including oxidants, can promote the sudden decomposition of TCE. In the presence of moisture, dichloroacetic acid and hydrochloric acid are formed. Such acidic products are highly corrosive and reactive with many metals. Ozone will react with TCE to yield an ozonide which is explosive and which decomposes to hydrogen chloride, phosgene, carbon monoxide, and chlorine peroxide (Hardie, 1971). Glycolic acid $(CH_2OHCOOH)$ is produced upon

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reaction of TCE under pressure at 150°C, with alkaline hydroxides. Monochloroacetic acid results when TCE is reacted with 90% sulfuric acid.

It should thus be obvious that the hazard from TCE must be judged not only on the basis of its own toxicity but also on those of the products that may be produced by reaction with other chemicals present during the processes in which TCE is used.

Stabilizers/Inhibitors - TCE readily undergoes free radical-type autooxidation which can be prevented by the addition of various stabilizers or inhibitors. The most common stabilizer in medical grade TCE is a mixture of thymol and ammonium carbonate, usually in concentrations of 0.01 and 0.02%, respectively (Aviado, 1972). Industrial grades of TCE may contain a variety of stabilizers. Among the stabilizers used in the past for industrial grade TCE have been substances having antioxidant properties, such as simple amines; those capable of fixing hydrochloric acid, such as epoxy compounds; and other compounds used mainly as metal deactivators, such as ethanolamine and aniline (Hardie, 1971). More recently, stabilizers have tended to be synergistic mixtures of antioxidant organic compounds. An example is the use of diisopropylamine plus an alkyl-p-hydroxyanisole (Huff, 1971). Other stabilizers which are effective inhibitors of oxidation include acetone, acetylenic compounds, aniline, borate esters, n-butane, o-cresol, ethyl acetate, hydrazine derivatives, isobutyl alcohol, lactones, o-nitrophenol, pyrazoles, stearates, and SO_2. Additional chemicals that have been patented for use as TCE stabilizing agents include epichlorohydrin (U.S. Patent 2,818,446, Dec. 31, 1957) and 1,4-dioxane (U.S. Patent 3,763,048, Oct. 2, 1973). Normally, stabilizers are effective at concentrations of less than 1 percent (by weight).

The ability of these agents to stabilize TCE is lost at temperatures above 130°C, especially in the presence of air, moisture, light, and common construction metals, which will corrode in such circumstances. At temperatures above 700°C, TCE vapor will decompose, even with oxidation inhibitors present in the liquid TCE, to yield a mixture of various organochlorine compounds, including methyl chloride, dichloroethylene, tetrachloroethylene, carbon tetrachloride, and chloroform. Vigorous heating in the presence of air will result in complete oxidation of TCE vapor to carbon dioxide and hydrogen chloride.

III. MANUFACTURE, PRODUCTION, USES, AND EXPOSURE

A. MANUFACTURE

Trichloroethylene was first synthesized by Fisher in 1864 by the reduction of hexachloroethane with hydrogen. In large-scale commercial production, TCE is usually manufactured from either of two starting materials: acetylene or ethylene. Chlorination of acetylene yields 1,1,2,2-tetrachloroethane ($CHCl_2CHCl_2$), which is dehydrochlorinated by alkaline hydrolysis (i.e., reaction with calcium hydroxide), or by pyrolysis (i.e., reaction with mixed metallic chlorides at 300-500°C), to yield TCE (Hardie, 1971). The yield of TCE from acetylene is approximately 94% of the theoretical, or 4.8 pounds of TCE per 1.0 pound of acetylene consumed in the reaction (Blackford, 1975).

Chlorination of ethylene yields 1,2-dichloroethane, which is then oxychlorinated (reaction with chlorine and oxygen) to yield tetrachloroethane. Dehydrochlorination to TCE is then accomplished as described above for acetylene (Hardie, 1971). It is estimated that 85% of the total TCE produced in 1963-67 was manufactured using acetylene as a starting material. This decreased to only 8% in 1973-74 (Blackford, 1975). Now most TCE (85%) is manufactured using ethylene as a starting material. This trend is due to the cost differential between acetylene and the less expensive ethylene as raw materials (NIOSH, 1973, 1976d).

B. PRODUCTION VOLUME

TCE was first produced commercially in 1908 in Austria and England and in 1910 in Germany but not until 1925 in the United States. Its first uses in this country were in extraction processes and the formulation of boot polish, printing ink drier, and similar products. In the 1930's new applications for TCE and advances made in metal degreasing and drycleaning resulted in an increasing demand for the chemical. A steady increase in U.S production of TCE continued through the 1960's, a peak annual production of 277 million kilograms (610 million pounds) being reached in 1970 by the five TCE manufacturers. During the next 6 years, as shown in Table 3, production of TCE declined at an average annual rate of about 9%, and is estimated to amount to about 117 million kilograms (257 million pounds) in 1977.

The U.S. capacity for producing TCE has also experienced a general decline, from about 352 million kilograms (775 million pounds) per year in 1968 to about 277 million kilograms (610 million pounds) per year in 1975 (Blackford, 1975). The declines

in production and capacity have resulted somewhat from a national economic recession but perhaps more from air pollution control legislation, such as Los Angeles' Rule 66 in 1966 and the 1970 Federal Clean Air Act. Such legislation, which might impose restrictions on the use of TCE, has caused uncertainty about this chemical's future. Already other chlorinated solvents have been substituted for TCE in certain processes, e.g., replacement by tetrachloroethylene in the drycleaning trade. Further, the recent announcement of positive carcinogenic test results for TCE by the National Cancer Institute (NCI, 1976) has prompted TCE's replacement in some food-processing operations, e.g., decaffeination of coffee. It is estimated that total domestic consumption of TCE will decline at an average annual rate of 2% through 1979 and that total U.S. production will decline at an average annual rate of 1.2% during that same period, with TCE exports accounting for most of the excess production (Blackford, 1975).

Table 3. U.S. production and consumption of trichloroethylene

Year	Production $x10^6kg$	Consumption* $x10^6kg$	Exports $x10^6kg$	Imports $x10^6kg$
1958	122.9	NA	NA	15.7
1962	161.5	NA	NA	29.5
1970	276.7	276.1	14.8	13.9
1971	233.5	214.1	23.6	4.2
1972	193.5	202.0	19.1	27.5
1973	204.9	208.6	17.8	21.5
1974	176.4	157.4	19.6	0.6
1975	132.8	121.2	15.4	3.8
1976	137.6	128.5	16.1	7.0
1977	116.6**	100.2	26.0	9.7***

* Represents production plus imports minus exports
** Estimated from 1st 5 months production data
*** Estimated from 1st 9 months of import/export data
Data from U.S. International Trade Commission (1971-1977), Blackford (1975), U.S. Exports, FT 410, U.S. Dept. of Commerce, Bureau of the Census (1975-77) and U.S. Imports for Consumption and General Imports, FT 246, U.S. Dept. of Commerce, Bureau of the Census (1975-77).
NA = Not Available

C. USES

Approximately 92% of the TCE produced by U.S. manufacturers is actually consumed in the U.S., the remaining 8% being exported. Of the amount consumed in the United States, approximately 95% is used as a vapor-degreasing solvent, 3% as an extraction solvent, and 2% for miscellaneous uses (Faith et al., 1975).

In the past TCE was by far the most popular solvent for vapor degreasing. However, its use in this industrial process has experienced a decline in recent years because of the restrictive air pollution control legislation and the depressed state of the U.S. economy. Consumption trends indicate that TCE's use in metal cleaning operations should decline at an average annual rate of 3% through 1979 (Blackford, 1975).

As an extraction solvent, TCE has been used in the processing of alkaloids, fish meal, leather, meat meal, oil-containing seeds, sheepskins, and soya and coffee beans. It should be noted that the largest U.S. producer of decaffeinated coffee abandoned the use of TCE soon after the NCI announcement (Fuller, 1976).

TCE is used in numerous other applications, including use as a drycleaning solvent, as a component of fungicides, adhesives, and lubricants, as a low-temperature heat transfer agent, as a chain terminator in the production of polyvinyl chloride, and as an analgesic and anesthetic (Fuller, 1976). As an anesthetic, TCE has been used mainly in short operative procedures, such as in obstetrics, dentistry, burn dressing, and cystoscopy, and in veterinary practice. As an analgesic it has been used mainly for treatment of trigeminal neuralgia, for women in labor, and for dental extraction. A 1975 NIOSH survey of 1,254 hospitals found that 5% were utilizing TCE in certain anesthetic procedures (NIOSH, 1977b). However, the only manufacturer of anesthetic-grade TCE has discontinued its production (Coakley, 1976) and no other company seems to have entered this market. Consumption trends indicate that TCE use in miscellaneous applications (including extraction) may grow at an average annual rate of 6% through 1979 (Blackford, 1975).

D. EXTENT OF OCCUPATIONAL EXPOSURE

From the National Occupational Hazard Survey ("NOHS"), NIOSH (1976e), estimates that approximately 3.5 million persons are occupationally exposed on a part- or full-time basis to TCE and, further, that approximately 92% of these people are exposed in operations where control measures specific for TCE are ineffective. NIOSH further estimates that approximately 100,000 persons are exposed on a full-time basis and that approximately 67% of these are working in operations where control measures are

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absent or inadequate. It should be noted that these estimates are based on information collected during the period 1972-74 and are thought to be more accurate than the estimate of 200,000 people exposed occupationally as presented in the 1973 NIOSH Criteria Document on TCE.

The NOHS also revealed that the greatest levels of exposure to TCE are in metal cleaning processes, especially in vapor degreasing. U.S. consumption rates show, however, that this trend is shifting (refer to Section III-3 on Use). Exact TCE-exposure estimates are difficult to obtain because of the fluctuation in use trends and because the TCE-component of many cleaning agents and industrial solvents may be masked by a trade name.

While the great majority of degreaser operators may be men, there are many women employed in operations in close proximity to degreasers. The actual exposure levels may, in general, be lower than that directly around the degreaser. However, the numbers of workers thus exposed may be greater. The NIOSH Health Hazard Evaluations and a survey of degreaser operations, to be discussed later, document such exposures of women. Thus, while past concern has been expressed primarily for effects of TCE on adults, consideration for fetal effects should also be included in any hazard assessment. Dow estimated that there were over 25,000-vapor degreasers in use in the United States in 1974, most of which were classified as open-top units (Skory et al., 1974). That figure is likely a realistic estimate of the current number of degreasers in use, with TCE one of the major solvents in use.

IV. BIOLOGIC EFFECTS

A. TOXICITY

As this review pertains to the issue of carcinogenicity, only a brief summary of other aspects of toxicity will be presented. Aviado et al. (1975), Fuller (1976), and Waters et al. (1977) have presented recent reviews which support the assessment of toxic effects of TCE as presented in the NIOSH Criteria Document on TCE (NIOSH, 1973).

Toxic effects on the central nervous and cardiovascular systems, skin, liver, and kidney have been attributed to exposure to TCE. However, reports on the type and severity of effects occurring following industrial exposures were often sketchy and in some cases contradictory, especially as regards latent manifestations, including hepatic and renal toxicity.

Effects on the CNS, principally depression, have been well documented. Among the symptoms most often described are: headache, nausea, vomiting, dizziness, vertigo, fatigue, mental dullness, sleepiness, feeling of light-headedness, insomnia and burning eyes. Trigeminal palsies have been reported, as have several cases of visual deterioration. Considerable evidence has accumulated that indicates that dichloroacetylene is the likely neuropathy-causing agent in TCE exposures. Reichert et al. (1975), by exposing mice to dichloroacetylene, demonstrated degenerative lesions in the brain considered parallel to those responsible for neurotoxic symptoms observed in man. High, acute doses have also resulted in cardiovascular and respiratory effects with a number of deaths attributed to respiratory arrest, cardiac arrhythmias, including ventricular fibrillation, and primary cardiac standstill. Respiratory distress has been observed often, especially following intermittent inhalation exposures, with such symptoms as chest tightness and labored breathing.

Dermal effects have long been noted, principally as a localized reddening or flushing of the skin, although generalized dermatitis has also often occurred as a result of exposure to TCE.

Intolerance to alcohol is a well-characterized phenomenon among TCE-exposed workers. Not only do many TCE workers become inebriated with consumption of small quantities of alcoholic beverages but they also are subject to vasodilation of superficial skin vessels, resulting in skin blotches, a condition known as "degreasers flush." Stewart et al. (1974), in order to study this phenomenon, repeatedly exposed seven male volunteers to TCE and then gave them small oral doses of ethanol. A transient vasodilation in the skin reached its maximum within 30 minutes and completely subsided by 60 minutes. Flushing was most

common on the face, neck, shoulders, and back. From the studies of Stewart et al., "degreasers flush" appears to be a benign dermal phenomenon which occurs primarily following repetitive exposures to TCE of at least 3 weeks' duration. Further, it seems not to be a universal problem, as some individuals are more sensitive than others to the effect. Sensitivity to alcohol may also be a long-lasting effect in that some of the volunteers exhibited the effect for several weeks after cessation of the TCE exposure. One of the volunteers continued to flush upon consumption of a small quantity of alcohol 6 weeks after exposure to TCE for 5 days at 200 ppm. Small quantities of ethanol have been shown to increase the concentration of TCE in the body, of practical importance in assessing the hazard of TCE (Muller et al., 1975).

The effects of chronic exposure of humans to TCE have not been extensively studied and thus are not well characterized. Studies with laboratory animals and a few clinical studies, demonstrated latent effects of the liver, kidney and nervous system. The degree and dose relationships of these effects is unclear, at least at low levels (< 100 ppm). The few animal studies that have been conducted with inhalation exposures to TCE for periods of at least several months and at concentrations near the current Federal occupational exposure limit (100 ppm), have given conflicting results. Mosinger and Fiorentini (1955) observed both liver and kidney changes in cats exposed by inhalation to levels of 20 ppm for 1-1.5 hours per day for 4-6 months. Seifter (1944) also observed liver injury in dogs as soon as 3 weeks of exposure by inhalation to levels of 500-750 ppm, 4-8 hours per day, 5 days a week. Other reports (Adams 1957; von Oettingen 1955) indicated evidence for slight liver changes, and fatty degeneration, and weight increase, and degenerative effects on bone marrow, heart, and central nervous system following chronic exposures to animals.

Observations of liver disfunction in workers exposed to TCE have been observed only infrequently; however, relatively little surveillance of exposed workers has been conducted to ascertain any latent effects. Thus, it is unlikely that the potential magnitude of any liver or kidney abnormalities in humans exposed for long periods to TCE are fully known.

Evidence for latent toxicity and liver and kidney damage because of TCE is available from exposures other than those occurring in the workplace. Several cases of ingestion of liquid TCE have occurred and have resulted in severe liver and kidney damage. This is in apparent contrast to the usually slight hepatic and renal effects observed after inhalation exposures. Whether the same effects would have been encountered if ingestion of TCE were spread over a period of time similar to that of an inhalation exposure is difficult to predict. However, Baerg and Kimberg (1970) did document centrilobular hepatic necrosis and acute hepatic and renal damage in teenagers repeatedly sniffing a

cleaning fluid containing TCE and petroleum distillates. The toxic effects were attributed by the authors to TCE. As the vapor concentrations were likely high and were inhaled only for a short period, the effect cannot be directly extrapolated to inhalation of the same total dose over a longer period of time, as in typical occupational exposures.

In another chronic exposure study, El Ghawabi et al. (1973), 30 workers exposed to TCE for a period of 1-5 years at levels ranging from 41 to 163 ppm reported long-lasting symptoms, headache being the most common, followed in frequency of occurrence by dizziness, sleepiness, nausea and vomiting, conjunctivitis and lacrimation, diminished libido, fatigue, skin rashes and itching. Workers continued to suffer. Even when on leave for 2 weeks, their headaches worsened in some cases. Knee and ankle jerks were exaggerated in one exposed worker. A slight bradycardia was also observed in exposed workers. The blood analysis and liver function test results were comparable to those obtained from a group of 20 matched controls not exposed to TCE or to any other solvent. Based upon these latter results, El Ghawabi et al. concluded that no chronic toxicity was evident.

In a study of 50 workers chronically exposed to TCE, Grandjean et al. (1955), also were unable to diagnose a single case of liver or kidney trouble without difficulty; however, based upon modifications in biochemical tests, they were of the opinion that 10% of the workers had slightly impaired liver function. Of more concern to these investigators was the findings of chronic nervous disorders in workers exposed to levels between 20 and 80 ppm. Based upon those results, they concluded that the allowable concentration of TCE should be fixed below 40 ppm.

In assessing possible toxic effects associated with working with TCE, one must be concerned not only with the toxicity of TCE and its metabolites, but also with that of other chemicals formed by its environmental degradation or of products of reaction between TCE and components of normal biological systems. One of the most serious concerns relates to the possible formation of the highly hazardous chemicals, phosgene and dichloracetylene, under certain conditions of TCE use (as discussed in Section II). TCE vapor around open flames or even drawn through lighted cigarettes may degrade to phosgene and CO. Acute exposures to phosgene at 10-15 ppm may be fatal, with severe distress occurring at even lower concentrations. NIOSH has recommended a phosgene TWA workplace exposure standard of 0.1 ppm with a 0.2 ppm ceiling limit for no more than 15 minutes (NIOSH 1976a). Smoking, open flames, or very hot surfaces should be excluded in TCE operations to avoid inadvertent formation of phosgene.

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B. PHARMACOKINETICS/METABOLISM

The NIOSH criteria document on TCE provided as thorough a discussion of the kinetics of its absorption, distribution, elimination, and metabolism as was known, at that time (1973). One omission, however, was the speculation about an epoxide intermediate metabolite, which has been proposed by several scientists who studied the metabolism of TCE. This issue is important to an assessment of carcinogenicity and will be discussed further in a subsequent section.

From the review in the NIOSH criteria document, as well as from a more recent one by Waters et al. (1977), a few general principles on the pharmacokinetics and metabolism of TCE may be stated: (1) trichloroethylene is readily absorbed after inhalation or ingestion and considerably less readily from the surface of the skin, (2) TCE is rapidly distributed via the blood stream throughout the body with accumulation mainly in fatty tissues, lungs, spleen, and liver, (3) the elimination of TCE following short-term exposures is primarily in the form of metabolites rather than as the parent TCE molecule and is largely via the urine, and (4) TCE is metabolized to, and excreted primarily as, two metabolites, trichloroacetic acid and trichloroethanol. The latter of these may be conjugated with glucuronic acid. A well-documented intermediate metabolite is chloral hydrate. Trichloroethanol and chloral hydrate are likely responsible for many of the toxic effects observed with TCE exposure. Other proposed metabolites are: chloroform, monochloroacetic acid, trichloroacetaldehyde, and TCE epoxide.

These general statements have been developed primarily on the basis of short-term animal experiments or brief exposures of human volunteers. Although very little is known about the effects of chronic exposure at various doses or concentrations on the pharmacokinetics of TCE, Leibman and McAllister (1967) demonstrated that repeated exposures to TCE modified the ability of rats to metabolize TCE. In those studies the conversion of TCE to chloral hydrate by rat liver microsomal preparations was shown to increase when the rats were repeatedly exposed to atmospheres containing TCE. The exposures were at 4000 ppm, 1/2 hour per day for 4 days. It is not possible to extrapolate from these results to effects of long-term exposures or to effects on other species, including humans.

A crucial issue in this report is that of the relevance of animal carcinogenicity test results to the predictability of carcinogenicity in man. In such tests with TCE (to be discussed later), the test animals were exposed to high levels of TCE by gastric intubation for 18 months. As no pharmacokinetic measurements were made in these studies, it is not possible to assess with certainty the relevance of the results to hazard assessment. On the other hand, to disregard such evidence would

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indeed run counter to all concepts of public health protection. There are several examples of animal test results obtained under similar conditions that accurately predicted potential hazard to man. Notable examples have been those obtained with vinyl chloride and benzidine, both considered at one time to be relatively innocuous.

An argument widely voiced is that high-dose levels utilized in such studies may saturate the usual metabolic pathways and lead to atypical metabolites and routes of metabolism. Gehring et al. (1976) conducted a series of studies with 1,4-dioxane and vinyl chloride to assess the dose-dependent fate of chemicals, especially as related to their metabolism, retention, and excretion. As might be expected, with high-dose levels, greater percentages of the chemicals were either excreted unchanged or retained in the body without undergoing metabolism. While Gehring et al. determined major differences in the kinetics of retention and elimination, they found no qualitative change in metabolites as the dose or exposure level was changed. They noted that the known pathways for vinyl chloride metabolism produce intermediate reactive metabolites that lead to the same end products.

A recent NIOSH review of vinyl chloride studies (NIOSH, 1977a) and the papers by Green and Hathway (1975) and by Reynolds et al. (1975) support the probability that two metabolic routes exist. These reports also propose that a dose-dependent depletion of liver glutathione may lead to decreased clearance of reactive electrophilic metabolites and to increased toxicity, including possible carcinogenicity. In studies conducted with rats, Watanabe et al. (1976) found that an exposure of at least 7 hours at 50 ppm vinyl chloride led to absorption and the metabolism of sufficient vinyl chloride to exceed the capacity of the liver to replenish the nonprotein sulfhydryl groups (glutathione and cysteine), so that presumably, free epoxidized vinyl chloride or some other reactive metabolite is available to react with nucleic acids.

Ample evidence exists that variations in exposure profiles, including different dose levels, periods, and durations of exposure, as well as concomitant exposure to other chemicals, modify the pharmacokinetics and metabolism of chemicals in the body. However, there is little evidence to support a generalization that a total shift to a more hazardous metabolite or pharmacokinetic pattern will result from exposure at high-dose levels. Results of pharmacokinetic studies with various doses of TCE, such as those described for vinyl chloride, have not been reported.

Related to this issue, however, are the studies of Ikeda et al. (1972), in which a decrease in the rate of urinary excretion of trichloroacetic acid was observed in workers with exposures above 50 ppm, essentially reaching a plateau at 100 ppm. In contrast, the levels of trichloroethanol excreted in urine

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continued to rise at a constant rate with increased exposure-levels of TCE. Ikeda et al., suggested that a shift in the pattern of metabolism occurred at higher levels, with the formation of relatively more trichloroethanol, the more toxic of the two main metabolites. Based on these results, they expressed concern with 100 ppm as a permissible level of exposure.

As illustrated in recent reviews of carcinogenicity testing methods and applications of these results, extrapolation from high dose levels may in some cases underestimate the true effect that could result at low-dose levels (Kraybill, 1977; Page, 1977). This might occur where exposure levels exceed the capacity of the body to absorb, or where an "inert" chemical is metabolized to an active carcinogen by a system of finite capacity. In such cases sequential increases in exposure levels may not result in incremental increases in effect. As of this time, data are insufficient with which to assess with certainty the effect in either direction for exposures to TCE.

With respect to uptake, two recent studies have been conducted to study the influence of exercise on the pharmacokinetics of TCE following inhalation exposure. In one, Monster et al. (1976) observed that working or exercising men absorbed 40% more TCE than resting men during 4-hour exposures at 70 and 140 ppm, but there was no influence of exercise on either the distribution or the metabolism of TCE. In the other study, when 15 healthy men were exposed to TCE at about 100 and 200 ppm for four 30-minute periods similar results were obtained (Astrand, 1976). Some of the men were allowed to rest while others were exercised strenuously on a bicycle ergometer. The uptake of TCE was about 55% of that available in the inhaled air prior to beginning the exercise regimen. While the rate of uptake of TCE decreased to about 25% during the fourth period of exposure for those men exercising most vigorously, the total dose absorbed increased since the effect of exercise was to increase pulmonary ventilation (2.5 times that at rest). The concentration of TCE in alveolar air was about twice that at rest while that in arterial blood more than doubled. The decline in percentage uptake with increasing work intensity was attributed to a rate of diffusion to the blood from the alveoli slower than the rate of supply of TCE to the alveoli. Monster et al. suggested that the relative insolubility of TCE in blood contributed to the low-diffusion rate.

Perhaps even more important than the relative changes in the kinetics of absorption, retention, and excretion of a chemical is that of the metabolites that can be formed. Of particular importance is the potential for formation of a highly reactive metabolite that can be responsible for specific toxic effects.

It has been well established that some indirectly acting carcinogens may be metabolized to activated carcinogenic intermediates via cytochrome P-450-dependent mixed-function oxidases. Such metabolites may then interact covalently with

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nucleophilic sites in nucleic acids and proteins, inducing carcinogenic lesions.

As long ago as 1945, Powell, and later, Daniel (1963), and Leibman (1965) speculated that TCE might be oxidized to an epoxide as an intermediate metabolite during its biotransformation. Renewed interest in this hypothesis resulted from the findings that vinyl chloride is carcinogenic in man and animals, and the observation that this in turn is likely due to the formation of an epoxide, chloroethylene oxide. The mechanism, proposed by Van Duuren (1975), gained support from findings of covalent binding of ^{14}C-vinyl chloride to tissue macromolecules, that it is catalyzed by rat liver microsomal preparations (Kappus et al., 1975), and by the formation of an alkylating metabolite, having an absorption spectrum identical with that of chloroethylene oxide, when vinyl chloride is passed through a mouse liver microsomal preparation (Barbin et al., 1975).

Since TCE is a structural homolog of vinyl chloride, a similar metabolic pathway and the production of TCE epoxide as an intermediate should be considered. This was proposed by Van Duuren (1975) and Corbett (1975). Such a postulation of an epoxide not only had been made as early as 1945, as indicated previously, but also was consistent with the earlier findings of McKinney (1955) on the autooxidation products of TCE.

Trichloroethylene epoxide has been synthesized by Kline and Van Duuren (1977) and by Derkosch (see: Bonse et al., 1975; Bonse and Henschler, 1976). Detection of, and thus proof of the existence of, such an epoxide in vivo has proved very difficult, primarily because of its instability, high reactivity and relatively short half-life. Presumptive evidence of its occurrence in vivo has been provided, however, by spectroscopic investigations (Uehleke et al., 1976). In Derkosch's studies, a synthesized TCE epoxide was found to have a half-life of 25 minutes in nonpolar solvents at 60°C. A much shorter half-life, 1.3 minutes, was measured by Kline and Van Duuren at pH 7.4. In-vitro, with heat, TCE epoxide thermally rearranges by migration of chlorine atoms to form dichloracetyl chloride. Opening of the oxirane-ring (epoxide) to form chloral hydrate does not occur in vitro in any considerable amount except in the presence of Lewis acids (Bonse et al., 1975). In-vivo, a somewhat different process occurs, as dichloroacetyl chloride apparently is not formed and chloral hydrate is the only observed primary intermediate, resulting from oxidation and intramolecular chlorine migration. According to Bonse et al. (1975), chloral hydrate may be evolved via formation of an oxirane (epoxide) through an interaction with the biological environment which prevents extra-molecular migration of chlorine and ring-opening to chloral, with further oxidation to trichloroacetic acid or reduction to trichloroethanol.

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As discussed previously, evidence has accumulated that strongly supports the contention that TCE may be metabolized through a reactive alkylating epoxide, trichloroethylene oxide, as an intermediate metabolite. The toxicity of an epoxide depends on its chemical electrophilic properties, its rate of formation, stability against spontaneous rearrangement, rate and mode of degradation and the concentration of antioxidants in the specific system (Daly et al., 1972). All of these factors must be considered in assessing the impact of TCE epoxide on toxicity.

Additional studies, by Van Duuren and Banerjee (1976), Kline and Van Duuren (1977), Bolt et al. (1977), and Uehleke and Poplawski-Tabarelli (1977), lend considerable support to the hypothesis of epoxide formation followed by potential nucleophilic and microsomal interactions and binding. Using rat liver microsomal preparations incubated in vitro with ^{14}C-TCE, Van Duuren and his coworkers have adequately demonstrated that TCE binds covalently to microsomal protein and that trichloroethylene epoxide reacts rapidly with a variety of nucleophiles. In recent studies, Bolt et al. (1977) compared the uptake of highly-purified TCE vapor by rat liver microsomes and covalent binding to microsomal protein in vitro with that previously measured for gaseous vinyl chloride (Kappus et al., 1975).

The studies involved incubating rat liver microsomes in a closed system using atmospheres containing different concentrations of TCE vapor. Experiments were also conducted using albumin solutions and liposomal suspensions in order to study the affinity of TCE for protein and lipid structures. The results of the studies indicate that rat liver microsomes rapidly take up TCE vapor, as they do that of VC; however, certain quantitative differences were found. Relatively more TCE than VC was dissolved by the same preparation, indicating an apparently higher affinity of microsomes for TCE, with higher uptake of TCE at high TCE levels. Considerably more TCE than VC is also bound by albumin solutions and liposomal suspensions. Thus more TCE would be expected to bind to the lipid-containing membrane structures with resulting higher concentrations of TCE than of VC at the site of metabolism, especially in microsomal systems.

In the opinion of Bolt et al., covalent binding of both TCE and VC is of the same order of magnitude, which tends to support Van Duuren's theory (1975) that TCE and VC should exert similar carcinogenic effects. In this context, however, it should be noted that the primary target tissue in the liver for VC would appear to be the endothelium of the blood vessels rather than the hepatocyte. Another study, by Kelly and Brown (1974), confirmed binding of TCE to the cytochrome P-450 system. These investigators suggested that the binding was via an epoxide or other related electrophilic species.

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A further assessment of the binding of ^{14}C-trichloroethylene both in vivo and in vitro has been made by Uehleke and Poplawski-Tabarelli (1977). Following intraperitoneal injection and oral gavage of TCE to male mice, radioactive-TCE became irreversibly bound to various portions of the hepatic protein, including (in order of degree of binding) that of the microsomes, mitochondria and cytosol. TCE also was bound to the hepatic lipids, both endoplasmic and mitochondrial. In the in vitro studies, the activity of rat liver microsomes was approximately 40% less than that of the mouse.

Banerjee and Van Duuren (1977) have demonstrated the covalent binding of a TCE-metabolite, most likely TCE epoxide, to DNA using in vitro methods and salmon sperm DNA. TCE was shown to covalently bind to microsomal proteins of not only the liver but also of the lung, stomach and kidney. Binding was also greater in mice than rats and in males over that of females. The significance of these observations is considered later in discussing the carcinogenicity results.

Henschler and his colleagues (Bonse et al., 1975; Greim et al., 1975; Henschler et al., 1975; Bonse and Henschler, 1976) have studied the chemical reactivity, metabolism, and mutagenicity of the chlorinated ethylene series, including vinyl chloride and TCE. They have demonstrated a rather remarkable correlation between biological activity and chemical structure in that those chlorinated ethylenes that are symmetrical (i.e., cis and trans -1,2 dichloroethylene and tetrachloroethylene) are relatively stable and not mutagenic. In contrast, the asymmetrical ethylenes, vinyl chloride, 1,1-dichloroethylene (vinylidene chloride) and TCE, are unstable and mutagenic. Although they acknowledged that oxiranes (epoxides) may be formed by all six chlorinated ethylenes, they concluded that the unsymmetrical oxiranes are far less stable than the symmetrical ones, are more highly electrophilic, and may react directly with nucleophilic constituents of cells, thereby exerting mutagenic or carcinogenic effects. The results of the mutagenic tests at this time correlate well with this structure/reactivity relationship.

Thus, there is strong presumptive evidence for the existence of TCE epoxide as an important intermediate step in TCE metabolism, and for the covalent binding of TCE metabolites to tissue macromolecules, including sulfhydryl nucleophiles. This is of great toxicological significance because of the possibility that alkylation of nuclear macromolecules may also occur. Further research is needed to confirm actual binding to nucleic acids under in vivo conditions. It should also be borne in mind that actual nuclear interactions may not necessarily be a prerequisite to cancer induction. Interaction between certain chlorinated hydrocarbons and the ergastoplasm, i.e., the endoplasmic reticulum holding nucleoprotein in the ribosomes attached to it, appear to result in nodule formation in the liver. Such nodules may develop into malignant tumors.

In order to produce a toxic effect, not only must a toxic chemical be present but it must also make contact with a vulnerable target tissue. Biotransformation processes may either enhance or decrease toxicity. The toxic effect, including carcinogenicity, may well depend upon the effectiveness of such detoxification mechanisms in inactivating reactive metabolites, including a possible epoxide. Indeed, studies by Moslen et al. (1977) suggest that hepatotoxic effects of TCE are related to glutathione loss and deactivation of cytochrome P-450 so that vulnerable cellular constituents are exposed to the activity of electrophilic TCE metabolites that might be formed. This suggestion, if true, would indicate a dose-dependent effect, low doses causing less effective depletion than higher ones. Such a relationship has been suggested for vinyl chloride as discussed earlier. As of this time this idea is no more than speculation as applied to TCE. Additional studies are necessary to verify that this can occur.

Along this same line, a reactive epoxide may be inactivated by a hepatic epoxide hydrase. Oesch et al. (1974), not only demonstrated such hydrase activity, but also compared the levels of humans with that of laboratory animals. Their results indicated that the hydrase activity in humans was 4 times that of mice, 2 times that of rats, about the same as that of guinea pigs, and markedly lower, about one-third, that of Rhesus monkeys. Styrene oxide was used as the substrate; however, Oesch and his colleagues have shown that the same purified epoxide hydrase can hydrate a large variety of other alkene and arene oxides.

Based upon this review the metabolic scheme presented in Figure 1 is proposed. It differs from that presented in the NIOSH criteria document only by describing events occurring in the conversion of TCE to chloral hydrate.

C. CARCINOGENIC POTENTIAL

On March 21, 1975, the National Cancer Institute reported preliminary results of a carcinogen bioassay which indicated no carcinogenic effects in rats but the induction of a highly significant number of hepatocellular carcinomas in both male and female mice (Saffiotti, 1975). These preliminary results were later confirmed and described in great detail (NCI, 1976).

An extensive literature review has not produced information on any other adequately conducted carcinogen test. Waters et al. (1977) listed four other toxicity studies, none of which revealed evidence for carcinogenicity (Adams et al., 1951; Mosinger and Fiorentini, 1955; Rudali, 1967; and Seifter, 1944). All, however, had major design weaknesses such as an inadequate period of exposure or observation, too few animals, and, in three studies, no deaths or data reported on any of the animals. None

Trichloroethylene   Trichloroethylene   Trichloroacetaldehyde
                              epoxide

```
 Cl      Cl                   Cl   Cl                  Cl      O
   \    /                     |    |                   |      //
    C = C        --->    Cl - C -  C - H   --->   Cl - C -  C
   /    \                      \  /                   |      \
 Cl      H                      O                     Cl      H
                                                      |
                                                      ↓
```

                Trichloroethanol   Chloral hydrate

```
          Cl   H                          Cl   OH
          |    |                          |    |
    Cl -  C -  C - OH      <---     Cl -  C -  C -H
          |    |                          |    |
          Cl   H                          Cl   OH
          |                               |
          ↓                               ↓
```

           Trichloroethanol   Trichloroacetic
             glucuronide   acid

```
          Cl   H                          Cl      O
          |    |                          |      //
    Cl -  C -  C - O -C6H9O6       Cl -  C -  C
          |    |                          |      \
          Cl   H                          Cl      OH
```
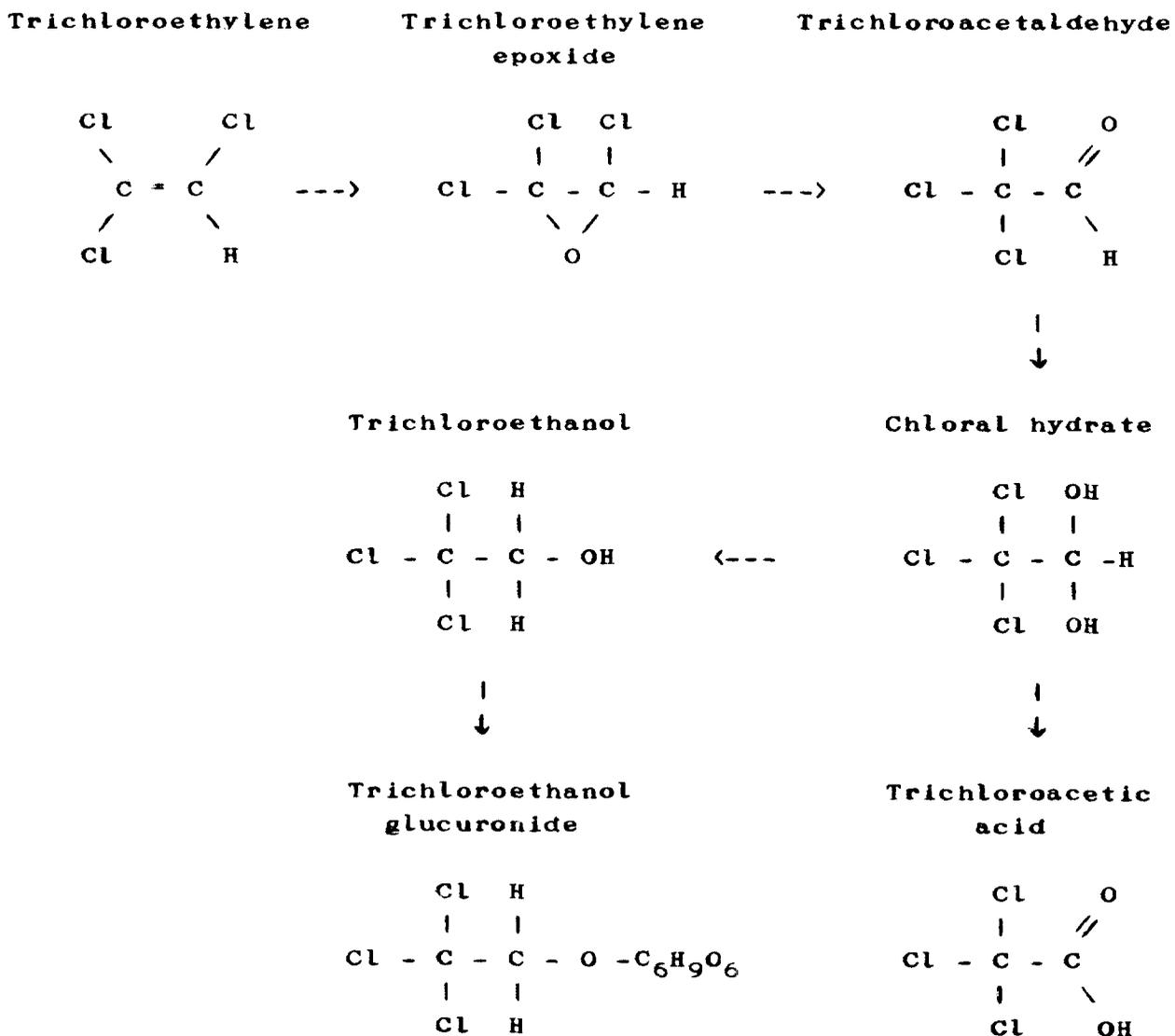
Figure 1.   Proposed metabolism of trichloroethylene

can qualify as an adequate carcinogenicity test and will receive no further consideration in this review. They are, however, summarized in Table 4.

A major carcinogenicity study is now underway, administered by the Manufacturing Chemists Association (Olson 1975a, 1975b; Clark 1977a). In these studies, male and female Charles River albino rats and B6C3F$_1$ mice are exposed to TCE (same commercial product tested by the NCI) by inhalation for a period of 24 months, beginning as young adults. Three dose levels, 100, 300, 600 ppm, are used with exposures for 6 hours per day, 5 days per week. Preliminary results, based upon rats and mice dying up to

21 months, and mice killed at 24 months, indicate an effect similar to that reported by the NCI, i.e., no evidence of tumorogenicity in rats with an apparent induction of liver cancer in mice (Clark, 1977b, 1977c).

Until the study supported by the MCA is completed, the only animal study that can be utilized in an evaluation of the carcinogenic potential of trichloroethylene is the one conducted for the NCI. The design can be summarized as follows: Rats and mice of both sexes were exposed once per day, 5 days/week to TCE, administered in corn oil by stomach tube, at two dose levels, beginning as weanlings and continuing for 78 weeks (18 months). At the end of 90 weeks (mice) or 110 weeks (rats), surviving animals were killed, necropsied, and submitted to an extensive gross and microscopic examination. Those dying or killed prior to the scheduled termination date were examined in the same manner. A total of 480 animals were employed in the chronic exposure study, consisting of groups of 50 TCE-exposed animals and of 20 controls (Table 5).

The observed incidences of hepatocellular carcinoma in mice were dose-related and highly significant ($p < .01$) at both dose levels in male mice and at the higher level in female mice (Table 6). The increase observed in low dose female mice was found to be significant at a p-value of 0.09.

A greater degree of confidence would be obtained if the control data for the entire colony were used, as opposed to the matched controls. The observed tumor incidences of 5% and 0% in the matched male and female control mice compares very favorably with incidences of 8.7% and 1.7% observed in over 2,000 colony controls of the same strain used in similar experiments by the NCI, (Page, 1977).

In reviewing these NCI test results, the response of male mice appeared to be greater than that of the female, not only in total incidence of hepatocellular carcinomas but also in shorter latency and in larger numbers of metastases to the lungs. These sex differences may have been more apparent than real, however, in as much as spontaneous hepatocellular carcinomas normally are not only of higher incidence in male controls but also appear earlier and metastasize with greater frequency.

As regards latency period, no hepatocellular carcinomas were found in female mice prior to the 90-week terminal killing. In comparison, 15 exposed males that died during the 90-week period had hepatocellular carcinomas. The first liver tumor was diagnosed at autopsy in a male mouse of the high-dose group that died after 27 weeks of exposure, with three others seen by the 36th week and six more by the end of the 78th week of exposure. By contrast, in the low-dose group, the first liver tumor was not observed until after 81 weeks in male mice. Thus, in male mice,

Table 4. Chronic toxicity studies of TCE reported in the literature other than the NCI studies

Species (Reference)	Route of Exposure	Exposure Regimen	Number Animals	Results	Comments
Mice (Rudali, 1967)	Gastric Intubation	0.1 ml in oil 2x/wk for unspecified period	28	No Tumors No Deaths	Insufficient data to judge adequacy - presumed to be inadequate
Rats	Inhalation	3000 ppm, 27 exposures	12	3 rats died No Tumors	Insufficient period of exposure/observation (too
Guinea Pigs	"	100 ppm, 132 exposures	11	No data	short for carcinogenicity
Monkeys	"	200 ppm, 148 exposures	2	No data	study)
Rabbits (Adams et al., 1951)	"	200 ppm, 178 exposures	4	No data	
Dogs (Seifter, 1944)	Inhalation	150-750 ppm in air; 20-48 hr/wk for 7-16 wks	16	No Tumors No Deaths	Insufficient period of exposure/observation
Cats (Mosinger and Fiorentini, 1955)	Inhalation	200 ppm for 75 min/day for 6 months	8	No Tumors No Deaths	Insufficient period of exposure/observation. Too few animals.

Table 5. Experimental design - NCI carcinogen bioassay of trichloroethylene

	Experimental design	Experimental Groups	Dose levels (mg/kg/day)[*]
Mice (B6C3F₁)		Males:	
Route of exposure:	Intragastric Intubation	Controls	0
Treatment mixture:	10-24% TCE in Corn Oil	Low Dose	1169
Frequency of exposure:	Once Daily, 5x/Week	High Dose	2339
Duration of exposure:	78 Weeks	Females:	
Additional observation:	12 Weeks	Controls	0
Total period:	90 Weeks	Low Dose	869
Microscopic examination:	About 30 tissues/all animals	High Dose	1739
Rats (Osborne-Mendel)		Males:	
Route of exposure:	Intragastric Intubation	Controls	0
Treatment mixture:	60% TCE in Corn Oil	Low Dose	549
Frequency of exposure:	Once Daily, 5x/Week	High Dose	1097
Duration of exposure:	78 Weeks	Females:	
Additional observation:	32 Weeks	Controls	0
Total period:	110 Weeks	Low Dose	549
Microscopic examination:	About 30 tissues/all animals	High Dose	1097

Reference: NCI, 1976

[*] Time-weighted average doses. Actual doses listed below:

Mice (M) - 12 weeks at 1000/2000 mg/kg/day; 66 weeks at 1200/2400 mg/kg/day.

Mice (F) - 12 weeks at 700/1400 mg/kg/day; 66 weeks at 900/1800 mg/kg/day.

Rats (M/F) - 7 weeks at 650/1300 mg/kg/day; 9 weeks at 750/1500 mg/kg/day; 62 weeks at 500/1000 mg/kg/day.

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Table 6. Incidence of hepatocellular carcinoma in B6C3F$_1$ mice
exposed to trichloroethylene

Males			
Matched controls	1/20	(05%)	
Low dose	26/50	(52%)	(P = 0.004)
High dose	31/48	(64%)	(P < 0.001)

Females			
Matched controls	0/20	(0%)	
Low dose	4/50	(8%)	(P = 0.090)
High dose	11/47	(23%)	(P = 0.008)

Reference: NCI, 1976.

the latency period for the appearance of tumors was shorter in the group receiving the higher dose level.

The incidences of no other types of tumors in mice and of no tumors in rats were significantly increased (p=.05) above those observed (and expected) in the control groups, although there were increased incidences of malignant lymphoid tumors 17/195 versus 2/40) and pulmonary tumors (18/195 versus 1/40) in mice. No hepatocellular carcinomas, like those diagnosed in mice, were observed in any of the exposed rats.

The NCI report acknowledges that there were several design features that may have exerted a modifying or contributing role in the experiment. The NCI followed the recommendations of expert panels on carcinogenesis testing (Page, 1977) in employing high-dose levels so as to provide maximum sensitivity in the screening assay. Supposedly "maximum tolerated" doses were chosen after an 8-week range-finding study. Unfortunately, the doses were not as well tolerated as had been predicted and considerable toxicity was evident. In an attempt to achieve the "maximum tolerated dose," some subsequent minor downward adjustments were made in dose levels or frequency of administration.

Mice developed alopecia, skin sores, and a hunched appearance after a few weeks exposure. Abdominal distension, attributed to developing liver pathology, was noticed after 50 weeks. Although toxicity was clinically evident, the mortality rate by 90 weeks was not sufficient to reduce seriously the effective number of animals.

Survival of both TCE-exposed and control rats was poor at 110 weeks, 82% of male controls and 60% of the control females

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having died by that time compared with 89 and 73% of the exposed male and female rats, respectively. In addition to an apparent exposure-related chronic nephropathy, the animals were afflicted with chronic respiratory disease. The renal pathology consisted essentially of degeneration of the epithelium of the proximal tubule, seen in the TCE-exposed animals only. No significant changes in the structure of the liver were observed. The NCI investigators concluded that the high mortality among the rats detracted from the usefulness of the experiment with that species in detecting carcinogenic potential.

Clinical signs of toxicity were observed in all exposed groups of rats, beginning in the first year and increasing in frequency progressively thereafter. Among the signs observed were rough haircoat, skin sores, reddish discharge from eyes, and a hunched appearance. While survival of all rats was poor, the exposed animals died earlier.

In addition to TCE-exposed animals, groups of animals to which other volatile chemicals had been administered were housed in the same room. Although the ventilation in the room conformed to the recommendations of the Institute of Laboratory Animal Resources (ILAR, 1976), it is possible that the TCE-exposed animals were also subjected to very low-level exposures to several other chemicals.

It should be pointed out that the NCI test had serious limitations as the ultimate test for the carcinogenic potential of TCE. As the exposure began when the animals were young adults, no assessment for transplacental carcinogenesis can be made. Tissues of the fetus or newborn animal are generally regarded as more sensitive to chemical carcinogenesis than those of older offspring. The tests were terminated at 90 and 110 weeks for mice and rats, respectively. It is possible that late developing tumors might have been observed had the animals been allowed to survive until they died or the study terminated after a longer period of observation. Over 80% of exposed and control mice and 70% of control rats were alive at time of termination. It should be noted that several expert committees have recommended that exposure begin prior to conception, continue during pregnancy, with exposure to offspring for life, especially for those chemicals to which the fetus may be exposed (FDA, 1971; Tomatis, 1974; Canada, 1975). The FDA further recommended that studies not be terminated until cumulative mortality has reached 75% in a group showing negative results. They also consider that sample sizes greater than 40-50 per group are required for testing weaker carcinogens. The NCI and MCA studies both suffer from failure to follow these guidelines.

Another design weakness of the NCI test, detracting from its sensitivity, was that the exposure levels were too high in the rat study, such that less than 15% of male rats and 25% of female rats survived after 110 weeks.

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While these deficiencies in basic design and performance detract somewhat from the confidence that one might attach to the NCI study, the differences observed in liver cancer rates between exposed and control mice are real. At this point, one must conclude that a carcinogenic potential in the mouse has been demonstrated for TCE under the test conditions. It then becomes necessary to examine several scientific issues to assess the probability that TCE would represent a cancer risk in the workplace under normal conditions of exposure.

Species Differences:

Differences in species responses to chemical carcinogens can often be attributed to differing metabolic pathways and metabolites, and to an inability of some species to effectively convert the test chemical to an active carcinogen. The high sensitivity of the $B6C3F_1$ mouse and the low sensitivity of the NCI strain of Osborne-Mendel rat (Table 7) not only to TCE but to the positive control, carbon tetrachloride (NCI 1976), and to tetrachloroethylene (NCI 1977b) indicate innate species differences in sensitivity to chlorinated aliphatic compounds.

Henschler (1977) is of the opinion that the difference in response of rats and mice might be attributed to the comparatively low activity of epoxide hydrase in mice, i.e., the decreased ability of the mouse to detoxify an epoxide, whether the product of metabolism or its presence in the administered TCE. Another obvious possibility is that of a difference in the degree of epoxide formation between the two species. Indeed, Banerjee and Van Duuren (1977) recently demonstrated, using in vitro methods, differences in the metabolism of TCE by the $B6C3F_1$ mouse and the Osborne-Mendel rat used in the NCI study. These differences agree well with the NCI carcinogenicity test results. The binding of TCE to liver microsomal protein was 46% higher in male $B6C3F_1$ mice than in the male Osborne-Mendel rat. Binding of TCE to liver microsomal proteins was 37% higher for males than that for female mice. Covalent binding of TCE to DNA was also much higher for microsomal proteins from male mice than from females. These differences correlate with the carcinogenic response in mice but not rats and a greater response in male mice over that of female mice in the NCI test. In an ancillary study, Banerjee and Van Duuren (1977) also substantiated the role of epoxide hydrase in the interaction of TCE and DNA. Enhanced covalent binding of TCE to DNA resulted from the addition of a known inhibitor of epoxide hydrase.

Based on the above observations, the greater metabolism of TCE, the larger covalent bindings of TCE to microsomal protein and to DNA, and the lower level of epoxide hydrase in mice are all factors which may have contributed to the greater carcinogenic response in the $B6C3F_1$ mouse, than in the Osborne-Mendel rat.

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Table 7. Incidence of hepatocellular carcinoma in rats exposed to trichloroethylene (TCE), tetrachloroethylene (PCE), chloroform ($CHCl_4$), and carbon tetrachloride (CCl_4).

	Male rats			Female rats		
	Controls	Low dose	High dose	Controls	Low dose	High dose
TCE	1/99	0/50	0/50	0/98	0/48	0/50
PCE	1/99	0/49	0/49	0/98	0/50	0/50
MCh	1/99	0/50	0/50	0/98	0/50	0/50
CHCL3	1/99	0/50	1/50	0/98	0/49	0/48
CCL4	1/99	2/50	2/50	0/98	4/49	1/49

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While it is possible that the epoxide hydrase level in humans is greater than that of rats and mice (Oesch et al., 1974), additional research is needed to compare the rate of formation, rate of detoxification and ultimate reactivity or alkylating potential of a carcinogenic chemical that might be formed in the metabolism of TCE by humans.

Significance of Mouse Liver Cancer as an Indicator of Carcinogenic Potential to Man:

One of the most controversial issues in cancer research in the past decade has been that of the relevance of liver cancer induction in mice as a predictor of carcinogenic potential in man. Indeed, in an effort to resolve the many uncertainties, two major working conferences have been held; in 1969 (IARC, 1971), and 1975 (Butler and Newberne, 1975). Neither has been able to provide clear guidance in the application of such data to risk assessment.

Challenges to the biological significance of mouse liver cancer and even to the use of the mouse in carcinogen testing have been primarily from the English pathologists Butler, Grasso, and Roe (Butler, 1971; Grasso and Crampton, 1972; Grasso and Hardy, 1975; Roe and Tucker, 1974). Recent support for their position has been expressed by Newberne (1974) of the United States.

In considering this issue, the World Health Organization in 1973 (WHO, 1974) agreed that "there is a serious lack of knowledge regarding the processes involved in the development of liver tumors by mice and that it would be unwise to classify a substance as a carcinogen solely on the basis of evidence of an increased incidence of tumors of a kind that may occur spontaneously with such a high frequency". In reviewing the basis for this conclusion, it appears that the concern is for use of animals in which the spontaneous incidence of liver tumors is very high. In the present case it does not appear that the 1.7 and 8.7% spontaneous incidences in female and male mice used by the NCI would engender this concern. In addition, the discussion cited largely pertains to hepatic nodules, considered benign liver tumors, rather than to hepatocellular carcinomas.

The issue of terminology may be more one of semantics than of substance, as the typical hepatocellular carcinoma diagnosed in the NCI study was of nodular appearance, and although it rarely invaded surrounding tissues, it frequently metastasized to the lungs. On the basis of both morphology and metastasis, they are truly malignant.

In the NCI study, approximately 12% (7 of 57) of the hepatocellular carcinomas in male mice were observed to have metastasized to the lungs. Of the 15 carcinomas in exposed female mice or the single hepatocellular carcinoma in control animals, none was found to have metastasized. The extent of

metastasis, however, was judged on the basis of single sections through each lung. There can be little doubt that a more thorough examination would be required to detect rare or early lesions, including metastatic foci of liver tumors in the lung. Kyriazis et al. (1974) illustrated the inadequacy of a cursory examination to detect such small lesions. A simple examination of randomly selected lung lobes revealed only 4% and 0% metastatic foci of diethylnitrosamine-induced hepatocellular carcinomas in male and female B6C3F$_1$ mice, respectively. Sections of the whole lung at two different levels detected foci in over 20% of animals with liver cancer. Additional sections may well have revealed an even higher rate of metastasis.

Pathologists have found it difficult to reach a consensus in the classification of liver tumors, and Terracini et al. (1973) stated that strict criteria for distinguishing between benign and malignant liver cell tumors were not available. Grasso and Hardy (1975) stated that the meaning of the term hepatoma in experimental cancer research is equivocal so that the reader is never certain whether investigators are using it to indicate benign tumors or hepatic cell carcinomas.

Andervont and Dunn (1952) transplanted hepatomas in mice and attempted to correlate the histologic structure of primary hepatomas with their ability to propagate in new hosts. Microscopic examination failed to reveal any consistent morphologic differences between tumors which did and did not grow.

In a dose response study of Dieldrin, Walker et al. (1973) distinguished two types of liver tumors. Benign hepatomas, or type A tumors, consisted of solid cords of closely packed parenchymal cells differing little in morphologic and staining characteristics from the rest of the parenchyma. The mitotic index was low and the lesion appeared to be growing by expansion with compression of normal adjacent liver parenchyma. Malignant, or type B, hepatomas were distinquished from type A by the presence of areas of papilliform or adenoid formations of liver cells with wide and irregular vascular channels. Nuclei showed a variable increase in size and enlarged nucleoli. The mitotic index was frequently increased and multinucleated forms were seen. Cytoplasmic alterations included hydropic and fatty changes and hyaline-droplet formation. Areas of necrosis were also present. Metastases were found in association with type B lesions only. In most other published series the incidence of metastases also was low.

Walker et al. (1973) did not distinguish between a hyperplastic nodule and a benign hepatoma. Lemon (1967) indicated that some weight should be given to the presence of portal tracts within the nodule in making the distinction between spontaneous nodular hyperplasia (small hepatoma) and an induced tumor.

Farber (1976) and Miller and Miller (1976), have reviewed the pathogenesis of liver cancer. From their reviews, it appears that the majority of experimental studies on the pathogenesis of chemically induced liver cancer have implicated proliferative stages, such as hyperplastic nodules, as probable precursor lesions.

Grasso and Crampton (1972) were of the opinion that induction of liver tumors in mice did not indicate chemical carcinogenicity, no matter what the tumor class. Reasons advanced were: possible presence of oncogenic viruses, unpredictable background or high spontaneous incidence of such tumors in untreated controls, and the ease of induction by carcinogens and other agents. Their concern seems to have been more related to the interpretation of benign lesions, often called hepatic nodules or hepatomas, rather than to that of such hepatocellular carcinomas as were observed in the NCI experiments.

Grasso and Hardy (1975) proposed that tissue injury and repair may be important in the development of hepatic nodular lesions. As examples they cited the efficacy of CCl_4 and chloroform in producing extensive necrosis as well as apparently increased incidences of liver tumors. Other factors, e.g., sex hormones and diet, have been suggested as possible modifiers of the carcinogenic activities of primary carcinogens and perhaps even of the natural occurrence of spontaneous liver tumors.

To evaluate this problem, Tomatis et al. (1973) surveyed the available literature and compiled a list of chemicals reported to induce liver tumors in mice. They then searched for test results in the rat and hamster with this list of chemicals in order to assess the correlation of induction of liver tumors in mice with the capability of the chemical to also induce tumors in the other two species. From this survey of 58 chemicals, a strong positive correlation existed when the chemical induced tumors of the liver in the mouse and also induced tumors in the liver or at another site in at least one of the other two species. Among the 58 chemicals considered, 7 were recognized or suspected to be human carcinogens. All seven were hepatocarcinogenic in the mouse and six were carcinogenic in the liver and/or other organs in the rat. Of the 58, 51 had been tested in rats and 29 in hamsters, of which 78% and 79% were positive, respectively in these species. Negative results were obtained in both rats and hamsters for only one chemical. Tomatis et al. concluded that the induction of liver tumors in the mouse should be considered to be as valid as the evidence obtained in the rat and/or the hamster at any site. These reviewers also demonstrated that target organs may differ in the rat and/or hamster (and perhaps man) from that or those in the mouse. Saffiotti (1977) undertook a critical evaluation of the tests used by Tomatis et al., and concluded that the correlation was even stronger than stated by the latter authors. In Saffiotti's opinion, there is no

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scientific basis to support the suggestion that the carcinogenicity of a chemical in mice is not representative of its activity in other species, including man.

As indicated in the preceeding discussion, many eminent scientists have disagreed about the validity of results obtained in the mouse for predicting carcinogenic activity in man. The opponents claim: (1) that factors unconnected with the administration of the test compound may have a considerable influence on the incidence of hepatomas in mice and (2) that a mechanism may be responsible for the effect which is unlikely to occur in humans exposed to the chemical at lower levels. In their opinion, additional evidence is required if claims of carcinogenicity based upon the induction of this type of tumor are to be seriously considered.

In contrast, proponents of the use of the mouse can point to the many results first obtained in the mouse which were later confirmed with other species, including humans. The mouse was the first animal used to demonstrate the carcinogenicity of coal tars, polynuclear aromatic hydrocarbons, azo dyes, aromatic amines, estrogenic hormones, and carbon tetrachloride. The mouse has been accepted by carcinogenesis researchers for years as the species of choice. As pointed out by Saffiotti (1977), serious questioning has arisen only after findings of carcinogenicity of organochlorine pesticides. The mouse, like the rat and other laboratory species, has strengths and limitations as an experimental model. Resolution of this controversy is beyond the scope of this review. However, we have chosen to adopt the approach of gathering all additional data that might either support or refute the animal bioassay results.

It should be noted, that while this discussion has focused on the induction of mouse liver tumors, a similarity exists in the interpretation of induced lung tumors of the mouse, mammary tumors in the rat and a number of other spontaneously occurring tumors in laboratory animals and humans. It should not be expected that an index for carcinogenicity is the induction of a tumor-type never observed as a spontaneously occurring one as the cell populations transformed are the same and since many so-called spontaneous tumors are possibly related to exposures to low-levels of chemicals in the animals' environment.

Route of Exposure:

In the NCI study, TCE was administered by gastric intubation whereas occupational exposures are predominantly by the inhalation and dermal routes. While the NCI did not measure gastrointestinal absorption, it is likely that a high concentration of TCE reached the liver via the portal circulation for a comparatively short time each day following intubation, as TCE is readily absorbed from the intestinal tract (Fabre and Truhaut, 1952; Barrett and Johnston, 1939). Because tumors

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appeared outside the intestinal tract, absorption of TCE and then systemic exposure of all tissues to TCE can be assumed. However, the relative distributions to other organs were not measured and would be difficult to estimate. It is worthy of note, however, that absorption from the gastrointestinal tract is the route that is the most likely to ensure that metabolites of TCE, rather than TCE itself, impinge upon not only the liver, but also other organs and tissues of the body. Here, the balance between activation and detoxication becomes of great importance also.

The kinetic relationships of absorption and distribution of TCE following inhalation and oral exposures are likely to be of a similar qualitative nature, with the liver the main organ responsible for biotransformation and detoxication in both situations. In the case of a chemical absorbed readily from either the lungs or the intestinal tract, and with an effect of a systemic nature, or at a site different than the point of initial contact or absorption, the results obtained with one route may be applicable generally to the other. NIOSH considers that the NCI test is appropriate for assessing the carcinogenic potential of TCE via inhalation. The inhalation studies underway, administered by the MCA, may provide useful data in assessing the route of exposure as a modifier of potential carcinogenicity of TCE. Preliminary results, recently released by the MCA, indicate a carcinogenic effect in mice similar to that found by the NCI after gavage.

Selection of Dose Levels:

Dose levels selected were to be the highest consistent with long-term survival. Such high doses have been referred to as "Maximum Tolerated Doses" in accordance with the methods proposed by Weisburger and Weisburger (1967). While such high levels may increase the probability of a tumorigenic response by the test system, objections to such levels are that they may introduce toxic conditions that interfere with survival and the carcinogenic process, or that they may introduce atypical metabolites by saturation of the usual metabolic pathways.

As indicated earlier, the doses used in the NCI study were too high, so that survival of the rats was poor and, consequently, the ability of the test to detect carcinogenicity was comparatively low. As regards the second objection to the use of high-dose levels, dose modifying effects on the pharmacokinetics of retention, metabolism and elimination have been demonstrated for vinyl chloride and dioxane (Gehring et al., 1976); however, an insufficient number of studies have been performed along this line to permit generalizations in this regard. As previously discussed in the metabolism section, Gehring et al. did not demonstrate qualitative or quantitative changes in metabolites as the exposure was changed. Unless a pathway is demonstrated to be the only one responsible for the

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carcinogenic effect, and unless that pathway is demonstrated to be completely lacking at low doses, then the modification of metabolism can only relate to some relative quantitative differences (of questionable value in extrapolation) and not an "all-or-none" effect. Data relevant to the NCI bioassay studies are not yet available.

Role of Exposure to Chemicals Other Than TCE:

TCE-exposed animals may have been exposed also to low levels of known carcinogens by way of additives or contaminants in the commercial grade TCE, the air, water, or the feed.

Trichloroethylene used in the NCI test was of a commercial grade, 99% pure, with a number of minor contaminants or additives. Those identified were 1,2-epoxybutane (0.19%), ethyl acetate (0.04%), epichlorohydrin (0.09%), N-methylpyrrole (0.02%) and diisobutylene (0.03%). Epichlorohydrin has carcinogenic and mutagenic potential (NIOSH 1977c), as does 1,2-epoxybutane (Walpole, 1958; Rosenkranz and Speck, 1975; McCann and Ames, 1976). Henschler et al. (1977) analyzed a sample of the TCE used by the NCI and identified contaminants amounting to 0.65%, including 0.22% epichlorohydrin and 0.20% epoxybutane.

Henschler et al. (1977) are of the opinion that the carcinogenic effect observed in the NCI study was predominantly, if not exclusively, due to the epoxides present in the TCE sample used in the test. While this possibility cannot be discounted, it should be noted that the TCE used in several positive mutation and cell transformation tests was highly-purified and without the epoxide stabilizers. An additional argument against implicating the epoxide stabilizers is that other chlorinated chemicals, e.g., tetrachloroethylene, have induced the same tumor response in mice and did not contain the epoxide stabilizers. While we are of the opinion that the carcinogenic effect is primarily related to exposure to TCE itself, the possible additive or modifying effects of other chemicals is recognized. As the TCE utilized in the MCA studies was the same grade as that used in the NCI test, possible effects of minor contaminants is also an issue.

In addition to TCE, 17 other chemicals were on test in the same room housing the TCE-exposed mice. Included in the group were five other chemicals which have carcinogenic potential: carbon tetrachloride, chloroform, tetrachlorethylene, 1,2-dibromo-3-chloropropane and 1,2-dibromoethane. The first three have been known to induce liver cancers similar to those observed in the TCE-exposed mice. The mice were maintained in filtered cages, the air in the room was changed 10-15 times per hour, and the chemicals were administered under a hood in a separate room. Even under these conditions it is possible that certain amounts of chemicals other than TCE were exhaled or excreted, so that contamination of the air within the room by low

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concentrations of other toxic substances may well have existed throughout most or all of the exposure to TCE. Sansone et al. (1977) have documented the spread of chemicals, mixed in feed, within and between animal rooms even when cages with filters and high-level containment practices were used. The escape and movement of volatile chemicals might be even greater than particulate matter. Thus, the TCE-exposed mice may well have been exposed also to low levels of other carcinogenic chemicals under test in the same room, especially to those of a relatively volatile nature. As no environmental measurements were made, these levels can not be estimated.

Artesian well water was provided to the mice ad libitum. This contained low levels of nitrate, nitrite, chloride, chromium and many other chemicals commonly present in water supplies. As the water was not chlorinated, the concentrations of chloroform or other chlorinated carcinogens were probably quite low. Very low levels of DDT, DDE, Aroclor 1254, and Dieldrin were present in some samples of the commercial feed used in the study.

The NCI concluded that there was no evidence that either the housing or the presence of other chemicals in the same room modified the results of the experiment. This conclusion was based on the lack of an unusual incidence of hepatocellular carcinomas in the controls kept in the same room, a dose-response relationship in the TCE-exposed groups, and the thousand-fold increase in dose levels achieved by gastric intubation versus that possible by any inadvertent inhalation of contaminants.

The possible role that exposure to these very low levels of other chemical carcinogens may have played in the NCI study is impossible to assess. As the controls were also exposed to the same air, diet, water, and room environment and since some tests conducted along with that of TCE did not reveal carcinogenic activity (NCI 1977a), a major effect of such minor exposures may be viewed as highly unlikely. However a cocarcinogenic effect or possible stimulatory activity on liver enzymes cannot be discounted. Other chemicals which affect the liver, such as phenobarbital and DDT, have been reported to be able to induce a significant enhancing effect with another liver carcinogen, 2-AAF (Peraino et al., 1975). The concentrations used in those studies were far in excess of those of the contaminant or incidental chemicals in the NCI tests.

Assessment of NCI Carcinogenicity Test:

The criteria for carcinogenicity developed by the National Cancer Advisory Board (NCAB, 1977) have been met by the NCI bioassay test in that: (1) the studies were adequately designed and conducted, (2) the increases in incidences of neoplasms were statistically significant, and (3) the only major experimental variable between control and experimental groups was the absence or presence of the test agent. In addition, positive results

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were observed in more than one group and the occurrence of neoplasms followed a dose-dependent relationship. In NIOSH's opinion, the use of high-dose levels, the gavage route of exposure, and the low-level contamination of air, food, and water with other chemicals do not negate the validity and usefulness of the test results as an indicator of carcinogenic potential. The NCI studies were designed in accordance with recommendations of expert international and academic committees and were conducted according to laboratory standards existing at the time.

Comparison of TCE Results With Studies of Other Organochlorine Chemicals:

Trichloroethylene was placed on carcinogenic bioassay as one of a series of short-chain organochlorine compounds. As of this time, results with four other structurally related chlorinated chemicals have been reported. These are carbon tetrachloride, chloroform, tetrachloroethylene and methyl chloroform. Of these, the first three induced hepatocellular carcinomas much like those induced by TCE. In addition, chloroform induced kidney cancers also. Methyl chloroform was tested at levels higher than used for the other chemicals. However, the mortality was excessive, which detracted from the confidence in that study. Table 8 presents information on this series of studies. While it is difficult to compare the results of these studies because of possible differences in absorption and mortality, it would appear from Figures 2 and 3 that the relative potency of TCE, as compared with those of the other chemicals capable of inducing liver cancer, may be somewhat less. This is based on the higher incidences of liver tumors at lower dose levels for the other three chemicals, and with the exception of the high-dose males in the TCE study, a shorter latency period.

D. MUTAGENICITY

Following the announcement of positive carcinogenic results by the NCI, considerable research was initiated to assess the mutagenic potential of TCE using in vitro systems. Initial tests proved negative. However, with the use of more sensitive test systems, to which metabolic activation systems were added, mutagenicity was demonstrated in four test systems: two bacteria, Salmonella typhimurium and E. coli, in yeast and in Tradescantia. In none of these systems, however, was a particularly strong response observed.

Simmon et al. (1977) found TCE to be weakly mutagenic in the S. typhimurium (Ames) bacterial system, using the TA100 tester strain coupled with liver homogenate. While positive results were obtained with Sprague-Dawley liver S-9 mix, the response was greater using liver homogenate obtained from male B6C3F$_1$ hybrid mice. The assay plates were placed in 9-liter

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Table 8. A comparison of NCI carcinogenesis bioassay tests of trichloroethylene (TCE). tetrachloroethylene (PCE), methyl chloroform (MCh), chloroform (CHCl$_3$), and carbon tetrachloride (CCl$_4$).

Chemical/expt'l group		Dose levels[1] (mg/kg)		Percent alive at 78 weeks		Hepatocellular carcinomas in mice	
		Rats	Mice	Rats	Mice	Percent incidence[2]	Time to 1st tumor (wks)
TCE	Males						
	Low dose	549	1169	60	80	52	81
	High dose	1097	2339	24	48	65	27
	Females						
	Low dose	549	869	40	82	8	90
	High dose	1097	1739	46	45	23	91
PCE	Males						
	Low dose	471	536	43	53	65	27
	High dose	941	1072	14	25	56	40
	Females						
	Low dose	474	386	50	25	40	41
	High dose	949	772	42	17	40	50
CHCl$_3$	Males						
	Low dose	90	138	78	86	36	80
	High dose	180	277	54	81	98	54
	Females						
	Low dose	100	238	56	86	80	66
	High dose	200	477	50	72	95	67
MCh	Males						
	Low dose	750	2807	2	42	0	–
	High dose	1500	5615	4	28	2	50
	Females						
	Low dose	750	2807	18	56	0	–
	High dose	1500	5615	24	28	0	–
CCl$_4$	Males						
	Low dose	47	1250	68	22	100	48
	High dose	94	2500	68	4	98	26
	Females						
	Low dose	80	1250	76	25	100	16
	High dose	159	2500	42	9	96	19

[1] Chemicals were administered by stomach intubation at predicted maximum tolerated dose levels for 78 weeks and observed for an additional 12 weeks (mice) or 32 weeks (rats).

[2] Incidence in all animals at end of experiment, i.e., 90 weeks for mice and 110 weeks for rats. Colony control incidence (n=2208) of hepatocellular carcinoma in B6C3F1 mice: Males = 8.7%; Females = 1.7% (Page 1977).
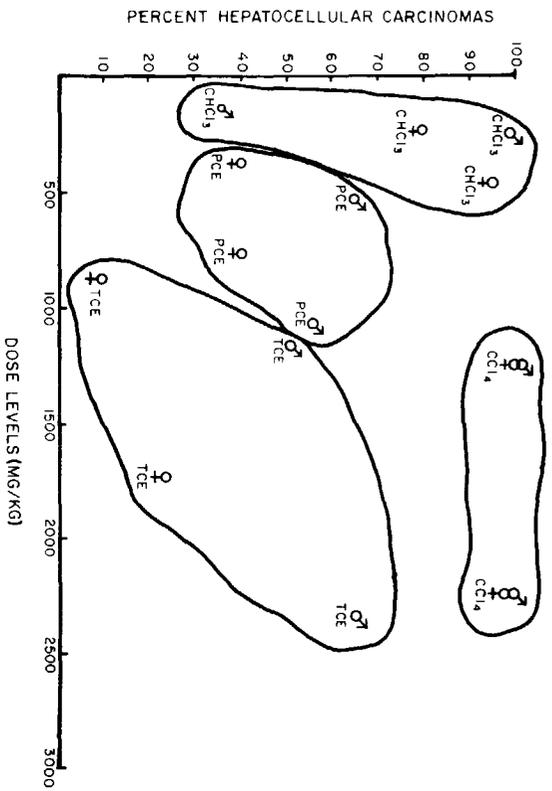
Figure 2. Relationship of hepatocellular carcinoma incidence with
dose levels for trichloroethylene (TCE), tetrachloroethylene
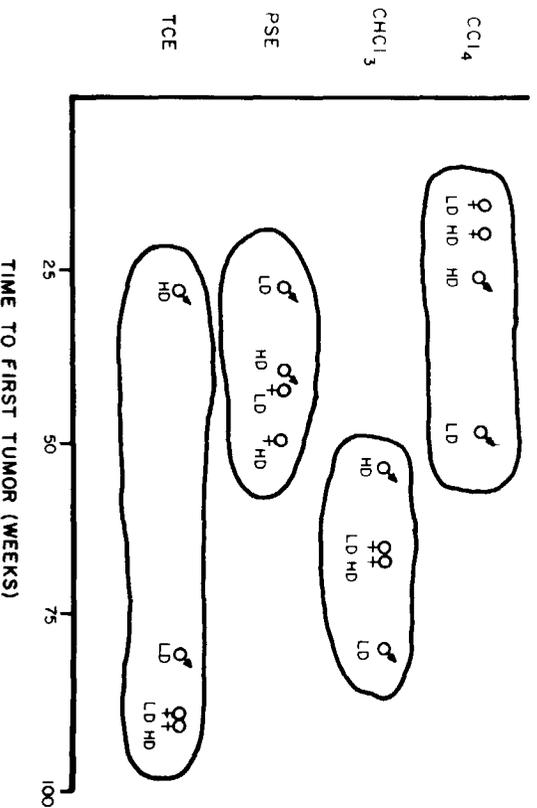(PCE), chloroform (ChCl3), and carbon tetrachloride (CCl4).

Figure 3. Initial tumor appearance with TCE, PCE, ChCl3, and CCl4.

desiccators and subjected to concentrations of up to 2,000 ppm of TCE for about 7 hours. A dose-related increase in revertants was observed up to about 1,500 ppm of TCE (1.5 ml). Higher dose levels resulted in a decrease in revertants because of toxicity and cell death. The increase in mutants was relatively small, but proved to be reproducible. The mutations detected in this system are histidine-requiring reverse gene mutations. High-purity, reagent grade TCE was used in the study. Chemical analysis did not detect either epichlorohydrin or 1,2-epoxybutane. Baden et al. (1976) had earlier alluded to these findings. Mutagenic activity was not found unless the liver homogenate was included in the system, indicating that TCE must be metabolized to an active agent for mutagenesis. In companion studies, both methyl chloroform and methylene chloride were found to be more active than TCE even without activation.

In a similar series of experiments also using the TA100 S. typhimurium strain, Bartsch et al. (1976) did not observe mutagenic activity even with the addition of human or mouse liver microsomes. In that series, vinyl chloride was the least active mutagen, less so than 1,1-dichloroethylene, vinyl bromide, 1- or 2- chloro-1,3 butadiene or 3,4-dichlorobutene-1. While epoxide formation by mouse liver microsomes was detected for vinyl chloride and vinyl bromide, such was not the case for TCE. Neither was an alkylating intermediate detected.

Greim et al. (1975) reported the induction of reverse mutations by analytical grade TCE using K12 E. coli bacteria coupled with a mouse liver microsomal enzyme activation system. The responding systems employed back mutation gal+ and arg+ mutants. Vinyl chloride and vinylidene chloride (1,1-dichloroethylene) were also positive, whereas tetrachloroethylene, cis 1,2-dichloroethylene and trans-1,2-dichloroethylene were not mutagenic. Because of toxicity (cell death), the concentration of TCE that could be used was only one-third that of vinyl chloride. Nevertheless, it was concluded that the mutagenicity of TCE was less than that of vinyl chloride but greater than that of vinylidene chloride. Without the liver microsomal enzyme system, no mutagenic activity of any of the chlorinated ethylenes was detected.

TCE has also been shown to induce both frameshift and base substitution mutations in the yeast, Saccharomyces cerevisiae, strain XV185-14C (Shanin and Von Borstel, 1977). In those studies, TCE was not mutagenic without activation but in the presence of mouse liver homogenate, it was considered to be a powerful mutagen. TCE was also very toxic in that system. Also using Saccharomyces cerevisiae (strains D4 and D7), Bronzetti et al. (1977) detected point mutations and mitotic gene conversions following both in vitro and in vivo exposures to certified, ACS grade TCE. In the in vitro study, no mutagenic activity was detected without activation; however, with added mouse liver homogenate, concentration dependent increases in mutations

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occurred. TCE concentrations of 10-40 mM were used. The in vivo, intrasanguinous or host-mediated assay, was used to assess mutagenicity from a single dose as well as repeated treatments of TCE. In the single-dose study, 400 mg/kg was administered by gavage to CD-1 mice, immediately after retroorbital sinus instillation with Saccharomyces cerevisiae. Four hours later the organisms harvested from the kidney and liver had high levels of mutation while those obtained from the lung revealed only few mutations.

In the multiple-dose study, 22 doses of TCE, each of 150 mg/kg, were administered over a 5-day period, followed by a dose of 400 mg/kg on the day of assay, total dose = 3,700 mg/kg. While the increase in the induced frequency of mutations of yeast recovered from the liver was greater (about 2X) than that found in the single-dose study, the increase in the kidneys was considerably greater (about 5X). A low response, like that in the single dose experiment, was found in the lung. The authors suggested that the results following multiple-doses may be indicative of either the retention of an active metabolite in the kidney or selective induction of kidney enzymes responsible for the metabolism of TCE to a mutagen. They further speculated that both the kidney and liver might be primary target organs for carcinogenicity.

In tests using Tradescantia (clone 4430), Sparrow (1976) observed TCE to be mutagenic following 6-hour exposures at levels as high as 30 ppm. The maximum response, however, was observed at 0.5 ppm, inasmuch as higher levels produced an inhibiting or interfering toxic effect.

PPG Industries, Inc. (Bell, 1977), recently reported a dominant lethal mutation study in which 15 male rats were exposed to inhalation of TCE at a level of 300 ppm, 6 hours per day, 5 days per week for 9 months. Following that exposure, the males were then each mated weekly to two unexposed virgin females for 8 consecutive weeks. As reproductive performances by the TCE-exposed and control rats were comparable, it was concluded that no dominant lethal mutagenic effect had resulted.

E.   CELL TRANSFORMATION

Using a highly sensitive in vitro cell system, Price et al. (1977) reported the transformation of Fischer rat embryo cells (F1706) to tumor producing cells upon exposure to TCE. The cells were phenotypically transformed, characterized by the appearance of progressively growing foci of cells lacking in contact inhibition and in orientation with growth of macroscopic foci in semisolid agar. Upon subcutaneous inoculation of the morphologically-changed cells into newborn Fischer rats (1×10^6 cells), undifferentiated fibrosarcomas developed within 55 days at the sites of inoculation in all animals. No spontaneous transformation was observed in media or acetone controls. The

TCE tested was of reagent grade (99.9% purity). Price et al. concluded that TCE has a carcinogenic potential on the basis of these results. The cell cultures were incubated for 48 hours with concentrations of 1.1×10^3 and 1.1×10^4 M of TCE. Three other chlorinated chemicals, tetrachloroethylene, methyl chloroform, and methylene chloride were also tested in this system and also induced transformation equal to or perhaps even more efficiently than TCE. In this system TCE was considerably less toxic than the other three halocarbons. The positive control, methylcholanthrene, was considerably more effective in transformation-frequency than any of the 4 halocarbons.

No other reports of cell transformation studies are known.

F. TERATOGENICITY/REPRODUCTIVE EFFECTS

Only two teratogenicity studies have been found in a literature review. In the first, Fink (1968), in a very limited study, exposed fertile chicken eggs to 1% TCE and observed a significant increase in anomalies in chick embryos (total 96) harvested on the 3d day of embryo development. The significance of results observed after only 3 days incubation is open to question. In the other, Schwetz et al. (1975), exposed 18 pregnant Sprague-Dawley rats and 12 pregnant Swiss Webster mice by inhalation to 300 ppm of commercial grade TCE for 7 hours per day on days 6-15 of gestation. Caesarian sections were performed on days 18 and 21, respectively, on the mice and rats. While all fetuses and dams were examined grossly for visible abnormalities, one-third of each litter was randomly selected for visceral exam and two-thirds from each litter for skeletal exam. All these were fixed in toto, sectioned, stained, and examined microscopically. The authors reported that exposure to TCE caused little or no maternal, embryonal or fetal toxicity as indicated by standard, visible abnormality criteria. An examination of the tables of data does, however, suggest three possible fetal effects among the mouse litters: hemorrhage into cerebral ventricles (17 in 2 litters versus 4 in 1 litter in controls), undescended testicles (17 in 2 litters versus none in controls), and split sternebrae (17 in 2 litters versus none in controls). The authors did not indicate whether the listed effects were observed in the same two litters. While the incidence of abnormalities was increased above that found in controls, these were not found to be significant by the investigators at P = 0.05. While these studies would have detected major teratogenic effects, they were not sufficiently sensitive or adequately designed to detect weak teratogens, especially using noninbred animals. Neither would teratogenic neurological effects have been detected.

In a study recently reported by the PPG Industries, Inc. (Bell, 1977), no teratogenic effects were observed in offspring from female Charles River albino rats exposed by inhalation to

300 ppm TCE, 6 hours each day, from the 6th to the 15th days of gestation. In this study, 17 pregnant females bore 138 offspring, of which 95 were examined for fetal skeletal development and 43 for fetal internal development. As in the previously discussed study, only gross skeletal or organ effects would have been observed. More subtle behavioral or latent teratogenic effects would not have been detected.

A few reports allege possible TCE-induced teratogenic effects in humans. In one, sacral agenesis was observed in five infants whose mothers were exposed during pregnancy to organic solvents (Kucera, 1968). As only one or two cases involved trichloroethylene, the causal relationship is not strong.

The other report pertained to the medical use of gaseous anesthetics (Corbett et al., 1973; NIOSH, 1977b). A higher rate of miscarriages was observed among operating room nurses than would be expected among women in the general population. Exposure to TCE may have been a contributing factor, although it was impossible to implicate any single chemical because of the wide variety of anesthetics in use in typical operating rooms over a long period.

In a somewhat related study, TCE was demonstrated to readily cross the placenta into the fetuses of sheep and goats, reaching a higher blood level than in the dam after only 16 minutes (Helliwell, 1950). As such a differential exposure to the fetus might also occur in humans, the possibility of reproductive or teratogenic effects warrants consideration.

Thus, while a teratogenic effect of TCE in humans has not been established, there is sufficient reason, based upon weak evidence from both animal and human studies, the ability of TCE to cross the placenta, and possibly expose the developing fetus, to be concerned about a teratogenic potential of this chemical. Further research is needed, especially to assess the occurrence of subtle latent effects, including neurological/behavioral effects and transplacental carcinogenesis.

V. ASSESSMENT OF CARCINOGENIC POTENTIAL OF TRICHLOROETHYLENE TO HUMANS

The predominant data on which to base suspicion of carcinogenic potential of TCE is that of the animal bioassay test conducted by the NCI, although the MCA inhalation test may well provide comparable results. Standard methodology was used by the NCI with highly significant positive results only in the mouse and only with regard to liver cancer. While there may have been contributing factors, the evidence clearly points to exposure to TCE as the primary causative factor. The nature of the results in mice, indicate the induction of liver tumors; however, they are also consistent with a promotional mechanism. In view of the scientific uncertainties surrounding those results, other evidence that might support or refute a carcinogenic association has been reviewed.

Mutagenicity has been demonstrated in three different test systems: microbial (Salmonella typhimurium and E. Coli), yeast (Saccharomyces cerevisiae), and Tradescantia. Malignant transformation of mammalian cells has also been observed. Enzyme activation systems were required for both mutation and transformation.

Based on the similarity of TCE to vinyl chloride in structure and on TCE's electrophilic activity, a certain suspicion that it might possess a potential for carcinogenicity had been expressed even prior to the generation of the animal and in vitro results. Metabolism to an epoxide (or oxirane), likely to impart alkylating potential, has now been reasonably well shown to be possible, adding additional support to the test data.

It would appear from the research conducted recently on species differences in metabolism of TCE to an epoxide, and the inactivation of the epoxide by hepatic epoxide hydrase, that the potential degree of epoxide activity might be in the order mice > rats > humans. On this basis, it is not to be expected that TCE is as potent a carcinogen in humans as has been found in mice.

As of this time, no evidence has been found to associate TCE with carcinogenicity in humans. However, a causal relationship in U.S. workers would be difficult to detect because of the generally transient employment of degreaser operators (the major occupationally exposed group), the likelihood of their exposure to several different chemicals during employment, and the inadequate records available on employment, exposure and health effects. Such is not the case in Sweden. Axelson et al. (1977), are monitoring the health experiences of a group of 518 men exposed to TCE prior to 1970 (and having 10 years latent period) and an additional 1,100 with exposure in 1970 and later. An epidemiologic study for carcinogenic risk because of TCE exposure

is feasible in Sweden as workers exposed to TCE have received periodic exposure measurements (trichloroacetic acid in urine) since the 1950's, with records available for review on the groups identified above. The cohort of 518 men is further subdivided into groups with high and low exposures, the high-exposure group excreting a mean of slightly more than 100 mg/l TCA in the urine. That level roughly corresponds to the Swedish standard of 30 ppm. The majority are in the low-exposure group, with 3,095 person-years of observation compared with 548 for the high-dose group at the time of the initial evaluation now being reported (Axelson et al., 1977). Current mortality statistics show a close agreement between the observed number of cancer cases in the TCE-exposed men and that expected from the incidences of cancer in the general population. However, only 49 deaths have occurred in the group of 518. Eleven of the decedents had tumors. The authors admit the low sensitivity of the study and conclude that the risk to man from induction of cancer by TCE can by no means be ruled out. In their opinion, however, the lack of an observed effect at this time makes it improbable that TCE is a very serious cancer hazard at low exposures.

Epidemiologic studies are also underway in Finland with vital statistics determined on 1868 workers exposed to TCE from 1965-1976. Preliminary analysis indicates 10 cases of cancer (no predominant type or site) in the 47 deaths that have occurred so far in the cohort. While there is no suggestion of an increased risk for cancer, exposure levels are not known with accuracy and the exposed population is quite young, 50% less than 40 years of age (Tola, 1977). It is important that both studies continue for several more years in view of the generally long latency period for cancer development in humans and the probability that TCE may not be a strong carcinogen. NIOSH so far has not been able to identify in this country a similarly appropriate worker population exposed to TCE for an epidemiologic investigation to test for such an association with cancer. Only the strongest of carcinogens could be detected without a well-designed and conducted epidemiologic study on an appropriate group of workers.

Based upon these considerations, the assessment for carcinogenicity must be based largely upon the animal and in vitro test results and on considerations of biochemical activity. A summary of evidence for the carcinogenic potential of TCE is presented in Table 9. Although NIOSH generally agrees that the weight of available evidence justifies considering trichloroethylene as a potential carcinogen, it notes that the bioassay does not provide information on the response at low levels of exposure; mutagenicity or transformation tests did not reveal strong responses, and the Swedish epidemiologic study would argue against a potent carcinogenic effect. The data so far available do not suggest that TCE should be viewed as a particularly strong carcinogen. The mechanism, i.e., induction or promotion, is not resolved.

Table 9.   Evidence for carcinogenicity of trichloroethylene

_____

Epidemiologic: None at this time[1]

Animal bioassay: Positive in mouse (liver cancer)
                      Not positive in rat

Mutagenicity:

- Salmonella typhimurium (TA100)
  - two weakly positive tests (Simmons; Greim)
  - negative test (Bartsch et al.)
- Escherichia coli, K12 - weakly positive test
- Saccharomyces cerevisiae - 2 positive tests
- Tradescantia (clone 4430) - positive test
- Host mediated assay (S. cerevisiae) - positive in rat
- Dominant lethal test - negative in rat

Cell transformation: Positive with Fisher rat embryo cells

Chemical activity:

- Reactive metabolite (epoxide)
- TCE covalent bonding to cellular macromolecules
- Electrophilic activity

_____
[1] Studies underway in Finland and Sweden (Tola, 1977;
       Axelson, 1977).

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VI. CHARACTERIZATION OF OCCUPATIONAL EXPOSURE

While estimates of the numbers of workers exposed and an evaluation of the biological effects of TCE have been stated earlier in this report, it is also necessary to address the nature of the occupational exposures to this chemical in assessing the overall hazard. Useful information from which such an analysis can be made comes primarily from occupational hazard surveys which attempt to assess the hazards under actual working conditions. From use and exposure information (Sections III C. and D.) it can be seen that most high-level occupational exposures to TCE arise from its use in metal cleaning operations and specifically from vapor degreasing. The following survey information helps to characterize the nature of the TCE exposures from this widely used industrial process.

A. EXPOSURE FROM THE VAPOR DEGREASING PROCESS

The commonly used open top vapor degreasers, as shown in Figures 4-6, consist basically of two sections: a lower section consisting of a reservoir containing liquid solvent and a heat source to boil the solvent creating a vapor and an upper section containing only the vapor and emission control items. Optional emission control items on some degreasers can include a cover to hold in vapor and reduce drafts, freeboard ventilator system to reduce vapor escaping from top of tank, and cooling coils around the freeboard to condense the vapor. Metal parts soiled with grease, oil, metal fines, etc., are lowered, usually by basket, into the solvent vapor-zone of the tank with the aid of a hand-operated or automatic crane. The hot vapor condenses onto the cooler metal parts and the condensate dissolves the soil, carrying it along as it drains back into the boiling liquid reservoir below. When the metal parts reach vapor temperature, the condensation stops. Parts should then be withdrawn from the vapor zone slowly, so as not to create updrafts of the vapor, and allowed to dry before raising above the top edge of the tank. The vapor-degreasing process takes advantage of the fact that the solvent boils at a much lower temperature than the oil and grease and if the temperature of the liquid reservoir is maintained at the boiling point of the solvent, only pure solvent vapor is found in the vapor zone of the degreaser. As water can interfere with the degreasing activity, degreasers are also equipped with a water drainoff valve. Other types of degreasers, such as in Figures 7-11, may be more enclosed or conveyorized as an integral step in a production line.

Several surveys, both by NIOSH and by industry, have been conducted to assess the nature and extent of TCE exposure problems associated with the vapor degreasing process. Fifteen

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NIOSH Health Hazard Evaluations have been conducted to evaluate health problems suspected to be associated with TCE exposure at specific workplaces, the findings of which are presented in Section B.

A recent field survey was also conducted by NIOSH personnel specifically to examine different models of degreasers as they were in use in a variety of working operations. Because of EPA's concurrent interest in controlling fugitive emissions of chlorinated solvents, a representative from that agency accompanied the NIOSH survey team. An attempt was made to evaluate the potential for exposure based upon the performance of the equipment and the procedures followed by degreasing operators. A variety of different industrial operations was visited, in which the major types of degreaser units, as depicted in Figures 4-11, were observed. Some of the facilities utilized degreasing solvents other than TCE. However, because of basic design and process similarities among degreasers, the observations made at all facilities are considered relevant. Although the survey involved only a limited sampling, it is likely that the findings throughout the industry would be similar to those observed in the survey.

A number of design features are used to contain the vapor, including partial process enclosure, vapor condensing coils, and local exhaust ventilation. The efficiency of such features varies with the degreaser model, some being less likely to cause exposure problems than others. However, improper operating procedures and negligence in regard to equipment maintenance or repair often negate the benefits of many features that are available. Such was found to be the case during the field survey. While many degreasers were properly installed and maintained and were being operated according to good procedures, many others were not. The highest concentrations of vaporized TCE, correlated with unsatisfactory operating conditions, as was expected.

Among the observations of unsatisfactory conditions made during the field survey, the following were considered most serious:

1. The vapor layer of several open-top degreasers lacked continuity because of excessive amounts of moisture in the solvent, poorly engineered or maintained ventilation systems, and drafts over the degreaser top. This situation lends itself to vapor loss and increased exposure risk to the operator.

2. In some cases, parts were not given adequate time to drain prior to their removal from the degreasing unit, allowing for increased concentrations of solvent vapor in the operators' breathing zones.
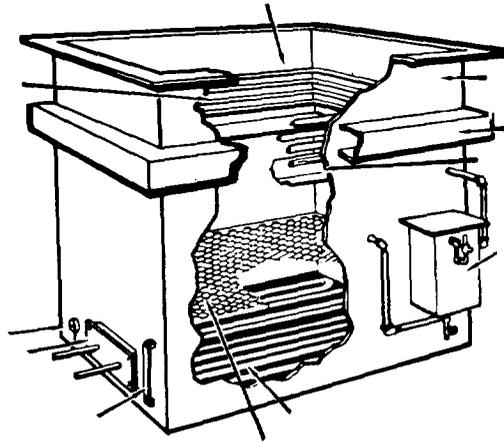
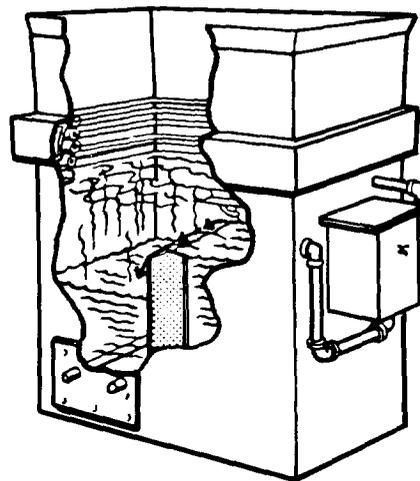Figure 4. A typical open top degreaser

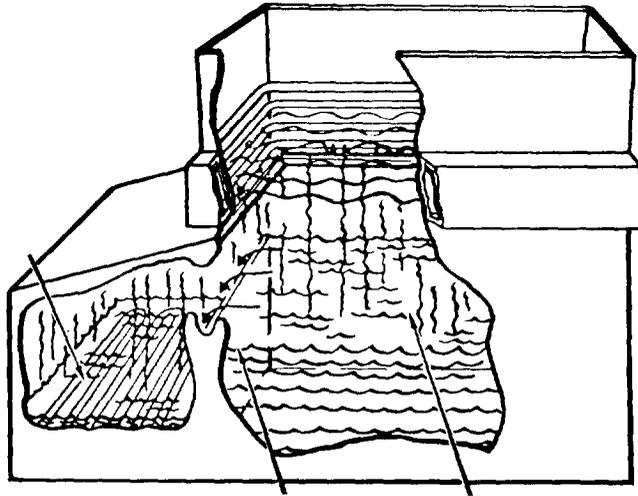Figure 5. A two-compartment open top degreaser

Figure 6. A two compartment open top degreaser with offset boiling chamber
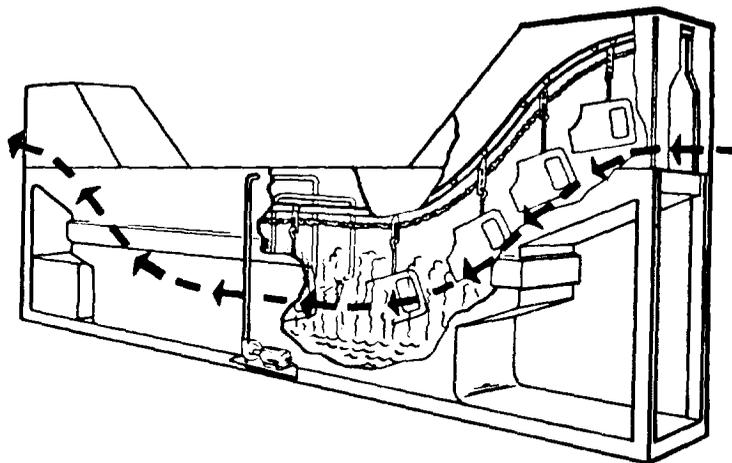

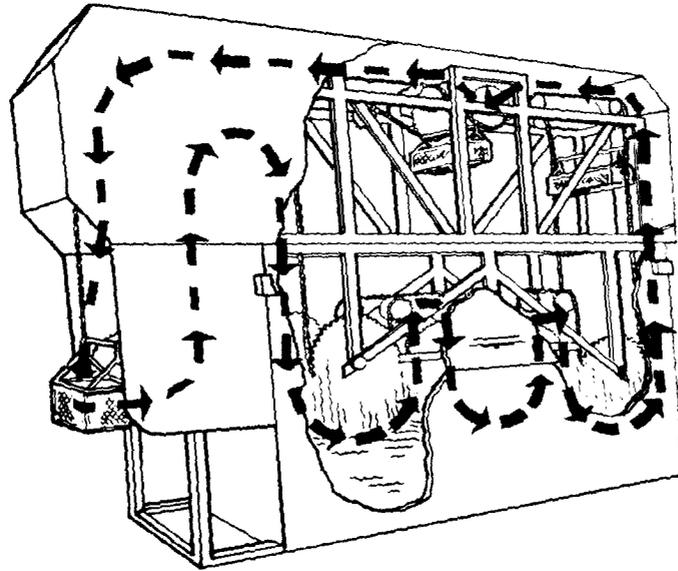Figure 7. A monorail conveyorized degreaser

Figure 8.   A cross-rod conveyorized degreaser
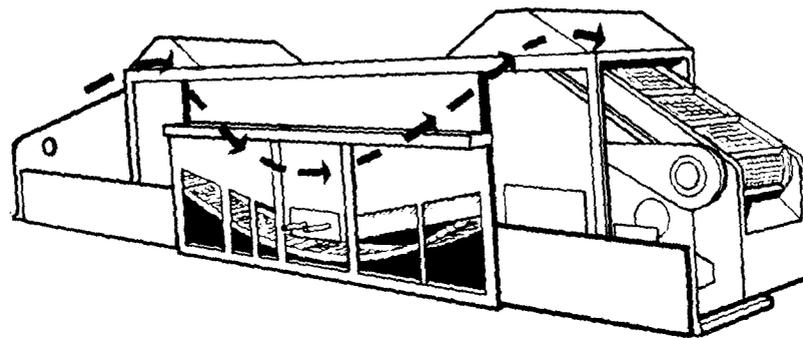

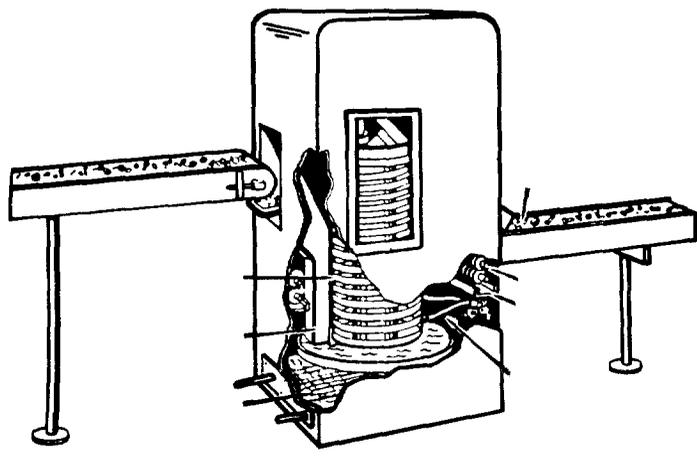Figure 9.   A mesh belt conveyorized degreaser

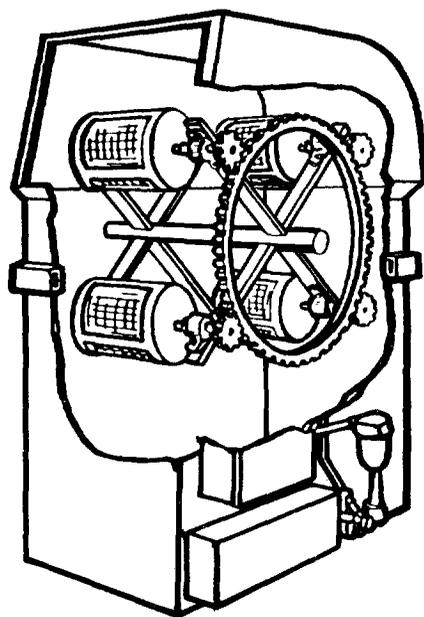Figure 10. A vibra degreaser

Figure 11. A ferris wheel degreaser

3. Disturbances of the vapor layer and solvent "dragout" also occurred from removing or introducing parts too quickly.

4. Freeboard exhaust ducts sometimes were badly in need of cleaning and were partially clogged, thereby interfering with proper exhaust.

5. In some cases, heat exchange coils on the compressor of freeboard chillers needed cleaning for the unit to operate effectively in condensing the vapor and containing it within the degeasing unit.

6. In most cases, degreaser covers were not in use. In some cases they had never been installed, while for others they had been removed or intentionally not used even while the unit was idling.

7. Employees were not always familiar with the solvent they were using, its potential hazards, and the appropriate precautionary measures.

In addition to the above observations, Draeger tube air samples were taken in the proximity of the operators' breathing zones. TCE concentrations of 20, 70, and 100 ppm were found at points of emissions from a monorail and two open-top degreasers, respectively. While such Draeger tube samples offer only very rough estimates of exposure levels, the above findings are in agreement with those of extensive surveys conducted by other groups.

Dow Chemical U.S.A. surveyed over 200 vapor degreasing facilities, using a Halide meter, and calculated the TWA exposure levels. They found that with existing control technology 37% of open-top degreasers using TCE maintained a 25 ppm exposure level, 58% were below a 50 ppm level, and 81% were in compliance with the current Federal standard of 100 ppm (Skory et al., 1974). These concentrations represent averages from what would be considered both good and poor operating conditions. A continuation of this survey to include over 1,000 vapor degreasing facilities has not resulted in changes of these estimates (Fulkerson, 1977).

Likewise, in a survey conducted by the Du Pont Company (Hargarten et al., 1961), very similar results were obtained. Data from air samples taken at 280 degreasers of various types and covering a 5-year period, 1952-57, showed that 48% of the units were below a 50 ppm exposure level and 86% were below a 100 ppm level. These figures represent exposure levels from degreasers which were operating under "problem" conditions. Data from a group of degreasers which were operating under "typical" conditions showed that 60% were under a 50 ppm level and 93% were under 100 ppm. As with the NIOSH and the Dow surveyors, the Du

Pont survey team concluded that most exposure problems could be substantially reduced by simple equipment maintenance and by proper use of the equipment and solvent by the operator. Based on their observations, the du Pont team developed the following list of common exposure-causes along with their relative frequency of occurrence:

Excessive drafts	55%
Dragout of solvent	48%
Overloading degreasers	43%
Spraying above vapor zone	21%
Excessive work speeds	13%
Poor machine maintenance	9%

Grandjean et al. (1955), evaluated the problem of dragout and determined that extending the time in which parts are allowed to drain and dry inside the tank, from 1/2-minute to 2-minutes, reduced the TCE emissions by 75%. Extending the period to 5-minutes resulted in a reduction of more than 85% from that of 1/2-minute.

Staheli (1972) conducted an experiment to test the effectiveness of certain engineering controls and work practices in eliminating some of the above problems. Specifically he tested the effectiveness of (1) using adequately trained personnel, (2) properly designed fans, blowers, and ventilation ducts, (3) baffles and shield to protect the degreasers from air currents, (4) use of a vapor zone freeboard height of 60% of the machine width, (5) use of a freeboard refrigerator device, commonly called a "freeboard chiller", (6) limiting entrance/removal speed for parts to 10 to 20 feet per minute, (7) eliminating overloading, (8) keeping cross sectional area of workload to less than 50% of the available machine area, and (9) removing work only when degreasing action is over. Vapor levels in the operator breathing zone were measured to compare the effectiveness of the various control measures with either TCE or methyl chloroform as the solvent. The results showed that with the freeboard chiller operating, even with no degreaser exhaust, ambient readings at the operators' breathing level were below 4 ppm for methyl chloroform and that zero stack emissions could be obtained. The test also showed a reduction in solvent consumption of 80% during a 6 month period because of the above controls (except the freeboard chiller). With the freeboard chiller, an additional reduction of 50% was obtained. For a continuously working degreaser, the freeboard chiller reduced TCE levels to as low as 12 ppm.

In a similar experiment, Esmen and Clearwater (1974) investigated the physical parameters influencing the physical formation of solvent vapors and subsequent emissions under laboratory conditions. Utilizing the experimental data obtained, they developed a mathematical model designed to predict emissions

following modifications of the physical characteristics of an actual industrial vapor degreaser under field conditions. The operating degreaser chosen to verify the model was of the open-top variety with a surface area of 28 x 58 inches; equipped with cooling coils, slot-type local ventilation powered by a 16-inch fan exhausting to the outside atmosphere; and a cover; and utilizing TCE as the solvent. TCE concentrations were measured under the following conditions: exhaust fan on, degreaser covered; exhaust fan off, degreaser covered; exhaust fan on, degreaser uncovered; and exhaust fan off, degreaser uncovered. Samples were taken both 6 inches above the freeboard and in the operators' breathing zone via personal sampling equipment. The most dramatic results were obtained when the fan was on and the degreaser covered. Under these conditions averages of 6 ppm and 13 ppm of TCE were found in the freeboard-area and operators' breathing zone. As is evident from the data presented in Table 10, a dramatic increase in exposure levels results when either the fan is shut off or when the degreaser is uncovered. When both were off, levels were further magnified and greatly exceeded the current OSHA standard. These findings, in actual operations, correlated well with the predictions of the mathematical model, prompting the investigators to emphasize the imperative nature of a degreaser cover in reducing solvent emissions. Esmen and Clearwater also demonstrated that the use of a cover reduced the solvent usage rate to only 7% of that previously required without a cover, a considerable economic savings to the industry. To overcome the operators' reluctance to use a cover and to reduce the potential fanning action sometimes associated with the conventional lid covers, they suggested the use of a roll-type design.

Table 10. Effect of local exhaust venting and cover in reducing trichloroethylene emissions from an operating degreaser

| Operating conditions | | Measurements (ppm) | |
Fan	Cover	6 " Above Freeboard	Operator's Breathing zone
On	On	6	13
Off	On	22	32
On	Off	89	55
Off	Off	633	163

Reference: Esmen and Clearwater (1974).

In support of all the above findings, is a survey by Ahlmark et al. (1963) of vapor degreasers in Sweden. Using a "Davies Halogen Detector" the investigators measured TCE concentrations in 570 degreasing plants over approximately a 10-year period. The samples were taken in the operators' breathing zones of predominantly open-top degreasers which utlized condensing coils and local exhaust ventilation to control vapor emissions. In taking 50 samples, every 30 seconds at each degreaser, over 35,000 individual checks were recorded. From analysis of these data the investigators found the average TCE concentration to be 16 ppm. Ahlmark et al. credit this performance to Swedish workers' conscientious adherence to safe work practices and proper engineering controls. The Swedish vapor degreasing industry emphasizes the importance of proper heating and condensing elements, adequate general and local ventilation, monitoring of workplace air, and employee training.

Other NIOSH surveys have gone one step further in characterizing occupational exposure to TCE by correlating biological effects with measured industrial-exposure levels.

B. RESULTS OF NIOSH HEALTH HAZARD EVALUATIONS

Fifteen surveys or Health Hazard Evaluations involving TCE use have been conducted by the NIOSH staff as the result of employee or employer requests. Most operations involved very low exposures (< 10 ppm) and no obvious toxic effects were noted. In three surveys where the concentrations of TCE in the workplace approached the current OSHA standard of 100 ppm (535 mg/m^3), however, consistent symptomatology was reported.

At one plant surveyed by Vandervort and Polakoff (1973), complaints of continued sickness involved employees in a pump room and metal fabrication area. During interviews, only one of 19 employees did not complain of a variety of illnesses, over one-half of them listed symptoms of eye irritation, tiredness, heart palpitation, coughing, weakness, dizziness, and changes in skin color. Some also indicated that they became severely intoxicated from small amounts of alcohol consumed when not on duty. The NIOSH surveyors also experienced nausea and weakness when making the survey. The obvious hazard was from TCE vapors arising from degreasing vats. Of 43 samples taken either in the personal breathing zone or as area samples, most were in the range of 37-75 ppm (200-400 mg/m^3) while directly over the degreasers the range was somewhat higher, 56-112 ppm (300-600 mg/m^3), for an 8-hour TWA.

The Vandervort and Polakoff survey noted several design or operational features which contributed to the release of TCE vapor from the degreasers. Among these were: (1) many parts had cavities that carried the solvent out of the degreaser when the parts were removed without tumbling to allow the solvent to drain out of these hollows, (2) there was no exhaust-controlled area in

which to place parts for evaporation of residual solvent, (3) parts were abruptly immersed into or raised from the solvent, causing splashing and vapor turbulence, (4) solvent was sprayed onto parts while they were held above the condensing coils of the degreaser, (5) the exhaust ventilator over the degreasers was operating at an airflow only one-half that recommended by the ACGIH (1971), and (6) the degreaser was near a brazing operation, which could result in the inadvertent formation of phosgene and HCl from degradation of TCE vapor. Also, one degreaser was near a space heater which could cause a similar situation. Many of the problems cited could be easily corrected by good administrative controls and improved ventilation.

In another survey by Bloom et al. (1974), medical interviews were conducted of 11 women employees who had previously reported illness, allegedly associated with TCE exposure. While a wide diversity in symptomatology was reported, over one-half complained of nausea and vomiting. Other symptoms registered were nervousness, irritability, headache, shortness of breath, sleepiness, cramps, depression, numbness of lips and head, crying, and a general feeling of heaviness of the body or extremities. Many illnesses coincided with the detection of an odor in the workplace. Generally, exposure concentrations were less than one-half the OSHA limit (ranges of 10-20 ppm at one degreaser and 20-100 ppm at the other). At one area where TCE-soaked rags had been piled, an airborne concentration of TCE of over 100 ppm was measured. One contributing factor causing escape of TCE vapor from the degreasers was the practice of placing a parts-basket at the "vapor line," thus interrupting the vapor lock created by the cooling coil. Employees were also potentially exposed to low levels of an epoxy anhydride curing agent. The surveyors and employees felt that TCE was the likely agent of concern. Relocation of the TCE tank and improved local ventilation resulted in a great decrease in employee complaints. This result supplies further support for the idea that TCE was the cause of the symptoms experienced.

In a third survey of a degreasing department, Hervin et al. (1974) found consistent symptoms of lightheadedness, headache, nausea, and tightness of the chest. Low levels of trichloroacetic acid and trichloroethanol were found in the urines of workers although the exposures were on the average much less than one-half the standard, ranging from 10-95 ppm (53 to 508 mg/m^3). The TWA concentration of airborne TCE for the degreaser operators was 47 ppm (253 mg/m^3). Employees who worked at some distance from the degreasers experienced effects also although they were exposed to lower TWA concentrations. TCE was detected throughout the plant, the result of obviously poor general and local ventilation.

In a fourth study (Okawa and Bodner, 1973), symptoms similar to those previously described were found among workers in an electrical company, where they were exposed to levels ranging

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from 13-40 ppm (average 25.3 ppm). Urine levels of trichloroethanol correlated well with exposures below 50% of the Federal limit. The exposures were intermittent and only for a portion of the working period. Even so, toxic effects were reported.

From these Health Hazard Evaluations there seems ample reason to challenge the current Federal standard based upon acute effects alone. Effects have been documented at levels of one-fourth to one-half the OSHA limit.

VII. SUMMARIZATION OF BIOLOGICAL AND EXPOSURE DATA

1. The toxicity of trichloroethylene has been adequately documented and in itself elicits concern regarding the adequacy of the present OSHA standard of 100 ppm TWA. Messite (1974) concluded, from a review of toxic effects other than cancer, that both the current Federal standard and that recommended in the NIOSH criteria document were inadequate. Most other countries, having assessed the toxicity and exposure to TCE, have established much lower permissible levels than the current U.S. standard.

2. Trichloroethylene has been demonstrated to be carcinogenic by gavage in the mouse but not in the rat. The studies are considered appropriate for assessing the potential of TCE for inducing occupational cancer although the doses were considerably higher and via a different route than encountered in the workplace.

3. Studies have indicated mutagenicity in four different systems in vitro, producing gene, frameshift, and base substitution mutations. In all, however, the effect was judged to be a relatively weak response in comparison with those produced by strong carcinogens. A positive response was obtained in a host-mediated assay with mice having an artificial saccharomycetemia. A negative response was obtained from a dominant lethal test with rats.

4. Transformation of cultured mammalian cells into malignant tumor cells has been produced, again with the response not as strong as that produced by more potent carcinogens or other chlorinated hydrocarbons.

5. Strong evidence exists that TCE may be metabolized to an epoxide having electrophilic activity, and the capability to react and bind to cellular macromolecules with potential for induction of carcinogenic lesions.

6. The evidence, as presented in this report, requires that TCE be considered as a potential carcinogen for humans; however, the animal and in vitro results do not warrant considering TCE as a potent carcinogen. The current occupational limit and control measures in use were established with no concern for carcinogenic potential and thus may be inadequate to assure worker protection from such a carcinogenic potential.

7. From inspection of a series of NIOSH Health Hazard Evaluations which were conducted in TCE degreasing facilities,

and from other surveys by NIOSH, Dow Chemical U.S.A., and the Du Pont Company, it appears that major exposure problems can be avoided through strict adherence to degreaser manufacturer's operating instructions. Further, it appears that with simple maintenance, repair and/or upgrading of existing engineering controls, substantial reductions in worker exposure could be effected even in facilities which are already operating below the current Federal standard. NIOSH believes that the existing engineering control technology is readily available to attain a TWA exposure level of 25 ppm, with the potential good for even further reductions.

VIII. EXPOSURE MEASUREMENT METHODS

A NIOSH-recommended sampling and analytical method for organic solvents (including TCE) can be found in the NIOSH Manual of Analytical Methods (1977d). This method involves sample collection by adsorption on charcoal, desorption with carbon disulfide and subsequent analysis by gas chromatography and an electron-capture detector. About 180 ug of TCE per sample should be collected for accurate measurement at 100 ppm TWA. A detailed discussion of this method can also be found in the NIOSH Criteria Document on TCE (NIOSH, 1973). Minor modifications to this method are required in order to measure at lower levels. For example, to sample for a 25 ppm TWA requires collection of 10 liters at a rate of 1 liter/minute. For a 10 ppm TWA, 10-100 liters are needed with a rate of 50-200 cc/minute. Further, NIOSH has published an efficiency evaluation of activated-charcoal tubes for TCE vapor collection (Reckner and Sachdev, 1975). This report addresses some of the pertinent aspects of TCE sampling such as pump calibration, flow rates and desorption factors, including their individual contributions to the overall analytical error associated with this sampling method. Other methods for analyzing TCE include spectrophotometry, neutron activation, spark source mass spectroscopy, and infrared spectroscopy. Gas chromatography offers the greatest specificity and sensitivity of the various methods of analysis and is therefore the recommended method (NIOSH, 1973).

It should be noted that direct reading instruments, i.e., detector tubes, for monitoring TCE workplace concentrations are available: Draeger tubes which detect down to 10 ppm; MSA tubes which are "certified" to 50 ppm; HNU Photoionization detector with a limit of measurability of 0.2 ppm; and the Wilks Miran Analyzers A1 and 101 with a limit of detection of 0.1 ppm.

Two methods for analyzing TCE exposure which utilize biological indicators also have been developed. Measurements of the amounts of trichloroethanol and/or trichloroacetic acid metabolites excreted in the urine over defined periods of time can be used to determine TCE exposures many hours, or even days, after the exposure to TCE has occurred; however, these measurements generally have led to wide ranges in the individual values reported (Grandjean et al., 1955; Stewart et al., 1974).

NIOSH has validated a method which uses the measurement of TCE present in the breath after exposure as an index of the magnitude of exposure (Stewart et al., 1974). Breath samples can easily be obtained from the workers and analyses of these samples are considered to yield reliable estimates of worker exposure to TCE. Measurements of TCE in the breath should be taken shortly after a known or suspected overexposure has occurred, however, as

the TCE concentration in the breath decreases to low levels rather rapidly. Experimentation has shown that 5 hours following exposure to 265 ppm of TCE for 83 minutes the concentration in the breath had declined to near the limit of detection, i.e., 0.8 ppm for the analytical method employed, i.e., infrared spectroscopy (Stewart et al., 1962). Further, a rather large percentage of a dose of TCE is metabolized by humans, with the result that the amount metabolized will be unavailable for excretion as the unchanged material in the expired air (Stewart et al., 1962).

It thus appears that biological sampling itself is not a reliable guide to the degree of exposure of workers but must be accompanied by air analysis.

IX. RECOMMENDED PREVENTIVE MEASURES

Preventive measures to reduce exposures and promote adequate surveillance for health effects can be organized into three main areas: engineering controls, surveillance activities, and work practices/education. Based upon staff surveys and recommendations of others, a number of much-needed improvements in the design and operation of solvent degreasers is necessary to provide for adequate worker protection. Many of the recommendations provided in this section can be implemented with little expense and effort by industry. Not only will improved emission controls reduce worker exposures, but an economic savings can be realized by the companies involved by a reduction in the amount of solvent required for usual operations. Particularly useful references for operating procedures are the Handbook of Vapor Degreasing, prepared by the American Society for Testing and Materials (ASTM, 1976), and Recommended Work Practices for Vapor Degreasing Operations prepared by the Industry Task Force on Solvent Vapor Degreasing (1976).

1. Permissible Exposure Limit: It is recommended that the permissible limit for occupational exposure to trichloroethylene be reduced and that TCE be controlled as an occupational carcinogen. Current information regarding engineering feasibility indicates that personnel exposures of 25 ppm, on a time-weighted-average, can be readily attained using existing engineering control technology. However, we do not feel that this should serve as a final goal. Rather, industry should pursue further reductions in worker exposure as advancements in technology research allow.

2. Engineering Controls: Proper design and operation of process equipment can substantially reduce emissions and is the most desirable method of achieving a safe work environment. Proper design and operation would include such items as full or partial process enclosures including covers, temperature control of vapor to include condensation coils or freeboard chiller, local exhaust ventilation, part removal rate from degreasing or cleaning tank, and proper part drainage. Federal regulations on certain aspects of equipment design and operation, including ventilation and the use of baffles and covers, are found in 29 CFR 1910.94. Further, NIOSH has developed criteria for the design of local exhaust ventilation systems which would assure the effective capture and removal of toxic contaminants emanating from open surface tanks (Flanigan et al., 1974). Other useful documents dealing with the subject of ventilation include: references NIOSH (1976f), ANSI (1971), Committee on Industrial Ventilation (1977), and EPA (1977). Engineering control

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technology and recommendations for further research on open surface tank-use have been made by NIOSH (Hagopian and Bastress, 1976). Adherance to the recommendations of those documents and to the degreaser manufacturers' operating instructions should further aid in controlling TCE exposures. Industry should take a leadership role in improving engineering control technology to control exposures to not only TCE but any solvent, especially where vaporization occurs.

3. Additional Exposure Control Measures: Workers may be exposed to toxic concentrations of TCE when engineering controls are not effective, when there is a need for open transfer of the liquid, when there is leakage from process equipment, and when maintenance or repair work on equipment or transfer systems is needed. Because of these exceptions, additional control measures are necessary. These additional control measures could include the following:

a. Location of degreasing equipment in large rooms with good general ventilation but no cross drafts, and away from sources of high temperature and high energy.

b. Use of personal protective clothing and respirators (when engineering controls fail).

(1) In operations where splashing, spilling, spraying, or skin contact with TCE may occur, employees should wear protective coveralls or other full-body protection, as opposed to bib-type aprons.

(2) If respirators are used, they should be selected from the following types only: (a) self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode, or (b) combination respirator which includes a type C supplied-air respirator with a full facepiece operated in pressure-demand or other positive pressure or continuous flow mode and an auxiliary self-contained breathing apparatus operated in pressure demand or positive mode. Where escape respirators are provided, any escape self-contained breathing apparatus is appropriate. Additional information concerning the above types of respirators for TCE can be found in reference: NIOSH (1976g).

c. Instituting procedures for cleanup of spills and disposal of chemical waste.

d. Establishing good general housekeeping and sanitation practices, e.g., food storage, preparation, and consumption should be prohibited in areas where TCE is handled, processed, or stored.

e. Establishing emergency procedures, including those necessary for fire fighting.

f. Instituting procedures for safe entry into such confined spaces as tanks, pits, process vessels, and trenches should be restricted to authorized personnel only and the following precautionary measures should be instituted:

(1). Confined spaces which have contained TCE should be inspected and tested for oxygen deficiency, TCE and other contaminants and should be thoroughly ventilated, cleaned, neutralized or washed, and then retested for TCE.

(2). Possible buildup of TCE vapor in the confined space while work is in progress should be prevented by positive means (e.g., forced-air ventilation of closed spaces during repair of leaks or equipment maintenance; securing intake valves or disconnecting intake lines).

(3). Individuals entering confined spaces where they may possibly be exposed to TCE should be equipped with the respiratory protective equipment outlined above. Each individual should also wear a suitable harness with a lifeline tended by another employee outside the space who should also be equipped with the necessary protective equipment, including the aforementioned respiratory apparatus. Communications (visual, voice, signal line, telephone, radio, or other suitable means) should be maintained by the standby person with the employee inside the enclosed space.

4. Recordkeeping and the Surveillance for Medical Effects and Exposures:

a. Keeping records on all measurements taken which pertain to worker exposure to TCE. Medical records, and personnel records relating to employee exposure should be retained for 30 years following termination of employment.

b. Medical surveillance should be conducted to detect symptoms related to TCE exposure.

c. Monitoring of environmental levels of TCE in the work area.

5. Warning of Potential Hazards:

a. Employees should be informed of the hazards of TCE, including the results from animal carcinogenicity or mutagenicity tests, as well as other forms of toxicity.

b. Labeling of containers and posting signs in TCE work areas which warn of its hazardous properties.

6. Substitution of less harmful solvents: NIOSH recommends against substitution of other materials because all known current replacements have associated health-related or environmental hazards of major concern. Hazard reviews or criteria document updates are to be prepared on the two main replacement chemicals, methyl chloroform and tetrachloroethylene.

One option which may be exercised by industry in order to comply with restrictive regulation on TCE is to switch to substitute chemicals for which regulations are either less stringent or are nonexistent. Past experience shows that chemical substitution for TCE has been a favored alternative for industry. This was demonstrated in California in 1966 when under the Los Angeles County Rule 66, TCE was placed on a list of restricted solvents which were held responsible for photochemical smog problems. As a result, some industries promptly switched from TCE to the use of exempt solvents such as methylene chloride, tetrachloroethylene, and methyl chloroform.

The decision by industry to substitute another solvent for TCE will likely come if the cost of compliance with regulations supersedes the benefits of continued use. The cost of compliance should vary among industries and will depend primarily upon their individual control technology needs in order to meet a lower environmental exposure limit. Analysis of the impact of such costs on industry and society in general does not fall within the immediate scope of this document.

While substitution must be considered a viable alternative in reducing TCE exposures, NIOSH recommends against substitution by chemicals which are not sufficiently well characterized for potential hazards and may unknowingly lead to further endangerment of worker health. Regarding chemicals for which preliminary data indicates positive carcinogenic, mutagenic or teratogenic activity, deferring their use as a substitute for TCE until further test data are available is the recommended course of action.

Of particular concern is the possibility that tetrachloroethylene and methyl chloroform may both possess carcinogenic and/or mutagenic potential based upon recent research results. As of this time, there is no assurance that these compounds represent less risk to workers than TCE. Concern is also expressed for their potential for having greater environmental effects than TCE. Like TCE, these two chemicals have demonstrated chronic effects of the liver and kidney, and may be degraded into hazardous substances, such as phosgene. An evaluation of these two chemicals will be undertaken in hazard reviews similar to this or by updating NIOSH criteria documents

for recommended occupational standards (NIOSH, 1976b; NIOSH, 1976c).

Rather than to substitute other chemicals for TCE, NIOSH recommends that industry exert a concerted effort to reduce exposures, not only to TCE but to all solvents, according to recommendations of this report and other references cited.

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