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MUTAGENIC AND POTENTIAL MUTAGENIC INDUSTRIAL  
CHEMICALS

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## MUTAGENIC AND POTENTIAL MUTAGENIC INDUSTRIAL CHEMICALS

by

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Synopsis

A spectrum of industrial chemicals (predominantly chlorinated aliphatic hydrocarbons) was reviewed in terms of the production quantities and/or use patterns, occurrence in the environment as well as germane aspects of their mutagenicity and/or carcinogenicity. The agents considered included: vinyl chloride, vinylidene chloride, trichloroethylene, tetrachloroethylene, carbon tetrachloride, chloroprene, haloethers (chloromethyl ether, bis(chloromethyl) ether, bis(2-chloroethyl) ether), chlorine, and chlorodioxins (2,3,7,8-tetrachlorodibenzo-p-dioxin).

The potential mutagenicity of a number of vinyl analogs (e.g., acrylamide, acrylonitrile, acrolein, acrylic acid, styrene) via the intact molecule per se or via an oxide or epoxide-intermediate or metabolic product was also noted.

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The spectrum of chemical burdens that man is subjected to is very broad indeed and can include use categories such as food and feed additives, drugs, pesticides and industrial chemicals (including their trace synthetic and/or degradation impurities), in various formulations including solid, liquid, suspensions, dusts and aerosols. The potential toxicants can enter the environment via air, water and soil as well as indirectly or directly into food.

It is estimated that about 500 chemicals are introduced each year<sup>1</sup>, adding to the burden of the more than approximately half million chemicals currently in use of which about 10,000 or so are produced annually in amounts between 500 and 1 million kilos<sup>2</sup>. It should be noted that more than 2 million chemicals have been registered for use, mostly in the last 3-4 decades<sup>1</sup>.

One striking feature of the chemical industry during the past two and a half decades has been in the enormous growth in the production of organic chemicals. For example, in 1950 world production (excluding Eastern bloc countries) totaled only approximately 7 million tons. By 1970 it had grown to 63 million tons and it is estimated that in 1985 it will total approximately 150 million tons<sup>3</sup>.

The majority of organic chemicals (approx. 75%) are further processed either in their place of manufacture or elsewhere. Over two thirds of the latter are used in the preparation of end-products such as plastics and resins, synthetic fibers, synthetic rubbers, and surf

coatings. (These are no longer "chemicals" in the usual accepted sense of the term.)

Of the remaining 25%, which consists of chemicals used as such, the largest part is further processed within industry itself to produce, either alone or in admixture with other materials such as detergents, glycols (e.g., antifreeze, brake fluids) and solvents (e.g., aerosol propellants).

Arising from these types of end-products, it has been speculated that at the present time a total amount of up to 20 million tons of manufactured organic chemicals may enter the environment annually<sup>3</sup>. It is not known with precision what percentage of these chemicals may be hazardous in terms of their potential carcinogenicity, mutagenicity, and teratogenicity.

Although the etiology of human neoplasia, with rare exceptions, is unknown, it has been estimated that 50% to 90% of cancer in man is caused by exposure to chemicals<sup>4,5</sup>. Most of the known chemical carcinogens are considered to be the product of increasing agricultural and technological sophistication<sup>4</sup>.

Not all chemical mutagens have been demonstrated to be carcinogenic, although most chemical carcinogens (several of which cause cancer in man), have been found to be mutagens when tested in one of the mutagenicity test procedures that combine microbial, mammalian, or other animal-cell systems as genetic targets with an in vitro or in vivo metabolic activation system<sup>6-8</sup>.

In recent years there has been recognized concern over the environmental and toxicological effects of a spectrum of halogenated hydrocarbons, primarily the organo chlorine insecticides, and related derivatives, e.g., DDT, dieldrin, Mirex, chlordane, heptachlor-epoxide and polychlorinated biphenyls (PCB's). This concern has now been extended to practically all of the major commercial chlorinated hydrocarbons, numerous members of which have extensive utility as solvents, aerosol propellants, degreasing agents, dry-cleaning fluids, fire extinguishers, etc., and hence are manufactured on a large scale.

Chlorinated aliphatic hydrocarbons have constituted and probably will continue to do so in the foreseeable future the most important class of organic solvents. Estimated world production capacities (1973) of the chlorinated aliphatics (Table I) illustrate the practical significance of this type of compounds, for economics as well as for toxicological and ecological consideration.

TABLE I

ESTIMATED WORLD PRODUCTION CAPACITIES (1973)  
OF MAJOR CHLORINATED HYDROCARBONS, IN  
10<sup>3</sup> TONS/YEAR

| (a)                     |      | (b)                  |        |
|-------------------------|------|----------------------|--------|
| Trichloroethylene       | 1010 | Vinyl Chloride       | 10,500 |
| Perchloroethylene       | 1050 | 1,2-Dichloroethane   | 19,500 |
| 1,1,1-Trichloroethane   | 480  | Carbon Tetrachloride | 1,000  |
| Methylene Chloride      | 400  | Chloroform           | 245    |
| Trichlorofluoromethane  | 485  | Methyl Chloride      | 350    |
| Dichlorodifluoromethane | 570  |                      |        |

Of the compounds in column (a), the fluorochloromethanes are extensively used as aerosol propellants and are almost completely lost after use. The others are employed principally as solvents in industrial or domestic applications.

The products listed in Table I are characterized by high volatility and low solubility in water. They enter the environment primarily by evaporation to the atmosphere. Some chlorinated hydrocarbons will, however, be found in aqueous effluents from factories handling them and even in household sewage, and hence will pass into municipal drainage systems and ultimate sinks.

The aliphatic chlorinated hydrocarbons listed in Table I have been found to exhibit a rapid transfer both from air to water, and from water to air. Irrespective of whether the initial loss of chlorinated hydrocarbon is to the atmosphere or the hydrosphere, the transfer processes will lead to a wide distribution of these compounds.

In terms of worker exposure, the predominant routes of exposure are via inhalation and dermal absorption and secondarily from ingestion of food and water.

Vinyl chloride (chloroethylene; ethylene monochloride) (VC; VCM) (vinyl chloride monomer), has attracted a considerable amount of attention since 1973, because of the recent discovery of its carcinogenic action in man<sup>9</sup>. Thirteen deaths due to angiosarcoma of the liver have been linked to occupational exposure to gaseous vinyl chloride during polyvinyl chloride (PVC) production operations in

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the plastics industry in the U.S.<sup>9,10</sup>. The total VCM work population in the U.S., past and present has been estimated to be about 20,000<sup>11</sup>. Thousands of companies, both large and small, and hundreds of thousands of workers are engaged in the manufacture of, and/or of, plastic products made from PVC<sup>10</sup>.

The hazard of vinyl chloride was originally belived to primarily concern workers in the plastic industries who may receive a particularly high exposure of VCM in certain operations (e.g., cleaning of polymerization kettles), or a long-term exposure to relatively low concentrations in air of VCM at different factory sites. It is now believed that much larger populations are at risk due to (a) significant losses of VCM to the atmosphere at selected sites with subsequent atmospheric transport, (2) populations within proximity of the VCM and PVC production areas per se, (3) consumption of food products containing leachable amounts of unreacted VCM from PVC packaged materials, and (4) ingestion of water containing unreacted VCM leached from PVC pipes.

World production of VCM in 1971 in various areas was estimated as follows (in millions of kg): United States 1,969; Western Europe 2,497; Japan 1,275; Eastern Europe 817; other areas 499<sup>1</sup> or a total of 7,057 million kilos<sup>12</sup>.

Polyvinyl chloride (PVC) is produced in the U.S. at a yearly rate of 2.4 billion kg (about one-third the Western Worlds' supply) via four major processes. (1) Suspension polymerization (78% of

total production); (2) Emulsion polymerization (12% of total production); (3) Bulk polymerization (6% of total production); and (4) solution (4% of total production).

The U.S. consumption of PVC resins in 1972 was as follows: building and construction industries (42%), household uses (15%), consumer goods (12%), electrical applications (11%), packaging (9%), and transportation (6%), with miscellaneous uses accounting for the remainder.

Information concerning VCM emission data from both VCM and PVC resin plants is scant. VCM loss estimates of approximately 6% have been reported, based primarily on material balance studies<sup>10</sup>. VCM is distributed into the atmosphere surrounding the emissions source in patterns that depend on the amount of VCM released, the nature of the plant area from which it is released and meteorological conditions. Currently, emissions of vinyl chloride from VCM and PVC plants are estimated to exceed 90 million kg annually with 90% of all vinyl chloride atmospheric emissions believed to emanate from PVC plants<sup>10</sup>. (Monomer plants emit less than 10% of the total).

While monomer plants emit less VCM per kg of product than polymer plants, this may partially be offset by the tendency for monomer plants to have larger production capacities than polymer plants.

This can be manifest in absolute VCM emission levels from polymer plants being in the range of 2 to 5 times those of monomer plants<sup>10</sup>.

Although emissions of VCM from fabricating plants and from fabricated

— products may also occur, there are apparently no current data to quantify these emissions.

The concentration of residual VCM monomer in PVC powder that is fabricated into final products is also an important determinant of VCM in the ppm range. The entrapped concentration is dependent upon the production process and can range from 0.1 to 5.8 thousand ppm, which can be liberated during fabrication, particularly when heated<sup>10</sup>.

An additional feature of the VCM and PVC industries (in the U.S.) that are of significance in terms of potential VCM concentration levels in the atmosphere are the "clustering" of plants, (e.g., on the Gulf Coast in the Pasadena-Deer, Texas and Baton Rouge, La. areas)<sup>10</sup>.

✓ It has been difficult to estimate the areas and quantities of VCM losses which come primarily from vent streams, the storage and transportation loading systems, and seepages from pumps. Limited atmospheric VCM concentration measurements have been made in the vicinity (0 to 8 km) of VCM/PVC production sources. In over 90% of the cases, the peak concentrations have been below 1 ppm. A few 24 hour average values of 1-3 ppm, at distances of 0.8-8 km measurements were below 1 ppm<sup>10</sup>. However, because of the sampling and analytical procedures used, the accuracy of these measurements may be no better than  $\pm 100\%$ <sup>10</sup>.

The principal route of exposure to vinyl chloride is believed to be via air inhalation, although exposure could occur from skin contact,

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as well as from ingestion of food and water. Occupational exposure studies have revealed a wide range of VCM concentrations, dependent on the manufacturing processes involved. Air concentration of VCM in a polymerization reactor prior to ventilation has been reported to be of the order of  $7800 \text{ mg/m}^3$  (600-1000 ppm).<sup>13</sup> Concentrations of  $1560\text{-}2600 \text{ mg/m}^3$  (600-1000 ppm) of VCM in a polymerization reactor after washing has also been reported<sup>14</sup>. Concentrations of 50-800  $\text{mg/m}^3$  (20-312 ppm) of VCM, with peaks up to  $87,300 \text{ mg/m}^3$  (34,000 ppm) in the working atmosphere of plants producing PVC have been reported<sup>15</sup>. PVC leaving certain manufacturing plants may contain 200-400 ppm VCM; on delivery to the customer, the level of VCM is about 250 ppm and after processing, levels of 0.5-20 ppm are reached, depending on the method of fabrication.

A number of potential non-factory exposures to VCM exist. Until recently, vinyl chloride has been widely employed as a propellant in aerosols for hair sprays, pesticides and room deodorants<sup>17, 18</sup>.

The use of aerosol products in enclosed spaces, even in short bursts (e.g., 30 seconds) could result in air concentrations of VCM as high as  $1000 \text{ mg/m}^3$  (400 ppm) and these levels could persist for several hours after spraying<sup>19</sup>.

The mutagenicity of vinyl chloride and/or its metabolites (e.g., chloroethylene oxide, chloroacetaldehyde, chloroethanol) has been demonstrated recently *in vitro*<sup>20-22</sup>, utilizing the reverse mutation system of *S. typhimurium* of Ames et al<sup>23</sup> (e.g., strains TA 1530,

TA 1535, and G 46 were specifically reverted to His+ prototrophy by single-base-pair substitutions or by base-pair insertions or deletions, "frameshifts" utilizing TA 1536, TA 1537, and TA 1538).

Loprieno et al<sup>24</sup> demonstrated that vinyl chloride in the presence of purified mouse-liver microsomes was converted to an active metabolite(s) producing gene mutation(s) in the yeast S. pombe and gene conversion(s) in two loci of a diploid strain of S. cerevisiae.

Vinyl chloride has also been found mutagenic in Drosophila melanogaster<sup>25</sup> and the mutagenicity in Chinese hamster V 79 cells of two vinyl chloride metabolites, chloroethylene oxide and chloroacetaldehyde has also been shown<sup>26</sup>.

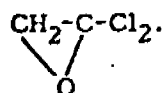
Chromosome aberrations in a small number of vinyl chloride exposed workers has also been demonstrated<sup>27, 28</sup>.

Vinylidene chloride (1,1-dichloroethylene:  $\text{CH}_2=\text{CCl}_2$ ) is used as a monomeric intermediate in the production of plastics, particularly the Saran type and has been reported to be an impurity in vinyl chloride monomer<sup>29</sup>.

The mutagenicity of vinylidene chloride (DCE) has been reported by Bartsch et al<sup>21</sup> in the previously described S. typhimurium strains of TA 1530 and TA 1535, DCE exhibited a higher mutagenic effect than that observed with vinyl chloride, when the compound was metabolically activated by rat or mouse microsomal liver enzymes<sup>30</sup>.

It is quite possible that analogous to vinyl chloride<sup>21</sup>, DCE may

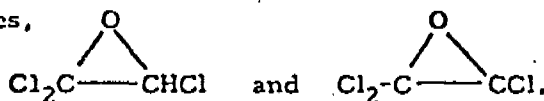
be mutagenic following activation to an epoxide intermediate, e.g.,



Trichloroethylene (trichloroethene;  $\text{ClCH}=\text{CCl}_2$ ) and tetrachloroethylene (perchloroethylene,  $\text{Cl}_2\text{C}=\text{CCl}_2$ ) are both widely employed as solvents, dry cleaning and degreasing agents, and in the manufacture of a variety of organic chemicals, such as polymerized resins of phenol-formaldehyde, urea-formaldehyde and epoxides in the production of special fiber glasses. Tetrachloroethylene is also used in comparatively small amounts as a commodity fumigant, and for food extractions including decaffeinating coffee, and removing oleoresins from spices<sup>31</sup>.

Preliminary evaluation tests at the National Cancer Institute in the U.S. indicates that trichloroethylene (when fed) induces tumors in mice, predominantly hepatocellular carcinomas with some metastases to the lungs<sup>31</sup>.

Mammalian metabolic pathways of trichloroethylene and tetrachloroethylene in the mouse and rat are believed to involve the intermediate epoxides,



respectively<sup>32, 33</sup>. Urinary metabolites found for trichloroethylene include: trichloroacetic acid, chloral (trichloroacetaldehyde) trichloroethanol and chloroform<sup>32-35</sup>. Chloralhydrate has been reported to induce point mutations in *Drosophila*<sup>36</sup>, bacteria<sup>37</sup> and chromosome aberrations in *Vicia faba*<sup>38</sup>.

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It should also be noted that the possibility exists of trichloroethylene per se and/or its oxide being mutagenic via considerations previously demonstrated above for vinyl chloride<sup>21,22</sup>.

It is generally acknowledged that emissions of commercial organic solvent vapors into the atmosphere have been increasing dramatically in the last decade<sup>39</sup>. McConnell et al<sup>39</sup> estimated the loss of trichloroethylene and perchloroethylene to the global environment in 1973 to be each over 1 million tons.

Solvent emissions, for example, are believed to account for over 20% of the total hydrocarbons emitted into the atmosphere in Los Angeles County and these emissions averaged about one-sixth pound per person annually in this county. The release rate of industrial effluents into the air over Los Angeles County has been estimated at 500 tons/day. These emissions are believed to be mainly solvents of which 25 tons are dry cleaning fluids and 95 tons are degreasing solvents; the remaining 380 tons are surface coating and miscellaneous compounds<sup>40, 41</sup>.

Carbon tetrachloride is produced in enormous quantities, e.g., over 1.0 billion pounds in the U.S. in 1970. In the U.S., the majority of the  $\text{CCl}_4$  produced in 1970 was employed in the production of fluorocarbons, e.g., approximately 700 million pounds (69%) for dichlorodifluoromethane ( $\text{CF}_2\text{Cl}_2$ ) and about 260 million pounds (26%) for trichlorofluoromethane ( $\text{CFCl}_3$ ). The remaining 5% of the production in the U.S. (in 1970) (approximately 50 million pounds)

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was used as : (a) grain fumigants (mixed with other chemicals); (b) fire extinguishers; (c) solvent for oils, fats, resins, and rubber cents; (d) cleaning agent for machinery and electrical equipment; (e) degreasing metal fabricated parts; and (f) organic chlorination processes.

Losses of carbon tetrachloride to the global environment were estimated by McConnell et al<sup>39</sup> to be in the order of 1 million tons in 1974.

Carbon tetrachloride has produced liver tumors in the mouse, hamster, and rat following several routes of administration, including inhalation and oral ingestion<sup>42</sup>. A number of cases of hepatomas appearing in men several years after CCl<sub>4</sub> poisoning have also been reported<sup>43,44</sup>. Bartholmess<sup>45</sup> in his survey of chemical mutagens in the environment has listed carbon tetrachloride as a chromosome breaking agent.

Chloroprene (1-chloro-2,3-butadiene;  $\text{CH}_2=\underset{\text{Cl}}{\text{C}}-\text{CH}=\text{CH}_2$ ) is the monomer for neoprene, the specialty rubber.

High rates of skin and lung cancer have been recently reported among workers in U.S. and USSR plants who have handled chloroprene and its derivatives<sup>46,47</sup>. Currently about 2500 workers in the United States are exposed to chloroprene<sup>47</sup>.

Haloethers represent an interesting category of alkylating carcinogens, as well as potential mutagens, of increasing interest. The

carcinogenicity of the  $\alpha$ -chloroethers, chloromethyl methyl ether (CMME), and bis(chloromethyl)ether (BCME) in mice and rats has been reported<sup>48-50</sup>. Suspected cases of lung cancer due to occupational exposure to CMME has also been cited<sup>51,52</sup>. CMME and BCME are widely used in the chemical industry as intermediates in organic synthesis and in the preparation of ion-exchange series. Commercial CMME contains 1 to 8% of BCME. BCME is very carcinogenic and CMME is also active but less so<sup>48,53</sup>.

Conflicting information exists as to the formation of BCME via the spontaneous reactions between HCl and formaldehyde in both gas and liquid phases<sup>54-56</sup>. NIOSH has confirmed the spontaneous formation of BCME from the reaction of formaldehyde and hydrochloric acid in some textile plants and is now investigating the extent of possible worker exposure to the carcinogen<sup>57</sup>.

Bis(2-chloroisopropyl)ether and bis(2-chloroethyl)ether (apparently arising from industrial outfall) appear to be rather widespread haloether pollutants in the rivers of the United States<sup>58,59</sup>.

Innes et al<sup>60</sup> reported the induction of hepatomas in mice fed bis(2-chloroethyl)-ether and bis(2-chloroethyl) ether has been found to be mutagenic in Drosophila<sup>61</sup>.

Approximately 250 million pounds of chlorinated hydrocarbon byproducts, known as still bottom material, accumulate each year from organic chemical manufacturing in the U.S.<sup>62</sup>.

A procedure which has been recommended for the decomposition of the above materials (as well as 2,4,5-T and DDT) is chlorinolysis, Int. Conf. on Air Poll.

whereby chlorine is added to the chemical residues, producing high yields of carbon tetrachloride, hydrochloric acid, and carbonyl chloride.

Recent concerns have been raised about the use of chlorination as a disinfecting technique<sup>63</sup>. An estimated 1,000 tons of chlorinated organic compounds, some of them known to induce cancer in laboratory animals (e.g., chloroform and carbon tetrachloride) are discharged annually into the U.S. waterways as a result of the chlorination of waste water. (It should be noted that the wastewater industry relies almost exclusively on chlorine as a disinfectant.) Recent Environmental Protection Agency (EPA) studies have indicated the presence of small quantities of 66 organic chemicals (many of them chlorinated hydrocarbons) in the nation's drinking water supply<sup>64</sup>.

The chromosomal effects of chlorine per se on mammalian cells in vitro have been reported by Mickey and Holden<sup>65</sup>.

Chlorodioxins (polychlorinated dibenzo-p-dioxins) include a large number of compounds, (some extremely toxic) which occur primarily as contaminants in technical products such as tri-, tetra-, and pentachlorophenol and a number of other related products. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) or other chlorinated dibenzodioxins or chlorinated dibenzofurans may be present in the waste products from chlorination of benzenes, phenols and polyphenyls since traces have been found in the commercial products<sup>66</sup>.

Conditions which enhance TCDD formation (as well as other chlorinated dioxins) are high temperature, high pressure, and

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alkalinity, are analogous to the conditions required for the production of pentachlorophenol (PCP) from hexachlorobenzene or in the production of tri-, tetra- and pentachlorophenol by the direct chlorination of phenol.

The mutagenic effects of TCDD on bacterial systems e.g., Salmonella typhimurium strain TA 1532 have been noted by Hussain et al<sup>67</sup>.

It is also important to note a number of vinyl analogs which have significant industrial utility as solvents, plastic and polymer monomers and synthetic utility may be potential mutagens via analogous considerations as described for vinyl chloride, vinylidene chloride and trichloroethylene, e.g., the intact molecule per se or via an oxide or epoxide intermediate or metabolic product. These agents include: acrylamide ( $\text{CH}_2=\text{CHCONH}_2$ ); acrylonitrile ( $\text{CH}_2=\text{CHCN}$ ); acrolein ( $\text{CH}_2=\text{CHCHO}$ ); acrylic acid ( $\text{CH}_2=\text{CHCOOH}$ ); styrene ( $\text{C}_6\text{H}_5\text{CH}=\text{CH}_2$ ); styrene oxide ( $\text{C}_6\text{H}_5\text{CH}-\text{CH}_2$ ), vinyl bromide ( $\text{CH}_2=\text{CHBr}$ ) and vinyl-  
 $\text{O}$   
 benzyl chloride ( $\text{CH}_2=\text{CHC}_6\text{H}_5\text{CH}_2\text{Cl}$ ).

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