III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

1,2-Dichloroethane, commonly known as ethylene dichloride, and also known as ethylene chloride and dichloroethane, is a colorless liquid at room temperature (25 C). [1] Minimal concentrations of ethylene dichloride in air that have been reported to be detected by odor vary from 3 to 100 ppm. [2-4] Selected properties of ethylene dichloride are listed in Table XII-1. [1,5-7]

There has been confusion in the literature because of similar names used for related chlorinated hydrocarbons. As examples, Ienistea and Mezincesco [8] cited 2 references to relate industrial intoxication to ethylene dichloride that actually were concerned with dichloroethylene, and Cetnarowicz, [9] cited a report about dichloroethylene as a chronic occupational exposure to ethylene dichloride.

Manufacturing processes are based on the chlorination of ethylene. The reaction between ethylene and chlorine yields a mixture of ethylene dichloride, 1,1-dichloroethane, and 1,1,2-trichloroethane. By controlling the temperature of the reaction and by using specific catalysts (ethyl bromide, metal chlorides), the production of addition products such as ethylene dichloride can be enhanced. Ethylene dichloride is also produced by hydrochlorination of ethylene and is obtained as a by-product of trichloroethylene synthesis. [10]

The United States production of ethylene dichloride increased from about 510 million pounds in 1955 to almost 8 billion pounds in 1972. [11-28] This 16-fold increase was mostly due to increased vinyl chloride

production, for which ethylene dichloride is one of the basic raw materials. [10]

Manufacture of ethylene dichloride has been reported by 15 companies in the United States. [10,28] Eleven of these also produce vinyl chloride in integrated operations and 7 other chemical companies have used ethylene dichloride in the production of vinyl chloride. [10,28] Thus many workers involved in the manufacture of vinyl chloride are potentially exposed to ethylene dichloride.

Although the principal use (about 75%) of ethylene dichloride is as a raw material in the production of vinyl chloride, it is used by at least 36 chemical companies in a variety of other applications, such as a constituent in antiknock mixtures of leaded fuels, as a fumigant-insecticide, and in the formulation of some degreaser compounds and rubber cements. [10,28,29]

Formulators of insecticide mixtures and agricultural workers involved in the fumigation of a variety of crops are potentially exposed to ethylene dichloride in their occupation. [30] At least 29 chemical companies manufacture at least 45 fumigant-insecticides which have ethylene dichloride as an ingredient. [31]

Formulators of antiknock compounds containing tetraethyl lead and tetramethyl lead might be exposed to ethylene dichloride which is a constituent of antiknock mixtures (as high as 20% by weight). There are 4 chemical companies in the United States involved in the formulation of such compounds, [10] and at least 6 different formulations of antiknock fuel additives are available on the market. [29]

Ethylene dichloride has been utilized as a component of degreasing mixtures for metal parts. [29] However, this application is now very limited since less toxic solvents have replaced ethylene dichloride for this use. [1] Another small scale use of ethylene dichloride is as a constituent of rubber cements, and some formulations of acrylic-type adhesives use it as a solvent. [29]

NIOSH estimates that 18,000 people are potentially exposed to ethylene dichloride in their working environment in the US.

Historical Reports

In 3 letters to the editor of the 1849 Provincial Medical and Surgical Journal, Nunneley [32-34] reported his experiments with ethylene dichloride as an anesthetic and discussed the work of others. He called the substance chloride of olefiant gas and mentioned the synonyms hydrochlorate of chloride of acetyle, oil of olefiant gas, Dutch oil, and oil of the Dutch chemists. [32] Contrary to reports of others with whom he had corresponded, Nunneley [33] found inhalation of the material to be agreeable to him and to 6 of his colleagues who were anesthetized by it, and he reported having successfully performed surgery on 4 patients under ethylene dichloride anesthesia. Nunneley [32-33] reported that, compared to chloroform, less ethylene dichloride was required to anesthetize his subjects and patients, and they were less uncomfortable afterwards. He [33] also discussed the experiences of others who found ethylene dichloride vapor to be very irritating to the throat of humans and lethal to mice. Subsequent information on the effects of ethylene dichloride inhalation suggests that perhaps Nunneley was working with something other than

ethylene dichloride.

Eulenberg [35] reported in 1876 that a young woman accidentally anesthetized by ethylene dichloride instead of its isomer, ethylidene dichloride (1,1-dichloroethane), developed a severe headache followed by repetitive vomiting for several hours. The next day she was still extremely tired and felt unwell.

Corneal opacities were reported in 1887 to have developed in dogs after anesthesia with ethylene dichloride. [36] The opacities developed 60-80 hours following single exposures of 1.5 hours duration and began to clear about 2 days later. The following year, Dubois [37] reported that the opacification and thickening deformity of the canine cornea were due to lymphatic infiltration of the vitreous humor, and Panas [38] independently confirmed these findings. It was shown more recently that corneal opacities from systemic intoxication following ethylene dichloride exposure developed in canine species but not in other animal species studied. [39] This distinction has not always been clearly stated in the literature, and it has been both inferred and erroneously stated [40, 41] that corneal opacities have occurred in humans from ethylene dichloride exposures, but these were unvarified extrapolations from animal data. Reports of corneal opacities developing in humans exposed to ethylene dichloride have not been found.

An experimental exposure of humans to ethylene dichloride was reported in 1930. Two subjects exposed at 1,200 ppm for 2 minutes reported a strong odor, but no other subjective or objective responses. [42]

Occupational hazards of working with ethylene dichloride were the subject of a letter by Murdock [43] to the editor of the Journal of the

American Medical Association in 1932. Murdock reported that men exposed to ethylene dichloride in a new oil refining process became nauseated, and he asked for further information on the toxicity of this chemical. The editor pointed out that: "Workmen with any considerable exposure may develop headache, dizziness, diarrhea, hemorrhage into the intestinal tract, hemorrhage into the lungs or pleural cavity, and irritation of the respiratory tract. Higher concentrations may lead to necrosis of the liver."

Two cases of occupational exposure that occurred in 1934 were reported by Hamilton and Hardy [44] in 1949. Two men spraying the interior of a brewery tank with a solvent containing ethylene dichloride became unconscious. Resuscitation was attempted on both, but one man died without regaining consciousness. An autopsy showed fat in the blood and urine and a defatted, parchment-like appearance of the pericardium and omentum.

In 1943, Brandt [45] reported that ethylene dichloride was a potential health hazard in degreasing operations, leather cleaning, rubber goods fabrication, and in the manufacture of parts for tanks. Exposures encountered in the latter industry were reported to have produced nausea and vomiting.

Effects on Humans

(a) Ingestion

Death has been the consequence in the majority of the reported cases of ethylene dichloride ingestion. [46-73] The progression of signs and symptoms of poisoning in these cases is presented in Table XII-2. There was usually a period of about one hour before onset of symptoms, followed by dizziness, nausea, vomiting, and unconsciousness. A rapid, weak pulse, dilated pupils, pulmonary edema, and increasing cyanosis were usual findings. Death was usually ascribed to circulatory and respiratory failure.

Occasionally, there was evidence of overt bleeding into the visceral organs [46,50,51,54,56,60,62,70] or into the lungs. [51,66] In many cases, autopsies revealed hyperemia and hemorrhagic lesions of most organs including the stomach, intestines, heart, brain, liver, and kidney. [46,47,49-52,54,56,57 59-62,64,66,67,70,72,73]

In 1969, prolonged bleeding from venipunctures was observed by Martin et al [64] in a patient 24 hours after ethylene dichloride ingestion. They then studied the clotting factors and found a maximal reduction in factors II, V, VII, VIII, and complete defibrination. The platelet count had dropped to 14,300/cu mm, fibrinolysis was increased to 4 times its normal value, and proactivator levels were below 10%. "Thrombin time" after fibrinogen substitution was 59 seconds as contrasted to the normal 12 seconds. The complex coagulation disorder with thrombocytopenia and reduced activity of the coagulation factors was attributed by the authors [64] to the depletion of these in a process of disseminated intravascular coagulation and to secondary hyperfibrinolysis. The post mortem

examination revealed thrombi in the pulmonary arterioles and capillaries, as well as hemorrhages into the mucosa of the esophagus, stump of the stomach, rectum, and in the subepicardial, subendocardial, and myocardial tissues.

The observations of Martin et al [64] became guidelines for Schonborn et al [65] in their treatment of an 18-year-old man who had ingested about 50 g of ethylene dichloride. Schonborn et al [65] began detailed studies of blood clotting in their patient 5.5 hours after the ingestion. They found a lengthening of the prothrombin time (according to Quick's test), a decrease in clotting factors II and V and in thrombocytes, but no increase in fibrinolysis. In this case, heparin given 5.5 hours after ingestion was not successful in preventing the initial clotting and subsequent loss of clotting factors as postulated by Martin et al. [64] The patient died from circulatory shock after 17 hours, and in the post mortem examination intravascular thromboses were not found.

Prothrombin time was reported to be slightly increased by Yodaiken and Babcock [66] in 1973, 2 hours after their patient ingested ethylene dichloride. The clotting ability of the blood progressively decreased, and on the 4th day, all clotting factors except VIII were markedly decreased. Blood glucose was 40 mg/100 ml on the 2nd day and glucose was given intravenously. In spite of this, blood glucose fell to 12 mg/100 ml on the 3rd day. Serum calcium concentrations rose to 16 mg/100 ml on the 5th day.

Internal organ changes were studied by Bryzhin [73] after 4 persons died from ingestion of 150-200 ml of ethylene dichloride. The deaths occurred at 10, 15, 33, and 35 hours after ingestion. Significant autopsy findings included punctate hemorrhaging in the epicardium, pleura, and

mucous membranes of the stomach and duodenum; varying degrees of liver damage with focal hemorrhaging in one case; yellow-white fibrinous bundles of blood in the heart cavities and lesser circulatory vessels; distinct icteric coloring of the endocardium, aortal intima, and dura mater; and evidence of decomposition of circulating erythrocytes. The author concluded that the jaundice was of hemolytic origin.

Bryzhin [73] analyzed the remainder of the liquid that the patients had drunk as well as the chemical found in the internal organs. Whereas the liquid that was ingested was clearly determined to be ethylene dichloride and the chemical in the internal organs was determined to be an organic chloride, ethylene dichloride itself was not found. Because of this and the fact that the clinical aspects of poisoning appeared 3-4 hours after the ingestion, Bryzhin concluded that ethylene dichloride rapidly underwent a chemical change in the organism.

Nonfatal cases of ethylene dichloride ingestion were reported by Ienistea and Mezincesco, [8] Bloch, [50] Stuhlert, [52] Flowtow, [55] Kaira, [62] Rohmann et al, [68] Gikalov et al, [69] Pavlova et al, [71] and Agranovich. [72] Ienistea and Mezincesco [8] reported that several soldiers who drank it developed headaches and became nauseated, but because they had ingested a small amount they did not become sick enough to seek medical help.

A man who claimed to have swallowed "only a small amount" began to vomit 2 hours later, developed bloody diarrhea that night, and was hospitalized on the second day after the ingestion according to Bloch. [50] He was slightly cyanotic on admission and coarse rales were heard over his chest. His heart beat was weak and "every 5th or 6th beat was

interrupted." The clinical diagnosis included kidney and liver damage. The kidney damage was based on clinical findings of oliguria, albumin and casts in the urine, and temporary retention of nitrogenous substances. The liver damage was evidenced by an enlarged liver, a slight increase in serum bilirubin, urobilin, and urobilinogen in the urine, and abnormal results in tests for galactose and alcohol load. The patient was considered to have recovered by 2 weeks after ingestion.

Temporary electroencephalographic (EEG) changes were reported by Rohmann et al [68] in a 2-year-old child 19 hours after ingestion of about 20 ml of a "nerve balsam" containing ethylene dichloride. The child did not vomit and, 9 hours after ingestion, there were no signs of poisoning and the EEG was normal. However, at 12 hours after ingestion there was a tendency to cramp (probably abdominal) and the EEG showed abortive spikes and waves with frontal and precentral leads.

Decreased albumin-globulin ratio and increased aldolase in the blood of persons poisoned by ethylene dichloride were found by Pavlova et al. [71] They also found increased bilirubin values which they attributed to a decreased hepatic transglucuronidase activity resulting from impaired hepatic function.

(b) Acute Inhalation Exposures with Fatalities

The effects of acute exposure to ethylene dichloride by inhalation are very similar to those found after ingestion. Headache, weakness, conjunctival irritation, cyanosis, nausea, and vomiting first appear, followed by unconsciousness and respiratory and circulatory failure. [72,74-85] Autopsy findings have included damage to the liver, kidneys, and lungs, [75-81] and there have been repeated reports of leukocytosis and

elevated serum bilirubin. [72,75,82,83,86] Many of the acute exposures were fatal. [74-81]

Exposure to a mixture of chlorinated solvents, including ethylene dichloride, was responsible for the death of a worker in a study reported by Wendel [74] in 1948. Two workers were painting the inner walls of a basement 1.5 meters underground which measured 3.5 x 2 x 3 meters. Five kg of ethylene dichloride had been mixed with the paint as thinner, the paint itself consisted of 13% polyvinyl chloride and 87% solvents, primarily methylene chloride and some cyclohexanone. While painting, both workers noticed a sweet taste, dizziness, and discomfort. After 5 hours, one of the workers was found unconscious and was rushed to the hospital, where he reported that he had become ill suddenly and lost all memory. He was somnolent, nauseated, and vomited frequently. He died 1.5 days later from circulatory failure, respiratory paralysis, and pneumonia. The second worker experienced nausea, weakness, vomiting, and diarrhea, but survived. The author [74] stated that ethylene dichloride was the most toxic of the chemicals inhaled and attributed the death of the worker to purulent pneumonia resulting from pulmonary irritation.

In 1949, Brass [75] reported 2 fatal cases of occupational ethylene dichloride poisoning which had occurred in a chemical plant in Germany in 1943. Two men, 65 and 39 years of age, were working in a 3.5-meter deep ditch repairing leaks in pipes that carried ethylene dichloride. The older man, wearing a gas mask, was working alone in the ditch when he collapsed. In a rescue attempt, the second worker, also wearing a gas mask, lost consciousness as he was climbing up a ladder with the first worker. Both workers were finally rescued 30 minutes later and regained consciousness

when brought into fresh air. Cyanosis and tachycardia were present and both men were taken to a clinic.

The first worker to collapse (the 65-year-old man) was examined and found to be sleepy; cyanosis of the visible mucous membranes and a paleness of the skin were noticeable. His breath smelled very strongly of ethylene dichloride. There were no abnormal findings in the lungs, heart, liver, spleen, and kidneys on physical examination and there were no unusual neurological findings. Blood analysis showed 114% Hgb, 5,460,000 RBC, 13,500 WBC, and a normal differential cell count. He reported feeling weakness of the limbs and considerable pressure in the bladder. [75] With continued supportive treatment, the patient began to improve, but felt thirsty, had an unpleasant taste in his mouth, and the pressure in the bladder area was increasing. A few ml of alkaline urine obtained by catheter the next day showed albumin and white and red blood cells. Circulatory weakness developed and the man died approximately 32 hours after the exposure. [75]

Extensive subepicardial, subendocardial, and a few subpleural hemorrhages were found at autopsy. The lungs were moderately edematous, the kidneys were swollen, there was generalized jaundice and multiple fist-sized cavernomas in the liver. [75] Microscopic examinations confirmed the presence of pulmonary inflammation and edema. The kidneys showed thickening of the perinephric capsule and only a few hyalinized glomeruli. The remaining glomeruli were swollen and filled with blood. Cells of the parietal and visceral capsules were swollen and their nuclei were occasionally karyolytic and pyknotic in appearance. In a few of these capsule formations, there was desquamated epithelium. The renal tubular

epithelium was swollen, and the tubules and lumina had many damaged cells. The straight portions of the epithelium were the most severely affected. [75] The liver showed individual or small groups of transparent cells and degenerative nuclear changes. There was considerable swelling of the reticuloendothelium, leukocytic infiltration, and moderate fatty degeneration.

The course of illness of the second worker (the 39-year-old man), who also died, followed a similar pattern with conspicuous jaundice and anuria. Autopsy findings included extensive subepicardial and subendocardial hemorrhages, a few subpleural hemorrhages, bilateral pleural effusion, slightly swollen kidneys, portal cirrhosis of the liver, and a generalized jaundice. [75] In both cadavers there was an intense, unique smell of all organs that was so strong people present at the autopsy felt uncomfortable and developed headaches. There was a profound rigor mortis and an absence of clots. The blood was described as intensely red and thick. Neither methemoglobin nor carboxyhemoglobin was found by spectroscopic analysis.

Hadengue and Martin [76] reported a case in 1953 in which a plant engineer died after being exposed to ethylene dichloride vapor for only a few minutes during a rescue attempt. A worker became unconscious while making repairs in a tank in which there was a mixture containing ethylene dichloride used in the production of carotene. The plant engineer entered the tank to rescue the man and he, too, lost consciousness. The worker suffered only temporary and minor problems, whereas the engineer, having been exposed to the same concentrations, died 6 hours after the accident. It is likely that skin absorption as well as inhalation contributed to the

exposure since the engineer's body had a yellow coating adhering to it when he was removed from the tank.

When brought to the hospital, the engineer did not seem to be in a particularly serious condition. However, he became comatose and died during the night. Autopsy findings included massive pulmonary edema, hepatic hypertrophy with yellowish color and distinct areas of degeneration, intense renal congestion, and small meningeal hemorrhages. Microscopic examination of the lungs indicated areas of emphysema and edema. Some of the alveoli contained erythrocytes and eosinophils, and the alveolar capillaries were moderately congested. The liver cells showed necrosis and fatty degeneration with moderate congestion of the capillaries. The renal convoluted tubules and Henle's loop showed granular degeneration and there were numerous hyaline and granular casts in the lumen. The cause of death was attributed to pulmonary edema. [76]

Ollivier et al [77] described a case in 1954 in which 4 workers were painting a boat with a compound containing ethylene dichloride. After a few hours, the workers became ill with general malaise and vomiting. They were taken to the hospital where they were treated with intravenous methylene blue. One worker died shortly after admission, and the other 3 workers were all discharged from the hospital the following morning. An autopsy revealed intense congestion of the deep and superficial vessels of the central nervous system, pulmonary edema, and congestive lesions in the liver, spleen, and kidneys. [77]

A case of poisoning by Granosan, a disinfestant composed of 30% carbon tetrachloride and 70% ethylene dichloride, was reported by Domenici [78] in 1955. A worker who spent 4 hours unloading empty sacks that had

been disinfested with Granosan felt tense after work. Two days later he did not report to work and on the 3rd day he had severe dyspnea and had to be hospitalized. Examination showed a cyanotic coloring, fast pulse, reduced respiratory rate, and heart sounds that were barely perceptible. He died 10 days after the initial contact with Granosan. The autopsy findings included pulmonary edema with signs of marginal emphysema, thickened pericardium, epicardiac thickening, necrosis and fatty degeneration of the liver and kidneys, renal congestion, and hyperemia throughout the digestive tract.

Fifteen cases of poisoning after inhalation of Granosan were reported by Salvini and Mazzucchelli [79] in 1958. Four persons had been involved in the fumigation of a warehouse and the other 11 persons lived nearby. The fumigation took place in the afternoon and that night most persons developed signs and symptoms that included malaise, nausea, vomiting, headache, anorexia, tiredness, asthenia, epigastric pain, and mild hepatomegaly. One of the workers involved in the fumigation procedure for 50 minutes became more seriously ill and was hospitalized with tachycardia, oliguria, and a decrease in renal and hepatic function (criteria of evaluation not mentioned). One person who did not participate in the disinfesting, but who lived near the warehouse, died on the 8th day after exposure. Autopsy findings included meningeal hemorrhaging, hyperemia in the cephalic parenchymal cortex, congested and edematous lungs, clots in the heart and a thickening of the myocardium, congestion of the liver and spleen, renal hyperemia, and centrilobular liver necrosis with binucleated cells. All of the other persons exposed to the fumigant mixture recovered. [79]

Guarino and Lioia [80] in 1958 reported a case in which a 50-year-old worker using a compound containing 70% ethylene dichloride to disinfest wheat died 12 days after the exposure. He was part of a working crew employed to disinfest grain stored in a rectangular shed. Five barrels of the Granosan compound, each containing 250 kg, were placed outside the building, and the liquid was then pumped through rubber hoses. Two workers, equipped with masks with filters, stood inside the shed and directed the spray. The first barrel was emptied in about 5 minutes. The pump then clogged, and one worker carried the insecticide in 2 buckets to the workers in the storage area. He reportedly removed his mask several times and continued to carry the compound in this manner for one hour. [80]

Four hours later, he developed severe frontal headaches and repeated vomiting which continued through the next morning. Oliguria developed and he was hospitalized. Slightly muffled heart sounds, rales, slight accentuation of the left patellar reflex, and slight abdominal tenderness were found by physical examination. Urinalysis showed albumin, urobilin, hyaline and granular casts, and erythrocytes. One week after the incident, his blood pressure was found to be 155/115, and an electrocardiogram revealed left ventricular prevalence. Ten days after the incident, he had profuse diarrhea, increased dyspnea, and amblyopia, and he died 2 days later. Autopsy findings included edema with areas of necrosis in the kidneys, splenic congestion, and necrosis of the liver. [80]

A fatal exposure of a 32-year-old man, employed for several years in a plant which manufactured ascorbic acid, was reported by Troisi and Cavallazzi [81] in 1961. The worker was exposed to ethylene dichloride during the process of loading and unloading a centrifuge, during which time

he wore rubber boots and a mask with a filter, defined only as neutralizing. The mask had been malfunctioning for several days, and during this time the employee complained of general malaise and was seen staggering about the workplace. On one particular day, he was loading the centrifuge when he became pale and started to vomit about 5.5 hours after he began work. A few hours later, he complained of chills. When he arrived home, vomiting continued, he developed hiccups, and the general malaise worsened. An epileptiform convulsion occurred about 3 hours after he left work; he lost consciousness and was rushed to the hospital where he was found to be comatose with cyanosis and dyspnea. His pupils did not react to light, rales were heard over his entire chest, there was mild tachycardia, muscular hypotonia with a complete absence of tendon reflexes, and he had repeated convulsions. Blood glucose was 310 mg/100 ml and urinalysis showed 1,250 mg glucose/ 100 ml and a trace of acetone. The patient's condition continued to decline and he died approximately 11 hours after he left work. [81]

An autopsy performed 3 days later showed intense cyanosis of the head and neck, a small blood clot in the right temporal region, congestion and edema in the cerebrum, hemorrhages in the trachea and bronchi, pulmonary edema and congestion, and fatty degeneration of the liver. Intense renal tubular degeneration was found on histological examination. [81]

(c) Acute Inhalation and Skin Exposures without Fatalities

Nonfatal acute exposures to ethylene dichloride have also been reported. [82-90]

One of the early reports of occupational poisoning was in 1939 when Wirtschafter and Schwartz [82] published a study of 3 employees in a

knitting factory who became acutely ill following a single exposure to ethylene dichloride. These men had no previous exposures to ethylene dichloride and had become ill while cleaning a shipment of yarn by immersing it in an open tank containing 20 gallons of ethylene dichloride. After soaking, the yarn was removed and wrung out by hand. The workroom had an exhaust fan and the temperature in the room was about 75 F. Four hours after the beginning of the exposure, the men became dizzy, nauseated, and vomited profusely. They were also weak and trembling and were removed from the exposure after the onset of vomiting. They were hospitalized one hour later, the vomiting having continued unabated.

One of the men, aged 60, was still vomiting when he arrived at the hospital and complained of epigastric pain. Other observations included furring of the tongue, tremor of the extremities, and severe dermatitis of the hands. The liver was neither tender nor palpable. [82]

The 2nd man, 51 years old, was also vomiting profusely when admitted to the hospital. There was a continuous generalized tremor, absence of breath sounds over the right anterior chest, left border of cardiac dullness 12 cm from the mid-sternal line, and severe dermatitis. Abdominal examination was negative. [82]

The 3rd worker was the most acutely ill with severe headache and weakness accompanying the nausea and vomiting. This 44-year-old man also had generalized tremor, moderate conjunctival congestion, occasional moist rales throughout both lungs, and severe dermatitis of the hands. The liver was palpable and tender. [82]

The icteric indices for the 3 men were 9.1, 14.5, and 8.6, respectively (normally 3-8). Leukocytosis was prominent in all 3 men and

blood sugar levels 72 hours after admission were 52.6, 55.0, and 74.0 mg/100 ml, respectively. [82]

The patients were administered 10% calcium gluconate solution intravenously upon admission to the hospital and were fed on a high calcium, high carbohydrate diet. All 3 men improved and were discharged after one week. The dermatitis persisted even after discharge from the hospital. [82]

Six cases of occupational intoxication were reported by Jordi [83] in 1944. Two men were working in a small room with closed windows dismantling and cleaning a compressor in ethylene dichloride which contained 5-6% methyl acetate. Both experienced headaches, a feeling of being intoxicated, and vomiting. One man had recovered by the following day but the other continued to feel tired and weak. He returned to work two days after the exposure even though he had not recovered. He also suffered from rheumatism and underwent treatment during that summer. One year after his exposure, his symptoms of tiredness, nervousness, insomnia, reduction in libido and potency, and generalized atrophy of muscles without abnormal findings in the organs were concluded to be consequences of the initial poisoning.

A 3rd worker in a factory which manufactured artificial rubber developed headaches and vomiting after a bottle of ethylene dichloride broke. [83] Two other cases of intoxication presented by Jordi [83] occurred in a room 20 cm below ground level where ethylene dichloride (sometimes mixed with methylene chloride and methyl acetate) was used as a solvent for a resin. A 33-year-old man developed nausea, the urge to vomit, and abdominal cramps when an obstruction developed in the

ventilation system. He recovered after 14 days. Another man who worked over an unventilated trough felt dizzy and nauseated for several days, then developed vomiting and cramps. He rested for 2 weeks but did not fully recover for over a month. [83]

The sixth case of occupational exposure to ethylene dichloride reported by Jordi [83] occurred when a worker attempted to disassemble an ethylene dichloride pump in a cellar. Four liters of the liquid spilled onto the floor, and one worker shoveled most of the material into a container, then mopped up the remainder. During this time, about one hour, he felt pressure in his head and dizziness. He then moved to a different room but the dizziness continued and he began to vomit. This continued for several hours and the next morning he was still nauseated and had headaches. The urge to vomit and a burning sensation in his stomach lasted for several days. On physical examination one month after the exposure, findings were normal except for leukocytosis and a slight sensitivity to touch in the epigastrium. [83]

A 33-year-old employee was reported in 1946 to have become ill after he was splashed with ethylene dichloride. [87] His overalls were saturated and some of the liquid entered one eye. When eye treatment was given, he was found to be dazed and 2 hours later he began to feel very sick. Three hours after the accident, there was retching and vomiting which persisted for 9 hours. The following 2 days, the man had violent epigastric pain which was aggravated by the intake of food. His physician diagnosed hepatitis with no jaundice, and recovery was complete.

A case of severe dermatitis and necrosis of the epidermis of the feet, accompanied by suppuration and delayed healing, was reported by

Rosenbaum [88] in 1947 in a worker who spilled ethylene dichloride on his socks, wrung them out and put them on again.

Agranovich, [72] in 1948, reported having investigated 10 cases of occupational poisoning by ethylene dichloride, one of which he summarized. He stated that all cases were mild and characterized by headache, nausea, and general weakness, often appearing after a delay of a few hours, and sometimes lasting several days. The liver was palpable in some and one worker had an insignificant increase in bilirubin in the blood.

In the case he summarized, a 29-year-old man became ill after having used ethylene dichloride to clean oil from a certain piece of equipment. [72] He left work, began to stagger about as if drunk, was confused, and soon began to vomit. He was brought to the clinic with a headache, slight nausea and general debility. Epigastric tenderness, scattered, dry rales, hypoglycemia 3 hours after administration of galactose, and urobilin in the urine were found. He was fully recovered when he was released from the clinic a week later.

An entire family was reported in 1950 to have been poisoned by ethylene dichloride, presumably from inhalation, after the floors of 2 rooms were treated with pure ethylene dichloride. [84] The wife was the 1st to develop nausea and a headache and she vomited repeatedly. Two children, the husband, and his sister became ill soon after. Another child showed cyanosis, continuous vomiting, elevated temperatures, and weak heart beats with almost no pulse for about 2 weeks. Two workers of the company making the cleanser also were intoxicated. Details of the workers' illnesses were not given.

Twenty-two workers were reported by Paparopoli and Cali in 1956 [85] to have become ill after unloading grain disinfested with a combination of carbon tetrachloride and ethylene dichloride from the hold of a ship. [85] Fifteen of the dock workers were hospitalized. The patients were between the ages of 18 and 50 and all presented the same initial subjective manifestations of poisoning, which appeared between the 2nd and 4th day of work. These included a burning sensation in the exposed mucous membranes, frontal headache, vertigo, nausea, epigastric pain, asthenia, and somnolence. Some of the workers experienced more serious signs of poisoning such as vomiting, diarrhea, and unconsciousness lasting from a few minutes to about an hour. Paparopoli and Cali [85] summarized their clinical findings on the 15 patients and did not describe each case separately. Most persons had manifestations of bronchial inflammation, infrequent, dry cough, nausea, and epigastric disturbances. The livers were slightly enlarged in all, and 2 cases showed a jaundiced coloration of the sclera and skin and urobilinuria. One person had cardiac arrhythmia, and hypocalcemia was present in several other individuals, but the number not stated. All patients were released from the hospital by the end of one month.

Menschick [86] reported in 1957 that four men became acutely ill from inhaling ethylene dichloride while applying a protective coating to the walls of a concrete tank. After the men complained about the odor, compressed air was supplied to the chamber. One worker became nauseated after about 15 minutes of exposure and sat down at the edge of the tank. His condition became worse, an ambulance was called, and by the time it arrived (25 minutes after exposure began) he had already lapsed into

unconsciousness. A second worker, who felt nauseated, also was placed in the ambulance. The remaining workers had no symptoms, but were seen by the factory physician. [86]

The first worker remained unconscious for 3 hours with severe tonic-clonic muscle spasms and profuse vomiting. His skin was pale, lips cyanotic, and conjunctiva were reddened. The following day, he was found to have leukocytosis, acute conjunctivitis, acute inflammation of the upper and lower airways, intestinal spasms, abdominal tenderness, anxiety, and precordial pain. The liver was enlarged, serum bilirubin was elevated, the Takata-Ara test of liver function was positive, and urinalysis showed albumin, hyaline and granular casts, few leukocytes and erythrocytes, and abundant sedimentation. Symptomatic treatment was continued and the man's condition was improved by the 4th day after exposure, although there was still abdominal and precordial pain, slight conjunctivitis, diffuse bronchitis, and the liver was still enlarged and sensitive to pressure. Three months after the intoxication, liver damage was still detectable as indicated by a positive Takata-Ara test and elevated bilirubin; 4 months after the exposure the patient was found to be clinically normal. [86]

The second painter had symptoms similar to the first man with pale skin, cyanotic lips, conjunctivitis, bronchitis, leukocytosis, a positive Takata-Ara test, and elevated bilirubin. His condition was reported as improved 5 weeks after the intoxication. [86]

The remaining 2 men had leukocytosis, a slightly elevated bilirubin, and a positive Takata-Ara test. Gastric X-ray showed acute gastritis and bulbar duodenal erosion in one man, and hypersecretion was also reported to

have been found. Five weeks later, the conditions of both men were reported to be improved. [86]

Smirnova and Granik [89] studied the long-range effects in 6 workers who had been acutely poisoned with ethylene dichloride. These 6 workers were among 35 follow-up case studies of workers acutely exposed to various substances at work because of accidents, violation of safety rules, or insufficiently sealed equipment. The occupations of the total group were machine operators, metal workers and lab workers. Their ages ranged from 20 to 60 years. Twenty-three of the workers had been exposed up to 5 years and 12 had been exposed for more than 5 years. More specific details about the occupations and ages of the 6 workers exposed to ethylene dichloride were not given. It was not entirely clear from the article that the exposures were only to ethylene dichloride. At least one of the ethylene dichloride exposures resulted in loss of consciousness. None of the 6 workers exposed to ethylene dichloride showed evidence of liver damage, but chronic changes were noted in the central nervous system and were manifested in 1-18 years. In the most serious case of ethylene dichloride poisoning, the illness was reported to be accompanied by signs of encephalitis with special injury to the subcortical region which improved slowly during 14 years.

(d) Repeated and Chronic Occupational Exposures

Repeated exposures to ethylene dichloride in the occupational environment have been associated with anorexia, nausea, vomiting, epigastric pain, irritation of the mucous membranes, and liver and kidney dysfunction. Although fatal cases have been reported less frequently with

chronic exposure than with acute exposure, chronic effects can progress unless the exposures are adequately reduced.

The experiences with ethylene dichloride during its first 3-4 years of use in Russian industries were discussed by Rosenbaum [91] in 1939. During that time, a number of mild cases of poisoning with symptoms lasting for several hours had been observed. In more severe cases, the illnesses lasted 1-3 days and occasionally 4-5 days. The symptoms included general debility, vertigo, headache, nausea, and vomiting. Irritation of the eyes and respiratory tract were common, and occasionally the workers perceived a buzzing sensation and developed reddening of the facial skin. Rosenbaum [91] reported that secondary symptoms almost never developed. About 90 persons from a number of Moscow factories were examined who had worked with ethylene dichloride at work-zone concentrations usually below 25 ppm. The author [91] reported that no pronounced chronic effects on the blood picture or on individual organs were established in these workers. The most characteristic and frequent findings were bradycardia (heart rate 60 beats/minute or less) and bright red, long-lasting dermographism which he considered to be transitory CNS effects.

In a 1947 report, Rosenbaum [88] discussed the experiences in Russian industries from 1934 to 1945. He noted that acute poisonings could develop rather rapidly with repeated exposures at concentrations of 75-125 ppm. He considered that the signs and symptoms of the acute poisonings included general weakness, headache, dizziness, vomiting (usually with a trace of bile), and irritation of the mucous membranes and skin. Some cases resulted in fatalities when the workers experienced these signs and symptoms of poisoning 2 or more times in a period of 2-3 weeks.

Two cases in which workers became ill after occupational exposure to ethylene dichloride were reported by McNally and Fostvedt [90] in 1941. There were no concentrations given in either case. One man had been employed in a packing plant as a cholesterol extraction process operator for 9 weeks, 40 hours/week. He ground spinal cords, a process in which he used 750-900 gallons of ethylene dichloride for each batch. Exposures to the vapor occurred during the centrifugation process to separate the cholesterol and during the emptying of barrels containing the cholesterol. The man complained that during the previous month he had experienced anorexia, nausea, and vomiting of 2 days' duration, drowsiness at work, and a weight loss of 10 pounds. Upon physical examination, the man appeared nervous, but not acutely ill. It was concluded that he had recovered from the ill effects of ethylene dichloride, except for the nervousness.

The second person, a 28-year-old male, worked in the cholesterol department of the packing plant for a period of 5 months. He complained of epigastric pain of 4 days' duration, nausea and vomiting for several days, and sleeplessness for 2 nights. Physical examination revealed a marked nystagmus to the left, fine tremor of the tongue, an injected and dry pharynx, chronic bronchitis, and a sluggish patellar reflex. [90]

A 55-year-old man died in 1942 after working 4-5 days with a varnish containing what was described as solvent benzol, testbenzin, and ethylene dichloride. [92] On the last work day, he was exposed for 5 hours to ethylene dichloride in a poorly ventilated pit. After work, he had to be carried home where he developed nausea, vomiting, and inflammation of the mucous membranes. He died the following day. Autopsy findings included bronchial irritation, fatty degeneration of the liver, and multiple

petechial hemorrhages. Death was attributed to inhalation of the combination of solvents.

The following year, 1943, Byers [93] reported that many persons exposed to ethylene dichloride reported delayed effects with the worst effects occurring after the evening meal. These varied from lassitude and malaise to nausea, vomiting, and abdominal pain. Byers [93] further stated that these workers were exposed at concentrations only slightly higher than 100 ppm for 7.5 hours daily when these symptoms were reported, and that the addition of ventilation which reduced the concentrations to an average of 70 ppm alleviated some but not all of the complaints.

In a 1947 letter to the Journal of the American Medical Association, Siegel [94] stated that a patient chronically exposed to ethylene dichloride as a finisher on celluloid products complained of nausea and weakness for several hours after contact with the fumes. His liver was also reported to be palpable about 2 inches below the costal margin.

In discussing health hazards in the pharmaceutical industry, Watrous [95] mentioned in 1947 that men working with ethylene dichloride developed symptoms referable to the gastrointestinal tract suggesting to him slight liver damage. These symptoms included anorexia, a heaviness in the epigastrium, and fatigue. Watrous [95] also stated that the urine may give a positive test for urobilinogen.

Rejsek and Rejskova [96] in 1947 reported 3 cases of poisoning in a printing shop in which a solution containing 95% ethylene dichloride was used frequently to wash rollers. The symptoms included irritation of the conjunctiva and mucous membranes of the respiratory tract, and an excitation resembling that of the early stages of alcohol intoxication.

The authors [96] estimated that the concentration at which the workers had been exposed was about 2,500 ppm (10 mg/liter) during the cleaning process.

Neurologic effects in 2 workers chronically exposed to ethylene dichloride were reported by Guerdjikoff [97] in 1955. The workers were involved in the manufacture of hexachlorophene. Ethylene dichloride was used as a catalyst in the process. Exposure to ethylene dichloride occurred at various times during the process.

Exposures associated with adding ethylene dichloride, trichlorophenol, and sulfuric acid to the reaction vat occurred for 2-3 minutes several times a day for a total of about 30 minutes. During the filling operations, the ethylene dichloride exposure concentrations were not measured but the worker wore an air-supplied face mask. In another operation which lasted 10 minutes 3-4 times/day, the exposure concentration of ethylene dichloride was about 120 ppm. Another exposure occurred daily for 10-15 minutes when the ethylene dichloride pipe was cleaned. The exposure concentrations during this time were not measured but Guerdjikoff [97] considered that they were more than 120 ppm.

The first person worked under the described conditions for 9 months. After 3 weeks, he experienced anorexia, epigastric pains, fatigue, irritability, and nervousness. As the exposure progressed he also developed headaches, sexual impotence, insomnia, feelings of drunkenness, and tingling sensations of the eyes. Examination revealed a 6-kg weight loss over 6 months, exaggerated dampness of the skin, deviation to the right in a blind walk, and a slight trembling of the hands. After 15 weeks of rest and treatment, the patient returned to work. [97]

The second case reported by Guerdjikoff [97] involved a worker who replaced the first worker. He was employed for 7 months. During that time he gradually experienced progressive difficulty in walking and other symptomatology similar to the first case. Neurological examination revealed sensory and motor abnormalities of the right cerebral hemisphere. Variability in the patient's responses and a psychiatric examination led to the conclusion that the patient suffered from initial sensory-motor disturbances followed by post-traumatic neurosis. The neurosis was still being treated 2 years after the exposure ceased. [97]

Delplace et al [98] reported in 1962 that they observed 16 cases of industrial intoxication due to ethylene dichloride in 1960 and 1961. In 5 cases, encephalitic disorders were noted, 2 were accompanied by respiratory difficulties, and 2 by digestive problems. The other 11 complaints were of eczema of the hand and arm which appeared within the first year of exposure. No exposure concentrations and no information of the types of exposures were given.

Ethylene dichloride was reported by Urosova [99] in 1953 to appear in the milk of nursing women who were occupationally exposed to ethylene dichloride through inhalation and skin absorption. In one experiment, Urosova [99] analyzed exhaled breath and milk samples taken immediately, after 30 minutes, 1, 1.5, 2, and 2.5 hours after the women left work. Exposure was assumed to be by skin absorption since gas masks were worn. Data were not presented, but it was stated that the concentrations of ethylene dichloride in milk increased after leaving work, reached a maximum after one hour, then diminished. The amount of ethylene dichloride in exhaled breath samples was highest just after exposure, then decreased with

In a second investigation, Urosova [99] measured the amounts of ethylene dichloride in milk and breath samples of a woman exposed at approximately 15.5 ppm (0.063 mg/liter) for an unspecified amount of time. The concentration in the breath was 14.5 ppm (0.058 mg/liter) and the concentrations in milk were found to be 0.54, 0.57, and 0.64 mg/100 ml. Eighteen hours after the woman left work, 0.195-0.63 mg/100 ml ethylene dichloride were found in her milk and 2-4 ppm (0.009-0.017 mg/liter) were found in her breath.

Suveev and Babichenko [100] reported in 1969 on 12 cases of ethylene dichloride poisoning observed over a 5-year period. Eleven men and one woman had become intoxicated while working indoors; the type of work and the time of exposure were not specified. The first symptoms to appear were headache, dizziness, irritation of the mucous membranes of the upper respiratory tract, a sweet taste in the mouth, and a burning sensation behind the sternum. They became nauseated 1-2 hours after the poisoning and vomited. The vomitus contained blood. They also developed pain in the substernal region, cough, weakness, and a partial loss of orientation.

All victims were brought to the clinic where they were found to be pale and in a cold sweat. Nine of the 12 patients had bradycardia (40-52 beats/minute) and 3 had tachycardia (up to 120 beats/minute). The blood pressures ranged from 100/60 to 80/40, heart sounds were muffled, and 5 patients had systolic murmur. Respiratory rate ranged from 30 to 40/minute, whistling sounds and rales were heard over the chest, the tongue was coated and dry, and there was epigastric pain. In 9 patients, the livers were enlarged by 2-5 cm and were soft and tender to pressure. After 2-3 days, 5 persons had diarrhea and in 3 of these the stool was mixed with

blood. Effects on the nervous system were also reported, including deafness, decrease in muscle tone, loss of reflexes, and a positive Romberg's sign. [100]

(e) Experimental Investigations

Borisova [4,101] studied the physiological effects of low concentrations of ethylene dichloride on man by determining the odor threshold, light sensitivity of the eye, and by plethysmographic and spirographic observations. To determine odor threshold, 20 subjects were used to make 1,256 tests. Thirteen subjects could detect ethylene dichloride at a concentration of about 6 ppm (23.2-24.9 mg/cu m), 6 persons could detect it at 4.5 ppm (17.5 mg/cu m), and 1 person at 3 ppm (12.2 mg/cu m).

An adapter was used to determine the intensification of light sensitivity during exposure to ethylene dichloride. Three persons were exposed at concentrations varying from 1 to 12.5 ppm (4-50 mg/cu m). The threshold at which light was perceived was lower during exposure to ethylene dichloride. As the concentration of ethylene dichloride increased from 1.5 to 12.5 ppm (6-50 mg/cu m), the threshold of perception decreased. At the concentration of 1 ppm (4 mg/cu m), there was no change in the light sensitivity of eyes. [4,101]

The effect of ethylene dichloride on the vascular system was investigated with the use of a plethysmograph, which enabled Borisova [4,101] to observe pulse fluctuations and changes in blood volume in limbs. Four subjects inhaled ethylene dichloride vapor concentrations of 1.5, 3, 6, and 12.5 ppm (6, 12, 23, and 50 mg/cu m) for 30 seconds or 15 minutes. A 30-second exposure at 1.5 ppm (6 mg/cu m) resulted in a temporary vasoconstriction in all 4 subjects. Exposure at 3 ppm (12 mg/cu m) caused

an even greater reaction in the vessels of the fingers of all subjects, and further observations at higher concentrations showed that the degree of response was proportional to the exposure concentration. [4,101]

Changes in respiration were also observed. Spirograms were obtained by introducing a tube into the nostril of each subject. Concentrations of 1, 1.5, 3, 6, and 12.5 ppm (4, 6, 12, 23, and 50 mg/cu m) were administered for 1 minute and concentrations of 1.5 ppm (6 mg/cu m) and greater produced a change in the depth of breathing as indicated by an increase in the height of the wave on the spirogram. [4,101]

Epidemiologic Studies

DiPorto and Padellaro [102] reported in 1959 on a study of 48 cases of poisoning by a fumigant containing 75% ethylene dichloride and 25% carbon tetrachloride. In 28 persons the effects were very mild, in 16 they were moderate to severe, and 4 persons died after exposure. Clinical findings included acute hepatorenal insufficiency with vomiting and circulatory failure; there was oliguria or anuria with urobilin albumin, casts, and blood cells being found in the urine. Necrotic and hemorrhagic lesions in the centrilobular cells of the liver, necrosis of the convoluted tubules of the kidneys, and proliferative changes in the glomeruli including many multinucleated cells were found in fatal cases.

Hematologic changes in ethylene dichloride workers were studied by Khubutiya in 1964. [103] Hemoglobin, red blood cell count, color index, and blood cell morphology were recorded. The presence of hyperchromic erythrocytes without megaloblasts in 29.2% of the red blood cells was reported in the workers examined. It was also reported that 48.9% of the

cases (the total number of workers was not stated) showed moderate and high figures for sedimentation rate induced by the increase in blood globulin, according to the author. [103] Leukopenia occurred with a reduction in the number of absolute neutrophils, with relative neutrophilia, and with absolute lymphopenia. The number of workers showing these blood changes was not mentioned. Cases of moderate and marked monocytosis were frequent and platelets were reduced. Turk cells were present in the peripheral blood in 18.8% of the cases. The author [103] concluded that the monocytosis and the presence of Turk cells was due to stimulation of the reticuloendothelial system, as a result of long exposures to ethylene dichloride. The concentrations to which these workers were exposed were not reported.

In 1959 Cetnarowicz [9] published a study of an oil refinery in Poland. The plant had introduced a new method of purifying mineral oils ("Barisol") which included mixing the oils with a solvent containing 80% ethylene dichloride and 20% benzene at 40 C. [9] The mixture was then cooled to -25 C and the paraffin was precipitated by centrifuging. After using the method for 6 months, the plant management requested that the Department of Occupational Diseases of the Cracow Academy of Medicine investigate the possibility of ethylene dichloride poisoning occurring in the workers. The concentration measurements were performed by the Institute of Occupational Medicine in Lodz.

Environmental concentrations ranged from 10 ppm (0.04 mg/liter) to 200 ppm (0.8 mg/liter). Repeated measurements in 4 work areas, as presented by the author, [9] are given in Table III-1.

Table III-1

CONCENTRATIONS OF ETHYLENE DICHLORIDE IN WORKROOM AIR

Location	ppm (mg/liter)		
Centrifuge room	64(0.26)	62(0.25)	200(0.8)
Pump room 1	16(0.066)	10(0.04)	17(0.07)
Pump room 2	25(0.10)	13(0.053)	-----
Crystallization room	30(0.12)	37(0.15)	-----

Derived from Cetnarowicz [9]

Benzene concentrations were in the range of 0.01-0.025 mg/liter (the current US federal standard is 0.08 mg/liter) and the authors considered it to be an insignificant contribution to any toxicity hazard. The ethylene dichloride concentrations, on the other hand, exceeded the maximum permissible concentration at that time of 12.5 ppm (0.05 mg/liter) in all but one measurement. Within the plant, the highest excursions were experienced in the centrifuge room. [9]

In order to investigate the possibility of ethylene dichloride poisoning, Cetnarowicz [9] examined a total of 42 workers from this plant. Six persons, seen in the plant clinic, complained of a sweetish aftertaste, dizziness, nausea, vomiting, and lack of appetite. Two of them had pain in the epigastrium and 3 had insignificantly enlarged livers which were tender to pressure. Cetnarowicz [9] judged that further clinical investigations were necessary and initiated a comprehensive study of 19 members of 1 shift.

The crew consisted of 18 men and 1 woman, ranging in age from 19 to 48 years. Medical examinations excluded 2 men from further study because

chronic appendicitis and a duodenal ulcer were found. The woman was excluded because of chronic cholecystitis and chronic ovaritis. The 16 remaining workers had been employed in the "Barisol" section of the plant for 2-8 months; 10 worked in the centrifuge room. Four of the workers in the centrifuge room did not complain of any symptoms; the other 6 stated they had dryness of the mouth, an unpleasant sweetish aftertaste, dizziness (compared to that state attained from vodka drinking), lassitude, sleepiness, nausea, vomiting, constipation, and poor appetite which was contributing to weight loss. All 10 workers from the centrifuge room had a burning sensation of the eyes and lacrimation which disappeared as they adapted to the atmosphere. Three workers also complained of pain in the epigastrium. All symptoms disappeared when the workers were removed from the workplace but returned when the workers were again exposed to the ethylene dichloride-containing atmosphere. Of the 6 workers employed in the pump and crystallization rooms, only one complained of the above-mentioned symptoms. [9]

Physical examinations indicated a general reduction in body weight of 2-10 kg below the expected weight. One worker had slight icteric coloration of the skin. Ophthalmologic examination revealed no eye damage and examination of the upper respiratory tract, lungs, and heart showed no significant changes. Four persons employed in the centrifuge room had livers which were tender when palpated and minimally enlarged, and 7 others had tenderness of the epigastrium.

Investigations by the Neurologic Clinic of the Medical Academy showed that 3 persons had augmented reflexes and what was reported as vegetative neurosis. Cetnarowicz [9] also reported that the majority of individuals

had elevated urobilinogen levels in the urine and in 3 of these the levels were grossly elevated. Blood analysis of 13 workers revealed normal erythrocytes and hemoglobin (Hgb) except in one worker with moderate hyperchromic anemia (3,430,000 erythrocytes/cubic mm and 60% hemoglobin). Reticulocytosis was found to average 0.1-0.3%, and in 4 persons ranged from 0.9 to 1.1%. The osmotic fragility of erythrocytes in sodium chloride was diminished in 6 workers, and one worker had slight leukocytosis (11,200/cu mm). The number of platelets was in the normal range in all but 2 workers (40,000-55,000/cu mm). A decrease to 50% polymorphonuclear neutrophils was found in one case and 40% in another. The number of lymphocytes oscillated around 45% and the number of monocytes varied around 16%. Six workers had increased number of neutrophils in the range of 70-78% with lymphocytes in the range of 15-25%. The numbers of monocytes in all investigated workers were in the upper part of the normal range. In general, only 9 workers in the investigated group had a normal percentile distribution of white blood cells. [9]

Bone marrow analysis in 5 workers showed an increased number of erythrocytes, increased percentage of polymorphonuclear neutrophils, and a mild stimulation of erythropoiesis with a less significant increase of leukopoiesis. It seems more likely that many of the blood changes reflect benzene poisoning rather than ethylene dichloride poisoning.

Chemical analyses of the blood were also done and abnormal values were found; serum bilirubin at 2.3 mg% in one worker, blood nonprotein nitrogen at 55 mg% in one worker, albumin in 6 workers had diminished amounts, globulin in 8 workers showed an increase, and fibrin content of the blood was diminished in 3 workers.

The Takata-Ara test of liver function was positive in 4 workers and borderline in 5 others, and the cadmium turbidity test was negative in 5 workers, borderline in 5, positive in 3, and strongly positive in 3 others. Blood glucose values were within normal limits for all workers, but in 8 persons, the glucose tolerance test showed a delayed return to normal values. X-rays of the gastrointestinal tract showed what was reported as chronic catarrh of the stomach with atrophy of the mucous membrane in 6 of the 16 workers and, in 3 of them, periodic spasm of the pylorus was also reported. [9]

A 35-year-old worker who had been employed for 4 months and who cleaned the centrifuges had the greatest degree of impairment of hepatic function, with icterus, an enlarged and tender liver, and highly elevated urine urobilinogen. Values obtained during blood analyses were generally within normal ranges except for a slight decrease in reticulocytes (0.2%), a slight increase in neutrophils (71%), a slight decrease in lymphocytes (19%), decreased albumin, and increased globulins. Bone marrow showed a mild stimulation of erythropoiesis. A glucose tolerance test showed a prolonged, elevated glucose level in the blood. The Takata-Ara and cadmium turbidity tests were strongly positive. Some of these blood and bone marrow changes may be caused by benzene. Bleeding time was 4.5 minutes, coagulation time was 7.5 minutes.

In his summary, Cetnarowicz [9] concluded that individual variation and susceptibility resulted in a range of effects but that in half of the crew (3/4 of those in the centrifuge room) liver function was compromised. In addition, there were changes in the gastrointestinal tract, sinus bradycardia in a third of the workers, and a variety of effects on the

hematopoietic system. He proposed to study the effect of a protective diet containing high levels of sulfhydryl groups on the health of the Barisol plant workers. By the time of this recommendation, the concentrations of ethylene dichloride in the workplace had been partially controlled but were still above permissible levels, and the entire crew had been replaced. For 6 months, 16 men and one woman had a diet supplemented with 5 mg methionine, choline, and 40 mg vitamin C. Nine of the workers were employed in the centrifuge room and 8 in other locations for an average of 8-12 months. Consequences of the dietary change are not apparent.

In 1954, Brzozowski et al [104] reported the work practices and health status of agricultural workers using ethylene dichloride as a fumigant in Poland and stated that skin absorption of ethylene dichloride was primarily responsible for producing symptoms such as nausea, weakness, and abdominal pain. It was reported that ethylene dichloride was brought to the fields in barrels and poured by hand into buckets. The worker handling the bucket had his face extremely close to the barrel during pouring and was therefore exposed to a high concentration. Workers then carried the open buckets to the place of application, meanwhile spilling quantities of the insecticide on their clothes and shoes. These clothes, often soaked with ethylene dichloride, were not changed. The actual application involved pouring the ethylene dichloride into a series of holes. Furthermore, the authors [104] stated that the workers used ethylene dichloride to wash their skin. This seems to confirm that skin absorption probably was as significant a contribution to exposure as inhalation.

An environmental sample representative of the working zone was collected in an unstated medium by midget impingers and analyzed by a modification of the alkaline hydrolysis method. Since the workers did not stay at one location for a sufficient amount of time to collect an entire sample, the collection apparatus was moved from place to place following the workers. Consequently, one environmental sample was collected from 10 locations. The concentration was found to be 4 ppm (16 mg/cu m). Because of the practical difficulties of sample collection, conditions were simulated in the laboratory and air was sampled and analyzed, resulting in concentrations of about 14.5-15 ppm (58-60 mg/cu m). A sample taken during the pouring of ethylene dichloride into buckets, considered to be the maximum exposure of a worker, was found to have 60 ppm ethylene dichloride. [104]

To establish the health status of the workers, the following investigations were performed: medical examinations, patch tests to detect sensitization, urinalyses and tests of liver function. Blood counts were also performed but the data were not reported. [104]

Among 118 workers using ethylene dichloride, signs and symptoms were reported in 90 persons, the most common being conjunctival congestion (82 of the workers), weakness (54), reddening of the pharynx (50), bronchial symptoms (43), metallic taste in the mouth (40), headache (39), dermatographism (37), nausea (31), cough (30), liver pain (29), burning sensation of the conjunctiva (24), tachycardia (21), and dyspnea after effort (21). [104]

The amounts of ethylene dichloride found in the urine of workers were not reported, but it was stated that ethylene dichloride was excreted very

fast, and that the amounts excreted did not correlate with the appearance of clinical symptoms. The Quick test for hippuric acid was used to measure liver function, and significantly abnormal findings were reported to occur in 40 of 56 investigations. Further detail was not reported. To determine skin sensitization, a piece of gauze was soaked in a 0.1% solution of ethylene dichloride in alcohol and was taped to the arm. The result was read after 40 hours, and in all cases the tests were negative. The same test was repeated using a 50% solution of ethylene dichloride in soybean oil and the results were again negative. [104]

The authors [104] concluded that the poor work practices including the spilling of ethylene dichloride on clothes and skin contributed significantly to the workers' exposure. They recommended the use of protective clothing and correction of work practices to decrease the exposure by skin absorption.

Rosenbaum [88] reported that in 100 factory workers exposed to ethylene dichloride for 6 months to 5 years at concentrations not in excess of 25 ppm (0.1 mg/liter), there were no changes in the blood or internal organ functions. However in a number of workers, there were nervous system functional disturbances of varying intensity. These disturbances included what was called heightened lability of the autonomic nervous system, diffuse red dermographism, muscular torus, bradycardia, increased hidrosis, and frequent complaints about fatigability, irritability, and sleeplessness. Information about the method of measuring ethylene dichloride was not given in the report.

The health of workers chronically exposed to ethylene dichloride in the Russian aircraft industry was studied for the years 1951-1955 and

reported in 1957 by Kozik. [105] The workers of concern comprised a large group employed in the shop where soft tanks were produced. Most of the workers in this shop were gluers who assembled the metal forms and attached rubber parts to them. A small number worked inside the completed tanks to dissassemble the forms. Rubber sheets were spread on tables situated in 4 rows and the metal forms were placed along the tables. During application of the glue to the large rubber sheets, ethylene dichloride, the solvent for the glue, was emitted to the air. The exit ducts of the ventilation system were located in the floor between the rows of tables and metal forms.

About 500 ethylene dichloride measurements were reported to have been taken for various purposes. The data for 3 operations in the shop are presented in Table XII-3 and summarized in Figures XII-1 and XII-2. Although the sampling and analytical methods were not mentioned, the design of the study and the extensiveness of the data presentation lend credibility to the study.

During application of the glue to the rubber sheets, concentrations of 5-40 ppm were reported. The author [105] reported that concentrations of 22-40 ppm were maintained for 5-6 minutes, after which they decreased to 17-22 ppm as the glue dried, and by the end of drying to 7.5-10 ppm, in 15 minutes. The gluing was done in the 1st half of the shift and the dried sheets were placed on the forms in the 2nd half. The author estimated that the array of ethylene dichloride concentrations reported for the gluing and drying operations occurred during 70-75% of the time. It can be estimated, from the data presented, that about 44% of the total exposure occurred during the gluing operations (Figure XII-2) when the TWA concentration was

about 28 ppm during application of the glue, and about 16 ppm when the glue was drying. During the 2nd half of the shift when other operations were performed, the ethylene dichloride concentration was about 11 ppm, and for the total shift the TWA was about 15 ppm.

A study was made of morbidity and temporary loss of working capacity in the group of workers engaged in the production of soft tanks and in the entire factory for the years 1951-1955. The morbidity indices are presented in Table III-2.

TABLE III-2

MORBIDITY AND LOST WORKDAYS OF WORKERS EXPOSED TO ETHYLENE DICHLORIDE
(Rates/100 Workers)

Year		Total Morbidity		Acute Gastro-intestinal Disorders		Neuritis and Radiculitis		Other Diseases	
		Plant	Shop	Plant	Shop	Plant	Shop	Plant	Shop
1951	Cases	120.2	159.8	5.1	11.6	5.2	13.0	34.4	43.2
	Days	995.8	1445.5	19.3	43.5	59.9	127.0	354.2	541.8
1952	Cases	124.0	137.6	4.2	5.7	5.0	9.7	34.0	40.8
	Days	960.9	996.0	15.1	23.1	44.8	94.5	335.2	378.7
1953	Cases	135.6	163.9	14.4	6.2	7.5	16.5	35.3	53.5
	Days	1040.8	1236.5	15.6	19.1	67.3	146.0	338.3	524.0
1954	Cases	150.7	191.8	5.3	9.6	7.9	16.7	40.8	63.8
	Days	1175.9	1563.2	19.3	31.8	73.8	182.8	386.4	596.2
1955	Cases	127.6	176.6	3.6	5.0	5.9	10.3	37.9	63.3
	Days	978.4	1462.4	12.1	15.3	51.1	90.2	345.7	640.5

From Kozik [105]

For each disease category considered, total morbidity, acute gastrointestinal disorders, neuritis, radiculitis, and other diseases, the indices of both cases of morbidity/100 workers and days of temporary loss of working capacity/100 workers were greater in the soft-tank shop than throughout the factory in each year, except cases of acute gastrointestinal disorders in 1953. Diseases of the muscles, tendons, and ganglia were considered by Kozik [105] to be associated with the many repetitive motions the workers had to make when applying the glue.

Eighty-three of the gluers were examined by the Department of Occupational Diseases of the Central Institute for Postgraduate Medicine. Diseases of the liver and bile ducts were found in 19 of the workers, neurotic conditions were found in 13, autonomic dystonia in 11, asthenic conditions in 5, and goiter and hyperthyroidism in 10 workers. Visual-motor reactions at the beginning and end of the working day were studied for 14 days in 17 gluers and 10 control machinists from the mechanical shop. The author stated that simple reaction, a complicated light differentiation reaction, and modifications of a complicated reaction were used; details of the tests were not given. The average values of the speeds of reaction were reported to have shown no substantial differences in the 2 groups before and after work. However, in the case of the complicated reaction, the majority of gluers made errors compared to no errors by the machinists. With the modified complicated reaction, 4 of 10 machinists made errors, but only at the end of the workday. Errors were committed by 15 of 17 gluers and the errors were committed both before and after work.

Animal Toxicity

(a) Toxicity Studies

In 1930, Sayers et al [42] exposed guinea pigs to ethylene dichloride to determine the acute effects resulting from a single exposure. The guinea pigs were exposed in groups of 3 or 6, for varying periods of time up to 8 hours. The exposure concentrations ranged from 600 to 60,000 ppm. The progression of pathological effects was observed by killing 1/3 of each group immediately after removal from the exposure chamber, 1/3 after 4 days, and 1/3 at the end of 8 days provided they did not die sooner. Control animals were also killed at these times. All the animals were killed by injecting 2 ml of saturated magnesium sulfate directly into the heart. Sayers [42] did not discuss gross or microscopic effects of ethylene dichloride on the heart.

The usual order of occurrence of signs of poisoning exhibited by the exposed animals were eye and nasal irritation manifested by squinting and lacrimation of the eyes and rubbing of the nose, apparent vertigo, static and motor ataxia, retching movements, apparent unconsciousness, incoordination of extremities, and marked changes in the respiration. [42]

Exposures at 60,000 ppm caused all these signs to occur in less than 10 minutes, and death in 30 minutes. Exposure at 10,000 ppm caused the signs to occur in 25 minutes with the possibility of death occurring a day or more following an exposure of 15-20 minutes. No signs of poisoning or deaths occurred following exposure at 1,200 ppm for 8 hours. In animals that died during exposure, congestion and edema of the lungs and generalized passive congestion throughout the visceral organs were found. [42]

Pulmonary congestion and edema and renal hyperemia were found in animals that died 1-8 days after the end of exposure. In animals killed immediately after exposure, there was congestion of the liver, spleen, lungs, and kidneys. In animals killed 3-4 days after exposure, the kidneys were hyperemic and the congestion and edema of the lungs were more pronounced than in those killed immediately after exposure. These conditions were partially resolved by 8 days after the end of exposure. Pulmonary involvement varied from mild congestion to actual scattered hemorrhages. [42] The severity of the pathological changes was proportional to the exposure time and concentration.

There was generalized visceral congestion, slight to moderate hepatic necrosis, and slight fatty degeneration of the renal tubular epithelium in the experiment reported in 1945 by Heppel et al [106] in rabbits, rats, and mice that died after exposure at 3,000 ppm ethylene dichloride for 7 hours. In addition to these effects, focal necrosis of the adrenal cortex, sometimes with hemorrhage, was found in guinea pigs exposed in the same experiment. In yet another exposure of guinea pigs at 3,000 ppm, Heppel et al [106] found fatty degeneration of the myocardium in 7 of the 8 animals. Single exposures at 3,000 ppm for 2-7 hours caused death of 75-100% of rabbits, guinea pigs, hogs, mice, and rats within 5 days. The 3 cats and 2 raccoons did not die from the exposure.

Hemorrhaging in the lungs, stomach, intestines, and adrenals, fatty degeneration of the myocardium, degenerative changes of the renal tubules, and congestion of the liver and intestines were common observations in rats, guinea pigs, rabbits, and dogs exposed at 1,500 ppm for 7 hours daily. Some animals of all exposed species had died after the first or

second exposure, and all exposed animals had died after 6 exposures except one rabbit and one dog. [106]

In 1946, Heppel et al [107] reported that most animals died when exposed at 1,000 ppm for 7 hours/day, 5 days/week. All 22 exposed mice died after a single exposure. One monkey died after 2 exposures and the other died after 32 exposures. Twenty of 26 rats, 5 of 6 rabbits, 36 of 41 guinea pigs, 2 of 6 dogs, and 2 of 6 cats died from exposure. The pathological changes were quite variable. In some rats and in the monkeys, there were degenerative changes in renal tubular epithelium, in 2 rats there was pulmonary congestion with focal extravasation of blood. Congestion and fatty metamorphosis of the liver were found in the 6 cats, and necrosis and fatty degeneration of the liver were found in the other. Focal myocarditis was found in one monkey and one dog. Chronic splenitis was present in all 26 rats. [107]

Mortality was also high in rabbits, guinea pigs, and rats exposed repeatedly 7 hours/day, 5 days/week for 177 days at 400 ppm by Heppel et al. [107] Pathological findings in animals that died or were killed were limited in number but varied widely, including pulmonary congestion in rats, and diffuse myocarditis and slight to moderate fatty degeneration of the liver, kidney, and heart in one rat. There was slight to moderate fatty degeneration of the liver and kidney in 5 guinea pigs, and slight fatty degeneration of the heart in two. Slight fatty metamorphosis of the livers was found in 5 dogs and of the kidney in one. [107]

Mortality in mice, rats, and guinea pigs continued to be high when the exposure concentration was reduced to 200 ppm for 7 hours/day, 5 days/week. [107] The 5 rabbits and 2 monkeys all survived 125 exposures, as

did 9 of 14 guinea pigs. Five of 12 Wistar strain rats survived 86 exposures and 4 of 12 Osborne-Mudd strain rats survived 28 exposures. Pathological findings were limited to pulmonary congestion in a few cases, fatty degeneration of the renal convoluted tubules in a rat, necrosis and hemorrhage into the liver and necrosis of the adrenal cortex in a guinea pig, and fine fat droplets in the liver and myocardium of both monkeys.

Thirty-nine rats and 16 guinea pigs were exposed at 100 ppm ethylene dichloride for 7 hours/day, 5 day/week for 4 months without any observed effects on clinical examination or at necropsy. [107]

Spencer et al [108] reported in 1951 on the results of a large number of single exposures of rats to ethylene dichloride. The exposure concentrations ranged from 200 to 20,000 ppm and the exposure times from 0.1 to 7 hours. No deaths were observed with exposure at 300 ppm for 7 hours. The authors [108] concluded that exposures at 300 ppm for 5.5 hours had adverse effects, but, from the way the data were presented, it is not possible to determine what these effects were. The authors [108] also concluded that a single exposure at 200 ppm for 7 hours had no adverse effects, but did not present the data from which this conclusion was reached.

Rats, guinea pigs, rabbits, and monkeys were exposed at 400 ppm ethylene dichloride 7 hours/day, 5 days/week for various periods. All female rats were killed by the 10th exposure and all males by the 40th exposure. All male guinea pigs were killed by the 10th exposure and all females by the 24th. One female and 2 male rabbits were exposed 165 times. The 2 monkeys were severely affected and were killed after 8 and 12 exposures. There were no pathological findings in the rabbits. Microscopic findings were slight cloudy swelling of the livers with a few

large fat vacuoles in rats and guinea pigs, and slight to moderate swelling of the renal tubular epithelium of the guinea pigs. The monkeys showed fatty degeneration of the liver and kidneys and increased plasma prothrombin time. [108]

Exposures of rats at 200 and 100 ppm were reported to be without effect. [108] Groups of 15 male and 15 female rats tolerated 151 exposures at 100 ppm. There was no evidence of adverse effects as judged by general appearance, behavior, mortality, growth, organ function, or blood chemistry at either exposure concentration.

Guinea pigs exposed 180 times at 200 and 100 ppm did not grow as well as the controls and had increased liver weight to body weight ratios. Other findings were normal. [108]

Hofmann et al [109] in 1971 reported one exposure of 4 cats, 4 rabbits, 10 guinea pigs and 10 rats at 500 ppm ethylene dichloride for 6 weeks. The exposures were for 6 hours/day, 5 days/week. A similar group of animals was also exposed at 100 ppm in the same way. At 500 ppm, 3 of the 4 rabbits died after 10-17 exposures; 9 of the 10 guinea pigs died after 4-14 exposures; the rats died after 1-5 exposures; all cats survived 30 exposures. At 100 ppm, there were no deaths.

At necropsy, dilated hearts were found in all cats and rabbits exposed at 500 ppm. Rats had hyperemia of the lungs and sometimes low grade edema. Fatty degeneration and necrosis of the myocardium, liver, kidney and adrenals were found in rats and guinea pigs. Blood urea rose to 114 mg/100 ml in cats. [109]

At 100 ppm, no pathologic changes were found at autopsy. One of the 4 rabbits showed a rise in blood urea and creatinine which the authors

[109] considered of doubtful relevance. The exposed cats did not grow as well as the control cats.

Groups of 10 rabbits were exposed at 3,000 ppm ethylene dichloride for 4 hours/day (acute exposures) and other groups of 10 were exposed at 3,000 ppm for 2 hours/day, 5 days/week for 90 days (chronic exposures). The results were presented in a series of reports in 1959 by Lioia et al [110, 111,112,114] and Guarino et al. [113] In acute exposures, no significant changes of the blood or bone marrow cells were found except for granulations in about 20% of the granulocytes. [110] In chronic poisoning there was constant anemia of varying degree accompanied by leukopenia and thrombocytopenia, and there was frequent hypoplasia of granuloblastic and erythroblastic parenchyma in the bone marrow. [110] Cytochemically, a reduction in leukolipids was found, but there was no change in polysaccharides, peroxidase, or ribonucleic acid. [111] Liver function tests showed a decrease in the albumin-globulin ratio, slightly elevated BSP retention, slightly elevated values in colloidal tests (cadmium and cholesterol), and normal Van den Berg and blood amino acid levels. [112] Histologically, congestive changes, vacuolar degeneration, and limited necrotic areas were found on microscopic examination of the livers and kidneys. [113] Kidney function was impaired as determined by creatinine clearance, portal blood flow, and glomerular filtration rate. [114]

Loscalzo et al [115] in 1959 reported a study of respiratory functions and arterial blood pressure changes during inhalation of a fatal concentration of ethylene dichloride and found a continual fall in blood pressure and the development of respiratory paralysis.

Dmitrieva and Kuleshov [116] studied the action of ethylene dichloride on 18 albino rats exposed at 1,235 ppm (5 mg/liter) over 3.5 months and reported their findings in 1971. Neither the number of exposures nor their duration and frequency were reported. Electroencephalograms of the animals were taken before exposure and once monthly during the exposure time. Silver and platinum electrodes were implanted in the skulls of the animals, and the assimilation of a rhythmic photic stimulus of constant intensity and pulse duration was the criterion for evaluation.

The EEG of animals exposed to ethylene dichloride showed a high degree of preservation of the frequency of rapid activity. The oscillation amplitude diminished progressively, the delta rhythm amplitude reached 50-70 μV (control values of delta rhythm were not given) and the beta rhythm amplitude decreased to 10-15 μV from 30-80 μV (amplitude of the control beta rhythm). The authors also noted loss of capacity to assimilate an imposed rhythm toward the end of the exposure. [116]

Andreuzzi and Capodaglio [117] reported in 1958 a study of the cardiovascular effects of acute inhalation to a fumigant insecticide containing 70% ethylene dichloride and 30% carbon tetrachloride at a concentration of 4,800 ppm in 8 rabbits. The responses of the cardiovascular system of intact animals was compared with those of heart-lung preparations from an additional group of 8 rabbits. The intact animals were sedated with pentobarbital (5 mg/kg), their tracheas were intubated, and artificial respiration was maintained during the experiment. The second group of 8 rabbits was anesthetized by injection of 0.1 g/kg of chloralose or 0.03 g of pentothal and ventilated in the same manner as the

first group. In these animals, a Sterling heart-lung preparation separated the heart and lung from the rest of the body. Ethylene dichloride was then administered to both groups of animals via a respiratory pump.

The cardiac output, measured in the heart-lung preparation, fell rapidly after the onset of exposure from 60 ml/minute to 20-30 ml/minute. In both groups of animals, there was a drop in blood pressure to a third of the preexposure value within one minute. The venous pressure increased simultaneously with the reductions in cardiac output and arterial pressure. After the initial drop in blood pressure, there was a continued gradual decrease to near zero in 4-6 minutes, and, in the heart-lung preparation, a gradual reduction in the systolic-diastolic pulse. In both groups of animals there were substantial ECG changes including arrythmias and changes in the repolarization phase (T wave). [117]

Since ethylene dichloride residues on grain feed can be a consequence of fumigation, Sykes and Klein [118] studied the accumulation of ethylene dichloride in cow milk and reported the results in 1957. The ethylene dichloride was administered in a solution of corn oil in the form of a sealed gelatin capsule. Five cows were used in the 22-day study. Two cows were fed ethylene dichloride equivalent to 100 ppm in the 7 kg of grain concentrate given daily, 2 cows were fed the equivalent of 500 ppm for the first 10 days of the study then 1,000 ppm for 12 days, and one cow served as a control. There was no reduction of appetite or milk production.

Seven milk samples were taken during the study period. In all experimental animals, the highest volumes of ethylene dichloride were found on the 2nd or 3rd sampling date, then the amounts in subsequent analyses gradually decreased. The concentrations of ethylene dichloride found in the milk are presented in Table III-3.

TABLE III-3

CONCENTRATIONS OF ETHYLENE DICHLORIDE IN COWS' MILK

	Ethylene dichloride concentrations, ppm	
Day	Diet	Milk*
3	100	0.13
	500	0.29
5	100	0.29
	500	0.23
9	100	0.25
	500	0.45
12	100	0.15
	1000	0.35
16	100	0.17
	1000	0.25
19	100	0.13
	1000	0.13
22	100	0.10
	1000	0.18

* Each value is the average for the 2 cows in each group.
Derived from Sykes and Klein [118]

The average control value was 0.06 ppm ethylene dichloride with a reported range of 0 to 0.10 ppm. The authors [118] found recovery of ethylene dichloride of 80% in the 1.5 ppm range and 90% in the 25-50 ppm range.

Sykes and Klein [118] also investigated the possibility that ethylene dichloride is degraded to a nonvolatile organic chlorine compound by the cow. No detectable amount of chloride could be found in milk from a cow fed 1,000 ppm ethylene dichloride for 12 days.

Specific studies of teratogenic properties of ethylene dichloride were not found in the literature. However, in the chronic exposure studies reported by Heppel et al, [107] 2 litters of guinea pigs were born during exposures of the parents to ethylene dichloride at 200 ppm. Three of the young guinea pigs were then subjected to 60 daily exposures at this concentration and survived. Fifteen of 16 female rats exposed to ethylene dichloride 7 hours/day, 5 days/week at 100 ppm became pregnant and some were bred twice. The young rats were exposed with their mothers after birth and their survival, growth and appearance were considered satisfactory by the investigators. [107] There was no mention of abnormalities in the offspring.

Other information relative to exposure of pregnant females comes from the reports of Alumot et al. [119,120] These investigators were concerned with ethylene dichloride residues in grain. Groups of rats and chickens were fed grain containing 250 or 500 ppm of ethylene dichloride. Because of the volatility of ethylene dichloride, the animals' consumption of ethylene dichloride was 60-70% of the nominal amounts.

Ethylene dichloride had a noticeable effect on egg production and egg weights of Leghorn chickens. Both experimental groups showed a persistent decrease in egg weights in the 3rd month of full laying activity and this continued to the end of the 2-year trial. Egg production was decreased in the group receiving 500 ppm ethylene dichloride mash. This began in the 4th month. The egg production was decreased because of both a decrease in the overall production rate and a decrease in the number of individual hens. [119] There were no effects on the fertility of the roosters, or of the eggs, or on hatchability.

Fertility tests with rats began after 6 weeks on the experimental diets and were conducted at intervals of about 2 months thereafter. [120] Seven fertility tests were made in the 2 years of the study. There was no adverse effect of the diets on the reproductive activity of either sex. Abnormalities in the offspring were not mentioned.

Rats and mice were fed ethylene dichloride as part of the National Cancer Institute bioassay program (EK Weisburger, written communication, January 1976). Male mice were fed 100 and 200 mg/kg and female mice received 150 and 300 mg/kg. Both male and female rats were fed 50 and 100 mg/kg. All feedings were 5 days/week for 78 weeks. At necropsy a few rats had tissue masses. No histopathological description was given, but most were reported as mammary tumors in the females. A few gross tumors were reported in the mice, but they were not further described.

(b) Metabolic Studies

Enzymatic dechlorination of ethylene dichloride was found to proceed slowly with an enzyme system prepared from rat liver by Heppel and Porterfield. [121] The enzyme system required activation by cyanide and either glutathione or cysteine, and was more active in nitrogen than oxygen. Using rabbit liver extracts, Bray et al [122] found less chloride liberated from ethylene dichloride after 4-24 hours of incubation than they found with any of the other 28 compounds they tested. These authors [122] were unable to conclude that the dechlorination was entirely enzymatic since they observed considerable dechlorination with most compounds without the liver extract. They [122] considered that the dechlorination reaction took place between the sulfhydryl compounds and the chlorine of the chlorinated compound. Van Dyke and Wineman [123] also found little

dechlorination of ethylene dichloride with their rat liver microsomal enzyme system which was active with 1,1-dichloroethane, 1,1,2-trichloroethane and 1,1,2,2-tetrachloroethane. This enzyme system required oxygen, NADPH, and small amounts of supernatant which was not glutathione.

A single oral dose of 4 mM/kg of ethylene dichloride to rats resulted in liver glutathione levels of 31-84% of control values when the rats were killed 2 hours later. [124] In this same experiment, it was found that 2-halogeno-ethanols were quite effective in reducing liver glutathione levels. 2-Chloroethanol at 0.67 mM/kg reduced the glutathione levels to 17% of control values. In an in vitro study, it was found that 2-chloroethanol reduced NAD in the presence of rat liver supernatant.

Bondi and Alumot [125] found that an enzyme system from the soluble supernatant from rat liver catalyzed a reaction between ethylene dichloride and glutathione to a small extent. The products of the reaction were S-(beta-hydroxyethyl)glutathione and S,S-ethylene-bis-glutathione. The quantitative study by Yllner [126] showed that these compounds could only be minor components of the metabolites.

Yllner [126] found that ethylene dichloride was metabolized by mice to monochloroacetic acid through 2-chloroethanol. Using carbon-14 labeled ethylene dichloride administered in oral doses of 0.05, 0.10, 0.14, and 0.17 g/kg, he found that about 95% of the dose was excreted in the first 24 hours. The percentage metabolized decreased with increasing dose. At 0.05 g/kg, 10.7% was excreted unchanged in the exhaled breath, and at 0.17 g/kg, 42.0% was excreted unchanged. The amount exhaled as carbon dioxide at the lower dose was 10.6% and at the higher dose, 4.2%. At the lower dose 71.3% of the administered radioactivity was recovered in the urine, and at the

Analysis of the urine radioactivity showed it to be distributed percentagewise among the metabolites as presented in Table III-4.

TABLE III-4

DISTRIBUTION OF RADIOACTIVITY AMONG ETHYLENE DICHLORIDE METABOLITES IN URINE

Metabolite	% Total Radioactivity
Monochloroacetic acid	16
S-Carboxymethylcysteine	45
Conjugated S-carboxymethylcysteine	3
Thiodiacetic acid	33
2-Chloroethanol	0.3
S,S'-Ethylene-bis-cysteine	0.9

Adapted from Yllner [126]

Yllner [126] also found that 2-chloroethanol was metabolized in vivo by mice to monochloroacetic acid, suggesting that the reaction with glutathione occurs after the monochloroacetic acid is formed.

Both 2-chloroethanol and monochloroacetic acid are several times more toxic than ethylene dichloride. [127-134] Dierker and Brown [128] determined that their fatal case had been exposed at about 300 ppm 2-chloroethanol for 2 hours. The symptoms at the end of the 2 hours were nausea and vertigo. Cyanosis, labored breathing, and rapid, irregular pulse developed and the patient died from respiratory failure 9 hours after the end of exposure. Autopsy findings were pulmonary edema, kidney and liver congestion, interstitial hemorrhages in the liver, engorgement of

blood vessels in the liver and kidneys, and parenchyma-cell damage in the renal tubules.

Bush et al [129] reported on 6 cases of chronic exposure to 2-chloroethanol, one of them fatal. Autopsy findings in the fatal case included severe fatty infiltration of the liver, marked edema of the brain, marked passive congestion and edema of the lung, dilation of the chambers of the right side of the heart, fatty degeneration of the myocardium, and petechial hemorrhages into the skin. The nonfatal cases experienced nausea, vomiting, and dizziness. Two of these were found to have a significant fall in blood pressure.

A 23-month-old male child died after drinking 1-2 ml of 2-chloroethanol. [130] After the ingestion, vomiting occurred immediately, cyanosis and respiratory difficulty developed, followed by convulsions, heart failure, and death 12 hours after ingestion. Autopsy findings included pulmonary edema and congestion, and petechiae in the subepicardium, thymus, and liver. Neither 2-chloroethanol nor monochloroacetic acid were found in the blood or tissues.

Exposure of rats at 2 ppm of 2-chloroethanol for 2 hours was not fatal in a single exposure but repeated exposure at this concentration caused paralysis in some rats and finally death. [131] Exposure at 7.5 ppm caused death within a short time.

The oral LD50 values of monochloroacetic acid were determined for rats, mice, and guinea pigs by Woodard et al [134] to be 76, 255, and 80 mg/kg body weight, respectively. Hayes et al [133] found an LD50 for rats of 108 mg/kg. These investigators [133] found that it was an uncompetitive inhibitor of acetate oxidation, that it did not significantly alkylate

sulfhydryl groups of cysteine in vitro, but that in vivo, total sulfhydryl concentration in rat liver and kidney was decreased at the LD90 doses. Brain and heart sulfhydryl values were not affected. Signs of toxicity included clonic and tonic convulsions, respiratory depression, and thirst.

No information on metabolism of ethylene dichloride by humans was found in the literature. The similarity of the human responses to exposure to ethylene dichloride and 2-chloroethanol and the pathologic findings after such exposures are not proof that ethylene dichloride is metabolized to 2-chloroethanol. With both compounds, the delay in onset of symptoms (Table XII-2) is indicative of metabolism to more toxic compounds. [128-130] Ethylene dichloride and 2-chloroethanol could share a common metabolic pathway to monochloroacetic acid with chloroacetaldehyde as an intermediate metabolite. (RA Van Dyke, written communication, February 1975)

McCann et al [135] tested the mutagenicity of ethylene dichloride, its metabolite chloroeacetic acid, and its possible metabolic intermediates, chloroethanol and chloroacetaldehyde, by their ability to revert a bacterial tester strain. Ethylene dichloride and 2-chloroethanol were described as weakly mutagenic compared to chloroacetaldehyde, which was hundreds of times more effective in causing reversions. Monochloroacetic acid showed no activity in the testing.

Correlation of Exposure and Effect

Ethylene dichloride has anesthetic properties but it was found to be too toxic to be used for this purpose. [32-35] Guinea pigs developed a state of unconsciousness in 0.5 hour with exposures of 4,000 and 4,500 ppm. [42] A monkey exposed at 4,500 ppm for 10 minutes became unable to

maintain itself on the perch of the cage. [42]

During a 7-hour exposure at 3,000 ppm, guinea pigs, rats, mice, and rabbits showed varying degrees of narcosis according to Heppel et al. [106] Spencer et al [108] considered that the inactivity or stupor and slowness of response to handling of rats exposed for up to 8 hours to a series of concentrations in the range of 300 to 3,000 ppm may have been due to toxic injury other than central nervous system depression.

Workers acutely poisoned by occupational exposure to ethylene dichloride developed symptoms indicative of central nervous system effects including headache, dizziness, feelings of drunkenness, and sometimes unconciousness. [74-77,80-82,86] In some cases workers who were not overcome during exposure became unconscious later. [81,86]

Because of the profound effects of other chlorinated hydrocarbons on the liver and kidneys, many of the clinical and epidemiologic studies with ethylene dichloride have been directed toward the detection of dysfunction and degeneration of these organs. Evidence of liver and kidney injuries have been noted following both ingestion and occupational exposure, as evidenced by increased serum bilirubin, [9,86] decreased blood glucose, [82] positive Takata-Ara tests, [9,86] tender and palpable liver, [9] and the presence in the urine of albumin, blood cells, and hyaline and granular casts. [86,102]

However, even repeated exposures at high concentrations in animals and accidental poisonings in humans produced only slight to moderate fatty degeneration in the liver and kidneys. [75,107,108] What was much more evident in these and other organs at autopsy was the hyperemia and

hemorrhaging into the tissues. [44,46,47,50,52,54,56,57,60,61,62,65, 66,68,75,76,77,81]

The effects of ethylene dichloride ingestion, vapor inhalation, and absorption through the skin were similar. Early signs of circulatory damage included bleeding into the visceral organs, [46,50,51,54,56,62,70], cyanosis, [46,50,52,54,55,57,59 60,65,75,81,84,86] and rapid and weak pulse. [46,50,52,56,59,74,81,84] Acute exposures, both by ingestion and inhalation, were often fatal. Death resulted from respiratory and circulatory failure, following a period of nausea, vomiting, and unconsciousness. Autopsies revealed hyperemia and hemorrhagic lesions in the stomach, intestines, heart, brain, liver, and kidneys. [46,47,49-52,54,56,57,59,61-62,64-66,70,72,73,75,76,81]

Disseminated intravascular coagulopathy (DIC) and hyperfibrinolysis were reported in 1969 by Martin et al [64] in a patient who had ingested ethylene dichloride. They first noticed prolonged bleeding from venipunctures 24 hours after the ingestion and then studied the clotting factors, finding a reduction in factors II, V, VII, and VIII and complete defibrination. Platelet count was low (14,300/cu mm), fibrinolysis was markedly increased, and proactivator levels were below 10% of normal. Autopsy examination revealed thrombi in the pulmonary arterioles and capillaries, and hemorrhages into the mucosa of the esophagus, stump of the stomach, rectum, subepicardial, subendocardial, and myocardial tissues.

A decrease in clotting factors II and V was also found by Schonborn et al [65] 5.5 hours after a person ingested ethylene dichloride. Yodaiken and Babcock [66] noted that 2 hours after a patient ingested ethylene dichloride the prothrombin time was increased and the clotting

ability of the blood continued to decrease. On the 4th day, all clotting factors except VIII were markedly decreased.

An absence of clots and intensely red, thick blood were among the autopsy findings in 2 workers following an acute occupational exposure. [75] Extensive subepicardial, subendocardial, and a few subpleural hemorrhages were also found.

Chronic occupational exposures have also resulted in ethylene dichloride intoxication. Repeated exposures have resulted in neurological changes, anorexia, nausea, vomiting, epigastric pain, irritation of the mucous membranes, possible liver and kidney dysfunction, and death. [88,90-98,105]

Cetnarowicz [9] investigated the possibility of ethylene dichloride poisoning in an oil refinery in Poland where the concentrations were in the range of 10-200 ppm. Ten workers employed in the centrifuge room, where 3 concentration measurements were 62, 64, and 200 ppm, complained of a burning sensation of the eyes and lacrimation. Six of the workers had dryness of the mouth, an unpleasant sweet aftertaste, dizziness, lassitude, sleepiness, nausea, vomiting, constipation, and loss of appetite. Three workers also complained of pain in the epigastrium. Of 6 workers employed in other sections of the plant, where concentrations ranged from 10 to 37 ppm, one worker complained of the above-mentioned symptoms.

Further clinical investigations showed liver tenderness upon palpation in 4 workers, epigastric pain in 7 persons, elevated urobilinogen levels in the majority of individuals, abnormal percentile distribution of white blood cells in 8 persons. Other abnormal findings included high serum bilirubin levels, elevated nonprotein nitrogen levels, diminished

amounts of albumin in the serum, elevated globulin levels, positive Takata-Ara tests, and delayed return to normal values in the glucose tolerance test.

Two reports [88,91] of years of experience with ethylene dichloride in Russia indicated that acute effects were found after exposure at 75-125 ppm. The symptoms of these acute effects included general weakness, headache, dizziness, vomiting (usually producing a trace of bile), and irritation of the skin and mucous membranes. When some workers experienced these signs and symptoms 2 or more times in a period of 2 to 3 weeks, fatalities resulted. However, there was no mention of the method of air sampling, of the number of people exposed, or the duration of exposure.

Byers [93] reported that delayed effects of ethylene dichloride, such as lassitude, nausea, vomiting, and abdominal pain, were experienced in the evening by workers exposed at 100 ppm or slightly higher for 7.5 hours daily. These effects were not completely alleviated when ventilation procedures reduced the ethylene dichloride concentration to 70 ppm.

Exposure conditions were more extensively described for the 2 cases of neurological involvement reported by Guerdjikoff. [97] These workers used a gas mask for the operation where higher ethylene dichloride concentrations were expected for 2-3 minutes about 10 times/day. In this operation, there was opportunity for occasional exposure if the mask was not worn properly. In another operation, the workers were exposed 3-4 times/day for 10 minutes each time at a concentration of about 120 ppm, and in another operation, they were exposed at a higher concentration for 10-15 minutes once/day. An estimate of the daily TWA for these workers was not made.

The workers developed sensory and motor problems during 6-9 months of exposure. [97] Anorexia, epigastric pains, fatigue, irritability, and nervousness appeared first after 3 weeks of exposure. Eventually each worker developed a difficulty in walking, trembling hands, and hyperhidrosis.

Heightened lability of the autonomic nervous system, diffuse red dermographism, increased hidrosis, fatigability, irritability, and insomnia were among the responses reported by Rosenbaum [88] in a group of 100 workers exposed to ethylene dichloride at less than 25 ppm for 6 months to 5 years.

Impairment of the central nervous system and increased morbidity, especially diseases of the liver and bile ducts, were found in workers chronically exposed to ethylene dichloride at concentrations below 40 ppm and averaging 10-15 ppm. [105]

An analysis of the data presented by the author indicated a TWA concentration of about 15 ppm (see Table XII-3 and Figures XII-1 and XII-2). There are reasons to suspect that this may be an overestimate of most of the workers' exposures. The author pointed out that an insignificant number of the workers were employed in disassembling the metal molds, washing the tanks, etc. During disassembly of the metal forms, the workers were inside the tanks where ethylene dichloride concentrations of about 45-52 ppm were found. These concentrations were included by the author in the array associated with gluing. The measurements were apparently not breathing zone measurements and the ventilation system was designed with the exhaust ducts on the floor. As a consequence, the author [105] found an average concentration of about 27 ppm near the gluing table, about 40

ppm at 1 meter from the floor, and about 6 ppm at 2 meters from the floor. From these considerations it would appear that a more realistic appraisal of the TWA exposures of the majority of workers is 10-15 ppm.

Ethylene dichloride was found in the milk of nursing women occupationally exposed at approximately 15.5 ppm for an unspecified time. [99] The concentrations of ethylene dichloride in the milk ranged from 0.54 to 0.64 mg %. Concentrations of about 14.5 ppm ethylene dichloride were found in the women's breath. Eighteen hours after exposure, the concentrations of ethylene dichloride in milk samples and breath were found to be 0.195-0.63 mg % and 2-4 ppm, respectively. This one report of ethylene dichloride concentrations in the milk of female workers is supported by one study of ethylene dichloride concentrations in the milk of cows fed 1.75 to 17.5 mg/kg (based on body weights of about 400 kg). Additional research on this subject is needed.

Brzozowski et al [104] considered that absorption of ethylene dichloride through the skin was primarily responsible for producing such symptoms as nausea, weakness, abdominal pain, irritation of the mucous membranes, and weakness in the agricultural workers they studied. The workers were exposed in the field at atmospheric concentrations of about 15 ppm. Exposures to about 60 ppm occurred during transfer of ethylene dichloride into buckets. The workers were exposed to direct contact with the liquid that was spilled in large quantities on their skin and clothes while carrying it to the field in open buckets and they used it to wash their skin.

Medical examinations were performed on 118 workers. Ninety of them had some positive findings, including conjunctival congestion, weakness,

reddening of the pharynx, bronchial symptoms, metallic taste in the mouth, headache, dermatographism, nausea, cough, liver pain, burning sensation of the conjunctiva, hastened pulse, and dyspnea after effort. The "hippuric acid Quick test" was used to measure liver dysfunction and was reported to be positive in 40 of 56 workers investigated. [104]

A mixture of 25% ethylene dichloride and 75% carbon tetrachloride is used for grain fumigation in the United States. There are no reports in the literature of poisoning from the use of this fumigant mixture. However, in Italy, where the proportions of ethylene dichloride and carbon tetrachloride are approximately reversed, there are many reports of fumigant intoxication. [78-80,85,102]

Experimental studies performed by Borisova [4,101] resulted in effects on the vascular and respiratory systems with short-term exposure at very low concentrations of ethylene dichloride. A 30-second exposure of 4 subjects at 1.5 ppm resulted in a temporary stenosis of the blood vessels in all 4 subjects. This reaction was generally more pronounced especially in the vessels of the fingers when the exposure was at 3 ppm.

Borisova [4,101] found that a 1-minute exposure at 1.5 ppm produced a change in the depth of breathing as indicated by an increase in the height of the wave of the spirogram.

Experimental exposures of animals have resulted in circulatory effects similar to those found in humans, including pulmonary congestion and edema with focal extravasation of blood, generalized congestion throughout the visceral organs, hyperemia, and hemorrhage into the lungs, stomach, intestines, liver, and adrenals. [42,106-109]

Guinea pigs were exposed at concentrations from 600 to 60,000 ppm ethylene dichloride for periods up to 8 hours by Sayers et al. [42] Congestion and edema of the lungs and generalized passive congestion of the visceral organs were found in animals that died during exposure at 30,000 or 60,000 ppm for 30-40 minutes. Pulmonary congestion and edema and renal hyperemia were found in animals exposed at concentrations greater than 1,200 ppm. No deaths or apparent symptoms resulted from 8-hour exposures at 1,200 ppm.

Pulmonary congestion and hemorrhage, generalized visceral congestion, hepatic necrosis, and slight fatty degeneration of the renal tubular epithelium were found by Heppel et al [106] in rabbits, rats, and mice that died from exposure at 3,000 ppm ethylene dichloride. Guinea pigs exposed at the same concentrations developed focal necrosis of the adrenal cortex, sometimes with hemorrhage, and fatty degeneration of the myocardium was found in 7 of 8 guinea pigs. Repeated 7-hour exposures at 1,500 ppm resulted in hemorrhage in the lungs, stomach, intestines, and adrenals, fatty degeneration of the myocardium, and congestion in the liver and intestines of rats, guinea pigs, rabbits, and dogs. [106]

Degenerative changes in the renal tubular epithelium, pulmonary congestion with focal extravasation of blood, congestion, hemorrhage and fatty changes in the liver, and focal myocarditis were among the effects noted by Heppel et al [107] after exposing various animals at 1,000 ppm for 7 hours/day, 5 days/week for up to 177 days. When the exposure concentration was lowered to 200 ppm, mortality remained high but only occasional pathological findings, varying from animal to animal, were observed. These included pulmonary congestion, fatty degeneration of the

renal convoluted tubules, necrosis and hemorrhage in the liver, necrosis of the adrenal cortex, and fine fat droplets in the liver and myocardium. [107]

Spencer et al [108] exposed a variety of animals at 400 ppm ethylene dichloride for 7 hours/day. One of 2 exposed monkeys died after 8 exposures and the other died after 12 exposures. Prothrombin time was increased and microscopic findings included fatty degeneration of the liver and kidneys.

No abnormal findings were observed grossly or microscopically in 2 male monkeys subjected to 148 7-hour exposures at 100 ppm ethylene dichloride in 212 days. [108]

Both male and female guinea pigs exposed at 100 ppm ethylene dichloride for as many as 162 7-hour exposures in 226 days had reduced growth rates and increased liver to body weight ratios compared to controls. Lung, heart, kidney, spleen, and testes organ weight to body weight ratios were normal. [108] Cats similarly exposed also had reduced growth rates. [109]

A summary of findings from animal exposures is presented in Table XII-4.

Ethylene dichloride was shown to be metabolized to monochloroacetic acid through 2-chloroethanol in mice. [126] Both of these compounds are more toxic than ethylene dichloride. [131,134] The signs of poisoning by 2-chloroethanol from both accidental and occupational exposures of humans and experimental exposures of animals are very similar to those resulting from ethylene dichloride poisoning. [127-131] This similarity of signs, symptoms, and microscopic findings provides evidence that the mechanism of

human poisoning from ethylene dichloride resides at least in part in its metabolic products. [124,131,133]

There were no reports found in the literature dealing directly with carcinogenic or teratogenic effects of ethylene dichloride.

A feeding study conducted by the National Cancer Institute (EK Weisburger, written communication, January 1976) showed that some female rats developed mammary tissue masses after receiving 50 and 100 mg/kg ethylene dichloride in their diet for 78 weeks. No statistical or histopathologic data were given concerning the tumors.

Ethylene dichloride and its known metabolic product, chloroacetic acid, showed low mutagenicity when tested by McCann et al [135] on a tester strain of bacteria. However, by comparison, the possible intermediate metabolites, chloroethanol and chloroacetaldehyde, were extremely potent mutagens.