

TECHNICAL BACKGROUND INFORMATION

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REPORT ON CARCINOGENESIS BIOASSAY OF 1,2-DICHLOROETHANE (EDC)

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Bioassay Results in Brief: In a carcinogenesis bioassay of the halogenated solvent 1,2-dichloroethane (ethylene dichloride, or EDC), oral administration of the compound produced cancers in rats and mice. In male rats, dosage with EDC caused forestomach cancers, hemangiosarcomas (vascularized cancers) of multiple organs, and subcutaneous fibromas (cancers beneath the skin). Female rats exposed to EDC developed mammary (breast) cancers--some in high-dose animals as early as the 20th week of the study. The chemical also caused breast cancers as well as uterine cancers in female mice, and respiratory tract cancers in both male and female mice.

Reasons for Bioassay: EDC is one of several chlorinated hydrocarbons, or halogenated solvents, selected for bioassay by the National Cancer Institute (NCI). The chemical is produced in large quantities, the major portion for use in manufacturing vinyl chloride monomer, which in turn is used in making polyvinyl chloride (PVC) plastic. There is considerable potential for human exposure in the workplace. Other industrial workers who may be exposed to EDC are those who make

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insecticides or antiknock agents, and who make or use metal degreasing compounds.

EDC also has been found as a contaminant in water and air. Because EDC is used as a soil and crop fumigant, agricultural workers are exposed to it. The general population may be exposed to EDC as a grain and food contaminant, through inhaling gasoline or exhaust fumes, and through contaminated water supplies. EDC also is used as an ingredient in cosmetics and as a food additive. It is highly toxic and potentially lethal when inhaled in large doses.

In the NCI effort to identify cancer-causing chemicals in the environment, approximately 300 chemicals are currently in long-term studies with laboratory animals, chiefly mice, rats and hamsters. The compounds under test include pesticides, pharmaceuticals, industrial chemicals, food additives, and naturally occurring substances. These studies provide data for use by Federal regulatory agencies, NCI research programs, other scientific and academic institutions, and for the information of the public.

The test series is directed by the Carcinogenesis Testing Program. The bioassay of 1,2-dichloroethane was conducted at Hazelton Laboratories America, Inc., Vienna, Virginia, initially under direct contract with NCI and later through the bioassay prime contractor, Tracor Jitco, Inc., Rockville, Maryland.

The Compound: EDC is a colorless, oily liquid with a chloroform-like odor. It is a source chemical from which other chemicals are made.

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These include vinyl chloride, methyl chloroform, vinylidene chloride, perchloroethylene, trichloroethylene (TCE), carbon tetrachloride, and the chlorofluorocarbons (Freon compounds). Formerly EDC was in extensive use as a commercial solvent and extraction solvent, but many of these applications have been taken over by methyl chloroform, TCE, and perchloroethylene--all made from EDC. EDC is used in making gasoline antiknock additives, although this use is declining as leaded gasolines are phased out. Other uses include metal degreasing and some textile drycleaning, for making adhesives, fumigating grain, and in paint removers. EDC may appear as a food additive as a result of its use to extract spices such as annatto, paprika and turmeric. Its use in cosmetics is reported to be limited to nail lacquers.

EDC was rated in the Condensed Chemical Dictionary as the sixteenth highest-volume chemical produced in 1975. Production is now estimated at about 10 billion pounds annually in the United States and, according to the Environmental Protection Agency (EPA), is projected to increase by about 4 percent annually through 1979. According to the National Occupational Hazard Survey conducted by the National Institute for Occupational Safety and Health (NIOSH), about 2 million workers are exposed to EDC annually in the United States, and of these, 33,675 receive full-time occupational exposure.

The Environmental Protection Agency estimates about 163 million pounds of EDC were lost into the environment through emissions in 1974.

In an EPA-sponsored study of surface waters near heavily industrialized areas, EDC was detected in 26 percent of the samples taken

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(53 of 204). The concentrations ranged from the detection limit of one part per billion (ppb) to a high of 90 ppb, found at a Pennsylvania site in the Delaware River Basin.

Toxicity in Animals and Humans: EDC can be taken into the body by ingestion, inhalation or skin absorption. By any of these means it can be highly toxic. Acute poisoning may cause headache, dizziness, feelings of drunkenness, loss of consciousness, internal bleeding, and death. Repeated exposures can bring on nausea, vomiting, stomach pain, irritated mucous membranes, loss of appetite, liver and kidney failure, and possible death. Numerous cases of EDC poisoning, both fatal and nonfatal, have been documented by the National Institute for Occupational Safety and Health. When EDC is ingested, the predominant characteristic is blood disorders, including clotting problems. With skin absorption or inhalation, the first effects are headache, weakness, eye irritation, cyanosis (blackening of skin), and nausea. EDC has been found in human milk and in the exhaled breath of nursing mothers who were exposed to the chemical.

Animal studies have demonstrated EDC effects similar to those in humans, including drowsiness, breathing difficulty, clotting disorders, and damage to liver, kidneys and adrenal glands.

Animals, Test Procedures, and Dosages: Osborne-Mendel rats and B6C3F1 mice were used for the study. Groups of 50 male and 50 female animals of each species were used for each of two dose levels of 1,2-dichloroethane mixed in corn oil and given orally through a stomach tube (gavage) five days per week.

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Groups of 20 mice and rats of each sex were placed on test as vehicle controls, and given corn oil alone in the same way and at the same times as dosed animals were given corn oil with EDC. In addition, 20 animals of each sex and each species were put on test as untreated controls, and were given neither corn oil nor EDC.

Short-term studies were made in order to establish the proper dose levels of EDC. The maximum tolerated dose sought was one that would demonstrate any cancer-causing potential of the chemical, but would not curtail the animals' lifespan or growth. This dose level would become the high dose for the test, while half this dose became the low dose.

EDC was administered to rats and mice for 78 weeks. Dosages were set at 100/mg/kg/day as high doses for both male and female rats, 50 mg/kg/day as the low dose. The initial high doses selected for mice were 150 mg/kg/day for males, 250 mg/kg/day for female mice. Low doses were 75 mg/kg/day for male mice, 125 mg/kg/day for female mice.

During the study, however, dosage adjustments were found necessary. At weeks seven and eight, dosages were increased for all animals, and later were reduced again for all groups except male mice. After the dosage periods, surviving animals were observed untreated until the termination date. Low-dose rats of both sexes were observed for 32 weeks. The last high-dose male rat died after 23 weeks of observation, and the last high-dose female rat after 15 weeks. All mice at both doses were observed for 12 or 13 weeks.

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Because of changes in EDC dosages, the net intakes of the test chemical were later calculated as time-weighted average doses. Thus, for high-dose male and female rats the time-weighted average (twa) dosage over the 78-week period was 95 mg/kg/day, and the low dose was 47 mg/kg/day. In male mice, the twa high dosage was 195 mg/kg/day, the low dose 97 mg/kg/day. Time-weighted average high dose in female mice was 299 mg/kg/day, low dose was 148 mg/kg/day.

During the test, animals were housed in temperature- and humidity-controlled, air-conditioned quarters. High standards of sanitation were maintained in housing, bedding, and feeding facilities. When placed on test, mice were about five weeks old, and rats were placed on test at approximately nine weeks of age.

The following tissues were taken from sacrificed mice and rats, and where possible from those found dead: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder and bile duct (in mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, brain, tunica vaginalis, uterus, mammary gland, and ovary.

Data Recording and Statistical Analysis: Data were recorded in the Carcinogenesis Bioassay Data System (CBDS), a computerized data system. Data Elements were those recommended by the International Union Against Cancer, and included details on the chemical, the animals, the design of the experiment, clinical observations, survival figures, animal

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weights, and individual pathology results for each animal. Data tables were prepared for statistical analysis. Final data are tabulated in a Carcinogenesis Technical Report.

Clinical Effects: As in other tests, doses of the test chemical were purposely set high, and just within toxic range. The purpose is to give maximum opportunity for development of cancer within the animal's lifespan, if the test chemical is capable of producing cancer.

Body weights of EDC-dosed rats were not significantly depressed when compared with vehicle control animals. Untreated controls, however, weighed more than other rat groups after the first six months of the study.

Body weights were not distinctly depressed in treated male mice or in low-dose females, when compared with both untreated and vehicle control animals. High-dose female mice began to show weight depression by the fifteenth week of the study.

Higher death rates could be related to EDC dosage in rats early in the study, and the difference in survival between high and low-dose rats was substantial after the first year. In mice, treated animals had earlier death rates only during the second year.

Pathology and Tumor Incidences: In rats, the types of cancer providing evidence for carcinogenicity of EDC were: squamous-cell carcinomas of the forestomach in 9 out of 50 (18 percent) high-dose males and in 3 of 50 (6 percent) low-dose males; hemangiosarcomas of the spleen in 6 of 49 (12 percent) low-dose male rats and in 2 of 49 (4 percent) of high-dose males; adenocarcinomas of the mammary gland in 18 of 50

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(36) percent) high-dose female rats; and subcutaneous fibromas in 6 of 50 (12 percent) high-dose male rats. High-dose female rats developed mammary gland cancers as early as the 20th week of dosage. Hemangiosarcomas occurred at lower rates in a variety of other body tissues in dosed animals, but no hemangiosarcomas at all were found in either male or female control animals. Forestomach cancers also were not found in control rats.

In mice, the cancers providing evidence for carcinogenicity of EDC were: mammary gland adenocarcinomas in 9 of 50 (18 percent) low-dose females and in 7 of 48 (15 percent) high-dose females, but in none of the control females; uterine adenocarcinomas in 4 of 47 (9 percent) high-dose female mice and in 3 of 49 (6 percent) low-dose females but in no controls; endometrial stromal sarcomas of the uterus in 3 of 47 (6 percent) high-dose and in 2 of 49 (4 percent) low-dose females but in no controls; and squamous cell carcinomas of the forestomach in 5 of 48 (10 percent) high-dose females, 2 of 50 (4 percent) low-dose females, but in only one control animal. In both male and female mice, alveolar-bronchiolar cancers were found at significant levels of 15 in 48 (31 percent) high-dose males and females alike, and in 7 of 50 (14 percent) low-dose females, but only in 1 in 47 (2 percent) low-dose males.

Other kinds of tumors of various organs and tissues occurred among all animal groups, with no distinct difference between the EDC-dosed and the untreated animals.

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