Environmental Health Criteria 176

1,2-DICHLOROETHANE (SECOND EDITION)

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The **International Programme on Chemical Safety** (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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ENVIRONMENTAL HEALTH CRITERIA FOR 1,2-DICHLOROETHANE

NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

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A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (Telephone No. 9799111).

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1. Summary

1.1 Identity, physical and chemical properties, and analytical methods

1,2-Dichloroethane (ethylene dichloride) is a synthetic chemical which is a colourless liquid at room temperature. It is also highly volatile, with a vapour pressure of 8.5 kPa (at 20 °C), and is soluble in water, with a solubility of 8690 mg/litre (at 20 °C). The log octanol/water partition coefficient is 1.76.

Analysis for 1,2-dichloroethane in environmental media is usually by gas chromatography, in combination with electron capture or flame ionization detection or mass spectrometry. Detection limits range from 0.016 to > 4 $\mu g/m^3$ in air, 0.001 to 4.7 μg/litre in water, and from 6 to 10 μg/kg in various foodstuffs.

1.2 Sources of human and environmental exposure

The principal use of 1,2-dichloroethane is in the synthesis of vinyl chloride monomer, and to a lesser extent in the manufacture of various chlorinated solvents. It is also incorporated into anti-knock gasoline additives (although this use is declining with the phase-out of leaded gasoline in some countries), and has been used as a fumigant. Total annual production of 1,2-dichloroethane in Canada in 1990 and the USA in 1991 was 922 and 6318 kilotonnes, respectively.

1.3 Environmental transport, distribution and transformation

The majority of 1,2-dichloroethane released to the environment is in emissions to air. It is moderately persistent in air; the estimated atmospheric lifetime is between 43 and 111 days. 1,2-Dichloroethane is transported to the stratosphere, where photolysis may produce chlorine radicals which may in turn react with ozone. Some 1,2-dichloroethane may be released in industrial effluents to the aquatic environment, from which it is removed rapidly by volatilization. 1,2-Dichloroethane may also leach to groundwater near industrial waste sites. It is not expected to bioconcentrate in aquatic or terrestrial species.

1.4 Environmental levels and human exposure

Mean concentrations of 1,2-dichloroethane in recent surveys of ambient air in non-source-dominated areas of cities range from 0.07 to 0.28 $\mu g/m^3$, while mean levels in residential indoor air are reported to range from < 0.1 to 3.4 $\mu g/m^3$. In drinking-water, mean concentrations are generally less than 0.5 μg/litre. 1,2-Dichloroethane has only rarely been detected in foodstuffs in recent surveys and, since it has low potential for bioaccumulation, food is unlikely to be a major source of exposure.

Based on estimates of mean exposure from various media, the predominant source of exposure to 1,2-dichloroethane by the general population is indoor and outdoor air, only minor amounts being contributed by drinking-water. Intake of 1,2-dichloroethane from food is probably negligible. The amount inhaled in ambient air may be greater in the vicinity of industrial sources.

1.5 Kinetics and metabolism in laboratory animals

1,2-Dichloroethane is readily absorbed following inhalation, ingestion or dermal exposure and is rapidly and widely distributed throughout the body. It is rapidly and extensively metabolized in rats and mice, with principally sulfur-containing metabolites being eliminated in the urine in a dose-dependent manner. Metabolism appears to be saturated or limited in rats at levels of exposure resulting in blood concentrations of 5 to 10 μg/ml. Levels of DNA alkylation were higher following exposure to a bolus dose by gavage than in the case of inhalation over a 6-h period.

1,2-Dichloroethane appears to be metabolized via two principal pathways; the first involves a saturable microsomal oxidation mediated by cytochrome P-450 to 2-chloroacetaldehyde and 2-chloroethanol followed by conjugation with glutathione. The second pathway entails direct conjugation with glutathione to form *S*-(2-chloroethyl)-glutathione, which may be non-enzymatically converted to a glutathione episulfonium ion; this ion can form adducts with DNA. Although DNA damage has been induced by the P-450 pathway *in vitro*, several lines of evidence indicate that the glutathione conjugation pathway is probably of greater significance than the P-450 pathway as the major route for DNA damage.

1.6 Effects on laboratory mammals and *in vitro* test systems

The acute toxicity of 1,2-dichloroethane is low in experimental animals. For example, inhalation LC_{50}s for rats exposed for 6 or 7.25 h ranged from 4000 mg/m³ to 6600 mg/m³, while oral LD_{50}s for rats, mice, dogs and rabbits ranged from 413 to 2500 mg/kg body weight.

The results of short-term and subchronic studies in several species of experimental animals indicate that the liver and kidneys are the target organs; reliable NOELs or LOELs were not attained in general due to inadequate documentation and the limited range of end-points examined in small groups of animals. In a series of early limited studies, morphological changes in the liver were observed in several species following subchronic exposure to airborne concentrations as low as 800 mg/m³. Increases in the relative liver weight have been observed in rats following subchronic oral administration of doses of 49 to 82 mg/kg body weight per day or more for 13 weeks. Little information was presented on non-neoplastic effects in available chronic studies. Changes in serum parameters indicative of liver and kidney toxicity were observed in rats exposed to airborne concentrations as low as 202 mg/m³ for 12 months, although histopathological examinations were not conducted in this study.

The carcinogenicity of 1,2-dichloroethane has been investigated in a few limited bioassays on experimental animals (limitations include short duration of exposure and high mortality). Significant increases were not reported in the incidence of any type of tumour in Sprague-Dawley rats or Swiss mice exposed to up to 607 mg/m³ for 78 weeks and observed until spontaneous death. Mortality was high in rats in this study, although it was not related to concentration, and the incidence rates were not adjusted for differential mortality among groups. There was a non-significant increase in the incidence of mammary gland adenomas and fibroadenomas in female Sprague-Dawley rats exposed to 200 mg/m³ for 2 years in an assay in which no other compound-related toxicity was observed.

In contrast, there was convincing evidence of increases in tumour incidence in two species following ingestion. Significant increases in the incidence of tumours at several sites (including squamous cell carcinomas of the stomach (males), haemangiosarcomas (males and females), fibromas of the subcutaneous tissue (males), adenocarcinomas and fibroadenomas of the mammary

gland (females)) were observed in Osborne-Mendel rats administered TWA daily doses of 47 or 95 mg/kg body weight per day by gavage for 78 weeks. Similar increases in the incidences of tumours at multiple sites (including alveolar/bronchiolar adenomas (males and females), mammary gland adenocarcinomas (females) and endometrial stromal polyp or endometrial stromal sarcoma combined (females) and hepatocellular carcinomas (males)) occurred in B6C3F1 mice administered TWA daily doses of 97 or 195 mg/kg body weight per day (males) or 149 or 299 mg/kg body weight per day (females) by gavage for 78 weeks.

The incidence of lung tumours (benign papillomas) was significantly increased in female mice following repeated dermal application of 1,2-dichloroethane for 440 to 594 days. Repeated intraperitoneal injections of 1,2-dichloroethane resulted in dose-related increases in the number of pulmonary adenomas per mouse in a susceptible strain, although none of these increases was significant. Concomitant exposure to inhaled 1,2-dichloroethane and disulfiram in the diet resulted in an increased incidence of intrahepatic bile duct cholangiomas and cysts, subcutaneous fibromas, hepatic neoplastic nodules, interstitial cell tumours in the testes and mammary adenocarcinomas in rats, compared to rats administered either compound alone or untreated controls. No potential to initiate or promote tumour development was evident in three bioassays, although the extent of histopathological examination was limited in these studies.

In *in vitro* assays, 1,2-dichloroethane has been consistently positive in mutagenicity bioassays in *Salmonella typhimurium*. Responses have been greater in the presence of an exogenous activation system (possibly due to activation by the cytochrome system) than in its absence, and mutagenicity was more than doubled in *S. typhimurium* expressing the human GSTA1-1 gene. In cultured mammalian cells, 1,2-dichloroethane forms adducts with DNA. It also induces unscheduled DNA synthesis in primary cultures of rodent and human cells and gene mutation in several cell lines. Mutation frequency in human cell lines has been correlated with differences in glutathione-*S*-transferase activity. In *in vivo* studies, 1,2-dichloroethane induced somatic cell and sex-linked recessive lethal mutations in *Drosophila melanogaster* and the compound bound to DNA in all reported studies in rats and mice. Although primary DNA damage in liver and sister chromatid exchange has been observed in studies in mice, there has been no evidence for micronucleus induction.

Based on the results of a limited number of studies, there is no evidence that 1,2-dichloroethane is teratogenic in experimental animals. There is also little convincing evidence that it induces reproductive or developmental effects at doses below those which cause other systemic effects. Available data on the immunotoxicity of 1,2-dichloroethane are limited.

7 Effects on humans

Acute incidental exposure to 1,2-dichloroethane by inhalation or ingestion has resulted in a variety of effects in humans, including effects on the central nervous system, liver, kidney, lung and cardiovascular system.

The potential carcinogenicity of 1,2-dichloroethane in exposed human populations has not been extensively investigated. Mortality due to pancreatic cancer was significantly increased in a group of workers at a chemical production plant who had been exposed principally to 1,2-dichloroethane (in combination with other chemicals). Mortality due to pancreatic cancer increased with duration of exposure. In addition, although the number of cases was small, and the association with duration of exposure was less consistent, mortality due to leukaemia was also increased in these workers. No association between occupational exposure to 1,2-dichloroethane and brain cancer was noted in a small case-control study. Although the incidence of colon and rectal cancer increased with the concentration of 1,2-dichloroethane in drinking-water in an inherently limited ecological study, concomitant exposure to other substances may have contributed to the observed effects.

8 Effects on non-target organisms in the laboratory and field

The effects of exposure to 1,2-dichloroethane on a number of other organisms in the laboratory and field have been investigated. For aquatic microorganisms, IC_{50}s or EC_{50}s for various end-points have been reported to range from 25 to 770 mg/litre. The lowest reported LC_{50} value for *Daphnia* was 220 mg/litre, while effects on reproductive success and growth were observed at 20.7 and 71.7 mg/litre, respectively. Based on available data, the most sensitive freshwater vertebrate species appears to be the northwestern salamander (*Ambystoma gracile*), in which 9-day larval survival (4 days post-hatch) was reduced at 2.54 mg/litre. Only limited data are available on the toxicity of 1,2-dichloroethane to terrestrial organisms.