WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Volume 60
Some Industrial Chemicals

Summary of Data Reported and Evaluation

Ethylene
Ethylene oxide
Propylene
Propylene oxide
Isoprene
Styrene
Styrene-7,8-oxide
4-Vinylcyclohexene
4-Vinylcyclohexene diepoxide
Vinyl toluene
Acrylamide
N-Methylolacrylamide
Methyl methacrylate
2-Ethylhexyl acrylate

Last updated: 13 April 1999

ETHYLENE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 60 (1994) (p. 45)
CAS No.: 74-85-1
Chem. Abstr. Name: Ethene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Ethylene, the petrochemical manufactured in largest volume worldwide, is produced primarily by the steam-cracking of hydrocarbons. It is used mainly as a chemical intermediate in the production of polymers and other industrial chemicals; small amounts are used to promote the ripening of fruits and vegetables. Ethylene is introduced into the environment from both natural and man-made sources, including emissions from vegetation, as a product of burning of organic material (such as cigarettes) and of incomplete combustion of fossil fuels, and in its production and use. Few data are available on levels of occupational exposure.

5.2 Human carcinogenicity data

The available data did not allow the Working Group to evaluate the carcinogenicity of ethylene to humans.

5.3 Animal carcinogenicity data

Ethylene was tested for carcinogenicity in one experiment in rats exposed by inhalation. No increase in tumour incidence was reported.

5.4 Other relevant data

Endogenous but unidentified sources of ethylene exist in man and experimental animals. Steady-state alveolar retention of ethylene is less than 10% in both man and rat. The biological half-time of ethylene in humans is about 0.65 h. In rats and man, the processes of uptake, exhalation and metabolism are described by first-order kinetics, at least up to 50 ppm; in rats, ethylene metabolism follows first-order kinetics up to about 80 ppm. The maximal rate of metabolism in rats is reached at about 1000 ppm, the initial metabolite being ethylene oxide; hydroxyethyl cysteine is a urinary metabolite in mice. Because ethylene metabolism can be saturated, the maximal possible concentration of ethylene oxide in rat tissues is about 0.34 nmol/ml (15 ng/g bw). Exposure to ethylene results in the formation of adducts with proteins. In nonsmokers, the background concentrations of the hydroxyethyl valine adduct of haemoglobin were 12-188 pmol/g haemoglobin. Environmental ethylene contributes to these concentrations; the endogenous contribution was calculated to be about 12 pmol/g haemoglobin in nonsmoking control subjects. The increment of N-terminal hydroxyethyl valine formed during a 40-h work week has been estimated as 100-120 pmol/g haemoglobin per part per million of ethylene. Tobacco smoke contributes to formation of this adduct: smoking 10-30 cigarettes/day was reported to result in 600-690 pmol/g haemoglobin. Background concentrations of 7-hydroxyethyl guanine were 8.5 nmol/g DNA in one study of human peripheral lymphocytes and ranged from 2 to 6 nmol/g DNA in various tissues of rats and mice. A single exposure of mice to 50 ppm ethylene for 1 h resulted in 0.1-0.2 nmol/g DNA. No data were available on the genetic and related effects of ethylene in exposed humans. In a single study, no micronuclei were induced in bone-marrow cells of mice and rats exposed *in vivo*. Gene mutation was not induced in *Salmonella typhimurium*. Although the genetic effects of ethylene have not been well studied, its metabolite, ethylene oxide, is genotoxic in a broad range of assays.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of ethylene.

There is *inadequate evidence* in experimental animals for the carcinogenicity of ethylene.

Overall evaluation

Ethylene is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 63)

Synonyms

- Acetene
- Bicarburetted hydrogen
- Elayl
- Olefiant gas

Last updated 08/26/1997

ETHYLENE OXIDE
(Group 1)

For definition of Groups, see Preamble Evaluation.

VOL.: 60 (1994) (p. 73)
CAS No.: 75-21-8
Chem. Abstr. Name: Oxirane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Ethylene oxide has been produced since the early 1900s, originally by the reaction of ethylene chlorohydrin with base and in recent years more commonly by catalytic oxidation of ethylene. It has been used as a chemical intermediate in the production of ethylene glycol, glycol ethers, nonionic surfactants and other industrial chemicals. Although much smaller amounts are used in sterilizing medical instruments and supplies in hospitals and industrially and for the fumigation of spices, it is during these uses that the highest occupational exposure levels have been measured.

5.2 Human carcinogenicity data

In epidemiological studies of exposure to ethylene oxide, the most frequently reported association has been with lymphatic and haematopoietic cancer. The populations studied fall into two groups - people using ethylene oxide as a sterilant and chemical workers manufacturing or using the compound. In general, people involved in sterilization are less likely to have occupational exposure to other chemicals.

Of the studies of sterilization personnel, the largest and most informative is that conducted in the USA. Overall, mortality from lymphatic and haematopoietic cancer was only marginally elevated, but a significant trend as found, especially for lymphatic leukaemia and non-Hodgkin's lymphoma, in relation to estimated cumulative exposure to ethylene oxide. For exposure at a level of 1 ppm [1.8 mg/m^3] over a working lifetime (45 years), a rate ratio of 1.2 was estimated for lymphatic and haematopoietic cancer. Three other studies of workers involved in sterilization (two in Sweden and one in the United Kingdom) each showed nonsignificant excesses of lymphatic and haematopoietic cancer.

In a study of chemical workers exposed to ethylene oxide at two plants in the USA, the mortality rate from lymphatic and haematopoietic cancer was elevated, but the excess was confined to a small subgroup with only occasional low-level exposure to ethylene oxide. Six other studies in the chemical industry (two in Sweden, one in the United Kingdom, one in Italy, one in the USA and one in Germany) were based on fewer deaths. Four found excesses of lymphatic and haematopoietic cancer (which were significant in two), and in two, the numbers of such tumours were as expected from control rates.

Because of the possibility of confounding occupational exposures, less weight can be given to the positive findings from the studies of chemical workers. Nevertheless, they are compatible with the small but consistent excesses of lymphatic and haematopoietic cancer found in the studies of sterilization personnel.

Some of the epidemiological studies of workers exposed to ethylene oxide show an increased risk for cancer of the stomach, which was significant only in one study from Sweden.

5.3 Animal carcinogenicity data

Ethylene oxide was tested for carcinogenicity in one experiment by oral administration in rats, in two

experiments by inhalation in mice and two experiments by inhalation in rats. It was also tested in single studies in mice by skin application and by subcutaneous injection.

In the experiment by intragastric intubation in rats, ethylene oxide produced tumours of the forestomach, which were mainly squamous-cell carcinomas. In one study in mice, inhalation of ethylene oxide resulted in increased incidences of alveolar/bronchiolar lung tumours and tumours of the Harderian gland in animals of each sex and of uterine adenocarcinomas, mammary carcinomas and malignant lymphomas in females. In a bioassay of pulmonary tumours in strain A mice, inhalation of ethylene oxide increased the number of pulmonary adenomas per mouse. In the two experiments in which rats of one strain were exposed by inhalation, ethylene oxide increased the incidences of mononuclear-cell leukaemia and brain tumours in animals of each sex and of peritoneal mesotheliomas in the region of the testis and subcutaneous fibromas in males. Ethylene oxide produced local sarcomas in mice following subcutaneous injection. In a limited study in mice treated by skin application, no skin tumours were observed.

5.4 Other relevant data

Inhaled ethylene oxide is readily taken up in man and rat, and aqueous ethylene oxide solutions can penetrate human skin. Ethylene oxide is uniformly distributed throughout the body of rats. Its half-life has been estimated as between 14 min and 3.3 h in the human body and about 6 min in rats. Exposure of rats to 5 ppm [9 mg/m^3] resulted in steady-state ethylene oxide levels in blood of 60 ng/g. Whole-body elimination of ethylene oxide from rats is described by first-order kinetics. It is excreted mainly in the urine as thioethers; at high doses, the proportion of thioethers is reduced, while the proportion of ethylene glycol increases. Rats conjugate ethylene oxide with glutathione to a greater extent than mice, while rabbits do not appear to be capable of this reaction.

Ethylene oxide was not teratogenic to rats or rabbits exposed by inhalation to concentrations up to 150 ppm [270 mg/m^3]. It was teratogenic to mice after intravenous injection in a single study. Surprisingly, brief exposure of dams around the time of fertilization to a high concentration (1200 ppm [2160 mg/m^3]) of ethylene oxide by inhalation induced teratogenic effects in mice. The effect was shown to be due to a direct action on the zygote.

Ethylene oxide forms adducts with proteins in both man and experimental animals and with DNA in experimental animals. Haemoglobin adducts have been used for biomonitoring, as there is a significant correlation between cumulative exposure over four months and levels of N-terminal hydroxyethyl valine in haemoglobin of exposed workers. The increment of hydroxyethyl valine adduct formed is about 3.5 pmol/g haemoglobin per ppm-h ethylene oxide. Higher proportions of hydroxyethyl histidine are formed. Hydroxyethyl haemoglobin adducts are also found in the absence of known exposure to ethylene oxide. Greater numbers of haemoglobin and DNA adducts occur per unit of exposure in rats and mice at high concentrations (> 33 ppm) than at lower concentrations. 7-Hydroxyethylguanine is quantitatively the most important DNA adduct formed. Its half-life varies from 1.0 to 6.9 days in mouse and rat tissues.

Studies of workers exposed to ethylene oxide in hospital and factory sterilization units and in ethylene oxide manufacturing and processing plants consistently showed chromosomal damage in peripheral blood lymphocytes, including chromosomal aberrations in 11 of 14 studies, sister chromatid exchange in 20 of 23 studies, micronuclei in three of eight studies and gene mutation in one study. Micronuclei were induced in the bone marrow of exposed workers in one study. In general, the degree of damage is correlated with level and duration of exposure. The induction of sister chromatid exchange appears to be more sensitive to exposure to ethylene oxide than is that of either chromosomal aberrations or micronuclei. In one study, chromosomal aberrations were observed in the peripheral lymphocytes of workers two years after cessation of exposure to ethylene oxide, and sister chromatid exchanges six months after cessation of exposure.

Chromosomal aberrations and sister chromatid exchange were induced in cynomolgus monkeys exposed to ethylene oxide. Ethylene oxide also induced gene mutation, specific locus mutation, sister chromatid exchange, chromosomal aberrations, micronuclei, dominant lethal mutation and heritable translocation in rodents treated *in vivo*. It induced unscheduled DNA synthesis, gene mutation, sister chromatid exchange and chromosomal aberrations in human cells and gene mutation, micronuclei, chromosomal aberrations and cell transformation in rodent cells *in vitro*.

Analogous genetic and related effects were observed in nonmammalian systems.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of ethylene oxide.

There is *sufficient evidence* in experimental animals for the carcinogenicity of ethylene oxide.

In making the overall evaluation, the Working Group took into consideration the following supporting evidence. Ethylene oxide is a directly acting alkylating agent that:

(i) induces a sensitive, persistent dose-related increase in the frequency of chromosomal aberrations and sister chromatid exchange in peripheral lymphocytes and micronuclei in bone-marrow cells of exposed workers;

(ii) has been associated with malignancies of the lymphatic and haematopoietic system in both humans and experimental animals;

(iii) induces a dose-related increase in the frequency of haemoglobin adducts in exposed humans and dose-related increases in the numbers of adducts in both DNA and haemoglobin in exposed rodents;

(iv) induces gene mutations and heritable translocations in germ cells of exposed rodents; and

(v) is a powerful mutagen and clastogen at all phylogenetic levels.

Overall evaluation

Ethylene oxide is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 205)

Synonyms

- Dihydrooxirene
- Dimethylene oxide
- 1,2-Epoxyethane
- Epoxyethane
- Ethene oxide
- EtO
- ETO
- Oxacyclopropane
- Oxane
- Oxidoethane

PROPYLENE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 60 (1994) (p. 161)
CAS No.: 115-07-1
Chem. Abstr. Name: 1-Propene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Propylene is a major chemical intermediate, produced by catalytic or thermal cracking of hydrocarbons or as a by-product of petroleum refining. It is used mainly in the preparation of alkylates for gasoline and in the production of polypropylene, acrylonitrile, propylene oxide and a number of other industrial chemicals. Propylene is introduced into the atmosphere from natural and man-made sources, including emissions from vegetation, burning of organic material and incomplete combustion of fossil fuels, and from its production and use. Few data are available on levels of occupational exposure.

5.2 Human carcinogenicity data

No relevant data were available to the Working Group.

5.3 Animal carcinogenicity data

Propylene was tested by inhalation in two studies in mice and in two studies in rats. A slight increase in the incidence of vascular tumours was observed in female mice in one study. In one study in rats, no treatment-related increase in tumour incidence was observed. In two studies in mice and rats exposed by inhalation, insufficient information was provided to allow an assessment of carcinogenicity.

5.4 Other relevant data

In rats exposed to 50 ppm propylene, about one-sixth of the inhaled material is absorbed, of which almost one-half is exhaled again, unchanged. The remainder is eliminated metabolically, through oxidation to propylene oxide, which is subsequently either conjugated with glutathione or, to a smaller extent, hydrated by epoxide hydrolase. Oxidation is a saturable reaction mediated by cytochrome P450 enzymes, whereas no saturation concentration has been identified for the hydration of propylene oxide. There is, therefore, a maximal attainable tissue concentration of propylene oxide in rats. Oxidation of propylene can occur in the rat nasal epithelium, where irritation, hyperplasia and metaplasia have been described after chronic exposure.

No data were available on the genetic and related effects of propylene in humans.

Alkylation products of the metabolite, propylene oxide, were found in haemoglobin and in DNA from mice exposed to propylene by inhalation. Although insufficient data are available to evaluate the genetic and related effects of propylene, its major metabolite, propylene oxide, is genotoxic in a broad range of assays.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of propylene.

There is *inadequate evidence* in experimental animals for the carcinogenicity of propylene.

Overall evaluation

Propylene is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of Groups, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 71)

Synonyms

- Methylethylene
- 1-Propylene

Last updated 08/26/1997

PROPYLENE OXIDE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 60 (1994) (p. 181)
CAS No.: 75-56-9
Chem. Abstr. Name: Methyloxirane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Propylene oxide is produced by dehydrochlorination of propylene chlorohydrin or by indirect oxidation of propylene. It is used primarily as a chemical intermediate to produce polyether polyols, propylene glycols and propylene glycol ethers. It is used to a lesser extent in the production of hydroxypropyl starch ethers, as a food additive and as a fumigant for certain dried fruits and nuts.

Occupational exposure occurs during the production of propylene oxide and its derivatives and during production of hydroxypropyl starch ethers.

5.2 Human carcinogenicity data

One case-control study provides information about cancer risk in relation to exposure to propylene oxide specifically but does not allow any firm conclusion regarding carcinogenicity.

5.3 Animal carcinogenicity data

Propylene oxide was tested by oral gavage in one study in rats, by inhalation in one study in mice and in three adequate studies in rats and by subcutaneous administration in one study in mice and in one study in rats. Propylene oxide administered by oral gavage to rats produced tumours of the forestomach, which were mainly squamous-cell carcinomas. In mice exposed by inhalation, propylene oxide produced haemangiomas and haemangiosarcomas of the nasal cavity and a few malignant nasal epithelial tumours. In a study in rats of each sex exposed by inhalation, papillary adenomas of the nasal cavity were observed in males and females and thyroid adenomas and carcinomas were found in females; in the second study, in males, papillary adenomas of the nasal cavity and an increased incidence of adrenal phaeochromocytomas were observed; in the third study, in females, increased incidences of mammary fibroadenomas and adenocarcinomas were observed. Subcutaneous administration of propylene oxide to mice produced local sarcomas; the study in rats was inadequate for evaluation.

5.4 Other relevant data

In rats exposed by inhalation, there is strong uptake of propylene oxide, which is then metabolized extensively and eliminated rapidly. Metabolism occurs predominantly by conjugation with glutathione. Propylene oxide can also be hydrolysed by epoxide hydrolase to 1,2-propanediol, which is subsequently metabolized to lactic and pyruvic acids. Propylene oxide forms adducts with proteins, including haemoglobin, in man, dog, rat and mouse. In mice, the concentration of the N-terminal valine adduct of propylene oxide in haemoglobin is linearly related to the administered dose. The alkylation efficiency in mice exposed by inhalation is about one-half that observed in rats and dogs.

In a seven-week study of rats exposed by inhalation, ataxia in the absence of muscular atrophy was observed, which was due to distal axonopathy in the central and peripheral nervous systems. Chronic and subchronic

exposure of rats to propylene oxide by inhalation induced proliferative lesions, irritation and toxicity in the nasal mucosa and respiratory epithelium.

Other than occasional reductions in fetal weight, no adverse effects on reproduction were observed in rats or rabbits exposed to propylene oxide at up to 500 ppm.

DNA adducts of propylene oxide are formed in various organs of mice, rats and dogs. Binding in mouse liver DNA was about one-twentieth that of ethylene oxide.

Dominant lethal mutations were not induced in rats or mice, and sperm abnormalities were not observed in mice exposed to propylene oxide *in vivo*. Micronuclei and, in single studies, chromosomal aberrations and sister chromatid exchange were induced in mouse bone marrow after intraperitoneal injection of propylene oxide. Neither sister chromatid exchange nor chromosomal aberrations were induced in monkeys exposed by inhalation to 300 ppm. Propylene oxide induced chromosomal aberrations and sister chromatid exchange in human lymphocytes and DNA damage, gene mutation, chromosomal aberrations and sister chromatid exchange in mammalian cells *in vitro*. It caused dominant lethal mutation in *Drosophila* and was mutagenic to yeast, fungi and bacteria.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of propylene oxide.

There is *sufficient evidence* in experimental animals for the carcinogenicity of propylene oxide.

Overall evaluation

Propylene oxide is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 328)

Synonyms

- Epoxypropane
- 1,2-Epoxypropane
- 2,3-Epoxypropane
- Methyloxacyclopropane
- Propene oxide
- Propylene epoxide
- 1,2-Propylene oxide

Last updated 08/26/1997

STYRENE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 60 (1994) (p. 233)
CAS No.: 100-42-5
Chem. Abstr. Name: Ethenylbenzene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Styrene has been produced since the 1920s by catalytic dehydrogenation of ethylbenzene. It is one of the most important monomers, worldwide, and finds major use in the production of polystyrene, acrylonitrile-butadiene-styrene resins, styrene-butadiene rubbers and latexes, and unsaturated polystyrene resins. Occupational exposure levels, measured both by air measurements and biological monitoring, have been highest in the manufacture of fibre glass-reinforced polyester products and lower in the production of styrene, polystyrene and styrene-based plastics and rubbers.

5.2 Human carcinogenicity data

Epidemiological studies of styrene have been done in three types of industry: production of glass-reinforced plastic products, production of styrene monomer and styrene polymerization and production of styrene-butadiene rubber. The malignancies observed in excess most frequently are of the lymphatic and haematopoietic system.

In a European multinational study of over 40 000 workers in the glass-reinforced plastics industry, no overall excess of deaths from lymphatic and haematopoietic cancers was observed in comparison with national controls. Within the cohort, the risks for these cancers were significantly related to average intensity of exposure and to years since first exposure but were not related to cumulative exposure.

A study of cancer incidence in the reinforced plastics industry in Denmark involved 12 800 male workers who had been included within the European multinational mortality study and a further 24 000 workers with lower probability of exposure to styrene. A nonsignificant overall increase in risk was seen for lymphatic and haematopoietic cancer. The increase was concentrated mainly in those workers not previously included in the international cohort, in short-term workers with at least 10 years since first employment and in those employed before 1970.

In a large study of the reinforced plastics industry in the USA, no overall increase in risk for lymphatic and haematopoietic cancer was seen, although a nonsignificant increase was found among workers with the highest exposure.

A study of chemical workers in the production of styrene and styrene derivatives in the USA found a nonsignificant association between exposure to styrene and lymphatic and haematopoietic cancers. A smaller study from the United Kingdom also found a nonsignificant association with cancers at this site but lacked detailed information on exposure.

A large cohort study of the styrene-butadiene rubber industry showed increased risks for lymphatic and haematopoietic malignancies, but a nested case-control analysis that evaluated exposure to both styrene and butadiene found no relationship with exposure to styrene. Two additional studies showed increased risks for lymphatic and haematopoietic cancers but provided little information on exposure to styrene.

Exposures to styrene are highest in the reinforced plastics industry, where less opportunity for confounding occurs than in the other industries studied. The two largest, most informative, but partly overlapping, studies of reinforced plastics manufacturers have certain features that are suggestive of a cancer hazard insofar as, in one, risk increased with average intensity of exposure and time since first exposure, and in the other risk was greatest in men employed at times when the highest exposures occurred. More importantly, however, they do not indicate an increase in risk with increasing cumulative exposure to styrene (as the excesses occurred mainly in short-term employees), and there is no overall increase in risk for lymphatic and haematopoietic cancer in studies of the reinforced plastics industry.

5.3 Animal carcinogenicity data

Styrene was tested for carcinogenicity in mice and rats by oral administration and in rats by inhalation exposure. Administration of styrene by gastric intubation resulted in a small increase in the incidence of pulmonary tumours in male mice and of hepatocellular adenomas in females and no increase in tumour incidence in rats. Prenatal exposure followed by postnatal gastric intubation of styrene resulted in a significant increase in the occurrence of pulmonary tumours in male and female mice of one strain and no increase in tumour incidence in rats. Exposure of rats to styrene by inhalation in one study was associated with an increase in the incidence of mammary tumours in females; however, because of limitations in the reporting of the data, the results of the study were considered to be inconclusive. Two studies by gastric intubation of a styrene/β-nitrostyrene mixture in mice and rats were of limited value for the evaluation.

5.4 Other relevant data

Styrene is absorbed by inhalation and dermal transfer in both man and rat. In man, 60-70% of inhaled styrene is absorbed. It is rapidly distributed throughout the body in treated rats. A large percentage of absorbed styrene is excreted as urinary mandelic and phenylglyoxylic acids, glutathione conjugates forming a minor fraction of the metabolites. Saturation of metabolic activation of styrene becomes apparent at concentrations above 200-300 ppm (850-1280 mg/m^3) in rats and mice, and above 100-200 ppm (430-850 mg/m^3) in humans. The dominant first metabolite is styrene-7,8-oxide, the formation of which appears to be catalysed in man principally by the cytochrome P450 isoenzyme CYP2B6 but also by CYP2E1 and CYP1A2. Isolated erythrocytes are also capable of nonenzymatic conversion of styrene to styrene-7,8-oxide. The amounts of styrene-7,8-oxide present in the blood of rats and mice exposed to styrene at concentrations below 100 ppm (430 mg/m^3) were about 5-20 fold greater than those in similarly exposed humans.

Exposure to styrene leads to the formation of both protein and DNA adducts in man, rat and mouse. The levels of the N-terminal valine adduct of haemoglobin, *N*-(1-hydroxy-2-phenylethyl)valine, have been found to be four times higher in styrene-exposed workers than in controls, and the levels of the DNA adduct, O^6-(2-hydroxy-1-phenylethyl)-2'-deoxy-guanosine-3'-monophosphate, have been found to be about five times higher than in controls.

Central and peripheral neurotoxicity have been described in workers, rats and rabbits exposed to styrene, but the mechanism has not been established.

No clear association was seen in a number of studies between occupational exposure of either mothers or fathers to styrene and the frequency of spontaneous abortions or congenital malformations. In rats and rabbits exposed to styrene at doses up to those that induce maternal toxicity, no adverse reproductive effect has been observed. Damage to seminiferous tubules and decreased sperm counts have been observed in male rats.

Some 25 studies on chromosomal aberrations, micronuclei and sister chromatid exchange have been performed in workers exposed to styrene in various countries and different industries. These have provided variable results with regard to the association between exposure to styrene and chromosomal damage. While clear dose-response relationships were not observed, those studies that showed effects were conducted in the reinforced plastics industry, where exposure to styrene is high; only one study was available on the styrene monomer and polystyrene manufacturing industries. Chromosomal aberrations were observed in 9 of 22, sister chromatid exchange in 3 of 12 and micronuclei in 3 of 11 studies.

The frequency of single-strand DNA breakage/alkali-labile sites was increased in workers exposed to styrene at less than 20 ppm (85 mg/m^3).

Chromosomal aberrations have not been seen in most studies in rodents, while several studies indicate weak induction of sister chromatid exchange in various tissues of rats and mice. Contradictory results have been obtained with regard to the induction of micronuclei in mice.

Significant increases have been observed consistently in the frequency of sister chromatid exchange and chromosomal aberrations in human lymphocytes *in vitro*. Most studies did not show mutation in bacteria, although mutation was seen in some studies in the presence of an exogenous metabolic activation system.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of styrene.

There is *limited evidence* in experimental animals for the carcinogenicity of styrene.

In making the overall evaluation, the Working Group took into consideration the following supporting evidence: Styrene is metabolized to styrene-7,8-oxide, which binds covalently to DNA and shows activity in various in-vitro and in-vivo assays for genetic effects. The genetic and related effects of styrene are therefore associated with its oxidation, which also occurs, e.g. in human whole blood cultures, where styrene induces dose-related responses of chromosomal damage at low concentrations. Styrene-7,8-oxide is detected in blood of workers exposed to styrene. Adducts in haemoglobin and DNA, DNA single-strand breaks/alkali-labile sites, as well as significant increases in the frequency of chromosomal damage have been found in workers exposed to styrene in the reinforced plastics industry. Positive results are associated with higher overall styrene levels and negative results with decreasing exposures to styrene. Although in human studies the role of other contaminants cannot be excluded, their occurrence is variable and their concentrations are very low in comparison with that of styrene.

Overall evaluation

Styrene is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 345)

Subsequent evaluation: Vol. 82 (2002)

Synonyms

- Cinnamene
- Phenethylene
- Phenylethene
- Phenylethylene
- Styrol
- Styrole
- Styrolene
- Vinylbenzene
- Vinylbenzol

Last updated 08/26/1997

STYRENE-7,8-OXIDE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 60 (1994) (p. 321)
CAS No.: 96-09-3
Chem. Abstr. Name: Phenyloxirane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Styrene-7,8-oxide is produced by cyclization of styrene chlorohydrin and by epoxidation of styrene with peroxyacetic acid. It is used mainly in the preparation of fragrances and as a reactive diluent in epoxy resin formulations. Few data are available on levels of occupational exposure to styrene-7,8-oxide. It has been detected in association with styrene, but at much lower levels, in industries where unsaturated polyester resins are used.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Styrene-7,8-oxide was tested for carcinogenicity in one experiment in mice and in two experiments in rats by oral gavage. It produced benign and malignant tumours of the forestomach in animals of each species and sex and induced hepatocellular tumours in male mice. It was also tested in one strain of rats by prenatal exposure followed by postnatal gastric intubation, producing benign and malignant tumours of the forestomach.

5.4 Other relevant data

Styrene-7,8-oxide is absorbed by rabbits and rats following its oral administration. In mice, the highest tissue concentrations are found in kidney, adipose tissue and blood. Styrene-7,8-oxide is hydrolysed rapidly in the acid environment of the stomach. Almost all of an administered dose of styrene-7,8-oxide is excreted in the urine of experimental animals. Styrene-7,8-oxide can be metabolized by epoxide hydrolase to the glycol or by glutathione *S*-transferase to glutathione conjugates. A small amount may be reduced to styrene. Styrene glycol is further metabolized to mandelic, phenyl glyoxylic and hippuric acids.

Styrene-7,8-oxide bound to histidine in haemoglobin and to cysteine in plasma proteins *in vitro*. Low levels of covalent binding to DNA were observed in the stomachs of orally dosed rats. In rat brain, it can decrease the activity of some neurotransmitters and monoamine oxidase, and it increases the availability of dopamine receptors. Glutathione *S*-transferase from human erythrocytes was inhibited by low concentrations of styrene-7,8-oxide.

No teratogenic effect was observed in rats or rabbits treated with doses of styrene-7,8-oxide up to the lethal level.

No data were available on the genetic and related effects of styrene-7,8-oxide in humans.

Both positive and negative results have been obtained with styrene-7,8-oxide for a variety of genetic end-points in vivo. Chromosomal aberrations and sister chromatid exchange were induced in mouse bone marrow

only after treatment with the S enantiomer and not with the R enantiomer. DNA damage, mutations and chromosomal aberrations have been observed consistently in mammalian and nonmammalian systems *in vitro*.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of styrene-7,8-oxide.

There is *sufficient evidence* in experimental animals for the carcinogenicity of styrene-7,8-oxide.

In making the overall evaluation, the Working Group took into consideration the following supporting evidence. Styrene-7,8-oxide:

(i) forms covalent adducts with DNA in humans, rats and mice;

(ii) induces gene mutation in bacteria and rodent cells *in vitro*;

(iii) induces chromosomal aberrations, micronuclei and sister chromatid exchange in human cells *in vitro*; and

(iv) induces chromosomal aberrations and sister chromatid exchange in mice *in vivo*.

Overall evaluation

Styrene-7,8-oxide is *probably carcinogenic to humans (Group 2A)*.

Previous evaluation: Suppl. 7 (1987) (p. 72)

For definition of the italicized terms, see Preamble Evaluation.

Synonyms

- 1,2-Epoxyethylbenzene
- 1,2-Epoxy-1-phenylethane
- Epoxystyrene
- α,β-Epoxystyrene
- Phenethylene oxide
- 1-Phenyl-1,2-epoxyethane
- Phenylethylene oxide
- 2-Phenyloxirane
- Styrene epoxide
- Styrene oxide
- Styryl oxide

Last updated 08/26/1997

4-VINYLCYCLOHEXENE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 60 (1994) (p. 347)
CAS No.: 100-40-3
Chem. Abstr. Name: 4-Ethenylcyclohexene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

4-Vinylcyclohexene is produced by catalytic dimerization of 1,3-butadiene. 4-Vinylcyclohexene has been used as a chemical intermediate for production of flame retardants, flavours and fragrances, in the manufacture of polyolefins, as a solvent and in the manufacture of its diepoxide. Low levels of occupational exposure have been measured during the production and use of 1,3-butadiene.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

4-Vinylcyclohexene was tested for carcinogenicity in one experiment in mice and in one experiment in rats by gastric intubation and in two skin application studies in mice. Administration of 4-vinylcyclohexene by gastric intubation produced granulosa-cell and mixed tumours of the ovary and adrenal subcapsular tumours in female mice. In male mice, there was an increase in the incidence of lymphoma and of lung tumours. Following gastric intubation in rats, increased incidences of squamous-cell tumours of the skin in males and of clitoral gland tumours in females were observed. The studies by skin application were inadequate for evaluation.

5.4 Other relevant data

4-Vinylcyclohexene is distributed mainly to adipose tissue in rodents. The ethylene carbons are eliminated mainly in urine and expired air. Metabolism primarily involves oxidation to 4-vinylcyclohexane-1,2-epoxide, which is formed 13 times faster by liver microsomes from mice and twice as fast by those from rats than by human microsomes. 4-Vinyl-1,2-epoxycyclohexane, 4-epoxyethylcyclohexene and, particularly, the diepoxide are more toxic to mouse oocytes than 4-vinylcyclohexene itself. Treatment with 4-vinylcyclo-hexene decreased the number of oocytes in mice but not in rats. The difference seemed to be due to the reduced ability of the rat to metabolize 4-vinylcyclohexene to epoxides.

No data were available on the genetic and related effects of 4-vinylcyclohexene in humans.

4-Vinylcyclohexene and its mono-epoxide metabolites were not mutagenic to *Salmonella typhimurium*. 4-Vinyl-1,2-epoxycyclohexane induced micronuclei but not hprt mutations in cultured Chinese hamster cells.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 4-vinylcyclohexene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 4-vinyl-

cyclohexene.

Overall evaluation

4-Vinylcyclohexene is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 73)

Synonyms

- 1-Vinyl-3-cyclohexene
- 4-Vinyl-1-cyclohexene

Last updated 08/26/1997

4-VINYLCYCLOHEXENE DIEPOXIDE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 60 (1994) (p. 361)
CAS No.: 106-87-6
Chem. Abstr. Name: 3-Oxiranyl-7-oxabicyclo[4.1.0]heptane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

4-Vinylcyclohexene diepoxide is produced by epoxidation of 4-vinylcyclohexene with peroxyacetic acid. It is used as a reactive diluent for other diepoxides and for epoxy resins. No data are available on levels of occupational exposure to 4-vinylcyclohexene diepoxide.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

4-Vinylcyclohexene diepoxide was tested for carcinogenicity by skin application in three studies in mice and in one study in rats. Skin application of 4-vinylcyclohexene diepoxide produced benign and malignant skin tumours in all studies in mice and in the study in rats. In one study in mice, it also increased the incidences of ovarian and lung tumours in females.

5.4 Other relevant data

4-Vinylcyclohexene diepoxide can be absorbed through the skin of rodents. Higher concentrations tend to be found in the ovary rather than in other organs, and virtually all elimination occurs via the urine. Its metabolism involves hydration to a mixture of glycols and conjugation with glutathione.

4-Vinylcyclohexene diepoxide is locally toxic and, when given orally, causes ovarian degeneration in both mice and rats and testicular degeneration in mice, as well as lesser effects in other organs.

No data were available on the genetic and related effects of 4-vinylcyclohexene diepoxide in humans.

4-Vinylcyclohexene diepoxide induced gene mutation, sister chromatid exchange and chromosomal aberrations but not micronuclei in mammalian cells *in vitro*. It was mutagenic in bacteria and caused gene conversion and mitotic crossing-over in *Saccharomyces cerevisiae*.

A metabolite of 4-vinylcyclohexene diepoxide, 4-epoxyethylcyclohexane-1,2-diol, was not mutagenic to *Salmonella typhimurium*.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 4-vinylcylcohexene diepoxide.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 4-vinyl-cyclohexene diepoxide.

Overall evaluation

4-Vinylcyclohexene diepoxide is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 63)

Synonyms

- 1,2-Epoxy-4-(epoxyethyl)cyclohexane
- 1-(Epoxyethyl)-3,4-epoxycyclohexane
- 3-(1,2-Epoxyethyl)-7-oxabicyclo[4.1.0]heptane
- Vinylcyclohexene diepoxide
- 4-Vinyl-1-cyclohexene diepoxide
- 4-Vinyl-1,2-cyclohexene diepoxide
- 4-Vinylcyclohexene dioxide
- 1-Vinyl-3-cyclohexene dioxide
- 4-Vinyl-1-cyclohexene dioxide

Last updated 08/26/1997

VINYL TOLUENE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 60 (1994) (p. 373)

CAS No.: 25013-15-4
Chem. Abstr. Name: Ethenylmethylbenzene

CAS No.: 611-15-4
Chem. Abstr. Name: 1-Ethenyl-2-methylbenzene

CAS No.: 100-80-1
Chem. Abstr. Name: 1-Ethenyl-3-methylbenzene

CAS No.: 622-97-9
Chem. Abstr. Name: 1-Ethenyl-4-methylbenzene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Vinyl toluene has been produced since the 1940s, as a mixture mainly of *meta* and *para* isomers, by dehydrogenation of *meta*- and *para*-ethyl toluene. It is used as a reactive monomer in the production of polymers and coatings. Few data are available on levels of occupational or environmental exposures to vinyl toluene.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Vinyl toluene (predominantly *para* isomer) was tested for carcinogenicity in one experiment in mice and one experiment in rats by intragastric intubation. The mixed isomers were tested in one experiment in mice and one experiment in rats exposed by inhalation. No increase in the incidence of tumours was observed in any of the experiments.

5.4 Other relevant data

Vinyl toluene is absorbed in rats exposed by inhalation; its neurotoxicity indicates that it is distributed to the brain in both man and rat. The vinyl moiety is first metabolized to form an epoxide, which is either conjugated with glutathione or further oxidized to a number of products, including carboxylic acids, which are conjugated with glycine. The methyl group can also be oxidized to a carboxylic acid and subsequently conjugated with glycine. Saturation of metabolic pathways in rats commences at a dose of 250 mg/kg bw.

No data were available on the genetic and related effects of vinyl toluene in humans.

Vinyl toluene induces sister chromatid exchange and chromosomal aberrations in cultured human lymphocytes and micronuclei in mouse bone-marrow cells *in vivo*.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of vinyl toluene.

There is *evidence suggesting lack of carcinogenicity* of vinyl toluene in experimental animals.

Overall evaluation

Vinyl toluene is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Synonyms for Ethenylmethylbenzene

- Methylstyrene
- Methylvinylbenzene
- Tolylethylene

Synonyms for 1-Ethenyl-2-methylbenzene

- 2-Ethenylmethylbenzene
- 2-Methylstyrene
- 1-Methyl-2-vinylbenzene
- 2- Vinyltoluene
- *ortho*-Vinyltoluene

Synonyms for 1-Ethenyl-3-methylbenzene

- 3-Ethenylmethylbenzene
- 3-Methylstyrene
- 1-Methyl-3-vinylbenzene
- 3-Vinyltoluene
- *meta*-Vinyltoluene

Synonyms for 1-Ethenyl-4-methylbenzene

- 4-Ethenylmethylbenzene
- 4-Methylstyrene
- 1-Methyl-4-vinylbenzene
- 1-*para*-Tolylethene
- 4-Vinyltoluene
- *para*-Vinyltoluene

Last updated 08/26/1997

ACRYLAMIDE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 60 (1994) (p. 389)
CAS No.: 79-06-1
Chem. Abstr. Name: 2-Propenamide

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Acrylamide has been produced since the 1950s by hydration of acrylonitrile. It is used mainly to produce water-soluble polyacrylamides used as flocculents for clarifying drinking-water, for treating municipal and industrial waste waters and as flow control agents in oil-well operations. Other major uses of acrylamide are in soil stabilization, in grout for repairing sewers and in acrylamide gels used in biotechnology laboratories. The major routes of exposure at the workplace appear to be dermal absorption of acrylamide monomer from solution and inhalation of dry monomer or aerosols of acrylamide solution. Exposure occurs during acrylamide and polyacrylamide manufacture, during acrylamide grouting and during laboratory preparation of polyacrylamide gels.

5.2 Human carcinogenicity data

Two cohort mortality studies were conducted among workers exposed to acrylamide. The first showed no significant excess of cancer but suffered from small size, short duration of exposure and short latency. In the other study, in one Dutch and three US plants, a nonsignificant increase was seen in deaths from pancreatic cancer, but there was no trend with increasing exposure.

5.3 Animal carcinogenicity data

Acrylamide was tested for carcinogenicity in one experiment in rats by oral administration. It increased the incidences of peritoneal mesotheliomas found in the region of the testis and of follicular adenomas of the thyroid in males and of thyroid follicular tumours, mammary tumours, glial tumours of the central nervous system, oral cavity papillomas, uterine adenocarcinomas and clitoral gland adenomas in females. In screening bioassays, acrylamide, given either orally or intraperitoneally, increased both the incidence and multiplicity of lung tumours in strain A mice.

Acrylamide was also tested as an initiating agent for skin carcinogenesis after oral, intraperitoneal and topical administration to mice of one strain and after oral administration to mice of another strain, followed by topical treatment with 12-*O*-tetradecanoylphorbol 13-acetate. It induced a dose-related increase in the incidence of squamous-cell papillomas and carcinomas of the skin in all four experiments.

5.4 Other relevant data

In occupational settings, acrylamide is taken up both through the skin and by inhalation. Damage to both the central and peripheral nervous systems has been reported on several occasions in exposed humans and has been thoroughly studied in animals.

Acrylamide is metabolized *in vitro* and *in vivo* in mice, rats and humans to the epoxide, glycidamide. Both substances are equally distributed throughout the tissues and have half-lives of about 5 h in rats; acrylamide itself has also been shown to be uniformly distributed between tissues in several other species. The

conversion of acrylamide to glycidamide is saturable, ranging from 50% at very low doses to 13% at 100 mg/kg bw in treated rats. Both agents are detoxified by glutathione conjugation, and glycidamide is also detoxified by hydrolysis. Both agents react directly with haemoglobin in vivo, but DNA adducts result only from the formation of glycidamide.

The presence of haemoglobin adducts of acrylamide was correlated with neurotoxicity in a group of highly exposed workers.

Acrylamide was not teratogenic to rats or mice after oral treatment of dams with doses up to the toxic level. It causes testicular atrophy, with damage to spermatids and mature spermatozoa. Reduced sperm motility, impaired fertility and dominant lethal mutations at the spermatozoa stage have also been reported in mice and rats. A single study in rats provides evidence that the testicular damage is not secondary to neurotoxicity, since testicular damage but not neurotoxicity was induced by injection of the reactive epoxide, glycidamide.

The genotoxicity of acrylamide has been studied extensively. It induces gene mutation, structural chromosomal aberrations, sister chromatid exchange and mitotic disturbances in mammalian cells *in vitro* in the presence or absence of exogenous metabolic systems. It induces structural chromosomal aberrations *in vivo* in both somatic and germ-line cells. Chromosomal aberrations and micronuclei were induced in mouse bone marrow and in premeiotic and postmeiotic cells. Treatment with acrylamide *in vivo* also caused somatic mutation in the spot test, heritable translocation and specific locus mutations in mice and dominant lethal mutations in both mice and rats in several studies. Acrylamide induces unscheduled DNA synthesis in rat spermatocytes *in vivo* but apparently not in rat hepatocytes; glycidamide induced unscheduled DNA synthesis in rat hepatocytes in one study *in vitro*. Acrylamide induces transformation in cultured mammalian cells. It does not induce mutation in bacteria, but glycidamide does in the absence of an exogenous metabolic system. Acrylamide induces sex-linked recessive lethal and somatic mutations in *Drosophila*.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of acrylamide.

There is *sufficient evidence* in experimental animals for the carcinogenicity of acrylamide.

In making the overall evaluation, the Working Group took into consideration the following supporting evidence:

(i) Acrylamide and its metabolite glycidamide form covalent adducts with DNA in mice and rats.

(ii) Acrylamide and glycidamide form covalent adducts with haemoglobin in exposed humans and rats.

(iii) Acrylamide induces gene mutations and chromosomal aberrations in germ cells of mice and chromosomal aberrations in germ cells of rats and forms covalent adducts with protamines in germ cells of mice *in vivo*.

(iv) Acrylamide induces chromosomal aberrations in somatic cells of rodents *in vivo*.

(v) Acrylamide induces gene mutations and chromosomal aberrations in cultured cells *in vitro*.

(vi) Acrylamide induces cell transformation in mouse cell lines.

Overall evaluation

Acrylamide is *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 56)

Synonyms

- Acrylic acid amide
- Acrylic amide
- Ethylenecarboxamide
- Propenamide
- Propenoic acid amide
- Vinyl amide

Last updated 08/26/1997

N-METHYLOLACRYLAMIDE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 60 (1994) (p. 435)
CAS No.: 924-42-5
Chem. Abstr. Name: *N*-(Hydroxymethyl)-2-propenamide

5. Summary of Data Reported and Evaluation

5.1 Exposure data

N-Methylolacrylamide is a bifunctional monomer used in the production of thermoplastic polymers and as a cross-linking agent in adhesives and binders for paper products and textiles. No data were available on occupational exposure to this compound.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

N-Methylolacrylamide was tested by oral gavage in one experiment in mice and one experiment in rats. In mice, it increased the incidences of Harderian gland adenomas, hepatocellular adenomas and carcinomas and alveolar-bronchiolar lung adenomas and carcinomas in animals of each sex and the incidence of benign granulosa-cell tumours of the ovary in females. In rats, no increase in tumour incidence was observed.

5.4 Other relevant data

N-Methylolacrylamide is absorbed by rats and mice after oral administration; no information was available regarding dermal application or inhalation. *N*-Methylolacrylamide administered to rats intravenously was distributed rapidly in body water; its distribution in tissues and subcellularly is similar to that of acrylamide. *N*-Methylolacrylamide reacts with glutathione, protein sulfhydryls and haemoglobin at rates similar to those of acrylamide, but it is not known if it is converted to acrylamide or an epoxide. Neurotoxicity developed in rats and mice exposed subchronically to *N*-methylolacrylamide.

No data were available on the genetic and related effects of *N*-methylolacrylamide in humans.

N-Methylolacrylamide did not induce micronuclei in mouse bone marrow in vivo but did induce chromosomal aberrations in Chinese hamster ovary cells *in vitro* and weakly increased the frequency of sister chromatid exchange. It was not mutagenic to *Salmonella typhimurium*.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of *N*-methylolacrylamide.

There is *limited evidence* in experimental animals for the carcinogenicity of *N*-methylolacrylamide.

Overall evaluation

N-Methylolacrylamide is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Synonyms

- *N*-MAM P
- *N*-Methanolacrylamide
- Monomethylolacrylamide
- NMA

Last updated 08/26/1997

METHYL METHACRYLATE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 60 (1994) (p. 445)
CAS No.: 80-62-6
Chem. Abstr. Name: 2-Methyl-2-propenoic acid, methyl ester

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Methyl methacrylate is produced mainly by a process based on the reaction of acetone with hydrogen cyanide. It is an important monomer used mainly in the production of acrylic sheeting, moulding powders and resins and surface coatings. Occupational exposures have been measured during its production and during its use in polymers, as a component of surgical bone cement, in denture fabrication and during the preparation of artificial fingernails.

5.2 Human carcinogenicity data

A large mortality study was conducted of workers in acrylic sheet manufacture in two US plants. A significant increase in mortality from colon cancers was seen in one plant and a nonsignificant increase in the other; a nonsignificant increase in mortality from rectal cancer was found in the first plant. The increases were most evident among workers employed during the earliest production period and in jobs entailing the highest exposure. Exposure was predominantly to methyl methacrylate, but workers were also exposed to ethyl acrylate and to volatile by-products of the polymerization process.

Another US study examined the mortality of workers employed in methyl methacrylate manufacture and polymerization and found no significant increase in the number of cancer deaths.

5.3 Animal carcinogenicity data

Methyl methacrylate was tested for carcinogenicity in one experiment in mice and one experiment in rats exposed by inhalation. No significant treatment-related increase in tumour incidence occurred. One study in rats by oral administration was inadequate for evaluation.

5.4 Other relevant data

Methyl methacrylate can be absorbed through the skin and is rapidly metabolized in man. In rats, it is first hydrolysed, and the dominant metabolic pathway is to fully oxidized carbons which are exhaled as carbon dioxide; a very small proportion is excreted as thioethers in the urine. Methyl methacrylate produces a number of toxic effects in man and experimental animals.

Exposure of mice and rats to methyl methacrylate by inhalation had no adverse reproductive effects.

No data were available on the genetic and related effects of methyl methacrylate in humans.

It caused chromosomal aberrations in rat bone marrow but did not induce micronuclei in mouse bone marrow *in vivo*. Gene mutation, sister chromatid exchange, micronuclei and chromosomal aberrations were induced in mammalian cells *in vitro*. Methyl methacrylate did not cause reverse gene mutation in bacteria but induced forward gene mutation in Salmonella typhimurium in a single study in the presence of an exogenous metabolic

activation system.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of methyl methacrylate.

There is *evidence suggesting lack of carcinogenicity* of methyl methacrylate in experimental animals.

Overall evaluation

Methyl methacrylate is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 66)

Synonyms

- 2-(Methoxycarbonyl)-1-propene
- Methyl 2-methylacrylate
- Methyl 2-methyl-2-propenoate
- MMA

Last updated 08/26/1997

2-ETHYLHEXYL ACRYLATE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 60 (1994) (p. 475)
CAS No.: 103-11-7
Chem. Abstr. Name: 2-Propenoic acid, 2-ethylhexyl ester

5. Summary of Data Reported and Evaluation

5.1 Exposure data

2-Ethylhexyl acrylate is produced by acid-catalysed esterification of acrylic acid with 2-ethylhexanol. Its major uses are in pressure-sensitive adhesives, in resins for latex paints and paper coatings and in the finishing of textiles. Occupational exposure to 2-ethylhexyl acrylate has been reported during its production and use.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

2-Ethylhexyl acrylate was tested by skin application in three experiments in mice. It increased the incidence of squamous-cell carcinomas of the skin in two experiments and of malignant melanomas in one experiment. In the third experiment, in a different strain of mice, 2-ethylhexyl acrylate did not increase skin tumour incidence, with or without subsequent application of 12-*O*-tetradecanoylphorbol 13-acetate.

5.4 Other relevant data

2-Ethylhexylacrylate is rapidly metabolized in rats; a small proportion is exhaled as carbon dioxide within 24 h, and a small proportion is excreted as thioethers in urine. No data were available on the genetic and related effects of 2-ethylhexylacrylate in humans. There is very little evidence for or against its genotoxicity in experimental systems.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of ethylhexyl acrylate.

There is *limited evidence* in experimental animals for the carcinogenicity of ethylhexyl acrylate.

Overall evaluation

Ethylhexyl acrylate is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Synonym

- 2-Ethylhexyl 2-propenoate

Last updated 08/26/1997