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Volume 71
Re-Evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide

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Vinylidene fluoride

Last updated: 8 April 1999

ACRYLONITRILE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 43)

CAS No.: 107-13-1
Chem. Abstr. Name: 2-Propenenitrile

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Acrylonitrile is a monomer used in high volume principally in the manufacture of acrylic fibres, resins (acrylonitrile–butadiene–styrene, styrene–acrylonitrile and others) and nitrile rubbers (butadiene–acrylonitrile). Other important uses are as an intermediate in the preparation of adiponitrile (for nylon 6/6) and acrylamide and, in the past, as a fumigant. Occupational exposures to acrylonitrile occur in its production and use in the preparation of fibres, resins and other products. It is present in cigarette smoke and has been detected rarely and at low levels in ambient air and water.

5.2 Human carcinogenicity data

The potential carcinogenicity of acrylonitrile in occupationally exposed populations has been investigated in several epidemiological studies. Studies carried out in the 1970s and 1980s suggested a possible increased risk of lung cancer among workers exposed to acrylonitrile. However, these were inconclusive because of one or more of the following actual or potential problems: small sample sizes, insufficient length of follow-up, incompleteness of follow-up, inadequate exposure assessment, potential confounding by other occupational carcinogens, and potential confounding by smoking. Consequently, larger and better studies were undertaken, in most cases building upon the same cohorts that had previously been assembled. Four such studies (two in the United States, one in the United Kingdom and one in the Netherlands) were carried out and these now provide the most relevant, informative data on which to base an evaluation. All of the studies made some attempt to establish exposure levels, although for the British study, this was rather cruder than for the others. The two studies from the United States were carried out in similar industries, but the range of cumulative exposure values was quite different between the two, raising questions about the inter-study comparability of methods of exposure assessment. The four studies employed different strategies for comparing exposed with unexposed. While the British study used a classic SMR comparison with national rates, the Dutch study did the same, but also compared the exposed with a different unexposed cohort. One of the studies from the United States compared the exposed with national rates and with rates of mortality and incidence in other plants of the same large company. The other compared the exposed with workers in the same plants who were unexposed to acrylonitrile. Typically, in each study, a number of analyses were carried out, varying comparison groups and other parameters.

There was no significant excess risk for any type of cancer when all exposed workers were compared with unexposed, or with an external comparison population. Further, when the study subjects were subdivided by levels of exposure (cumulative exposure when feasible), for no site but lung was there any hint that risk increased with exposure. For lung cancer, there was an indication that workers with the highest exposures had relative risk estimates greater than 1.0. This finding was strongest in the largest of the studies, which had one of the most intensive exposure assessment protocols, but the other studies gave either negative or only weakly supportive results. Even in the largest study (where the relative risk in the highest exposure quintile ranged from 1.2 to 1.7 depending on the parameters in the analysis), the finding was not consistently statistically significant; there was no coherent dose–response pattern throughout the range of exposures and the risk in the highest decile of exposure was lower than that in the second highest decile. On balance and

given the largely unsupportive findings from the other studies, the evidence from this one study was not considered to be sufficiently strong to conclude that there was a credible association between acrylonitrile and lung cancer. Thus, the earlier indications of an increased risk among workers exposed to acrylonitrile were not confirmed by the recent, more informative studies.

5.3 Animal carcinogenicity data

Acrylonitrile has been tested for carcinogenicity in one study in rats by inhalation with pre- and postnatal exposure. This study confirmed the findings of increased incidences of glial cell tumours of the central nervous system found in several previous studies that had not been fully reported and also found increases in malignant mammary tumours, Zymbal gland carcinomas, benign and malignant hepatocellular tumours and extrahepatic angiosarcomas.

5.4 Other relevant data

Acrylonitrile forms adducts with proteins and glutathione. It also forms DNA adducts *in vitro*, but only after cytochrome P450 bioactivation, most likely through its epoxide metabolite (cyanoethylene oxide), which is also formed *in vivo*. Acrylonitrile–haemoglobin adducts have been detected in exposed workers.

Both acrylonitrile and cyanoethylene oxide can conjugate with glutathione, leading to detoxification of these reactive compounds. At high doses of acrylonitrile, as used in animal studies, glutathione in certain tissues may be depleted. Such glutathione depletion will probably not occur at low-level human exposure.

Acrylonitrile is mutagenic *in vitro*; in *Salmonella* systems, bioactivation (to cyanoethylene oxide) is required, but in *Escherichia coli* and in rodent systems, bioactivation by an added microsomal system is not required. The results of genotoxicity experiments *in vivo* have in most cases been negative, although acrylonitrile is mutagenic in *Drosophila*.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 19 (1979) (Acrylonitrile and copolymers); Suppl. 7 (1987)

Synonyms

- AN
- Cyanoethylene
- Propenenitrile
- VCN
- Vinyl cyanide

1,3-BUTADIENE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 109)

Butadiene

CAS No.: 106-99-0
Chem. Abstr. Name: 1,3-Butadiene

Diepoxybutane

CAS No.: 1464-53-5
Chem. Abstr. Name: 2,2′-Bioxirane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

1,3-Butadiene is a monomer used in high volume in the manufacture of a wide range of polymers, including styrene–butadiene rubber, polybutadiene, nitrile rubber, acrylonitrile–butadiene–styrene resins and styrene–butadiene latexes. It is also an intermediate in the production of various other chemicals.

Occupational exposure to 1,3-butadiene occurs in the production of monomeric 1,3-butadiene and of 1,3-butadiene-based polymers and 1,3-butadiene-derived products. The mean full-shift, time-weighted average exposure levels measured for workers in these industries have usually been below 10 ppm [22 mg/m^3], although that level may be exceeded during some short-term activities. Recent data from monomer extraction and styrene–butadiene rubber plants showed lower average concentrations (< 5 ppm [< 11 mg/m^3]. 1,3-Butadiene is not usually found at detectable levels in workplace air during manufacture of finished rubber and plastic products.

The general population may be exposed to very low levels of 1,3-butadiene due to its occurrence in engine exhausts and cigarette smoke.

5.2 Human carcinogenicity data

One cohort study of workers in the United States who manufactured 1,3-butadiene monomer showed a moderate and significant excess of lymphohaematopoietic cancers based on 42 deaths. Persons employed before 1950 were especially at increased risk, but there was no convincing association with a cumulative exposure score. A total of 13 leukaemia cases only slightly and insignificantly contributed to the excess of the lymphohaematopoietic cancers.

A small cohort study of 1,3-butadiene production workers showed a significant excess of lymphosarcoma and reticulosarcoma, based on four cases. There was also an excess of stomach cancer, although represented by only five cases. Two leukaemia cases were found: this was slightly more than expected.

Several reports have been published on follow-up of styrene–butadiene rubber workers at eight plants in the United States and Canada. The most recent follow-up showed a consistent excess of leukaemia and a

significant dose–response relationship with cumulative exposure to 1,3-butadiene, which remained after adjustment for exposure to styrene.

Evaluation of the human carcinogenicity of 1,3-butadiene hinges on evidence regarding leukaemia risks from one large and well conducted study and two smaller studies. The smaller studies neither support nor contradict the evidence from the larger study. The larger, United States–Canada study shows that workers in the styrene–butadiene rubber industry experienced an excess of leukaemia and that those with apparently high 1,3-butadiene exposure had higher risk than those with lower exposure. The evidence from this study strongly suggests a hazard, but the body of evidence does not provide an opportunity to assess the consistency of results among two or more studies of adequate statistical power. Further, while 1,3-butadiene was a major exposure in this cohort, there were others, and it remains possible that even if there is an increased risk of cancer in the styrene–butadiene rubber industry, it may be due to occupational exposures other than 1,3-butadiene.

5.3 Animal carcinogenicity data

1,3-Butadiene was tested for carcinogenicity by inhalation exposure in four experiments in mice and one experiment in rats.

In the studies in mice, tumours were induced in multiple organs at all exposure concentrations studied, ranging from 6.25 to 1250 ppm [13.8–2760 mg/m^3]. The tumours induced included malignant lymphomas and heart haemangiosarcomas. Neoplasms at multiple organ sites were induced in mice after as little as 13 weeks of exposure at exposure levels of 625 ppm.

In one inhalation study in rats, 1,3-butadiene increased the incidence of tumours at several sites. The tumour increases were mainly in organs in which tumours develop spontaneously. The response was seen mainly at 8000 ppm [17 700 mg/m^3].

The initial metabolite of 1,3-butadiene, 1,2-epoxy-3-butene, yielded equivocal results in carcinogenicity tests, whereas the subsequent metabolite, 1,2:3,4-diepoxybutane, was carcinogenic to mice and rats when administered by skin application or by subcutaneous injection.

5.4 Other relevant data

1,3-Butadiene is metabolized in experimental animals and human liver microsomes to epoxide metabolites, initially 1,2-epoxy-3-butene and subsequently 1,2:3,4-diepoxybutane, by cytochrome P450. The epoxides can be inactivated by epoxide hydrolase and glutathione *S*-transferases. Adducts formed by reaction of 1,2-epoxy-3-butene and 3,4-epoxy-1,2-butanediol with haemoglobin and urinary mercapturic acids derived from 1,2-epoxy-3-butene have been detected in 1,3-butadiene-exposed workers. There are significant species differences in the metabolism of 1,3-butadiene both *in vitro* and *in vivo*. The in-vitro data are consistent with modelled and measured concentrations of 1,2-epoxy-3-butene and 1,2:3,4-diepoxybutane in 1,3-butadiene-exposed mice and rats. In these animals, blood and tissue levels of 1,2-epoxy-3-butene are several times higher in mice than in rats and those of 1,2:3,4-diepoxybutane up to 100 times higher in mice than in rats. There is considerable interindividual variability in the ability of human liver microsomes to metabolize 1,3-butadiene and 1,2-epoxy-3-butene *in vitro.* Mechanistic data suggest that the much higher carcinogenic potency of 1,3-butadiene in mice than in rats results predominantly from the high burden of 1,2:3,4-diepoxybutane.

The haemoglobin-binding index of 1,2-epoxy-3-butene can be considered as a dose surrogate for this metabolite; corresponding haemoglobin-binding indices have been published for mouse and rat. Haemoglobin-binding indices in occupationally exposed humans have also been estimated. In agreement with model predictions, these data demonstrate binding indices for 1,3-butadiene-exposed humans more than one order of magnitude lower than those in exposed rats.

There are conflicting results on whether 1,3-butadiene increases *hprt* mutations in lymphocytes from 1,3-

butadiene-exposed humans compared with non-exposed controls. Sister chromatid exchanges, micronuclei, chromosomal aberrations and DNA strand breaks were not significantly elevated above control levels in peripheral blood lymphocytes of occupationally exposed workers. 1,3-Butadiene induced DNA adducts and damage in both mice and rats *in vivo*, although the damage was significantly greater in mice than in rats. 1,3-Butadiene is mutagenic in virtually all test systems both *in vitro* and *in vivo*. Where a direct comparison between rats and mice could be made for the same end-point, positive effects were observed primarily in mice.

Activated K-*ras* oncogenes have been detected in lymphomas and in liver and lung tumours induced in mice by 1,3-butadiene. Mutations in the *p53* tumour-suppressor gene have been detected in mouse lymphomas.

1,2-Epoxy-3-butene was directly mutagenic in bacteria and induced gene mutations, chromosomal aberrations and sister chromatid exchanges *in vivo* in rodents. Micronuclei were induced in both somatic and germ cells of mice and rats *in vivo*. It induced gene mutations and sister chromatid exchanges in cultured human lymphocytes but did not induce unscheduled DNA synthesis, micronuclei or chromosomal aberrations in mouse or rat cells *in vitro.*

1,2:3,4-Diepoxybutane is a potent bifunctional alkylating agent which reacts with DNA *in vitro* and *in vivo*. As a result, it is mutagenic in virtually all test systems including effects in somatic and germ cells of mammals exposed *in vivo*. *In vivo*, it induced DNA adducts, dominant lethal mutations and gene mutations in mice; chromosomal aberrations and sister chromatid exchanges in Chinese hamsters and mice; and micronuclei in splenocytes and spermatids of rats and mice. It induced gene mutations, chromosomal aberrations and sister chromatid exchanges in human and mammalian cell cultures. In one study, 1,2:3,4-diepoxybutane induced DNA–DNA cross-links in murine hepatocytes *in vitro*. It induced somatic and sex-linked recessive lethal mutations, chromosomal deletions and heritable translocations in *Drosophila.* Gene mutations were induced in bacteria in the mouse host-mediated assay and *in vitro*. 1,2:3,4-Diepoxybutane also induced bacterial prophage and DNA repair.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of 1,3-butadiene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,3-butadiene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,2:3,4-diepoxybutane.

Overall evaluation

1,3-Butadiene is *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Butadiene: Vol. 39 (1986); Suppl. 7 (1987); Vol. 54 (1992); diepoxybutane: Vol. 11 (1976); Suppl. 7 (1987)

Synonyms

Butadiene

- Biethylene
- Bivinyl
- 1,3-Butadiene
- Buta-1,3-diene
- α,γ-Butadiene

- *trans*-Butadiene
- Divinyl
- Erythrene
- Pyrrolylene
- Vinylethylene

Diepoxybutane

- Butadiene dioxide
- 1,2:3,4-Diepoxybutane

Last updated: 12 April 1999

CHLOROPRENE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 227)

CAS No.: 126-99-8
Chem. Abstr. Name: 2-Chloro-1,3-butadiene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Chloroprene is a monomer used almost exclusively for the production of polychloroprene elastomers and latexes. It readily forms dimers and oxidizes at room temperature. Occupational exposures occur in the polymerization of chloroprene and possibly in the manufacture of products from polychloroprene latexes.

Although few data are available on environmental occurrence, general population exposures are expected to be very low or negligible.

5.2 Human carcinogenicity data

The risk of cancer associated with occupational exposure to chloroprene has been examined in two well conducted studies, one in the United States and one in Russia. These investigations do not indicate a consistent excess of cancer at any site.

5.3 Animal carcinogenicity data

Chloroprene was tested for carcinogenicity in two studies in mice, in two studies in rats and in one study in hamsters, all by inhalation with samples of purity > 99%. Exposure of mice to chloroprene produced lung tumours in one study in which the lung was the only organ examined. In another study in mice, chloroprene produced neoplasia in the lung, circulatory system, Harderian gland, mammary gland, liver, kidney, skin, mesentery, forestomach and Zymbal gland. In one study in rats, chloroprene caused increased incidences of tumours of the oral cavity, thyroid gland, lung, mammary gland and kidney. In another study in a different strain of rats, the incidence of mammary tumours was increased in high-dose females only when mammary tumours of all types were combined. No increase in neoplasia was seen in hamsters.

5.4 Other relevant data

The observation of excretion of mercapturates of chloroprene indicates that glutathione conjugation occurs in rats.

Genetic toxicity assays with chloroprene may often have been complicated by impurities derived either from added stabilizers or from degradation and polymerization products. Consequently, positive and negative results have been reported for most assays, and it is notable that, often, the negative results were obtained using the higher dose levels of chloroprene.

5.5 Evaluation

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

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

Overall evaluation

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

Previous evaluations: Vol. 19 (1979) (Chloroprene and polychloroprene); Suppl. 7 (1987)

Synonyms

- 2-Chlorobutadiene
- β-Chloroprene

Last updated: 8 April 1999

DICHLOROMETHANE
(Group 2B)

VOL.: 71 (1999) (p. 251)

CAS No.: 75-09-2
Chem. Abstr. Name: Dichloromethane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Dichloromethane is used principally as a solvent, in paint removers, degreasers and aerosol products, and in the manufacture of foam polymers. Widespread exposure occurs during the production and industrial use of dichloromethane and during the use of a variety of consumer products containing dichloromethane. Substantial losses to the environment lead to ubiquitous low-level exposures from ambient air and water.

5.2 Human carcinogenicity data

Seven cohort studies have examined the risk of cancer among populations exposed to dichloromethane. Two studies observed an excess of pancreatic cancer, but the three others which reported on this tumour did not. One study observed an excess of liver and biliary tract cancers among longer-term employees. One study observed an excess of prostate cancer that appeared to increase with level of exposure. One study observed an excess of breast cancer and gynaecological cancers among women with the highest likelihood of exposure and another study observed an excess of cervical cancer. With the exception of the prostate cancer excess observed in one study, all the excesses were based on small numbers. No estimates of exposure levels were available for two of the six studies.

Three case–control studies have examined the risk of cancer associated with dichloromethane exposure and provided data adequate for evaluation. One observed an association between estimated intensity, probability and duration of exposure and the risk of astrocytic brain tumours. A second, which focused on female breast cancer, observed an elevated risk in the highest exposure category but no association with probability of exposure. The third indicated an increased risk of rectal cancer and possibly lung cancer.

For no type of cancer was there a sufficiently consistent elevation of risk across studies to make a causal interpretation credible.

5.3 Animal carcinogenicity data

Dichloromethane was tested by oral administration in the drinking-water in one study in mice and one study in rats, by inhalation exposure in two studies in mice, three studies in rats and one study in hamsters and by intraperitoneal injection in a lung adenoma assay in mice. In the study in mice by oral administration, no increase in tumour incidence was observed. The study in rats by oral administration gave inconclusive results. In the two inhalation studies in mice, increased incidences of benign and malignant lung and liver tumours were observed in both sexes. In the three inhalation studies in rats, the incidence of benign mammary tumours was increased in one study in females of a strain in which the incidence of spontaneous mammary tumours is low, and the multiplicity was increased in two studies in females of a high-incidence strain. In one study, in males, the incidence of mammary gland adenomas and fibroadenomas was increased. Negative results were obtained in the lung adenoma test in mice and in the inhalation study in hamsters.

5.4 Other relevant data

Two dose-dependent alternative pathways involving cytochrome P450 and glutathione *S*-transferases are responsible for the metabolism of dichloromethane in human and rodent cells.

Dichloromethane is consistently mutagenic in microorganisms. Weaker and less consistent responses are seen in mammalian systems, predominantly in mice, both *in vitro* and *in vivo*.

It induced sister chromatid exchanges, chromosome breakage and chromosome loss *in vitro* in human cells. In-vitro results in rodent cells were inconclusive or negative.

Dichloromethane induced DNA single-strand breaks in mammalian cell cultures, but inconclusive or negative effects were reported for induction of gene mutations. It did not induce unscheduled DNA synthesis either *in vivo* in rodents or in human fibroblast cultures. It was genotoxic in fungi but not in *Drosophila* in the sex-linked recessive lethal assay.

Mechanistic studies have established a link between glutathione *S*-transferase-mediated metabolism of dichloromethane and its genotoxicity and carcinogenicity in mice. The glutathione *S*-transferase responsible for the metabolism of dichloromethane is expressed to significantly greater extents in mouse tissues than in rat, hamster or human tissues.

The available data suggest a plausible mechanism for the development of liver and lung tumours which occur in mice but not in rats exposed to dichloromethane.

5.5 Evaluation

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

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

Overall evaluation

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

Previous evaluations: Vol. 20 (1979); Vol. 41 (1986); Suppl. 7 (1987)

Synonyms

- Methane dichloride
- Methylene bichloride
- Methylene chloride
- Methylene dichloride

Last updated: 12 April 1999

ACETALDEHYDE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 319)

CAS No.: 75-07-0
Chem. Abstr. Name: Acetaldehyde

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to acetaldehyde may occur in its production, and in the production of acetic acid and various other chemical agents. It is a metabolite of sugars and ethanol in humans and has been detected in plant extracts, tobacco smoke, engine exhaust, ambient and indoor air, and in water.

5.2 Human carcinogenicity data

An increased relative frequency of bronchial and oral cavity tumours was found among nine cancer cases in one study of chemical workers exposed to various aldehydes. Oesophageal tumours have been associated with genetically determined, high metabolic levels of acetaldehyde after drinking alcohol.

Three case–control studies assessed the risk of oral, pharyngeal, laryngeal and oesophageal cancer following heavy alcohol intake, according to genetic polymorphism of enzymes involved in the metabolism of ethanol to acetaldehyde (alcohol dehydrogenase 3) and in the further metabolism of acetaldehyde (aldehyde dehydrogenase 2 and glutathione *S*-transferase M1). Despite limitations in the study design and the small size of most of the studies, these studies consistently showed an increased risk of alcohol-related cancers among subjects with the genetic polymorphisms leading to higher internal doses of acetaldehyde following heavy alcohol intake as compared to subjects with other genetic polymorphisms.

5.3 Animal carcinogenicity data

Acetaldehyde was tested for carcinogenicity in rats by inhalation exposure and in hamsters by inhalation exposure and by intratracheal instillation. It produced tumours of the respiratory tract following inhalation, particularly adenocarcinomas and squamous-cell carcinomas of the nasal mucosa in rats and laryngeal carcinomas in hamsters. In hamsters, it did not cause an increased incidence of tumours following intratracheal instillation. Inhalation of acetaldehyde enhanced the incidence of respiratory-tract tumours produced by intratracheal instillation of benzo[*a*]pyrene.

5.4 Other relevant data

Acetaldehyde is metabolized to acetic acid. During inhalation exposure of rats, degeneration of nasal epithelium occurs and leads to hyperplasia and proliferation.

Acetaldehyde causes gene mutations in bacteria and gene mutations, sister chromatid exchanges, micronuclei and aneuploidy in cultured mammalian cells, without metabolic activation. *In vivo*, it causes mutations in *Drosophila melanogaster* but not micronuclei in mouse germ cells. It causes DNA damage in cultured mammalian cells and in mice *in vivo*. Acetaldehyde–DNA adducts have been found in white blood cells from human alcohol abusers.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 36 (1985); Suppl. 7 (1987)

Synonyms

- Acetic aldehyde
- ‘Aldehyde’
- Ethanal
- Ethylaldehyde

Last updated: 12 April 1999

AZIRIDINE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 337)

CAS No.: 151-56-4
Chem. Abstr. Name: Aziridine

5. Summary of Data Reported and Evaluation

N.B. - Summary (but not the evaluation) prepared by the Secretariat after the meeting.

5.1 Exposure data

Aziridine is a highly reactive and volatile chemical. Exposure to the compound may occur during its use as an intermediate and monomer in the production of cationic polymers.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Aziridine was tested for carcinogenicity in mice by oral administration, producing an increased incidence of liver-cell and pulmonary tumours. Subcutaneous injection of single doses in suckling mice produced an increased incidence of lung tumours in males. In one experiment in rats it increased the incidence of tumours at the injection site following injection in oil.

5.4 Other relevant data

Aziridine produces genetic damage in bacteria, insects and mammalian cells in culture, as well as dominant lethal effects in mice. Opening of the aziridine ring appears to be an important metabolic step in its mutagenic action.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of aziridine were available.

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

Overall evaluation

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

In making the overall evaluation, the Working Group took into consideration that aziridine is a direct-acting alkylating agent which is mutagenic in a wide range of test systems and forms DNA adducts that are promutagenic.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 9 (1975); Suppl. 7 (1987)

Synonyms

- Azacyclopropane
- Dimethylenimine
- Ethyleneimine
- Ethylenimine

Last updated: 12 April 1999

BENZOYL PEROXIDE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 345)

CAS No.: 94-36-0
Chem. Abstr. Name: Dibenzoyl peroxide

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to benzoyl peroxide may occur in its manufacture and use as an initiator in polymer production, food bleaching and rubber curing. Consumer exposure occurs from acne medications and dental products containing benzoyl peroxide.

5.2 Human carcinogenicity data

Two case–control studies have evaluated exposure to benzoyl peroxide among cases of malignant melanoma. One of these studies (the smallest) (among chemists) suggested a greater frequency of exposure among cases than controls. A third large population-based case–control study, designed specifically to evaluate the possible risk of benzoyl peroxide used as an acne medication among young persons, included largely cases of basal-cell carcinoma of the skin. There was no association with use of benzoyl peroxide in this study.

5.3 Animal carcinogenicity data

Benzoyl peroxide was tested in two studies by skin application in strains of mice susceptible to the development of skin papillomas and in several skin-painting studies in mice and in one study in hamsters in combination with known carcinogens. In one study by skin application in mice, it induced benign and malignant skin tumours and, in the other study, benign skin tumours. Benzoyl peroxide was active as a skin tumour promoter in several strains of mice.

5.4 Other relevant data

Benzoyl peroxide forms radicals that are involved in its covalent binding to macromolecules. Its biological effects are inhibited by antioxidants.

Its genotoxic properties have received little attention. DNA damage has been observed in treated mammalian cells, but it is not mutagenic in bacteria and does not cause chromosomal damage in cultured mammalian cells or dominant lethal effects in mice.

5.5 Evaluation

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

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

Overall evaluation

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

Previous evaluations: Vol. 36 (1985); Suppl. 7 (1987)

Synonyms

- Benzoic acid, peroxide
- Benzoperoxide
- Benzoyl superoxide
- Diphenylglyoxal peroxide

Last updated: 8 April 1999

n-BUTYL ACRYLATE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 359)

CAS No.: 141-32-2
Chem. Abstr. Name: 2-Propenoic acid, butyl ester

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to *n*-butyl acrylate may occur in its manufacture and its use in the production of polymers and other chemical products. It has been detected at low levels in ambient air and water.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

n-Butyl acrylate was tested in one study in mice by skin application and in one study in rats by inhalation exposure. No carcinogenic effect was observed.

5.4 Other relevant data

n-Butyl acrylate is rapidly absorbed and hydrolysed in experimental animals exposed orally. Exposure of rats to *n*-butyl acrylate vapours leads to hyperplasia of the nasal mucosa. In assays for genotoxicity/mutagenicity considered, results for *n*-butyl acrylate were generally negative.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of *n*-butyl acrylate were available.

There is *inadequate evidence* in experimental animals for the carcinogenicity of *n*-butyl acrylate.

Overall evaluation

n-Butyl acrylate is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 39 (1986); Suppl. 7

Synonyms

- Acrylic acid, n-Butyl ester
- Butyl 2-propenoate

Last updated: 12 April 1999

γ-BUTYROLACTONE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 367)

CAS No.: 96-48-0
Chem. Abstr. Name: Dihydro-2(3-*H*)-furanone

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to γ-butyrolactone may occur in its production and use as an intermediate and as a solvent. It has been detected in alcoholic beverages, tobacco smoke, coffee and several foodstuffs.

5.2 Human carcinogenicity data

No adequate data were available to the Working Group.

5.3 Animal carcinogenicity data

γ-Butyrolactone was tested for carcinogenicity in two studies in mice and two studies in rats by oral administration. It was also tested in mice by skin application in two studies and by subcutaneous injection in mice and rats in single studies. No carcinogenic effect was observed.

5.4 Other relevant data

γ-Butyrolactone rapidly hydrolyses in blood to γ-hydroxybutyric acid. γ-Butyrolactone has been extensively studied in in-vitro genetic toxicity tests in which the overwhelming majority of results did not indicate activity. Positive results were obtained in one study for chromosomal aberrations and sister chromatid exchanges in a Chinese hamster cell line. No mutagenic activity was observed *in vivo* in *Drosophila* or in mouse bone marrow micronucleus tests.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of γ-butyrolactone.

There is *evidence suggesting lack of carcinogenicity* of γ-butyrolactone in experimental animals.

Overall evaluation

γ-Butyrolactone is *not classifiable as to its carcinogenicity to humans* (Group 3).

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 11 (1976); Suppl. 7 (1987)

Synonyms

- γ-BL
- 1,4-Butanolide
- Butyric acid lactone
- 4-Butyrolactone

Last updated: 12 April 1999

CAPROLACTAM
(Group 4)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 383)

CAS No.: 105-60-2
Chem. Abstr. Name: Hexahydro-2*H*-azepin-2-one

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to caprolactam, a monomer used in high volume, can occur in its manufacture and the manufacture of nylon 6. It has been detected in surface water, groundwater and drinking-water.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Caprolactam was tested for carcinogenicity by oral administration in the diet of mice and rats. No increase in the incidence of tumours was observed. Caprolactam was also tested for promoting effects in two multistage studies in male rats. In one, oral administration of caprolactam in the diet after treatment with several carcinogens showed no modifying effect on carcinogenicity in any organ or on glutathione *S*-transferase (placental form) (GST-P)-positive foci of the liver. In the other study, oral administration of caprolactam in the diet with a two-thirds partial hepatectomy after treatment with *N*-nitrosodiethylamine did not increase the numbers or areas of GST-P-positive foci in the liver.

5.4 Other relevant data

Caprolactam is metabolized in rats to a number of metabolites including 4-hydroxy caprolactam. In rats, it exhibits some hepatotoxicity at high doses.

Caprolactam was not mutagenic to rodents *in vivo.* It induced chromosomal aberrations and aneuploidy in human lymphocytes *in vitro*, but no other evidence of mutagenicity has been found in a variety of tests with rodent cell cultures. Results for morphological transformation in mammalian cells were inconclusive. Caprolactam was mutagenic in somatic and to a lesser degree to germ cells in *Drosophila melanogaster*. Caprolactam was not genotoxic in bacteria.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of caprolactam were available.

There is *evidence suggesting a lack of carcinogenicity* of caprolactam in experimental animals.

Overall evaluation

Caprolactam is *probably not carcinogenic to humans (Group 4)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 19 (1979); Vol. 39 (1986); Suppl. 7 (1987)

Synonyms

- Hexahydro-2*H*-azepin-2-one
- 2-Ketohexamethylenimine
- 2-Oxohexamethylenimine

Last updated: 8 April 1999

CARBON TETRACHLORIDE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

Vol.: 71 (1999) (p. 401)

CAS No.: 56-23-5
Chem. Abstr. Name: Tetrachloromethane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to carbon tetrachloride may occur in its production, in the production of refrigerants, in laboratories and during degreasing operations. It has been detected at low levels in ambient air and water.

5.2 Human carcinogenicity data

The risk of cancer from carbon tetrachloride has been examined in five occupational populations. In three of four studies that collected information on non-Hodgkin lymphoma (two cohort investigations and one independent nested case–control study), associations with exposure to carbon tetrachloride were suggested. However, not all of these studies distinguished exposure to carbon tetrachloride specifically, and the associations were not strong statistically. In the fourth study (another cohort investigation), few men were exposed to carbon tetrachloride and the risk of non-Hodgkin lymphoma was not reported. A nested case–control study of lung cancer in a cohort of chemical workers showed no association with exposure to carbon tetrachloride.

Four population-based case–control studies have examined associations of carbon tetrachloride with chronic lymphocytic leukaemia, brain cancer, female breast cancer and intraocular melanoma. Findings were generally unremarkable. In a fifth case–control study, which examined several cancers, no association was found with non-Hodgkin lymphoma, although the power to detect an increased risk was low.

5.3 Animal carcinogenicity data

Carbon tetrachloride was tested for carcinogenicity by various routes of administration. It produced liver neoplasms in mice and rats and mammary neoplasms in rats following subcutaneous injection. In one study in mice by inhalation, an increased incidence of phaeochromocytomas was reported. In experiments involving administration of carbon tetrachloride after known carcinogens, the occurrence of tumours and/or preneoplastic lesions of the liver in mice, rats and hamsters was enhanced.

5.4 Other relevant data

Carbon tetrachloride is metabolized by CYP2 enzymes; several reactive metabolites have been postulated, including radicals and phosgene. *In vitro*, DNA binding of carbon tetrachloride is observed in several cellular systems; no such binding *in vivo* has been reported.

Carbon tetrachloride induces hepatic cell proliferation and DNA synthesis.

Carbon tetrachloride has a mutagenic effect and induces aneuploidy in several in-vitro systems.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 1 (1972); Vol. 20 (1979); Suppl. 7 (1987)

Synonyms

- Benzinoform
- Carbona

Last updated: 8 April 1999

CATECHOL
(Group 2B)

VOL.: 71 (1999) (p. 433)

CAS No.: 120-80-9
Chem. Abstr. Name: 1,2-Benzenediol

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to catechol may occur in its production, in the production of insecticides, perfumes and drugs, in metal plating and in coal processing. Catechol occurs naturally in fruits and vegetables. It is present in cigarette smoke and has been detected at low levels in ambient air and water.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Catechol was tested for carcinogenicity by oral administration in one study in mice and in two studies in rats. No increase in the incidence of malignant tumours was found in mice. In rats, it induced adenocarcinomas in the glandular stomach in several strains. In one study in mice by skin application, no skin tumour was observed. In several experiments in rats involving administration with known carcinogens, catechol enhanced the incidence of papillomas of the tongue, carcinomas of the oesophagus, squamous-cell carcinomas of the forestomach and adenocarcinomas of the glandular stomach.

5.4 Other relevant data

Catechol is oxidized by peroxidases to the reactive intermediate benzo-1,2-quinone, which binds to protein. The acute toxicity of catechol is relatively low. In humans, the irritant action of catechol can lead to dermatitis and other dermal lesions. Chronic oral treatment of rodents causes hyperplasia of the forestomach and pyloric mucosa.

Catechol was shown to cause gene mutations in mammalian cells *in vitro*. Chromosomal aberrations and sister chromatid exchanges were reported in mammalian cells in culture. After application to mice, catechol was negative in one and positive in three studies of micronucleus formation in bone marrow.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of catechol were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 15 (1977); Suppl. 7 (1987)

Synonyms

- Catechin
- 1,2-Dihydroxybenzene
- Pyrocatechol

Last updated: 12 April 1999

α-CHLORINATED TOLUENES AND BENZOYL CHLORIDE (COMBINED EXPOSURES) (Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 453)

Benzyl chloride
CAS No.: 100-44-7
Chem. Abstr. Name: (Chloromethyl)benzene

Benzal chloride
CAS No.: 98-87-3
Chem. Abstr. Name: (Dichloromethyl)benzene

Benzotrichloride
CAS No.: 98-07-7
Chem. Abstr. Name: (Trichloromethyl)benzene

Benzoyl chloride
CAS No.: 98-88-4
Chem. Abstr. Name: Benzoyl chloride

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Little information on occupational or environmental exposures to these chemicals was available to the Working Group.

5.2 Human carcinogenicity data

Small cohort studies of occupational exposures to α-chlorinated toluenes and benzoyl chloride in the United States and England each noted an approximately three-fold excess of lung cancer.

5.3 Animal carcinogenicity data

Benzyl chloride, benzal chloride, benzotrichloride and benzoyl chloride have been studied by skin application to mice. Small numbers of skin tumours were produced by benzyl chloride and benzoyl chloride, while clear increases in skin tumours were produced by benzal chloride and benzotrichloride. Following subcutaneous injections to rats, benzyl chloride produced some injection site tumours. Administration by gavage of benzyl chloride to mice and rats produced forestomach tumours in mice and a few neoplasms of the forestomach were observed in male rats. Benzotrichloride administered by gavage to mice produced tumours of the forestomach and lungs. In addition, benzotrichloride and benzoyl chloride were administered by inhalation to mice: benzotrichloride produced increases in the incidences of tumours of the lung and skin, whereas no significant increase in tumour incidence was observed after benzoyl chloride administration.

5.4 Other relevant data

No studies were available on the disposition of benzotrichloride, benzal chloride or benzoyl chloride. Benzyl chloride is rapidly absorbed and distributed from the gastrointestinal tract. Excretion is mainly in urine as *S*-benzyl-*N*-acetylcysteine, benzyl alcohol and benzaldehyde.

All of the compounds are irritant to the skin and mucous membranes.

Benzyl chloride, benzal chloride and benzotrichloride, but not benzoyl chloride, are bacterial mutagens. Only benzyl chloride has been more extensively tested. It is genotoxic to fungi, *Drosophila melanogaster* and cultured mammalian cells, but did not increase the frequency of micronuclei in mice.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of α-chlorinated toluenes and benzoyl chloride.

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

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

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

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

Overall evaluation

Combined exposures to α-chlorinated toluenes and benzoyl chloride are *probably carcinogenic to humans (Group 2A)*.

Previous evaluations: Vol. 29 (1982) (benzoyl chloride); Suppl. 7 (1987) (benzoyl chloride)

Synonyms

Benzyl chloride

- Chloromethyl benzene
- Chlorophenylmethane
- α-Chlorotoluene
- α-Tolyl chloride

Benzal chloride

- Benzyl dichloride
- Benzylene chloride
- Benzylidine chloride
- Chlorobenzal
- (Dichloromethyl)benzene
- Dichlorophenylmethane
- Dichlorotoluene
- α,α-Dichlorotoluene

Benzotrichloride

- Benzenyl chloride
- Benzenyl trichloride
- Benzylidyne chloride
- Benzyl trichloride
- Phenyl chloroform
- Phenyltrichloromethane
- Toluene trichloride
- Trichloromethylbenzene
- α,α,α-Trichlorotoluene

Benzoyl chloride

- Benzene carbonyl chloride

Last updated: 12 April 1999

1,2-DIBROMO-3-CHLOROPROPANE (Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 479)

CAS No.: 96-12-8
Chem. Abstr. Name: 1,2-Dibromo-3-chloropropane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to 1,2-dibromo-3-chloropropane has occurred during its production and use as a pesticide, nematocide and soil fumigant; however, production is believed to have ceased. It has been detected at low levels in ambient air, water and soil.

5.2 Human carcinogenicity data

Four cohort studies and one population-based case–control study have examined the risk of cancer among populations exposed to 1,2-dibromo-3-chloropropane, among other chemicals. In two of the cohort studies, an excess of lung cancer was observed based on small numbers of cases. In a third cohort study, an excess of liver and biliary tract cancers was found, while in the fourth an excess of cervical cancer and a non-significant excess of melanoma and leukaemia were observed. However, in both of the last two studies, it was unclear what proportion of the population was exposed to 1,2-dibromo-3-chloropropane, and there was exposure to multiple pesticides. In the case–control study, there was a non-significant association of gastric cancer and leukaemia with exposure to 1,2-dibromo-3-chloropropane in groundwater.

5.3 Animal carcinogenicity data

1,2-Dibromo-3-chloropropane has been tested by oral administration and inhalation in mice and rats. After oral administration, it produced squamous-cell carcinomas of the forestomach in animals of each species and adenocarcinomas of the mammary gland in female rats. After inhalation, it induced nasal cavity and lung tumours in mice, and nasal cavity and tongue tumours in rats of each sex and pharynx in females. In fish, an increased incidence of liver tumours was found.

5.4 Other relevant data

1,2-Dibromo-3-chloropropane is metabolically activated via cytochrome P450-catalysed oxidation and glutathione conjugation to form several protein- and DNA-binding products in the rat and mouse. It is also activated in human testicular cells *in vitro*. It disturbs spermatogenesis and has caused male infertility in humans. 1,2-Dibromo-3-chloropropane is a bacterial mutagen in the presence of metabolic activation. It causes DNA damage and genotoxicity in animal cells *in vitro* and *in vivo*.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 1,2-dibromo-3-chloropropane.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,2-dibromo-3-chloropropane.

Overall evaluation

1,2-Dibromo-3-chloropropane is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 15 (1977); Vol. 20 (1979); Suppl. 7 (1987)

Synonyms

- DBCP
- Dibromochloropropane

Last updated: 12 April 1999

1,2-DICHLOROETHANE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 501)

CAS No.: 107-06-2
Chem. Abstr. Name: 1,2-Dichloroethane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

1,2-Dichloroethane is used mainly in the production of vinyl chloride. It is no longer registered as a fumigant. It has been detected at low levels in ambient and urban air, groundwater and drinking-water.

5.2 Human carcinogenicity data

Five cohort studies and one nested case–control study of brain tumours have examined the risk of cancer among workers with potential exposure to 1,2-dichloroethane. Excesses of lymphatic and haematopoietic cancers were observed in three studies and of stomach cancer in one study, while an excess of pancreatic cancer was observed in one study. All the cohort studies included workers with potential exposure to multiple agents and were not able to examine the excess risk associated with 1,2-dichloroethane.

5.3 Animal carcinogenicity data

1,2-Dichloroethane was tested in one experiment in mice and in one in rats by oral administration. In mice, it produced benign and malignant tumours of the lung and malignant lymphomas in animals of each sex, hepatocellular carcinomas in males and mammary and uterine adenocarcinomas in females. In rats, it produced carcinomas of the forestomach in males, benign and malignant mammary tumours in females and haemangiosarcomas in animals of each sex. No increase in tumour incidence was found after inhalation exposure in two experiments in rats or in one experiment in mice, but these studies were considered to be inadequate. In two other inhalation studies, one in mice and one in rats, 1,2-dichloroethane increased the incidence of tumours at various sites including the liver, lung and mammary gland.

In a multistage study measuring γ-glutamyl transpeptidase (γ-GT)-positive foci in the liver of male rats, single administration of 1,2-dichloroethane by gavage after a two-thirds partial hepatectomy followed by treatment with phenobarbital (initiation study) or repeated administration of 1,2-dichloroethane by gavage after a two-thirds partial hepatectomy and initiation by *N*-nitrosodiethylamine (promotion study) did not increase the number of γ-GT-positive foci. In a two-stage mouse-skin assay, 1,2-dichloroethane was not active as an initiator of skin carcinogenicity.

5.4 Other relevant data

1,2-Dichloroethane is easily absorbed by humans and animals and is metabolized extensively by rats and mice via cytochrome P450 and glutathione *S*-transferase.

No teratogenic effect was seen in rats, rabbits or mice.

1,2-Dichloromethane is mutagenic in bacteria, *Drosophila melanogaster* and mammalian cells. It induces DNA

damage in liver cells *in vivo* and binds to DNA, RNA and proteins in animals.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 1,2-dichloroethane.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,2-dichloroethane.

Overall evaluation

1,2-Dichloroethane is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 20 (1979); Suppl. 7 (1987)

Synonym

- Ethylene dichloride

Last updated: 12 April 1999

DIMETHYLCARBAMOYL CHLORIDE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 531)

CAS No.: 79-44-7
Chem. Abstr. Name: Dimethylcarbamic chloride

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to dimethylcarbamoyl chloride may occur during its manufacture and its use as an intermediate in the manufacture of a number of pharmaceuticals and pesticides.

5.2 Human carcinogenicity data

No deaths from cancer were reported in a small study of workers exposed for periods ranging from six months to 12 years.

5.3 Animal carcinogenicity data

Dimethylcarbamoyl chloride was tested for carcinogenicity in rats and hamsters by inhalation exposure, producing malignant tumours of the nasal cavity. It was also tested in mice by skin application and by subcutaneous and intraperitoneal injection, producing local tumours.

5.4 Other relevant data

No data were available on the metabolism of dimethylcarbamoyl chloride, but it rapidly decomposes on contact with water to dimethylamine, hydrochloric acid and carbon dioxide.

Dimethylcarbamoyl chloride when inhaled by rats damages the nasal mucous membrane, throat and lung.

It has a wide spectrum of genotoxic activity, which is expressed as a result of its direct alkylating activity.

5.5 Evaluation

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

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

Overall evaluation

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

In making the overall evaluation, the Working Group took into consideration that dimethylcarbamoyl chloride is

a direct-acting alkylating agent with a wide spectrum of genotoxic activity, including activity in somatic cells *in vivo*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 12 (1976); Suppl. 7 (1987)

Last updated: 8 April 1999

DIMETHYLFORMAMIDE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 545)

CAS No.: 68-12-2
Chem. Abstr. Name: *N*,*N*-Dimethylformamide

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposures to dimethylformamide occur during its production and during the production of inks, adhesives, resins, fibres, pharmaceuticals, synthetic leather, and its use as a purification or separation solvent in organic synthesis. It has been detected in ambient air and water.

5.2 Human carcinogenicity data

Case reports of testicular cancer in aircraft repair and leather tannery facilities suggested possible association with dimethylformamide. Further research has failed to confirm this relationship. A screening effort at a leather tannery, where a cancer cluster had been noted, identified no additional cases. Mortality and cancer incidence studies and nested case–control investigations of testicular cancer and several other anatomical sites at several facilities with exposure to dimethylformamide noted no convincing associations.

5.3 Animal carcinogenicity data

Dimethylformamide was adequately tested for carcinogenicity by inhalation in one study in mice and one study in rats. No increase in tumours was found.

5.4 Other relevant data

Acute exposure of humans or experimental animals to relatively high concentrations of dimethylformamide causes hepatotoxicity as a major toxic effect.

Reports on chromosomal damage in workers exposed to dimethylformamide either failed to take into account smoking as a bias factor or were documented incompletely.

Dimethylformamide has been extensively tested in a broad range of in-vitro and in-vivo genotoxicity assays. Results have been consistently negative in well controlled studies.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 47 (1989)

Synonym

- DMF

Last updated: 12 April 1999

DIMETHYL SULFATE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 575)

CAS No.: 77-78-1
Chem. Abstr. Name: Sulfuric acid, dimethyl ester

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to dimethyl sulfate may occur during its manufacture and its use as a methylating agent.

5.2 Human carcinogenicity data

No epidemiological studies were available to the Working Group. A small number of cases of, mainly, bronchial carcinoma has been reported.

5.3 Animal carcinogenicity data

Dimethyl sulfate was tested for carcinogenicity in rats by inhalation, subcutaneous and intravenous injection, and following prenatal exposure. It produced local sarcomas and tumours of the nervous system.

5.4 Other relevant data

Dimethyl sulfate rapidly decomposes on contact with water, as a result of which it very rapidly disappears from the circulation of dosed rats.

It is corrosive or irritant to the skin, eyes and respiratory tract of exposed people, and may result in death caused by respiratory failure.

Dimethyl sulfate is embryotoxic to rats and causes malformations among surviving foetuses.

Workers exposed to dimethyl sulfate have developed chromosomal aberrations in their circulating lymphocytes. Dimethyl sulfate has been subjected to a broad range of in-vitro tests for genotoxic activity, in which positive results were consistently found without the need for exogenous metabolic activation systems. It has also consistently produced positive responses in the small number of in-vivo tests to which it has been subjected. It forms a variety of alkylated bases with DNA *in vitro* and the same alkylated bases are formed *in vivo*.

5.5 Evaluation

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

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

Overall evaluation

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

In making the overall evaluation, the Working Group took into consideration that dimethyl sulfate is a potent genotoxic chemical which can directly alkylate DNA both *in vitro* and *in vivo*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 4 (1974); Suppl. 7 (1987)

Synonyms

- Dimethyl monosulfate
- Methyl sulfate

Last updated: 12 April 1999

1,4-DIOXANE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 589)

CAS No.: 123-91-1
Chem. Abstr. Name: 1,4-Dioxane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to 1,4-dioxane may occur during its manufacture and its use as a solvent in a wide range of organic products. It has been detected in ambient air.

5.2 Human carcinogenicity data

Deaths from cancer were not elevated in a single, small prospective study of workers exposed to low concentrations of dioxane.

5.3 Animal carcinogenicity data

1,4-Dioxane was tested for carcinogenicity by oral administration in mice, rats and guinea-pigs. It produced an increased incidence of hepatocellular adenomas and carcinomas in mice, tumours of the nasal cavity, liver subcutaneous tissues, mammary gland and peritoneal mesotheliomas in rats and tumours of the liver and gall-bladder in guinea-pigs. No increase in tumours was seen in rats following inhalation exposure. In the mouse-lung adenoma assay, intraperitoneal injection of 1,4-dioxane increased the incidence of lung tumours in males; no such effect was seen following oral administration. In a two-stage liver foci assay in rats, 1,4-dioxane showed promoting activity.

5.4 Other relevant data

1,4-Dioxane is rapidly absorbed upon inhalation or after oral administration, but its penetration of skin is poor. The major metabolite is β-hydroxyethoxyacetic acid, which is rapidly excreted. In rats, the elimination of 1,4-dioxane and its metabolites is progressively delayed as doses are increased, indicating saturation of metabolism.

No clinical signs or changes in mortality were found in a cohort of exposed workers. In rats, 1,4-dioxane produces degenerative and necrotic changes in liver and renal tubules. High doses can significantly increase the total hepatic cytochrome P450 content.

No reproductive effects of 1,4-dioxane exposure of rats have been reported.

Most of the broad of tests for genotoxic activity have produced negative results, but positive results were obtained in a cell transformation assay and conflicting results were obtained in mouse bone-marrow cell tests for micronucleus induction.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 1,4-dioxane.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,4-dioxane.

Overall evaluation

1,4-Dioxane is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 11 (1976); Suppl. 7 (1987)

Synonyms

- 1,4-Diethylene dioxide
- *para*-Dioxane

Last updated: 12 April 1999

EPICHLOROHYDRIN
(Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 603)

CAS No.: 106-89-8
Chem. Abstr. Name: (Chloromethyl)oxirane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to epichlorohydrin may occur during the production and use of resins, glycerine and propylene-based rubbers and its use as a solvent. It has been detected at low levels in water.

5.2 Human carcinogenicity data

The risk of cancer has been investigated among four populations exposed to epichlorohydrin. In one cohort study, an excess of lung cancer was observed among the small number of workers employed in the production of epichlorohydrin. A nested case–control study within this population found a weak association between epichlorohydrin and lung cancer but risk was not related to level of exposure. In another nested case–control study based on the same cohort, a weak association with central nervous system tumours was observed which appeared to be related to the level of exposure. A small excess of lung cancer was observed in another cohort, but in a third no excess of cancer was observed. In a case–control study of lung cancer nested within a further cohort of chemical workers, a significantly decreased risk of lung cancer was associated with epichlorohydrin exposure. All results were based on relatively small numbers.

5.3 Animal carcinogenicity data

Epichlorohydrin was tested in rats by oral administration, inducing papillomas and carcinomas of the forestomach, and by inhalation, inducing papillomas and carcinomas of the nasal cavity. It was also tested in mice by skin application and by subcutaneous and intraperitoneal injection; it gave negative results after continuous skin painting but was active as an initiator on skin. It produced local sarcomas after subcutaneous injection and was active in a mouse-lung tumour bioassay by intraperitoneal injection.

5.4 Other relevant data

Epichlorohydrin is itself a reactive epoxide and is metabolized by binding to glutathione and by hydration via epoxide hydrolase. The same haemoglobin adduct has been detected in humans and rats. In man, epichlorohydrin causes local damage upon contact exposure. In rodents, toxicity to kidneys, liver and forestomach has been observed. After inhalation, the most sensitive target organ is the nasal turbinates. Epichlorohydrin induces genetic damage in most bacterial and mammalian tests *in vitro* or *in vivo*, not requiring the presence of a metabolic activation system.

5.5 Evaluation

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

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

Overall evaluation

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

In making the overall evaluation, the Working Group took into consideration the known chemical reactivity of epichlorohydrin and its direct activity in a wide range of genetic tests.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 11 (1976); Suppl. 7

Synonyms

- 1-Chloro-2,3-epoxypropane
- Chloropropylene oxide

Last updated: 13 April 1999

1,2-EPOXYBUTANE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 629)

CAS No.: 106-88-7
Chem. Abstr. Name: Ethyloxirane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to 1,2-epoxybutane may occur in its production and use as a monomer, chemical intermediate and stabilizer.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

1,2-Epoxybutane was tested for carcinogenicity by inhalation exposure in one study in mice and in one study in rats, producing nasal papillary adenomas in rats of both sexes and pulmonary alveolar/bronchiolar tumours in male rats. It did not induce skin tumours when tested by skin application in one study in mice.

5.4 Other relevant data

1,2-Epoxybutane induced morphological transformation, sister chromatid exchanges, chromosomal aberrations and mutation in cultured animal cells; however, in a single study, it did not induce unscheduled DNA synthesis in rat primary hepatocytes. It induced sex-linked recessive lethal mutations and translocations in *Drosophila melanogaster*, mitotic recombination in yeast, and mutations in yeast and fungi. 1,2-Epoxybutane induced DNA damage and mutations in bacteria.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of 1,2-epoxybutane were available.

There is *limited evidence* in experimental animals for the carcinogenicity of 1,2-epoxybutane.

Overall evaluation

1,2-Epoxybutane is *possibly carcinogenic to humans (Group 2B)*.

In making the overall evaluation, the Working Group took into consideration that 1,2-epoxybutane is a direct-acting alkylating agent which is mutagenic in a range of test systems.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 47 (1989)

Synonyms

- 1-Butene oxide
- 1,2-Butene oxide
- 1,2-Butylene epoxide
- α-Butylene oxide
- 1-Butylene oxide
- 1,2-Butylene oxide
- Epoxybutane
- Ethyl ethylene oxide
- 2-Ethyloxirane

Last updated: 13 April 1999

ETHYLENE DIBROMIDE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 641)

CAS No.: 106-93-4
Chem. Abstr. Name: 1,2-Dibromoethane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to ethylene dibromide (1,2-dibromoethane) may occur in pest control, petroleum refining and waterproofing. Dermal exposure is possible when handling leaded gasoline containing ethylene dibromide. It has been detected at low levels in air and water.

5.2 Human carcinogenicity data

Three cohort studies have included workers exposed to ethylene dibromide, but because of their low statistical power and/or lack of information about individual exposures, little can be concluded about the carcinogenicity of this compound in humans.

5.3 Animal carcinogenicity data

Ethylene dibromide has been tested for carcinogenicity by oral administration in mice, rats and fish, by inhalation in mice and rats and by skin application in mice. Following its oral administration, it produced squamous-cell carcinomas of the forestomach in rodents of both species, an increased incidence of alveolar/bronchiolar lung tumours in mice of each sex, haemangiosarcomas in male rats, oesophageal papillomas in female mice and liver and stomach tumours in fish. Following its inhalation, ethylene dibromide produced adenomas and carcinomas of the nasal cavity, haemangiosarcomas, mammary gland tumours, subcutaneous mesenchymal tumours, an increased incidence of alveolar/bronchiolar lung tumours in animals of each species and an increased incidence of peritoneal mesotheliomas in male rats. It induced skin and lung tumours in mice after skin application.

5.4 Other relevant data

In rodents and humans, ethylene dibromide is metabolized both by cytochrome P450 and GST enzymes; the latter seem to be responsible for DNA adduct formation. In rodents, covalently bound radioactivity has been detected in the epithelial lining of a number of organs.

In humans, acute high-dose exposure leads to liver and kidney damage. In rodents, inhalation exposure causes primarily proliferative lesions in nasal cavities. After intragastric administration, liver and kidney were the main target organs. Some evidence of adverse effects on reproduction was observed both in humans and rodents.

Ethylene dibromide is mutagenic in bacteria and *Drosophila*, and in rodent and human cells *in vitro*. It induced DNA breakage but not chromosomal aberrations or micronuclei *in vivo* in rodents. It gave negative results in dominant lethal tests in mice and rats. It did not induce either chromosomal aberrations or sister chromatid exchange in humans *in vivo*.

Ethylene dibromide binds to DNA *in vitro* and *in vivo* in rodents.

5.5 Evaluation

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

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

Overall evaluation

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

In making the overall evaluation, the Working Group took into consideration that ethylene dibromide is genotoxic in a broad range of in-vitro and in-vivo assays and binds covalently with DNA *in vivo*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 15 (1977); Suppl. 7 (1987)

Synonyms

- 1,2-Dibromoethane
- EDB

Last updated: 13 April 1999

HYDROGEN PEROXIDE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 671)

CAS No.: 7722-84-1

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Hydrogen peroxide is produced in moderately high volume and is widely used. Its primary uses are as a chemical intermediate, as a bleaching agent in the textile and paper and pulp industry and in water treatment operations. It occurs naturally at low levels in the air and water, in human and plant tissues and bacteria, and in food and beverages.

5.2 Human carcinogenicity data

No adequate data on the carcinogenicity of hydrogen peroxide were available to the Working Group.

5.3 Animal carcinogenicity data

Hydrogen peroxide was tested in mice by oral administration, skin application and subcutaneous administration and in hamsters by topical application to oral mucosa. In mice, adenomas and carcinomas of the duodenum were found following oral administration. The other studies in mice and the study in hamsters were inadequate for evaluation. One study in mice and one study in hamsters showed no promoting activity of hydrogen peroxide.

5.4 Other relevant data

Hydrogen peroxide is formed intracellularly as a result of certain enzymatic reactions. Hydrogen peroxide, either from this source or externally applied, generates hydroxyl radicals that initiate lipid peroxidation chain reactions within exposed cells and can lead to DNA damage and cell death. DNA damage has been demonstrated in bacteria and in cultured mammalian cells. In addition, hydrogen peroxide induced mutations in bacteria, yeast and other fungi and there is some evidence that it can do so in Chinese hamster V79 and mouse lymphoma L5178Y cells at the *hprt* locus. Chromosomal aberrations and sister chromatid exchanges are induced in both human and other mammalian cells *in vitro*, but it did not induce chromosomal aberrations in the bone-marrow cells of exposed rats.

5.5 Evaluation

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

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

Overall evaluation

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

Previous evaluations: Vol. 36 (1985); Suppl. 7 (1987)

Synonyms

- Dihydrogen dioxide
- Hydrogen dioxide
- Hydrogen oxide
- Hydroperoxide
- Peroxide

Last updated: 13 April 1999

HYDROQUINONE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 691)

CAS No.: 123-31-9
Chem. Abstr. Name: 1,4-Benzenediol

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to hydroquinone may occur during its production, its use as an inhibitor, antioxidant and intermediate in the production of dyes, paints, motor fuels and oils, and in black-and-white photographic processing. Hydroquinone occurs naturally in certain plant species. It is used as a topical treatment for skin hyperpigmentation.

5.2 Human carcinogenicity data

A cohort of workers with definite and lengthy exposure to hydroquinone had low cancer rates compared with two comparison populations; the reason for the lower than expected rates is unclear. A cohort of lithographers, some of whom had worked with hydroquinone, had an excess of malignant melanoma based on five cases; only two of the cases had reported exposure to hydroquinone.

5.3 Animal carcinogenicity data

Hydroquinone was tested for carcinogenicity in two studies in mice and two studies in rats by oral administration. It was also tested in rats for promoting activity in assays for bladder, stomach, liver, lung, oesophagus and kidney carcinogenesis and in one study in hamsters for pancreatic carcinogenesis.

In mice, hydroquinone induced hepatocellular adenomas in females in one study and in males in another study. In rats it induced renal tubule adenomas in males in two studies.

Hydroquinone had no promoting activity in most assays; an increase in the multiplicity of oesophageal tumours was observed in one study and in the multiplicity of renal cell tumours in another study. No promoting effect on pancreatic carcinogenesis was observed in the study in hamsters.

5.4 Other relevant data

Hydroquinone is metabolized mainly to conjugates, but a small percentage may be converted to 1,4-benzoquinone, conjugated with glutathione or form DNA adducts *in vitro*.

It caused toxicity in several organs, notably the kidney and forestomach.

Hydroquinone was mutagenic in many in-vitro systems using a variety of end-points. Also, after intraperitoneal administration, it caused genotoxicity or chromosomal aberrations in bone marrow.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 15 (1977); Suppl. 7 (1987)

Synonym

- Benzoquinol

Last updated: 13 April 1999

METHYL BROMIDE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 721)

CAS No.: 74-83-9
Chem. Abstr. Name: Bromomethane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to methyl bromide may occur in its production, in pest control and in fumigation of soil. Methyl bromide is naturally produced in oceans. It is commonly detected in ambient air and at low levels in water.

5.2 Human carcinogenicity data

One cohort study of workers at three chemical manufacturing plants included a subgroup with potential exposure to methyl bromide, among whom there were two deaths from testicular cancer (0.11 expected).

5.3 Animal carcinogenicity data

Methyl bromide was tested by oral administration in rats and by inhalation in mice and rats. In one 90-day study by oral administration in rats, methyl bromide was reported to produce squamous-cell carcinomas of the forestomach. In a second, 25-week study designed to investigate further the findings of the previous study, early hyperplastic lesions of the forestomach developed after 25 weeks of continuous treatment by gavage. In two inhalation studies in mice, no significant increase in the incidence of tumours was observed. In one inhalation study in rats, an increase in the incidence of adenomas of the pituitary gland was observed in high-dose male rats. In another study in rats, no increase in tumour incidence was observed.

5.4 Other relevant data

Methyl bromide is metabolized by glutathione conjugation and excreted as carbon dioxide. In animal studies, it caused toxicity and irritation and organ toxicity in many organs. It binds covalently to DNA *in vitro* and also in various organs in the rat *in vivo*. Methyl bromide is mutagenic in bacteria; it induces gene mutations and sister chromatid exchanges *in vitro* in mammalian cells. Methyl bromide gave positive results for several genetic activity end-points in *Drosophila*.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 41 (1986); Suppl. 7 (1987)

Synonyms

- Bromomethane
- Monobromomethane

Last updated: 13 April 1999

METHYL CHLORIDE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 737)

CAS No.: 74-87-3
Chem. Abstr. Name: Chloromethane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to methyl chloride may occur in its production, and in the production of silicones and various other chemical products. Methyl chloride is produced naturally, primarily in oceans, and it is widely detected in ambient air and water.

5.2 Human carcinogenicity data

Two small cohort studies evaluated the mortality experience of workers employed in facilities using or producing methyl chloride. No clear mortality excess occurred, and the small size and mixed exposures of these studies limited their utility for assessing the carcinogenicity of methyl chloride.

5.3 Animal carcinogenicity data

No adequate data were available to the Working Group.

5.4 Other relevant data

The toxicokinetics of methyl chloride have been studied in human volunteers. It can be converted by human erythrocytes to *S*-methylglutathione, a metabolite also observed in animal studies; alternatively, it is metabolized by CYP2E1. Carbon dioxide is a major metabolite.

Methyl chloride causes toxicity in rodents in the liver, kidney and central nervous system. It may deplete glutathione in tissues.

Methyl chloride is mutagenic to bacteria. It was genotoxic in a number of mammalian cell systems *in vitro* and gave positive results in the dominant lethal test in rats *in vivo*.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity of methyl chloride to humans.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 41 (1986); Suppl. 7 (1987)

Synonyms

- Chloromethane
- Monochloromethane

Last evaluated: 13 April 1999

PHENOL
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 749)

CAS No.: 108-95-2
Chem. Abstr. Name: Phenol

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Phenol is a basic feedstock for the production of phenolic resins, bisphenol A, caprolactam, chlorophenols and several alkylphenols and xylenols. Phenol is also used in disinfectants and antiseptics. Occupational exposure to phenol has been reported during its production and use, as well as in the use of phenolic resins in the wood products industry. It has also been detected in automotive exhaust and tobacco smoke.

5.2 Human carcinogenicity data

A study of Finnish woodworkers found a high risk of lung cancer among those exposed to phenol, although the excess risk was stronger in short-term than in long-term workers. This result was not replicated in three other studies which reported results on phenol and lung cancer, although two of them had very low statistical power. In the three studies reporting associations with multiple cancer sites, a few elevated risks were reported, but not at any cancer site in two or more studies. The pattern of results fails to demonstrate a risk of cancer due to phenol exposure.

5.3 Animal carcinogenicity data

Phenol was tested for carcinogenicity by oral administration in rats in one study and in mice in one study. An increased incidence of leukaemia was reported in male rats treated with the lower dose but not in high-dose rats or in mice or female rats. Phenol was a promoter of mouse skin carcinogenesis in two-stage protocols.

5.4 Other relevant data

Phenol is well absorbed from the gastrointestinal tract and through the skin of animals and humans. It is metabolized principally by conjugation (by sulfation and glucuronidation) with a minor oxidation pathway leading to quinone-related reactive intermediates which bind covalently to protein and are detoxified by conjugation with glutathione. Topically applied phenol is a skin irritant and systemic toxicity is seen in liver and kidney after topical and oral dosing.

After in-vivo administration, phenol induced micronuclei in mice and chromosomal aberrations in rats. It also caused oxidative DNA damage in mice, and it bound covalently to rat DNA. In cultured mammalian cells, phenol caused mutations, sister chromatid exchanges and micronuclei. It bound to cellular protein (but not to DNA) and inhibited intercellular communication. It did not induce recessive lethal mutations in *Drosophila melanogaster* and had only a weak effect in inducing segregation in *Aspergillus nidulans*. Phenol was not mutagenic in bacteria.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 47 (1989)

Synonyms

- Carbolic acid
- Hydroxybenzene

Last updated: 13 April 1999

POLYCHLOROPHENOLS AND THEIR SODIUM SALTS (Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 769)

CAS No.: 120-83-2
Chem. Abstr. Name: 2,4-Dichlorophenol

CAS No.: 95-95-4
Chem. Abstr. Name: 2,4,5-Trichlorophenol

CAS No.: 88-06-2
Chem. Abstr. Name: 2,4,6-Trichlorophenol

CAS No.: 58-90-2
Chem. Abstr. Name: 2,3,4,6-Tetrachlorophenol

CAS No.: 87-86-5
Chem. Abstr. Name: Pentachlorophenol

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposures to chlorophenols and their salts have occurred in their production, in the production of some phenoxy acid herbicides, in the wood industry, the textile industry and tanneries. They have been detected at low levels in ambient air and water.

5.2 Human carcinogenicity data

Mortality and/or cancer incidence has been analysed in several cohort studies of chemical manufacturers, almost all of which have been incorporated within a multicentre international collaborative study, and also in a case–control study nested within this cohort. Two other cohort studies have focused on leather tanneries in Sweden and sawmills in Canada where chlorophenols were used. In addition, case–control studies have examined the association of chlorophenols with soft-tissue sarcoma (one study in New Zealand, four in Sweden and one in the United States), non-Hodgkin lymphoma (one study in New Zealand, one in Sweden and one in the United States), thyroid cancer (one study in Sweden), nasal and nasopharyngeal cancer (one study in Sweden), colon cancer (one study in Sweden) and liver cancer (one study in Sweden).

These investigations have shown significant associations with several types of cancer, but the most consistent findings have been for soft-tissue sarcoma and non-Hodgkin lymphoma. Although the odds ratios in some case–control studies may have been inflated by recall bias, this cannot explain all of the findings. Nor are they likely to have arisen by chance. It is not possible, however, to exclude a confounding effect of polychlorinated dibenzo-*para*-dioxins which occur as contaminants in chlorophenols.

5.3 Animal carcinogenicity data

2,4-Dichlorophenol was tested in one study in mice and in two studies in rats by oral administration. No increase in the incidence of tumours was found.

2,4,5-Trichlorophenol has not been adequately tested for carcinogenicity.

2,4,6-Trichlorophenol was tested in one study in mice and in one study in rats by oral administration and in one study in mice in a screening test for lung tumours. In mice, it increased the incidences of benign and malignant tumours of the liver and in rats mononuclear cell leukaemia. It did not induce lung adenomas in mice.

No data on the carcinogenicity of tetrachlorophenols in experimental animals were available to the Working Group.

Three different pentachlorophenol formulations were tested for carcinogenicity by oral administration in two experiments in mice and in one study in rats. In mice, a dose-related increase in the incidence of hepatocellular adenomas and carcinomas was observed in males exposed to either formulation and of hepatocellular adenomas in females exposed to one of the formulations. A dose-related increase in the incidence of adrenal phaeochromocytomas was observed in male mice exposed to either formulation, and an increase was also seen in females exposed to one of the formulations at the highest dose. A dose-related increase in the incidence of malignant vascular tumours of the liver and spleen was seen in female mice exposed to either formulation. In rats, no increase in tumours was seen following oral administration of pentachlorophenol for 24 months. However, in rats in the same study receiving a higher concentration for 12 months and held for an additional year, an increased incidence of mesotheliomas of the tunica vaginalis was observed.

5.4 Other relevant data

Chlorophenols are absorbed fairly rapidly, distributed mainly to the kidney and liver and excreted principally via urine; low chlorine-substituted compounds are conjugated with sulfate and glucuronide to a greater extent than the more highly chlorine-substituted compounds. Chlorinated *para*-hydroquinone formation is a minor metabolic pathway but not for 2,3,5,6-tetrachlorophenol and pentachlorophenol. In rats, the liver is the main target organ. Otherwise, few remarkable effects have been observed.

2,4,6-Trichlorophenol may exhibit weak aneugenic and clastogenic activity. Information on other chlorophenols is inadequate to allow assessment of their genotoxicity.

Pentachlorophenol, after metabolic activation, may exhibit weak clastogenic activity by enhancing oxidative DNA damage.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of combined exposures to polychlorophenols or to their sodium salts.

There is *evidence suggesting lack of carcinogenicity* of 2,4-dichlorophenol in experimental animals.

There is *inadequate evidence* in experimental animals for the carcinogenicity of 2,4,5-trichlorophenol.

There is *limited evidence* in experimental animals for the carcinogenicity of 2,4,6-trichlorophenol.

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

Overall evaluation

Combined exposures to polychlorophenols or to their sodium salts are *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 20 (1979); Vol. 41 (1986) (Occupational Exposures to Chlorophenols); Suppl. 7 (1987); Vol. 53 (Pentachlorophenol)

Synonyms

2,4-Dichlorophenol

- 2,4-Dichlorophenic acid

2,4,5-Trichlorophenol

- TCP

Pentachlorophenol

- Chlorophenasic acid
- PCP

Last updated: 13 April 1999

1,1,2,2-TETRACHLOROETHANE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 817)

CAS No.: 79-34-5
Chem. Abstr. Name: 1,1,2,2-Tetrachloroethane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

1,1,2,2-Tetrachloroethane is used as a solvent. It has been detected at low levels in urban and ambient air and in drinking-, ground- and wastewater.

5.2 Human carcinogenicity data

The available epidemiological data are inadequate for evaluation.

5.3 Animal carcinogenicity data

1,1,2,2-Tetrachloroethane was tested in one experiment in mice and in one in rats by oral administration. In mice, it produced hepatocellular carcinomas in males and females. It was inadequately tested by intraperitoneal administration in mice. In one small experiment in rats, no initiating but promoting activity of 1,1,2,2-tetrachloroethane was found.

5.4 Other relevant data

1,1,2,2-Tetrachloroethane bound covalently to DNA but did not induce unscheduled DNA synthesis in mice *in vivo*. It induced sister chromatid exchanges and cell transformation, but not chromosomal aberrations or unscheduled DNA synthesis, in rodent cells *in vitro*. It induced gene conversion and mutation in yeast and aneuploidy, but not genetic crossing-over, in fungus. 1,1,2,2-Tetrachloroethane induced DNA damage and showed some evidence of being mutagenic in bacteria.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 1,1,2,2-tetrachloroethane.

There is *limited evidence* in experimental animals for the carcinogenicity of 1,1,2,2-tetrachloroethane.

Overall evaluation

1,1,2,2-Tetrachloroethane is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 20 (1979); Suppl. 7 (1987)

Synonym

- Acetylene tetrachloride

Last updated: 13 April 1999

TOLUENE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 829)

CAS No.: 108-88-3
Chem. Abstr. Name: Methylbenzene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Toluene is an industrial chemical produced in high volume, that is used in blending gasoline and as a solvent. Occupational exposure to toluene is extensive and occurs in its production and during the manufacture and use of toluene-containing paints, thinners, cleaning agents, coatings and adhesives. It is commonly detected in ambient air and at low levels in water.

5.2 Human carcinogenicity data

Toluene was mentioned as an exposure in eight studies. Two were community-based case–control studies, one of which involved brain cancer and one involved several types of cancer. Of the six industry-based studies, three were analysed as cohort studies and three were configured as nested case–control studies of one or a few types of cancer. In two of the studies, that of shoe-manufacturing workers in the United States and particularly that of Swedish rotogravure printers, it was believed that toluene was the predominant exposure; in the other studies, there were probably concomitant exposures. Cancers of most sites were not significantly associated with toluene exposure in any study. Stomach cancer mortality was significantly elevated in the Swedish rotogravure printers study, it was slightly, though not significantly, elevated in two other studies, and it was not associated at all in a fourth. Rates of lung cancer were significantly elevated in the cohort of shoe manufacturers and in the Swedish cohort of rotogravure printers, but was not associated at all in two other studies. Colorectal cancer was significantly elevated in the Swedish rotogravure printers study and in the Canadian case–control study, and colon cancer was nonsignificantly elevated in the shoe manufacturers cohort. While results on leukaemias and lymphomas generally showed no association, these were based on small numbers. Considering the multiple exposure circumstances in most studies and the weak consistency of findings, these results are not strong enough to conclude that there is an association.

5.3 Animal carcinogenicity data

Toluene was tested for carcinogenicity by inhalation exposure in one study in mice and in one study in rats. No significant increase in the incidence of tumours was observed. Repeated application of toluene to the skin of mice did not result in an increased incidence of skin tumours.

5.4 Other relevant data

Toluene is mainly converted to benzyl alcohol and excreted as hippurate. Its toxicokinetics in humans have been extensively studied.

Toluene toxicity is most prominent in the central nervous system after acute and chronic exposure. Reproductive toxicity has been observed in exposed humans and rats.

In the more recent cytogenetic studies in occupationally exposed populations, increases in chromosomal aberrations (two studies), micronuclei (one study) and of DNA strand breaks (one study) have been described. These effects have also been observed in rats and mice in some studies and in cultured mammalian cells. DNA adducts have not been detected.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 47 (1989)

Synonyms

- Methylbenzol
- Phenylmethane

Last updated: 13 April 1999

TOLUENE DIISOCYANATES
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 865)

Commercial toluene diisocyanate mixtures
CAS No.: 26471-62-5
Chem. Abstr. Name: 1,3-Diisocyanatomethylbenzene

2,4-Toluene diisocyanate
CAS No.: 584-84-9
Chem. Abstr. Name: 2,4-Diisocyanato-1-methylbenzene

2,6-Toluene diisocyanate
CAS No.: 91-08-7
Chem. Abstr. Name: 1,3-Diisocyanato-2-methylbenzene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Toluene diisocyanates are industrial chemicals produced in large volumes. Exposure to toluene diisocyanates may occur during their production and in the processing and handling of polyurethane foams.

5.2 Human carcinogenicity data

The risk of cancer associated with occupational exposure to isocyanates has been examined in three industrial cohort studies and in a population-based case–control study of several types of cancer. No strong association or consistent pattern has emerged.

5.3 Experimental data

Commercial mixtures of 2,4- and 2,6-toluene diisocyanates were tested for carcinogenicity in mice and rats by gavage and by inhalation exposure. Administration by gavage induced a dose-related increase in the incidence of subcutaneous fibromas and fibrosarcomas (combined) in male rats, together with an increase in the incidence of pancreatic acinar-cell adenomas in male rats and in pancreatic islet-cell adenomas, neoplastic nodules of the liver and mammary gland fibroadenomas in female rats. In female mice, dose-related increases in the combined incidence of haemangiomas and haemangiosarcomas and of hepatocellular adenomas were observed; no treatment-related tumour was seen in male mice, possibly due to poor survival. No treatment-related tumour was observed after exposure of mice or rats to commercial toluene diisocyanate by inhalation, although the results of the study with rats have not been reported fully.

5.4 Other relevant data

Toluene diisocyanates are metabolized to toluene diamines in humans and rats. Toluene diisocyanates are irritants and respiratory sensitizers in humans and rats.

Toluene diisocyanate did not induce micronuclei in mammalian erythrocytes *in vivo*. It induced DNA damage and chromosomal aberrations but not sister chromatid exchanges in human lymphocytes *in vitro*. It induced

gene mutation and sister chromatid exchanges but not DNA damage or chromosomal aberrations in rodent cells *in vitro*. It induced sex-linked mutations in *Drosophila* and in some experiments was mutagenic in bacteria. The presence of an exogenous metabolic activation system led to inconsistent results, sometimes enhancing and at other times eliminating the genotoxic effects of toluene diisocyanate.

5.5 Evaluation

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

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

Overall evaluation

Toluene diisocyanates are *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Synonyms

Toluene diisocyanate

- 1,3-Diisocyanatomethylbenzene
- Diisocyanatotoluene
- Isocyanic acid, methyl-*meta*-phenylene ester
- TDI

2,4-Toluene diisocyanate

- 2,4-Diisocyanatotoluene
- Isocyanic acid, 4-methyl-*meta*-phenylene ester
- 2,4-TDI
- 2,4-Toluene diisocyanate

2,6-Toluene diisocyanate

- 2,6-Diisocyanatotoluene
- Isocyanic acid, 2-methyl-*meta*-phenylene ester
- 2,6-TDI
- 2,6-Toluene diisocyanate

Previous evaluations: Vol. 39 (1986); Suppl. 7 (1987)

Last updated: 13 April 1999

1,1,1-TRICHLOROETHANE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 881)

CAS No.: 71-55-6

5. Summary of Data Reported and Evaluation

5.1 Exposure data

1,1,1-Trichloroethane is a solvent. It has been detected in waste-, ground, drinking- and ambient water as well as in ambient and urban air.

5.2 Human carcinogenicity data

An increased risk for central nervous system and multiple myeloma was reported from a cohort study of workers exposed to 1,1,1-trichloroethane in Finland. These findings were not confirmed by two case–control studies carried out in the United States and Canada, while an increased risk for cancer of the lung and kidney was shown in the Canadian study.

5.3 Animal carcinogenicity data

1,1,1-Trichloroethane was tested for carcinogenicity by oral administration in rats in two experiments and in mice in one experiment. Although leukaemia was seen in both sexes of rats in one study and a few liver tumours occurred in male mice, the results of these studies were considered to be inadequate for evaluation. 1,1,1-Trichloroethane was tested by inhalation in rats in two experiments and in mice in one experiment. No chemically related increase in tumour incidence was observed in either rats or mice in one adequate study. Another inhalation study was considered to be inadequate.

In a multistage study for γ-glutamyltranspeptidase (γ-GT)-positive foci in the liver of male rats, neither single administration of 1,1,1-trichloroethane by gavage after a two-thirds partial hepatectomy followed by treatment with phenobarbital (initiation study) nor repeated administration of 1,1,1-trichloroethane by gavage after a two-thirds partial hepatectomy and initiation with *N*-nitrosodiethylamine (promotion study) increased the number of γ-GT-positive foci.

5.4 Other relevant data

Absorption of 1,1,1-trichloroethane vapour is mainly through the respiratory tract. It is rapidly eliminated from blood. Metabolism plays a minor role in this process, more than 90% being eliminated unchanged, both in exposed people and rodents. The main metabolites are trichloroethanol, trichloroacetic acid and carbon dioxide.

1,1,1-Trichloroethane is neurotoxic and hepatotoxic, following exceptionally high exposure concentrations of people and also in rodents. No structural damage has been reported in reproductive toxicity studies in rats and mice, but delayed development, particularly of neurological attributes, has been reported in one study with mice.

1,1,1-Trichloroethane covalently bound to DNA, RNA and protein in mice and rats but did not induce

micronuclei or abnormal sperm head morphology in mice *in vivo*. It induced chromosomal aberrations and cell transformation in mammalian cell cultures and it showed inconclusive evidence of sister chromatid exchange induction. It did not induce unscheduled DNA synthesis or gene mutation in mammalian cells *in vitro*. 1,1,1-Trichloroethane did not cause mutation in plants or sex-linked mutation in *Drosophila*. It did not induce DNA damage, gene conversion, mutation or aneuploidy in yeast or genetic crossing-over or aneuploidy in fungi, but it was mutagenic to some bacterial strains.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity of 1,1,1-trichloroethane in humans.

There is *inadequate evidence* for the carcinogenicity of 1,1,1-trichloroethane in experimental animals.

Overall evaluation

1,1,1-Trichloroethane is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 20 (1979); Suppl. 7 (1987)

Synonyms

- Chloroethene
- Methyl chloroform

Last updated: 13 April 1999

TRIS(2,3-DIBROMOPROPYL) PHOSPHATE (Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 905)

CAS No.: 126-72-7
Chem. Abstr. Name: 2,3-Dibromo-1-propanol phosphate (3:1)

5. Summary of Data Reported and Evaluation

5.1 Exposure data

During the 1970s, tris(2,3-dibromopropyl) phosphate was produced in low volumes, with occupational exposure likely to have occurred in its production and use in the textile industry. It does not appear to have been produced since then. The primary exposure to the general population appears to have been through wearing clothing treated with the chemical.

5.2 Human carcinogenicity data

A small cohort study of workers exposed to tris(2,3-dibromopropyl) phosphate was uninformative.

5.3 Animal carcinogenicity data

Tris(2,3-dibromopropyl) phosphate was tested for carcinogenicity in mice and rats by oral administration. In mice, it produced benign and malignant tumours of the forestomach and lung in animals of each sex, benign and malignant liver tumours in females and benign and malignant tumours of the kidney in males. In rats, it produced benign and malignant tumours of the kidney in males and benign kidney tumours in females. In a study of limited duration in male rats, benign tumours of the colon were reported. After skin application to female mice, it produced tumours of the skin, lung, forestomach and oral cavity.

A metabolite of tris(2,3-dibromopropyl) phosphate, bis(2,3-dibromopropyl) phosphate, was tested for carcinogenicity in rats by oral administration and another metabolite, 2,3-dibromo-1-propanol, was tested in mice and rats by skin application. They produced a variety of tumours, including skin, forestomach and hepatocellular tumours, in mice and rats and tumours of the oesophagus, intestine, nasal mucosa and Zymbal glands in rats.

5.4 Other relevant data

Tris(2,3-dibromopropyl) phosphate and its metabolites bis(2,3-dibromopropyl)-phosphate and mono(2,3-dibromopropyl) phosphate are nephrotoxic in rodents.

Tris(2,3-dibromopropyl) phosphate is mutagenic in bacteria and causes genetic damage in cultured mammalian cells, *Drosophila melanogaster* and mice, probably via metabolism to a number of intermediates of which 2-bromoacrolein may be particularly important.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of tris(2,3-dibromopropyl) phosphate.

There is *sufficient evidence* in experimental animals for the carcinogenicity of tris(2,3-dibromopropyl) phosphate.

Overall evaluation

Tris(2,3-dibromopropyl)phosphate *is probably carcinogenic to humans (Group 2A)*.

In making the overall evaluation, the Working Group took into consideration that tris(2,3-dibromopropyl) phosphate is consistently active in a wide range of mammalian in-vivo and in-vitro test systems.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 20 (1979); Suppl. 7 (1987)

Synonyms

- 2,3-Dibromo-1-propanol phosphate
- Phosphoric acid, tris(2,3-dibromopropyl) ester
- Tris

Last updated: 13 April 1999

VINYL BROMIDE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 923)

CAS No.: 593-60-2
Chem. Abstr. Name: Bromoethene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Occupational exposure may occur during the production of vinyl bromide and its polymers.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Vinyl bromide was tested in female mice by skin application and by subcutaneous injection, and in rats by inhalation exposure. In the inhalation study in rats, there was a dose-related increase in the incidence of liver angiosarcomas and Zymbal gland carcinomas; an increased incidence of liver neoplastic nodules and hepatocellular carcinoma was also noted.

5.4 Other relevant data

Vinyl bromide was mutagenic to *Salmonella typhimurium* and *Drosophila melanogaster*.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of vinyl bromide were available.

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

Overall evaluation

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

In making the overall evaluation, the Working Group took into consideration that all available studies showed a consistently parallel response between vinyl bromide and vinyl chloride. In addition, both vinyl chloride and vinyl bromide are activated via a P450-dependent pathway to their corresponding epoxides. For both vinyl chloride and vinyl bromide, the covalent binding of these compounds to DNA forms the respective etheno adducts. The weight of positive evidence for both compounds was also noted among the studies for genotoxicity, although the number and variety of tests for vinyl bromide were fewer.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 19 (1979); Vol. 39 (1986); Suppl. 7

Synonym

- Bromoethylene

Last updated: 13 April 1999

1,3-DICHLOROPROPENE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 933)

CAS No.: 542-75-6
Chem. Abstr. Name: 1,3-Dichloro-1-propene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

1,3-Dichloropropene is used in organic synthesis and as a soil fumigant. It can be released into the air and waste water and can occur to some extent in ground water.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Technical-grade 1,3-dichloropropene (containing 1.0% epichlorohydrin), when given by gavage, produced tumours of the urinary bladder, lung and forestomach in mice and of the liver and forestomach in rats. Inhalation exposure produced an increase in the incidence of bronchioalveolar adenomas in mice. No increase in tumours was seen in rats. After subcutaneous administration to mice, the *cis*-isomer produced malignant tumours at the site of injection.

5.4 Other relevant data

The principle metabolic pathway of 1,3-dichloropropene is conjugation with glutathione and elimination as mercapturic acids. Enzymatic conjugation with glutathione and nonenzymatic alkylation proceed more rapidly with the *cis*-isomer than with the *trans*-isomer. At the concentrations used in rodent carcinogenicity studies by inhalation, significant morphological alterations in the nasal tissues were observed. No teratogenic or embryotoxic effects were observed in rats and rabbits exposed by inhalation to the mixed isomers.

1,3-Dichloropropene induces micronuclei in the bone marrow of female mice, as well as sister chromatid exchanges and DNA damage in cultured mammalian cells. It is mutagenic to bacteria.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of 1,3-dichloropropene were available.

There is *sufficient evidence* in experimental animals for the carcinogenicity of mixed isomers of 1,3-dichloropropene (technical grade).

Overall evaluation

1,3-Dichloropropene (technical-grade) is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 41 (1986); Suppl. 7 (1987)

Last updated: 13 April 1999

1,2-DIMETHYLHYDRAZINE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 947)

CAS No.: 540-73-8
Chem. Abstr. Name: 1,2-Dimethylhydrazine

5. Summary of Data Reported and Evaluation

5.1 Exposure data

1,2-Dimethylhydrazine is believed to be used only as a laboratory chemical. No information on potential human exposure is available.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

1,2-Dimethylhydrazine was studied for carcinogenicity in many experiments in rats and mice, mainly by subcutaneous, infrequently by oral and rarely by other routes of administration.

Whatever the route of administration, 1,2-dimethylhydrazine, if given at an appropriate dosage, produced in mice and rats a high incidence of adenomas and adenocarcinomas of the colon and, to a lesser extent, of the small bowel. When given with drinking water or by gavage at low single doses, it produced a high incidence of vascular tumours.

In some experiments in rats, it produced ear duct papillomas and carcinomas, hepatocarcinomas, kidney adenomas, carcinomas and fibrosarcomas. When given to rats at very high single doses, it produced high incidences of nephroblastomas.

In some strains of mice, it produced a high incidence of hormone-dependent angiosarcomas of the kidney capsule (males only), uterine sarcomas or vascular tumours and tumour-like lesions of the ovary.

5.4 Other relevant data

1,2-Dimethylhydrazine is readily absorbed. It can be *N*-demethylated, yielding formaldehyde, and can be oxidized through several steps to yield methylazoxymethanol. It binds covalently to protein, DNA and RNA in many mammalian tissues. The colon of rats is a target organ for 1,2-dimethylhydrazine toxicity, where it can produce aberrant crypts. In developmental studies, it is embryo- and feto-toxic in rats.

1,2-Dimethylhydrazine formed DNA adducts and induced gene mutations, DNA breaks and micronuclei *in vitro* and *in vivo* in rodents. *In vitro* it formed DNA adducts and induced unscheduled DNA synthesis and gene mutations in mammalian cells. Conflicting evidence has been obtained for its genotoxicity in bacteria.

Although the activating pathway has not been clarified in detail, there is good evidence that human tissues,

cells and subcellular preparations can activate 1,2-dimethylhydrazine in a similar manner to the corresponding rodent models.

1,2-Dimethylhydrazine requires bioactivation to become mutagenic and alkylates DNA in several species *in vivo*. It is not genotoxic in bacteria, but it is mutagenic for various endpoints in virtually all somatic test systems examined *in vitro* and *in vivo*.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of 1,2-dimethylhydrazine were available.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,2-dimethylhydrazine.

Overall evaluation

1,2-Dimethylhydrazine is *probably carcinogenic to humans (Group 2A)*.

In making the overall evaluation, the Working Group took into account that 1,2-dimethylhydrazine is consistently mutagenic in a wide range of test systems and gives rise to a similar pattern of DNA damage in human and animal tissues *in vitro*.

Previous evaluations: Vol. 4 (1974); Suppl. 7 (1987) (p. 62)

Synonyms

- DMH
- Hydrazomethane

Last updated: 9 April 1999

HYDRAZINE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 991)

CAS No.: 302-01-2
Chem. Abstr. Name: Hydrazine

5. Summary of Data Reported and Evaluation

N.B. - Summary (but not evaluation) prepared by the Secretariat after the meeting

5.1 Exposure data

Exposure to hydrazine may occur in its production, and in the production of chemical blowing agents, agricultural chemicals and in water treatment. It has been detected at low levels in wastewater.

5.2 Human carcinogenicity data

The cancer risk of men exposed to hydrazine was investigated in two small cohort studies. In neither of these studies was an elevated risk observed for all cancers combined or for any specific cancer type.

5.3 Animal carcinogenicity data

Hydrazine was tested for carcinogenicity by oral administration to mice in several experiments, producing mammary and lung tumours. When tested by oral administration or inhalation exposure in rats, it produced lung, liver and nasal tumours and a few colon tumours. In hamsters, it produced liver tumours and thyroid adenomas following oral or inhalation exposure.

5.4 Other relevant data

Following subcutaneous administration of hydrazine to rats, maximum tissue concentrations were reached in about 30 min. Most urinary elimination was as unchanged hydrazine, with acetylhydrazine being the main metabolite but a minor elimination product. Tissue retention was longest in kidney, mainly due to the presence of acetylhydrazine. Hydrazine is metabolized and detoxified by at least three microsomal cytochrome P450 isoenzymes in rat liver (CYP2E1, CYP2B1 and CYP1A1/2), ultimately yielding molecular nitrogen.

Human exposure to hydrazine has resulted in severe effects upon the central nervous system, liver and kidneys. In rats, hydrazine is hepatotoxic, causing accumulation of triglycerides, inhibition of protein synthesis and the formation of macromitochondria.

Hydrazine induces gene mutations in bacteria, yeast and *Drosophila* and in-vivo treatment of mice, rats and Syrian hamsters results in the formation of *N*7-methylguanine and O^6-methylguanine in liver DNA.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 4 (1974); Suppl. 7 (1987)

Last updated: 13 April 1999

ISOPRENE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1015)

CAS No.: 78-79-5
Chem. Abstr. Name: 2-Methyl-1,3-butadiene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to isoprene occurs in the production of the monomer and in the production of synthetic rubbers. Isoprene occurs in the environment due to emissions from vegetation and the production of ethylene by naphtha cracking.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Isoprene was tested for carcinogenicity in mice and rats by inhalation exposure. In two studies in mice, exposure to isoprene resulted in increased combined incidences of benign and malignant tumours of the lung and liver and of Harderian gland adenomas. In one study, haemangiosarcomas of the heart and spleen and histiocytic sarcomas were also found in male mice, as well as increased incidences of pituitary adenomas and Harderian gland adenomas in female mice. In one adequate study with rats, increased incidences were observed for benign neoplasms in the mammary gland in males and females and in the kidney and testis in males.

5.4 Other relevant data

Both rats and mice exhibited saturation kinetics when exposed to concentrations above 300 ppm [840 mg/m^3]. The maximal rate of metabolism *in vivo*, which occurs via monoepoxides and diepoxide and subsequent epoxide hydration, is more than three times greater in mice than in rats. In-vitro studies and a physiological toxicokinetic model suggest that the rates of metabolism in humans is lower.

At high inhalation exposures, proliferative lesions in olfactory epithelium and lung were observed. Forestomach epithelial hyperplasia was detected at lower exposure levels in rats and mice. Adverse effects in reproductive organs of male and female mice were detected after high inhalation doses.

Isoprene did not induce mutations in bacteria or sister chromatid exchanges or chromosomal aberrations in animal cells *in vitro*. Isoprene induced sister chromatid exchanges and micronuclei in bone-marrow cells after inhalation exposure of mice.

Isoprene binds covalently to haemoglobin *in vivo.*

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of isoprene were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 60 (1994)

Synonym

- Isopentadiene

Last updated: 13 April 1999

ISOPROPANOL
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1027)

CAS No.: 67-63-0

5. Summary of Data Reported and Evaluation

N.B. - Summary (but not the evaluation) prepared by the Secretariat after the meeting.

5.1 Exposure data

Exposure to isopropanol may occur in its production, in the production of acetone and during its use as a solvent.

5.2 Human carcinogenicity data

An increased incidence of cancer of the paranasal sinuses and laryngeal cancer was observed in workers at factories where isopropanol was manufactured by the strong-acid process. One case–control study investigated the risk associated with occupational exposure to isopropanol, but for none of the investigated cancer sites was a significant increase in risk observed.

5.3 Animal carcinogenicity data

Isopropanol was tested for carcinogenicity in mice and rats by inhalation exposure. Although no increase in tumours was observed in mice, the study had some limitations in design and adequacy. A slight increase in interstitial cell adenomas of the testis was observed in male rats.

5.4 Other relevant data

Isopropanol is rapidly absorbed from the human gastrointestinal tract, whereas absorption through the skin is slow. It is metabolized by aldehyde dehydrogenase to acetone, but following human exposure, a large proportion is excreted unchanged in expired air and urine. It is a human sensitizer and is irritant to the eyes and rhinopharynx. Isopropanol is a central nervous system depressant and prolonged inhalation exposure of rats can produce degenerative changes in the brain. There is no evidence for genetic toxicity.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 15 (1977); Suppl. 7 (1987)

Synonym

- 2-Propanol

Last evaluated: 13 April 1999

MALONALDEHYDE (MALONDIALDEHYDE) (Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1037)

Chem. Abstr. Serv. Reg. No.: 542-78-9
Chem. Abstr. Name: Propanedial

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Malonaldehyde is found in many foodstuffs and can be present at high levels in rancid foods. It is present as a lipid metabolite in human and animal tissues. It is probably used only as a research chemical.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Malonaldehyde sodium salt was tested for carcinogenicity in one experiment in mice and in one experiment in rats by oral administration. No increase in tumour incidence was found in mice. In rats, the incidence of follicular-cell tumours of the thyroid was increased in both sexes at the high dose and the incidence of pancreatic islet-cell adenomas was increased in low-dose males.

Malonaldehyde, its bis(dimethylacetal) and its sodium salts were tested for carcinogenicity in mice by skin application; no carcinogenic activity was observed.

5.4 Other relevant data

Background exposures to malonaldehyde occur in experimental animals and humans, as determined by the presence of specific DNA adducts in blood and other tissues. It is mutagenic to bacteria.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of malonaldehyde were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 36 (1985); Suppl. 7 (1987)

Last updated: 13 April 1999

4,4′-METHYLENEDIPHENYL DIISOCYANATE AND POLYMERIC 4,4′-METHYLENEDIPHENYL DIISOCYANATE (Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1049)

CAS No.: (a) 101-68-8 (monomer) and (b) 26447-40-5
Chem. Abstr. Name: 1,1′-Methylenebis(4-isocyanatobenzene)

5. Summary of Data Reported and Evaluation

5.1 Exposure data

4,4′-Methylenediphenyl diisocyanate is used for the production of polyurethane coatings and elastomers.

5.2 Human carcinogenicity data

The risk of cancer associated with occupational exposure to isocyanates has been examined in three industrial cohort studies and in a population-based case–control study of several types of cancer. No strong association or consistent pattern has emerged.

5.3 Animal carcinogenicity data

Polymeric 4,4′-methylenediphenyl diisocyanate containing 44.8–50.2% monomeric 4,4′-methylenediphenyl diisocyanate was tested for carcinogenicity by inhalation in rats. An increased incidence of lung tumours was observed.

5.4 Other relevant data

The major urinary metabolites of 4,4′-methylenediphenyl diisocyanate are 4,4′-methylenedianiline and *N*-acetyl-4,4′-methylenedianiline, both of which also form haemoglobin adducts in exposed workers and rats. 4,4′-Methylenediphenyl diisocyanate is an irritant and a sensitizer; exposure by inhalation produces asthma among workers.

4,4′-Methylenediphenyl diisocyanate forms low-level DNA adducts *in vivo* and induces mutations in bacteria and chromosomal aberrations and sister chromatid exchanges in human lymphocyte cultures.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity of 4,4′-methylenediphenyl diisocyanate or polymeric 4,4′-methylenediphenyl diisocyanate in humans.

There is *limited evidence* in experimental animals for the carcinogenicity of a mixture containing monomeric and polymeric 4,4′-methylenediphenyl diisocyanate.

Overall evaluation

4,4′-Methylenediphenyl diisocyanate (industrial preparation) is *not classifiable as to its carcinogenicity to humans (Group 3).*

Previous evaluations: Vol. 19 (1979); Suppl. 7 (1987)

For definition of the italicized terms, see Preamble Evaluation.

Synonyms

For 101-68-8 (monomer)

- Bis(1,4-isocyanatophenyl)methane
- Diphenylmethane diisocyanate
- Isocyanic acid, methylenedi-*para*-phenylene ester
- MDI
- Methylenedi-*para*-phenylene isocyanate

For 26447-40-5

- Crude MDI
- Polymeric MDI
- PMDI
- Generic MDI
- Non-isomeric-specific MDI

Last updated: 13 April 1999

METHYL METHANESULFONATE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1059)

CAS No.: 66-27-3
Chem. Abstr. Name: Methanesulfonic acid, methyl ester

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Methyl methanesulfonate is a laboratory chemical that has been produced for research purposes. No information was available to the Working Group on potential human exposures.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Methyl methanesulfonate was tested in rats by inhalation exposure and by subcutaneous and intraperitoneal administration, producing nasal tumours, tumours of the nervous system and tumours at the injection site. In rats, it was carcinogenic after administration of a single dose as well as following prenatal exposure. Following instillation into the bladder of rats, it potentiated the effect of *N*-methyl-*N*-nitrosourea. In one study, following oral administration in mice, it increased the incidence of lung tumours and of lymphomas. A subsequent experiment with oral and intraperitoneal administration to mice failed to increase the incidence of lung adenomas in A/J mice. In a multistage mouse skin model, it was not an initiator but was found to be a stage I tumour promoter. It accelerated the occurrence of thymic lymphomas in AKR mice.

5.4 Other relevant data

Methyl methanesulfonate caused an increased frequency of resorptions and congenital malformations after treatment of females 1–25 h after mating.

Methyl methanesulfonate induced mouse germ cell mutations and chromosomal aberrations, and DNA damage, micronuclei, sister chromatid exchanges and chromosomal aberrations in somatic cells of rodents *in vivo*. It increased the frequency of DNA damage, gene mutation, sister chromatid exchanges and micronuclei in human and rodent cell cultures, as well as chromosomal aberrations in rodent cells *in vitro*. Methyl methanesulfonate induced somatic and sex-linked mutations in *Drosophila.* It induced DNA damage in *Escherichia coli* and was mutagenic in bacteria.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of methyl methanesulfonate were available.

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

Overall evaluation

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

In making the overall evaluation, the Working Group took into consideration that methyl methanesulfonate is a direct-acting methylating agent which is mutagenic in a wide range of in-vivo and in-vitro test systems.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 7 (1974); Suppl. 7 (1987)

Synonym

- MMS

Last updated: 13 April 1999

2-NITROPROPANE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1079)

CAS No.: 79-46-9
Chem. Abstr. Name: 2-Nitropropane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

2-Nitropropane is produced in low volume and occupational exposures occur primarily in its production and use as a solvent in inks, adhesives, paints and coatings. Exposures of the general population may occur in ambient air and water near industrial sites manufacturing or using 2-nitropropane, in cigarette smoke, and possibly from its solvent uses.

5.2 Human carcinogenicity data

No adequate epidemiological data were available to the Working Group.

5.3 Animal carcinogenicity data

2-Nitropropane was tested for carcinogenicity in one experiment in rats by oral administration and two experiments in rats by inhalation exposure. It induced benign and malignant liver tumours following oral administration and hepatocellular carcinomas in one inhalation experiment and an increased incidence of hepatocellular nodules in the other. 2-Nitropropane showed initiating activity in rat liver in two experiments.

5.4 Other relevant data

Nitropropane shows mainly hepatotoxicity in rats.

It is mutagenic in a wide variety of in-vitro and in-vivo systems by a direct action. It leads to formation of 8-hydroxydeoxyguanosine in DNA *in vivo*.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity of 2-nitropropane in humans.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 2-nitropropane.

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 29 (1982); Suppl. 7 (1987)

Synonyms

- Dimethylnitromethane
- Isonitropropane

Last updated: 13 April 1999

1,3-PROPANE SULTONE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1095)

CAS No.: 1120-71-4
Chem. Abstr. Name: 1,2-Oxathiolane, 2,2-dioxide

5. Summary of Data Reported and Evaluation

5.1 Exposure data

1,3-Propane sultone has been used as an intermediate in the production of a variety of chemical products.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

1,3-Propane sultone is carcinogenic in rats by all routes of administration (oral, dermal, intravenous, subcutaneous or prenatal), producing tumours at various sites including the brain and mammary gland. In mice, it was carcinogenic after skin application and subcutaneous injection producing local tumours.

5.4 Other relevant data

1,3-Propane sultone is mutagenic in bacteria. It is positive for many genetic activity end-points *in vitro* in rodent and human cells. 1,3-Propane sultone induces DNA strand breaks *in vivo* in rat brain cells.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of 1,3-propane sultone were available.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,3-propane sultone.

Overall evaluation

1,3-Propane sultone is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 4 (1974); Suppl. 7 (1987)

Synonyms

- 3-Hydroxy-1-propanesulfonic acid, γ-sultone

- Propane sultone

Last updated: 13 April 1999

β-PROPIOLACTONE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1103)

CAS No.: 57-57-8
Chem. Abstr. Name: 2-Oxetanone

5. Summary of Data Reported and Evaluation

5.1 Exposure data

The main use of β-propiolactone has been as an intermediate in the production of acrylic acid and its esters. It has also been used for the sterilization of vaccines and blood products.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

β-Propiolactone was tested for carcinogenicity in mice by skin application and subcutaneous or intraperitoneal injection and in rats by inhalation exposure and subcutaneous injection, producing local tumours. The results obtained in studies in hamsters and guinea-pigs were equivocal.

5.4 Other relevant data

β-Propiolactone is a direct-acting alkylating agent. It forms DNA adducts. It is mutagenic in a wide variety of in-vitro and in-vivo systems, both in somatic and germ cells.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of β-propiolactone were available.

There is *sufficient evidence* in experimental animals for the carcinogenicity of β-propiolactone.

Overall evaluation

β-Propiolactone is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 4 (1974); Suppl. 7 (1987)

Synonyms

- Hydracrylic acid, β-lactone
- 3-Hydroxypropionic acid, lactone
- 3-Hydroxypropionic acid, β-lactone
- Propanolide
- 3-Propanolide
- Propiolactone
- 3-Propiolactone
- β-Propionolactone

Last updated: 13 April 1999

RESORCINOL
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1119)

CAS No.: 108-46-3
Chem. Abstr. Name: 1,3-Benzenediol

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to resorcinol may occur in its production, in the manufacture of adhesives, rubber, wood products, dyes and pharmaceuticals. It has been detected at low levels in groundwater and occurs in wood smoke and tobacco smoke.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Resorcinol was tested for carcinogenicity in one experiment in mice and in one experiment in rats by oral administration. It was also tested in mice by skin application. No carcinogenic effect was observed in these experiments.

In several experiments in rats and hamsters, resorcinol was tested for promoting activity after initiation by known carcinogens. It did not enhance the incidence of tumours of the bladder, forestomach, liver or kidney.

In one study, resorcinol increased the incidence of tongue and oesophageal tumours after initiation with *N*-nitrosomethyl-*n*-amylamine.

5.4 Other relevant data

Resorcinol is water-soluble and readily conjugated and eliminated. The chemical has no known potential for formation of electrophilic reactive intermediates comparable to those derived from the other dihydroxybenzenes. Resorcinol was tested in various genetic toxicology assays, including in-vitro bacterial and mammalian assays and in-vivo mammalian assays. It gave negative results in all studies, with the exception of a positive response in the two in-vitro studies that assessed chromosomal aberrations in human lymphocytes from whole blood cultures; however, resorcinol did not induce chromosomal aberrations in human fibroblasts.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of resorcinol were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 15 (1977); Suppl. 7 (1987)

Synonyms

- *meta*-Benzenediol
- Resorcin

Last updated: 13 April 1999

1,1,1,2-TETRACHLOROETHANE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1133)

CAS No.: 630-20-6
Chem. Abstr. Name: 1,1,1,2-Tetrachloroethane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

1,1,1,2-Tetrachloroethane is an intermediate in one process for the manufacture of trichloroethylene and tetrachloroethylene and has been reported to occur as an impurity in these widely used products. It has been detected at low levels in ambient air and in drinking-water.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

1,1,1,2-Tetrachloroethane was tested for carcinogenicity by oral administration by gavage in one study in mice and one study in rats. An increased incidence of hepatocellular adenomas was observed in mice of each sex and of hepatocellular carcinomas in females. The experiment in male rats gave negative results and that in female rats was inconclusive. In one small experiment in rats, no initiating or promoting activity of 1,1,1,2-tetrachloroethane was demonstrated.

5.4 Other relevant data

In a single study, 1,1,1,2-tetrachloroethane bound covalently to DNA in rats and mice *in vivo*. It induced gene mutations, sister chromatid exchanges and aneuploidy, but not chromosomal aberrations, in rodent cell cultures. It did not induce sex-linked recessive mutation in *Drosophila* or mutations or aneuploidy in yeast. 1,1,1,2-Tetrachloroethane induced gene conversion in yeast, genetic crossing-over and aneuploidy in fungus and gene mutations in bacteria.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of 1,1,1,2-tetrachloroethane were available.

There is *limited evidence* in experimental animals for the carcinogenicity of 1,1,1,2-tetrachloroethane.

Overall evaluation

1,1,1,2-Tetrachloroethane is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 41 (1986); Suppl. 7 (1987)

Synonym

- (Chloromethyl)trichloromethane

Last updated: 13 April 1999

TETRAFLUOROETHYLENE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1143)

CAS No.: 116-14-3
Chem. Abstr. Name: Tetrafluoroethene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Tetrafluoroethylene is used in the manufacture of polytetrafluoroethylene and other polymers. No information on potential human exposure is available.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Tetrafluoroethylene was tested for carcinogenicity in one study in mice and one study in rats by inhalation. In both sexes of mice, it increased the incidence of hepatocellular carcinomas, histiocytic sarcomas and haemangiosarcomas in the liver. In rats of both sexes, it increased the incidence of hepatocellular carcinomas and kidney tubule cell adenomas.

5.4 Other relevant data

Tetrafluoroethylene is metabolized by hepatic glutathione *S*-transferase and the resulting cysteine conjugate is further metabolized by renal β-lyase. This pathway results in the formation of a reactive thiol that causes kidney toxicity in rats.

Tetrafluoroethylene did not induce micronuclei in mouse erythrocytes and the metabolite tetrafluoroethylcysteine was not mutagenic in *Salmonella typhimurium*.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of tetrafluoroethylene were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 19 (1979); Suppl. 7 (1987)

Synonyms

- Perfluoroethene
- Perfluoroethylene
- 1,1,2,2-Tetrafluoroethylene

Last updated: 13 April 1999

1,1,2-TRICHLOROETHANE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1153)

CAS No.: 79-00-5
Chem. Abstr. Name: 1,1,2-Trichloroethane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

1,2-Trichloroethane is used in the manufacture of vinylidene chloride. It has been detected in ground-, drinking-, waste- and ambient water and ambient air.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

1,1,2-Trichloroethane was tested for carcinogenicity in a two-year study in male and female B6C3F$_1$ mice and Osborne-Mendel rats by oral administration and in Sprague-Dawley rats by subcutaneous injection. In the study by oral administration, 1,1,2-trichloroethane produced hepatocellular neoplasms and adrenal phaeochromocytomas in mice of each sex but did not significantly increase the proportion of rats with neoplasms at any site relative to untreated controls. In the study in rats by subcutaneous injection, 1,1,2-trichloroethane did not increase the incidence of neoplasms.

5.4 Other relevant data

1,1,2-Trichloroethane bound to DNA, RNA and protein and caused strong S-phase induction but not unscheduled DNA synthesis in rodents *in vivo*. It induced DNA damage and micronuclei in human lymphocytes and cell transformation in BALB/c-3T3 cells *in vitro*. 1,1,2-Trichloroethane caused chromosomal malsegregation in fungi and showed some evidence of mutagenicity in bacteria.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of 1,1,2-trichloroethane were available.

There is *limited evidence* in experimental animals for the carcinogenicity of 1,1,2-trichloroethane.

Overall evaluation

1,1,2-Trichloroethane is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 20 (1979); Suppl. 7 (1987); Vol. 52 (1991)

Synonym

- Vinyl trichloride

Last updated: 13 April 1999

VINYLIDENE CHLORIDE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1163)

CAS No.: 75-35-4
Chem. Abstr. Name: 1,1-Dichloroethene

5. Summary of Data Reported and Evaluation

N.B. - Summary (but not the evaluation) prepared by the Secretariat after the meeting.

5.1 Exposure data

Exposure to vinylidene chloride may occur during its production and in the production of copolymers. It has been detected in wastewater.

5.2 Human carcinogenicity data

Two cohort studies were performed in workers exposed to vinylidene chloride. Both studies have major limitations and do not allow evaluation of the carcinogenicity of the compound.

No specific association was found between exposure to vinylidene chloride and an excess of lung cancer observed in a synthetic chemical plant in the United States.

5.3 Animal carcinogenicity data

Vinylidene chloride was tested for carcinogenicity in mice and rats by oral administration and inhalation exposure, in mice by subcutaneous administration and topical application and in hamsters by inhalation. Studies in mice and rats by oral administration gave negative results. In inhalation studies, no treatment-related neoplasm was observed in rats or hamsters. In mice, treatment-related increases in the incidence of kidney adenocarcinomas were observed in male mice, as were increases in mammary carcinomas in females and pulmonary adenomas in male and female mice. In skin-painting studies in female mice, vinylidene chloride showed activity as an initiator, but in a study of repeated skin application, no skin tumour occurred. No tumour at the injection site was seen in mice given repeated subcutaneous administration.

5.4 Other relevant data

Vinylidene chloride is oxidized principally by CYP2E1, the activity of this cytochrome P450 being higher in those tissues (particularly mouse Clara cells and male mouse kidney) that are targets for toxicity of vinylidene chloride. Glutathione levels and conjugation are important in its inactivation and protect against covalent binding. It causes gene mutations in microorganisms, but its genetic activity has not been extensively studied in mammalian cells.

5.5 Evaluation

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

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

For definition of the italicized terms, see Preamble Evaluation.

Overall evaluation

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

Previous evaluations: Vol. 19 (1979); Vol. 39 (1986); Suppl. 7 (1987)

Synonyms

- Asym-dichloroethylene
- 1,1-Dichloroethylene

Last updated: 13 April 1999

N-VINYL-2-PYRROLIDONE AND POLYVINYL PYRROLIDONE
N-VINYL-2-PYRROLIDONE (Group 3)
POLYVINYL PYRROLIDONE (Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1181)

CAS No.: 88-12-0
Chem. Abstr. Name: 1-Ethenyl-2-pyrrolidinone

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Little information was available to the Working Group regarding potential exposures to *N*-vinyl-2-pyrrolidone.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

N-Vinyl-2-pyrrolidone was tested for carcinogenicity in one experiment in rats by inhalation exposure. It produced adenomas and adenocarcinomas of the nasal cavity, squamous carcinomas of the larynx and hepatocellular carcinomas in both sexes. Another 12-month inhalation experiment in rats of the same strain indicated occurrence of adenomas of the nasal cavity and foci of cellular alteration of the liver.

Polyvinyl pyrrolidone was tested for carcinogenicity in mice, rats and rabbits by several routes of administration, producing local tumours.

5.4 Other relevant data

N-Vinyl-2-pyrrolidone metabolites and polyvinyl pyrrolidone are excreted mainly in urine. Inhalation of low concentrations of *N*-vinyl-2-pyrrolidone by rats can cause nasal cavity inflammation, atrophy of olfactory epithelium and hyperplasia of the basal cells of the respiratory and olfactory epithelium. In humans and experimental animals, polyvinyl pyrrolidone accumulates in vacuoles of cells of many organs and, in humans, may be accompanied by pulmonary fibrosis and pneumonia. There have been no genetic toxicity studies with either compound.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of *N*-vinyl-2-pyrrolidone or polyvinyl pyrrolidone were available.

There is *limited evidence* for the carcinogenicity of *N*-vinyl-2-pyrrolidone in experimental animals.

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

Overall evaluation

N-Vinyl-2-pyrrolidone is *not classifiable as to its carcinogenicity to humans (Group 3)*.

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 19 (1979); Suppl. 7 (1987)

Synonyms

- Vinylbutyrolactam
- Vinylpyrrolidinone
- 1-Vinylpyrrolidinone
- *N*-Vinylpyrrolidinone
- 1-Vinyl-2-pyrrolidinone
- *N*-Vinyl-2-pyrrolidinone
- Vinylpyrrolidone
- *N*-Vinylpyrrolidone
- 1-Vinyl-2-pyrrolidone

Last updated: 13 April 1999

XYLENES
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1189)

CAS No.: 1330-20-7
Chem. Abstr. Name: Dimethylbenzene

CAS No.: 95-47-6
Chem. Abstr. Name: 1,2-Dimethylbenzene

CAS No.: 108-38-3

Chem. Abstr. Name: 1,3-Dimethylbenzene

CAS No.: 106-42-3
Chem. Abstr. Name: 1,4-Dimethylbenzene

5. Summary of Data Reported and Evaluation

N.B. - Summary (but not the evaluation) prepared by the Secretariat after the meeting.

5.1 Exposure data

Exposure to xylenes may occur during their production and in the production of aviation gasoline and protective coatings, and during their use in petroleum products, e.g., solvents, and as intermediates in organic synthesis. Natural sources include petroleum, forest fires and volatile substances in plants.

5.2 Human carcinogenicity data

Xylene was mentioned as an exposure in four studies. Two were community-based case–control studies, one of which involved brain cancer and one involved several types of cancer. The two industry-based studies were configured as nested case–control studies, one of central nervous system tumours and one of several sites. In none of these studies was xylene the sole or predominant exposure. Cancers at most sites were not significantly associated with xylene exposure in any study. Incidence of colorectal cancer was significantly elevated in the Canadian case–control study, but no other study reported colorectal cancer results. Hodgkin's disease was elevated in one study; non-Hodgkin lymphoma was elevated in one study, but not in another. Most results were based on small numbers. In view of the multiple exposure circumstances in most studies, the multiple inference context of these studies, and the weak consistency of the findings, these results are not strong enough to establish whether there is an association with xylene exposure.

5.3 Animal carcinogenicity data

Xylene (technical grade or mixed xylenes) was tested for carcinogenicity in one strain of mice and in two strains of rats by gavage. One study in rats with mixed xylenes was considered inadequate for evaluation. No increase in the incidence of tumours was observed in either mice or rats following the administration of a technical-grade xylene.

No data were available on the indidivual isomers.

5.4 Other relevant data

Xylenes are absorbed after inhalation and dermal exposure. Elimination after human exposure is rapid and mostly as urinary metabolites after oxidation to the methylbenzyl alcohols, methylbenzoic acids and their glycine and glucuronic acid conjugates. In mice inhaling *para*-xylene, methylhippurate accumulated in the nasal mucosa and olfactory bulb.

Renal and hepatic toxicity has been described following human accidental poisonings and experimental exposure of rats and mice. In rats, hepatic cytochrome P450 content, particularly of CYP2B1, and the activities of certain conjugation enzymes are increased upon inhalation exposure to *meta*-xylene. Although xylenes have been studied extensively, there is no confirmed evidence of genetic activity for any of the isomers.

5.5 Evaluation

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

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

Overall evaluation

Xylenes are *not classifiable as to their carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 47 (1989)

Synonyms

Dimethylbenzene

- Xylene
- Xylol

1,2-Dimethylbenzene

- *ortho*-Xylene
- *ortho*-Xylol

1,3-Dimethylbenzene

- *meta*-Xylene
- *meta*-Xylol

1,4-Dimethylbenzene

- *para*-Xylene
- *para*-Xylol

Last updated: 13 April 1999

ACETAMIDE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1211)

CAS No.: 60-35-5

5. Evaluation

No epidemiological data relevant to the carcinogenicity of acetamide were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 7 (1974); Suppl. 7 (1987)

Last updated: 13 April 1999

ACRYLIC ACID
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1223)

CAS No.: 79-10-7

5. Evaluation

No epidemiological data relevant to the carcinogenicity of acrylic acid were available.

No experimental data relevant to the carcinogenicity of acrylic acid were available.

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 19 (1979)

Synonym

- 2-Propenoic acid

Last updated: 13 April 1999

ALLYL CHLORIDE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1231)

CAS No.: 107-05-1
Chem. Abstr. Name: 3-Chloro-1-propene

5. Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 36 (1985)

Synonyms

- 3-Chloropropene
- 3-Chloropropylene
- 2-Propenyl chloride

Last updated: 13 April 1999

ALLYL ISOVALERATE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1241)

CAS No.: 2835-39-4

5. Evaluation

No epidemiological data relevant to the carcinogenicity of allyl isovalerate were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 36 (1985)

Synonym

- Butanoic acid, 3-methyl-, 2-propenyl ester

Last updated: 13 April 1999

1,4-BENZOQUINONE (*para*-QUINONE) (Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1245)

CAS No.: 106-51-4

5. Evaluation

No epidemiological data relevant to the carcinogenicity of 1,4-benzoquinone were available.

There is *inadequate evidence* in experimental animals for the carcinogenicity of 1,4-benzoquinone.

Overall evaluation

1,4-Benzoquinone is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 15 (1977)

Synonyms

- *para*-Benzoquinone
- 2,5-Cyclohexadiene-1,4-dione

Last updated: 13 April 1999

1,4-BENZOQUINONE DIOXIME
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1251)

CAS No.: 105-11-3

5. Evaluation

No epidemiological data relevant to the carcinogenicity of 1,4-benzoquinone dioxime were available.

There is *limited evidence* in experimental animals for the carcinogenicity of 1,4-benzoquinone dioxime.

Overall evaluation

1,4-Benzoquinone dioxime is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 29 (1982)

Synonyms

- *para*-Benzoquinone dioxime
- 2,5-Cyclohexadiene-1,4-dione, dioxime

Last updated: 13 April 1999

BENZYL ACETATE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1255)

CAS No.: 140-11-4

5. Summary of Data Reported and Evaluation

5.1 Exposure data

There is widespread human exposure to benzyl acetate by ingestion, skin application and inhalation.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Benzyl acetate was tested for carcinogenicity by gavage in one experiment in mice and in one experiment in rats, and by administration in the diet in two studies in rats and in one study in mice. In the gavage study in mice, increased incidences of liver adenomas and of combined liver adenomas and carcinomas were oberved in animals of each sex. An increased incidence of forestomach tumours was observed in mice of each sex. An increased incidence of acinar-cell adenomas of the pancreas was observed in male rats administered benzyl acetate by gavage. Benzyl acetate did not increase the incidence of tumours in either mice or rats when administered in the diet. A low incidence of pancreatic carcinomas *in situ* was reported in one study.

Benzyl acetate was tested in two studies for promotion of pancreatic carcinogenesis in rats and was found to be inactive.

5.4 Other relevant data

Benzyl acetate is hydrolysed to benzoic acid and acetate. It is metabolized similarly by humans and rodents. Except for one positive result *in vitro*, findings on genotoxicity *in vitro* and *in vivo* were negative.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of benzyl acetate were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 40 (1986)

Synonym

- Acetic acid, phenylmethyl ester

Last updated: 13 April 1999

BIS(2-CHLOROETHYL)ETHER
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1265)

CAS No.: 111-44-4

5. Evaluation

There is *inadequate evidence* for the carcinogenicity of bis(2-chloroethyl)ether in humans.

There is *limited evidence* in experimental animals for the carcinogenicity of bis(2-chloroethyl)ether.

Overall evaluation

Bis(2-chloroethyl)ether is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 9 (1975)

Synonym

- 1,1′-Oxybis(2-choro)ethane

Last updated: 13 April 1999

1,2-BIS(CHLOROMETHOXY)ETHANE (Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1271)

CAS No.: 13483-18-6

5. Evaluation

No epidemiological data relevant to the carcinogenicity of 1,2-bis(chloromethoxy)ethane were available.

There is *limited evidence* in experimental animals for the carcinogenicity of 1,2-bis(chloromethoxy)ethane.

Overall evaluation

1,2-Bis(chloromethoxy)ethane is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 15 (1977)

Synonym

- 1,2-Bis(chloromethoxy)ethane

Last updated: 13 April 1999

1,4-BIS(CHLOROMETHOXYMETHYL)BENZENE (Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p.1273)

CAS No.: 56894-91-8

5. Evaluation

No epidemiological data relevant to the carcinogenicity of 1,4-bis(chloromethoxymethyl)benzene were available.

There is *limited evidence* in experimental animals for the carcinogenicity of 1,4-bis(chloromethoxymethyl)benzene.

Overall evaluation

1,4-Bis(chloromethoxymethyl)benzene is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 15 (1977)

Synonym

- 1,4-Bis(chloromethoxymethyl)benzene

Last updated: 13 April 1999

BIS(2-CHLORO-1-METHYLETHYL)ETHER (Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1275)

CAS No.: 108-60-1

5. Evaluation

No epidemiological data relevant to the carcinogenicity of bis(2-chloro-1-methylethyl)ether were available.

There is *limited evidence* in experimental animals for the carcinogenicity of bis(2-chloro-1-methylethyl)ether.

Overall evaluation

Bis(2-chloro-1-methylethyl)ether is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 41 (1986)

Synonym

- 2,2′-Oxybis(1-chloropropane)

Last updated: 13 April 1999

BIS(2,3-EPOXYCYCLOPENTYL)ETHER (Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1281)

CAS No.: 2386-90-5

5. Evaluation

No epidemiological data relevant to the carcinogenicity of bis(2,3-epoxycyclopentyl)ether were available.

There is *limited evidence* in experimental animals for the carcinogenicity of bis(2,3-epoxycyclopentyl)ether.

Overall evaluation

Bis(2,3-epoxycyclopentyl)ether is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 47 (1989)

Synonym

- 2,2′-Oxybis(6-oxabicyclo[3.1.0]hexane)

Last updated: 13 April 1999

BISPHENOL A DIGLYCIDYL ETHER
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1285)

CAS No.: 1675-54-3

5. Evaluation

No epidemiological data relevant to the carcinogenicity of bisphenol A diglycidyl ether were available.

There is *limited evidence* in experimental animals for the carcinogenicity of bisphenol A diglycidyl ether.

Overall evaluation

Bisphenol A diglycidyl ether is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 47 (1989) (Some Glycidyl ethers)

Synonym

- 2,2′-[(1-Methylethylidene)bis(4,1-phenyleneoxymethylene)]bis(oxirane)

Last updated: 13 April 1999

BROMOCHLOROACETONITRILE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1291)

CAS No.: 83463-62-1

5. Evaluation

No epidemiological data relevant to the carcinogenicity of bromochloroacetonitrile were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 52 (1991) (Halogenated acetonitriles)

Last updated: 13 April 1999

BROMODICHLOROMETHANE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1295)

CAS No.: 75-27-4

5. Evaluation

No epidemiological data relevant to the carcinogenicity of bromodichloromethane were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 52 (1991)

Last updated: 13 April 1999

BROMOETHANE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1305)

CAS No.: 74-96-4

5. Evaluation

No epidemiological data relevant to the carcinogenicity of bromoethane were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 52 (1991)

Synonym

- Ethyl bromide

Last updated: 13 April 1999

BROMOFORM
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1309)

CAS No.: 75-25-2

5. Evaluation

No epidemiological data relevant to the carcinogenicity of bromoform were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 52 (1991)

Synonym

- Tribromomethane

Last updated: 13 April 1999

β-BUTYROLACTONE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1317)

CAS No.: 3068-88-0

5. Evaluation

No epidemiological data relevant to the carcinogenicity of β-butyrolactone were available.

There is *sufficient evidence* in experimental animals for the carcinogenicity of β-butyrolactone.

Overall evaluation

β-Butyrolactone is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 11 (1976)

Synonym

- 4-Methyl-2-oxetanone

Last updated: 13 April 1999

CARBAZOLE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1319)

CAS No.: 86-74-8

5. Evaluation

No epidemiological data relevant to the carcinogenicity of carbazole were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 32 (1983)

Synonym

- 9H-Carbazole

Last updated: 13 April 1999

CHLOROACETONITRILE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1325)

CAS No.: 107-14-2

5. Evaluation

No epidemiological data relevant to the carcinogenicity of chloroacetonitrile were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 52 (1991) (Halogenated acetonitriles)

Last updated: 13 April 1999

CHLORODIBROMOMETHANE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1331)

CAS No.: 124-48-1

5. Evaluation

No epidemiological data relevant to the carcinogenicity of chlorodibromomethane were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 52 (1991)

Last updated: 13 April 1999

CHLORODIFLUOROMETHANE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1339)

CAS No.: 75-45-6

5. Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 41 (1986); Suppl. 7 (1987)

Last updated: 13 April 1999

CHLOROETHANE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1345)

CAS No.: 75-00-3

5. Evaluation

No epidemiological data relevant to the carcinogenicity of chloroethane were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 52 (1991)

Synonym

- Ethyl chloride

Last updated: 13 April 1999

CHLOROFLUOROMETHANE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1351)

CAS No.: 593-70-4

5. Evaluation

No epidemiological data relevant to the carcinogenicity of chlorofluoromethane were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 41 (1986)

Last updated: 13 April 1999

2-CHLORO-1,1,1-TRIFLUOROETHANE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1355)

CAS No.: 75-88-7
Chem. Abstr. Name: 2-Chloro-1,1,1-trifluoroethane

5. Evaluation

No epidemiological data relevant to the carcinogenicity of 2-chloro-1,1,1-trifluoroethane were available.

There is *limited evidence* in experimental animals for the carcinogenicity of 2-chloro-1,1,1-trifluoroethane.

Overall evaluation

2-Chloro-1,1,1-trifluoroethane is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 41 (1986)

Last evaluated: 13 April 1999

CYCLOHEXANONE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1359)

CAS No.: 108-94-1

5. Evaluation

No epidemiological data relevant to the carcinogenicity of cyclohexanone were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 47 (1989)

Last updated: 13 April 1999

DECABROMODIPHENYL OXIDE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1365)

CAS No.: 1163-19-5
Chem. Abstr. Name: Benzene, 1,1′-oxybis[2,3,4,5,6-pentabromo]-

5. Evaluation

No epidemiological data relevant to the carcinogenicity of decabromodiphenyl oxide were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 48 (1990)

Last updated: 13 April 1999

DIBROMOACETONITRILE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1369)

CAS No.: 3252-43-5
Chem. Abstr. Name: Dibromoacetonitrile

5. Evaluation

No epidemiological data relevant to the carcinogenicity of dibromoacetonitrile were available.

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

Overall evaluation

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

Previous evaluation: Vol. 52 (1991) (Halogenated acetonitriles)

Last evaluated: 13 April 1999

DICHLOROACETONITRILE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1375)

CAS No.: 3018-12-0
Chem. Abstr. Name: Dichloroacetonitrile

5. Evaluation

No epidemiological data relevant to the carcinogenicity of dichloroacetonitrile were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 52 (1991)

Last updated: 13 April 1999

DICHLOROACETYLENE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1381)

CAS No.: 7572-29-4
Chem. Abstr. Name: Dichloroethyne

5. Evaluation

No epidemiological data relevant to the carcinogenicity of dichloroacetylene were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 39 (1986)

Last updated: 9 April 1999

trans-1,4-DICHLOROBUTENE (Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1389)

CAS No.: 110-57-6
Chem. Abstr. Name: *trans*-1,4-Dichloro-2-butene

5. Evaluation

No epidemiological data relevant to the carcinogenicity of *trans*-1,4-dichlorobutene were available.

There is *inadequate evidence* in experimental animals for the carcinogenicity of *trans*-1,4-dichlorobutene.

Overall evaluation

trans-1,4-Dichlorobutene is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 15 (1977)

Last updated: 13 April 1999

1,2-DICHLOROPROPANE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1393)

CAS No.: 78-87-5
Chem. Abstr. Name: 1,2-Dichloropropane

5. Evaluation

No epidemiological data relevant to the carcinogenicity of 1,2-dichloropropane were available.

There is *limited evidence* in experimental animals for the carcinogenicity of 1,2-dichloropropane.

Overall evaluation

1,2-Dichloropropane is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 41 (1986)

Last updated: 13 April 1999

1,2-DIETHYLHYDRAZINE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1401)

CAS No.: 1615-80-1
Chem. Abstr. Name: *N*,*N*′-Diethylhydrazine

5. Evaluation

No epidemiological data relevant to the carcinogenicity of 1,2-diethylhydrazine were available.

There is *sufficient evidence* for the carcinogenicity of 1,2-diethylhydrazine in experimental animals.

1,2-Diethylhydrazine is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 4 (1974)

Last updated: 13 April 1999

DIETHYL SULFATE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1405)

CAS No.: 98503-29-8
Chem. Abstr. Name: Sulfuric acid, diethyl ester

5. Evaluation

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

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

Overall evaluation

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

In making the overall evaluation, the Working Group took into account that diethyl sulfate is a strong direct-acting alkylating agent which ethylates DNA and that, as a result, it is genotoxic in virtually all test systems examined, including induction of potent effects in somatic and germ cells of mammals exposed *in vivo*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 54 (1992)

Last updated: 13 April 1999

DIGLYDICYL RESORCINOL ETHER
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1417)

CAS No.: 101-90-6
Chem. Abstr. Name: Oxirane, 2,2′-[phenylenebis(oxymethylene)]bis-

5. Evaluation

No epidemiological data relevant to the carcinogenicity of diglycidyl resorcinol ether were available.

There is *sufficient evidence* for the carcinogenicity of a technical grade of diglycidyl resorcinol ether in experimental animals.

Overall evaluation

Diglycidyl resorcinol ether (technical grade) is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 36 (1985)

Last updated: 13 April 1999

DIISOPROPYL SULFATE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1421)

CAS No.: 2973-10-6
Chem. Abstr. Name: Sulfuric acid, bis(1-methylethyl)ester

5. Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 54 (1992)

Last updated: 13 April 1999

1,1-DIMETHYLHYDRAZINE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1425)

CAS No.: 57-14-7
Chem. Abstr. Name: 1,1-Dimethylhydrazine

5. Evaluation

No epidemiological data on the carcinogenicity of 1,1-dimethylhydrazine were available.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,1-dimethylhydrazine.

Overall evaluation

1,1-Dimethylhydrazine is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 4 (1974)

Synonyms

- Dimazine
- Dimazin
- UDMH

Last updated: 13 April 1999

DIMETHYL HYDROGEN PHOSPHITE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1437)

CAS No.: 868-85-9
Chem. Abstr. Name: Dimethyl phosphonate

5. Evaluation

No epidemiological data relevant to the carcinogenicity of dimethyl hydrogen phosphite were available.

There is *limited evidence* for the carcinogenicity of dimethyl hydrogen phosphite in experimental animals.

Overall evaluation

Dimethyl hydrogen phosphite is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 48 (1990)

Last updated: 13 April 1999

3,4-EPOXY-6-METHYLCYCLOHEXYLMETHYL 3,4-EPOXY-6-METHYLCYCLOHEXANE CARBOXYLATE (Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1441)

CAS No.: 141-37-7

5. Evaluation

No epidemiological data relevant to the carcinogenicity of 3,4-epoxy-6-methylcyclohexylmethyl 3,4-epoxy-6-methylcyclohexane carboxylate were available.

There is *limited evidence* in experimental animals for the carcinogenicity of 3,4-epoxy-6-methylcyclohexylmethyl 3,4-epoxy-6-methylcyclohexane carboxylate.

Overall evaluation

3,4-Epoxy-6-methylcyclohexylmethyl 3,4-epoxy-6-methylcyclohexane carboxylate is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 11 (1976)

Synonym

- 4-Methyl-7-oxabicyclo[4.1.0]heptane-3-carboxylic acid, 4-methyl-7-oxabicyclo[4.1.0]hept-3-yl methyl ester

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Last updated: 13 April 1999

cis-9,10-EPOXYSTEARIC ACID (Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1443)

CAS No.: 2443-39-2

5. Evaluation

No epidemiological data relevant to the carcinogenicity of *cis*-9,10-epoxystearic acid were available.

There is *inadequate evidence* in experimental animals for the carcinogenicity of *cis*-9,10-epoxystearic acid.

Overall evaluation

cis-9,10-Epoxystearic acid is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 11 (1976)

Synonym

- *cis*-3-Octyl-oxiraneoctanoic acid

Last updated: 13 April 1999

ETHYL ACRYLATE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1447)

CAS No.: 140-88-5
Chem. Abstr. Name: 2-Propenoic acid, ethyl ester

5. Evaluation

No epidemiological data relevant to the carcinogenicity of ethyl acrylate were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 39 (1986)

Synonyms

- Acrylic acid, ethyl ester
- Ethyl propenoate

Last updated: 13 April 1999

GLYCIDALDEHYDE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1459)

CAS No.: 765-34-4

5. Evaluation

No epidemiological data relevant to the carcinogenicity of glycidaldehyde were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 11 (1976)

Synonym

- Oxirane-carboxaldehyde

Last updated: 13 April 1999

HEXAMETHYLPHOSPHORAMIDE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1465)

CAS No.: 680-31-9

5. Evaluation

No epidemiological data relevant to the carcinogenicity of hexamethylphosphoramide were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 15 (1977)

Synonym

- Hexamethylphosphoric triamide

Last updated: 13 April 1999

ISOPROPYL OILS
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1483)

5. Evaluation

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

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

Overall evaluation

Isopropyl oils are *not classifiable as to their carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 15 (1977) (Isopropyl alcohol and isopropyl oils); Suppl. 7 (1987)

Last updated: 13 April 1999

LAUROYL PEROXIDE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1485)

CAS No.: 105-74-8

5. Evaluation

No epidemiological data relevant to the carcinogenicity of lauroyl peroxide were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 36 (1985)

Synonym

- Peroxide, bis(1-oxododecyl)

Last updated: 13 April 1999

METHYL ACRYLATE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1489)

CAS No.: 96-33-3
Chem. Abstr. Name: 2-Propenoic acid, methyl ester

5. Evaluation

No epidemiological data relevant to the carcinogenicity of methyl acrylate were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 39 (1986)

Synonyms

- Acrylic acid, methyl ester
- Methyl propenoate

Last updated: 13 April 1999

2-METHYLAZIRIDINE (PROPYLENEIMINE) (Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1497)

CAS No.: 75-55-8

5. Evaluation

No epidemiological data relevant to the carcinogenicity of 2-methylaziridine were available.

There is *sufficient evidence* for the carcinogenicity in experimental animals of 2-methylaziridine.

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Vol. 9 (1975)

Synonym

- Propylene-1,2-imine

Last updated: 13 April 1999

METHYL IODIDE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1503)

CAS No.: 74-88-4
Chem. Abstr. Name: Iodomethane

5. Evaluation

No epidemiological data relevant to the carcinogenicity of methyl iodide were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 41 (1986)

Last updated: 13 April 1999

MORPHOLINE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1511)

CAS No.: 110-91-8
Chem. Abstr. Name: Morpholine

5. Evaluation

No epidemiological data relevant to the carcinogenicity of morpholine were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 47 (1989)

Last updated: 13 April 1999

1,5-NAPHTHALENE DIISOCYANATE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1515)

CAS No.: 3173-72-6
Chem. Abstr. Name: 1,5-Diisocyanatonaphthalene

5. Evaluation

No epidemiological data relevant to the carcinogenicity of 1,5-naphthalene diisocyanate were available.

No experimental data relevant to the carcinogenicity of 1,5-naphthalene diisocyanate were available.

Overall evaluation

1,5-Naphthalene diisocyanate is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 19 (1979)

Synonym

- Isocyanic acid, 1,5-naphthylene ester

Last updated: 13 April 1999

PENTACHLOROETHANE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1519)

CAS No.: 76-01-7

5. Evaluation

No epidemiological data relevant to the carcinogenicity of pentachloroethane were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 41 (1986)

Last updated: 13 April 1999

PHENYL GLYCIDYL ETHER
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1525)

CAS No.: 122-60-1

5. Evaluation

No epidemiological data relevant to the carcinogenicity of phenyl glycidyl ether were available.

There is *sufficient evidence* in experimental animals for the carcinogenicity of phenyl glycidyl ether.

Overall evaluation

Phenyl glycidyl ether is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 47 (1989) (Some Glycidyl Ethers)

Synonym

- (Phenoxymethyl)oxirane

Last updated: 13 April 1999

TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM SALTS (Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1529)

Tetrakis(hydroxymethyl)phosphonium sulfate
CAS No.: 55566-30-8
Chem. Abstr. Name: Phosphonium, tetrakis(hydroxymethyl)-, sulfate (2:1) (salt)

Tetrakis(hydroxymethyl)phosphonium chloride
CAS No.: 124-64-1
Chem. Abstr. Name: Phosphonium, tetrakis(hydroxymethyl)-, chloride

Tetrakis(hydroxymethyl)phosphonium acetate/phosphate
CAS No.: 55818-96-7
Chem. Abstr. Name: Phosphonium, tetrakis(hydroxymethyl)-, acetate (salt), mixture with tetrakis(hydroxymethyl)phosphonium phosphate (3:1) (salt)

5. Evaluation

No epidemiological relevant to the carcinogenicity of tetrakis(hydroxymethyl)phosphonium salts were available.

There is *inadequate evidence* in experimental animals for the carcinogenicity of tetrakis(hydroxymethyl)phosphonium salts.

Overall evaluation

Tetrakis(hydroxymethyl)phosphonium salts are *not classifiable as to their carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 48 (1990)

Last updated: 13 April 1999

TRICHLOROACETONITRILE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1533)

CAS No.: 545-06-2

5. Evaluation

No epidemiological data relevant to the carcinogenicity of trichloroacetonitrile were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 52 (1991) (Halogenated Acetonitriles)

Last updated: 13 April 1999

TRIETHYLENE GLYCOL DIGLYCIDYL ETHER (Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1539)

CAS No.: 1954-28-5

5. Evaluation

No epidemiological data relevant to the carcinogenicity of triethylene glycol diglycidyl ether were available.

There is *inadequate evidence* for the carcinogenicity of triethylene glycol diglycidyl ether in experimental animals.

Overall evaluation

Triethylene glycol diglycidyl ether is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 11 (1976)

Synonym

- 2,2′-(2,5,8,11-Tetraoxadodecane-1,12-diyl)bisoxirane

Last updated: 13 April 1999

TRIS(2-CHLOROETHYL) PHOSPHATE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1543)

CAS No.: 115-96-8

5. Evaluation

No epidemiological data relevant to the carcinogenicity of tris(2-chloroethyl) phosphate were available.

There is *limited evidence* for the carcinogenicity of tris(2-chloroethyl) phosphate in experimental animals.

Overall evaluation

Tris(2-chloroethyl) phosphate is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 48 (1990)

Synonym

- Tris(2-chloroethyl) phosphate

Last updated: 13 April 1999

1,2,3-TRIS(CHLOROMETHOXY)PROPANE (Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1549)

CAS No.: 38571-73-2

5. Evaluation

No epidemiological data relevant to the carcinogenicity of 1,2,3-tris(chloromethoxy)propane were available.

There is *limited evidence* for the carcinogenicity of 1,2,3-tris(chloromethoxy)propane in experimental animals.

Overall evaluation

1,2,3-Tris(chloromethoxy)propane is *not classifiable as to its carcinogenicity to humans (Group 3)*.

Synonym

- 1,2,3-Tris(chloromethoxy)propane

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 15 (1977)

Last updated: 13 April 1999

VINYLIDENE FLUORIDE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 71 (1999) (p. 1551)

CAS No.: 75-38-7

5. Evaluation

No epidemiological data relevant to the carcinogenicity of vinylidene fluoride were available.

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

Overall evaluation

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

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 39 (1986)

Synonym

- 1,1-Difluoroethene

Last updated: 14 April 1999