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Some Industrial Chemicals

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Last updated: 22 August 2000

DI(2-ETHYLHEXYL) PHTHALATE (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 77 (2000) (p. 41)

CAS No.: 117-81-7

Chem. Abstr. Name: 1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Di(2-ethylhexyl) phthalate is a liquid of low volatility, widely used as a plasticizer in flexible poly(vinyl chloride) products at concentrations of up to 40%, as well as in a number of other minor applications. Occupational exposure occurs mainly by inhalation as an aerosol during its manufacture and its use as a plasticizer in poly(vinyl chloride) product manufacturing plants, at concentrations usually below 1 mg/m³.

Di(2-ethylhexyl) phthalate is ubiquitous in the general environment as a result of its widespread use in poly(vinyl chloride) products. It is found in ambient air at levels usually below 100 ng/m³. The highest levels of di(2-ethylhexyl) phthalate in foods are found in milk products, meat and fish and in other products with a high fat content, where concentrations up to 10 mg/kg have been reported. The leaching of di(2-ethylhexyl) phthalate from flexible plastics used in medical devices, such as during dialysis and transfusion, can result in large direct exposures.

5.2 Human carcinogenicity data

One small study of workers in a di(2-ethylhexyl) phthalate production plant did not show any excess of cancer mortality. However, this study did not have adequate power to detect a potential excess risk.

5.3 Animal carcinogenicity data

Di(2-ethylhexyl) phthalate was tested for carcinogenicity by oral administration in the diet in two experiments in mice and six experiments in rats. Hepatocellular tumours were produced consistently in both species.

In a number of initiation/promotion studies in strains of mice susceptible to liver carcinogenesis, administration of di(2-ethylhexyl) phthalate following administration with known carcinogens enhanced the incidences of hepatocellular preneoplastic foci, adenomas and carcinomas. In a number of similar studies in rats and in one study in hamsters, in general, no promoting activity of di(2-ethylhexyl) phthalate was demonstrated. No initiating activity of di(2-ethylhexyl) phthalate was found in the liver of mice or rats. In two *N*-nitrosamine-initiation target organ models in rats, one showed enhancement of renal tubule tumours by di(2-ethylhexyl) phthalate, whereas the other showed no promotion of urinary bladder tumours.

5.4 Other relevant data

The absorption and disposition of di(2-ethylhexyl) phthalate has been investigated extensively in humans and laboratory animals. In all species studied, the compound underwent rapid metabolism, with the urine and faeces being the major routes of excretion. Following oral administration, the bulk of a di(2-ethylhexyl) phthalate dose was absorbed as the monoester, mono(2-ethylhexyl) phthalate. This ester is also formed by esterases in the body following intravenous administration and is subject to extensive oxidative metabolism by the cytochrome P450 system.

The peroxisome-proliferating effects of di(2-ethylhexyl) phthalate in susceptible species (e.g., rats and mice) have primarily been related to mono(2-ethylhexyl) phthalate and two other specific metabolites. However, while species differences have been observed in the absorption and disposition of di(2-ethylhexyl) phthalate, they do not provide an explanation for the species differences in hepatic peroxisome-proliferating activity.

The literature on potential toxic effects of di(2-ethylhexyl) phthalate following human exposure is limited. Taken together, the data indicate that di(2-ethylhexyl) phthalate does not cause observable toxicity following oral and intravenous exposure, but do not contribute information relevant to the evaluation of human carcinogenicity.

A considerable amount of information on the hepatic effects of orally administered di(2-ethylhexyl) phthalate indicates that it causes hepatic peroxisome proliferation (ultrastructural effects and enzyme induction), hepatomegaly and increased replicative DNA synthesis in rats and mice. At a lower magnitude in Syrian hamsters, enzyme induction and hepatomegaly have been observed (ultrastructural effects and replicative DNA synthesis have not been evaluated). Guinea-pigs, marmosets and cynomolgus monkeys evaluated under the same or similar experimental conditions did not exhibit peroxisome proliferation responses. Studies of di(2-ethylhexyl) phthalate metabolites in primary rat, mouse and, to a lesser extent, Syrian hamster hepatocyte cultures *in vitro* elicited markers of peroxisome proliferation, while the same or similar experimental conditions did not elicit markers of peroxisome proliferation in primary cultures of either guinea-pig, rabbit, dog, cynomolgus monkey, marmoset or, most notably, human hepatocytes.

Hepatic peroxisome proliferation depends on a nuclear receptor, PPAR α , to mediate these responses in mice, based on lack of response to peroxisome proliferators in PPAR α -deficient mice. In one study with another peroxisome proliferator, WY-14,643, carcinogenesis was shown to be dependent on the same receptor. Oral administration of di(2-ethylhexyl) phthalate failed to elicit markers of peroxisome proliferation in PPAR α -deficient mice, while the same treatment elicited this response in normal mice. Metabolites of di(2-ethylhexyl) phthalate caused activation of PPAR α -mediated gene expression in mammalian cell co-transfection assays. Differences between responsive rodents and humans in various aspects of PPAR α -mediated regulation of gene expression are consistent with the lack of activity of di(2-ethylhexyl) phthalate metabolites in hepatocyte cultures from 12 people studied to date.

No data on reproductive and developmental effects in humans were available.

Oral exposure of rats and mice to di(2-ethylhexyl) phthalate during organogenesis caused malformations and fetal death. A study in knock-out mice suggested that the developmental effects are not PPAR α -mediated.

Irreversible testicular damage has been observed in male rat pups exposed prenatally and during suckling via maternal exposure to drinking water containing the compound.

Oral exposure of adult rats and mice caused effects on fertility in males and females and serious effects on the testicles. Young animals were much more sensitive to gonadal effects than adults and in some cases, the onset of occurrence of the testicular effects was earlier in young animals. Dose-dependent testicular effects were seen in young rats exposed to di(2-ethylhexyl) phthalate in the diet.

In one study using small groups of adult marmosets, oral exposure did not cause testicular toxicity at doses higher than those producing testicular effects in adult rats.

The Sertoli cells in the testes appear to be the main target of the testicular toxicity. Proposed mechanistic hypotheses relate to reduced testicular zinc levels, altered hormonal status, altered metabolic function and altered follicle-stimulating hormone reactivity.

Di(2-ethylhexyl) phthalate has been studied extensively for its genotoxic effects in a wide range of test systems, both *in vitro* and *in vivo*. The majority of these studies did not reveal any activity. No mutagenic activity was observed in bacteria. In fungi, all but two studies failed to show any evidence of recombinational

events or mutation. A single study in yeast for aneuploidy was positive. Low levels of mutation were induced in *Drosophila melanogaster* in somatic cells in some studies, but no germ-cell mutations or DNA damage were induced in these insects. In cultured mammalian cells, no primary DNA damage, mutation, sister chromatid exchange or chromosomal aberrations were induced (except in a single study for DNA strand breakage), whereas transformation of cells was induced in a number of different systems.

In vivo, neither covalent binding to DNA nor DNA strand breakage was induced in several studies on rat liver, and unscheduled DNA synthesis was not induced in the liver of either rats or mice. Gene mutations were not induced in the liver of dosed mice in a single study and there was no evidence for induction of chromosomal aberrations in mice or rats. Aberrations were induced, however, in the embryos of dosed pregnant Syrian hamsters. Dominant lethal effects were reported to be induced in male mice, but re-evaluation of these data did not confirm this conclusion.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of di(2-ethylhexyl) phthalate.

There is *sufficient evidence* in experimental animals for the carcinogenicity of di(2-ethylhexyl) phthalate.

Overall evaluation

Di(2-ethylhexyl) phthalate is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

In making its overall evaluation of the carcinogenicity to humans of di(2-ethylhexyl) phthalate, the Working Group took into consideration that (a) di(2-ethylhexyl) phthalate produces liver tumours in rats and mice by a non-DNA-reactive mechanism involving peroxisome proliferation; (b) peroxisome proliferation and hepatocellular proliferation have been demonstrated under the conditions of the carcinogenicity studies of di(2-ethylhexyl) phthalate in rats and mice; and (c) peroxisome proliferation has not been documented in human hepatocyte cultures exposed to di(2-ethylhexyl) phthalate nor in the liver of exposed non-human primates. Therefore, the mechanism by which di(2-ethylhexyl) phthalate increases the incidence of hepatocellular tumours in rats and mice is not relevant to humans.

Previous evaluations: [Vol. 29 \(1982\)](#); [Suppl. 7 \(1987\) \(p. 62\)](#) (Group 2B)

Synonyms:

- Bis(2-ethylhexyl) 1,2-benzenedicarboxylate
- Bis(2-ethylhexyl) *ortho*-phthalate
- Bis(2-ethylhexyl) phthalate
- DEHP
- Dioctyl phthalate
- Di-sec octyl phthalate
- Ethylhexyl phthalate
- 2-Ethylhexyl phthalate
- Octyl phthalate
- Phthalic acid, bis(2-ethylhexyl) ester
- Phthalic acid di(2-ethylhexyl) ester
- Phthalic acid dioctyl ester

DI(2-ETHYLHEXYL) ADIPATE (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

Vol.: 77 (2000) (p. 149)

CAS No.: 103-23-1

Chem. Abstr. Name: Hexanedioic acid, bis(2-ethylhexyl) ester

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Di(2-ethylhexyl) adipate is a liquid of low volatility, widely used as a plasticizer in flexible poly(vinyl chloride) products, notably food films, as well as in other plastics and in a number of other minor applications, such as lubricants and cosmetics. Occupational exposure may occur by inhalation of di(2-ethylhexyl) adipate as an aerosol during its manufacture and its use. Meat-wrapping workers may be exposed while cutting poly(vinyl chloride) film across a heated cutter. Food is the major source of exposure of the general population to di(2-ethylhexyl) adipate because of migration from poly(vinyl chloride) packaging, particularly into fatty foods such as cheese and meat.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Di(2-ethylhexyl) adipate was tested for carcinogenicity by oral administration in one experiment in mice and one experiment in rats. In mice, liver adenomas and carcinomas were produced in both males and females. No treatment-related tumours were observed in rats.

5.4 Other relevant data

Di(2-ethylhexyl) adipate is rapidly and completely absorbed after oral administration, rapidly and extensively metabolized and rapidly excreted in humans and experimental animals. It is hydrolysed in the gastrointestinal tract before absorption.

No data on the toxic effects of di(2-ethylhexyl) adipate in humans were available to the Working Group.

In mice and rats, di(2-ethylhexyl) adipate induced hepatic markers of peroxisome proliferation (ultrastructural and biochemical) as well as hepatomegaly and increased replicative DNA synthesis. The species differences in carcinogenicity assays of di(2-ethylhexyl) adipate (increased hepatocellular tumours in mice, not rats) are consistent with a higher intake of di(2-ethylhexyl) adipate and a greater extent of peroxisome proliferation and associated responses in livers of mice compared with rats fed the same dietary doses.

In hepatocytes isolated from rats and mice, treatment of primary cultures with metabolites of di(2-ethylhexyl) adipate increased peroxisomal palmitoyl-coenzyme A oxidation activity. The same treatment of primary cultures of hepatocytes from guinea-pigs and marmosets failed to cause any similar increase in activity.

No data on reproductive and developmental effects in humans were available to the Working Group.

Exposure of rats to di(2-ethylhexyl) adipate during organogenesis caused an increased frequency of variations and retardations in the fetuses at doses below the maternally toxic range.

No effects on male or female fertility were found in rats given di(2-ethylhexyl) adipate in the feed. The body weight gain of the pups at the highest dose was reduced throughout the postnatal period. In mice, a single high intraperitoneal dose given to males before mating was associated with a reduced percentage of pregnancies and increased number of fetal deaths.

No data on the genetic and related effects of di(2-ethylhexyl) adipate in humans or human cells were available to the Working Group.

Di(2-ethylhexyl) adipate did not bind covalently to mouse liver DNA *in vivo*. One report showed evidence of oxidative damage in rat liver DNA *in vivo* but not in rat kidney DNA. A weak dominant lethal effect has been reported in male mice. Analyses of mouse bone marrow after treatment with di(2-ethylhexyl) adipate *in vivo* found no induction of micronuclei in one study and no induction of chromosomal aberrations in one study. Urine from rats treated with di(2-ethylhexyl) adipate by gavage was not mutagenic to *Salmonella typhimurium*.

Di(2-ethylhexyl) adipate did not induce gene mutations, sister chromatid exchanges, chromosomal aberrations or micronuclei in rodent cells *in vitro*. It did not induce sex-linked recessive lethal mutations in *Drosophila* when administered either by diet or injection. Di(2-ethylhexyl) adipate was not mutagenic to either *Photobacterium phosphoreum* or *Salmonella typhimurium* in the presence or absence of exogenous metabolic activation.

These data indicate that di(2-ethylhexyl) adipate is not genotoxic.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of di(2-ethylhexyl) adipate were available.

There is *limited evidence* in experimental animals for the carcinogenicity of di(2-ethylhexyl) adipate.

Overall evaluation

Di(2-ethylhexyl) adipate is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluations: [Vol. 29 \(1982\)](#); Suppl. 7 (1987) (p. 62)

Synonyms

- Adipic acid bis(2-ethylhexyl) ester
- BEHA
- Bis(2-ethylhexyl) adipate
- DEHA
- Dioctyl adipate
- DOA
- Hexanedioic acid, dioctyl ester
- Octyl adipate

CINNAMYL ANTHRANILATE

(Group 3)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 77 (2000) (p. 177)

CAS No.: 87-29-6

Chem. Abstr. Name: 3-Phenyl-2-propen-1-ol, 2-aminobenzoate

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Cinnamyl anthranilate was used as a synthetic flavouring and fragrance agent. It has not been commercially available since 1985. No information was available on its occurrence in the workplace or in the environment.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Cinnamyl anthranilate was tested for carcinogenicity in one experiment in mice and in one experiment in rats by oral administration in the diet. In mice, a dose-related increase in the incidence of hepatocellular tumours was found, but there was no increased incidence of tumours in rats. In a mouse lung tumour bioassay, an increased multiplicity of lung tumours was found.

5.4 Other relevant data

Cinnamyl anthranilate is metabolized by hydrolysis to anthranilic acid and cinnamyl alcohol, which is oxidized to benzoic acid. In mice, but not in rats or humans, the hydrolysis is saturated at high doses, leading to excretion of unchanged cinnamyl anthranilate in the urine.

Cinnamyl anthranilate has the characteristic effects of a peroxisome proliferator on mouse liver, increasing the activity of peroxisomal fatty acid-metabolizing enzymes and microsomal CYP4A and increasing hepatocellular proliferation. These effects are mediated by the intact ester, and were not seen after administration of the hydrolysis products, cinnamyl alcohol and anthranilic acid. The corresponding effects on rat liver were very much weaker. No relevant data from humans were available.

The only standard genotoxicity assay in which cinnamyl anthranilate was active was the mouse lymphoma mutation assay.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of cinnamyl anthranilate were available.

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

Overall evaluation

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

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluations: [Vol. 16 \(1978\)](#); [Vol. 31 \(1983\)](#); Suppl. 7 (1987) (p. 60)

Synonyms

- Anthranilic acid, cinnamyl ester
- Cinnamyl alcohol anthranilate
- 3-Phenyl-2-propenyl 2-aminobenzoate
- 3-Phenyl-2-propenyl anthranilate

Last updated: 21 August 2000

COUMARIN

(Group 3)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 77 (2000) (p. 193)

CAS No.: 91-64-5

Chem. Abstr. Name: 2*H*-1-Benzopyran-2-one

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Coumarin is a natural product occurring in the essential oils of a large number of plants, such as cinnamon, cassia, lavender and woodruff. It is used for its fragrance in many personal care products (perfumes, deodorants, soaps) and in tobacco, in household and industrial products to mask unpleasant odours and, in some countries, as a flavouring agent in food and beverages. It has also been used to treat several medical conditions. Exposure to coumarin may occur from its production, its natural presence in many plants and essential oils, and its several industrial, medical and consumer uses.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Coumarin has been adequately tested by oral administration in two experiments in mice and in one experiment in rats. In mice of one strain, it produced increases in lung tumours (adenomas and carcinomas) in both males and females and in hepatocellular adenomas in females. There was no increase in tumour incidences in another strain of mouse. In one study in rats, coumarin produced a low incidence of renal tubule adenomas in males, seen only after step-sectioning of the kidney. Three other studies in rats could not be evaluated.

5.4 Other relevant data

Coumarin is rapidly and extensively absorbed after topical or oral administration to human subjects. It undergoes very extensive metabolism along two major pathways, 7-hydroxylation and ring-opening to *ortho*-hydroxyphenylacetaldehyde. There are numerous minor metabolites, many of which are secondary products from the primary metabolites. The relative extent of these two major pathways is highly variable between species. Ring-opening predominates in rodents, while 7-hydroxylation is particularly evident in humans.

In humans exposed to coumarin for treatment of various clinical conditions, a few cases of hepatotoxicity have been reported. However, a clear relationship between the dose of coumarin and the hepatotoxic responses observed has not been established. The target organs for coumarin toxicity are primarily the liver in rats and the liver and lung in mice. There are marked species differences in these responses, with the mouse being particularly susceptible to coumarin-induced Clara cell injury. Coumarin is hepatotoxic in rats and mice. Hamsters and gerbils are resistant to acute coumarin-induced hepatotoxicity. *In vitro*, coumarin is toxic in either hepatocytes or liver slices from rats, mice, rabbits and guinea-pigs, whereas monkey and human cells and/or slices appear to be resistant.

No data on reproductive and developmental effects in humans were available. No signs of teratogenicity were observed in mice, rats, rabbits or miniature pigs.

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

Coumarin did not induce micronuclei in mice *in vivo* and was not mutagenic in *Drosophila melanogaster*. It was weakly positive in induction of micronuclei in human cells *in vitro*, but failed to induce unscheduled DNA synthesis in human liver cells *in vitro*. Coumarin induced sister chromatid exchanges without metabolic activation and chromosomal aberrations with metabolic activation, but not micronuclei or gene mutations in mammalian cells *in vitro*. It was mutagenic in only two out of 11 *Salmonella typhimurium* strains tested, with metabolic activation.

Coumarin was antimutagenic in various assays, but also had co-mutagenic properties.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluations: [Vol. 10 \(1976\)](#); Suppl. 7 (1987) (p. 61)

Synonyms

- 1,2-Benzopyrone
- 5,6-Benzo-2-pyrone
- Benzo- α -pyrone
- *cis-ortho*-Coumarinic acid lactone
- Coumarinic anhydride
- *ortho*-Hydroxycinnamic acid lactone

ETHYLBENZENE

(Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

Vol.: 77 (2000) (p. 227)

CAS No.: 100-41-4

Chem. Abstr. Name: Ethylbenzene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Ethylbenzene is a major industrial chemical produced by alkylation of benzene. The pure chemical is used almost exclusively for styrene production. It is also present at up to 25% in technical grades of mixed xylenes and up to 15% in gasoline.

Occupational exposure to ethylbenzene may occur by inhalation during its production and use. Most occupational exposures are related to technical grades of mixed xylenes used as solvents in various paints and coatings, inks, insecticides and in rubber and plastic production, as well as from the production and handling of gasoline and bitumen. Ethylbenzene from these sources as well as from vehicle emissions is ubiquitous at $\mu\text{g}/\text{m}^3$ levels in ambient air. It is a component of tobacco smoke and of several household products. These various sources contribute to indoor air levels that are often higher than adjacent outdoor levels. Ethylbenzene is only rarely found in drinking-water but is found at $\mu\text{g}/\text{kg}$ levels in a variety of foodstuffs.

5.2 Human carcinogenicity data

Two studies of workers potentially exposed to ethylbenzene in a production plant and a styrene polymerization plant were available. In the first study, no excess of cancer incidence was found but the description of methods was insufficient to allow proper evaluation of this finding. In the second study, no cancer mortality excess was observed during the follow-up of 15 years.

5.3 Animal carcinogenicity data

Ethylbenzene was tested by inhalation exposure in single experiments in mice and rats. In mice, it increased the incidence of lung adenomas in males and of liver adenomas in females. In male rats, it increased the incidence of renal tubule adenomas and carcinomas. An increase in the incidence of renal adenomas was seen in females only after step-sectioning. A study in rats by oral administration could not be evaluated. A metabolite of ethylbenzene, 1-phenylethanol, increased the incidence of renal tubule adenomas in male rats.

5.4 Other relevant data

Ethylbenzene is well absorbed from the skin, lungs and gastrointestinal tract. It is virtually completely metabolized, the primary pathways being hydroxylation of the two carbons of the side-chain, followed by further oxidation to a range of metabolites that are excreted principally in the urine. The fate of ethylbenzene is similar in animals and humans.

Limited data were available to evaluate the toxic effects of ethylbenzene in humans. Liver and kidney weights were increased in rats following exposure to ethylbenzene with no signs of hepatic necrosis. Cytochrome P450 enzymes were induced in both liver and kidney of ethylbenzene-exposed rats. Ethylbenzene caused changes in dopamine levels in brain and prolactin secretion in rats exposed for three to seven days. In rat brain cell

cultures, ethylbenzene decreased the activity of several integral membrane enzymes.

No data on reproductive or developmental effects of ethylbenzene in humans were available. In rats and mice, developmental retardation and an increased incidence of variations were reported after inhalation exposure during pregnancy. Reduced numbers of live pups per litter or abortions were reported in rabbits exposed during pregnancy. No changes in sperm motility or oestrous cyclicity were found in rats or mice exposed to ethylbenzene for 13 weeks.

Ethylbenzene was non-mutagenic in bacteria, yeast and insects. In mammalian cells, it was inactive in inducing sister chromatid exchanges in Chinese hamster embryo cells but very weakly positive in cultured human lymphocytes. It did not induce micronuclei *in vivo*, although it was positive in Syrian hamster embryo cells *in vitro*. It also caused cell transformation in these cells. Ethylbenzene induced mutations in the mouse lymphoma assay, but only at the highest non-lethal concentration tested.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms

- EB
- Ethylbenzol
- α -Methyltoluene
- Phenylethane

***ortho*-TOLUIDINE**

(Group 2A)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 77 (2000) (p. 267)

***ortho*-Toluidine**

CAS No.: 95-53-4

Chem. Abstr. Name: 2-Methylbenzenamine

***ortho*-Toluidine hydrochloride**

CAS No.: 636-21-5

Chem. Abstr. Name: 2-Methylbenzenamine hydrochloride

5. Summary of Data Reported and Evaluation

5.1 Exposure data

ortho-Toluidine and its hydrochloride salt have been widely produced commercially throughout the twentieth century for use in manufacture of dyestuffs, pigments, optical brighteners, rubber chemicals, pharmaceuticals and pesticides. Human exposure has been reported during its use in production of dyestuffs and rubber chemicals. Non-occupational exposure to *ortho*-toluidine may result from its occurrence in certain foods and from exposure to tobacco smoke.

5.2 Human carcinogenicity data

Five studies were available for evaluation. Two mortality studies were conducted in the 1980s among dye production workers in Italy and in the United States. In each case, the subgroups of workers exposed to *ortho*-toluidine were small. Two recent cohort studies in Germany, the United Kingdom and a larger study in the United States among workers in 4-chloro-*ortho*-toluidine production and in rubber chemical manufacturing looked at bladder cancer incidence. Of these five studies, four observed a very high excess of bladder cancer among *ortho*-toluidine-exposed workers. The fifth study had limited power to detect a risk. In the two studies with data on duration of exposure to *ortho*-toluidine, the highest risk was observed in the subgroup with the longest duration of exposure. In none of these studies, however, could confounding by concomitant exposure to various other potential bladder carcinogens be ruled out with confidence, although co-exposures differed between studies.

5.3 Animal carcinogenicity data

ortho-Toluidine was tested for carcinogenicity as its hydrochloride salt in two experiments in mice and in three experiments in rats and as the free base in one limited experiment in hamsters. After oral administration to mice, it induced an increased incidence of haemangiomas and haemangiosarcomas and hepatocellular carcinomas or adenomas. In rats, oral administration of *ortho*-toluidine increased the incidence of tumours in multiple organs, including fibromas, sarcomas, mesotheliomas, mammary fibroadenomas and transitional-cell carcinomas of the urinary bladder.

5.4 Other relevant data

ortho-Toluidine undergoes extensive metabolism *in vivo*, with the bulk of the dose being excreted in the urine within 24 h. Like other aromatic amines, it is thought to undergo metabolic activation initially via *N*-hydroxylation, leading to covalent binding to tissue macromolecules. Evidence that *ortho*-toluidine undergoes

metabolic activation *in vivo* is supported by the fact that it forms both haemoglobin and albumin adducts in laboratory animals and haemoglobin adducts in humans.

In rats, repeated administration of *ortho*-toluidine led to haemosiderosis, splenic congestion, bone marrow and splenic proliferation and splenic fibrosis consistent with a response to erythrocyte destruction.

Bacterial or bacteriophage assay systems showed negative or inconsistent data or, at most, weakly positive results. In the yeast *Saccharomyces cerevisiae*, *ortho*-toluidine caused reverse mutation at some loci and occasionally recombinational events. It caused gain or loss of whole chromosomes and mutation of mitochondrial DNA. In cultured mammalian cells, it generally caused sister chromatid exchanges and sometimes also increased gene mutations, chromosomal aberrations and micronuclei. It induced aneuploidy and increased cell transformation in such cells. *ortho*-Toluidine may inhibit intercellular communication. It has been demonstrated to be a mutagen but not a recombinogen in *Drosophila melanogaster*. In rodent models *in vivo*, it enhanced sister chromatid exchanges but gave equivocal results for micronuclei and sperm morphology.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of *ortho*-toluidine.

There is *sufficient evidence* in experimental animals for the carcinogenicity of *ortho*-toluidine.

Overall evaluation

ortho-Toluidine is *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluations: [Vol. 16 \(1978\)](#); [Vol. 27 \(1982\)](#); [Suppl. 7 \(1987\)](#)

Synonyms

ortho-Toluidine

- 1-Amino-2-methylbenzene
- 2-Amino-1-methylbenzene
- 2-Aminotoluene
- *ortho*-Aminotoluene
- 2-Methyl-1-aminobenzene
- 2-Methylaniline
- *ortho*-Methylaniline
- *ortho*-Methylbenzenamine
- 2-Methylphenylamine
- *ortho*-Tolylamine

ortho-Toluidine hydrochloride

- 1-Amino-2-methylbenzene hydrochloride
- 2-Amino-1-methylbenzene hydrochloride
- 2-Aminotoluene hydrochloride
- *ortho*-Aminotoluene hydrochloride
- 2-Methyl-1-aminobenzene hydrochloride
- 2-Methylaniline hydrochloride

- *ortho*-Methylaniline hydrochloride
- *ortho*-Methylbenzenamine hydrochloride
- 2-Methylphenylamine hydrochloride
- *ortho*-Tolylamine hydrochloride

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4-CHLORO-*ortho*-TOLUIDINE (Group 2A)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 77 (2000) (p. 323)

4-Chloro-*ortho*-toluidine

CAS No.: 95-69-2

Chem. Abstr. Name: 4-Chloro-2-methylbenzenamine

4-Chloro-*ortho*-toluidine hydrochloride

CAS No.: 3165-93-3

Chem. Abstr. Name: 4-Chloro-2-methylbenzenamine hydrochloride

5. Summary of Data Reported and Evaluation

5.1 Exposure data

4-Chloro-*ortho*-toluidine and its hydrochloride salt were produced commercially in substantial amounts as intermediates in the manufacture of azo dyes and chlordimeform, an insecticide. Since the 1980s, production and use of 4-chloro-*ortho*-toluidine have been discontinued in most countries.

5.2 Human carcinogenicity data

Three small cohort studies of workers exposed to 4-chloro-*ortho*-toluidine, one each among dye, 4-chloro-*ortho*-toluidine and chlordimeform production workers, were available. Two of them showed high relative risks of bladder cancer. Despite problems in the cohort definitions in these two studies, the high relative risks observed for bladder cancer most likely represent a true excess. However, confounding cannot be excluded due to the presence of other exposures including potential bladder carcinogens. The third study had limited power to detect a risk due to use of mortality data only in a small cohort.

5.3 Animal carcinogenicity data

4-Chloro-*ortho*-toluidine or its hydrochloride was tested for carcinogenicity by oral administration in two experiments in mice and in two experiments in rats. The compounds increased the incidence of haemangiosarcomas in the spleen and adipose tissue in both male and female mice, but no increase in the incidence of tumours was observed in rats.

5.4 Other relevant data

4-Chloro-*ortho*-toluidine undergoes extensive metabolism in rodents *in vivo*. Like other aromatic amines, it undergoes metabolic activation via initial formation of the *N*-hydroxy derivative. The further metabolic processing of this metabolite has not been investigated.

In humans, 4-chloro-*ortho*-toluidine induces acute toxicity in the urinary bladder and causes methaemoglobinaemia. In rodents, 4-chloro-*ortho*-toluidine and/or its metabolites bind to macromolecules in liver cells.

4-Chloro-*ortho*-toluidine gave variable results in the majority of bacterial tests for mutagenicity. While most of the mammalian tests were positive, chromosomal aberration assays gave conflicting results. These data overall indicate that 4-chloro-*ortho*-toluidine causes DNA damage in mammalian cells.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of 4-chloro-*ortho*-toluidine.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 4-chloro-*ortho*-toluidine.

Overall evaluation

4-Chloro-*ortho*-toluidine is *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluations: Vol. 16 (1978) (p. 277); Vol. 30 (1983) (p. 61); Suppl. 7 (1987) (p. 60); [Vol. 48 \(1990\)](#)

Synonyms

4-Chloro-*ortho*-toluidine

- 2-Amino-5-chlorotoluene
- 3-Chloro-6-aminotoluene
- 5-Chloro-2-aminotoluene
- 4-Chloro-2-methylaniline
- 4-Chloro-6-methylaniline
- 4-Chloro-2-toluidine
- *para*-Chloro-*ortho*-toluidine
- 2-Methyl-4-chloroaniline
- 2-Methyl-4-chlorobenzeneamine

4-Chloro-*ortho*-toluidine hydrochloride

- 4-Chloro-2-methylaniline hydrochloride
- C.I. Azoic Diazo Component 11
- 2-Methyl-4-chloroaniline hydrochloride
- *para*-Chloro-*ortho*-toluidine hydrochloride

5-CHLORO-*ortho*-TOLUIDINE

(Group 3)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 77 (2000) (p. 341)

CAS No.: 95-79-4

Chem. Abstr. Name: 5-Chloro-2-methylbenzenamine

5. Summary of Data Reported and Evaluation

5.1 Exposure data

5-Chloro-*ortho*-toluidine is an aromatic amine which is produced in relatively small quantities as an intermediate in the manufacture of some pigments and azo dyes. No data were available on human exposure.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

5-Chloro-*ortho*-toluidine was tested for carcinogenicity by oral administration in one experiment in mice and in one experiment in rats. In mice, it increased the incidence of haemangiosarcomas (mostly of adipose tissue) and of hepatocellular carcinomas in both males and females. In rats, no carcinogenic effect was observed.

5.4 Other relevant data

5-Chloro-*ortho*-toluidine undergoes an initial metabolic activation step, probably via *N*-oxidation, to form a nitrosoarene that can bind covalently to haemoglobin.

The few available genotoxicity test results on 5-chloro-*ortho*-toluidine were negative.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of 5-chloro-*ortho*-toluidine were available.

There is *limited evidence* in experimental animals for the carcinogenicity of 5-chloro-*ortho*-toluidine.

Overall evaluation

5-Chloro-*ortho*-toluidine is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms

- 2-Amino-4-chlorotoluene

- 4-Chloro-2-aminotoluene
- 3-Chloro-6-methylaniline
- 5-Chloro-2-methylaniline
- 5-Chloro-2-toluidine
- 2-Methyl-5-chloroaniline

Last updated: 22 August 2000

DIETHANOLAMINE (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 77 (2000) (p. 349)

CAS No.: 111-42-2

Chem. Abstr. Name: 2,2'-Iminobis[ethanol]

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Diethanolamine is a viscous liquid widely used as a chemical intermediate and as a corrosion inhibitor and surface-active agent in various products including metalworking fluids, oils, fuels, paints, inks, cosmetic formulations and agricultural products. Occupational exposure may occur by inhalation and dermal contact, particularly in metal-machining occupations. No data were available on environmental exposure to this substance. The general population may be exposed through contact with a variety of personal care products.

5.2 Human carcinogenicity data

Two cohort studies and two nested case-control studies looked at cancer mortality or incidence among workers using metalworking fluids with ethanolamines as additives, with or without sodium nitrite. Small excesses were observed for cancers at various sites, in particular the stomach, oesophagus and larynx. In most of these studies, only associations with use of soluble oils or synthetic fluids were presented and no results were given specifically in relation to diethanolamine exposure. It is difficult to draw conclusions regarding diethanolamine using data from studies of exposures to these complex mixtures.

5.3 Animal carcinogenicity data

Diethanolamine was tested for carcinogenicity by dermal application in one study in mice and in one study in rats. In the mouse study, there was a treatment-related increase in the incidences of both hepatocellular adenomas and carcinomas in both males and females, as well as an increase in the incidence of hepatoblastomas in males. There was also a marginal increase of renal tubule adenomas in males. In rats, no treatment-related increase in the incidence of tumours was seen in either males or females.

In a Tg.AC transgenic mouse model using similar doses to the first mouse study, there was no treatment-related increase in the incidence of skin tumours after skin application.

5.4 Other relevant data

Diethanolamine is metabolized by biosynthetic routes common to endogenous alkanolamines (ethanolamine and choline) and incorporated into phospholipids. It is excreted predominantly unchanged with a half-life of approximately one week in urine. In the absence of sodium nitrite, no conversion to *N*-nitrosodiethanolamine is observed. Diethanolamine competitively inhibits the cellular uptake of choline *in vitro* and hepatic changes in choline homeostasis, consistent with choline deficiency, are observed *in vivo*.

No data on reproductive and developmental effects in humans were available.

Oral or dermal exposure of rats to diethanolamine during organogenesis was not associated with any sign of developmental toxicity, while inhalation exposure to diethanolamine aerosols caused signs of developmental

toxicity. Dermal exposure of rabbits during organogenesis caused no sign of developmental toxicity.

Testicular effects have been found after exposure of rats to diethanolamine in the drinking water.

No data on genetic and related effects of diethanolamine in humans were available to the Working Group.

Diethanolamine induced cell transformation in Syrian hamster embryo cells *in vitro* in two studies but not in another. It did not induce gene mutations, sister chromatid exchanges or chromosomal aberrations. Diethanolamine did not induce micronucleus formation in larval newt blood cells in either the absence or presence of sodium nitrite or nitrate. It was without effect on gene conversion in yeast and was not mutagenic in bacteria.

The limited data available to the Working Group do not indicate that diethanolamine is genotoxic.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms

- Bis(hydroxyethyl)amine
- Bis(2-hydroxyethyl)amine
- *N,N*-Bis(2-hydroxyethyl)amine
- DEA
- *N,N*-Diethanolamine
- 2,2' -Dihydroxydiethylamine
- Di(β -hydroxyethyl)amine
- Di(2-hydroxyethyl)amine
- Diolamine
- 2-(2-Hydroxyethylamino)ethanol
- Iminodiethanol
- 2,2' -Iminodiethanol
- *N,N'* -Iminodiethanol
- 2,2' -Iminodi-1-ethanol

TRIETHANOLAMINE

(Group 3)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 77 (2000) (p. 381)

CAS No.: 102-71-6

Chem. Abstr. Name: 2,2',2''-Nitrilotris[ethanol]

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Triethanolamine is a viscous liquid widely used as a corrosion inhibitor, a surface-active agent and an intermediate in various products including metalworking fluids, oils, fuels, paints, inks, cement, cosmetic and personal products, as well as herbicide and algicide formulations. Occupational exposure may occur by inhalation and dermal contact, particularly in metal-machining occupations. No data were available on environmental exposure to this substance. The general population may be exposed through contact with a variety of personal care products.

5.2 Human carcinogenicity data

Two cohort studies, two proportionate mortality studies and two nested case–control studies looked at cancer mortality or incidence among workers using metalworking fluids with ethanolamines as additives, with or without sodium nitrite. Small excesses were observed for cancers at various sites, in particular, stomach, oesophagus and larynx. In most of these studies, only associations with use of soluble oils or synthetic fluids were presented and no results were given specifically in relation to triethanolamine exposure. It is difficult to draw conclusions regarding triethanolamine using data from studies of exposures to these complex mixtures.

5.3 Animal carcinogenicity data

Triethanolamine was adequately tested for carcinogenicity in one study in mice and in one study in rats by oral administration in the drinking-water. No increase in the incidence of tumours was observed. It was also tested by dermal application in one study in rats and no increase in the incidence of tumours was found.

In a Tg.AC transgenic mouse model, dermal application of triethanolamine produced no increase in tumours.

5.4 Other relevant data

Triethanolamine is rapidly absorbed and excreted in rodent urine (about 60%) and faeces (about 20%), mainly in the unchanged form. Biodegradation of triethanolamine to monoethanolamine or diethanolamine or to any other putative metabolite has not been shown in rodents, nor has its incorporation into endogenous macromolecules. There is no evidence for formation of *N*-nitrosodiethanolamine from triethanolamine under physiological conditions.

In humans, triethanolamine is reported to be a skin sensitizer. Repeated dermal application of high concentrations of triethanolamine to rats led to a necrotizing inflammatory process in the skin.

Data on reproductive and developmental effects in humans were not available. No reproductive or developmental effects were produced when rats and mice were exposed by topical administration. Other routes of exposure have not been studied.

No data on the genetic and related effects of triethanolamine in humans were available to the Working Group.

Triethanolamine did not induce mutations in bacteria, unless nitrite was also present. It did not influence the frequency of micronuclei in mouse peripheral blood *in vivo* after dermal application. Triethanolamine did not induce unscheduled DNA synthesis, sister chromatid exchange, chromosomal aberrations or cell transformation in rodent cells *in vitro*. Triethanolamine had no effect on sex-linked recessive lethal mutations in *Drosophila melanogaster* or on gene conversion in *Saccharomyces cerevisiae*.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms

- Alkanolamine 244
- Nitrioltriethanol
- 2,2',2''-Nitrioltriethanol
- TEA
- TEA (amino alcohol)
- TEOA
- Triethanolamin
- Tris(β -hydroxyethyl)amine
- Tris(2-hydroxyethyl)amine

N-NITROSODIETHANOLAMINE

(Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 77 (2000) (p. 403)

CAS No.: 1116-54-7

Chem. Abstr. Name: 2,2' -(Nitrosoimino)bis[ethanol]

5. Summary of Data Reported and Evaluation

5.1 Exposure data

N-Nitrosodiethanolamine is a contaminant formed by the action of nitrites on ethanolamines in a wide range of products including metalworking fluids, pesticides, antifreeze and personal care products. Occupational exposure by inhalation and dermal contact may occur from water-diluted metalworking fluids contaminated with *N*-nitrosodiethanolamine. General population exposure is possible through contact with a variety of personal care products and the use of some tobacco products. Contamination levels in both metalworking fluids and personal care products have considerably decreased since the 1980s.

5.2 Human carcinogenicity data

Four studies showed inconsistent increases in cancer mortality or incidence at various sites among workers using metalworking fluids containing ethanolamines and sodium nitrite. Only one of them attempted indirectly to estimate exposure to nitrosamines, showing an increased risk for oesophageal cancer with increasing duration of exposure, but there was concomitant exposure to biocides, also associated with an increased risk for oesophageal cancer in this study.

5.3 Animal carcinogenicity data

N-Nitrosodiethanolamine was tested for carcinogenicity by addition to drinking-water in six studies in rats. It was also tested in hamsters by subcutaneous injection in three studies and in single studies by topical or buccal administration. In rats, it consistently produced liver tumours (principally hepatocellular carcinomas). It also produced adenocarcinomas and squamous-cell carcinomas of the nasal cavity. In hamsters, *N*-nitrosodiethanolamine consistently induced adenocarcinomas of the nasal cavity.

In a mouse lung screening assay, *N*-nitrosodiethanolamine increased the incidence and multiplicity of lung tumours.

5.4 Other relevant data

N-Nitrosodiethanolamine is metabolized *in vivo* slowly and only to a small extent, being principally eliminated unchanged in human and rodent urine. Bioactivation of *N*-nitrosodiethanolamine is associated with α - and β -hydroxylation pathways involving the enzymes CYP2E1 and alcohol dehydrogenase, resulting in DNA adduct formation.

Two studies have examined the potential genotoxic hazard of occupational exposure to *N*-nitrosodiethanolamine. The larger one, measuring DNA damage, indicated an association between single-strand breakage and the presence of *N*-nitrosodiethanolamine in the air of the workplace, but the effects of other exposures could not be excluded. The small study measuring chromosome damage in tool-room workers did not find any significant effect.

N-Nitrosodiethanolamine is mutagenic to bacteria. Studies using cultured cells *in vitro* found induction of DNA single-strand breakage after exposure to *N*-nitrosodiethanolamine in human buccal cells and in rat, hamster and pig hepatocytes. Chromosomal damage was detected in human lymphocytes without exogenous metabolic activity in one study; sister chromatid exchange frequency alone was increased and was detected at lower doses in another study with an exogenous metabolic system including alcohol dehydrogenase.

5.5 Evaluation

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

There is *sufficient evidence* in experimental animals for the carcinogenicity of *N*-nitrosodiethanolamine.

Overall evaluation

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

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluations: [Vol. 17 \(1978\)](#); Suppl. 7 (1987) (p. 67)

Synonyms

- Diethanolnitrosamine
- *N,N*-Diethanolnitrosamine
- NDELA
- *N*-Nitrosobis(2-hydroxyethyl)amine
- Nitrosodiethanolamine
- 2,2' -Nitrosoiminodiethanol

2,3-DIBROMOPROPAN-1-OL (Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 77 (2000) (p. 439)

CAS No.: 96-13-9

Chem. Abstr. Name: 2,3-Dibromo-1-propanol

5. Summary of Data Reported and Evaluation

5.1 Exposure data

2,3-Dibromopropan-1-ol was used as an intermediate to produce the flame retardant tris(2,3-dibromopropyl) phosphate. In the past, it was detected in the urine of children wearing nightwear treated with tris(2,3-dibromopropyl) phosphate. It is still produced for use in the manufacture of other chemicals (possibly flame retardants, insecticides and pharmaceuticals).

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

2,3-Dibromopropan-1-ol was tested by skin application in one experiment in mice and in one experiment in rats. In mice, it produced tumours of the skin at the site of application and forestomach in both males and females and tumours of the liver in males. In rats, it produced tumours of the skin at the site of application and of the digestive tract including the mouth, oesophagus, forestomach and intestines, nasal mucosa and Zymbal gland in both males and females, and tumours of the liver, mammary gland and clitoral gland in females.

5.4 Other relevant data

Two mercapturic acid metabolites of 2,3-dibromopropan-1-ol have been identified in the urine of treated rats.

Application of 2,3-dibromopropan-1-ol to the skin of rats and mice for 13 weeks caused kidney lesions in male rats, liver lesions in female rats and liver and lung lesions in both male and female mice.

2,3-Dibromopropan-1-ol was mutagenic in bacterial assays both in the presence and absence of exogenous metabolic systems. It gave positive results in a mammalian cell mutagenesis assay and induced sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells. It was mutagenic in *Drosophila melanogaster*. It was inactive in an in-vivo bone-marrow micronucleus assay in male mice.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of 2,3-dibromopropan-1-ol were available.

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

Overall evaluation

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

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms

- DBP
- DBP (flame retardant)
- 1,2-Dibromopropan-3-ol
- 2,3-Dibromopropyl alcohol

Last updated: 22 August 2000

2,2-BIS(BROMOMETHYL)PROPANE-1,3-DIOL (Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 77 (2000) (p. 455)

CAS No.: 3296-90-0

Chem. Abstr. Name: 2,2-Bis(bromomethyl)propane-1,3-diol

5. Summary of Data Reported and Evaluation

5.1 Exposure data

2,2-Bis(bromomethyl)propane-1,3-diol is a flame retardant used in polyester resins and polyurethane foams. No data on human exposure to this substance were available.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

2,2-Bis(bromomethyl)propane-1,3-diol was tested for carcinogenicity as a commercial mixture (FR-1138®) containing 80% of the parent compound in one experiment in mice and in two experiments in rats by oral administration in the diet. In mice, it increased the incidence of tumours of the Harderian gland, forestomach and lung in both males and females and of subcutaneous sarcomas in females. In one study in male rats, it increased the incidences of tumours of the skin, subcutaneous tissue, mammary gland, Zymbal gland, oral cavity, oesophagus, forestomach, small and large intestine, peritoneum, lung and thyroid. In female rats the incidences of oesophageal, mammary gland and thyroid follicular tumours were increased.

5.4 Other relevant data

No data on the metabolism of 2,2-bis(bromomethyl)propane-1,3-diol were available.

Histopathological changes were observed in the kidney and the urinary bladder of rats and mice administered 2,2-bis(bromomethyl)propane-1,3-diol for 13 weeks.

No data on reproductive and developmental effects in humans were available.

No effects were observed, after 13 weeks' exposure, on sperm parameters or vaginal cytology in mice or rats. However, in a mouse continuous breeding study, exposure to 2,2-bis(bromomethyl)propane-1,3-diol in feed caused a female-specific decrease in reproductive capacity.

2,2-Bis(bromomethyl)propane-1,3-diol was mutagenic in only one of several bacterial strains tested, and only with metabolic activation. In cultured mammalian cells, it was only weakly active in tests for chromosomal aberrations and sister chromatid exchanges. Micronucleus formation, indicative of chromosomal damage, was induced in cells from mice exposed to 2,2-bis(bromomethyl)propane-1,3-diol *in vivo*.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of 2,2-bis(bromomethyl)propane-1,3-diol were available.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 2,2-bis(bromomethyl)propane-1,3-diol.

Overall evaluation

2,2-Bis(bromomethyl)propane-1,3-diol is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms

- 1,3-Dibromo-2,2-dihydroxymethylpropane
- 1,3-Dibromo-2,2-dimethylolpropane
- 2,2-Dibromomethyl-1,3-propanediol
- Dibromoneopentyl glycol
- Pentaerythritol dibromide
- Pentaerythritol dibromohydrin

Last updated: 22 August 2000

GLYCIDOL (Group 2A)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 77 (2000) (p. 469)

CAS No.: 556-52-5

Chem. Abstr. Name: Oxiranemethanol

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Glycidol is an epoxide used as a chemical intermediate in the production of functional epoxides, glycidyl urethanes, pharmaceuticals and other products. It is also used as a reactive diluent in epoxy resin systems and as a sterilant. Occupational exposure may occur during its production and use. No data were available on environmental exposure to glycidol.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Glycidol has been tested by oral administration in one study in mice, in one study in rats and in one study in hamsters. It was also tested by skin application in one study in mice. After oral administration to mice, it produced increases in tumours of the Harderian gland in both males and females, of the forestomach, lung, liver and skin in males, and of the mammary gland and subcutaneous tissue in females. In rats, it produced increases in the incidence of gliomas of the brain and forestomach tumours in both males and females. Mesotheliomas of the tunica vaginalis/peritoneum, as well as tumours of the intestine, skin, thyroid gland and Zymbal gland were increased in males. Tumours of the clitoral gland, mammary gland and oral mucosa as well as leukaemia were increased in females.

In hamsters, there was a marginal increase in the incidence of splenic haemangiosarcomas after oral administration.

No skin tumours were observed in mice after skin application.

5.4 Other relevant data

Glycidol is an alkylating agent which reacts readily with glutathione. It causes a decrease in glutathione content in rat liver, probably reflecting its binding to glutathione. In rats, it is metabolized to oxidative and glutathione-derived products. No toxicokinetic data on humans were available.

No data on developmental and reproductive effects in humans were available to the Working Group.

No effects on fertility or development were observed in mice given intraperitoneal injections of glycidol 24 h before mating or orally during organogenesis. In contrast, when a single dose of glycidol was administered to female mice within 25 h after mating, the numbers of fetal deaths and anomalies were increased. Intra-amniotic injection of glycidol on day 13 of gestation in rats increased the frequency of resorptions and, at high

doses, limb malformations.

Glycidol has been shown to be genotoxic using assays covering a wide range of end-points. *In vitro*, it did not require metabolic activation to elicit positive responses.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of Groups, see [Preamble Evaluation](#).

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

Synonyms

- Allyl alcohol oxide
- Epihydrin alcohol
- 1,2-Epoxy-3-hydroxypropane
- 2,3-Epoxypropan-1-ol
- 2,3-Epoxy-1-propanol
- (±)-2,3-Epoxy-1-propanol
- Glycide
- (±)-Glycidol
- (RS)-Glycidol
- dl-Glycidol
- Glycidyl alcohol
- Hydroxy-1,2-epoxypropane
- 1-Hydroxy-2,3-epoxypropane
- 2-(Hydroxymethyl)oxirane
- 3-Hydroxypropylene oxide
- Oxiranylmethanol
- Racemic glycidol

NITROMETHANE (Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 77 (2000) (p. 487)

CAS No.: 75-52-5

Chem. Abstr. Name: Nitromethane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Nitromethane is a volatile liquid that is added in small amounts to many halogenated solvents and aerosol propellants as a stabilizer. It is also used as a polar solvent for certain polymers and resins, in specialized fuels and in explosives. Exposures may occur from the use of solvents, propellants and fuels containing nitromethane.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Nitromethane was tested for carcinogenicity by inhalation in one experiment in mice and in two experiments in rats. In mice, it increased the incidence of Harderian gland and lung tumours in males and females as well as of hepatocellular adenomas in females. In one experiment in rats, nitromethane increased the incidence of benign and malignant mammary gland tumours in females, but produced no increase in the incidence of tumours in a second study in a different strain of rat.

5.4 Other relevant data

Nitromethane produces histidinaemia in rats by decreasing hepatic histidase activity, leading to increased tissue levels of histidine.

Neurological effects were observed in nitromethane-exposed rats.

Nitromethane caused mild degeneration of the olfactory epithelium of exposed rats and mice and microcytic anaemia with minimal to mild hyperplasia of the bone marrow in rats.

No data on reproductive or developmental effects in humans were available.

In rats and mice, dose-related decreases in sperm motility were found after inhalation of nitromethane. In females, estrous cycle length was increased in mice but not in similarly exposed rats.

Nitromethane gave negative results in all short-term tests for genetic effects, with the exception of a cell transformation assay in which it was positive at high concentration.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonym

- Nitrocarbol

Last updated: 22 August 2000

PYRIDINE (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 77 (2000) (p. 503)

CAS No.: 110-86-1

Chem. Abstr. Name: Pyridine

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Pyridine is an organic liquid of disagreeable odour, produced from coal-tar or by chemical synthesis. It is widely used as a solvent and intermediate in the production of piperidine, agricultural chemicals, drugs, dyestuffs, paints, rubber products, polycarbonate resins and textile water-repellents, as well as in laboratories. Occupational exposure may occur through inhalation and dermal contact during its production and its various uses as well as during the processing of oil-shale and at coke-oven works. It is rarely detected in ambient air or drinking water but is frequently found in indoor air. It is present in cigarette smoke and in the volatile components of certain foodstuffs.

5.2 Human carcinogenicity data

One mortality study of workers at a 4,4'-bipyridyl manufacturing plant using pyridine as a starting material showed a small non-significant excess of lung cancer mortality. This excess could not be attributed to specific chemical exposures within the plant, and it was not clear if the risk associated with pyridine exposure was specifically assessed.

5.3 Animal carcinogenicity data

Pyridine was tested for carcinogenicity by oral administration in the drinking-water in one experiment in mice and in two experiments in rats and by subcutaneous injection in one experiment in rats. In male and female mice, it increased incidences of hepatocellular carcinomas and hepatoblastomas. In male Fischer 344 rats, it increased the incidence of renal tubule adenomas but not in male Wistar rats. No increase in tumour incidence at any site was observed in rats following subcutaneous injection of pyridine for one year and a subsequent observation period of six months.

In two studies with genetically modified mice, there was no treatment-related increase in the incidence of tumours.

5.4 Other relevant data

Pyridine is well absorbed from the gastrointestinal tract in mammals, and undergoes extensive metabolism by C- and N-oxidation and by N-methylation, giving the quaternary ion N-methylpyridinium.

In humans, acute pyridine intoxication affects the central nervous system, leading to dizziness, headache, nausea and anorexia. There is one case report of lethality after a high dose. Further symptoms include abdominal pain and pulmonary congestion. Pyridine was hepatotoxic in Fischer 344 and Wistar rats and caused an increase in granular casts and renal tubule hyaline degeneration in male Fischer 344 rats. Inhalation of pyridine can cause necrotic damage of the nasal epithelium. In rats and rabbits, pyridine is an inducer of CYP2E1 in the liver and kidney.

No data on reproductive and developmental effects in humans were available.

Exposure to pyridine in drinking-water led to reduction of sperm motility at all dose levels in mice and increased estrous cycle length at the highest dose level in rats.

Apart from positive responses in the sex-linked recessive lethal assay in *Drosophila melanogaster* and for aneuploidy in a fungal system, all tests, covering a range of end-points, for genetic toxicology of pyridine gave negative results.

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms

- Azabenzene
- Azine