



WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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Volume 73

Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents and Some Other Substances

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Last updated: 29 September 1999

ALLYL ISOTHIOCYANATE

(Group 3)

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

VOL.: 73 (1999) (p. 37)

CAS No.: 57-06-7

Chem. Abstr. Name: 3-Isothiocyanato-1-propene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to allyl isothiocyanate occurs as a result of its presence in foods as the chief constituent of mustard oil and as a flavouring agent.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Allyl isothiocyanate was tested for carcinogenicity in one experiment in mice and one experiment in rats by oral administration. No increase in tumour incidence was observed in mice. An increased but low incidence of transitional-cell hyperplasia and papillomas of the urinary bladder was observed in male rats, and there was a low incidence of subcutaneous fibrosarcomas in female rats given the high dose.

5.4 Other relevant data

Major sex- and species-related differences in the tissue distribution of allyl isothiocyanate were restricted to the urinary bladder, where higher concentrations of allyl isothiocyanate-derived radiolabel were found in the bladders of male rats than in mice or female rats. Rodents and humans both metabolize allyl isothiocyanate to *N*-acetyl-*S*-(*N*-allyl thiocarbamoyl)-*L*-cysteine. Allyl isothiocyanate appears to be an irritant in both rodents and humans.

Allyl isothiocyanate was not teratogenic to mice, rats, hamsters or rabbits, but resorptions were seen in mice and rats.

No data were available on the genetic and related effects of allyl isothiocyanate in humans. The available data do not allow a conclusion about the genotoxicity of allyl isothiocyanate in experimental systems *in vivo*. There is evidence for genotoxic effects in mammalian cells *in vitro*. It was not mutagenic to bacteria.

5.5 Evaluation

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

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

Overall evaluation

Allyl isothiocyanate 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) (p. 56)

Synonyms

- AITC
- Allyl mustard oil
- Allyl senevolum
- Allyl thioisocyanate
- 3-Isothiocyanato-1-propene
- Isothiocyanic acid, allyl ester
- Mustard oil
- Oleum sinapis
- 2-Propenyl isothiocyanate
- Volatile mustard oil
- Volatile oil of mustard

Last updated: 1 October 1999

***ortho*-ANISIDINE (Group 2B)**

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

VOL.: 73 (1999) (p. 49)

CAS No.: 90-04-0

Chem. Abstr. Name: 2-Methoxybenzenamine

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to *ortho*-anisidine may occur during its production and its use as a chemical intermediate, a corrosion inhibitor and an industrial antioxidant.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

ortho-Anisidine hydrochloride was tested for carcinogenicity in one study in mice and one study in rats by oral administration in the diet. It produced transitional-cell carcinomas of the urinary bladder in animals of each species and sex.

5.4 Other relevant data

Limited information was available to the Working Group on the metabolism of *ortho*-anisidine. It was shown to be *O*-dealkylated in rat liver microsomes.

ortho-Anisidine at a high dose increased the incidence of hyperplasia of the bladder in male and female mice.

No data were available on the developmental and reproductive effects of *ortho*-anisidine.

No data were available on the genetic and related effects of *ortho*-anisidine in humans. No conclusion can be drawn about its genotoxicity in experimental animals *in vivo*; however, *ortho*-anisidine induced gene mutation in bladder cells in an assay in transgenic mice. There is no evidence that it has genotoxic effects in mammalian cells *in vitro*. *ortho*-Anisidine was not mutagenic to bacteria.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of *ortho*-anisidine.

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

Overall evaluation

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

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

Previous evaluations: [Vol. 27 \(1982\)](#); Suppl. 7 (1987) (p. 57)

Synonyms

- *ortho*-Aminoanisole
- 2-Aminoanisole
- *ortho*-Aminomethoxybenzene
- 2-Aminomethoxybenzene
- 1-Amino-2-methoxybenzene
- 2-Methoxy-1-aminobenzene
- *ortho*-Methoxyaniline
- 2-Methoxyaniline
- 2-Methoxybenzenamine
- *ortho*-Methoxyphenylamine
- 2-Methoxyphenylamine

Last updated: 30 September 1999

ATRAZINE

(Group 3)

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

VOL.: 73 (1999) (p. 59)

CAS No.: 1912-24-9

Chem. Abstr. Name: 6-Chloro-*N*-ethyl-*N'*-(1-methylethyl)-1,3,5-triazine-2,4-diamine

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Atrazine is a triazine herbicide widely used on a variety of crops, notably maize, sorghum and sugar-cane, for the pre- and post-emergent control of broad-leaved weeds. Occupational exposure may occur through both inhalation and dermal absorption during its manufacture, its formulation and its application by spraying. It is found widely, together with its dealkylated degradation products, in rivers, lakes, estuaries, groundwater and reservoirs. In drinking-water, the levels rarely exceed 1 µg/L. Surveys of various foods and feeds have generally indicated no detectable atrazine residue.

5.2 Human carcinogenicity data

A combined analysis of the results of two cohort studies of agricultural chemical production workers in the United States showed decreased mortality from cancers at all sites combined among the subset of workers who had had definite or probable exposure to triazine. Site-specific analyses in this subset of workers yielded no significant findings; a non-significant increase in the number of deaths from non-Hodgkin lymphoma was seen, but was based on very few observed cases.

A pooled analysis of the results of three population-based case–control studies of men in Kansas, eastern Nebraska and Iowa–Minnesota, United States, in which the risk for non-Hodgkin lymphoma in relation to exposure to atrazine and other herbicides on farms was evaluated, showed a significant association; however, the association was weaker when adjustment was made for reported use of phenoxyacetic acid herbicides or organophosphate insecticides. A sub-analysis of results for farmers in Nebraska, the State in which the most detailed information on atrazine use was available, showed no excess risk for non-Hodgkin lymphoma among farmers who had used atrazine for at least 15 years, after adjustment for use of other pesticides. In a case–control study of non-Hodgkin lymphoma among women in eastern Nebraska, a slight, nonsignificant increase in risk was seen. In all these studies, farmers tended to have an increased risk for non-Hodgkin lymphoma, but the excess could not be attributed to atrazine.

Less information was available to evaluate the association between exposure to atrazine and other cancers of the lymphatic and haematopoietic tissues. One study of Hodgkin disease in Kansas, one study of leukaemia in Iowa–Minnesota and one study of multiple myeloma from Iowa gave no indication of excess risk among persons handling triazine herbicides.

In a population-based study in Italy, definite exposure to triazines was associated with a two- to threefold increase of borderline significance in the risk for ovarian cancer. The study was small, and potential confounding by exposure to other herbicides was not controlled for in the analysis.

5.3 Animal carcinogenicity data

Atrazine was tested for carcinogenicity in one study in mice by oral administration in the diet. No increase in

tumour incidence was observed. It was also tested by oral administration in two studies in Fischer rats and in five studies in Sprague-Dawley rats, including a comparison of intact and ovariectomized females of the latter strain. In Fischer rats, no increase in tumour incidence was observed in one adequate study. The incidence of mammary tumours was increased in intact Sprague-Dawley females in four studies, but no increase was seen in ovariectomized Sprague-Dawley females. Atrazine was also tested by intraperitoneal injection in one study in mice; an increased incidence of lymphomas was reported.

5.4 Other relevant data

N-Dealkylation and conjugation with glutathione are the main metabolic pathways for atrazine in various species *in vivo*. There do not appear to be qualitative differences in the metabolism of atrazine between the strains and species studied that would explain the fact that mammary gland tumours develop in Sprague-Dawley rats but not in Fischer 344 rats or CD-1 mice.

Atrazine has been tested for developmental toxicity in rats and rabbits. No teratogenic effects have been observed. Fetal loss and reduced fetal body weights were seen in rabbits; the incidences of some minor skeletal variants were elevated in exposed fetal rats. No developmental effects were seen in a study of mice and rats exposed to groundwater contaminants that included atrazine.

The evidence from biological assays (e.g. uterine weight, stromal cell proliferation, epithelial cell height) and from *in-vitro* assays of oestrogen receptors indicates that atrazine does not have intrinsic oestrogenic activity.

Long-term administration of atrazine enhances the onset of reproductive senescence in female Sprague-Dawley (but not Fischer 344) rats, resulting in an earlier onset of persistent oestrus and tissue changes characteristic of long-term exposure to elevated oestrogen levels. Atrazine appears to disrupt neuroendocrine pathways in the hypothalamus by as yet undetermined mechanisms, resulting in attenuation of the luteinizing hormone surge that normally results in ovulation. These hormonal imbalances seen after atrazine administration were associated with an increased incidence and earlier onset of mammary tumours in some but not all studies of carcinogenicity in Sprague-Dawley rats, and not in Fischer 344 rats or CD-1 mice. Ovariectomized Sprague-Dawley rats exposed for two years to the highest dose of atrazine used in the bioassay in which ovariectomized and intact animals were compared did not develop either tumours or other proliferative lesions in the mammary gland.

In contrast to the hormonal changes in Sprague-Dawley rats, reproductive senescence in women is characterized by depletion of the ovarian oocyte content and reduced oestrogen secretion.

No data were available on the genetic and related effects of atrazine in humans. There is weak evidence for genotoxic effects in mammalian cells *in vivo* and *in vitro*. Atrazine was mutagenic in *Drosophila*, yeast and plant cells but was not mutagenic to bacteria. Overall, the results of genotoxicity testing would not appear to bear directly on the strain-specific tumour induction in female Sprague-Dawley rats.

5.5 Evaluation

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

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

Overall evaluation

In making its overall evaluation, the Working Group concluded that the mammary tumours associated with exposure to atrazine involve a non-DNA-reactive, hormonally mediated mechanism. In reaching the conclusion, the following evidence was considered:

(a) Atrazine produces mammary tumours (fibroadenomas, adenocarcinomas) only in intact female Sprague-Dawley rats (not in Fischer 344 rats, CD-1 mice or ovariectomized Sprague-Dawley rats) and does not increase the incidences of other tumour types.

(b) Atrazine affects neuroendocrine pathways of the hypothalamus to accelerate the onset of reproductive senescence in female Sprague-Dawley but not Fischer 344 rats.

(c) Atrazine does not have intrinsic oestrogenic activity.

(d) There are critical interspecies differences in the hormonal changes associated with reproductive senescence.

Therefore, there is strong evidence that the mechanism by which atrazine increases the incidence of mammary gland tumours in Sprague-Dawley rats is not relevant to humans.

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

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

Previous evaluation: [Vol. 53 \(1991\)](#)

Synonyms

- 2-Chloro-4-(ethylamino)-6-(isopropylamino)triazine
- 2-Chloro-4-(ethylamino)-6-(isopropylamino)-s-triazine
- 2-Chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine
- 6-Chloro-*N*²-ethyl-*N*⁴-isopropyl-1,3,5-triazine-2,4-diamine

Last updated: 30 September 1999

BUTYL BENZYL PHTHALATE

(Group 3)

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

VOL.: 73 (1999) (p. 115)

CAS No.: 85-68-7

Chem. Abstr. Name: 1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to butyl benzyl phthalate occurs during its production and use as a plasticizer, mainly in polyvinyl chloride products. It has been detected at low levels in indoor air, water and a few foods.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Butyl benzyl phthalate was tested for carcinogenicity by oral administration in one experiment in mice and three experiments in rats, including two studies with dietary restriction. No increase in the incidence of tumours was observed in mice. A marginal increase in the incidence of bladder tumours was observed in female rats after 32 months of dietary restriction. An increased incidence of benign pancreatic tumours was seen in one conventional study in male rats, but not after dietary restriction, despite extension of the period of dosing to 32 months.

In one study in rats, butyl benzyl phthalate inhibited mammary carcinogenesis produced by prior administration of 7,12-dimethylbenz[a]anthracene.

5.4 Other relevant data

Butyl benzyl phthalate is hydrolysed in the gastrointestinal tract to mono-*n*-butyl phthalate and monobenzyl phthalate, which are absorbed, further metabolized, glucuronidated and excreted in the urine. Butyl benzyl phthalate weakly stimulated hepatic peroxisome proliferation. Although the compound binds weakly to oestrogen receptors *in vitro*, it had no oestrogenic activity *in vivo* in tests which included uterotrophic effects and vaginal cornification.

Butyl benzyl phthalate has been tested for developmental toxicity in mice by administration in the diet and in rats by administration in the diet, by gavage and in drinking-water. Malformations and embryonic deaths were observed in both species, generally at maternally toxic doses. In rats, alterations in ovarian and/or uterine function appeared to be involved in the decreased embryonic viability. Testicular toxicity has been observed in male rats exposed to butyl benzyl phthalate.

No data were available on the genetic and related effects of butyl benzyl phthalate in humans. Butyl benzyl phthalate was not genotoxic in experimental systems, except for weak clastogenicity in bone-marrow cells of mice treated *in vivo* in one study.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of butyl benzyl phthalate.

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

Overall evaluation

Butyl benzyl phthalate 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. 59)

Synonyms

- BBP
- Benzyl butyl phthalate
- Benzyl *n*-butyl phthalate
- Phthalic acid, benzyl butyl ester

Last updated: 30 September 1999

CHLOROFORM (Group 2B)

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

VOL.: 73 (1999) (p. 131)

CAS No.: 67-66-3

Chem. Abstr. Name: Trichloromethane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Occupational exposure to chloroform may occur during its production and use as a solvent and chemical intermediate. The general population may be exposed as a result of its presence in chlorinated drinking-water, ambient air and some foods.

5.2 Human carcinogenicity data

Two cohort studies of cancer and drinking-water quality were carried out in the United States. One conducted in Maryland showed excess mortality from cancers of the liver and breast in association with water chlorination, while that conducted in Iowa showed increased risks for cancers of the colon and lung and skin melanoma associated with chloroform concentrations in drinking-water.

Eight case-control studies have been reported on bladder cancer in relation to chlorinated drinking-water in the United States. Significant results were obtained in five studies, but there was little consistency in the risk pattern in subgroups defined by sex or surrogate measures of chloroform intake. Significant increasing trends in the risk for bladder cancer were seen in two studies. The study in Colorado showed increasing risk with years of exposure to chlorinated water; the study in Iowa showed increasing risk with lifetime intake of trihalomethanes (from drinking-water), but only in men and not in women.

Seven case-control studies addressed the risk for cancers of the large bowel in association with consumption of chlorinated water. In two of these studies, lifetime exposure to trihalomethanes was assessed. Two studies showed significant associations with rectal cancer. Overall, however, the results were inconsistent with regard to the subsite of the large bowel and sex, and the quality of the studies varied widely.

Exposure to chloroform in the workplace was addressed in two case-control studies, both of which had limited statistical power. The study on brain cancer gave negative results. The other included a number of sites (but not the brain) and showed associations with cancers of the prostate and lung, but no association was seen with bladder cancer.

The presence of various water chlorination by-products, including trihalomethanes, is likely to be highly correlated. Although chloroform is the most ubiquitous, the other by-products therefore may act as confounders in studies of water-mediated exposure. In addition, important sources of chloroform other than drinking-water were ignored in the majority of the studies.

Although the epidemiological evidence for an association between consumption of chlorinated drinking-water and the risk for some cancers, particularly those of the urinary bladder and rectum and possibly of the colon, seems to favour an interpretation of mild excess, a causal inference cannot be made with regard to chloroform because of incomplete control for confounding by other water impurities and other factors and lack of concordance in the results for men and women. Use of surrogate indicators for exposure to chloroform adds to

the uncertainty.

5.3 Animal carcinogenicity data

Chloroform was tested for carcinogenicity in several experiments in mice, rats and dogs. In three studies by oral administration and in one study by inhalation exposure in mice, it produced renal tubule tumours and, in one study, hepatocellular tumours. In three studies by oral administration in Osborne-Mendel rats, chloroform produced renal tubule tumours. No increased incidence of tumours was observed in one study in dogs.

5.4 Other relevant data

Chloroform is metabolized by oxidative and reductive pathways. Under normal conditions, oxidative metabolism is the major pathway, and reductive metabolism does not play a significant role. Oxidative metabolism of chloroform results in the generation of phosgene, which either reacts with water to give carbon dioxide and hydrogen chloride or binds covalently to tissue macromolecules. The formation of carbon dioxide as a metabolite of chloroform has been shown in a number of studies in both rodents and humans *in vivo*.

The metabolism of chloroform is more rapid in mice than in rats, and human tissues (liver and kidney) have the lowest activity. CYP2E1 is the predominant enzyme involved in the metabolism of chloroform in both rodent and human tissues.

There is a consistent, tissue-, species-, strain- and sex-specific pattern in the rate of metabolism, cytotoxicity and cell proliferation produced by chloroform in rodent liver and kidney. Under the conditions of the high-dose regimens used in cancer bioassays in which tumours are produced, chloroform induced cytotoxicity and regenerative cell proliferation in the target organs for cancer. These findings are consistent with a mode of action for tumorigenesis in the liver and kidney of rodents that involves cytotoxicity.

Chloroform has been tested for developmental toxicity in mice and rats by gavage and inhalation. Fetal toxicity in the form of growth retardation has been observed in several studies, concurrent with evidence of maternal toxicity. Malformations were observed in one study in rats exposed by inhalation. In a continuous breeding study, no reproductive effects were noted.

No data were available on the genetic and related effects of chloroform in humans. There is weak evidence for the genotoxicity of chloroform in experimental systems *in vivo* and in mammalian cells, fungi and yeast *in vitro*. It was not mutagenic to bacteria.

5.5 Evaluation

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

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

Overall evaluation

Chloroform 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

- HCC 20
- R 20
- R 20 (refrigerant)
- Trichloroform

Last updated: 30 September 1999

CHLOROTHALONIL (Group 2B)

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

VOL.: 73 (1999) (p. 183)

CAS No.: 1897-45-6

Chem. Abstr. Name: 2,4,5,6-Tetrachloro-1,3-benzenedicarbonitrile

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to chlorothalonil may occur during its production and during its application as a fungicide, bactericide and nematocide. It has been detected in some foods.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Chlorothalonil was tested by oral administration in the diet in three experiments in mice and three experiments in rats. It produced renal tubular tumours (adenomas and carcinomas) in males of each species and in female rats. The incidences of forestomach papillomas and carcinomas were increased in males and females of each species.

5.4 Other relevant data

Chlorothalonil is metabolized in rats by conjugation to glutathione in the gastrointestinal tract and liver. After biliary excretion, uptake and metabolism of these conjugates in the kidney by the action of γ -glutamyl transpeptidase and cysteine-conjugate β -lyase results in the production of di- and tri-thiols, which are thought to be responsible for the toxicity seen in the kidney. Sustained cytotoxicity and the resultant regenerative response in the kidney are found in conjunction with tumour formation after long-term exposure.

There may be less activity of γ -glutamyl transpeptidase and cysteine-conjugate β -lyase in humans than in rats.

Forestomach tumours produced by chlorothalonil were associated with squamous hyperplasia and local irritation.

No data were available on reproductive or developmental effects.

No data were available on the genetic and related effects of chlorothalonil in humans or in rodents *in vivo*. In one study, 8-oxydeoxyguanosine products were observed in the livers of mice exposed *in vivo*. There is some evidence for genotoxicity in mammalian cells *in vitro*. Chlorothalonil was not mutagenic to bacteria.

5.5 Evaluation

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

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

Overall evaluation

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

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

Previous evaluations: [Vol. 30 \(1983\)](#); Suppl. 7 (1987) (p. 60)

Synonyms

- 1,3-Dicyanotetrachlorobenzene
- Tetrachlorobenzene-1,3-dicarbonitrile
- 2,4,5,6-Tetrachloro-1,3-dicyanobenzene
- Tetrachloroisophthalonitrile
- 2,4,5,6-Tetrachloroisophthalonitrile
- 2,4,5,6-Tetrachloro-1,3-isophthalonitrile

Last updated: 30 September 1999

CYCLAMATES (Group 3)

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

VOL.: 73 (1999) (p. 195)

Cyclamic acid

CAS No.: 100-88-9

Chem. Abstr. Name: Cyclohexylsulfamic acid

Sodium cyclamate

CAS No.: 139-05-9

Chem. Abstr. Name: Cyclohexylsulfamic acid, monosodium salt

Calcium cyclamate

CAS No.: 139-06-0

Chem. Abstr. Name: Cyclohexylsulfamic acid, calcium salt (2:1)

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Cyclamates are widely used as non-caloric sweeteners, the average daily dietary intake generally being less than 3 mg/kg bw.

5.2 Human carcinogenicity data

Use of cyclamates was analysed separately in only four of the studies summarized in the monograph on saccharin and its salts. No increase in the risk for urinary bladder cancer was seen.

5.3 Animal carcinogenicity data

Sodium cyclamate was tested by oral administration in two experiments in mice, one of which was a multigeneration study, and in three experiments in rats. No treatment-related increase in tumour incidence was found. Sodium cyclamate was also tested by oral administration in other experiments in mice, rats, hamsters and monkeys, but these experiments could not be evaluated because of various inadequacies or incomplete reporting.

Pellets containing sodium cyclamate induced bladder tumours in mice after implantation into the bladder; however, the protocol was considered to be inadequate for determining carcinogenicity.

Calcium cyclamate was tested by oral administration in a two-generation experiment in rats; no difference in tumour incidence was seen between treated and control animals.

In two studies in rats, sodium cyclamate was administered orally after a known carcinogen. The incidence of urinary bladder tumours was increased in one study, whereas only slight enhancement was found in a second study.

5.4 Other relevant data

Cyclamates are incompletely absorbed from the gastrointestinal tract of humans and other mammals. Most is excreted in the urine unchanged. Cyclamates are partially converted by gastrointestinal microflora to cyclohexylamine, which is absorbed. Cyclamates and cyclohexylamine can produce testicular toxicity in rats.

Cyclamates have not been observed to produce developmental toxicity in mice, rats, rabbits, hamsters, dogs or rhesus monkeys. Negative results were obtained in a number of short-term assays for teratogenicity *in vitro* and *in vivo*. Cyclamates were not teratogenic in mice, rats or rhesus monkeys, but there were some indications of reduced growth and viability of embryos in some studies. Rat embryos exposed *in vitro* showed altered morphological development in one study.

Cyclamates did not produce chromosomal aberrations in peripheral lymphocytes of volunteers. Cyclamates were not genotoxic in rodents *in vivo* but were genotoxic in mammalian cells *in vitro*.

5.5 Evaluation

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

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

Overall evaluation

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

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

Previous evaluations: [Vol. 22 \(1980\)](#); [Suppl. 7 \(1987\)](#)

Synonyms

Cyclamic acid

- Cyclamate
- Cyclohexanesulfamic acid
- Cyclohexylamidodisulfuric acid
- Cyclohexylaminesulfonic acid
- *N*-Cyclohexylsulfamic acid
- Hexamic acid
- Sucaryl
- Sucaryl acid

Sodium cyclamate

- Cyclamate sodium
- Cyclohexanesulfamic acid, monosodium salt cyclohexylsulfamate sodium
- *N*-Cyclohexylsulfamic acid sodium salt
- Sodium cyclohexanesulfamate
- Sodium cyclohexylaminesulfonate
- Sodium cyclohexylsulfamate
- Sodium sucaryl
- Sucaryl sodium

Calcium cyclamate

- Calcium cyclohexanesulfamate
- Calcium sucaryl
- Cyclohexanesulfamic acid, calcium salt (2:1)

Last updated: 30 September 1999

DICHLOROBENZENES

ortho-Dichlorobenzene (Group 3)
meta-Dichlorobenzene (Group 3)
para-Dichlorobenzene (Group 2B)

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

VOL.: 73 (1999) (p. 223)

ortho-Dichlorobenzene

Chem. Abstract No.: 95-50-1

Chem. Abstr. Name: 1,2-Dichlorobenzene

meta-Dichlorobenzene

Chem. Abstr. No.: 541-73-1

Chem. Abstr. Name: 1,3-Dichlorobenzene

para-Dichlorobenzene

Chem. Abstr. No.: 106-46-7

Chem. Abstr. Name: 1,4-Dichlorobenzene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Dichlorobenzenes are chemical intermediates used widely in the manufacture of dyes, pesticides and various industrial products. *ortho*-Dichlorobenzene is further used as a solvent and an insecticide. *para*-Dichlorobenzene is used widely as a moth repellent and an air deodorizer and also as a pesticide.

Occupational exposure to dichlorobenzenes may occur during their manufacture and use, at levels reaching up to a few hundred milligrams per cubic meter in the case of *para*-dichlorobenzene. *ortho*-Dichlorobenzene and *para*-dichlorobenzene are found in ambient air at levels usually below 1 μ g/m³; in indoor air, *para*-dichlorobenzene is typically found at a level an order of magnitude higher. These two isomers have been detected in some drinking-water supplies at levels usually below 1 μ g/L and in some foods at levels up to 10 μ g/kg. Concentrations of 5–30 μ g/kg *ortho*- and *para*-dichlorobenzene have been reported in human milk.

meta-Dichlorobenzene is produced in smaller quantities than the *ortho* and *para* isomers and is used primarily as a chemical intermediate. The data on exposure to this chemical are limited.

5.2 Human carcinogenicity data

In a cohort study from the United States, no association was observed between occupational exposure to *ortho*-dichlorobenzene and mortality from multiple myeloma or non-Hodgkin lymphoma; however, the risk estimates were based on exceedingly few observations.

5.3 Animal carcinogenicity data

ortho-Dichlorobenzene was tested by oral administration in one well-conducted study in mice and one well-conducted study in rats. No increased incidence of tumours was observed.

meta-Dichlorobenzene has not been adequately tested for potential carcinogenicity in laboratory animals.

para-Dichlorobenzene was tested by oral administration and inhalation in mice and rats. After oral administration, it increased the incidence of adenomas and carcinomas of the liver in male and female mice and of renal tubular carcinomas in male rats. Studies in mice and rats exposed by inhalation were judged to be inadequate. *para*-Dichlorobenzene did not promote hepatic foci in a two-stage model of carcinogenesis in rats.

5.4 Other relevant data

No data were available on the absorption, distribution, metabolism or excretion of *ortho*-, *meta*- or *para*-dichlorobenzene in humans.

The major route of biotransformation of *ortho*-dichlorobenzene in male rats was via the glutathione pathway; most of the urinary metabolites were mercapturic acids. Other metabolites were conjugates of 2,3- and 3,4-dichlorophenol. A high dose of *ortho*-dichlorobenzene results in depletion of glutathione. The major metabolite of *para*-dichlorobenzene is 2,5-dichlorophenol. After administration of a high oral dose of *para*-dichlorobenzene to male rats, dichlorohydroquinone was identified in the urine only after acid hydrolysis.

No data were available to evaluate the toxicity of *meta*-dichlorobenzene in humans. Occupational exposure to *ortho*- and *para*-dichlorobenzene caused ocular irritation; *ortho*-dichlorobenzene also caused irritation in the upper respiratory tract.

para-Dichlorobenzene was reported to be hepatotoxic at doses of 600 mg/kg bw and higher in rats. *ortho*-Dichlorobenzene was found to be a more potent hepatotoxicant in rats than *para*-dichlorobenzene. *para*-Dichlorobenzene was reported to cause a mitogenic response in both mouse and rat liver under the dosing conditions used in the cancer bioassay.

para-Dichlorobenzene causes male rat-specific nephrotoxicity resulting from accumulation of the male rat-specific protein α_{2u} -globulin. Both *para*-dichlorobenzene and its major metabolite, 2,5-dichlorophenol, bind reversibly to α_{2u} -globulin. *para*-Dichlorobenzene causes sustained cell proliferation in proximal renal tubular cells, and the dose-response relationships for tumour outcome, enhanced cell proliferation and other histopathological end-points typical of α_{2u} -globulin nephropathy are similar. Female rats, male rats of strains that do not express this protein and mice are not susceptible to the nephrotoxic action of *para*-dichlorobenzene.

ortho-Dichlorobenzene did not cause developmental toxicity in rats or rabbits exposed by inhalation during gestation. After administration by gavage to rats during gestation, decreased fetal growth and an increased incidence of extra ribs were observed. *para*-Dichlorobenzene did not cause developmental toxicity in rabbits exposed during gestation.

A statistically significant, fourfold increase in the frequency of persistent chromosomal aberrations was observed in peripheral blood lymphocytes of individuals accidentally exposed to *ortho*-dichlorobenzene. No data were available on the genetic and related effects of *meta*-dichlorobenzene or *para*-dichlorobenzene in humans.

ortho-Dichlorobenzene induced micronuclei in the bone marrow of mice treated *in vivo*. Radiolabelled *ortho*-dichlorobenzene was found to bind covalently to DNA, RNA and proteins of the liver, kidney, lung and stomach of treated rats and mice. It bound to DNA *in vitro* in the presence but not in the absence of metabolic activation. It was mutagenic to yeast and fungi but not to bacteria.

meta-Dichlorobenzene increased the frequency of micronuclei in the bone marrow of mice treated *in vivo*. It caused gene conversion in yeast. It was not mutagenic to bacteria but gave contradictory results with respect to DNA damage.

para-Dichlorobenzene bound to DNA in liver, lung and kidney of mice but not of male rats. It induced DNA damage in liver and spleen but not in kidney, lung or bone marrow of mice. No conclusion can be drawn from the few data on genotoxicity *in vivo*. There is weak evidence for the genotoxicity of *para*-dichlorobenzene in mammalian cells *in vitro*. It was not mutagenic to bacteria. Overall, the results of tests for genotoxicity do not support a mechanism for renal-cell tumour induction in male rats that involves a direct interaction between *para*-dichlorobenzene or its metabolites and DNA.

5.5 Evaluation

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

There is *evidence suggesting lack of carcinogenicity* in experimental animals of *ortho*-dichlorobenzene.

There is *inadequate evidence* in experimental animals for the carcinogenicity of *meta*-dichlorobenzene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of *para*-dichlorobenzene.

Overall evaluation

In making its overall evaluation of the carcinogenicity of *para*-dichlorobenzene to humans, the Working Group concluded that *para*-dichlorobenzene produces renal tubular tumours in male rats by a non-DNA-reactive mechanism, through an $\alpha_2\mu$ -globulin-associated response. Therefore, the mechanism by which *para*-dichlorobenzene increases the incidence of renal tubular tumours in male rats is not relevant to humans.

para-Dichlorobenzene caused a high incidence of liver tumours in male and female mice. Supporting evidence that its mechanism of carcinogenesis may be relevant for humans includes evidence that it causes DNA damage in liver and spleen of mice and weakly binds to DNA in mouse liver.

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

meta-Dichlorobenzene is *not classifiable as to its carcinogenicity to humans (Group 3)*.

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

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

Previous evaluations of *ortho*-dichlorobenzene and *para*-dichlorobenzene: [Vol. 29 \(1982\)](#); [Suppl. 7 \(1987\)](#)

Synonyms

ortho-Dichlorobenzene

- Cloroben
- *o*-Dichlorobenzene
- *o*-Dichlorobenzol
- Dilatin DB
- Dowtherm E.

***meta*-Dichlorobenzene**

- *m*-Dichlorobenzene
- *m*-Dichlorobenzol
- *m*-Phenylene dichloride

***para*-Dichlorobenzene**

- *p*-Chlorophenyl chloride
- *p*-Dichlorobenzene
- Paradichlorobenzene
- PDB
- Di-chloricide
- Dichlorocide
- Evola
- Paradi
- Paradow
- Paramoth
- Persia-Perazol
- Santochlor

Last updated: 30 September 1999

HEXACHLOROBUTADIENE (Group 3)

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

VOL.: 73 (1999) (p. 277)

Chem. Abstr. No.: 87-68-3

Chem. Abstr. Name: 1,1,2,3,4,4-Hexachloro-1,3-butadiene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to hexachlorobutadiene has occurred principally as a result of its production and release as a by-product from the manufacture of chlorinated solvents and related products. It has been widely detected in ambient air, water, foods and human tissues.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Hexachlorobutadiene was tested by oral administration in one study in rats, by skin application in mice and inadequately in one experiment in mice by intraperitoneal injection. After oral administration in rats, it produced benign and malignant tumours in the kidneys of animals of each sex. It did not produce skin tumours after repeated application or show initiating activity in a two-stage initiation–promotion study in mice. It enhanced the incidence of renal tubular tumours induced by *N*-nitrosoethylhydroxyethylamine in a two-stage model of renal carcinogenesis.

5.4 Other relevant data

Hexachlorobutadiene is metabolized exclusively by glutathione conjugation and γ -glutamyl transpeptidase to its corresponding cysteine *S*-conjugate, *S*-(1,2,3,4,4-pentachloro-1,3-butadienyl)-L-cysteine, which is concentrated in the renal proximal tubules. This conjugate is partly acetylated to the corresponding mercapturic acid and excreted in urine. It is also a substrate for β -lyases, which have high activity in this part of the nephron and cleave the *S*-conjugate to produce a reactive thioketene, which can acylate proteins and DNA. This toxification pathway is responsible for the kidney-specific toxicity and carcinogenicity of hexachlorobutadiene in rodents. The metabolism of hexachlorobutadiene has not been investigated in humans; however, the demonstrated formation of mercapturic acids from the structurally related haloalkenes tri- and tetrachloroethylene in humans indicates that hexachlorobutadiene would be metabolized in humans in a manner similar to that in rodents.

In rats exposed during development, fetal growth retardation has been observed, usually at maternally toxic doses. Malformations have not been reported. Negative results were obtained in a short-term assay to screen for teratogenicity in mice exposed by gavage.

No data were available on the genetic and related effects of hexachlorobutadiene in humans or in rodents *in vivo*. There is weak evidence for its genotoxicity in mammalian cells *in vitro*. The findings for mutagenicity in bacteria are equivocal.

5.5 Evaluation

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

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

Overall evaluation

Hexachlorobutadiene 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) (p. 64)

Synonyms

- HCB
- Hexachloro-1,3-butadiene
- Perchloro-1,3-butadiene
- Perchlorobutadiene

Last updated: 30 September 1999

HEXACHLOROETHANE (Group 2B)

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

VOL.: 73 (1999) (p. 295)

CAS No.: 67-72-1

Chem. Abstr. Name: Hexachloroethane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to hexachloroethane may occur during its production and use in metal refining, in fire suppression and in other minor uses.

5.2 Human carcinogenicity data

One cohort study of workers at aluminium foundries and aluminium smelters in Sweden showed no significant association between exposure to hexachloroethane and cancer incidence.

5.3 Animal carcinogenicity data

Hexachloroethane was tested in one experiment in mice and two experiments in rats by oral administration. It produced liver tumours in mice of each sex. In rats, it produced a statistically significantly increased incidence of renal tubular tumours in males in one study and a marginal increase in the incidence of renal tubular tumours in another study, also only in males. In a two-stage liver initiation–promotion assay in rats, hexachloroethane showed promoting but no initiating activity.

5.4 Other relevant data

No data were available to the Working Group on the absorption, distribution, metabolism or excretion of hexachloroethane in humans. It is absorbed in rats after oral administration, is concentrated in kidney and fat and is excreted by apparent first-order kinetics.

In humans, exposure by inhalation to hexachloroethane (10–20 mg/m³) produced mild irritation of the skin and mucous membrane. Inhalation produced respiratory irritation in rodents.

After short-term exposure, hexachloroethane caused renal toxicity in male rats and hepatocellular necrosis in both male and female rats.

The data on reproductive toxicity were inadequate for evaluation.

No data were available on the genetic and related effects of hexachloroethane in humans. Hexachloroethane was found to bind to DNA in mouse liver after intraperitoneal injection; no other data were available on its genetic effects in experimental systems *in vivo*. It induced sister chromatid exchange in one study but did not induce chromosomal damage in mammalian cells *in vitro*. It induced gene mutation in *Drosophila* and yeast but was not mutagenic to bacteria.

5.5 Evaluation

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

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

Overall evaluation

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

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

Previous evaluations: [Vol. 20 \(1979\)](#); Suppl. 7 (1987) (p. 64)

Synonyms

- Ethane hexachloride
- Hexachloroethane
- 1,1,1,2,2,2-Hexachloroethane
- Hexachloroethylene

Last updated: 30 September 1999

***d*-LIMONENE**

(Group 3)

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

VOL.: 73 (1999) (p. 307)

Chem. Abstr. No.: 5989-27-5

Chem. Abstr. Name: (R)-1-Methyl-4-(1-methylethenyl)cyclohexene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

d-Limonene is a terpene which occurs naturally in citrus and a variety of other plants. Exposure occurs from its presence in foods and its use as a solvent. It is being evaluated in clinical trials for use as a cancer chemotherapeutic agent.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

d-Limonene was tested for carcinogenicity by oral gavage in mice and rats and in several two-stage experiments with multi-organ carcinogens. It significantly increased the incidence of renal tubular tumours (adenomas and carcinomas) and induced atypical renal tubular hyperplasia in male rats, which normally synthesize α_{2u} -globulin in the liver, but not in female rats or in mice of either sex. It consistently enhanced the incidences of renal tubular tumours and atypical renal tubular hyperplasia initiated by carcinogens in two-stage carcinogenesis assays in male rats of a strain conventionally used in bioassays, but not in a strain that lacks hepatic synthesis of α_{2u} -globulin.

d-Limonene was tested as a cancer-preventive agent in other experimental models with known carcinogens. It inhibited lung carcinogenesis in mice, preneoplastic stages of colon carcinogenesis in rats and pancreatic carcinogenesis in hamsters.

5.4 Other relevant data

d-Limonene is metabolized in humans and experimental animals to a variety of metabolites, including perillic acid and *d*-limonene-1,2-diol. *d*-Limonene causes a male rat-specific nephrotoxicity resulting from accumulation of the male rat-specific protein α_{2u} -globulin. *d*-Limonene-1,2-epoxide binds reversibly to α_{2u} -globulin. *d*-Limonene causes sustained cell proliferation in renal proximal tubular cells, and the dose-response relationships for tumour outcome, enhanced cell proliferation and other histopathological end-points typical of α_{2u} -globulin nephropathy are similar. Female rats, male rats of strains that do not express this protein and other species are not susceptible to the nephrotoxic action of *d*-limonene.

Developmental toxicity in the form of delayed prenatal growth has been observed in mice, rats and rabbits exposed to *d*-limonene during gestation. Skeletal anomalies have also been observed in the fetuses of exposed mice and rabbits.

The few available data indicate that *d*-limonene and its 1,2-epoxide metabolite are not genotoxic.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of *d*-limonene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of *d*-limonene.

Overall evaluation

In making its overall evaluation of the carcinogenicity to humans of *d*-limonene, the Working Group concluded that *d*-limonene produces renal tubular tumours in male rats by a non-DNA-reactive mechanism, through an α_2 -globulin-associated response. Therefore, the mechanism by which *d*-limonene increases the incidence of renal tubular tumours in male rats is not relevant to humans.

d-Limonene is *not classifiable as to its carcinogenicity to humans (Group 3)*.

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

Previous evaluation: [Vol. 56 \(1993\)](#)

Synonyms

- (+)-Dipentene
- (R)-4-Isopropenyl-1-methyl-1-cyclohexene
- D-Limonene
- d-(+)-Limonene
- D-(+)-Limonene
- (+)-Limonene
- (+)- α -Limonene
- (+)-(R)-Limonene
- (+)-(4R)-Limonene
- (R)-Limonene
- (R)-(+)-Limonene
- (4R)-(+)-Limonene
- (+)-*para*-Mentha-1,8-diene
- (R)-(+)-*para*-Mentha-1,8-diene
- (R)-*p*-Mentha-1,8-diene
- (R)-(+)-*para*-Mentha-1,8-diene

MELAMINE (Group 3)

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

VOL.: 73 (1999) (p. 329)

Chem. Abstr. Reg. No.: 108-78-1

Chem. Abstr. Name: 1,3,5-Triazine-2,4,6-triamine

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to melamine may occur during its production and use in the manufacture of synthetic resins with formaldehyde.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Melamine has been studied for carcinogenicity in mice and rats of each sex by oral administration. It produced urinary bladder and ureteral carcinomas in male rats but only urinary bladder hyperplasia in male mice. The occurrence of urinary bladder tumours in male rats correlated strictly with calculus formation and exposure to high doses. The dose dependence was confirmed by subsequent studies in male rats in which concomitant administration of sodium chloride to increase urinary output resulted in a decreased tumour yield.

5.4 Other relevant data

There is no evidence that melamine undergoes biotransformation. The urinary bladder tumours seen in male rats exposed to high doses of melamine appear to be produced by a non-DNA-reactive mechanism involving epithelial hyperplasia secondary to the presence of melamine-containing bladder stones. Consequently, bladder tumours would not be expected in either rodents or humans except at doses that produce bladder calculi.

No data were available on the reproductive or developmental toxicity of melamine.

No data were available on the genetic and related effects of melamine in humans. It was not genotoxic in experimental systems.

5.5 Evaluation

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

There is *sufficient evidence* in experimental animals for the carcinogenicity of melamine under conditions in which it produces bladder calculi.

Overall evaluation

In making its overall evaluation, the Working Group noted that the non-DNA-reactive mechanism by which melamine produced urinary bladder tumours in male rats occurred only under conditions in which calculi were produced.

Melamine 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 (1987) (p. 65)

Synonyms

- Cyanuramide
- Cyanurotriamide
- Cyanurotriamine
- Isomelamine
- Triaminotriazine
- 2,4,6-Triaminotriazine
- Triamino-s-triazine
- 2,4,6-Triamino-1,3,5-triazine
- 2,4,6-s-Triazinetriamine
- 1,3,5-Triazine-2,4,6(1*H*,3*H*,5*H*)-triimine

METHYL *tert*-BUTYL ETHER (Group 3)

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

VOL.: 73 (1999) (p. 339)

Chem. Abstr. Serv. Reg. No.: 1634-04-4

Chem. Abstr. Name: 2-Methoxy-2-methyl-propane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Methyl *tert*-butyl ether is a volatile synthetic chemical that has been used widely since the 1980s in proportions up to 15% as a component of gasolines for its octane-enhancing and air pollution-reducing properties. Exposure to methyl *tert*-butyl ether may occur through inhalation and skin contact during its production, formulation, distribution and use, either as methyl *tert*-butyl ether or in gasoline. In the petroleum industry, the average exposure is generally below 5 ppm (20 mg/m³), although higher exposure occurs during some operations. In service stations where fuels containing > 10% methyl *tert*-butyl ether are delivered, the average concentration to which attendants are exposed is about 0.5 ppm (2 mg/m³). The ambient air concentrations in regions where methyl *tert*-butyl ether-rich gasoline is used are usually 1–5 ppb (4–20 µg/m³), while in other regions they are below 1 ppb (4 µg/m³). During self-service refuelling, individuals may be exposed to levels up to 10 ppm (40 mg/m³) or more for a few minutes. Methyl *tert*-butyl ether has been detected in a small percentage of drinking-water samples in the United States.

5.2 Human carcinogenicity data

Although methyl *tert*-butyl ether has been in commercial use for gasoline blending since the 1970s, no analytical epidemiological studies have addressed a possible association of methyl *tert*-butyl ether with human cancer.

5.3 Animal carcinogenicity data

Methyl *tert*-butyl ether was tested for carcinogenicity in a non-standard protocol in rats by gavage. The incidences of Leydig-cell tumours of the testis in males and of lymphomas and leukaemias combined in females were increased. Methyl *tert*-butyl ether was tested by inhalation in one experiment in mice and in one experiment in rats. It increased the incidence of hepatocellular adenomas in female mice and that of renal tubular tumours in male rats in a non-dose-related manner.

tert-Butyl alcohol, a metabolite of methyl *tert*-butyl ether, marginally increased the incidence of follicular-cell adenomas of the thyroid in female mice.

5.4 Other relevant data

Methyl *tert*-butyl ether is metabolized in humans and rodents to *tert*-butyl alcohol. In both species, methyl *tert*-butyl ether is cleared from blood rapidly whereas *tert*-butyl alcohol accumulates and is cleared at a slower rate than the parent compound. In rats exposed to methyl *tert*-butyl ether, the metabolites identified in urine include *tert*-butyl alcohol, its sulfate and glucuronide conjugates, 2-methyl-1,2-propanediol and 2-hydroxyisobutyrate.

No significant acute effects on human health were seen after exposure of volunteers by inhalation to methyl *tert*-butyl ether itself or of service-station attendants to gasoline.

In male rats, methyl *tert*-butyl ether-induced kidney lesions were associated with α_{2u} -globulin nephropathy, a male rat-specific response. Exposure of female mice to 8000 ppm methyl *tert*-butyl ether in air was mitogenic to the liver and caused changes in oestrogen-regulated tissues.

Methyl *tert*-butyl ether did not induce developmental toxicity in rats or rabbits exposed via inhalation to concentrations that affected maternal food consumption. In one study in mice, increased incidences of postimplantation loss and cleft palate were seen at doses that also induced hypoactivity, ataxia and reduced food consumption in the dams. Another study in mice, conducted at lower doses that were less toxic to dams, did not provide evidence of developmental toxicity.

No data were available on the genetic and related effects of methyl *tert*-butyl ether in humans. The few available data indicate that methyl *tert*-butyl ether is not genotoxic in experimental systems.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of methyl *tert*-butyl ether.

There is *limited evidence* in experimental animals for the carcinogenicity of methyl *tert*-butyl ether.

Overall evaluation

Methyl *tert*-butyl ether is *not classifiable as to its carcinogenicity to humans (Group 3)*.

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

Synonyms

- *t*-Butyl methyl ether
- *tert*-Butyl methyl ether
- *tert*-Butoxymethane
- 1,1-Dimethylethyl methyl ether
- Methyl 1,1-dimethylethyl ether
- 2-Methyl-2-methoxypropane
- Methyl tertiary butyl ether
- MTBE

NITRILOTRIACETIC ACID AND ITS SALTS (Group 2B)

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

VOL.: 73 (1999) (p. 385)

Nitrilotriacetic acid

CAS No.: 139-13-9

Chem. Abstr. Name: *N,N*-Bis(carboxymethyl)glycine

Nitrilotriacetic acid, sodium salt

CAS No.: 10042-84-9

Chem. Abstr. Name: *N,N*-Bis(carboxymethyl)glycine, sodium salt

Nitrilotriacetic acid, monosodium salt

CAS No.: 18994-66-6

Chem. Abstr. Name: *N,N*-Bis(carboxymethyl)glycine, monosodium salt

Nitrilotriacetic acid, disodium salt

CAS No.: 15467-20-6

Chem. Abstr. Name: *N,N*-Bis(carboxymethyl)glycine, disodium salt

Nitrilotriacetic acid, disodium salt, monohydrate

CAS No.: 23255-03-0

Chem. Abstr. Name: *N,N*-Bis(carboxymethyl)glycine, disodium salt, monohydrate

Nitrilotriacetic acid, trisodium salt

CAS No.: 5064-31-3

Chem. Abstr. Name: *N,N*-Bis(carboxymethyl)glycine, trisodium salt

Nitrilotriacetic acid, trisodium salt, monohydrate

CAS No.: 18662-53-8

Chem. Abstr. Name: *N,N*-Bis(carboxymethyl)glycine, trisodium salt, monohydrate

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to nitrilotriacetic acid and its salts occurs during their production, formulation and use in synthetic laundry and dishwashing detergents and related products as metal chelating and sequestering agents.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Nitrilotriacetic acid was tested for carcinogenicity by oral administration in the diet to mice and rats. It induced renal tubular tumours (adenomas and adenocarcinomas) in mice of each sex and in male rats and transitional-cell and squamous-cell carcinomas of the urinary bladder, hepatocellular adenomas and adrenal

phaeochromocytomas in female rats.

The trisodium salt was tested for carcinogenicity in mice and rats by oral administration. When administered in the diet as the monohydrate, it induced haematopoietic tumours in male mice and benign and malignant tumours of the urinary system (kidney, ureter and bladder) in rats of each sex. When administered in drinking-water to male rats, it induced renal tubular adenomas and adenocarcinomas.

In two-stage studies of carcinogenicity in male rats treated by oral administration, nitrilotriacetic acid and its trisodium salt increased the incidence of urinary-tract tumours after pretreatment with various *N*-nitrosamines.

5.4 Other relevant data

Nitrilotriacetic acid is absorbed in mammals, but it is not metabolized and is excreted rapidly by filtration in the kidney.

Orally administered nitrilotriacetic acid and its trisodium salt were nephrotoxic to rats and mice of each sex. Toxicity occurs at high doses and appears to be due to Zn⁺⁺ accumulation secondary to the chelating properties of nitrilotriacetic acid; administration of Zn⁺⁺ accentuated the nephrotoxicity of the acid. Urothelial cytotoxicity and regenerative hyperplasia were seen in male and female rats but not in mice, and only at doses higher than those that produced nephrotoxicity. The mechanism is unclear but appears to involve cellular Ca⁺⁺ depletion secondary to the chelating effect of nitrilotriacetic acid. Urinary microcrystals were also produced.

Nitrilotriacetic acid does not induce developmental toxicity in rats, rabbits or mice exposed during gestation and gave negative results in short-term assays to screen for teratogenesis in two cellular assays in *Drosophila* larvae and frog embryos.

No data were available on the genetic and related effects of nitrilotriacetic acid or its salts in humans. Nitrilotriacetic acid and its disodium and trisodium salts were not genotoxic in experimental systems *in vivo*, except that the acid induced aneuploidy in mouse germ cells. Neither the acid nor its salts were genotoxic in mammalian cells *in vitro* and they were not mutagenic to bacteria.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of nitrilotriacetic acid and its salts.

There is *sufficient evidence* in experimental animals for the carcinogenicity of nitrilotriacetic acid and its salts.

Overall evaluation

Nitrilotriacetic acid and its salts *are possibly carcinogenic to humans (Group 2B)*.

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

Previous evaluation: [Vol. 48 \(1990\)](#)

Synonyms

Nitrilotriacetic acid

- Nitrilo-2,2',2''-triacetic acid

- Nitrilotris(methylenecarboxylic acid)
- NTA
- Triglycine
- Triglycollamic acid
- $\alpha, \alpha', \alpha''$ -Trimethylaminetricarboxylic acid

Nitrilotriacetic acid, sodium salt

- Nitrilotriacetic acid sodium salt
- NTA Sodium salt
- NTA, Sodium salt
- Sodium aminotriacetate
- Sodium nitriloacetate
- Sodium nitrilotriacetate
- Sodium NTA

Nitrilotriacetic acid, monosodium salt

- Monosodium nitrilotriacetate
- NTA, monosodium salt

Nitrilotriacetic acid, disodium salt

- Disodium hydrogen nitrilotriacetate
- Disodium nitrilotriacetate
- Nitrilotriacetic acid disodium salt
- NTA, disodium salt

Nitrilotriacetic acid, disodium salt, monohydrate

- Disodium nitrilotriacetic acid monohydrate
- NTA, disodium salt, monohydrate

Nitrilotriacetic acid, trisodium salt

- Nitrilotriacetic acid trisodium salt
- NTA Trisodium salt
- NTA, Trisodium salt
- Trisodium nitrilotriacetate

- Trisodium 2,2',2''-nitrilotriacetate
- Trisodium NTA

Nitrilotriacetic acid, trisodium salt, monohydrate

- NTA, trisodium salt, monohydrate
- Trisodium nitrilotriacetate monohydrate

Last updated: 30 September 1999

PARACETAMOL (Group 3)

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

VOL.: 73 (1999) (p. 401)

Chem. Abstr. No.: 103-90-2

Chem. Abstr. Name: *N*-(4-Hydroxyphenyl)acetamide

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Paracetamol (acetaminophen) is widely used as an analgesic and antipyretic at daily doses up to 4000 mg, with minor uses as an intermediate in the chemical and pharmaceutical industries. Occupational exposure may occur during its production and its use.

5.2 Human carcinogenicity data

In the previous monograph on paracetamol, a positive association with cancer of the ureter (but not of other sites in the urinary tract) was observed in an Australian case-control study. None of the other three case-control studies showed an association with cancer in the urinary tract. Nine new—mainly population-based—case-control studies of cancers of the urinary tract have been published, many of which addressed more than one subsite.

None of six studies from Australia, Europe and North America, including a very large international study, found a consistent association between renal-cell cancer and regular intake of paracetamol at any level. In one study from the United States which included patients with renal cancer (type not specified), the risk increased with increasing cumulative intake of paracetamol, to reach statistical significance at the highest exposure; however, this result was not adjusted for intake of other analgesics.

In one study from Australia which included patients with cancer of the renal pelvis, a nonsignificant twofold increase in risk was seen among people in the highest exposure category, with no excess risk in the two lower exposure categories. Another, large case-control study of cancer of the renal pelvis and ureter from the United States showed no association with regular intake of paracetamol.

Of the three new studies that included patients with urinary bladder cancer, that conducted in Sweden showed an elevated risk without providing details. The other two (both from the United States) showed only a slight or no association.

5.3 Animal carcinogenicity data

Paracetamol was tested for carcinogenicity by oral administration in mice and rats. An early study indicated an increased incidence of liver adenomas and carcinomas at a markedly toxic dose in mice of one strain; however, this result was not corroborated in a later study in mice, also at a dose greater than the maximal tolerated dose. A more recent, well-conducted study showed no evidence of a carcinogenic effect in mice. Paracetamol had no carcinogenic effect in rats of several strains, but in rats of one inbred strain, increased incidences of liver and bladder neoplasms were recorded in males at the high dose and an increased incidence of bladder tumours in females at the low dose. A more recent, well-conducted study showed no treatment-related carcinogenic effect in rats. Paracetamol did not promote urinary bladder carcinogenesis in rats and reduced the incidence of intestinal tumours in a two-stage model of intestinal carcinogenesis in rats. It

enhanced the incidence of renal adenomas induced by one renal carcinogen but not those induced by another.

5.4 Other relevant data

Activation of a relatively small percentage of paracetamol to *N*-acetyl-*para*-benzoquinone imine by cytochrome P450, predominantly CYP 2E1, has been found to be involved in the mechanism of hepatic and, perhaps, renal toxicity. Most paracetamol is metabolized by glucuronidation, sulfation and conjugation with glutathione, which protects the liver at therapeutic doses. Doses of 300 mg/kg bw per day paracetamol and higher saturate conjugation reactions, deplete glutathione and result in binding of the benzoquinone imine to cellular proteins; this has been proposed to be the mechanism of hepatocellular injury in rodents and humans. Several protein adducts have been found in humans and rodents *in vivo* after exposure to paracetamol. DNA adducts were not observed in mice.

In humans, an association was reported in two case–control studies between daily use of paracetamol and renal disease; however, a causal relationship has not been established. Humans and rodents exposed to doses of paracetamol well above the therapeutic range have experienced centrilobular hepatotoxicity and nephrotoxicity involving the proximal renal tubule. In experimental animals, hepatic, renal and testicular damage occurred only at oral doses that exceeded 300 mg/kg bw per day in rats and 900 mg/kg bw per day in mice. At lower doses, toxic effects in rodents are minimal or absent.

Paracetamol does not present a teratogenic risk to humans at doses associated with severe maternal toxicity. It did not affect reproductive performance of mice in a continuous breeding protocol, although growth and birth weights were reduced. Sperm abnormalities have been observed in mice.

The results of studies of the cytogenetic effects of paracetamol in humans are inconclusive. Paracetamol induced sister chromatid exchange in human cells *in vivo*, and it was aneugenic and induced chromosomal aberrations but not micronuclei in mammalian cells *in vivo*. It induced DNA single-strand breaks in mice treated *in vivo*. Paracetamol induced sister chromatid exchange and chromosomal aberrations in human cells *in vitro*. It weakly induced cell transformation in a mouse cell line. It induced chromosomal aberrations, micronuclei and sister chromatid exchange in mammalian cells *in vitro*. It did not induce gene mutation, and the results of tests in mammalian cells *in vitro* for unscheduled DNA synthesis and DNA damage were inconclusive. Overall, paracetamol was genotoxic in mammalian cells *in vivo* and *in vitro*. It was not mutagenic to insects but was clastogenic in plant cells. It was not mutagenic in any standard assay in bacteria.

5.5 Evaluation

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

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

Overall evaluation

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

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

Previous evaluation: [Vol. 50 \(1990\)](#)

Synonyms

- 4-Acetamidophenol
- Acetaminophen
- 4-Acetaminophenol

- 4-(Acetylamino)phenol
- 4-(*N*-Acetylamino)phenol
- 4-Hydroxyacetanilide
- 4'-Hydroxyacetanilide
- 4'-Hydroxyacetanilide
- *N*-(4-Hydroxyphenyl)acetamide

Last updated: 30 September 1999

***ortho*-PHENYLPHENOL AND ITS SODIUM SALT**
***ortho*-PHENYLPHENOL (Group 3)**
SODIUM *ortho*-PHENYLPHENATE (Group 2B)

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

VOL.: 73 (1999) (p. 451)

***ortho*-Phenylphenol**

Chem. Abstr. No.: 90-43-7

Chem. Abstr. Name: (1,1' -Biphenyl)-2-ol

Sodium *ortho*-phenylphenate

Chem. Abstr. No.: 132-27-4

Chem. Abstr. Name: (1,1' -Biphenyl)-2-ol, sodium salt

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to *ortho*-phenylphenol and its sodium salt may occur during their production and use as industrial and agricultural fungicides, germicides and disinfectants, and as chemical intermediates. *ortho*-Phenylphenol has been detected in some groundwater and drinking-water samples as well as in some fruits and juices.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

ortho-Phenylphenol was tested for carcinogenicity in one experiment in mice and two experiments in rats by administration in the diet. Benign and malignant bladder tumours were induced at significant incidence in male rats in one study. Sodium *ortho*-phenylphenate was tested in mice in one study and in rats in two studies. It induced tumours of the bladder and renal pelvis in male rats in both studies and a marginal increase in the incidence of bladder tumours in female rats in one of the studies. There was no evidence of carcinogenicity in mice.

Bladder carcinogenesis induced in male rats by administration of *N*-nitrosobutyl(4-hydroxybutyl)amine was enhanced by sodium *ortho*-phenylphenate but not by *ortho*-phenylphenol. In one study, dermal application of sodium *ortho*-phenylphenate enhanced skin tumorigenesis in mice given 7,12-dimethylbenz[*a*]anthracene.

5.4 Other relevant data

The major urinary metabolites of sodium *ortho*-phenylphenate are the glucuronide and sulfate conjugates of *ortho*-phenylphenol and phenylhydroquinone. The capacity of male rats to metabolize sodium *ortho*-phenylphenate is several times greater than that of females.

Urothelial toxic effects and increased regenerative cell proliferation in the bladder epithelium are induced in rats. Although the mechanism of toxicity is unknown, the higher pH induced by the sodium salt may enhance the toxic effect of sodium *ortho*-phenylphenate in comparison with that of *ortho*-phenylphenol.

In a study of rats exposed to *ortho*-phenylphenol by oral gavage during gestation, the high dose resulted in delayed skeletal maturation of pups but had no effect on their viability, growth or morphological appearance.

No data were available on the genetic and related effects of *ortho*-phenylphenol and its sodium salt in humans. Mixed results were found in assays with *ortho*-phenylphenol for genotoxicity in rodents *in vivo* and in cultured mammalian cells *in vitro*. It induced gene mutation in mammalian cells *in vitro*. It was not mutagenic to bacteria or *Drosophila* but induced aneuploidy in fungi.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of *ortho*-phenylphenol and sodium *ortho*-phenylphenate.

There is *limited evidence* in experimental animals for the carcinogenicity of *ortho*-phenylphenol.

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

Overall evaluation

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

Sodium *ortho*-phenylphenate is *possibly carcinogenic to humans (Group 2B)*.

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

Previous evaluations: [Vol. 30 \(1983\)](#); [Suppl. 7 \(1987\) \(sodium *ortho*-phenylphenate\)](#)

Synonyms *ortho*-Phenylphenol

- *ortho*-Biphenylol
- 2-Biphenylol
- *ortho*-Diphenylol
- *ortho*-Hydroxybiphenyl
- 2-Hydroxybiphenyl
- 2-Hydroxy-1,1' -biphenyl
- *ortho*-Hydroxydiphenyl
- 2-Hydroxydiphenyl
- 2-Phenylphenol
- *ortho*-Xenol

Sodium *ortho*-phenylphenate

- 2-Biphenylol, sodium salt
- *ortho*-Hydroxybiphenyl sodium salt

- 2-Hydroxybiphenyl sodium salt
- 2-Hydroxydiphenyl sodium
- *ortho*-Phenylphenol sodium salt
- 2-Phenylphenol sodium salt
- Sodium 2-biphenylolate
- Sodium 2-phenylphenate
- Sodium 2-phenylphenoxide
- Sodium *ortho*-phenylphenol
- Sodium *ortho*-phenylphenolate
- Sodium *ortho*-phenylphenoxide
- SOPP

Last updated: 30 September 1999

POTASSIUM BROMATE

(Group 2B)

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

VOL.: 73 (1999) (p. 481)

Chem. Abstr. No.: 7758-01-2

Chem. Abstr. Name: Bromic acid, potassium salt

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to potassium bromate may occur during its production and use as a dough conditioner and food additive. Bromate may also be found in some drinking-water samples as a by-product of ozone disinfection.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Potassium bromate has been tested by oral administration in several studies in rats and in one study each in mice and hamsters. In rats, it produced renal tubular tumours (adenomas and carcinomas) and thyroid follicular tumours in animals of each sex and peritoneal mesotheliomas in males. In mice, it produced a low incidence of renal tubular tumours in males. In hamsters, the incidence of renal tubular tumours was marginally increased. Potassium bromate did not increase tumour incidence in bioassays in newborn rats and mice, but it enhanced the induction of kidney tumours by *N*-nitrosoethylhydroxyethylamine in several experiments.

5.4 Other relevant data

No data were available on the absorption, distribution, metabolism or excretion of potassium bromate in humans, and limited information was available on rats. Bromate was found to be rapidly absorbed in rats and eliminated (or degraded).

A number of case reports of acute poisoning by potassium bromate have been reported. Potassium bromate is highly toxic. It produces lipid peroxidation and oxidative DNA damage in rat kidney. There is also evidence that it increases the amount of α_2 -globulin in male rat kidney. The available data, including evidence of genetic toxicity, indicate, however, that potassium bromate causes renal tumours through a mechanism involving oxidative damage.

No data were available on the developmental and reproductive effects of potassium bromate. However, in a single, short-term assay to screen for reproductive toxicity, involving exposure of male and female rats to sodium bromate before and during gestation, no developmental toxicity was observed. A decrease in epididymal sperm concentration was found in males.

No data were available on the genetic and related effects of potassium bromate in humans. It is genotoxic in experimental systems *in vivo* and in rodent cells *in vitro*. No conclusion could be drawn with respect to its mutagenicity to bacteria.

5.5 Evaluation

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

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

Overall evaluation

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

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

Previous evaluations: [Vol. 40 \(1986\)](#); Suppl. 7 (1987) (p. 70)

Last updated: 30 September 1999

QUERCETIN (Group 3)

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

VOL.: 73 (1999) (p. 497)

Chem. Abstr. No.: 117-39-5

Chem. Abstr. Name: 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-1-benzopyran-4-one

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to quercetin may occur during its production and use in dyes and from its presence in a variety of fruits and vegetables.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Quercetin was tested in several studies in rats by oral administration in the diet and by topical application in mice. Carcinogenicity was seen in only two studies in rats. Quercetin increased the incidences of intestinal and urinary bladder tumours in one study, but this effect was not seen in subsequent studies. Quercetin produced a low but significant increase in the incidence of renal tubular neoplasms, primarily adenomas in male rats, which was observed only after step-sectioning of renal tissue. When tested in several two-stage models of organ carcinogenesis, quercetin did not significantly enhance tumour incidence, except that of renal tumours induced by oestradiol in a model in hamsters.

5.4 Other relevant data

Although the metabolism of quercetin appears to be similar in humans and rabbits (the same three metabolites were identified in urine), no information on rats or mice was available for comparison. No information was available on the toxicity of quercetin in humans.

Quercetin increased the frequency of DNA damage and lipid peroxidation in liver nuclei of rats *in vitro*. In long-term studies in rats, there were no treatment-related clinical signs of toxicity, but renal hyperplasia occurred in males.

Quercetin inhibited cytochrome P450 enzymes in both human and rodent microsomes *in vitro*.

Fetal growth retardation was observed in a study in rats exposed to quercetin by oral gavage.

No data were available on the genetic and related effects of quercetin in humans. It was not genotoxic in experimental systems *in vivo*. It produced cytogenetic damage in human and rodent cells *in vitro*, but conflicting results were obtained in assays for gene mutation. It was mutagenic to *Drosophila*.

5.5 Evaluation

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

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

Overall evaluation

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

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

Previous evaluations: [Vol. 31 \(1983\)](#); Suppl. 7 (1987) (p. 71)

Synonyms

- CI 75670
- CI Natural Yellow 10
- 3,3',4',5,7-Pentahydroxyflavone
- 3,4',5,5',7-Pentahydroxyflavone
- 3,5,7,3',4' -Pentahydroxyflavone
- Quercetine

Last updated: 30 September 1999

SACCHARIN AND ITS SALTS (Group 3)

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

VOL.: 73 (1999) (p. 517)

Saccharin

Chem. Abstr. No.: 81-07-2

Chem. Abstr. Name: 1,2-Benzisothiazol-3(2*H*)-one, 1,1-dioxide

Sodium saccharin

Chem. Abstr. No.: 128-44-9

Chem. Abstr. Name: 1,2-Benzisothiazol-3(2*H*)-one, 1,1-dioxide, sodium salt

Calcium saccharin

Chem. Abstr. No.: 6485-34-3

Chem. Abstr. Name: 1,2-Benzisothiazol-3(2*H*)-one, 1,1-dioxide, calcium salt

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Saccharin and its salts have been used as sweeteners for nearly a century. Saccharin (acid form), sodium saccharin and calcium saccharin are widely used as non-caloric table-top sweeteners, in beverages and foods, in personal care products and in a variety of non-food applications. The average daily dietary intake is generally less than 1 mg/kg bw.

5.2 Human carcinogenicity data

Case-control studies of the carcinogenicity of artificial sweeteners have been reported only for the urinary bladder or lower urinary tract. Most of the studies were published between 1975 and 1985, so that any association would be to sweeteners that were on the market over 25 years ago. The studies varied widely in the detail with which information on the source and nature of artificial sweeteners was identified, collected and presented. The terms used in the various studies include 'table-top', 'dietetic beverages', 'saccharin' and 'artificial sweeteners' with no further characterization; only the salts of saccharin are used in these ways. Eight of the studies considered were hospital-based, which raises uncertainty about the representativeness of the controls' consumption of artificial sweeteners in relation to the general population. The results of the population-based studies must also be viewed with caution, owing to the sizable proportion of non-respondents, which might reflect the occurrence of health-related conditions associated with the use of replacements for sugar.

A statistically significant relative risk in the order of 1.6 for the association between use of artificial sweeteners (and saccharin salts as such) and bladder cancer and a dose-response relationship between intake and odds ratio were found for men but not for women in an early study in Canada. In subsequent population-based studies, including a study of several thousand people in the United States, estimates for the entire population of each study did not confirm the existence of an association. In some studies, estimates of the strength of the association between consumption of sweeteners and bladder cancer differed between smokers and non-smokers, but the direction of the difference and its distribution between the sexes was inconsistent over the studies.

In spite of the fact that three studies showed high, statistically significant relative risks for small subsets of consumers of very large amounts of artificial sweeteners, the finding was limited to men in one study and to women in the other two. In addition, no consistent pattern of dose-response relationship between use of

artificial sweeteners and cancers of the urinary bladder or lower urinary tract is apparent in the available literature.

5.3 Animal carcinogenicity data

Sodium saccharin was tested by oral administration in numerous experiments in rats and mice and in a few studies in hamsters, guinea-pigs and monkeys.

Sodium saccharin produced urinary bladder tumours in male rats in four two-generation studies, in one study in male rats in which administration commenced at birth and in one study commencing at 30 days of age. Sodium saccharin was not carcinogenic for the urinary bladder in several one-generation studies in male and female rats or in mice.

Saccharin (acid form) did not produce tumours in one study in male and female mice, in one study in male rats or in one study in female rats. Calcium saccharin did not produce tumours in one study in male rats.

A few studies with sodium saccharin in hamsters and guinea-pigs also showed no induction of bladder tumours but were considered inadequate. In one long-term (up to 23 years) study in monkeys in which oral administration of sodium saccharin was begun shortly after birth, no bladder tumours were observed, but a relatively low dose (25 mg/kg bw) and relatively few animals were used.

Sodium saccharin has been studied in numerous experiments in adult rats involving administration concurrently or, more frequently, sequentially with other chemicals or treatments. Enhanced bladder tumorigenesis has been observed after prior treatment with known urinary bladder carcinogens. In one study, saccharin (acid form) did not significantly enhance the incidence of bladder carcinogenesis, while calcium saccharin produced a marginal increase.

Thus, the only organ affected by sodium saccharin is the urinary bladder and only in rats exposed for periods including pre- and/or postnatal periods and/or when exposure was begun by 30 days of age.

5.4 Other relevant data

Studies in humans and rodents reveal that, after absorption, saccharin and sodium saccharin are excreted unchanged in the urine. Excretion occurs relatively rapidly with no evidence of accumulation. The strong nucleophilic character of the saccharin anion and the lack of metabolism are consistent with the lack of DNA reactivity. The urinary concentration of the saccharin anion is similar, regardless of the form administered.

Sodium saccharin has been shown to enhance urothelial cell proliferation in rats, primarily in males, resulting in hyperplasia. This regenerative cell proliferation follows urothelial cytotoxic effects. Administration of saccharin (acid form) does not produce these effects in rats. Sodium saccharin at doses that enhance cell proliferation in rats does not do so in other species, including mice, hamsters and guinea-pigs. Hyperplasia was not produced in non-human primates, although the dose used in this study was lower than that used in the studies in rodents.

The cytotoxicity has been shown to result from formation of a calcium phosphate-containing precipitate in rat urine after administration of high doses of sodium saccharin or a variety of other sodium salts. A combination of factors in urine composition appears to be critical for formation of the precipitate, including a pH of 6.5 or greater, high urinary concentrations of calcium phosphate and protein and high urinary osmolality. This combination of critical factors appears to be unique to the rat and is consistent with the species-specific urothelial proliferative and tumorigenic effects in rats.

Saccharin, generally as the sodium salt, has been tested for developmental and reproductive toxicity in mice, rats, hamsters and rabbits. The effects have generally been limited to reductions in body weights at high dietary concentrations. With the exception of a test in *Drosophila* larvae, no effects have been reported in a variety of short-term assays to screen for teratogenicity *in vivo* and *in vitro*.

Saccharin (acid form) was not genotoxic in human or rodent cells *in vitro*. It weakly induced DNA single-strand breaks in rat hepatocyte cultures. It induced aneuploidy in yeast but was not mutagenic to bacteria.

Sodium saccharin induced dominant lethality in three of seven studies in mice *in vivo*; it did not induce heritable translocations, chromosomal aberrations in spermatocytes or embryos or altered sperm morphology in rodents *in vivo*. Negative or conflicting results were obtained in most studies of chromosomal damage in bone marrow, somatic mutation and sister chromatid exchange in rodents *in vivo*. Sodium saccharin was mutagenic in host-mediated and body fluid assays and caused DNA single-strand breaks in hepatic and renal cells of mice; however, bile from rats exposed to sodium saccharin was not mutagenic. Sodium saccharin did not cause DNA damage and did not bind covalently to DNA of rat liver or bladder. It induced genotoxic effects in human and rodent cells and in *Drosophila* and yeast. It was not mutagenic to bacteria.

The positive results for genotoxicity found with sodium saccharin in mammalian cells *in vitro* have been hypothesized to result from increased osmolality (i.e. nonspecific ionic effects). This hypothesis would appear to explain some but not all of the findings of sister chromatid exchange, chromosomal aberrations and gene mutations *in vitro*. The few positive results seen in mice treated with sodium saccharin *in vivo* would not be readily explained by ionic influences.

Impurities in the test materials could explain the positive results obtained in some studies in mice treated with high doses of sodium saccharin. It is notable that no data are available on the genetic effects of saccharin or its salts in rats; however, the available evidence indicates no binding of sodium saccharin to DNA in rat bladder or liver. Overall, the results of tests for genotoxicity do not support a mechanism for the induction of urothelial-cell tumours in rats involving direct interaction of sodium saccharin with DNA.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of saccharin salts used as sweeteners.

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

There is *inadequate evidence* in experimental animals for the carcinogenicity of saccharin (acid form) and calcium saccharin.

Overall evaluation

In making its evaluation, the Working Group concluded that sodium saccharin produces urothelial bladder tumours in rats by a non-DNA-reactive mechanism that involves the formation of a urinary calcium phosphate-containing precipitate, cytotoxicity and enhanced cell proliferation. This mechanism is not relevant to humans because of critical interspecies differences in urine composition.

Saccharin and its salts are *not classifiable as to their carcinogenicity to humans (Group 3)*.

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

Previous evaluations: [Vol. 22 \(1980\)](#); [Suppl. 7 \(1987\)](#)

Synonyms

Saccharin

- Acid saccharin
- Anhydro-*ortho*-sulfaminebenzoic acid

- [Azucaretas]
- Benisothiazolin-3-one, 1,1-dioxide
- 1,2-3-Benisothiazolinone 1,1-dioxide
- *ortho*-Benzoic acid sulfimide
- Benzoic sulfimide
- *ortho*-Benzoic sulfimide
- Benzoic sulphinide
- Benzosulfimide
- *ortho*-Benzosulfimide
- *ortho*-Benzoyl sulfimide
- Benzosulfinide
- 1,1-Dioxo-1,2-benisothiazol-3(2*H*)-one
- 1,2-Dihydro-2-ketobenisosulfonazole
- 2,3-Dihydro-3-oxobenisosulfonazole
- 3-Hydroxybenisothiazole-S,S-dioxide
- Dulcibona
- Garantose
- Glucid
- Gluside
- Hollandia
- Maca
- Necta Sweet
- Saccharimide
- Saccharin acid
- Saccharin insoluble
- Saccharine
- Saccharinol
- Saccharinose
- Saccharol
- Sakarin
- Saxin
- Slim & Sweet
- Sucredulcor
- [Sucrettes]
- Sucrosa
- Suita
- Sukrettine
- Suktar-Maró
- *ortho*-Sulfobenzimide
- *ortho*-Sulfobenzoic acid imide
- Sweeta
- Sweetex
- Syncal

Sodium saccharin

- 1,2-Benisothiazolin-3-one, 1,1-dioxide, sodium salt
- *ortho*-Benzoylsulfimide sodium salt
- Cristallose
- Cristalasetas
- Crystallose
- Dagutan
- [Edulcorant Pege]
- [Gaosucryl]
- Hermesetas
- Kristallose
- [Luetta]
- [Oda]
- Ril-Sweet

- Saccharin sodium
- Saccharin Sodium Oral Solution USP 23
- Saccharin sodium salt
- Saccharin soluble
- Saccharin Sodium Tablets USP 23
- [Sanix]
- Saxin
- Sodium *ortho*-benzosulfimide
- Sodium saccharide
- Sodium saccharinate
- Sodium saccharine
- Soluble saccharin
- [Sucromat]
- Sugarina
- Suita Presta
- [Sun-Suc]
- Sweeta
- Sykose
- Willosetten
- Zero

Calcium saccharin

- 1,2-Benzisothiazolin-3-one, 1,1-dioxide, calcium salt
- Calcium *ortho*-benzosulfimide
- Calcium saccharinate

[Names in brackets are for formerly manufactured products]

Last updated: 30 September 1999

SIMAZINE (Group 3)

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

VOL.: 73 (1999) (p. 625)

Chem. Abstr. No.: 122-34-9

Chem. Abstr. Name: 6-Chloro-*N,N*-diethyl-1,3,5-triazine-2,4-diamine

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to simazine occurs during its production, formulation and use as a herbicide. Simazine and its degradation products have been detected at low levels in ambient rural and urban air, rainwater, surface and groundwater and, less frequently, in drinking-water samples.

5.2 Human carcinogenicity data

No data were available on simazine alone (see the monograph on atrazine).

5.3 Animal carcinogenicity data

Simazine was tested for carcinogenicity in one experiment by oral administration to Sprague-Dawley rats. It increased the incidences of benign and malignant mammary gland tumours in females.

5.4 Other relevant data

Simazine is metabolized by dealkylation. No interaction with an oestrogen receptor was seen *in vitro*. In Sprague-Dawley rats, simazine was not uterotrophic but prolonged the duration of the oestrus cycle. Long-term administration resulted in haematological effects in rats and dogs.

Simazine did not show developmental toxicity in one study by inhalation in rats, but it was embryolethal and decreased fetal body weights in a study in which it was administered orally.

No data were available on the genetic and related effects of simazine in humans. Simazine was not genotoxic to rodents *in vivo* or in cultured mammalian cells, yeast or bacteria. It induced genetic damage in *Drosophila* and in plants.

5.5 Evaluation

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

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

Overall evaluation

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

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

Previous evaluation: [Vol. 53 \(1991\)](#)

Synonyms

- 2,4-Bis(ethylamino)-6-chloro-*s*-triazine
- 4,6-Bis(ethylamino)-2-chlorotriazine
- 2-Chloro-4,6-bis(ethylamino)-*s*-triazine

Last updated: 30 September 1999