



WORLD HEALTH ORGANIZATION  
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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## Volume 27

# Some Aromatic Amines, Anthraquinones and Nitroso Compounds, and Inorganic Fluorides Used in Drinking-water and Dental Preparations

Summary of Data Reported and Evaluation

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### Aromatic Amines

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### Inorganic fluorides used in drinking-water and dental preparations

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# ANILINE AND ANILINE HYDROCHLORIDE

VOL.: 27 (1982) (p. 39)

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Aniline hydrochloride was tested in mice by dietary administration, producing no carcinogenic effects. It was also tested by oral administration in rats; in one experiment by dietary administration it produced fibrosarcomas, sarcomas and haemangiosarcomas of the spleen or the peritoneal cavity.

Aniline was inactive in bacterial and mammalian DNA repair assays, in tests for mitotic recombination with yeast and in cell transformation assays. It did not induce chromosomal aberrations in mammalian cells or in animals. It was not mutagenic for the silkworm; nor was it mutagenic to *Salmonella typhimurium* unless both norharman and hepatic microsomes were present. Urines from treated rats were mutagenic for *S. typhimurium* with metabolic activation. Aniline induced sister chromatid exchanges in cultured mammalian cells.

### 5.2 Human data

Aniline has been produced commercially since 1847. Its numerous applications as a chemical intermediate could result in occupational exposure. Contamination of the general environment has been reported to occur.

The high risk of bladder cancer observed originally in workers in the aniline dye industry was probably due to exposure to chemicals other than aniline. Studies of individuals exposed to aniline but to no other known bladder carcinogens have shown little evidence of increased risk. The best of these reported one death from bladder cancer in 1223 men producing or using aniline, with 0.83 deaths expected from population rates. The degree of confidence which can be placed in the negative results obtained in the other studies is difficult to assess because of the absence of estimates of expected numbers of bladder cancers and the presumed lack of follow-up of workers who had left the industry.

### 5.3 Evaluation

There is *limited evidence* for the carcinogenicity of aniline hydrochloride in experimental animals. The available epidemiological data are insufficient to allow a conclusion as to the carcinogenicity of aniline. On the basis of all the available data, no evaluation could be made of the carcinogenicity of aniline to humans.

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

**Previous evaluation:** [Vol. 4 \(1974\)](#)

**Subsequent evaluation:** [Suppl. 7 \(1987\)](#)

# ***ortho*- AND *para*-ANISIDINE AND THEIR HYDROCHLORIDES**

**VOL.:** 27 (1982) (p. 63)

## ***ortho*-Anisidine**

**CAS No.:** 90-04-0

**Chem. Abstr. Name:** Benzenamine, 2-methoxy-

## ***ortho*-Anisidine hydrochloride**

**CAS No.:** 134-29-2

**Chem. Abstr. Name:** Benzenamine, 2-methoxy-, hydrochloride

## ***para*-Anisidine**

**CAS No.:** 104-94-9

**Chem. Abstr. Name:** Benzenamine, 4-methoxy-

## ***para*-Anisidine hydrochloride**

**CAS No.:** 20265-97-8

**Chem. Abstr. Name:** Benzenamine, 4-methoxy-, hydrochloride

## **5. Summary of Data Reported and Evaluation**

### **5.1 Experimental data**

*ortho*-Anisidine hydrochloride was tested in mice and rats by dietary administration. It was carcinogenic in both species, producing transitional-cell carcinomas of the urinary bladder. *para*-Anisidine hydrochloride, tested in the same way, did not produce carcinogenic effects in mice, and the data in rats were inadequate for evaluation; there is, in addition, some doubt about the nature of the compound tested.

While *ortho*-anisidine hydrochloride was mutagenic for *Salmonella typhimurium*, *para*-anisidine was not. *para*-Anisidine did not transform morphologically BHK21 cells in culture.

### **5.2 Human data**

*ortho*-Anisidine has been produced commercially for over 50 years. Its use as an intermediate in the manufacture of dyes, pigments and synthetic guaiacol could result in occupational exposure. *para*-Anisidine has been produced commercially since at least 1937. Its use as a dye intermediate could result in occupational exposure.

No case report or epidemiological study was available to the Working Group.

### **5.3 Evaluation**

There is *sufficient evidence* for the carcinogenicity of *ortho*-anisidine hydrochloride in experimental animals. In the absence of data on humans, *ortho*-anisidine should be regarded, for practical purposes, as if it presented a carcinogenic risk to humans.

The available data were inadequate to evaluate the carcinogenicity of *para*-anisidine hydrochloride in experimental animals. No evaluation of the carcinogenicity of *para*-anisidine to humans could be made.

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

**Subsequent evaluations:** Suppl. 7 (1987) (p. 57: *ortho*-Anisidine - Group 2B; *para*-Anisidine - Group 3); Vol. 73 (1999) (*ortho*-Anisidine)

### Synonyms for *ortho*-Anisidine

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

### Synonyms for *ortho*-Anisidine hydrochloride

- 2-Aminoanisole hydrochloride
- *ortho*-Aminoanisole hydrochloride
- 1-Amino-2-Methylbenzene hydrochloride
- 2-Anisidine hydrochloride
- *ortho*-Anisylamine hydrochloride
- C.I. 37115
- Fast Red BB Base
- 2-Methoxy-1-aminobenzene hydrochloride
- 2-Methoxy-aniline hydrochloride
- *ortho*-Methoxyaniline hydrochloride
- 2-Methoxybenzenamine hydrochloride
- *ortho*-Methoxyphenylamine hydrochloride

### Synonyms for *para*-Anisidine

- 4-Aminoanisole
- *para*-Aminoanisole
- 1-Amino-4-methoxybenzene
- 4-Anisidine
- *para*-Anisylamine
- 4-Methoxy-1-aminobenzene
- 4-Methoxyaniline
- *para*-Methoxyaniline
- 4-Methoxybenzenamine
- *para*-Methoxyphenylamine

### Synonyms for *para*-Anisidine hydrochloride

- 4-Aminoanisole hydrochloride
- *para*-Aminoanisole hydrochloride
- 1-Amino-4-methoxybenzene hydrochloride
- 4-Anisidine hydrochloride
- *para*-Anisidine monohydrochloride
- *para*-Anisylamine hydrochloride
- 4-Methoxy-1-aminobenzene hydrochloride
- 4-Methoxyaniline hydrochloride

- *para*-Methoxyaniline hydrochloride
- 4-Methoxybenzeneamine hydrochloride
- *para*-Methoxyphenylamine hydrochloride

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# 4-CHLORO-*ortho*-PHENYLENEDIAMINE AND 4-CHLORO-*meta*-PHENYLENEDIAMINE

VOL.: 27 (1982) (p. 81)

## 4-Chloro-*ortho*-phenylenediamine

CAS No.: 95-83-0

Chem. Abstr. Name: 1,2-Benzenediamine, 4-chloro-

## 4-Chloro-*meta*-phenylenediamine

CAS No.: 5131-60-2

Chem. Abstr. Name: 1,3-Benzenediamine, 4-chloro-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Both 4-chloro-*ortho*-phenylenediamine and 4-chloro-*meta*-phenylenediamine were tested for carcinogenicity in mice and rats by dietary administration. 4-Chloro-*ortho*-phenylenediamine was carcinogenic in mice, producing hepatocellular carcinomas in animals of both sexes, and in rats of both sexes, producing benign and malignant tumours of the urinary bladder. The results of the studies with 4-chloro-*meta*-phenylenediamine in mice were inconclusive; those in rats were not indicative of a carcinogenic effect.

4-Chloro-*ortho*-phenylenediamine was mutagenic to *Salmonella typhimurium* after metabolic activation. No data were available on the mutagenicity of 4-chloro-*meta*-phenylenediamine.

### 5.2 Human data

4-Chloro-*ortho*- and 4-chloro-*meta*-phenylenediamine have been produced commercially since the early 1940s. The extent of present human exposure is unknown. Both have been patented for use as hair-dye components.

No case report or epidemiological study was available to the Working Group, but see Appendix 1, in this volume.

### 5.3 Evaluation

There is *sufficient evidence* for the carcinogenicity of 4-chloro *ortho*-phenylenediamine in experimental animals. In the absence of data on humans, 4-chloro-*ortho*-phenylenediamine should be regarded, for practical purposes, as if it presented a carcinogenic risk to humans.

The available data were *inadequate* to evaluate the carcinogenicity of 4-chloro-*meta*-phenylenediamine in experimental animals. No evaluation of the carcinogenicity of 4-chloro-*meta*-phenylenediamine to humans could be made.

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

**Subsequent evaluation:** Suppl. 7 (1987) (p. 60: 4-chloro-*ortho*-phenylenediamine - **Group 2B**; 4-chloro-*meta*-phenylenediamine - **Group 3**)

**Synonyms for 4-Chloro-*ortho*-phenylenediamine**

- 2-Amino-4-chloroaniline
- 4-Chloro-1,2-diaminobenzene
- 4-Chloro-1,2-phenylenediamine
- *para*-Chloro-*ortho*-phenylenediamine
- C.I. 76015
- 1,2-Diamino-4-chlorobenzene
- 3,4-Diaminobenzene
- 3,4-Diamino-1-chlorobenzene
- Ursol Olive 6G

#### **Synonyms for 4-Chloro-*meta*-phenylenediamine**

- 1-Chloro-2,4-diaminobenzene
- 4-Chloro-1,3-phenylenediamine
- C.I. 76027

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Last updated: 8 April 1998

# *meta*- AND *para*-CRESIDINE

VOL.: 27 (1982) (p. 91)

## *meta*-Cresidine

CAS No.: 102-50-0

Chem. Abstr. Name: Benzenamine, 4-methoxy-2-methyl-

## *para*-Cresidine

CAS No.: 120-71-8

Chem. Abstr. Name: Benzenamine, 2-methoxy-5-methyl-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

*meta*- and *para*-Cresidine (technical grades) were tested in mice and rats by dietary administration. In the only experiment in rats with *meta*-cresidine, it produced an increased incidence of transitional-cell carcinomas of the urinary bladder in males. The results of the study in mice were inconclusive. *para*-Cresidine produced malignant tumours of the urinary bladder in both mice and rats, olfactory neuroblastomas in rats of both sexes and liver tumours in male rats; it also produced nasal cavity tumours in male mice and liver-cell tumours in female mice.

Technical-grade *meta*-cresidine was not mutagenic to *Salmonella typhimurium* or *Escherichia coli*. *para*-Cresidine was mutagenic to *S. typhimurium* after metabolic activation.

### 5.2 Human data

Although *meta*-cresidine is produced commercially, the extent to which humans are exposed to it is unknown.

*para*-Cresidine has been produced commercially since 1926. Its use as a dye intermediate could result in occupational exposure, and such exposure may have increased markedly in recent years as a result of the greater production of *para*-cresidine-based food dyes.

No case report or epidemiological study was available to the Working Group.

### 5.3 Evaluation

The available data were *inadequate* to evaluate the carcinogenicity of *meta*-cresidine in experimental animals. No evaluation of the carcinogenicity of *meta*-cresidine to humans could be made.

There is *sufficient evidence* for the carcinogenicity of *para*-cresidine in experimental animals. In the absence of data on humans, *para*-cresidine should be regarded, for practical purposes, as if it presented a carcinogenic risk to humans.

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

**Subsequent evaluation:** Suppl. 7 (1987) (p. 61: *meta*-Cresidine - **Group 3**; *para*-Cresidine - **Group 2B**)

**Synonyms for *meta*-Cresidine**

- 4-Methoxy-2-methylaniline
- 2-Methyl-*para*-anisidine
- 2-Methyl-4-methoxyaniline

### Synonyms for *para*-Cresidine

- *meta*-Amino-*para*-cresol, methyl ether
- 1-Amino-2-methoxy-5-methylbenzene
- 3-Amino-4-methoxytoluene
- Azoic Red 36
- C.I. Azoic Red 83 (Component)
- Cresidine
- Kresidin
- 2-Methoxy-5-methylaniline
- 4-Methyl-2-aminoanisole
- 5-Methyl-*ortho*-anisidine

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# 2,4-DIAMINOANISOLE AND 2,4-DIAMINOANISOLE SULPHATE

VOL.: 27 (1982) (p. 103)

## 2,4-Diaminoanisole

CAS No.: 615-05-4

Chem. Abstr. Name: 1,3-Benzenediamine, 4-methoxy-

## 2,4-Diaminoanisole sulphate

CAS No.: 39156-41-7 (6219-67-6 for the salt with an unknown ratio of sulphuric acid to diamine)

Chem. Abstr. Name: 1,3-Benzenediamine, 4-methoxy, sulfate (1:1)

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

2,4-Diaminoanisole sulphate (technical-grade) was tested by dietary administration in one experiment in mice and in two experiments in one strain of rats. Benign or malignant tumours of the thyroid gland were induced in rats and mice with the highest dose tested; tumours of the skin and of the preputial, clitoral and Zymbal glands were also induced in rats. It was also tested in a hair-dye formulation by skin application in mice and rats, but the studies were considered to be inadequate for evaluation.

2,4-Diaminoanisole or its sulphate was mutagenic for *Salmonella typhimurium*, cultured mouse lymphoma cells and *Drosophila melanogaster*. The sulphate produced mitotic recombination in yeast. Neither 2,4-diaminoanisole nor its sulphate induced micronuclei, sperm abnormalities, or dominant lethal mutations in rodents.

### 5.2 Human data

2,4-Diaminoanisole and its sulphate have been used in hair dyes for over 60 years. In addition to the consumer and occupational exposure resulting from this use, past use of 2,4-diaminoanisole as a chemical intermediate and as a fur-dye component could have resulted in other occupational exposure.

No case report or epidemiological study was available to the Working Group, but see Appendix 1, in this volume.

### 5.3 Evaluation

There is *sufficient evidence* for the carcinogenicity of 2,4-diaminoanisole sulphate in experimental animals.

In the absence of epidemiological studies relating specifically to 2,4-diaminoanisole, it should be regarded, for practical purposes, as if it presented a carcinogenic risk to humans.

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

**Previous evaluation:** [Vol. 16 \(1978\)](#)

**Subsequent evaluation:** [Suppl. 7 \(1987\) \(p. 61: Group 2B\)](#); [Vol. 79 \(2001\)](#)

**Synonyms for 2,4-Diaminoanisole**

- C.I. 76050
- C.I. Oxidation Base 12
- 2,4-DAA
- 2,4-Diaminoanisol
- 2,4-Diaminoanisole base
- *meta*-Diaminoanisole 1,3-diamino-4-methoxybenzene
- 2,4-Diamino-1-methoxybenzene
- Furro L
- *para*-Methoxy-*meta*-phenylenediamine
- 4-MMPD
- Pelagol DA
- Pelagol Grey L
- Pelagol L

### Synonyms for 2,4-Diaminoanisole sulphate

- BASF Ursol SLA
- C.I. 76051
- C.I. Oxidation Base 12A
- 2,4-DAA sulphate
- 2,4-Diaminoanisol sulphate
- 1,3-Diamino-4-methoxybenzene sulphate
- 2,4-Diamino-1-methoxybenzene sulphate
- Durafur Brown MN
- Fouramine BA
- Furrine 76
- Furrine SLA
- Furro SLA
- *para*-Methoxy-*meta*-phenylenediamine sulphate
- 4-MMPD sulphate
- Nako TSA
- Pelagol BA
- Pelagol Grey SLA
- Pelagol SLA
- Renal SLA
- Ursol SLA
- Zoba SLE

# 4,4'-METHYLENEBIS(*N,N*-DIMETHYL)BENZENAMINE

VOL.: 27 (1982) (p. 119)

CAS No.: 101-61-1

Chem. Abstr. Name: Benzenamine, 4,4'-methylenebis(*N,N*-dimethyl)-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

4,4'-Methylenebis(*N,N*-dimethyl)benzenamine was tested in one experiment in mice and in one experiment in rats by dietary administration. It produced liver-cell adenomas in female mice and thyroid follicular-cell carcinomas in male and female rats given the highest dose.

4,4'-Methylenebis(*N,N*-dimethyl)benzenamine was positive in *Escherichia coli* repair tests. It was mutagenic to *Salmonella typhimurium*, both *in vitro* and in the murine host-mediated assay. It did not induce mitotic recombination in yeast, but caused morphological transformation in hamster embryo cells.

### 5.2 Human data

4,4'-Methylenebis(*N,N*-dimethyl)benzenamine has been produced commercially since at least 1921. Its use as a dye intermediate could result in occupational exposure.

No case report or epidemiological study was available to the Working Group.

### 5.3 Evaluation

There is *limited evidence* for the carcinogenicity of 4,4'-methylenebis(*N,N*-dimethyl)benzenamine in experimental animals.

No evaluation of the carcinogenicity of 4,4'-methylenebis(*N,N*-dimethyl)benzenamine to humans could be made.

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

**Subsequent evaluation:** Suppl. 7 (1987) (p. 66: **Group 3**)

### Synonyms

- 4,4'-Bis(dimethylamino)diphenylmethane
- *para,para'*-Bis(dimethylamino)diphenylmethane
- Bis[4-(dimethylamino)phenyl]methane
- Bis[4-(*N,N*-dimethylamino)phenyl]methane
- Bis[*para*-(dimethylamino)phenyl]methane
- Bis[*para-N,N*-(dimethylamino)phenyl]methane
- Methane base
- Michler's Base
- Michler's hydride
- Michler's methane
- Tetrabase

- Tetramethyldiaminodiphenylmethane
- 4,4'-Tetramethyldiaminodiphenylmethane
- *para,para'*-Tetramethyldiaminodiphenylmethane
- *N,N,N',N'*-Tetramethyl-4,4'-diaminodiphenylmethane
- *N,N,N',N'*-Tetramethyl-*para,para'*-diaminodiphenylmethane

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# 1,5-NAPHTHALENEDIAMINE

VOL.: 27 (1982) (p. 127)

CAS No.: 2243-62-1

Chem. Abstr. Name: 1,5-Naphthalenediamine

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

1,5-Naphthalenediamine (technical grade) was tested in one experiment in mice and in one experiment in rats by dietary administration. It produced adenomas of the thyroid in male mice and carcinomas and adenomas of the thyroid and lungs and carcinomas of the liver in female mice. The experiment in rats was inadequate for evaluation.

1,5-Naphthalenediamine (technical-grade) was mutagenic to *Salmonella typhimurium*.

### 5.2 Human data

1,5-Naphthalenediamine has been produced commercially since at least 1957. Its use as an intermediate in the manufacture of 1,5-naphthalene diisocyanate and of dyes could result in occupational exposure.

No case report or epidemiological study was available to the Working Group.

### 5.3 Evaluation

There is *limited evidence* for the carcinogenicity of 1,5-naphthalenediamine in experimental animals.

No evaluation of the carcinogenicity of 1,5-naphthalenediamine to humans could be made.

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

**Subsequent evaluation:** Suppl. 7 (1987) (p. 67: **Group 3**)

### Synonyms

- 1,5-Diaminonaphthalene
- 1,5-Naphthylenediamine

# 5-NITRO-*ortho*-ANISIDINE

**VOL.:** 27 (1982) (p. 133)

**CAS No.:** 99-59-2

**Chem. Abstr. Name:** Benzenamine, 2-methoxy-5-nitro-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

5-Nitro-*ortho*-anisidine was tested for carcinogenicity in one experiment in mice and in one experiment in rats by dietary administration. It produced skin carcinomas in male rats, carcinomas of the Zymbal gland or skin of the ear in male and female rats, mammary adenocarcinomas in female rats and adenomas or carcinomas of the preputial and clitoral glands in male and female rats, respectively. The experiment in mice was inadequate for evaluation.

5-Nitro-*ortho*-anisidine was mutagenic to *Salmonella typhimurium*.

### 5.2 Human data

5-Nitro-*ortho*-anisidine has been produced commercially since at least 1937. Its principal use as a dye intermediate could result in occupational exposure.

No case report or epidemiological study was available to the Working Group.

### 5.3 Evaluation

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

No evaluation of the carcinogenicity of 5-nitro-*ortho*-anisidine to humans could be made.

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

**Subsequent evaluation:** Suppl. 7 (1987) (p. 67: **Group 3**)

### Synonyms

- 2-Amino-1-methoxy-4-nitrobenzene
- 2-Amino-4-nitroanisole
- *ortho*-Anisidine nitrate
- Azoamine Scarlet K
- Azogene Ecarlate R
- Azoic Diazo Component 13, Base
- 2-Methoxy-5-nitroaniline
- 3-Nitro-6-methoxyaniline
- 5-Nitro-2-methoxyaniline

# 2,2',5,5'-TETRACHLOROBENZIDINE

VOL.: 27 (1982) (p. 141)

CAS No.: 15721-02-5

Chem. Abstr. Name: (1,1'-Biphenyl)-4,4'-diamine, 2,2',5,5'-tetrachloro-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

2,2',5,5'-Tetrachlorobenzidine (of unknown purity) was tested for carcinogenicity by dietary administration in mice and rats. The available data were insufficient for evaluation.

2,2',5,5'-Tetrachlorobenzidine was mutagenic to *Salmonella typhimurium* with metabolic activation.

### 5.2 Human data

2,2',5,5'-Tetrachlorobenzidine has been produced commercially since at least 1965. Its use as an intermediate in the manufacture of organic pigments could result in occupational exposure.

No case report or epidemiological study was available to the Working Group.

### 5.3 Evaluation

The available data were *inadequate* for an evaluation of the carcinogenicity of 2,2',5,5'-tetrachlorobenzidine in experimental animals.

No evaluation of the carcinogenicity of this compound to humans could be made.

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

**Subsequent evaluation:** Suppl. 7 (1987) (p. 72: **Group 3**)

### Synonyms

- 3,3',6,6'-Tetrachlorobenzidine
- 2,2',5,5'-Tetrachloro-4,4'-diaminodiphenyl

# 4,4'-THIODIANILINE

**VOL.:** 27 (1982) (p. 147)

**CAS No.:** 139-65-1

**Chem. Abstr. Name:** Benzenamine, 4,4'-thiobis-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

4,4'-Thiodianiline was tested adequately for carcinogenicity in one experiment in mice and in one experiment in rats by dietary administration. It was carcinogenic for animals of both sexes of both species. In mice, it produced hepatocellular carcinomas and carcinomas or adenomas of the thyroid gland in animals of both sexes. In rats, it produced metastatic thyroid gland carcinomas in animals of both sexes, hepatocellular carcinomas and ear-canal papillomas or carcinomas in males and adenocarcinomas of the uterus in females.

4,4'-Thiodianiline was mutagenic to *Salmonella typhimurium* with metabolic activation.

### 5.2 Human data

4,4'-Thiodianiline was first produced commercially in the early 1940s. Its use as a dye intermediate could lead to occupational exposure.

No case report or epidemiological study was available to the Working Group.

### 5.3 Evaluation

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

In the absence of data on humans, 4,4'-thiodianiline should be regarded, for practical purposes, as if it presented a carcinogenic risk to humans.

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

**Previous evaluation:** [Vol. 16 \(1974\)](#)

**Subsequent evaluation:** Suppl. 7 (1987) (p. 72: **Group 2B**)

### Synonyms

- Bis(4-aminophenyl)sulphide
- 4,4'-Diaminodiphenyl sulphide
- *para,para'*-Diaminodiphenyl sulphide
- 4,4'-Diaminophenyl sulphide
- Di(*para*-aminophenyl)sulphide
- Thioaniline
- 4,4'-Thiobis(aniline)
- *para,para'*-Thiodianiline
- Thiodi-*para*-phenylenediamine

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# ***ortho*-TOLUIDINE AND *ortho*-TOLUIDINE HYDROCHLORIDE**

**VOL.:** 27 (1982) (p. 155)

## ***ortho*-Toluidine**

**CAS No.:** 95-53-4

**Chem. Abstr. Name:** Benzenamine, 2-methyl-

## ***ortho*-Toluidine hydrochloride**

**CAS No.:** 636-21-5

**Chem. Abstr. Name:** Benzenamine, 2-methyl-, hydrochloride

## **5. Summary of Data Reported and Evaluation**

### **5.1 Experimental data**

*ortho*-Toluidine hydrochloride was tested in several experiments, but only two experiments in mice and two experiments in rats by oral administration were adequate. It was carcinogenic in mice, producing hepatocellular carcinomas or adenomas in females and haemangiosarcomas at all sites in males of one strain and haemangiosarcomas and haemangiomas of abdominal viscera in animals of both sexes of another strain. It was carcinogenic in rats: in animals of one strain it produced sarcomas of multiple organs in animals of both sexes, fibromas of the subcutaneous tissue and mesotheliomas in males; and sarcomas of the spleen, transitional-cell papillomas and carcinomas of the urinary bladder and mammary gland fibroadenomas and adenomas in females. In male rats of another strain it produced subcutaneous fibromas and fibrosarcomas as well as a slight increase in the incidence of multiple tumours, including transitional-cell carcinomas of the urinary bladder.

*ortho*-Toluidine gave positive results in *Escherichia coli* DNA-repair and phage-induction assays, but it was not mutagenic in *Salmonella typhimurium* unless tested in the presence of both norharman and a metabolic activation system. Urine concentrates from rats treated with *ortho*-toluidine were mutagenic for *S. typhimurium* with metabolic activation.

### **5.2 Human data**

*ortho*-Toluidine has been produced commercially since 1880. Its use as an intermediate in the manufacture of dyes and other chemicals as well as its occurrence as an impurity in some formulated corrosion inhibitors could result in occupational exposure.

The epidemiological studies available to the Working Group dealt only with workers who had been exposed to *ortho*-toluidine in combination with other chemicals. The majority were case reports and did not provide estimates of the population at risk. In one follow-up study, five cases of bladder cancer (0.08 expected) occurred in 53 men exposed to *ortho*-toluidine and to other possibly carcinogenic agents in the manufacture of Fuchsine and Safranine T.

### **5.3 Evaluation**

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

An increased incidence of bladder cancer has been observed in workers exposed to *ortho*-toluidine, but as all were exposed to other possibly carcinogenic chemicals, *ortho*-toluidine cannot be identified specifically as the responsible agent.

*ortho*-Toluidine should be regarded, for practical purposes, as if it presented a carcinogenic risk to humans.

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

**Previous evaluation:** [Vol. 16 \(1974\)](#)

**Subsequent evaluation:** [Suppl. 7 \(1987\)](#); [Vol. 77 \(2000\)](#)

### **Synonyms for *ortho*-Toluidine**

- 1-Amino-2-methylbenzene
- 2-Amino-1-methylbenzene
- 2-Aminotoluene
- *ortho*-Aminotoluene
- C.I. Azoic Brown 29 (Component)
- C.I. 37077
- 1-Methyl-2-aminobenzene
- 2-Methyl-1-aminobenzene
- 2-Methylaniline
- *ortho*-Methylaniline
- 2-Methylbenzenamine
- *ortho*-Methylbenzenamine
- *ortho*-Toluidin
- 2-Toluidine
- *ortho*-Tolylamine

### **Synonyms for *ortho*-Toluidine hydrochloride**

- 1-Amino-2-methylbenzene hydrochloride
- 2-Amino-1-methylbenzene hydrochloride
- 2-Aminotoluene hydrochloride
- *ortho*-Aminotoluene hydrochloride
- 1-Methyl-2-aminobenzene hydrochloride
- 2-Methyl-1-aminobenzene hydrochloride
- 2-Methylaniline hydrochloride
- *ortho*-Methylaniline hydrochloride
- 2-Methylbenzenamine hydrochloride
- *ortho*-Methylbenzenamine hydrochloride
- *ortho*-Toluidin hydrochloride
- 2-Toluidine hydrochloride
- *ortho*-Tolylamine hydrochloride

# 2,4,5- AND 2,4,6-TRIMETHYLANILINE AND THEIR HYDROCHLORIDES

VOL.: 27 (1982) (p. 177)

## 2,4,5-Trimethylaniline

CAS No.: 137-17-7

Chem. Abstr. Name: Benzenamine, 2,4,5-trimethyl-

## 2,4,5-Trimethylaniline hydrochloride

CAS No.: 21436-97-5

Chem. Abstr. Name: Benzenamine, 2,4,5-trimethyl-, hydrochloride

## 2,4,6-Trimethylaniline

CAS No.: 88-05-1

Chem. Abstr. Name: Benzenamine, 2,4,6-trimethyl-

## 2,4,6-Trimethylaniline hydrochloride

CAS No.: 6334-11-8

Chem. Abstr. Name: Benzenamine, 2,4,6-trimethyl-, hydrochloride

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

2,4,5-Trimethylaniline and its hydrochloride were tested in two experiments in mice and in two experiments in rats by dietary administration. In one experiment in mice, 2,4,5-trimethylaniline produced an increased incidence of hepatocellular carcinomas in female mice. The other experiment in mice was considered inadequate for an evaluation. In one experiment in rats it produced an increased incidence of liver carcinomas and lung adenomas. In the other experiment in rats no significantly increased incidence of tumours was observed.

2,4,6-Trimethylaniline hydrochloride was tested in one experiment in mice and in one experiment in male rats. These experiments were considered inadequate for evaluation.

2,4,5-Trimethylaniline was mutagenic to *Salmonella typhimurium* with metabolic activation. The available data were inadequate to evaluate the mutagenicity of 2,4,6-trimethylaniline.

### 5.2 Human data

2,4,5-Trimethylaniline has been produced commercially in the past. 2,4,6-Trimethylaniline is believed to be produced in commercial quantities, but its uses and the extent of human exposure are unknown. The hydrochloride salts of these two compounds are not produced commercially.

No case report or epidemiological study was available to the Working Group.

### 5.3 Evaluation

There is *limited evidence* for the carcinogenicity of 2,4,5-trimethylaniline in experimental animals. No evaluation of the carcinogenicity of 2,4,5-trimethylaniline to humans could be made.

The available data were *inadequate* for an evaluation of the carcinogenicity of 2,4,6-trimethylaniline in experimental animals to be made. No evaluation of the carcinogenicity of 2,4,6-trimethylaniline to humans could be made.

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

**Subsequent evaluation:** Suppl. 7 (1987) (p. 73: **Group 3**)

#### **Synonyms for 2,4,5-Trimethylaniline**

- 1-Amino-2,4,5-trimethylbenzene
- *psi*-Cumidine
- Pseudo-cumidine
- 1,2,4-Trimethyl-5-aminobenzene

#### **Synonyms for 2,4,5-Trimethylaniline hydrochloride**

- 1-Amino-2,4,5-trimethylbenzene hydrochloride
- *psi*-Cumidine hydrochloride
- Pseudocumidine hydrochloride
- 1,2,4-Trimethyl-5-aminobenzene hydrochloride

#### **Synonyms for 2,4,6-Trimethylaniline**

- Aminomesitylene
- 2-Aminomesitylene
- 2-Amino-1,3,5-trimethylbenzene
- Mesidin
- Mesidine
- Mesitylamine

#### **Synonyms for 2,4,6-Trimethylaniline hydrochloride**

- Aminomesitylene hydrochloride
- 2-Aminomesitylene hydrochloride
- 2-Amino-1,3,5-trimethylbenzene hydrochloride
- Mesidin hydrochloride
- Mesidine hydrochloride
- Mesitylamine hydrochloride

# 2-AMINOANTHRAQUINONE

VOL.: 27 (1982) (p. 191)

CAS No.: 117-79-3

Chem. Abstr. Name: 9,10-Anthracenedione, 2-amino-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

2-Aminoanthraquinone (technical grade of low purity) was tested in one experiment in mice and in one experiment in rats by dietary administration. It produced hepatocellular carcinomas in mice of both sexes and in male rats.

Purified 2-aminoanthraquinone was not mutagenic to *Salmonella typhimurium*.

### 5.2 Human data

2-Aminoanthraquinone has been produced commercially since at least 1921. Its use as an intermediate in the manufacture of dyes and pigments could result in occupational exposure.

No case report or epidemiological study was available to the Working Group.

### 5.3 Evaluation

There is *limited evidence* for the carcinogenicity in experimental animals of the material tested, which was technical-grade 2-aminoanthraquinone of low purity.

In view of the uncertain purity of the compound tested and in the absence of data on humans, no evaluation of the carcinogenicity of 2-aminoanthraquinone could be made.

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

**Subsequent evaluation:** Suppl. 7 (1987) (p. 56: **Group 3**)

### Synonyms

- 2-Amino-9,10-anthraquinone
- $\beta$ -Aminoanthraquinone
- Aminoanthraquinone
- $\beta$ -Anthraquinonylamine

# 1-AMINO-2-METHYLANTHRAQUINONE

**VOL.:** 27 (1982) (p. 199)

**CAS No.:** 82-28-0

**Chem. Abstr. Name:** 9,10-Anthracenedione, 1-amino-2-methyl-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

1-Amino-2-methylantraquinone (technical grade, maximum purity 68%) was tested in one experiment in mice and one experiment in rats by dietary administration. This material increased the incidence of hepatocellular carcinomas in rats of both sexes and of kidney adenomas and adenocarcinomas in males. The experiment in mice was inadequate for evaluation.

No data on the mutagenicity of this compound were available.

### 5.2 Human data

1-Amino-2-methylantraquinone was first produced commercially in 1948. It has been used as a dye intermediate in the US and is still produced in commercial quantities in western Europe. Its continued production could lead to occupational exposure.

No case report or epidemiological study was available to the Working Group.

### 5.3 Evaluation

There is *limited evidence* for the carcinogenicity in experimental animals of the material tested, which was technical-grade 1-amino-2-methylantraquinone of low purity.

In view of the uncertain purity of the compound tested and in the absence of data on humans, no evaluation of the carcinogenicity of 1-amino-2-methylantraquinone could be made.

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

**Subsequent evaluation:** Suppl. 7 (1987) (p. 57: **Group 3**)

### Synonyms

- Acetate Fast Orange R
- Acetoquinone Light Orange JL
- Artisil Orange 3RP
- Celliton Orange R
- C.I. Disperse Orange 11
- C.I. 60700
- Cilla Orange R
- Disperse Orange
- Disperse Orange (anthraquinone dye)
- Duranol Orange G
- Microsetile Orange RA

- 2-Methyl-1-anthraquinonylamine
- Nyloquinone Orange JR
- Perliton Orange 3R
- Serisol Orange YL
- Supracet Orange R

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Last updated: 8 April 1998

# 2-METHYL-1-NITROANTHRAQUINONE

VOL.: 27 (1982) (p. 205)

CAS No.: 129-15-7

Chem. Abstr. Name: 9,10-Anthracenedione, 2-methyl-1-nitro-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

2-Methyl-1-nitroanthraquinone (of uncertain purity/impurity) was tested in one experiment in mice and one experiment in rats by dietary administration. It was carcinogenic in mice of both sexes, producing haemangiosarcomas, and in rats, producing hepatocellular carcinomas in males and subcutaneous fibromas in animals of both sexes.

2-Methyl-1-nitroanthraquinone was mutagenic to *Salmonella typhimurium*.

### 5.2 Human data

2-Methyl-1-nitroanthraquinone was first produced commercially in 1946. Its probable use as a dye intermediate could result in occupational exposure.

No case report or epidemiological study was available to the Working Group.

### 5.3 Evaluation

There is *sufficient evidence* for the carcinogenicity in experimental animals of the material tested, which was 2-methyl-1-nitroanthraquinone of uncertain purity/impurity.

In view of the uncertain purity/impurity of the compound tested and in the absence of data on humans, no evaluation of the carcinogenicity of 2-methyl-1-nitroanthraquinone could be made.

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

**Subsequent evaluation:** Suppl. 7 (1987) (p. 66: **Group 2B**)

### Synonym

- 1-Nitro-2-methylantraquinone

# N-NITROSODIPHENYLAMINE

VOL.: 27 (1982) (p. 213)

CAS No.: 86-30-6

Chem. Abstr. Name: Benzenamine, *N*-nitroso-*N*-phenyl-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

*N*-Nitrosodiphenylamine was adequately tested in one experiment in mice and in one experiment in rats by dietary administration. No carcinogenic effects were observed in mice. It was carcinogenic for male and female rats, producing transitional-cell carcinomas of the urinary bladder in animals given the high dose. In other experiments the results were not indicative of carcinogenic effects, but there were various inadequacies in the conducting and/or reporting of these experiments.

*N*-Nitrosodiphenylamine has been extensively tested in short-term assays in prokaryotes and eukaryotes for mutagenicity and other chromosomal effects. It was not mutagenic and did not induce unscheduled DNA synthesis or chromosomal damage under any test condition employed.

### 5.2 Human data

*N*-Nitrosodiphenylamine has been produced commercially since at least 1945. Its use as a chemical intermediate and as a rubber processing chemical could result in occupational exposure.

No case report or epidemiological study was available to the Working Group.

### 5.3 Evaluation

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

No evaluation of the carcinogenicity of *N*-nitrosodiphenylamine to humans could be made.

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

**Subsequent evaluation:** Suppl. 7 (1987) (p. 67: **Group 3**)

### Synonyms

- Curetard A
- Delac J
- Diphenylnitrosamine
- Diphenyl *N*-nitrosoamine
- *N,N*-Diphenylnitrosamine
- Naugard TJB
- NDPA
- NDPhA
- Nitrosodiphenylamine
- *N*-Nitroso-*N*-phenylaniline
- Nitrous diphenylamide

- Redax
- Retarder J
- TJB
- Vulcalent A
- Vulcatard A
- Vulkalent A
- Vultrol

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Last updated: 8 April 1998

# ***para*-NITROSODIPHENYLAMINE**

**VOL.:** 27 (1982) (p. 227)

**CAS No.:** 156-10-5

**Chem. Abstr. Name:** Benzenamine, 4-nitroso-*N*-phenyl-

## **5. Summary of Data Reported and Evaluation**

### **5.1 Experimental data**

*para*-Nitrosodiphenylamine (technical grade) was tested in mice and rats by dietary administration. It produced lesions described as neoplastic nodules in the livers of male rats. The results of the study in mice were inconclusive.

No data on the mutagenicity of *para*-nitrosodiphenylamine were available.

### **5.2 Human data**

*para*-Nitrosodiphenylamine has been produced commercially since at least 1970. Its use as a chemical intermediate could result in occupational exposure.

No case report or epidemiological study was available to the Working Group.

### **5.3 Evaluation**

The available data are insufficient for an evaluation of the carcinogenicity of *para*-nitrosodiphenylamine in experimental animals.

In view of the few data in experimental animals and in the absence of data on humans, no evaluation of the carcinogenicity of *para*-nitrosodiphenylamine to humans could be made.

**Subsequent evaluation:** Suppl. 7 (1987) (p. 68: **Group 3**)

### **Synonyms**

- Naugard TKB
- 4-Nitroso-*N*-phenylaniline
- *para*-Nitroso-*N*-phenylaniline
- *N*-Phenyl-*para*-nitrosoaniline
- TKB

# INORGANIC FLUORIDES USED IN DRINKING-WATER AND DENTAL PREPARATIONS

VOL.: 27 (1982) (p. 237)

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Sodium fluoride was tested in three experiments in three different strains of mice by oral administration. The available data are insufficient to allow an evaluation to be made. Sodium fluoride was not mutagenic to *Salmonella typhimurium* or *Drosophila melanogaster* and did not induce gene conversion in *Saccharomyces cerevisiae*.

### 5.2 Human data

Significant mining of fluorspar (calcium fluoride) started in about 1775. The natural occurrence of some inorganic fluorides and their use in water fluoridation and anti-caries dental products results in widespread exposure of the general population. In addition, the numerous industrial applications of these chemicals result in significant occupational exposure and emissions to the environment.

Only studies on water fluoridation and cancer were reviewed. The relationship between cancer mortality or incidence and both natural and artificial fluoride in drinking-water has been investigated in a large number of descriptive epidemiological studies of population aggregates, carried out in Australia, Canada, New Zealand, Norway, the United Kingdom and the United States. Because of the uneven distribution of natural fluoride in the earth's crust, and the fact that local communities make independent decisions with regard to fluoridation, some of these studies could be viewed roughly as natural experiments. When proper account was taken of the differences among population units, in demographic composition, and in some cases also in their degree of industrialization and other social factors, none of the studies provided any evidence that an increased level of fluoride in water was associated with an increase in cancer mortality.

### 5.3 Evaluation

The available data are *inadequate* for an evaluation of the carcinogenicity of sodium fluoride, the only inorganic fluoride tested, in experimental animals.

Variations geographically and in time in the fluoride content of water supplies provide no evidence of an association between fluoride ingestion and mortality from cancer in humans.

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

**Subsequent evaluation:** [Suppl. 7 \(1987\)](#)