



WORLD HEALTH ORGANIZATION  
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

# Volume 4

## Some Aromatic Amines, Hydrazine and Related Substances, *N*-Nitroso Compounds and Miscellaneous Alkylating Agents

Summary of Data Reported and Evaluation

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### Aromatic Amines

Aniline  
3,3'-Dimethoxybenzidine  
3,3'-Dichlorobenzidine  
4,4'-Methylene bis(2-methylaniline)  
4,4'-Methylenedianiline  
1-Naphthylamine  
2-Naphthylamine  
4-Nitrobiphenyl  
*N,N*-Bis(2-chloroethyl)-2-naphthylamine

### Hydrazine and Related Substances

Hydrazine  
1,1-Dimethylhydrazine  
1,2-Dimethylhydrazine  
1,2-Diethylhydrazine  
Isonicotinic acid hydrazide  
Maleic hydrazide

### *N*-Nitroso Compounds

*N*-Methyl-*N'*-Nitro-*N*-nitrosoguanidine  
*N*-Nitroso-di-*n*-butylamine  
*N*-Nitroso-*N*-methylurethane  
Streptozotocin

### Miscellaneous Alkylating Agents

Bis(chloromethyl)ether  
Chloromethyl methyl ether

1,4-Butanediol dimethanesulfonate

1,3-Propane sultone

$\beta$ -Propiolactone

Dimethyl sulphate

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Last updated: 13 April 1999

# ANILINE

VOL.: 4 (1974) (p. 27)

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

There is no adequate data to indicate that aniline is carcinogenic in experimental animals.

### 5.2 Human carcinogenicity data

At the present time, the weight of epidemiological evidence suggests that aniline is not a carcinogen for the human bladder.

**Subsequent evaluations:** [Vol. 27 \(1982\)](#); [Suppl. 7 \(1987\)](#)

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Last updated: 16 March 1998

## 3,3'-DIMETHOXYBENZIDINE (*o*-DIANISIDINE)

VOL.: 4 (1974) (p. 41)

### 5. Summary of Data Reported and Evaluation

#### 5.1 Animal carcinogenicity data

3,3'-Dimethoxybenzidine (*o*-Dianisidine) was shown to have a carcinogenic effect in rats following oral administration. The findings obtained in the hamster by the same route suggest a similar effect.

#### 5.2 Human carcinogenicity data

No conclusive epidemiological studies have been reported concerning the carcinogenicity of *o*-dianisidine alone in man.

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

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Last updated: 16 March 1998

# 3,3'-DICHLOROBENZIDINE

VOL.: 4 (1974) (p. 49)

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

3,3'-Dichlorobenzidine is carcinogenic in the rat following oral and subcutaneous administration and in the hamster after oral administration.

### 5.2 Human carcinogenicity data

No epidemiological data are available, but as 3,3'-dichlorobenzidine and benzidine may be made in the same plant, the possibility cannot be excluded that 3,3'-dichlorobenzidine has contributed to the incidence of bladder cancer attributed to benzidine.

**Subsequent evaluations:** [Vol. 29 \(1982\)](#); [Suppl. 7 \(1987\)](#)

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Last updated: 16 March 1998

# 4,4'-METHYLENE BIS(2-METHYLANILINE)

VOL.: 4 (1974) (p. 73)

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

4,4'-Methylene bis(2-methylaniline) is carcinogenic in the rat after oral administration, the only species and route tested.

### 5.2 Human carcinogenicity data

No epidemiological data are available to the Working Group.

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

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Last updated: 16 March 1998

# 4,4'-METHYLENEDIANILINE

VOL.: 4 (1974) (p. 79)

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

The available experimental evidence in the rat, the only species tested, does not permit a definite conclusion regarding the carcinogenicity of 4,4'-methylenedianiline in this species.

### 5.2 Human carcinogenicity data

No epidemiological data are available to the Working Group.

**Subsequent evaluation:** [Vol. 39 \(1986\)](#); Suppl. 7 (1987) (p. 66: **Group 2B**)

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

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Last updated: 16 March 1998

# 1-NAPHTHYLAMINE

VOL.: 4 (1974) (p. 87)

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

No carcinogenic effect of 1-naphthylamine was observed in the hamster following oral administration. The results obtained after oral and subcutaneous administration to mice are inconclusive. The experiments in dogs demonstrate that 1-naphthylamine, if carcinogenic at all, is less so to the bladder in this species than is the 2-isomer.

### 5.2 Human carcinogenicity data

Occupational exposure to commercial 1-naphthylamine containing 4-10% 2-naphthylamine is strongly associated with bladder cancer. A number of case reports from several countries support this association. It is not possible on present evidence to decide whether 1-naphthylamine free from the 2-isomer is carcinogenic to man.

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

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Last updated: 16 March 1998

# 2-NAPHTHYLAMINE

VOL.: 4 (1974) (p. 97)

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

2-Naphthylamine is carcinogenic in the mouse, hamster, dog and monkey. Given orally it has produced bladder carcinomas in the dog and monkey, and, at high dosage levels, in the hamster. By this route, it has increased the incidence of hepatomas in the mouse; in the rat and rabbit, it has little, if any, carcinogenic effect.

### 5.2 Human carcinogenicity data

Epidemiological studies have shown that occupational exposure to 2-naphthylamine, either alone or when present as an impurity in other compounds, is strongly associated with the occurrence of bladder cancer. There is no doubt that 2-naphthylamine is a human bladder carcinogen.

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

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Last updated: 16 March 1998

# 4-NITROBIPHENYL

VOL.: 4 (1974) (p. 113)

CAS No.: 92-93-3

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

4-Nitrobiphenyl induced carcinomas of the bladder when given orally to dogs, the only species and route known to have been tested.

### 5.2 Human carcinogenicity data

There are no data on the carcinogenicity of 4-nitrobiphenyl in man. However, it has been used in the production of 4-aminobiphenyl, which is a recognized human bladder carcinogen.

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

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

### Synonyms

- *p*-Nitrobiphenyl
- *p*-Nitrodiphenyl
- 4-Nitrodiphenyl
- 4-Phenyl-nitrobenzene
- *p*-Phenyl-nitrobenzene
- PNB

# ***N,N*-BIS(2-CHLOROETHYL)-2-NAPHTHYLAMINE (CHLORNAPHAZINE)**

**VOL.:** 4 (1974) (p. 119)

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

### **5.1 Animal carcinogenicity data**

*N,N*-Bis(2-chloroethyl)-2-naphthylamine is carcinogenic to the mouse lung by the intraperitoneal route and has a local carcinogenic effect in rats following subcutaneous injection.

### **5.2 Human carcinogenicity data**

This drug has been administered to man with <sup>32</sup>P sodium phosphate for the treatment of polycythaemia and of neoplasias of the haemopoietic system in doses of up to 400 mg/day. Follow-up studies have shown that under these conditions, the drug is carcinogenic, producing bladder tumours after administration of total doses as low as 4 g.

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

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Last updated: 16 March 1998

# 1,1-DIMETHYLHYDRAZINE

**VOL.:** 4 (1974) (p. 137)

**CAS No.:** 57-14-7

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

1,1-Dimethylhydrazine (UDMH) is carcinogenic in mice after oral administration. The observation of a few liver tumours after high oral doses of UDMH occurring in rats after a long latent period does not allow a proper evaluation of the carcinogenic effect in this species.

### 5.2 Human carcinogenicity data

No epidemiological data are available to the Working Group.

**Subsequent evaluation:** [Vol. 71 \(1999\)](#)

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

### Synonyms

- Asymmetrical-dimethylhydrazine
- Dimazine
- Dimethylhydrazine
- *N,N*-Dimethylhydrazine
- UDMH
- UNS-dimethylhydrazine
- Unsymmetrical dimethylhydrazine

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# 1,2-DIETHYLHYDRAZINE

**VOL.:** 4 (1974) (p. 153)

**CAS No.:** 1615-80-1

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

1,2-Diethylhydrazine (SDEH) is carcinogenic in rats by subcutaneous administration and transplacental exposure, the only species and routes tested.

### 5.2 Human carcinogenicity data

No epidemiological data are available to the Working Group.

**Subsequent evaluation:** [Vol. 71 \(1999\)](#)

### Synonyms

- *N,N'*-Diethylhydrazine
- Hydrazoethane
- SDEH
- Symmetrical-diethylhydrazine

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# ISONICOTINIC ACID HYDRAZIDE (ISONIAZID)

VOL.: 4 (1974) (p. 159)

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

Isonicotinic acid hydrazide (INH) is carcinogenic in mice after oral, subcutaneous and intraperitoneal administration. The observation of tumours in rats in only one of several oral studies is inconclusive. INH failed to produce tumours in hamsters when given orally.

### 5.2 Human carcinogenicity data

Available evidence from the first 15 years of human exposure has not suggested that INH is carcinogenic in man in the doses applicable to treatment and prophylaxis of tuberculosis.

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

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Last updated: 16 March 1998

# MALEIC HYDRAZIDE

**VOL.:** 4 (1974) (p. 173)

**CAS No.:** 123-33-1

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

No carcinogenic effect was observed in adult mice and rats following oral or subcutaneous administration of maleic hydrazide. The significance of hepatomas obtained in newborn mice cannot be assessed because of the contamination of maleic hydrazide with hydrazine.

### 5.2 Human carcinogenicity data

No epidemiological data are available to the Working Group.

**Subsequent evaluation:** Suppl. 7 (1987) (p. 65: **Group 3**)

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

### Synonyms

- 1,2-Dihydropyridazine-3,6-dione
- 1,2-Dihydro-3,6-pyridazinedione
- 6-Hydroxy-3-(2*H*)pyridazinone
- MAH
- Malazide
- Maleic acid hydrazide
- Maleic hydrazine
- *N,N*-Maleoylhydrazine
- MH
- Regulox

# ***N*-METHYL-*N'*-NITRO-*N*-NITROSOGUANIDINE**

**VOL.:** 4 (1974) (p. 183)

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

### **5.1 Animal carcinogenicity data**

*N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) is carcinogenic in all species tested: mouse, rat, hamster, rabbit and dog. It has a predominantly local carcinogenic effect following administration by oral and other routes. It is carcinogenic in single-dose experiments.

### **5.2 Human carcinogenicity data**

No epidemiological data are available to the Working Group.

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

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Last updated: 17 March 1998

# N-NITROSO-DI-*n*-BUTYLAMINE

VOL.: 4 (1974) (p. 197)

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

*N*-Nitroso-di-*n*-butylamine (DBNA) is carcinogenic in all animal species tested: mouse, rat, hamster and guinea pig. It is carcinogenic by oral and other routes, and it is particularly effective as a bladder carcinogen after subcutaneous injection. It is carcinogenic after exposure to a single dose.

### 5.2 Human carcinogenicity data

No epidemiological data are available to the Working Group.

**Subsequent evaluations:** [Vol. 17 \(1978\)](#); Suppl. 7 (1987) (p. 67: **Group 2B**)

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

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Last updated: 17 March 1998

# N-NITROSO-N-METHYLURETHANE

VOL.: 4 (1974) (p. 211)

CAS No.: 615-53-2

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

*N*-Nitroso-*N*-methylurethane is carcinogenic in all species tested: mouse, rat, hamster, guinea-pig. It has a local as well as a systemic carcinogenic effect, producing tumours at different sites by oral and other routes of administration. It is carcinogenic in single-dose experiments and following pre-natal exposure.

### 5.2 Human carcinogenicity data

No epidemiological data are available to the Working Group.

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

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

### Synonyms

- Ethyl ester of methylnitroso-carbamic acid
- *N*-Methyl-*N*-nitroso-ethylcarbamate
- *N*-Methyl-*N*-nitrosourethan
- MNUN
- NMUT

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Last updated: 17 March 1998

# STREPTOZOTOCIN

VOL.: 4 (1974) (p. 221)

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

Streptozotocin is carcinogenic in rats and hamsters following intravenous injection, the only route tested. It is active in single dose experiments.

### 5.2 Human carcinogenicity data

No epidemiological data are available to the Working Group.

**Subsequent evaluations:** [Vol. 17 \(1978\)](#); Suppl. 7 (1987) (p. 72: **Group 2B**)

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

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Last updated: 17 March 1998

# BIS(CHLOROMETHYL)ETHER

VOL.: 4 (1974) (p. 231)

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

Bis(chloromethyl)ether (BCME) is carcinogenic to mice following inhalation, skin application and subcutaneous administration. In newborn mice it is carcinogenic after a single subcutaneous exposure. In the rat it is carcinogenic by inhalation and subcutaneous administration.

### 5.2 Human carcinogenicity data

A high incidence of predominantly oat-cell carcinoma in a small population of laboratory workers exposed to BCME strongly suggests that exposure to this compound constitutes a serious human lung cancer hazard.

There is also epidemiological evidence to suggest that exposure to BCME may constitute a lung cancer risk amongst workers exposed to it as a contaminant in the manufacture of the related chloromethyl methyl ether (CMME) (see separate monograph on CMME).

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

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Last updated: 17 March 1998

# CHLOROMETHYL METHYL ETHER

VOL.: 4 (1974) (p. 239)

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

Chloromethyl methyl ether (CMME) is almost invariably contaminated by bis(chloromethyl)ether (BCME), and the latter may be responsible for at least part of the observed carcinogenic activity. Such contaminated CMME has been found to be carcinogenic on subcutaneous injection in the mouse and possibly to be an initiator for mouse skin tumours. Inhalation in mice and subcutaneous injection in the rat produced equivocal evidence of carcinogenic activity.

### 5.2 Human carcinogenicity data

One study based on 4 cases of oat cell lung cancer observed amongst 111 workers exposed to CMME (and its associated BCME impurity), followed for 5 years, suggests an increased risk of lung cancer.

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

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Last updated: 17 March 1998

# 1,4-BUTANEDIOL DIMETHANESULFONATE (MYLERAN)

VOL.: 4 (1974) (p. 247)

## 5. Summary of Data Reported and Evaluation

### 5.1 Animal carcinogenicity data

Administration of 1,4-butanediol dimethanesulfonate (Myleran) to the mouse by intraperitoneal injection and to the rat by oral administration did not significantly increase the incidence of tumours. Intravenous administration in the mouse significantly increased the incidence of thymic lymphomas and ovarian tumours. Myleran in conjunction with X-rays further augmented the incidence of thymic lymphomas. The increased incidences of thymic lymphomas and ovarian tumours are difficult to assess with respect to the carcinogenicity of Myleran in the mouse.

### 5.2 Human carcinogenicity data

Although there is evidence that histological and cytological changes are associated with Myleran therapy, there is no firm evidence of an increased cancer risk among those treated.

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

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