



WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Volume 1

Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, *N*-Nitroso Compounds and Natural Products

Summary of Data Reported and Evaluation

Inorganic Substances

Haematite and iron oxide
Lead salts

Chlorinated Hydrocarbons

Carbon tetrachloride
Chloroform

Aromatic Amines

Auramine
4-Aminobiphenyl
Benzidine
3,3'-Dimethylbenzidine (*o*-Tolidine)

N-Nitroso Compounds

N-Nitrosodimethylamine
N-Nitrosodiethylamine
Nitrosomethylurea
Nitrosoethylurea
N-Methyl-*N*,4-Dinitrosoaniline

Natural Products

Cycasin
Safrole, isosafrole and dihydrosafrole
Sterigmatocystin

Miscellaneous

[N\[4-\(5-Nitro-2-furyl\)-2-thiazolyl\]acetamide](#)

Last updated: 13 April 1999

HAEMATITE AND IRON OXIDE

VOL.: 1 (1972) (p. 29)

5. Summary of Data Reported and Evaluation

5.1 Animal carcinogenicity data

Iron oxide given by inhalation or by intratracheal route has not been found to be carcinogenic in the hamster, the mouse or the guinea-pig.

5.2 Human carcinogenicity data

On the basis of epidemiological evidence, exposure to haematite dust may be regarded as increasing the risk of lung cancer development in man. The risk is manifest in underground workers but not surface workers, and it is not known whether the excess risk is due to radioactivity in the air of mines, the inhalation of iron oxide or silica, or to a combination of these or other factors. There is no evidence that iron-ore dust (haematite) or iron oxide influences the incidence of cancers at sites other than the lungs.

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

Last updated: 12 March 1998

LEAD SALTS

VOL.: 1 (1972) (p. 40)

5. Summary of Data Reported and Evaluation

5.1 Animal carcinogenicity data

Lead acetate is carcinogenic in rats and mice; lead subacetate and lead phosphate are carcinogenic in the rat. Given orally, they produce benign and malignant tumours of the kidney. The observation that exposure of rats to lead subacetate may result in an increased frequency of gliomas needs confirmation, as well as the observation of a high frequency of tumours of the testis, adrenal, thyroid, pituitary and prostate, together with renal tumours, in rats receiving lead acetate. No induction of tumours was reported to occur following exposure to lead arsenate or lead carbonate, but the evidence cannot be held as conclusive.

The pattern of absorption metabolism and storage of lead in the body seems to be similar in all animal species that have been studied. The kidney is a target from the point of view of toxicity in all animal species studied. Renal enlargement and the appearance of intranuclear inclusion bodies in the epithelial cells occur in all laboratory animal species and in man in the same way.

5.2 Human carcinogenicity data

There is no evidence to suggest that exposure to lead salts causes cancer of any site in man. However, only one epidemiological study of the relationships between exposure to lead and the occurrence of cancer has been reported. It must be noted that the level of human exposure equivalent to the levels of lead acetate producing renal tumours in rats is 810 mg per day (550 mg Pb). This level appears to exceed by far the maximum tolerated dose for man.

Subsequent evaluations: [Vol. 23 \(1980\)](#); [Suppl. 7 \(1987\)](#)

Last updated: 12 March 1998

CHLOROFORM

VOL.: 1 (1972) (p. 61)

5. Summary of Data Reported and Evaluation

5.1 Animal carcinogenicity data

The carcinogenicity of chloroform has been investigated only in mice in experiments involving a small number of animals at risk. Nevertheless among these the frequency of liver tumours was high. There is no evidence of carcinogenicity for organs other than the liver, but the experiments were shorter than the life-span of the animals. An experiment involving single or a few exposures of newborn mice gave negative results. An assessment of the carcinogenicity of chloroform awaits further experimental evidence.

5.2 Human carcinogenicity data

Chloroform entails several sources of exposure for humans. No long-term follow-up studies in men exposed to chloroform have been reported.

Subsequent evaluations: [Vol. 20 \(1979\)](#); [Suppl. 7 \(1987\)](#); [Vol. 73 \(1999\)](#)

Last updated: 30 September 1999

AURAMINE

VOL.: 1 (1972) (p. 69)

5. Summary of Data Reported and Evaluation

5.1 Animal carcinogenicity data

Auramine is carcinogenic in the mouse and rat. Given orally, it has produced liver tumours in these two species. No tumours were obtained in the only experiment in the dog and in the rabbit. The purity of the auramine used in these experiments is not known.

5.2 Human carcinogenicity data

One epidemiological study indicates that the open manufacture of auramine presents an occupational bladder cancer risk. .

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

Last updated: 12 March 1998

4-AMINOBIIPHENYL

VOL.: 1 (1972) (p. 74)

5. Summary of Data Reported and Evaluation

5.1 Animal carcinogenicity data

4-Aminobiphenyl is carcinogenic in the mouse, rat, rabbit and dog. Following its oral administration it has produced bladder and liver tumours in mice and bladder papillomas and carcinomas in rabbits and dogs.

5.2 Human carcinogenicity data

In the epidemiological studies, confined to one series of workers occupationally exposed to commercial 4-aminobiphenyl, a high incidence of bladder carcinomas was reported. In consequence one can say that bladder cancer was strongly associated with occupational exposure to 4-aminobiphenyl.

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

Last updated: 12 March 1998

BENZIDINE

VOL.: 1 (1972) (p. 80)

5. Summary of Data Reported and Evaluation

5.1 Animal carcinogenicity data

Benzidine is carcinogenic in the mouse, rat and hamster, and possibly the dog. Given orally, it has produced bladder carcinoma in the dog after a long latent period and liver tumours in the rat and hamster.

5.2 Human carcinogenicity data

The epidemiological studies showed that occupational exposure to commercial benzidine alone was strongly associated with bladder cancer. In the same studies, exposure to 2-naphthylamine alone was similarly associated with bladder cancer. A number of case reports from several countries support the relationship between this neoplasm and occupational exposure to benzidine.

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

Last updated: 12 March 1998

3,3'-DIMETHYLBENZIDINE (*o*-TOLIDINE)

VOL.: 1 (1972) (p. 87)

CAS No.: 119-93-7

5. Summary of Data Reported and Evaluation

5.1 Animal carcinogenicity data

Purified *o*-tolidine is a systemic carcinogen in the rat when given subcutaneously. The oral experiment in the rat is of doubtful significance because of the small number of animals involved. In feeding experiments, the commercial product failed to produce tumours in hamsters.

5.2 Human carcinogenicity data

No epidemiological studies are available.

Subsequent evaluation: Suppl. 7 (1987) (p. 62: **Group 2B**)

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

Synonyms

- 4,4'-Diamino-3,3'-dimethylbiphenyl
- 4,4'-Diamino-3,3'-dimethyldiphenyl
- 3,3'-Dimethyl-4,4'-biphenyldiamine
- 3,3'-Dimethyl-4,4'-diphenyldiamine
- 3,3'-Dimethylbiphenyl-4,4'-diamine
- 3,3'-Dimethyldiphenyl-4,4'-diamine
- 3,3'-Tolidine
- 4,4'-Bi-*o*-toluidine
- 4,4'-Di-*o*-toluidine
- Diaminoditoly
- Fast dark blue base R
- C.I. azoic diazo component 113

N-NITROSODIMETHYLAMINE

VOL.: 1 (1972) (p. 95)

5. Summary of Data Reported and Evaluation

5.1 Animal carcinogenicity data

N-Nitrosodimethylamine (DMN) is carcinogenic in all seven animal species tested. The main target organs are the liver and the kidney. It induces tumours following different routes of administration, including ingestion and inhalation. It is carcinogenic following prenatal exposure and in single-dose experiments. Similarities in metabolism in human and rat liver tissues have been reported.

5.2 Human carcinogenicity data

DMN has been used in the chemical industry. The extent of such use at present is not known.

Many data on occurrence have been obtained by inadequate analytical methods and must await confirmation. Considerable progress has been made in the development of adequate and specific methods for trace analysis of nitrosamines, and reliable information is to be expected in the near future. Recent results, which have been confirmed by mass spectrometry, indicate that DMN does occur in certain food products at the 5-10 ppb level. There is some indication that DMN might be formed from ingested dimethylamine and nitrosating agents *in vivo*. Both precursors can occur in food.

No long-term follow-up studies of human subjects exposed to DMN are known.

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

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

Last updated: 12 March 1998

N-NITROSODIETHYLAMINE

VOL.: 1 (1972) (p. 107)

5. Summary of Data Reported and Evaluation

5.1 Animal carcinogenicity data

N-Nitrosodiethylamine (DEN) is carcinogenic in all ten animal species tested, including sub-human primates. The main target organs are the nasal cavity, trachea, lung, oesophagus and liver. It induces tumours following different routes of administration, including ingestion, inhalation and skin painting. It is carcinogenic in single-dose experiments and following prenatal exposure.

5.2 Human carcinogenicity data

Many data on the occurrence in the human environment have been obtained by inadequate analytical methods and must await confirmation. Considerable progress has been made in the development of adequate and specific methods for trace analysis and more information is to be expected in the near future.

The possibility of a formation of DEN from precursors, diethylamine and nitrosating agents, *in vivo*, must receive further attention. No long-term studies of human subjects exposed to DEN are known.

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

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

NITROSOMETHYLUREA

VOL.: 1 (1972) (p. 125)

5. Summary of Data Reported and Evaluation

5.1 Animal carcinogenicity data

Nitrosomethylurea (NMU) is carcinogenic in all six animal species tested. It has a local as well as a systemic carcinogenic effect, producing tumours at different sites, including the nervous tissue. It induces tumours following different routes of administration, including ingestion. It is carcinogenic in single-dose experiments and following prenatal exposure.

5.2 Human carcinogenicity data

The compound may be formed *in vivo* from methylurea and nitrite or other nitrosating agents. No data on direct human exposure are available.

Subsequent evaluations: [Vol. 17 \(1978\)](#); Suppl. 7 (1987) (p. 66: **Group 2A**)

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

Last updated: 12 March 1998

NITROSOETHYLUREA

VOL.: 1 (1972) (p. 135)

5. Summary of Data Reported and Evaluation

5.1 Animal carcinogenicity data

Nitrosoethylurea is carcinogenic in all four animal species tested. The main target organs are the kidney, nervous system and lympho-reticular system. Tumours have been induced following different routes of administration, including single oral doses. Prenatal exposure to the substance has been shown to be particularly effective in producing tumours of the nervous system.

5.2 Human carcinogenicity data

The compound can be formed from ethylurea by nitrosation *in vivo*. No data on direct human exposure are available.

Subsequent evaluations: [Vol. 17 \(1978\)](#); Suppl. 7 (1987) (p. 63: **Group 2A**)

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

Last updated: 12 March 1998

***N*-METHYL-*N*,4-DINITROSOANILINE**

VOL.: 1 (1972) (p. 141)

CAS No.: 99-80-9

5. Summary of Data Reported and Evaluation

Although there is some evidence of carcinogenic activity of *N*-methyl-*N*,4-dinitrosoaniline in the rat, the data available are considered insufficient for an evaluation.

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

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

Synonyms for *N*-Methyl-*N*,4-Dinitrosoaniline

- *N*,4-Dinitroso-*N*-methyl-aniline
- Elastopar
- *N*-Methyl-*N*-*p*-dinitrosoaniline
- Methyl-(4-nitrosophenyl)nitrosamine
- *N*-Nitroso-*N*-methyl-4-nitroso-aniline
- Nitrozan K

Last updated: 12 March 1998

CYCASIN

VOL.: 1 (1972) (p. 157)

5. Summary of Data Reported and Evaluation

5.1 Animal carcinogenicity data

Cycasin is carcinogenic in five animal species, inducing tumours in various organs. Following oral exposure, it is carcinogenic in the rat, hamster, guinea-pig and fish. By this route, the data in the mouse is of borderline significance and the negative experiment in chickens only lasted 68 weeks. It is active in single-dose experiments and following prenatal exposure. The carcinogenicity of its metabolite, methylazoxymethanol, has been demonstrated in the rat and the hamster and that of a closely related synthetic substance, methylazoxymethanol acetate, in the rat.

5.2 Human carcinogenicity data

Nuts prepared in Guam in the usual way (leached with water and sun-dried) were reported still to contain 160 ppb of cycasin. In another report, chips of dried kernels of cycad nuts did not contain cycasin. The epidemiological study in the Miyako Islands involved a follow-up after heavy exposure in 1959 for the years 1961 to 1966, which may have been too short for a carcinogenic effect to be observed. However, there was also chronic exposure prior to 1959 in this population. It is noteworthy that an increased mortality from cirrhosis was observed. This negative result concerning cancer in the only epidemiological study performed to date is insufficient to exclude a possible carcinogenic effect of cycasin on man.

Subsequent evaluation: [Vol. 10 \(1976\)](#); [Suppl. 7 \(1987\)](#) (p. 61: **Group 2B**)

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

Last updated: 12 March 1998

SAFROLE, ISOSAFROLE AND DIHYDROSAFROLE

VOL.: 1 (1972) (p. 169)

5. Summary of Data Reported and Evaluation

5.1 Animal carcinogenicity data

Safrole and isosafrole are liver carcinogens for the mouse and the rat when administered orally or subcutaneously. Dihydrosafrole is carcinogenic for the oesophagus of the rat following oral administration.

5.2 Human carcinogenicity data

Man may ingest small amounts of safrole and isosafrole through essential oils in which they occur.

No epidemiological data are available on the effects of human exposure.

Subsequent evaluation: [Vol. 10 \(1976\)](#); Suppl. 7 (1987) (p. 62: Dihydrosafrole - **Group 2B**; p. 65: Isosafrole - **Group 3**; p. 71: Safrole - **Group 2B**)

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

Last updated: 16 March 1998

STERIGMATOCYSTIN

VOL.: 1 (1972) (p. 175)

5. Summary of Data Reported and Evaluation

5.1 Animal carcinogenicity data

Sterigmatocystin is carcinogenic in the rat. It has produced liver tumours following oral administration and local sarcomas following subcutaneous administration.

5.2 Human carcinogenicity data

Sterigmatocystin-producing fungi are known to be present in food grains, but surveys of human foods have not produced evidence of exposure.

Subsequent evaluations: [Vol. 10 \(1976\)](#); Suppl. 7 (1987) (p. 72: **Group 2B**)

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

Last updated: 16 March 1998

***N*-[4-(5-NITRO-2-FURYL)-2-THIAZOLYL]ACETAMIDE**

VOL.: 1 (1972) (p. 181)

5. Summary of Data Reported and Evaluation

5.1 Animal carcinogenicity data

N-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide (NFTA) given orally produced tumours of the forestomach in mice and mammary gland, lung and other tumours in rats. Two dogs given NFTA orally developed tumours.

5.2 Human carcinogenicity data

The major source of exposure is its use in therapeutics. There is no information on the long-term effects of NFTA in humans.

Subsequent evaluations: [Vol. 7 \(1974\)](#); Suppl. 7 (1987) (p. 67: **Group 2B**)

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

Last updated: 16 March 1998