

CHEMICAL AGENTS AND RELATED OCCUPATIONS

VOLUME 100 F
A REVIEW OF HUMAN CARCINOGENS

This publication represents the views and expert
opinions of an IARC Working Group on the
Evaluation of Carcinogenic Risks to Humans,
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IARC MONOGRAPHS
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OF CARCINOGENIC RISKS
TO HUMANS

AURAMINE AND AURAMINE PRODUCTION

Auramine and auramine production were considered by previous IARC Working Groups in 1971, 1987, and 2008 ([IARC, 1972, 1987, 2010](#)). Since that time new data have become available, which have been incorporated in this *Monograph*, and taken into consideration in the present evaluation.

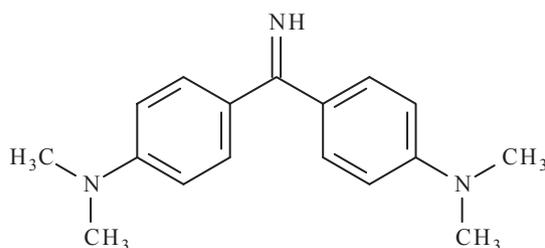
1. Exposure Data

1.1 Identification of the agent

Chem. Abstr. Serv. Reg. No.: 492-80-8

CAS Name: 4,4'-Carbonimidoylbis[*N,N*-dimethylbenzenamine]

Synonyms: C.I. 41000B; C.I. Solvent Yellow 34; 4,4'-dimethylaminobenzophenonimide; 4,4'-(imidocarbonyl)bis(*N,N*-dimethylaniline); glauramine; Solvent Yellow 34; yellow pyoctanine



$C_{17}H_{21}N_3$

Relative molecular mass: 267.37

Description: Yellow flakes or powder, decomposes at $>70\text{ }^{\circ}\text{C}$.

Solubility: as base: insoluble in water, soluble in ethanol and diethyl ether; as the hydrochloride: soluble in water, ether, ethanol and chloroform.

1.2 Manufacture and use

Auramine is manufactured industrially from *N,N*-dimethylaniline and formaldehyde, which react to form Michler's base (tetramethyldiaminodiphenylmethane). This base is subsequently converted to auramine by heating with sulfur and ammonium chloride in the presence of ammonia. It was reported that a 98% pure auramine contains salts, water and Michler's ketone, an hydrolysis product ([Kirsch *et al.*, 1978](#)).

Production of auramine took place first in Europe (Switzerland, Germany, the United Kingdom, and France), and later also in the United States of America (USA). Production in these countries has generally been discontinued. Auramine manufacturing is currently mainly located in India and the People's Republic of China.

Auramine colourants are used for dyeing of leather, jute, tanned cotton, and paints, and as dye components in inking ribbons, ballpoint pastes, oils and waxes, and carbon paper. The most important applications are in paper dyeing and flexographic printing ([IARC, 2010](#)). More detailed information on the use of auramine dyes and auramine compounds is provided in the recent *Monograph* ([IARC, 2010](#)).

1.3 Human exposure

1.3.1 Occupational exposure

The only well described groups of workers exposed during auramine production include those in the United Kingdom ([Case & Pearson, 1954](#)) and Germany ([Kirsch et al., 1978](#); [Thiess et al., 1982](#)). Results from exposure measurements in the workplace or from biological samples of workers employed in the production of auramine are not available.

The manufacture of auramine involves potential exposure to its process chemicals (e.g. dimethyl-aniline, formaldehyde, sulfur, ammonium chloride, ammonia, Michler's base), as well as to other chemicals that may be used and produced at the same location (e.g. benzidine, 1-naphthylamine, 2-naphthylamine, magenta, aniline) ([Case & Pearson, 1954](#)).

2. Cancer in Humans

Auramine was last reviewed in *IARC Monograph* Volume 99 ([IARC, 2010](#)). A 13-fold excess of bladder tumours was observed among men engaged in the manufacture of auramine ($P < 0.005$), compared with mortality rates for the male population in England and Wales ([Case & Pearson, 1954](#); see Table 2.1, available at <http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-07-Table2.1.pdf>). Although care had been taken to eliminate from the analysis those workers who were recorded as also having been in contact with 1- or 2-naphthylamine or benzidine, exposure to non-auramine bladder carcinogens could not be entirely excluded. A cohort-mortality study of auramine workers at the 'Badische Anilin und Soda-Fabrik' (BASF) in Germany ([Kirsch et al., 1978](#)) identified two bladder cancer deaths, with < 0.4 expected. Case reports of bladder cancer among Swiss auramine-production workers have also been published ([Von Müller, 1933](#)).

3. Cancer in Experimental Animals

Studies on the carcinogenicity of auramine in the mouse, rat, and rabbit after oral administration or subcutaneous injection were reviewed in previous *IARC Monographs* ([IARC, 1972, 1987, 2010](#)). There have been no additional carcinogenicity studies in experimental animals reported since the most recent evaluation ([IARC, 2010](#)).

Auramine was tested for carcinogenicity by oral administration in two experiments in mice, two in rats, one in rabbits, and one in dogs, and by subcutaneous administration in one experiment in rats. Results of adequately conducted carcinogenicity studies are summarized in [Table 3.1](#).

Oral administration of auramine caused a significant increase in the incidence of hepatomas in male and female mice and in male rats ([Bonser et al., 1956](#); [Williams & Bonser, 1962](#); [Walpole, 1963](#)), and of lymphomas in female mice ([Bonser et al., 1956](#)). The subcutaneous-injection study in rats (in which local sarcomas were observed) and the oral studies in rabbits and dogs were found to be inadequate for the evaluation of the carcinogenic hazards of auramine.

For data on Michler's base and Michler's ketone, see [IARC \(2010\)](#).

4. Other Relevant Data

A general Section on "Aromatic amines: metabolism, genotoxicity, and cancer susceptibility" appears as Section 4.1 in the *Monograph* on 4-aminobiphenyl in this volume.

While no studies were found on the metabolism of auramine in laboratory animals or humans, the finding that auramine-induced intrachromosomal recombination in *Saccharomyces cerevisiae* was reduced in the presence of a free-radical scavenger (*N*-acetylcysteine) suggests that auramine may induce genotoxic effects in yeast by generating

Table 3.1 Carcinogenicity studies of auramine in experimental animals

Species, strain (sex) Duration Reference	Route Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Strain NR (M, F) Lifetime Bonser et al. (1956)	Feed A group of 15 M and 15 F mice were fed a diet containing 0.1% auramine for 52 wk (total dose, 728 mg/mouse). A group of 30 M and 30 F mice received twice weekly a subcutaneous injection of arachis oil, and served as controls	Hepatomas: M-0/30, 4/15; F-0/30, 3/15 Lymphomas: M-1/30, 3/15; F-4/30, 8/15	[<i>P</i> < 0.05, both sexes] [<i>P</i> < 0.01, F]	Age NR, purity NR (commercial grade). Small number of animals per group. High mortality during study, especially in females. Inadequate controls.
Mouse, "Stock" albino and CBA (M, F) Lifetime Williams & Bonser (1962) , Walpole (1963)	Feed A group of 15 M and 15 F "Stock" mice were fed a diet containing 0.1% auramine for 52 wk (total dose ~1820 mg/mouse). Sixteen M and F mice served as untreated controls. A group of 12 M and 15 F CBA mice were fed a diet containing 0.2% auramine for 52 wk (total dose ~3640 mg/mouse). Ninety M and F mice served as untreated controls	Hepatoma: "Stock" mice M-0/8, 4/7 F-0/8, 3/10 CBA mice M-4/35, 7/12 F-3/55, 11/15	[<i>P</i> < 0.05] [NS] [<i>P</i> < 0.005] [<i>P</i> < 0.0001]	Purity NR (commercial grade) Animals at risk are the animals surviving ≥ 50 wk.
Rat, Wistar-Kyoto (M) Lifetime Williams & Bonser (1962) , Walpole (1963)	Feed Groups of 12 M rats were given a basic diet for life or a diet containing 0.1% auramine for 87 wk (estimated total auramine intake, 10 g/rat)	Hepatoma: 0/12, 11/12	NR, [<i>P</i> < 0.0001]	Purity NR (commercial grade) Animals at risk are the animals surviving ≥ 90 wk.
Rat, Sprague-Dawley (M, F) 24 mo Kirsch et al. (1978)	Feed Groups of 20 M and F rats were given a diet containing auramine (technical grade) at 0, 50, 100 and 200 ppm	All sites (benign and malignant): M-6/20, 13/20, 8/20, 10/20 F-19/20, 18/20, 15/20, 19/20	NS	Purity, 87% (technical grade) Age NR

F, female; M, male; mo, month or months; NR, not reported; NS, not significant; wk, week or weeks

free radicals (Brennan & Schiestl, 1998). Commercial preparations of auramine were mutagenic in several strains of *S. typhimurium*, when tested with metabolic activation systems. Other *in vitro* effects of auramine include induction of deletions and aneuploidy in *Saccharomyces cerevisiae*, DNA strand breaks in rat hepatocytes, unscheduled DNA synthesis in rat and hamster hepatocytes, mutations in Chinese hamster ovary cells, and micronucleus formation and transformation of Syrian hamster embryo cells. DNA strand breaks were induced in liver, kidney, and urinary bladder cells of exposed rats (Parodi *et al.*, 1982; Martelli *et al.*, 1998) and in liver and bone-marrow cells of exposed mice (Parodi *et al.*, 1982; Sasaki *et al.*, 1997).

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of auramine production. Auramine production causes cancer of the urinary bladder.

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

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

There are insufficient mechanistic data relevant to the carcinogenicity of auramine in humans. Auramine induces DNA strand-breaks in experimental animals.

Auramine production is *carcinogenic to humans (Group 1)*.

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

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