4,4'-Methylene bis(N,N'-dimethyl)aniline; CASRN 101-61-1

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR 4,4'-Methylene bis(N,N'-dimethyl)aniline

File First On-Line 08/01/1989

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	08/01/1989*

*A comprehensive review of toxicological studies was completed (July 17, 2006) - please see section II.D.2. for more information.

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — 4,4'-Methylene bis(N,N'-dimethyl)aniline
CASRN — 101-61-1

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — 4,4'-Methylene bis(N,N'-dimethyl)aniline
CASRN — 101-61-1

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 4,4'-Methylene bis(N,N'-dimethyl)aniline
CASRN — 101-61-1
Last Revised — 08/01/1989

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — B2; probable human carcinogen

Basis — sufficient evidence from animal experiments: thyroid tumors in male and female rats, and liver carcinoma/adenoma in the female mice with a significant positive trend in male mice. There is evidence of mutagenic activity. There are no human data.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Sufficient. NCI (1979a) conducted a bioassay of 4,4'-methylenebis(N,N- dimethylaniline) in rats and mice. Groups of 50 male and 50 female F344 rats were given 375 and 750 ppm of the chemical in the diet for 59 weeks followed by a 45-week observation period. Twenty animals of each sex served as the controls. The MTD was achieved in the high-dose group as indicated by a 20% decrease in weight gain in contrast to the control group. The survival rates after 104 weeks were comparable for the control and treated groups and ranged from 74 to 85% for females and 78 to 88% for males.

In male rats, a dose-related increase in the incidence of follicular cell carcinoma of the thyroid was observed. Individual incidences were 1/18, 4/50, and 21/46 in the 0, 375, and 750 ppm groups, respectively, with a statistically significant increase at the high dose. Combined follicular cell adenoma/carcinoma incidences were 1/18 in the control group, 4/50 in the low- dose group, and 34/36 in the high-dose group; the increase in the high-dose animals was statistically significant.

In the female rats, there were significant trends in the incidence of follicular cell carcinomas alone (0/20, 3/46, and 23/45 for controls, low-dose and high-dose animals, respectively) and when combined with the adenomas (0/20, 4/46, and 36/45 for controls, low-dose, and high-dose rats, respectively); pairwise comparisons of high-dose to control groups were also significant.

As part of the same study (NCI, 1979a), 50 male and 50 female B6C3F1 mice were administered 1250 and 2500 ppm in the diet for 78 weeks followed by a 13- week observation period. Twenty animals of each sex served as controls. Survival was comparable among control and treated animals; the treated animals had a decrease in weight gain.

In both male and female mice there was a significant dose-related trend in the incidence of hepatocellular carcinoma/adenoma; incidences were 5/20, 12/50, and 22/48 in males in the control, low- and high-dose groups, respectively, and the incidences in females were 1/19, 19/49, and 23/46 in the control, low- and high-dose groups, respectively. Statistical analyses in the males showed no significant elevation among the groups by pair wise comparison. In the females, however, pair wise comparisons between the high- dose group and the control group and the low-dose group and the control group indicated that there was a statistically significant elevation in both dose groups.

II.A.4. Supporting Data for Carcinogenicity

Maronpot et al. (1983) reported that 4,4'-methylenebis(N,N- dimethylaniline) administered at the maximum tolerated dose was negative in the Strain A mouse pulmonary tumor assay. The authors noted, however, that of 54 chemicals that had tested positive in a 2-year rodent bioassay, 50% showed negative results in the mouse lung tumor bioassay; 78% of the aromatic amines tested (14/18) were negative. (The Strain A mouse pulmonary assay is not considered a reliable indicator of carcinogenic potential.)

4,4'-Methylenebis(N,N-dimethylaniline) was found to be mutagenic in Salmonella typhimurium strains TA98 and TA100 in the presence of hepatic microsomal preparations from mice and rats (Dunkel and Simmon, 1980; Waalkens et al., 1981; McCarthy et al., 1983). Positive results were produced in host- mediated assays in the mouse using S. typhimurium TA1538 (Simmon et al., 1979; Legator et al., 1982). It also produced a slight increase in sister chromatid exchange in cultured rabbit lymphocytes (Waalkens et al., 1981) and induced transformation of a hamster embryo cell line. In addition, positive results were obtained in several mammalian cell systems for mutagenesis, DNA damage, and cell transformation (Pienta and Kawalek, 1981; Williams et al., 1982; Mitchell et al., 1982).

This compound is structurally related to 4,4'-methylenedianiline and 4-4'- bis(dimethylamino) benzophenone (Michler's ketone), which are carcinogenic in rats and mice (NCI, 1979b; Weisburger et al., 1984).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 4.6E-2 per (mg/kg)/day

Drinking Water Unit Risk — 1.3E-6 per ug/L

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	8E+1 ug/L
E-5 (1 in 100,000)	8 ug/L
E-6 (1 in 1,000,000)	8E-1 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type — thyroid, follicular cell carcinoma/adenoma
Test animals — rat/F344, female
Route — diet
Reference — NCI, 1979a

Administered Dose (ppm)	Animal Transformed Dose (mg/kg)/day	Human Equivalent (mg/kg)/day	Tumor Incidence
0	0	0	0/20
375	10.64	1.63	4/46
750	21.27	3.25	36/45

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Modeling was conducted using an exposure duration of 59 weeks averaged over the study length and animal lifetime of 104 weeks. Food consumption equivalent to 5% of the body weight, a human body weight of 70 kg and the reported animal weight of 0.25 kg were used. Note that the slope factor presented differs from that described in the 1985 Health and Environmental Effects Profile (1.2E-1 per (mg/kg)/day). The preferred value of 4.6E-2 per (mg/kg)/day was obtained by use of Global 86 which selected a 3-stage solution.

The unit risk should not be used if the water concentration exceeds 8E+3 ug/L, since above this concentration the slope factor may differ from that stated.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Adequate numbers of animals were treated for about half their lifetime and observed for a period of time approximating their natural lifespan.

There is uncertainty associated with adjusting for an experimental dose administered for a relatively short exposure duration over the lifetime of the animal. The uncertainty is such that if the chemical acts during the early stages of carcinogenesis, the risk will be overestimated, whereas if it acts during the later stages, the risk will be underestimated.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1985

The 1985 Health and Environmental Effects Profile for 4,4'-Methylenebis(N,N-dimethylaniline) received OHEA review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 05/04/1988, 01/04/1989, 04/05/1989

Verification Date — 04/05/1989

A comprehensive review of toxicological studies published through July 2006 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing carcinogenicity assessment for 4,4'-Methylene bis(N,N'-dimethyl)aniline and a change in the assessment is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — 4,4'-Methylene bis(N,N'-dimethyl)aniline
CASRN — 101-61-1

VI.A. Oral RfD References

None

VI.B. Inhalation RfD References

None

VI.C. Carcinogenicity Assessment References

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VII. Revision History

Substance Name — 4,4'-Methylene bis(N,N'-dimethyl)aniline
CASRN — 101-61-1

Date	Section	Description
08/01/1989	II.	Carcinogen summary on-line
12/03/2002	II.D.2.	Screening-Level Literature Review Findings message has been added.
09/28/2006	II.D.2.	Screening-Level Literature Review Findings message has been removed and replaced by comprehensive literature review conclusions.

VIII. Synonyms

Substance Name — 4,4'-Methylene bis(N,N'-dimethyl)aniline
CASRN — 101-61-1
Last Revised — 08/01/1989

- 101-61-1
- ANILINE, 4,4'-METHYLENEBIS(N,N-DIMETHYL-
- BAZE MICHLEROVA (Czech)
- BENZENAMINE, 4-4'-METHYLENEBIS(N,N-DIMETHYL)-
- p,p'-BIS(DIMETHYLAMINO)DIPHENYLMETHANE
- 4,4'-BIS(DIMETHYLAMINO)DIPHENYLMETHANE
- BIS(p-DIMETHYLAMINOPHENYL)METHANE
- BIS(4-(DIMETHYLAMINO)PHENYL)METHANE
- BIS(p-(N,N-DIMETHYLAMINO)PHENYL)METHANE
- BIS(4-(N,N-DIMETHYLAMINO)PHENYL)METHANE
- p,p'-BIS(N,N-DIMETHYLAMINOPHENYL)METHANE
- p,p-DIMETHYLAMINODIPHENYLMETHANE
- DIPHENYLMETHANE, TETRAMETHYLDIAMINO-
- METHANE BASE
- METHANE, BIS(p-(DIMETHYLAMINO)PHENYL)-

- METHYLENE BASE
- 4,4'-METHYLENEBIS(N,N-DIMETHYLANILINE)
- 4,4'-METHYLENEBIS(N,N-DIMETHYL)BENZENAMINE
- MICHLER'S BASE
- MICHLER'S HYDRIDE
- MICHLER'S METHANE
- NCI-C01990
- REDUCED MICHLER'S KETONE
- TETRA-BASE
- TETRAMETHYLDIAMINODIPHENYLMETHANE
- p,p-TETRAMETHYLDIAMINODIPHENYLMETHANE
- N,N,N'N'-TETRAMETHYL-p,p'-DIAMINODIPHENYLMETHANE
- N,N,N'N'-TETRAMETHYL-4,4'-DIAMINODIPHENYLMETHANE