N,N-Dimethyl-para-toluidine

Document History
Published: 2009
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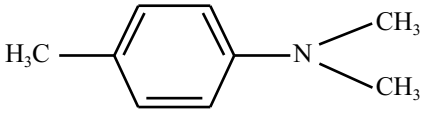
I. IDENTIFICATION

Chemical Name: N,N-Dimethyl-para-toluidine
Synonyms: DMPT, N,N,4-trimethylaniline; 4-Dimethylaminotoluene; N,N,4-Trimethyl benzenamine
CAS Number: 99-97-8
Molecular Formula: $C_9H_{13}N_1$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1–6]

Physical State and Appearance: Colorless to light yellow liquid
Odor Description: Sweet
Odor Threshold: No data found
Molecular Weight: 135.2
Conversion Factors: 1.0 ppm = 5.53 mg/m³
1.0 mg/m³ = 0.181 ppm
Melting Point: -6.6°C (20°F)
Boiling Point: 211°C (412°F) at 760 mm Hg
Vapor Pressure: 0.178 mm Hg at 25°C (77°F)
Saturated Vapor Concentration: 230 ppm at 25°C (77°F)
Flammability Limits: LEL: No data found
Flash Point: (closed cup) 83°C (181°F)
Autoignition Temperature: No data found
Specific Gravity: 0.937 at 20°C (68°F)
Solubility in Water: ~350–460 ppm by weight at 25°C (77°F)
Stability: Stable
Reactivity and Incompatibilities: Strong oxidizers
Partition Coefficient (Log $K_{o/w}$) = 2.81 at 25°C (77°F)

III. USES

N,N-Dimethyl-para-toluidine is used as a polymerization accelerator for bone cements, dental materials, artificial fingernail formulations, and cyanoacrylate adhesives.[3]

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. *Oral Toxicity*

LD_{50} – Rat: 1650 mg/kg[3,6]

Methemoglobinemia was noted.

LD_{50} – Rat: Between 400 and 3200 mg/kg[7]

Animals were dosed by gavage at 400, 800, 1600 or 3200 mg/kg, one animal at each dose. No autopsies were conducted and no further information was reported.

2. *Eye Irritation*

One manufacturer reported N,N-dimethyl-para-toluidine to be "moderately irritating." No further data was provided.[3]

3. *Skin Absorption*

LD_{50} – Rabbit >2000 mg/kg[6]

There was "no evidence of skin absorption" based upon normal weight gain over 14-day observation period following application of 0.5 mL of test material, under occluded wrap for 24 hours, on depilated abdomen of guinea pigs.[7]

4. *Skin Irritation*

One manufacturer reported it as "moderately irritating." No further data was provided.[3]

Another report indicated a moderate skin irritation response following application of 0.5 mL of test material, under occluded wrap for 24 hours, on depilated abdomen of guinea pigs.[7]

5. *Skin Sensitization*

One manufacturer reported having observed both positive and negative guinea pig sensitization studies, but no details are available.[3]

6. Inhalation Toxicity

LC_{50} – Rat (4-hours): 1400 mg/m^3 (250 ppm)[3,6,8]

Ten animals per group were exposed at concentrations of 300, 990, 1730, and 5270 mg/m^3 (54, 180, 312, and 953 ppm) for 4 hours. Effects in the high dose animals and the number of surviving animals in each group were not reported, except that mottled lungs and gas-filled gastrointestinal organs were reported to have been observed in both the 1730 and 5270 mg/m^3 exposure groups. Conditions of rats in the 1730 mg/m^3 exposure group were reported to include hypoactivity, prostrate/comatose condition, dyspnea or rapid respiration and salivation. At 990 or 300 mg/m^3 animals were observed most frequently to have nasal discharge and red material around the nose. No gross lesions were observed at either 300 or 990 mg/m^3.[8]

B. Subacute Toxicity:

No data found for N,N-dimethyl-para-toluidine.

For the similar compound para-toluidine (see section on Metabolism and Pharmacokinetics), rats were fed diets containing an equivalent dose of 14, 67 or 125 mg/kg-day. At the highest dose the authors observed reduced weight gain and at the middle and high doses they observed increased relative liver weight. A no-observed-adverse-effect-level (NOAEL) of 14 mg/kg-day was reported.[9]

In an inhalation study using another very similar compound, aniline, male rats (16 per group) were exposed to 0, 17, 45, or 87 ppm of aniline in air for 6 hours per day, 5 days per week for 2 weeks. Methemoglobin levels were significantly elevated in the animals exposed to 45 or 87 ppm, but were not statistically elevated in the animals exposed at 17 ppm. Multiple effects were observed in the animals exposed to either 45 or 87 ppm, including anemia and increased relative spleen weight. Minimal splenic histopathology was noted in the 17 ppm animals. The authors concluded that 17 ppm approximates a no-effect level under the conditions of this study.[10]

C. Subchronic Toxicity:

No data was found for N,N-dimethyl-para-toluidine.

The very similar compound, N,N-dimethyl aniline was the subject of an oral toxicity study using rats and mice. The study was intended to determine the maximum tolerated dose for a subsequent 2-year bioassay. Animals were dosed by gavage at levels of 0, 31, 62, 125, 250, and 500 mg/kg/day, 5 days per week, for 13 weeks. In rats, even at the lowest dose, adverse effects were seen in the spleen, liver, kidney, and bone marrow. In mice, adverse effects were seen in the liver, spleen, and kidneys, however, effects were equivocal at 31 mg/kg/day.[11]

D. Chronic Toxicity/Carcinogenicity:

In a lifetime feeding study reported in 1954, male and female rats from three different strains (28 animals per strain) were fed diets providing a nominal dose of 7 mg/day (about 28 mg/kg-day) of N,N-dimethyl-para-toluidine. The authors concluded that the compound did not induce tumors.[12]

In a lifetime bioassay of the very similar compound N,N-dimethyl aniline, rats were dosed by gavage at 3 or 30 mg/kg-day for 2 years. High dose animals were found to have a significant increase in hematopoiesis in the spleen. This effect was slightly elevated in low dose animals as well, but not to a statistically significant degree. There was a significant increase in hemosiderosis in the spleen at both dose levels. High dose males also were found to have statistically significantly increased fibrosis of the spleen. Mice dosed at 15 or 30 mg/kg-day did not show these effects. N,N-dimethyl aniline was found to have some evidence of carcinogenicity in male rats (sarcomas of the spleen and osteosarcomas), equivocal evidence of carcinogenicity in female mice (squamous cell papillomas of the forestomach) and no evidence of carcinogenicity in female rats or male mice.[11]

In a lifetime bioassay of another very similar compound, ortho-toluidine (hydrochloride), rats were fed diets containing 3000 or 6000 ppm (approximately 150 or 300 mg/kg-day) for 2 years. Survival and weight gain were decreased and non-neoplastic effects were seen in the spleen and liver. Mice fed at either 1000 or 3000 ppm (approximately 390 or 780 mg/kg-day) were found to have adverse effects on the spleen and ovaries, and also had decreased survival and weight gain. Ortho-Toluidine was found to be carcinogenic in both male and female rats (sarcoma of the spleen in both sexes, mesotheliomas of the abdominal cavity and scrotum in males and transitional cell carcinomas of the bladder in females), and in male and female mice (hemangiosarcomas in males and hepatocellular carcinomas or adenomas in females).[13]

E. Reproductive/Developmental Toxicity

No was data found for N,N-dimethyl-para-toluidine.

For the similar compound aniline, a study was conducted in which female rats were dosed by gavage on Days 7 through 20 of gestation at levels of 10, 30, or 100 mg/kg-day. This resulted in increased methemoglobin levels in the dams and in increased relative liver weight and erythrocyte size in the pups at the highest dose. No teratogenic or embryotoxic effect was seen at any of the dose levels.[14]

F. Genotoxicity/Mutagenicity

N-N-Dimethyl-para-toluidine was not genotoxic in an Ames assay using *S. typhimurium* strains TA-97, 98, or 100, with or without S-9 metabolic activation.[15] It was found to be positive in an Ames assay using *S. typhimurium* strain TA-1535, either with or without S-9 activation.[3] Another report of an Ames assay indicated negative findings in strains TA-98, TA-100, TA-1535, TA-1537 and TA-1538, with or without S-9 activation.[16] Although a full report was not available at the time of this writing, an NTP summary also reports negative findings in Ames Assays.[17]

N-N-Dimethyl-para-toluidine was judged positive for inducing chromosomal aberrations and micronuclei in an assay using V-79 Chinese hamster cells *in vitro*.[15] It was also determined to be positive *in vitro* in a standard mouse lymphoma TK +/- assay, with or without S-9 activation.[16]

Although a full report is not available at the time of this writing, a summary report indicates negative findings in a mouse micronucleus assay (*in vivo*) using B6C3F1 mice.[18]

G. Metabolism/Pharmacokinetics

In a study of the metabolism of N,N-dimethyl-para-toluidine, it was found that the primary metabolites are para-(N-acetyl hydroxyamino) hippuric acid, dimethyl-para-toluidine N-oxide and N-methyl-para-toluidine. The primary significance is that this is very similar to the metabolism of similar compounds such as N,N-dimethyl aniline or para-toluidine.[19]

Rats and mice were dosed via gavage to ^{14}C labeled N,N-dimethyl-para-toluidine and closely monitored for 24 hours. At the end of 24 hours, 88–97% of the dose was determined to have been excreted in the urine either as a metabolite or as the parent compound. 3–9% was in the feces. Less than 1% was excreted as volatile organic compounds and 4–9% stayed within the body. Conversion to CO_2 was negligible.[20]

H. Structure/Activity Relationships

A number of toluidines have been tested under National Toxicology Program and National Cancer Institute programs. NTP reports that 12 compounds structurally similar to N,N-dimethyl-para-toluidine had been screened for data relevant to carcinogenicity or genotoxicity as of 1999. NTP reported that six of seven toluidines tested for carcinogenicity were positive in at least one species. Ten of 12 structurally similar compounds were reported to be positive in at least one genotoxicity assay.[3]

V. HUMAN USE AND EXPERIENCE

A 16-month-old child accidentally ingested a mixture containing N,N-dimethyl-para-toluidine, resulting in a dose estimated at about 6 mg/kg. There was marked cyanosis upon admission to the hospital. The pO_2 was 67% and the methemoglobin level was determined to be 43%. The appearance of cyanosis did not occur until about 2 ½ hours after the ingestion occurred, indicating that metabolic conversion of the N,N-dimethyl-para-toluidine had to occur before methemoglobin formed. This is consistent with what is also observed for aniline and other organic amines with similar structures.[21]

There have been a number of anecdotal reports of possible sensitization in humans either as a result of exposure via bone cements in hip replacement surgery or in dental restoration work.[22–25]

It has been reported for the similar compound, toluidine, that exposure to 40 ppm for 60 minutes resulted in “severe intoxication,” while “prolonged” exposure at 10 ppm was also reported to result in mild symptoms.[9]

For another similar compound, aniline, a secondary reference cites exposures of 7 to 53 ppm for several hours as resulting in slight symptoms while exposure to 100 to 160 ppm for one hour resulted in “serious disturbances.”[26]

VI. RATIONALE

While there are relatively few studies explicitly on the effects of N,N-dimethyl-para-toluidine, the available metabolic data indicates that its effects can be anticipated to be very similar to related compounds such as aniline, N,N-dimethyl aniline or toluidine. A considerable number of chronic and sub-chronic animal studies and several reports of human experience are available for closely related compounds.

Evidence from an accidental human exposure indicates that an oral dose as low as 6 mg/kg can result in significantly elevated methemoglobin levels. An airborne exposure in the range of 8 ppm over an 8-hour day would be sufficient to deliver a dose in this range.

Analogy to human exposure data available for similar compounds, specifically aniline and toluidine, indicates

that airborne exposures in the 10 ppm range over several hours could result in mild symptoms.

Chronic and subchronic animal studies of similar compounds demonstrated significant effects on the spleen, and other organs. Rats dosed orally at approximately 30 mg/kg-day with N,N-dimethyl aniline were found have significant effects on the spleen. Milder effects in rats were reported in the same study at doses as low as 3 mg/kg-day. For an 8-hour day, exposure to about 4 ppm would be sufficient to deliver a dose of 3 mg/kg-day. Mice dosed at 15 or 30 mg/kg-day did not show such effects.

Review of effects of similar compounds indicates that N,N-dimethyl-para-toluidine is unlikely to be embryotoxic or teratogenic.

There is insufficient evidence to draw any conclusion regarding potential carcinogenicity. Genotoxicity studies indicate both positive and negative findings. However, most similar compounds that have been tested have been found to have at least some degree of carcinogenic potential in bioassays. Most similar compounds have also been found to be genotoxic in at least one assay. While negative, the only chronic study specifically for N,N-dimethyl-para-toluidine was published in 1954 and is not a GLP study. While the weight of the evidence is inconclusive, potential for carcinogenicity remains a concern for this substance.

While there is anecdotal evidence of sensitization, there is insufficient evidence to indicate whether or not it is a significant concern in the workplace setting.

The acute dermal LD_{50} for N,N-dimethyl-para-toluidine is over 2000 mg/kg indicating that this material is not readily absorbed via the dermal route in toxicologically significant amounts.

An OEL of 0.5 ppm is recommended to provide a reasonable margin of protection against elevated methemoglobin levels in exposed workers and the potential chronic effects (primarily in the spleen) that long term animal testing indicates is likely be associated with such elevated methemoglobin levels. An eight-hour limit in this range is also sufficiently low to effectively prevent adverse effects that would be expected to be associated with excursions, so a short-term limit is not needed.

VII. RECOMMENDED OEL

0.5 ppm (~3 mg/m^3) as an 8-hour time weighted average.

VIII. REFERENCES

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