

N-Nitroso-N-Methylaniline (*N-Methyl-N-nitrosobenzenamine*)

N-Nitroso-N-methylaniline (NMA) is used in rubber manufacturing and is found in smoked meat. NMA is also used in the laboratory for studying enzymatic denitrosation.

N-Nitroso-N-methylaniline passed the animal data screen, underwent a preliminary toxicological evaluation, and is being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation

Epidemiological data

- No cancer epidemiology studies were identified.

Animal carcinogenicity data

- Long-term studies
 - 50-week drinking water exposure (5 days/week) studies in F 344 rats followed by natural death: Kroeger-Koepke *et al.* (1983)
 - *Increase in esophageal tumors (mostly carcinomas) (by pairwise comparison) in male and female rats*
 - 20-week drinking water exposure (6 days/week) study in F344 female rats followed by natural death: Michejda *et al.* (1986)
 - *Increase in esophageal squamous cell carcinoma (by pairwise comparison) in female rats*
 - Lifetime drinking water studies in male and female rats: Boyland *et al.* (1964)
 - *Increase malignant esophageal tumors (by pairwise comparison) in male and female rats*
 - 50-week gavage study exposing once/week in female Syrian golden hamster followed by natural death: Lijinsky and Kovatch (1988)
 - *Increase in liver tumors and spleen hemangiosarcoma (by pairwise comparison)*

Other relevant data

- Genotoxicity
 - Reverse mutation assay in *Salmonella typhimurium* with or without rat or hamster liver S-9 activation (*negative*): Andrews *et al.* (1984)
 - Gene conversion and reverse mutation in *Sacchamomyces cerevisiae* (*positive*): Mehta and Borstel (1984)
 - N-Nitroso-N-methylaniline activated with microsomes forms DNA adducts: Stiborova *et al.* (1999)

- Structure-activity considerations
 - Similarity to 23 Proposition 65 N-nitroso carcinogens, including 16 nitrosamines:
 - N-Nitrosomethylethylamine
 - N-Carboxymethyl-N-nitrosourea
 - 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea
 - N-Methyl-N'-nitro-N-nitrosoguanidine
 - N-Nitrosodi-*n*-butylamine
 - N-Nitrosodiethanolamine
 - N-Nitrosodiethylamine
 - N-Nitrosodimethylamine
 - *p*-Nitrosodiphenylamine
 - N-Nitrosodiphenylamine
 - N-Nitrosodi-*n*-propylamine
 - N-Nitroso-N-ethylurea
 - 3-(N-Nitrosomethylamino)-1-(3-pyridyl)1-butanone
 - N-Nitroso-N-methylurea
 - N-Nitroso-N-methylurethane
 - N-Nitroso-N-methylvinylamine

References¹

Andrews AW, Lijinsky W. (1984). N-nitrosamine mutagenicity using the Salmonella/mammalian microsome mutagenicity assay. In: genotoxicity of N-nitroso compounds (Rao, TK, Lijinsky W, Epler JL eds) Plenum press. New York.

¹ Excerpts or the complete publication (presenting epidemiology or toxicology information) have been provided to members of the Carcinogen Identification Committee, in the order in which they are discussed in this document.

Boyland E, Roe FJC, Gorrod JW, Mitchley BCV (1964). The carcinogenicity of nitrosoanabasine, a possible constituent of tobacco smoke. *BJC* **18**(2) 265-270.

Kroeger-Koepke MB, Reuber MD, Iype PT, Lininsky W, Michejda CJ (1983). The effect of substituent in the aromatic ring on carcinogenicity of N-nitrosomethylaniline in F344 rats. *Carcinogenesis* **4**(2): 157-160

Lijinsky W, Kovatch RM (1988). Comparative carcinogenesis by nitrosomethylalkylamines in Syrian hamsters. *Can Res* **48**: 6648-6652.

Michejda CJ, Kroeger-Koepke MB, Kovatch RM (1986). Carcinogenic effects of sequential administration of two nitrosamines in Fischer 344 rats. *Can Res* **46**: 2252-2256.

Mehta RD, Borstel RC (1984). Genetic activity in yeast assay of reputed non mutagenic, carcinogenic N-nitroso compounds and methapyrilene hydrochloride. *IARC Sci Publ* **57**: 721-729.

Stiborova M, Schmeiser HH, Wiessler M, Frei E (1999). Direct evidence for the formation of deoxyribonucleotide adducts from carcinogenic N-nitroso-N-methylaniline revealed by the ³²P-postlabeling technique. *Can Lett* **138**: 61-66.