

## 2,6-Dimethyl-n-nitrosomorpholine

2,6-Dimethyl-n-nitrosomorpholine is a cyclic nitrosamine. It is formed by nitrosation of cyclic secondary amines and their derivatives, and occupational exposure is expected to occur in certain industrial environments. These include the rubber industry and machine workshops where metal-working fluids are used.

2,6-Dimethyl-n-nitrosomorpholine 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 in hamsters
  - Gavage studies in male and female Syrian golden hamsters (once/per week for life): Reznik *et al.* (1978); Mohr *et al.* (1977)
  - Gavage studies in male and female European hamsters (once/per week for life): Althoff *et al.* (1985)
  - Subcutaneous injection studies in male and female Syrian golden hamsters (once/per week for life): Althoff *et al.* (1978)
  - Subcutaneous injection studies in male and female European hamsters (once/per week for life): Althoff *et al.* (1985)
  - Continuous exposure for one week via a subcutaneous implanted osmotic pump in male Syrian golden hamsters (observed for 25 weeks): Kokkinakis and Scarpelli (1989)
  
- Long-term studies in rats
  - Drinking water studies in male and female Sprague-Dawley rats (five days per week for 30 weeks, and observed for life): Lijinsky and Taylor (1975)
  - Drinking water studies in male and female Fischer 344 rats (five days per week for life): Lijinsky and Reuber (1982)
  - Subcutaneous injection studies in male and female Sprague-Dawley rats (once/per week for life): Ovelar *et al.* (1981)
  - Single intraperitoneal injection study in male Wistar rats (observed for 55 weeks): Konishi *et al.* (1987)
  
- Long-term gavage studies in guinea pigs
  - Study in males (dosed weekly for 23 weeks and observed for up to 54 weeks): Rao *et al.* (1980)
  - Study in males (dosed twice per week for either 12 weeks or 35 weeks, and observed for life): Cardy and Lijinsky (1980)

- Long-term feeding studies in Rainbow trout
  - Nine and 18-month studies: Hendricks *et al.* (1995)
- Short-term rat hepatocarcinogenesis assay
  - Liver tumor initiation study of endogenously formed 2,6-dimethyl-n-nitrosomorpholine: Yamamoto *et al.* (1995)

### Other Relevant Data

- Genotoxicity
  - *Salmonella* reverse mutation assays: Andrews *et al.* (1978); Andrews and Lijinsky (1984, see Table V); Mori *et al.* (1983); Mori *et al.* (1987)
  - *In vivo* male Lewis rat pancreatic acinar cell single strand DNA break assay: Curphey *et al.* (1987)
  - *In vivo* male Syrian golden hamster pancreatic acinar cell single strand DNA break assay: Curphey *et al.* (1987)
- Structure activity considerations
  - Structurally similar to three other cyclic nitrosamines that are Proposition 65 carcinogens: N-Nitrosopiperidine, N-Nitrosopyrrolidine, and N-Nitrosomorpholine
  - Structurally similar to N-nitrosohexamethyleneimine,<sup>1</sup> another cyclic nitrosoamine with positive evidence of carcinogenicity

### References<sup>2</sup>

Althoff J, Grandjean C, Gold B (1978). Carcinogenic effects of subcutaneously administered N-nitroso-2,6-dimethylmorpholine in Syrian golden hamster. *J Natl Cancer Inst* **60**:197-199.

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<sup>1</sup> See material prepared for this chemical, also in this CIC consultation package

<sup>2</sup> Copies of these listed references, as either the abstract, the relevant sections of the publication, or the complete publication, have been provided to members of the Carcinogen Identification Committee. These references have been provided in the order in which they are discussed in this document.

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Rao MS, Scarpelli DG, Lijinsky W (1980). N-nitroso-2, 6-dimethylmorpholine-induced hemangiosarcomas in the liver of random bred pigs. *J Natl Cancer Inst* **64**:529-531.

Reznik G, Mohr U, Lijinsky W (1978). Carcinogenic effect of N-nitroso-2,6-dimethylmorpholine in Syrian golden hamster. *J Natl Cancer Inst* **60**:371-377.

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