9	CAS No.: 62-75-9	Substance: *N*-Nitrosodimethylamine

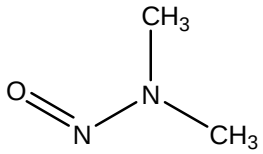
Chemical Substances Control Law Reference No.:

PRTR Law Cabinet Order No.:

Molecular Formula: $C_2H_6N_2O$

Molecular Weight: 74.08

Structural formula:



1. General information

The water solubility of this substance is 1×10^6 mg/L, the partition coefficient (1-octanol/water) (log K_{ow}) is -0.57, and the vapor pressure is 5.48 mmHg (=730 Pa) (25°C). There is a report of biodegradability showing more than 50% remained (14 days, colorimeter method). In addition, the substance was not hydrolyzed in lake water (3.5 months).

In the past, this substance was used as an intermediate for manufacturing rocket fuel, as a soil nitrification inhibitor, as a plasticizer in the manufacture of rubbers and polymers, as a solvent in the fiber and plastic industries, as an antioxidant, as a softening agent for copolymers, and as a lubricating oil additive.

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2. Exposure assessment

Because this substance is not classified as a Class 1 Designated Chemical Substance the Law Concerning Reporting, etc. of Releases to the Environment of Specific Chemical Substances and Promoting Improvements in Their Management (PRTR Law), release and transfer amounts could not be obtained. Predictions of distribution by medium using a Mackay-type level III fugacity model indicated that if equal quantities were released to the atmosphere, water bodies, and soil, the proportions distributed to soil and water bodies would be greater.

Data for setting the predicted maximum exposure to humans via inhalation could not be obtained. The predicted maximum oral exposure was estimated to be around 0.00012 μg/kg/day based on data from calculations for drinking water. Data for setting the predicted maximum exposure to humans via inhalation could not be obtained. The predicted daily exposure was estimated to be 0.00015 μg/kg/day based on calculations from data for drinking water, albeit for a limited area, while the daily exposure calculated from a past eating study for a limited area was 0.016 μg/kg/day.

The predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, could not be obtained. While the past data, public freshwater concentration and seawater concentration were less than around 0.02 μg/L. In addition, there is a report of 1.1 μg/L for public freshwater bodies from an environmental study of a limited area.

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3. Initial assessment of health risk

This substance is irritating to eyes, skin and respiratory tract, and it may cause jaundice through its effects on liver. When inhaled, it may cause sore throat, coughing, nausea, diarrhea, vomiting, headache and weakness, and when orally taken, it may also cause gastrospasm. Contact of eyes and skin with the substance makes them red and causes pain.

As for its non-carcinogenic effects, information on its general toxicity and reproductive/developmental toxicity has been obtained. Animal experiments have provided evidences for its carcinogenicity, so the substance is likely to be carcinogenic to humans. Initial assessments have been conducted both on its carcinogenic and non-carcinogenic effects.

As for its non-carcinogenic effect from oral exposure, a NOAEL of 0.005 mg/kg/day (for nodular hyperplasia in liver) obtained from mid- and long-term toxicity tests on rats was identified as the lowest reliable dose of the substance without any effect. As there was no information to indicate the threshold of its carcinogenic effects, a NOAEL of 0.005 mg/kg/day for its non-carcinogenic effects was deemed to be its ‘non-toxic level*’. As for carcinogenicity of the substance, 1.5 to 5.1 ∗ 10 $(mg/kg/day)^{-1}$ was identified as its slope factor for liver tumor from experiments on Colworth rats, when it was assumed that there was no threshold for the carcinogenicity. Since the present assessment is an initial

one, 5.1 * 10 $(mg/kg/day)^{-1}$ was identified as a conservative slope factor. As for other approach, TD_{05} required for calculation of EPI (Exposure/Potency Index) has been reported to be 0.034 mg/kg/day by experiments on Colworth rats (for biliary cystadenoma). As for its non-carcinogenic effects from inhalation exposure, its 'non-toxic level*' could not be identified. As for its carcinogenic effect, 1.4 * 10^{-2} $(\mu g/m^3)^{-1}$ was identified as its unit risk, when it was assumed that there was no threshold for the carcinogenicity. This unit risk, however, was obtained by conversion of the slope factor for oral exposure to the slope factor for inhalation exposure, so this is not adopted in the present initial assessment.

As for its oral exposure, its mean exposure would be less than around 0.00004 μg/kg/day and its predicted maximum exposure would be 0.00012 μg/kg/day, respectively, if its intakes through drinking water were assumed.

The MOE would be 420 when calculated from the 'non-toxic level*' of 0.005 mg/kg/day and the predicted maximum exposure, divided by 10 for conversion of the 'non-toxic level*' from animal experiments to an equivalent concentration for humans, and further divided by 10 for consideration of carcinogenicity of the substance. On the other hand, the excess incidence rate of its carcinogenicity would be 6.1 ∗ 10^{-6} for the predicted maximum exposure when calculated from the slope factor. For reference, EPI would be 3.5 ∗ 10^{-6} when calculated from TD_{05}. For information, the MOE, excess incidence rate and EPI would be 330, 7.7 ∗ 10^{-6}, and 4.4 ∗ 10^{-6}, respectively, when calculated for the maximum exposure of 0.00015 μg/kg/day reported for some location for exposure through intakes of drinking water. In addition, the MOE, excess incidence rate and EPI would be 3, 8.2 ∗ 10^{-4}, and 4.7 ∗ 10^{-4}, respectively, when calculated for the maximum exposure of 0.016 μg/kg/day reported for some location in 1982 for exposure through food intakes. Therefore, collection of information would be required to assess health risk from oral exposure to the substance.

As for its inhalation exposure, lack of available information on its 'non-toxic levels*', unit risk and exposure concentrations did not allow its health risk assessment. However, its relatively high vapor pressure, and its potential synthesis from reaction of dimethylamine and nitrogen oxide in the ambient air at night suggest that collection of information on its inhalation exposure would be required to assess its health risk from exposure to the substance in the ambient air, after its concentrations in the ambient air are understood.

Toxicity				Exposure assessment			Result of risk assessment			Judgment
Exposure Path	Criteria for risk assessment	Animal	Criteria for diagnoses (endpoint)	Exposure Medium	Predicted maximum exposure dose and concentration					
Oral				Drinking water	0.00012	μg/kg/day	MOE	420	○	▲
	Non-toxic level * ' 0.005 mg/kg/day	Rats	Nodular hyperplasia in liver				Excess incidence rate	6.1×10^{-6}	▲	
	Slope factor 51 $(mg/kg/day)^{-1}$	Rats	Liver tumor	Groundwater	—	μg/kg/day	MOE	—	×	
							Excess incidence rate	—	×	
Inhalation				Ambient air	—	$\mu g/m^3$	MOE	—	×	(▲)
	Non-toxic level * ' — mg/m^3	—	—				Excess incidence rate	—	×	
	Slope factor — $(\mu g/m^3)^{-1}$	—	—	Indoor air	—	$\mu g/m^3$	MOE	—	×	×
							Excess incidence rate	—	×	

Non-toxic level *

・When a LOAEL is available, it is divided by 10 to obtain a level equivalent to NOAEL.

・When an adverse effect level for the short-term exposure is available, it is divided by 10 to obtain a level equivalent to an adverse effect level for the long-term exposure.

4.Initial assessment of ecological risk

With regard to acute toxicity, the following reliable data were obtained: a 96-h LC_{50} of 280,000 μg/L for the crustacean *Gammarus limnaeus* (gammarid amphipod); and a 96-h LC_{50} of 940,000 μg/L for the fish *Pimephales promelas* (fathead minnow). Also obtained was a 96-h LC_{50} of 1,365,000 μg/L flatworm *Dugesia dorotocephala*. Accordingly, based on these acute toxicity values and an assessment factor of 1,000, a predicted no effect concentration (PNEC) of 280 μg/L was obtained. Reliable data for chronic toxicity values could not be obtained and for this reason, this 280 μg/L obtained from the crustacean acute toxicity was used as the PNEC for this substance.

Ecological risk could not be judged because data concerning environmental concentrations could not be obtained. Further, while not based on data obtained within the past 10 years, there is a report of less than around 0.02 μg/L for freshwater bodies and seawater, and the ratio of PNEC and this concentration is less than 0.00007. Furthermore, there is also a report of a maximum of 1.1 μg/L for public freshwater bodies from an environmental survey of a limited area. The ratio of PNEC with this concentration is 0.004. Accordingly, the need to gather further data regarding this substance is considered to be minimal.

Hazard assessment (basis for PNEC)			Assessment factor	Predicted no effect concentration PNEC (μg/L)	Exposure assessment		PEC/ PNEC ratio	Judgment based on PEC/PNEC ratio	Assessment result
Species	Acute/ chronic	Endpoint			Water body	Predicted environmental concentration PEC (μg/L)			
Crustacean *Gammarus limnaeus*	Acute	LC_{50} mortality	1,000	280	Freshwater	−	−	×	○
					Seawater	−	−		

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5. Conclusions

	Conclusions		Judgment
Health risk	Oral exposure	Requiring information collection.	▲
	Inhalation exposure	Further information collection would be required for risk characterization.	(▲)
Ecological risk	Need to gather further data considered minimal.		○

［Risk judgments］○: No need for further work ▲: Requiring information collection

■: Candidates for further work ×: Impossibility of risk characterization

(○) : Though a risk characterization cannot be determined, there would be little necessity of collecting information.

(▲) : Further information collection would be required for risk characterization.