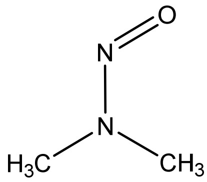
6	CAS No.: 62-75-9	Substance: *N*-Nitrosodimethylamine

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 aqueous 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 730 Pa (25°C). In terms of biodegradability (aerobic degradation), a report indicated that more than 50% of this substance remained (test duration: 14 d; test method: colorimetry). Another report indicates no breakdown in lake water (test duration: 108 d, 30°C).

The main uses of this substance were as an intermediate for rocket propellant manufacture, a soil nitrification inhibitor, a plasticizer in rubber and polymer manufacture, a solvent for the fiber and plastics industries, an antioxidant, a copolymer softening agent, and a lubricant additive. The production and import quantity could not be obtained.

---

2. Exposure assessment

Because this substance is not classified as a Class 1 Designated Chemical Substance under the PRTR Law, release and transfer quantities could not be obtained. Predictions of proportions distributed to individual media by use of a Mackay-type level III fugacity model indicate that if equal quantities were released to the atmosphere, water bodies, and soil, the proportion distributed to soil would be largest.

The maximum expected concentration of exposure to humans via inhalation, based on ambient atmospheric data, was around 0.30 µg/m^3. Data for groundwater, food, and soil to assess oral exposure could not be obtained. Thus, assuming intake solely from potable water gives a maximum expected exposure of around 0.00004 µg/kg/day, while assuming intake solely from public freshwater bodies gives a maximum expected exposure of around 0.00032 µg/kg/day.

Further, albeit based on data for a limited area, calculations for potable water gave a maximum daily exposure value of 0.0004 µg/kg/day. In addition, albeit based on data for a limited area, calculations for public freshwater bodies gave a maximum daily oral exposure value of around 0.0076 µg/kg/day. Finally, albeit past data (more than ten years old) for a limited area, a maximum daily exposure value of around 0.044 µg/kg/day was reported.

In addition, with regards to oral exposure from intake of food, this substance is potentially formed via cooking of food. Therefore, oral exposure cannot be calculated using the duplicate diet method or market basket method. Instead, it was calculated using actual data from seafood as reference values. Albeit past data, a maximum value of 0.00089 µg/kg/day was obtained from the sum of oral exposure from intake of fish species (0.00086 µg/kg/day) and shellfish species (less than 0.000028 µg/kg/day) estimated based on average daily intake values (fish: 61.3 g/capita/day (total); shellfish: 2.8 g/ capita /day (total)) and maximum concentrations in fish (0.0007 µg/g) and shellfish (less than 0.0005 µg/g). Adding this to the oral exposure of 0.00032 µg/kg/day calculated from public freshwater body data of 0.00032 µg/kg/day gives a maximum of 0.0012 µg/kg/day.

The predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, was around 0.0081 µg/L for public freshwater bodies, and less than around 0.06 µg/L for seawater.

Further, albeit based on data for a limited area, a maximum value of around 0.19 µg/L has been reported for public freshwater bodies. In addition, albeit past data (more than ten years old) for a limited area, a value of 1.1 µg/L has been reported for public freshwater bodies.

---

3. Initial assessment of health risk

This substance irritates the eyes, the skin as well as the respiratory tract, and may cause effects on the liver, resulting in jaundice. Inhalation will cause sore throat, cough, nausea, diarrhea, vomiting, headache, and weakness. Ingestion will cause abdominal cramps in addition to the same symptoms as inhalation. Contact to the skin and the eyes will cause redness and pain.

Though the information was not available on the carcinogenicity of the substance to humans, this substance is probably carcinogenic to humans, because of the mechanisms of carcinogenesis. Considering the above, the initial assessment was conducted for both non-carcinogenic and carcinogenic effects.

The non-carcinogenic NOAEL of 0.005 mg/kg/day for oral exposure (based on nodular hyperplasia of the liver), determined from toxicity tests in rats, was deemed to be the lowest reliable dose and was identified as the 'non-toxic level' of the substance for oral exposure. The cancer slope factor for oral exposure of 5.1 × 10 $(mg/kg/day)^{-1}$ (based on hepatic tumors), determined from carcinogenicity tests in rats, was adopted assuming no threshold. As an alternative risk assessment approach, TD_{05} of 0.034 mg/kg/day (based on biliary cystadenoma), determined from carcinogenicity tests in rats, was adopted to derive the EPI (Exposure/Potency Index). The 'non-toxic level' for inhalation exposure could not be identified. The unit risk for cancer of 5×10^{-2} $(\mu g/m^3)^{-1}$ was adopted assuming no threshold. This value was calculated from the long-term Environmental Assessment Level of 0.2 ng/m^3 (based on tumors in the nasal cavity) recommended by the Environment Agency in the UK, which corresponds to the lifetime excess cancer incidence rate of 10^{-5}.

Regarding oral exposure, the predicted maximum exposure level would be 0.00004 µg/kg/day, approximately, assuming that the substance is absorbed via drinking water, while it would be 0.00032 µg/kg/day, approximately, assuming that the substance is absorbed via public freshwater bodies. The MOE (Margin of Exposure) would be 1,300 which is calculated from the former exposure level and the 'non-toxic level' of 0.005 mg/kg/day, and subsequently divided by a factor of 10 to account for extrapolation from animals to humans, and by another factor of 10 to take into consideration the carcinogenicity. The MOE would be 160 which is calculated from the latter exposure level. The excess cancer incidence rates corresponding to the predicted maximum exposure levels of 0.00004 µg/kg/day and 0.00032 µg/kg/day would be 2.0×10^{-6} and 1.6×10^{-5}, respectively, which are calculated from the cancer slope factor. The EPIs corresponding to the predicted maximum exposure levels, for reference, would be 1.2×10^{-6} and 9.4×10^{-6}, respectively, which are calculated from the TD_{05}. These assessment results would lead to the health risk judgment that this substance is a candidate for further work. In addition, the MOE, the excess cancer incidence rate, and EPI would be 42, 6.2×10^{-5}, and 3.5×10^{-5}, respectively, which are calculated from the maximum exposure level of 0.0012 µg/kg/day. This maximum exposure level is the sum of the predicted maximum exposure level via public freshwater bodies and the oral exposure level via food estimated from the past data (in 1989) on seafood. Therefore, as a comprehensive judgment, this substance is a candidate for further work.

Regarding inhalation exposure, the predicted maximum exposure concentration in ambient air was 0.30 $\mu g/m^3$, approximately. Due to the lack of identified 'non-toxic level', the MOE could not be calculated. The excess cancer incidence rate, corresponding to the predicted maximum exposure concentration, would be 1.5×10^{-2}, which is calculated from the unit risk. In addition, the excess cancer incidence rate, corresponding to the second highest concentration of 0.0028 $\mu g/m^3$ in 2015 when the predicted maximum exposure concentration was observed, would be 1.4×10^{-4}. These assessment results would lead to the health risk judgment that this substance is a candidate for further work. Furthermore, the excess cancer incidence rate, corresponding to the highest concentration in Japan of 0.0023 $\mu g/m^3$ in 2019, four years after the predicted maximum exposure concentration was observed, would be 1.2×10^{-4}. Therefore, as a comprehensive judgment, this substance is a candidate for further work to assess the health risk via inhalation in ambient air.

Toxicity						Exposure assessment			MOE & Excess incidence rate		Comprehensive judgment
Exposure Path	Criteria for risk assessment			Animal	Criteria for diagnoses (endpoint)	Exposure medium	Predicted maximum exposure dose and concentration				
Oral	'Non-toxic level'	0.005	mg/kg/day	Rats	Nodular hyperplasia of the liver	Drinking water	0.00004	µg/kg/day	MOE	1,300	■
									Excess incidence rate	2.0×10^{-6}	
	Slope factor	5.1×10	$(mg/kg/day)^{-1}$	Rats	Hepatic tumors	Public freshwater bodies	0.00032	µg/kg/day	MOE	160	
									Excess incidence rate	1.6×10^{-5}	

Inhalation	'Non-toxic level'	-	mg/m³	-	-	Ambient air	0.30 µg/m³	MOE	-	■
								Excess incidence rate	1.5×10^{-2}	
	Unit risk	5×10^{-2}	(µg/m³)$^{-1}$	Rats	Tumors in the nasal cavity	Indoor air	- µg/m³	MOE	-	×
								Excess incidence rate	-	

Non-toxic level *

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

・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 species *Gammarus limnaeus*, a 96-h LC_{50} of 940,000 µg/L for the fish species *Pimephales promelas* (fathead minnow), and a 96-h LC_{50} of 1,365,000 µg/L for the dugesiid triclad *Dugesia dorotocephala* (flatworm). 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 chronic toxicity data could not be obtained. Therefore, the value of 280 µg/L obtained from the acute toxicity to the crustacean species was used as the PNEC for this substance.

The PEC/PNEC ratio is 0.00003 for freshwater bodies and less than 0.0002 for seawater. Further work to assess the ecological risk of this substance is considered unnecessary at this time.

Further, a maximum value of around 0.19 µg/L was reported, albeit for a limited area. The ratio of this value to PNEC is 0.0007. In addition, albeit past data (more than ten years old) for a limited area of public water bodies, a maximum value of 1.1 µg/L has been reported. The ratio of this value to PNEC is 0.004. Accordingly, based on a comprehensive review of the above findings, there is little need to collect new data regarding this substance.

Hazard assessment (basis for PNEC)			Assessment coefficient	Predicted no effect concentration PNEC (µg/L)	Exposure assessment		PEC/ PNEC ratio	Comprehensive judgment
Species	Acute/ chronic	Endpoint			Water body	Predicted environmental concentration PEC (µg/L)		
Crustacean *Gammarus minus*	Acute	LC_{50} Mortality	1,000	280	Freshwater	0.0081	0.00003	○
					Seawater	<0.06	<0.0002	

---

5. Conclusions

		Conclusions	Judgment
Health risk	Oral exposure	Candidate for further work	■
	Inhalation exposure	Candidate for further work	■
Ecological risk	No need for further work		○

[Risk judgments] ○: No need for further work ▲: Requiring information collection
■: Candidates for further work ×: Impossibility of risk characterization

* Note: Number after revision of law to be implemented on April 1, 2023