5	CAS No.: 55-18-5	Substance: *N*-Nitrosodiethylamine

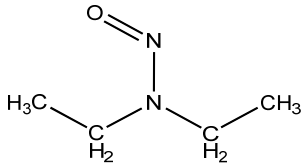
Chemical Substances Control Law Reference No.:

PRTR Law Cabinet Order No.:

Molecular Formula: $C_4H_{10}N_2O$

Molecular Weight: 102.14

Structural Formula:



1. General information

The aqueous solubility of this substance is 1.06×10^5 mg/1,000 g (24°C), the partition coefficient (1-octanol/water) (log K_{ow}) is 0.48, and the vapor pressure is 120 Pa (20°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).

Information could not be obtained regarding this substance's uses. In addition, the production and import quantity could not be obtained.

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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 0.011 μg/m^3. Data for potable water, groundwater, food, and soil to assess oral exposure could not be obtained. Assuming intake solely from public freshwater bodies, a maximum expected exposure of around 0.000064 μg/kg/day was obtained. Further, albeit based on data for a limited area, calculations for potable water and public freshwater bodies gave daily exposure reference values of less than 0.00008 μg/kg/day and around 0.0010 μg/kg/day, respectively.

In addition, with regard 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 0.00050 μg/kg/day was obtained from the sum of oral exposure from intake of fish species (0.00049 μg/kg/day) and shellfish species (less than 0.0000056 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 (0.0004 μg/g) and shellfish (less than 0.0001 μg/g). Adding this to the oral exposure calculated from public freshwater body data of 0.000064 μg/kg/day gives a maximum of 0.00056 μg/kg/day.

The predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, was around 0.0016 μg/L for public freshwater bodies. A PEC for seawater could not be set due to lack of data. Further, albeit based on data for a limited area for public water bodies and seawater, a maximum value of around 0.0026 μg/L μg/L has been reported. In addition, albeit based on past data for public water bodies and seawater, a maximum value of less than around 0.01 μg/L has been reported.

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3. Initial assessment of health risk

No information was available on acute symptoms in humans caused by this substance. However, rats exposed to an oral dose of this substance displayed hypermotility of the gastrointestinal tract, diarrhea, degeneration of the fatty liver, decrease in body weight, and suppression of body weight gain, and exposed mice displayed somnolence.

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 0.008 mg/kg/day for oral exposure (based on the increased relative weight of the liver), determined from toxicity tests in rats, was divided by a factor of 10 to account for extrapolation to chronic exposure. The calculated value of 0.0008 mg/kg/day 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 1.5×10^{2} $(mg/kg/day)^{-1}$ (based on hepatic tumors), determined from carcinogenicity tests in rats, was adopted assuming no threshold. Neither 'non-toxic level' nor unit risk could be identified for inhalation exposure.

Regarding oral exposure, assuming that the substance is absorbed via public freshwater bodies, the predicted maximum exposure level would be 0.000064 μg/kg/day, approximately. The MOE (Margin of Exposure) would be 130 which is calculated from the predicted maximum exposure level and the 'non-toxic level' of 0.0008 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 excess cancer incidence rate corresponding to the predicted maximum exposure level would be 9.6×10^{-6} which is calculated from the slope factor. These estimations would lead to the health risk judgment that the collection of information would be required. The maximum exposure level was estimated to be less than 0.00008 μg/kg/day based on data in a certain area on drinking water, while it was estimated to be 0.0010 μg/kg/day, approximately, based on data in a certain area on public freshwater bodies. The MOE and the excess cancer incidence rate, for reference, would be more than 100 and less than 1.2×10^{-5}, respectively, which are calculated from the former exposure level, and would be 8 and 1.5×10^{-4}, respectively, which are calculated from the latter. In addition, the MOE and the excess cancer incidence rate would be 14 and 8.4×10^{-5}, respectively, which are calculated from another estimation of the maximum exposure level of 0.00056 μg/kg/day. This 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, the collection of information would be required to assess the health risk of this substance via oral exposure, starting from identification of the sources of production and emission to enhance the data on the levels in public freshwater bodies and seafood.

Regarding inhalation exposure, due to the lack of identified 'non-toxic level' and exposure concentrations, the health risk could not be assessed. However, the tentative 'non-toxic level' for inhalation exposure of 0.003 mg/m^3 was derived from the conversion of the 'non-toxic level' for oral exposure, assuming that 100% of the inhaled substance is absorbed. The MOE for reference would be 3 which is calculated from the tentative 'non-toxic level' for inhalation exposure and the predicted maximum exposure concentration in ambient air of 0.011 $\mu g/m^3$, approximately, 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 excess cancer incidence rate for reference, corresponding to the predicted maximum exposure concentration of 0.011$\mu g/m^3$, approximately, would be 4.7×10^{-4} which is calculated from the tentative unit risk of 4.3×10^{-2} $(\mu g/m^3)^{-1}$, derived from the conversion of the slope factor for oral exposure. Therefore, as a comprehensive judgment, the collection of information would be required to assess the health risk of this substance via inhalation in ambient air, starting from an examination of the validity of the toxicity data for inhalation exposure converted from those for oral exposure, as well as identification of the sources of production and emission to enhance the data on the concentrations 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' 0.0008 mg/kg/day	Rats	The increased relative weight of the liver	Drinking water	- μg/kg/day	MOE	-	▲
						Excess incidence rate	-	
	Slope factor 1.5×10^{2} $(mg/kg/day)^{-1}$	Rats	Hepatic tumors	Public freshwater bodies	0.000064 μg/kg/day	MOE	130	
						Excess incidence rate	9.6×10^{-6}	

Inhalation	'Non-toxic level'	-	mg/m^3	-	-	Ambient air	0.011	µg/m^3	MOE	-	▲
									Excess incidence rate	-	
	Unit risk	-	(µg/m3)$^{-1}$	-	-	Indoor air	-	µg/m^3	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.

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4. Initial assessment of ecological risk

With regard to acute toxicity, the following reliable data were obtained: a 96-h LC_{50} of 500,000 µg/L for the crustacean species *Gammarus limnaeus*, a 96-h LC_{50} of 775,000 µg/L for the fish species *Pimephales promelas* (fathead minnow), and a 96-h of LC_{50} 1,490,000 µg/L for the dugesiid triclad (flatworm) *Dugesia dorotocephala*. Accordingly, based on these acute toxicity values and an assessment factor of 1,000, a PNEC of 500 µg/L was obtained.

Reliable chronic toxicity data could not be obtained. Therefore, the value of 500 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. Further work to assess the ecological risk of this substance is considered unnecessary at this time. Further, a maximum value of around 0.026 µg/L was reported, albeit for a limited area of public freshwater bodies. The ratio of this value to the PNEC is 0.00005. In addition, albeit past data (more than ten years old), a maximum value of less than 0.01 µg/L has been reported for public freshwater bodies and seawater. The ratio of this value and PNEC was less than 0.00002. 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	500	Freshwater	0.0016	0.000003	○
					Seawater	—	—	

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5. Conclusions

	Conclusions		Judgment
Health risk	Oral exposure	Requiring information collection	▲
	Inhalation exposure	Requiring information collection	▲
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