9	CAS No.: 110-85-0	Substance: Piperazine

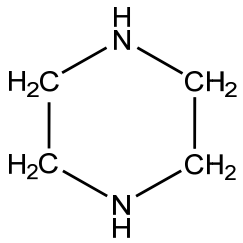
Chemical Substances Control Law Reference No.: 5-953

PRTR Law Cabinet Order No.: 1-341

Molecular Formula: $C_4H_{10}N_2$

Molecular Weight: 86.14

Structural Formula:



1.General information

The aqueous solubility of this substance is 1.5×10^5 mg/L (20°C), the partition coefficient (1-octanol/water) (log K_{ow}) is –1.50 (pH=13.0), and the vapor pressure is 0.160 mmHg (=21.3 Pa) (20°C). The biodegradability (aerobic degradation) is characterized by a BOD degradation rate of 1.4%, and bioaccumulation is thought to be nonexistent or low. In addition, this substance does not possess any hydrolyzable groups and therefore does not undergo hydrolysis.

This substance is classified as a Class 1 Designated Chemical Substance under the PRTR Law. It is mainly used as a raw material for pharmaceuticals and as an epoxy resin curing agent. It is also used as a raw material for parasitic worm and threadworm therapeutic agents (ascaricides), a detecting agent for antimony and other metals, and a synthesis catalyst for production of urethanes. The production and import quantity in fiscal 2016 was 1,000 t. The production and import category under the PRTR Law is more than 100 t.

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2. Exposure assessment

Total release to the environment in fiscal 2016 under the PRTR Law was approximately 4.4 t, of which approximately 2.0 t or 45% of total release was reported. In addition, approximately 13 t was transferred to waste and approximately 2.9 t to sewage. The oil and natural gas extraction and warehouse industries reported large releases to the atmosphere, while the electrical machinery manufacturing industry reported large releases to public water bodies The largest releases to the environment including unreported releases were to water bodies. A multi-media model used to predict the proportions distributed to individual media in the environment indicates that in regions where the largest quantities were estimated to have been released to the environment overall or public water bodies in particular, the predicted proportion distributed to water bodies was 98.6%. Where the largest quantities were estimated to have been released to the atmosphere, the predicted proportion distributed to water bodies was 98.4%.

The maximum expected concentration of exposure to humans via inhalation could not be determined because ambient atmospheric and indoor air quality data could not be obtained. The mean annual value for the atmospheric concentration in fiscal 2016 was calculated by use of a plume-puff model on the basis of releases to the atmosphere reported according to the PRTR Law; this model predicts a maximum level of 0.076 μg/m^3.

Data for potable water, ground water, food and soil to assess oral exposure could not be obtained. Thereupon, assuming intake solely from public freshwater bodies, the maximum expected concentration of exposure was calculated to be around 0.00088 μg/kg/day. However, when releases to public freshwater bodies in fiscal 2016 reported under the PRTR Law were divided by the ordinary water discharge of the national river channel structure database, estimating the concentration in rivers by taking into consideration only dilution gave a maximum value of 8.1 μg/L. Using this estimated concentration for rivers to calculate oral exposure gives 0.32 μg/kg/day. However, transfer to sewage greatly exceeded releases to public water bodies. When this transfer to sewage is included in the previous calculation, a

maximum value of 200 μg/L is obtained, and the resulting oral exposure becomes 8 μg/kg/day. The risk of exposure to this substance by intake from an environmental medium via food is considered slight, given its nonexistent or low bioaccumulation.

The predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, was reported to be around 0.022 μg/L for public freshwater bodies and around 0.023 μg/L for seawater. When releases to public freshwater bodies in fiscal 2016 reported according to the PRTR Law were divided by the ordinary water discharge of the national river channel structure database, estimating the concentration in rivers by taking into consideration only dilution gives a maximum value of 8.1 μg/L. However, transfer to sewage greatly exceeded releases to public water bodies. When this transfer to sewage is included in the previous calculation, a maximum value of 200 μg/L is obtained

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3. Initial assessment of health risk

This substance is corrosive. Inhalation of the substance causes burning sensation, cough, sore throat, shortness of breath, labored breathing and wheezing, and may cause lung edema. Ingestion causes burning sensation, abdominal pain, nausea, vomiting, headache, weakness, convulsions and shock or collapse, and ingestion of the substance in a large amount may result in impaired functions. Contact with the eyes causes redness, pain and severe burns. Contact with the skin causes skin burns, pain and blisters.

As sufficient information on the carcinogenicity of the substance was not available, the initial assessment was conducted on the basis of information on its non-carcinogenic effects.

The NOAEL of 25 mg/kg/day for oral exposure (no observed effect at the highest dose), determined from medium-term toxicity tests in dogs, was divided by a factor of 10 to account for extrapolation to chronic exposure. The calculated value of 2.5 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 ‘non-toxic level*’ for inhalation exposure could not be identified.

With regard to oral exposure, assuming the substance is absorbed via public freshwater bodies, the predicted maximum exposure level would be 0.00088 μg/kg/day, approximately. The MOE (Margin of Exposure) would be 280,000, when calculated from the predicted maximum exposure level and the ‘non-toxic level*’of 2.5 mg/kg/day, and subsequently divided by a factor of 10 to account for extrapolation from animals to humans. On the other hand, the maximum exposure level, when estimated according to the concentration in effluents from the high discharging plants reported in FY 2016 under the PRTR Law, would be 0.32 μg/kg/day. The MOE would be 780, when calculated from this level. When transfers to sewage are considered, the maximum exposure level would be 8 μg/kg/day, giving an MOE of 31, falling below 100. Since exposure to the substance in environmental media via food is presumed to be limited, including it in the calculation would not change the MOE significantly. Therefore, collection of information would be required to assess the health risk of this substance via oral exposure, starting from data on concentrations in public freshwater bodies with consideration of transfers to sewage.

With regard to inhalation exposure, owing to the lack of identified ‘non-toxic level*’ and exposure concentrations, the health risk could not be assessed. Assuming that 100% of the inhaled substance is absorbed, the ‘non-toxic level*’ for inhalation exposure, derived from the conversion of the ‘non-toxic level*’ for oral exposure, would be 8.3 mg/m^3. The maximum concentration (annual mean) in ambient air near the operators releasing large amount of the substance was estimated to be 0.076 μg/m^3 based on the releases to air reported in FY 2016 under the PRTR Law. The MOE would be 11,000, when calculated from these values, and subsequently divided by a factor of 10 to account for extrapolation from animals to humans. Therefore, collection of further information would not be required to assess the health risk of this substance via inhalation in ambient air.

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	'Non-toxic level*' 2.5 mg/kg/day	Dogs	No observed effect at the highest dose	Drinking water	- μg/kg/day	MOE	-	(▲)
				Public freshwater bodies	0.00088 μg/kg/day	MOE	280,000	
Inhalation	'Non-toxic level*' - mg/m^3	-	-	Ambient air	- $\mu g/m^3$	MOE	-	○
				Indoor air	- $\mu g/m^3$	MOE	-	×

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 72-h EC_{50} of 132,000 μg/L for growth inhibition in the green alga *Pseudokirchneriella subcapitata*, a 48-h EC_{50} of 21,000 μg/L for swimming inhibition in the crustacean *Daphnia magna*, and a 96-h LC_{50} exceeding 100,000 μg/L for the fish species *Oryzias latipes* (medaka). Accordingly, based on these acute toxicity values and an assessment factor of 100, a predicted no effect concentration (PNEC) of 210 μg/L was obtained.

With regard to chronic toxicity, the following reliable data were obtained: a 72-h NOEC of 34,200 μg/L for growth inhibition in the green alga *P. subcapitata* and a 21-d NOEC of 32,700 μg/L for reproductive inhibition in the crustacean *D. magna*. Accordingly, based on these chronic toxicity values and an assessment factor of 100, a PNEC of 320 μg/L was obtained.

The value of 210 μg/L obtained from the acute toxicity to the crustacean was used as the PNEC for this substance.

The PEC/PNEC ratio is 0.0001 for freshwater bodies and seawater. When releases to public freshwater bodies in fiscal 2016 reported according to the PRTR Law were divided by the ordinary water discharge of the national river channel structure database, estimating the concentration in rivers by taking into consideration only dilution gives a maximum value of 8.1 μg/L and the ratio of this value to the PNEC is 0.04. However, transfer to sewage greatly exceeded releases to public water bodies. When this transfer to sewage is taken into account in the previous calculation, a maximum value of 200 μg/L is obtained and the ratio of this value with PNEC is 0.95; accordingly, efforts to collect data are needed, and environmental concentration data needs to be augmented taking into consideration emission sources.

Hazard assessment (basis for PNEC)			Assessment coefficient	Predicted no effect concentration PNEC (μg/L)	Exposure assessment		PEC/ PNEC ratio	Assessment result
Species	Acute/ chronic	Endpoint			Water body	Predicted environmental concentration PEC (μg/L)		
Crustacean *Daphnia magna*	Acute	EC_{50} swimming inhibition	100	210	Freshwater	0.022	0.0001	(▲)
					Seawater	0.023	0.0001	

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5. Conclusions

	Conclusions		Judgment
Health risk	Oral exposure	Further efforts to collect data required based on comprehensive review of existing relevant data.	(▲)

	Inhalation exposure	No need for further work.	○
Ecological risk	Further efforts to collect data required based on comprehensive review of existing relevant data.		（▲）

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

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

（▲）: Further efforts to collect data required based on comprehensive review of existing relevant data

（■）: Candidate for further work based on comprehensive review of existing data