10	CAS No.: 124-09-4	Substance: Hexamethylenediamine

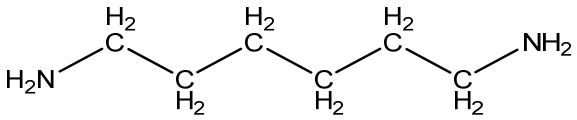
Chemical Substances Control Law Reference No.: 2-153

PRTR Law Cabinet Order No.: 1-390

Molecular Formula: $C_6H_{16}N_2$

Molecular Weight: 116.20

Structural Formula:



1.General information

The aqueous solubility of this substance is 9.6×10^6 mg/1,000g (30°C), the partition coefficient (1-octanol/water) (log K_{ow}) is 0.02, and the vapor pressure is 0.38 mmHg (=50 Pa) (25°C). The biodegradability (aerobic degradation) is characterized by a BOD degradation rate of 55.5%, and the substance exhibits good degradability. In addition, this substance does not possess any hydrolyzable chemical bonds.

This substance is classified as a Class 1 Designated Chemical Substance under the PRTR Law. This substance is used as a raw material for polyamide resins such as polyamide 66, and polyamide fiber. The production and import quantity in fiscal 2016 was 90,000 t. The production and import quantity in fiscal 2016 was 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 4.3 t, of which approximately 4.3 t or more than 99% of total releases were reported. The majority of reported releases were to the atmosphere. In addition, approximately 2.8 t was transferred to waste and 0.003 t to sewage. The chemical industry reported large releases to the atmosphere and public water bodies. The largest releases to the environment including unreported releases were to the atmosphere. A multi-media model used to predict the proportions distributed to individual media in the environment indicated that in regions where the largest quantities were estimated to have been released to the environment overall or the atmosphere in particular, the predicted proportion distributed to soil was 52.0% and that to water bodies was 44.8%.

The average expected concentration of exposure to humans via inhalation, based on ambient atmospheric data, was around less than 0.00091 μg/m^3 and the corresponding maximum expected concentration was around 0.0018 μg/m^3. 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 1.3 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 were calculated to be around 0.11 μg/kg/day. However, 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 96 μg/L. Using this estimated concentration for rivers to calculate oral exposure gives 3.8 μg/kg/day. The risk of exposure to this substance by intake from an environmental medium via food is considered slight, given the low bioaccumulation of the substance expected on the basis of its physicochemical properties.

The predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, was reported to be around 2.7 μg/L for public freshwater bodies and around less than 0.0043 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 96 μg/L.

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3. Initial assessment of health risk

This substance is corrosive to the eyes, skin and respiratory tract. Inhalation of the substance causes burning sensation, cough, labored breathing, shortness of breath and sore throat, and may cause lung edema. Ingestion of the substance demonstrates corrosiveness and may cause abdominal cramps, abdominal pain, burning sensation and shock or collapse. Contact with the skin causes redness, skin burns, pain and blisters. Contact with the eyes causes redness, pain and severe deep burns.

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 150 mg/kg/day for oral exposure (based on suppression of body weight gain), determined from medium-term toxicity tests in rats, was divided by a factor of 10 to account for extrapolation to chronic exposure. The calculated value of 15 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 NOAEL of 5 mg/m^3 for inhalation exposure of dihydrochloride of this substance (based on tissue degeneration in the nasal cavity), determined from toxicity tests in rats and mice, was adjusted according to exposure conditions to obtain 0.89 mg/m^3 , which is equivalent to 0.55 mg/m^3 of hexamethylenediamine, and subsequently divided by a factor of 10 to account for extrapolation to chronic exposure. The calculated value of 0.055 mg/m^3 was deemed to be the lowest reliable dose and was identified as the 'non-toxic level*' of the substance for inhalation exposure.

With regard to oral exposure, assuming the substance is absorbed via public freshwater bodies, the predicted maximum exposure level would be 0.11 μg/kg/day, approximately. The MOE (Margin of Exposure) would be 14,000, when calculated from the predicted maximum exposure level and the 'non-toxic level*'of 15 mg/kg/day, and subsequently divided by a factor of 10 to account for extrapolation from animals to humans. Alternatively, the maximum exposure level, estimated according to the concentration in effluents from the high discharging plants reported in FY 2016 under the PRTR Law, would be 3.8 μg/kg/day. The MOE would be 390, when calculated from this level. 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, no further work would be required at present to assess the health risk of this substance via oral exposure.

With regard to inhalation exposure, the predicted maximum exposure concentration in ambient air was 0.0018 μg/m^3, approximately. The MOE would be 3,100, when calculated from the predicted maximum exposure concentration and the 'non-toxic level*'of 0.055 mg/m^3, and subsequently divided by a factor of 10 to account for extrapolation from animals to humans. On the other hand, the maximum concentration (annual mean) in ambient air near the operators releasing large amount of this substance was estimated to be 1.3 μg/m^3 based on the releases to air reported in FY 2016 under the PRTR Law. The MOE would be 4, falling below 100, when calculated from this concentration. Therefore, collection of information would be required to assess the health risk of this substance via inhalation in ambient air, starting from data on concentrations in ambient air near the operators releasing large amount of this substance.

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*' 15 mg/kg/day	Rats	Suppression of body weight gain	Drinking water	- μg/kg/day	MOE	-	○
				Public freshwater bodies	0.11 μg/kg/day	MOE	14,000	
Inhalation	'Non-toxic level*' 0.055 mg/m^3	Rats, Mice	Tissue degeneration in the nasal cavity	Ambient air	0.0018 μg/m^3	MOE	3,100	(▲)
				Indoor air	- μg/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 70,000 μg/L for growth inhibition in the green alga *Pseudokirchneriella subcapitata*, a 48-h EC_{50} of 19,800 μg/L for swimming inhibition in the crustacean *Daphnia magna*, and a 96-h LC_{50} of 70,700 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 190 μg/L was obtained.

With regard to chronic toxicity, the following reliable data were obtained: a 72-h NOEC of 10,000 μg/L for growth inhibition in the green alga *P. subcapitata* and a 21-d NOEC of 4,160 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 41 μg/L was obtained.

The value of 41 μg/L obtained from the chronic toxicity to the crustacean was used as the PNEC for this substance.

The PEC/PNEC ratio is 0.07 for freshwater bodies and less than 0.0001 for seawater. However, 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 gave a maximum value of 96 μg/L and the ratio of this value to the PNEC is 2; 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*	Chronic	NOEC reproductive inhibition	100	41	Freshwater	2.7	0.07	(▲)
					Seawater	<0.0043	<0.0001	

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5. Conclusions

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

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