11	CAS No.: 100-97-0	Substance: Hexamethylenetetramine				
Chemical	Substances Control Law Referen	ce No.: 5-1155				
PRTR Lav	v Cabinet Order No.: 1-258					
Molecular	Molecular Formula: C ₆ H ₁₂ N ₄ Structural Formula:					
Molecular	Weight: 140.19					

1.General information

This substance is freely miscible with water, the partition coefficient (1-octanol/water) (log K_{ow}) is -2.18 (20°C) (pH=7–9), and the vapor pressure is 4.00×10^{-3} mmHg (=0.533 Pa) (25°C). The biodegradability (aerobic degradation) is characterized by a BOD degradation rate of 22%, and degradability is judged to be good. Further, hydrolyzability depends on the pH of the medium and degradation is expected within a few hours for acidic media.

This substance is classified as a Class 1 Designated Chemical Substance under the PRTR Law. The main uses of this substance are as agricultural chemical additives, curing accelerators for thermosetting plastics, and reaction accelerators for the production of rubber products. The production and import quantity in fiscal 2016 was 6,000 t. The production and import category under the PRTR Law is more than 100 t.

2. Exposure assessment

Total release to the environment in fiscal 2016 under the PRTR Law was approximately 79 t, of which approximately 1 t was reported. In addition, approximately 2,600 t was transferred to waste, and 0.015 t to sewage. Industries with large reported releases were the ceramics and soil and stone product manufacturing, chemical and transportation equipment manufacturing industries for the atmosphere, and the chemical industry for public water bodies. The largest releases to the environment including unreported releases were to soil.

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 soil in particular, the predicted proportion distributed to soil was 88.0%. Where the largest quantities were estimated to have been released to the atmosphere, the predicted proportion distributed to soil was 73.6% and to water bodies was 26.1%. Where the largest quantities were estimated to have been released to public water bodies, the predicted proportion distributed to soil was 25.5%.

The maximum expected concentration of exposure to humans via inhalation could not be defined 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 $0.11 \,\mu g/m^3$.

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, a maximum expected concentration of exposure of around 2.6 μ g/kg/day was obtained. Furthermore, a reference value of around less than 0.04 μ g/kg/day was obtained for maximum expected concentration of exposure based on data measured for drinking water, albeit for a limited area. 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 2.2 μ g/L. Calculating oral exposure based on this gives 0.088 μ g/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 65 μ g/L for public water bodies. Seawater data capable of withstanding assessment could not be obtained and therefore, a PEC could not be set 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 2.2 μ g/L.

3. Initial assessment of health risk

Inhalation of this substance causes cough. Ingestion of the substance causes abdominal pain, nausea and vomiting. Contact with the eyes or skin causes redness and pain with mild irritation.

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 27 mg/kg/day for oral exposure (no observed adverse effect dose) determined from human studies 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 2.6 μ g/kg/day, approximately. The MOE (Margin of Exposure) would be 10,000, when calculated from the predicted maximum exposure level and the 'non-toxic level*' of 27 mg/kg/day. 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 0.088 μ g/kg/day. The MOE would be 310,000, 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, 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 90 mg/m³. The maximum concentration (annual mean) in ambient air near the operators releasing large amount of the substance was estimated to be $0.11 \ \mu g/m^3$ based on the releases to air reported in FY 2016 under the PRTR Law. The MOE would be 820,000, when calculated from this exposure concentration and the converted 'non-toxic level*' for inhalation exposure. 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				
Exposure Path	Criteria fo	r risk as	sessment	Animal	Criteria for diagnoses (endpoint)	Exposure medium	exposu	d maximum re dose and entration	Result assess		Judgment
Qual	'Non-toxic	27		Humans	The dose with no observed	Drinking water	-	µg/kg/day	MOE	-	0
Oral	level*'	27	mg/kg/day	riumans	adverse effect	Public freshwater bodies	2.6	µg/kg/day	MOE	10,000	0
Inhalation	'Non-toxic level*'	- mg/m ³	_		Ambient air	-	$\mu g/m^3$	MOE	-	0	
midiation			mg/m	-	-	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.

4. Initial assessment of ecological risk

With regard to acute toxicity, the following reliable data were obtained: a 72-h EC₅₀ exceeding 100,000 μ g/L for growth inhibition in the green alga *Pseudokirchneriella subcapitata*, a 48-h EC₅₀ exceeding 104,000 μ g/L for swimming inhibition in the crustacean *Daphnia magna*, and a 96-h LC₅₀ exceeding 101,000 μ g/L for the fish species *Oryzias latipes* (medaka). A PNEC value could not be set based on these acute toxicity values because they were obtained from limit tests that investigated the presence of effects at a designated concentration.

With regard to chronic toxicity, the following reliable data were obtained: a 72-h of NOEC 100,000 μ g/L for growth inhibition in the green alga *P. subcapitata* and a 21-d NOEC of 99,100 μ g/L for reproductive inhibition in the crustacean *D. magna*. A PNEC value could not be set based on these chronic toxicity values because they were obtained from limit tests.

The toxicity selected for each organisms was obtained from limit tests that investigated the presence of effects at a designated concentration. For this reason, PNEC values were not set.

Provisionally, based on the lowest of these toxicity values, namely the chronic toxicity towards the crustacean of 99,100 μ g/L, and an assessment factor of 100, a PNEC of 990 μ g/L is obtained, and the ratio of this value to the PEC is 0.07 for freshwater. A concentration of less than 0.2 μ g/L was reported for a single location for seawater and the ratio of this value to the PNEC is less than 0.0002. Further, 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 2.2 μ g/L and the ratio of this value to the provisional PNEC value is 0.002; accordingly, further work is considered unnecessary at this time.

Hazard ass	Hazard assessment (basis for PNEC)			Predicted no	Exposure assessment				
Species	Acute/ chronic	Endpoint	Assessment coefficient	effect concentration PNEC (μg/L)	Water body	Predicted environmental concentration PEC (µg/L)	PEC/ PNEC ratio	Assessment result	
					Freshwater	65	—		
					Seawater	—	_	0	

5. Conclusions

	Conclusions Judgmen					
Health risk	Oral exposure	No need for further work.	0			
Health HSK	Inhalation exposure	No need for further work.	0			
Ecological risk	No need for further work.					

[Risk judgments] O: No need for further work

▲: Requiring information collection

×: Impossibility of risk characterization

■: Candidates for further work >

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

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