

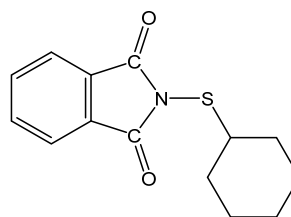
Chemical Substances Control Law Reference No.: 5-3358

PRTR Law Cabinet Order No.:1-155 (number after law revision*: 2-45)

Molecular Formula: C₁₄H₁₅NO₂S

Molecular Weight: 261.34

Structural Formula:



1. General information

The aqueous solubility of this substance is 12.4 mg/L (20°C) (pH = 4.74–5), the partition coefficient (1-octanol/water) (log K_{ow}) is 2.82–3.56 (25°C) (pH = 6.9), and the vapor pressure is 3.47×10^{-7} Pa (25°C) (calculated value). Its biodegradability (aerobic degradation) is 15.6% (mean value) based on oxygen consumption. In addition, the substance hydrolyzes (half-life: 23.3 h, 25°C, pH=7) to form *N*-(cyclohexylthio)phthalamide.

N-(cyclohexylthio)phthalimide is classified as a Class 1 Designated Chemical Substance under the PRTR Law, but it will be reclassified as a Class 2 Designated Chemical Substance by the Cabinet Order partially revising the Enforcement Order for the Act on the Assessment of Releases of Specified Chemical Substances in the Environment and the Promotion of Management Improvement promulgated on October 20, 2021, that will come into force on April 1, 2023.

The main use of this substance is as a synthetic rubber chemical (anti-scorching agent). The production and import quantity in fiscal 2019 was less than 1,000 t, and the production and import category under the PRTR Law was over 100 t.

2. Exposure assessment

Total release to the environment in fiscal 2019 under the PRTR Law was approximately 0.92 t, of which approximately 0.41 t or 44% of overall releases were reported. The majority of reported releases were to public water bodies. In addition, approximately 16 t was transferred to waste materials. The rubber products manufacturing industry reported releases to the atmosphere. The chemical industry reported releases to public water bodies. Releases to the environment, including unnotified releases, were to water bodies. 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 to public water bodies in particular, the predicted proportion distributed to water bodies was 96.9%. Where the largest quantity was estimated to have been released to the atmosphere, the predicted proportion distributed to water bodies was 96.8%.

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. Further, the mean annual value for atmospheric concentration in fiscal 2019 was calculated by use of a plume-puff model on the basis of releases to the atmosphere reported under the PRTR Law; this model predicts a maximum level of 0.0031 $\mu\text{g}/\text{m}^3$.

Data for potable water, groundwater, public freshwater bodies, seawater, food, and soil to assess oral exposure could not be obtained. However, when reported releases to public freshwater bodies in fiscal 2019 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 12 $\mu\text{g}/\text{L}$, and the oral exposure calculated thereof was 0.47 $\mu\text{g}/\text{kg}/\text{day}$. 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.

Exposure to aquatic organisms based on measured water quality data could not be estimated. When reported releases to public freshwater bodies in fiscal 2019 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 12 $\mu\text{g}/\text{L}$.

3. Initial assessment of health risk

No information was available on acute symptoms in humans. Somnolence and excitement were observed in mice and rabbits exposed to this substance by ingestion.

Since not enough information was available on the carcinogenicity of the substance, the initial assessment was conducted based on information on its non-carcinogenic effects.

The NOAEL of 3.8 mg/kg/day for oral exposure (based on the increased relative weight of kidneys), determined from toxicity tests in rats, was divided by a factor of 10 to account for extrapolation to chronic exposure. The calculated value of 0.38 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 LOAEL of 2.7 mg/m³ for inhalation exposure (based on degeneration and regeneration of tubular epithelium, granular casts, etc.), determined from toxicity tests in rats, was divided by a factor of 10 to account for uncertainty in using a LOAEL, and by another factor of 10 to account for extrapolation to chronic exposure. The calculated value of 0.027 mg/m³ was deemed to be the lowest reliable concentration and was identified as the ‘non-toxic level’ of the substance for inhalation exposure.

Regarding oral exposure, due to the lack of identified exposure levels, the health risk could not be assessed. However, the maximum exposure level was estimated to be 0.47 µg/kg/day according to the concentration in effluents from the high discharging plants based on the releases to public freshwater bodies reported in FY 2019 under the PRTR Law. The MOE (Margin of Exposure) for reference would be 81 which is calculated from the estimated maximum exposure level and the ‘non-toxic level’ of 0.38 mg/kg/day, and subsequently divided by a factor of 10 to account for extrapolation from animals to humans. Since exposure to the substance in environmental media via food is presumed to be limited, despite the lack of exposure level via food, including it in the calculation would not change the MOE significantly. 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 data on exposure based on the current releases.

Regarding inhalation exposure, due to the lack of identified exposure concentrations, the health risk could not be assessed. However, the maximum concentration (annual mean) in ambient air, near the operators that are releasing a large amount of the substance, was estimated to be 0.0031 µg/m³, based on the releases to air reported in FY 2019 under the PRTR Law. The MOE for reference would be 870 which is calculated from the estimated concentration in ambient air and the ‘non-toxic level’ of 0.027 mg/m³, and subsequently divided by a factor of 10 to account for extrapolation from animals to humans. Therefore, as a comprehensive judgment, the collection of further information would not be required to assess the health risk of this substance via inhalation in ambient air.

Toxicity				Exposure assessment		MOE		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’ 0.38 mg/kg/day	Rats	The increased relative weight of kidneys	Drinking water	- µg/kg/day	MOE	-	▲
				Groundwater	- µg/kg/day	MOE	-	
Inhalation	‘Non-toxic level’ 0.027 mg/m ³	Rats	Degeneration and regeneration of tubular epithelium, granular casts, etc.	Ambient air	- µg/m ³	MOE	-	○
				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.

4. Initial assessment of ecological risk

With regard to acute toxicity, the following reliable data were obtained: a 48-h EC₅₀ exceeding 142 µg/L for growth inhibition in the green alga species *Raphidocelis subcapitata*, a 48-h EC₅₀ of 1,210 µg/L for swimming inhibition in the crustacean species *Daphnia magna*, and a 96-h LC₅₀ of 690 µg/L for the fish species *Poecilia reticulata* (guppy).

Accordingly, based on these acute toxicity values and an assessment factor of 100, a predicted no effect concentration

(PNEC) of 6.9 µg/L was obtained.

With regard to chronic toxicity, the following reliable data were obtained: a 48-h NOEC of 142 µg/L for growth inhibition in the green alga species *R. subcapitata*, and a 21-d NOEC of 142 µg/L for reproductive inhibition in the crustacean species *Daphnia magna*. Accordingly, based on these chronic toxicity values and an assessment factor of 100, a PNEC of 1.4 µg/L was obtained.

The value of 1.4 µg/L obtained from the chronic toxicity to the crustacean was used as the PNEC for this substance.

An assessment of ecological risk could not be conducted because data for setting the predicted environmental concentration (PEC) could not be obtained

When reported releases to public freshwater bodies in fiscal 2019 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 12 µg/L. The ratio of this value to PNEC is 9 Accordingly, based on a comprehensive review of the above findings, efforts to collect data are considered necessary.

Efforts to elucidate releases to the environment, production and import quantities of this substance are required; data on environmental concentrations in the vicinity of major emission sources need to be augmented.

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)		
Green algae / Crustacean <i>Daphnia magna</i>	Chronic	NOEC Growth inhibition / Reproductive inhibition	100	1.4	Freshwater	—	—	▲
					Seawater	—	—	

5. Conclusions

	Conclusions		Judgment
Health risk	Oral exposure	Collection of further information would be required.	▲
	Inhalation exposure	No need for further work	○
Ecological risk	Requiring information collection		▲

[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