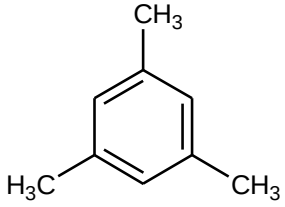
17	CAS No.: 108-67-8	Substance: 1,3,5-Trimethylbenzene

Chemical Substances Control Law Reference No.: 3-7 (tri- or tetra-methylbenzene), 3-3427 (trialkyl (C=1–4) benzene)

PRTR Law Cabinet Order No.: 1-224 (Cabinet Order No. after revision*: 1-297)

Molecular Formula: C_9H_{12} Structural Formula:

Molecular Weight: 120.19



*Note: No. according to revised order enacted on October 1, 2009.

1. General information

The aqueous solubility of this substance is 50 mg/1000 g (25°C), the partition coefficient (1-octanol/water) (log K_{ow}) is 3.42, and the vapor pressure is 2.48 mmHg (=330 Pa) (25°C). The biodegradability (aerobic degradation) is characterized by a BOD degradation rate of 0%, and bioaccumulation is thought to be nonexistent or low.

This substance was designated as a Class 1 Designated Chemical Substance under the Law Concerning Reporting, etc. of Releases to the Environment of Specific Chemical Substances and Promoting Improvements in Their Management (PRTR Law), and this continues to be the case after the revision of substances regulated by the PRTR Law (enacted on October 1, 2009). This substance is a component of petroleum, and it is found in gasoline and other fuels. It is primarily used as a solvent, paint thinner, and antioxidant, while it is also used as a raw material for dyestuffs and pigments, and as a raw material for pharmaceuticals and industrial chemicals. The production and import category under the PRTR Law is 1,000 t. The production quantity of this substance as reported by the OECD is 100,000 to <1,000,000 t/y, and the import quantity is <1,000 t/y.

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2. Exposure assessment

Total release to the environment in fiscal 2006 under the PRTR Law was approximately 5,800 t, of which approximately 1,600 t, or 28% of overall releases, was reported. The major destination of reported releases was the atmosphere. Besides this, approximately 380 t was transfer to waste. Industry types that reported large releases to the atmosphere were the transportation machinery manufacturing industry, the general tools and machinery manufacturing industry, and the metal products manufacturing industry. Those that reported releases to water for public use were the apparel and other textile product manufacturing industry and the petroleum product and coal product manufacturing industry. Including non-reported releases, releases to the atmosphere are estimated to have been the greatest. A multi-media model used to predict the distribution into each medium in the environment indicated that in regions where the largest quantity was estimated to have been released to the atmosphere, the proportion distributed to the atmosphere would be 96.5%. In regions where the largest estimated releases were to public water bodies, the predicted proportion distributed to the atmosphere was 80.7%.

The predicted maximum exposure to humans via inhalation, based on general environmental atmospheric data, was approximately 2.3 μg/m^3. In addition, the predicted maximum exposure for indoor air was around 11 μg/m^3. On the other hand, the mean annual value for atmospheric concentration in fiscal 2006 calculated using a plume-puff model based on reported releases to the atmosphere according to the PRTR Law was a maximum of 10 μg/m^3.

Data for calculating the predicted maximum oral exposure to humans could not be obtained, but calculations from public freshwater body data for a limited area gave a provisional value of around 0.056 μg/kg/day. On the other hand, when reported releases to public freshwater bodies in fiscal 2006 according to the PRTR Law are divided by the

ordinary water discharge of the national river structure database, estimating the concentration in rivers solely taking dilution into consideration gives a maximum value of 55 μg/L. Using this estimated concentration for rivers to calculate oral exposure gives 2.2 μg/kg/day. The risk of exposure to this substance by intake from an environmental medium via food is considered slight.

The predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, could not be set because water quality data could not be obtained, but there is a report of a maximum of around 1.4 μg/L for public freshwater bodies in a limited area. River concentration estimated using reported releases based on the PRTR Law was a maximum of 55 μg/L.

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3. Initial assessment of health risk

This substance is irritating to the eyes, skin and respiratory tract and may cause effects on the central nervous system. This substance may cause chemical pneumonia if swallowed in its liquid form as it is absorbed into the lungs. Inhalation or oral exposure causes confusion, cough, dizziness, lethargy, headache, sore throat and vomiting. Redness and dryness of the skin and redness and painful irritation in the eyes are caused by contact with this substance.

Sufficient information could not be obtained on its carcinogenicity, and its initial assessment was conducted on the basis of data on its non-carcinogenic effects.

As for its oral exposure, its no-observed-adverse-effect-level (NOAEL) of 200 mg/kg/day (for increase in relative liver weight, etc.) was obtained from its mid-term and long-term toxicity tests for rats. It was then adjusted for exposure conditions to provide 143 mg/kg/day. This was divided by 10 due to their short test periods to provide 14 mg/kg/day as its 'non-toxic level*'.

As for inhalation exposure to this substance, its 'non-toxic level' could not be identified. However, its LOAEL of 25 ppm or 123 mg/m^3 had been obtained for effects on the central nervous system from mid-term and long-term toxicity tests for rats. When adjusted for exposure conditions, it would be 22 mg/m^3. This was divided by 100 (divided by 10 due to their short test periods, and divided by 10 again as is always the case with LOAEL) to provide 0.22 mg/m^3 as its 'non-toxic level*'.

As for its oral exposure, data at national-level were not available, and its health risk could not be assessed. Its maximum exposure was estimated to be around 0.056 μg/kg/day from the report for some location, when intakes of freshwater in public water bodies were assumed. Its margin of exposure (MOE) would be 25,000, when calculated from its 'non-toxic level*' of 14 mg/kg/day and its estimated maximum exposure, and then divided by 10 due to the fact that the 'non-toxic level*' was obtained from animal experiments. Since risk associated with exposure to this substance through food intakes from the environment is presumed to be minimal, this exposure will not increase MOE significantly. If MOE were calculated from its concentration of 2.2 μg/kg/day in river water estimated from reports of its discharges under the Law Concerning Reporting, etc. of Releases to the Environment of Specific Chemical Substances and Promoting Improvements in Their Management, it would be 640. It would not be required to collect information on its oral exposure for the assessment of health risk associated with oral exposure to this substance.

As for its inhalation exposure, its 'non-toxic level *' could not be identified, and its health risk could not be assessed. The 'non-toxic level' for its oral exposure, if 100% absorption is assumed for it, turns to be the 'non-toxic level' of 47 mg/m^3 for its inhalation exposure. This is approximately 20 times higher than the 'non-toxic level*' of 2.2 mg/m^3 for inhalation exposure of 1,2,4-trimethylbenzene, an isomer of this substance. The reason for the determination of the endpoint can be that the region is directly exposed to the substance (degeneration of the peribronchial region). Much lower 'non-toxic level' for inhalation exposure of 1,2,4-trimethylbenzene would be attributed to its endpoint, or the effect on peribranchial parts (degeneration) under its direct exposure. 'Non-toxic level' of 10 mg/kg/day for oral exposure of 1,2,4-trimethylbenzene was similar to the 'non-toxic level' of this

substance. Its "non-toxic level" for inhalation exposure, therefore, was assumed to be 2 mg/m^3 as same as 1,2,4-trimethylbenzene, and MOE of 87 was obtained from the predicted maximum exposure of 2.3 μg/m^3 to this substance in the ambient air. On the other hand, the predicted maximum concentration for exposure in the indoor air is estimated to be 11 μg/m^3, and MOE will be 18. If MOE were calculated from its concentration of 10μg/m^3 in ambient air estimated from reports of its discharges under the Law Concerning Reporting, etc. of Releases to the Environment of Specific Chemical Substances and Promoting Improvements in Their Management, it would be 20. Its LOAEL of 25 ppm or 123 mg/m^3 had been obtained from mid-term and long-term toxicity tests for rats. This LOAEL would produce its 'non-toxic level' of 0.22 mg/m^3, and its MOE would be as low as one-tenth of the above-mentioned value.

Therefore, collection of information on its inhalation exposure would be required to assess health risk associated with its inhalation both in the ambient air and indoor air.

Information of toxicity				Exposure assessment		Result of risk assessment			Judgment
Exposure Path	Criteria for risk assessment	Animal	Criteria for diagnoses (endpoint)	Exposure medium	Predicted maximum exposure quantity and concentration				
Oral	'Non-toxic level*' 14 mg/kg/day	Rats	Increase in relative liver weight, etc.	Drinking water	– μg/kg/day	MOE	–	×	(○)
				Freshwater	– μg/kg/day	MOE	–	×	
Inhalation	'Non-toxic level*' – mg/m^3	–	–	Ambient air	2.3 μg/m^3	MOE	–	×	(▲)
				Indoor air	11 μg/m^3	MOE	–	×	(▲)

Non-toxic level *

- When a LOAEL is available, it is divided by 10 to obtain a level equivalent to NOAEL.
- When an adverse effect level is available for the short-term exposure, 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 48-h median effective concentration (EC_{50}) of 53,000 μg/L for growth inhibition in the green algae *Desmodesmus subspicatus;* a 24-h median lethal concentration (LC_{50}) of 14,200 μg/L for the crustacean *Artemia salina* (brine shrimp); and a 96-h LC_{50} of 12,500 μg/L for the fish species *Carassius auratus* (goldfish). Accordingly, based on these acute toxicity values and an assessment factor of 100, a predicted no effect concentration (PNEC) of 130 μg/L was obtained. With regard to chronic toxicity, reliable data of a 21-d no observed effect concentration (NOEC) of 400 μg/L was obtained for reproductive inhibition in the crustacean *Daphnia magna*. Accordingly, based on this chronic toxicity value and an assessment factor of 100, a predicted no effect concentration (PNEC) of 4 μg/L was obtained. The value of 4 μg/L obtained from the chronic toxicity to the crustacean was used as the PNEC for this substance.

At this point in time, data of environmental concentrations could not be obtained, and for this reason, judgment of ecological risk cannot be made. If the PEC for the limited area of 1.4 μg/L is provisionally used, the PEC/PNEC ratio is then 0.4. Furthermore, when taking the river concentration of 55 μg/L estimated using reported releases based on the PRTR Law as the PEC, the PEC/PNEC ratio is 14. Accordingly, reassessment of this substance is considered necessary after measuring its concentration in the environment.

Hazard assessment (basis for PNEC)			Assessment factor	Predicted no effect concentration PNEC (μg/L)	Exposure assessment		PEC/ PNEC ratio	Result of assessment
Species	Acute/ chronic	Endpoint			Water body	Predicted environmental concentration PEC (μg/L)		
Crustacean (water flea)	Chronic	NOEC Reproductive inhibition	100	4	Freshwater	-	-	× (▲)
					Seawater	-	-	

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5. Conclusions

	Conclusions		Judgment
Health risk	Oral exposure	Though a risk characterization cannot be determined, there would be little necessity of collecting information.	（○）
	Inhalation exposure	Impossibility of risk characterization. Collection of information considered necessary.	（▲）
Ecological risk	Impossibility of risk characterization. Reassessment of this substance is considered necessary after measuring its concentration in the environment.		（▲）

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

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

（○）: Though a risk characterization cannot be determined, there would be little necessity of collecting information.

（▲）: Further information collection would be required for risk characterization.