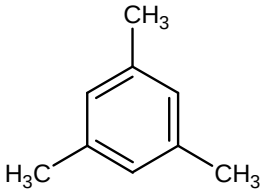
13	CAS No.: 108-67-8	Substance: 1,3,5-Trimethylbenzene

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

PRTR Law Cabinet Order No.: 1-297

Molecular Formula: C_9H_{12} Structural Formula:

Molecular Weight: 120.19



1. General information

The aqueous solubility of this substance is 50 mg/1,000 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). Biodegradability (aerobic degradation) is characterized by a BOD degradation rate of 0%, and bioaccumulation is judged to be non-existent or low.

This substance is 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). The main uses of this substance are as a solvent, paint thinner, antioxidant, and as a raw material for dyestuffs, pigments, pharmaceuticals, and industrial chemicals. The production and import quantity in fiscal 2010 as tri- or tetra-methyl benzene 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 2010 under the PRTR Law was approximately 4,000 t, of which approximately 1,200 t or 31% of overall releases were reported. The major destination of reported releases was the atmosphere. In addition, 270 t was transferred to waste materials, and approximately 0.53 t was transferred to sewage. Industry types with large reported releases were the transportation equipment and machinery manufacturing industry, the shipbuilding and repair industry, the marine engine manufacturing industry, the metal products manufacturing industry, and the plastic products manufacturing industry for the atmosphere, and the metal products manufacturing industry and the fiber industry for public water bodies. The largest release among releases to the environment including those unreported was 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 to the atmosphere in particular, the predicted proportion distributed to the atmosphere was 87.9%. In regions where the largest estimated releases were to public water bodies, the predicted proportions distributed to the atmosphere and soil were 67.6% and 31.8%, respectively. In regions where the largest estimated releases were to soil, the predicted proportions distributed to the atmosphere and soil were 61.5% and 37.4%, respectively.

The maximum expected concentration of exposure to humans via inhalation, based on general environmental atmospheric data, was around 1.6 μg/m^3 (roadside). The maximum expected exposure from indoor air was around 21 μg/m^3. The mean annual value for atmospheric concentration in fiscal 2010 was calculated by using a plume-puff model on the basis of reported releases to the atmosphere according to the PRTR Law; this model predicted a maximum level of 26 μg/m^3.

The maximum expected oral exposure was estimated to be around less than 0.0018 μg/kg/day on the basis of calculations from data for public freshwater bodies. In addition, a maximum expected oral exposure of around

0.056 μg/kg/day is calculated from data for public freshwater bodies in a limited area. When reported releases to public freshwater bodies in fiscal 2010 according to the PRTR Law were divided by the ordinary water discharge of the national river channel structure database, estimating the concentration in rivers t while taking into consideration only dilution gave a maximum value of 5.3 μg/L. Using this estimated concentration for rivers to calculate oral exposure gave 0.21 μg/kg/day. The risk of exposure to this substance by intake from an environmental medium via food is considered slight, based on estimates of oral exposure obtained by using estimated concentrations in fish species.

The predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, was around less than 0.044 μg/L for both public freshwater bodies and seawater. Note that albeit for a limited area, a maximum of around 1.4 μg/L has been reported for public freshwater bodies. The maximum river concentration was estimated to be 5.3 μg/L from reported releases to public freshwater bodies under the PRTR Law.

3.Initial assessment of health risk

This substance may cause irritation to eyes, skin and respiratory tract, and it may even affect the central nervous system. If its liquid is swallowed, aspiration into lungs may lead to chemical pneumonia. When inhaled or orally ingested, confusion, coughing, dizziness, lethargy, headache or vomiting may occur. Red or dry skin and eye redness and pain may occur if they accidentally come into direct contact with the substance.

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

With regard to oral exposure to the substance, a NOAEL of 200 mg/kg/day (for increased relative liver weight, etc.) obtained from its mid-term and long-term toxicity tests on rats was adjusted fro their durations to provide 143 mg/kg/day for its intermittent to continuous exposure, and divided by a factor of 10 due to their short test periods. 14 mg/kg/day derived was identified to be the reliable lowest dose of the substance as its ‘non-toxic level*’. With regard to inhalation exposure to the substance, its ‘non-toxic level*’ could not be determined. However, when a LOAEL of 25 ppm (or 123 mg/m^3; for effects on the central nervous system) obtained from its mid-term and long-term toxicity tests on rats was adjusted for their durations to provide 22 mg/m^3 for its intermittent to continuous exposure, and divided by a factor of 100 due to their short test periods and the use of a LOAEL, its ‘non-toxic level*’ of 0.22 mg/m^3 was produced.

Additionally, as for oral exposure to the substance, its maximum exposure was predicted to be below about 0.00018 μg/kg/day when intakes of freshwater from public water bodies were assumed. The MOE (Margin of Exposure) would be above 7,800,000 when calculated from its ‘non-toxic level*’ of 14 mg/kg/day and the maximum exposure predicted from animal experiments, and further divided by a factor or 10 to convert animal data to human. In addition, its maximum exposure would be approximately 0.056 μg/kg/day for some area when intakes of freshwater from public water bodies were assumed, and this would provide the MOE of 25,000. Its maximum exposure level was calculated to be 0.21 μg/kg/day from concentrations of the substance in river water with effluents from operators discharging high concentrations of the substance, reported in FY 2010 under the PRTR Law, and this would provide the MOE of 6,700. As exposure to the substance in the environment through food intakes would be limited, the MOE would not change significantly even when this exposure was included. Therefore, no further action would be required at this moment to assess health risk from its oral exposure.

As for inhalation exposure to the substance, as its ‘non-toxic level*’ could not be identified, its health risk could not be assessed accordingly. However, if 100 % absorption were assumed, the ‘non-toxic level*’ for oral exposure would be converted to 47 mg/m^3 for inhalation exposure. This is 20 times higher than the ‘non-toxic level*’ (2.2 mg/m^3) of its isomer, 1,2,4-Trimethylbenzene for inhalation exposure. This was attributed to the fact

that the 'non-toxic level*' (for degeneration of bronchial area) for inhalation exposure to the 1,2,4-isomer is for the body surface exposed directly. Assuming that the 'non-toxic level*' (10 mg/kg/day) of 1,3,5-Trimethylbenzene for inhalation exposure were same as that of the 1,2,4-isomer (as obtained from animal experiments), the 'non-toxic level*' of 1,3,5-Trimethylbenzene for inhalation exposure would be 2 mg/m^3. The MOE would be 130 when calculated from its predicted maximum exposure of approximately 1.6 μg/m^3 (as contained in roadside soils).

In addition, its maximum (annual mean) concentration in the ambient air near operators with its emissions in high concentrations was calculated to be was 26 μg/m^3 from its emissions reported in FY 2010 under the PRTR Law, and this would provide the MOE of 8.

With regard to its concentrations in the indoor air, the maximum exposure was predicted to be approximately 21 μg/m^3, and this would provide the MOE of 9.5. In addition, a LOAEL of 25 ppm (123 mg/m^3) obtained from mid-term and long-term toxicity tests on rats would produce its 'non-toxic level*' of 0.22 mg/m^3, and the MOE would be much smaller by about 1/10. Therefore, collection of further information would be required to assess health risk from its inhalation exposure both in the ambient air and in the indoor 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 doseand concentration				
Oral	'Non-toxic level*', 14 mg/kg/day	Rat	Increased relative liver weight, etc.	Drinking water	— μg/kg/day	MOE	—	×	○
				Freshwater	< 0.00018 μg/kg/day	MOE	> 7,800,000	○	
Inhalation	'Non-toxic level*' — mg/m^3	—	—	Ambient air	1.6 μg/m^3	MOE	—	×	(▲)
				Indoor air	21 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 48-h EC_{50} of 53,000 μg/L for growth inhibition in the green alga *Desmodesmus subspicatus*, a 24-h LC_{50} of 14,200 μg/L for the crustacean *Artemia* sp. (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, a 21-d NOEC of 400 μg/L for reproductive inhibition in the crustacean *Daphnia magna* was obtained as a reliable finding. Accordingly, based on these chronic toxicity values and an assessment factor of 100, a 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.

The PEC/PNEC ratio was less than 0.01 for both freshwater bodies and seawater. However, the maximum river concentration was estimated to be 5.3 μg/L from reported releases under the PRTR Law, and locations with concentrations that are higher than the PNEC may exist.

Accordingly, there is a need to collect data on this substance, and to augment environmental concentration data by taking PRTR data into consideration.

Hazard assessment (basis for PNEC)			Assessment factor	Predicted no effect concentration PNEC (μg/L)	Exposure assessment		PEC/PNEC ratio	Judgment based on PEC/PNEC ratio	Assessment result
Species	Acute/ chronic	Endpoint			Water body	Predicted environmental concentration PEC (μg/L)			
Crustacean *Daphnia magna*	Chronic	NOEC reproductive inhibition	10	4	Freshwater	<0.044	<0.01	○	▲
					Seawater	<0.044	<0.01		

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5. Conclusions

	Conclusions		Judgment
Health risk	Oral exposure	No need for further work.	○
	Inhalation exposure	Although risk to human health could not be identified, collection of further information would be required.	(▲)
Ecological risk	Requiring information collection.		▲

［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.