11	CAS No.: 99-76-3	Substance: Methyl 4-hydroxybenzoate

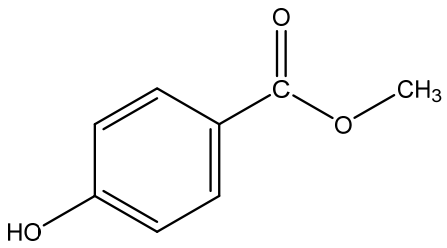
Chemical Substances Control Law Reference No.: 3-1585（Alkyl hydroxybenzoate (C=1–22)）

PRTR Law Cabinet Order No.: 1-334

Molecular Formula: $C_8H_8O_3$

Molecular Weight: 152.15

Structural Formula:



1. General information

The aqueous solubility of this substance is 2.4×10^3 mg/1000 g (25°C), the partition coefficient (1-octanol/water) (log K_{ow}) is 1.96, and the vapor pressure is 7.00×10^{-2} mmHg (= 9.33 Pa) (25°C). The biodegradability (aerobic degradation) is 89% based on the quantity of CO_2 emitted.

This substance is classified as a Class 1 Designated Chemical Substance under the PRTR Law. The main uses of this substance are as a preservative for pharmaceuticals and an additive in quasi-drugs (anti-mold agents for cosmetics). The production and import quantity of alkyl hydroxybenzoates (C=1–22) in fiscal 2017 was 4000 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 2017 under the PRTR Law was approximately 0.63 t, of which approximately 0.35 t or 56% was reported. Most reported releases were to public water bodies. In addition, approximately 17 t was transferred to waste and 0.30 t to sewage. The chemical industry was the main reporter of releases to the atmosphere, while the pulp & paper/paper products industry was the main reporter of releases to public water bodies. The largest releases to the environment, including unreported releases, were to water bodies. A multimedia 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 to public water bodies in particular, the predicted proportion distributed to water bodies was 99.5%. Where the largest quantities were estimated to have been released to the atmosphere, the predicted proportion distributed to water bodies was 54.5%, and that to the atmosphere was 29.1%.

The maximum expected concentration of exposure to humans via inhalation, based on general environmental atmospheric data, was around less than 0.0027 μg/m^3. The mean annual value for the atmospheric concentration in fiscal 2017 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 0.013 μg/m^3.

Data for setting the predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, could not be obtained. Further, albeit based on past data, calculations for public freshwater bodies gave a daily oral exposure of roughly less than 0.00008 μg/kg/day. In addition, albeit based data for a limited area, calculations for public freshwater bodies gave a maximum exposure of around 0.014 μg/kg/day. Conversely, when releases reported under the PRTR Law in fiscal 2017 to public freshwater bodies estimated from the reported transfer to public freshwater bodies 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 0.068 μg/L. Calculating oral exposure based on this gives 0.0027 μg/kg/day. Further, when transfer to sewage is included in the previous calculation, a maximum value of 1.7 μg/L is obtained, and the resulting oral exposure becomes 0.069 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.

Data for setting the predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, could not be obtained. Further, past data indicated a maximum value of generally less than 0.002 μg/L for public freshwater

bodies. In addition, albeit obtained from a survey of a limited area, indicate maximum values of around 0.36 μg/L for public freshwater bodies and generally 0.0079 μg/L for seawater. When releases reported under the PRTR Law in fiscal 2017 to public freshwater bodies estimated from the reported transfer to public freshwater bodies 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 0.068 μg/L. Further, when transfer to sewage is included in the previous calculation, a maximum value of 1.7 μg/L is obtained.

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3. Initial assessment of health risk

It has been reported that putting 0.1% solution of this substance in the mouth caused tongue paralysis and reduced sensation in a few minutes.

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 250 mg/kg/day for oral exposure (based on reduction in the relative weight of ovaries and increase in the relative weight of thyroid gland, adrenal gland and liver, etc.) determined from toxicity tests in rats, was divided by a factor of 10 to account for extrapolation to chronic exposure. The calculated value of 25 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 'non-toxic level' for inhalation exposure could not be identified.

With regard to oral exposure, owing to the lack of identified exposure levels, the health risk could not be assessed. However, the MOE (Margin of Exposure) for reference would be 180,000, when calculated from the estimated maximum exposure level of 0.014 μg/kg/day and the 'non-toxic level' of 25 mg/kg/day, and subsequently divided by a factor of 10 to account for extrapolation from animals to humans. This maximum exposure level was estimated according to the data on public freshwater bodies reported in a restricted area. Alternatively, the MOE for reference would be 930,000, when calculated from the estimated maximum exposure level of 0.0027 μg/kg/day. This maximum exposure level was estimated according to the concentration in effluents from the high discharging plants reported in FY 2017 under the PRTR Law. When transfers to sewage are considered, the maximum exposure level would be 0.069 μg/kg/day, giving an MOE of 36,000. Since exposure to the substance in environmental media via food is presumed to be limited in spite of data unavailability, including it in the calculation would not change the MOE significantly. Therefore, as a comprehensive judgment, collection of further information would not be required 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', the health risk could not be assessed. However, the MOE for reference would exceed 3,100,000, when calculated from the tentative 'non-toxic level' for inhalation exposure of 83 mg/m^3 and the predicted maximum exposure concentration in ambient air of 0.0027 μg/m^3, and subsequently divided by a factor of 10 to account for extrapolation from animals to humans. The tentative 'non-toxic level' for inhalation exposure above was derived from the conversion of the 'non-toxic level' for oral exposure, assuming that 100% of the inhaled substance is absorbed. Alternatively, the MOE for reference would be 640,000, when calculated from the concentration in ambient air of 0.013 μg/m^3. This concentration was estimated as the maximum concentration (annual mean) in ambient air near the operators releasing large amount of the substance based on the releases to air reported in FY 2017 under the PRTR Law. Therefore, as a comprehensive judgment, 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' 25 mg/kg/day	Rats	Reduction in the relative weight of ovaries and increase in the relative weight of thyroid gland, adrenal gland and liver etc.	Drinking water	- μg/kg/day	MOE	-	○
				Groundwater	- μg/kg/day	MOE	-	
Inhalation	'Non-toxic level' - mg/m^3	-	-	Ambient air	<0.0027 $\mu g/m^3$	MOE	-	○
				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.

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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 55,600 μg/L for growth inhibition in the alga *Raphidocelis subcapitata*, a 48-h EC_{50} of 11,200 μg/L for swimming inhibition in the crustacean *Daphnia magna*, and a 96-h LC_{50} of 59,500 μg/L for the fish *Oryzias latipes* (medaka). Accordingly, based on these acute toxicity values and an assessment factor of 100, a predicted no effect concentration (PNEC) of 110 μg/L was obtained.

With regard to chronic toxicity, the following reliable data were obtained: a 72-h NOEC of 16,600 μg/L for growth inhibition in the green alga *R. subcapitata* and a 21-d NOEC of 200 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 2.0 μg/L was obtained.

The value of 2.0 μg/L obtained from the chronic toxicity to the crustacean was used as the PNEC for this substance.

Data for setting the predicted environmental concentration (PEC) could not be obtained for this substance. Accordingly, an assessment of ecological risk could not be made.

However, past data, albeit obtained from a survey of a limited area, indicate maximum values of around 0.36 μg/L for public freshwater bodies and generally 0.0079 μg/L for seawater. The ratios to the PNEC are 0.18 for freshwater and 0.004 for seawater.

When releases reported under the PRTR Law in fiscal 2017 to public freshwater bodies estimated from the reported transfer to public freshwater bodies 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 0.068 μg/L, and the ratio of this value to the PNEC is 0.03. Further, when transfer to sewage is included in the previous calculation, a maximum value of 1.7 μg/L is obtained, and the ratio of this value to the PNEC is 0.85; accordingly, based on a comprehensive review of the above findings, efforts to collect data are needed.

Environmental concentration data for this substance needs to be augmented taking into consideration chronic toxicity towards fish species and environmental concentrations in the vicinity of major emission sources.

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)		
Crustacean *Daphnia magna*	Chronic	NOEC Reproductive inhibition	100	2.0	Freshwater	—	—	▲
					Seawater	—	—	

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5. Conclusions

	Conclusions		Judgment
Health risk	Oral exposure	No need for further work.	○
	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