7	CAS No.: 94-13-3	Substance: Propyl 4-hydroxybenzoate

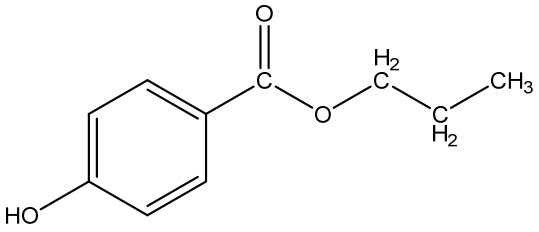
Chemical Substances Control Law Reference No.: 3-1585 (Alkyl hydroxybenzoate (C=1–22))

PRTR Law Cabinet Order No.:

Molecular Formula: $C_{10}H_{12}O_3$

Molecular Weight: 180.20

Structural Formula:



1.General information

The aqueous solubility of this substance is 400 mg/1,000 g (25°C), the partition coefficient (1-octanol/water) (log K_{ow}) is 3.01 (pH=7.5), and the vapor pressure is 1.97×10^{-5} mmHg (=2.63×10^{-3} Pa) (33.7°C). The biodegradability (aerobic degradation) is characterized by a BOD degradation rate of 91.5%.

The main uses of this substance is as a preservative added to pharmaceuticals, medicated products and food products. Further, the production and import quantity of alkyl hydroxybenzoate (C=1–22) in fiscal 2018 was 5,000 t.

2.Exposure assessment

Because this substance is not classified as a Class 1 Designated Chemical Substance under the PRTR Law, release and transfer quantities could not be obtained. Predictions of proportions distributed to individual media by use of a Mackay-type level III fugacity model indicate that if equal quantities were released to the atmosphere, water bodies, and soil, the proportion distributed to soil would be largest.

The maximum expected concentration of exposure to humans via inhalation was not established because neither data measured for the ambient atmosphere nor indoor air could be obtained.

Data for potable water, ground water, food, and soil to assess oral exposure could not be obtained. Thus, assuming intake solely from public freshwater bodies, a maximum expected concentration of exposure of around 0.00064 μg/kg/day. Further, albeit based on data for a limited area, calculations for public freshwater bodies gave a daily oral exposure value of around 0.0072 μg/kg/day. In addition, because this substance may be added to food as a preservative, market basket-type survey findings were not used to assess oral exposure via food. Instead, measured data for fish species were used as a reference. Albeit past data, the average daily intake of fish and shellfish (65.1 g/capita/day) was used to estimate exposure by intake from an environmental medium via food (fish and shellfish) to be less than 0.003 μg/kg/day. Further, a reference value of a maximum of less than 0.01 μg/kg/day for oral exposure was calculated from public freshwater bodies and food (fish and shellfish) for a limited area.

The predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, was reported to be around 0.016 μg/L for public freshwater bodies and around less than 0.014 μg/L for seawater. Further, albeit for a limited area, a maximum of around 0.18 μg/L was reported for public freshwater bodies.

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3. Initial assessment of health risk

It has been reported that putting 0.03% solution of this substance in the mouth caused tongue paralysis and reduced sensation within a few minutes.

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

The LOAEL of 100 mg/kg/day for oral exposure (based on increase in the ALT, AST, etc. and effects on liver tissue), 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 1.0 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.

Regarding the oral exposure, assuming that the substance is absorbed via public freshwater bodies, the predicted maximum exposure level would be 0.00064 μg/kg/day, approximately. The MOE (Margin of Exposure) would be 160,000, when calculated from the predicted maximum exposure level and the 'non-toxic level' of 1.0 mg/kg/day, and subsequently divided by a factor of 10 to account for extrapolation from animals to the humans. This would lead to the health risk judgment that no further work would be required at present. In addition, the MOE for reference would exceed 10,000, when calculated from the estimated maximum exposure level of less than 0.01 μg/kg/day. This maximum exposure level was estimated assuming that the substance is absorbed via fish and public freshwater bodies in a certain area, due to the lack of exposure level via food. Therefore, as a comprehensive judgment, no further work would be required at present to assess the health risk of this substance via oral exposure.

Regarding the inhalation exposure, due to the lack of identified 'non-toxic level' and exposure concentrations, the health risk could not be assessed. The vapor pressure of the substance is low, and predictions of the multimedia fugacity model indicated that the proportion distributed to air was little. In addition, considering the current use and the observed concentrations in urea samples, the exposure level of this substance is not presumed to exceed that of 4-Hydroxybenzoic acid methyl substantially. The MOE would exceed 120,000, when calculated from the tentative 'non-toxic level' for inhalation exposure of 3.3 mg/m^3 and the predicted maximum exposure concentration of 4-Hydroxybenzoic acid methyl of less than 0.0027 μg/m^3, approximately (see vol. 18), and subsequently divided by a factor of 10 to account for extrapolation from animals to the humans. The tentative 'non-toxic level' 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 would be 25,000, when calculated from the estimated maximum concentration of 0.013 μg/m^3 in ambient air near the operators that are releasing large amount of 4-Hydroxybenzoic acid methyl. The calculated MOEs are sufficiently higher than 100. 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' 1.0 mg/kg/day	Rats	Increase in the ALT, AST, etc. and effects on liver tissue.	Drinking water	- μg/kg/day	MOE	-	○
				Public freshwater bodies	0.00064 μg/kg/day	MOE	160,000	
Inhalation	'Non-toxic level' - mg/m^3	-	-	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 72-h EC_{50} of 15,000 μg/L for growth inhibition

in the alga *Raphidocelis subcapitata*, a 96-h LC_{50} of 114 μg/L for the crustacean *Tigriopus japonicus*, a 96-h LC_{50} of 6,400 μg/L for the fish species *Danio rerio* (zebra fish), and a 96-h LC_{50} of 12,300 μg/L for the dugesiid triclad *Dugesia japonica*. Accordingly, based on these acute toxicity values and an assessment factor of 100, a predicted no effect concentration (PNEC) of 1.1 μg/L was obtained.

With regard to chronic toxicity, the following reliable data were obtained: a 72-h NOEC of 2,100 μg/L for growth inhibition in the alga *R. subcapitata* and a 21-d NOEC of 5 μg/L for reproductive inhibition in the crustacean *T. japonicus*. Accordingly, based on this chronic toxicity value and an assessment factor of 100, a PNEC of 0.05 μg/L was obtained.

The value of 0.05 μg/L obtained from the chronic toxicity to the crustacean was used as the PNEC for this substance.

The PEC/PNEC ratio is 0.3 for freshwater bodies and less than 0.3 for seawater. Accordingly, efforts to collect data for assessment of ecological risk are needed.

Further, albeit for a limited area, a maximum of around 0.18 μg/L was reported for public freshwater bodies. The ratio of this value to the PNEC is 3.6. Accordingly, based on a comprehensive review of the above findings, efforts to collect data are needed.

Efforts to augment data regarding chronic toxicity towards fish species and environmental concentration taking into consideration major emission sources are needed.

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 *Tigriopus japonicus*	Chronic	NOEC Reproductive inhibition	100	0.05	Freshwater	0.016	0.3	▲
					Seawater	<0.014	<0.3	

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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