7	CAS No.: 119-90-4	Substance: 3,3'-Dimethoxybenzidine

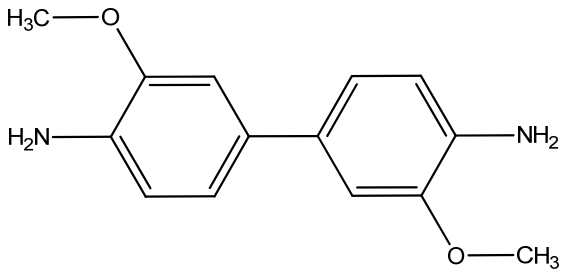
Chemical Substances Control Law Reference No.:

PRTR Law Cabinet Order No.:

Molecular Formula: $C_{14}H_{16}N_2O_2$

Molecular Weight: 244.29

Structural Formula:



1.General information

The aqueous solubility of this substance is 60 mg/1,000 g (25°C), the partition coefficient (1-octanol/water) (log K_{ow}) is 1.81, and the vapor pressure is 7.1×10^{-6} mmHg (=9.5×10^{-4} Pa) (25°C, calculated value). Biodegradability (aerobic degradation) is low and the substance does not possess any hydrolyzable groups. The main use of this substance is as an intermediate for pharmaceuticals and dyestuffs (Fast Blue B base). The production quantity in fiscal 2014 was approximately 200 t (estimated).

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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 could not be determined because ambient atmospheric and indoor air quality data could not be obtained.

Data for potable water, ground water, food and soil to assess oral exposure could not be obtained. Thereupon, assuming intake solely from public freshwater bodies, a maximum expected concentration of exposure of generally less than 0.000084 μg/kg/day was obtained.

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.

The predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, was reported to be generally less than 0.0021 μg/L for public freshwater bodies.

Data capable of withstanding assessment could not be obtained and therefore, a PEC could not be set for seawater.

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3. Initial assessment of health risk

Inhalation of this substance causes cough and contact with the eyes causes redness.

As sufficient information on the carcinogenicity in humans was not available, it could not be determined whether the substance is carcinogenic to humans or not. However, significant and dose-dependent tumorigenesis was observed in diverse organs in all dose-groups in the carcinogenesis study by oral administration in rats. Considering the above, assessment of the carcinogenic risk was deemed necessary as well, and initial assessment was conducted for both non-carcinogenic and carcinogenic effects.

The LOAEL of 4.6 mg/kg/day for oral exposure (based on increased hematopoiesis in the liver and spleen,

hepatocellular degeneration and necrosis, etc.), determined from long-term toxicity tests in rats, was divided by a factor of 10 to account for uncertainty in using a LOAEL. The calculated value of 0.46 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 cancer slope factor for oral exposure of 4.8 $(mg/kg/day)^{-1}$ (based on total tumors), determined from carcinogenicity tests in rats, was adopted assuming no threshold. Neither the 'non-toxic level*' nor the unit risk of the substance for inhalation exposure could be identified.

With regard to oral exposure, assuming the substance is absorbed via public freshwater bodies, the predicted maximum exposure level would be less than 0.000084 μg/kg/day, approximately. The MOE (Margin of Exposure) would exceed 110,000, when calculated from the predicted maximum exposure level and the 'non-toxic level*'of 0.46 mg/kg/day, and subsequently divided by a factor of 10 to account for extrapolation from animals to humans and by another factor of 5 to take into consideration the carcinogenicity in animals. The excess cancer incidence rate corresponding to the predicted maximum exposure level would be less than 4.0×10^{-7}, when calculated from the slope factor. Since exposure to the substance in environmental media via food is presumed to be limited, including it in the calculation would change neither the MOE nor the excess incidence rate significantly. Therefore, no further work would be required at present 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*' and exposure concentrations, the health risk could not be assessed. The vapor pressure of the substance is low, and the half-life in air is as short as several hours. The substance was not detected in samples collected from public water bodies. Given these facts, the concentration of the substance in ambient air is not likely to become a major concern. Therefore, collection of further information would not be required to assess the health risk of this substance via inhalation in ambient 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 dose and concentration				
Oral	'Non-toxic level*'	0.46	mg/kg/day	Rats	Increased hematopoiesis in the liver and spleen, etc.	Drinking water	-	μg/kg/day	MOE	-	○
									Excess incidence rate	-	
	Slope factor	4.8	$(mg/kg/day)^{-1}$	Rats	Total tumors	Public freshwater bodies	<0.000084	μg/kg/day	MOE	>110,000	
									Excess incidence rate	$<4.0\times10^{-7}$	
Inhalation	'Non-toxic level*'	-	mg/m^3	-	-	Ambient air	-	$\mu g/m^3$	MOE	-	○
									Excess incidence rate	-	
	Unit risk	-	$(\mu g/m^3)^{-1}$	-	-	Indoor air	-	$\mu g/m^3$	MOE	-	×
									Excess incidence rate	-	

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 13,800 μg/L for growth inhibition in the green alga *Pseudokirchneriella subcapitata*, a 48-h EC_{50} of 6,100 μg/L for swimming inhibition in the

crustacean *Daphnia magna*, and a 96-h LC_{50} of 25,800 μg/L for the fish species *Oryzias latipes* (medaka). Accordingly, based on these acute toxicity values and an assessment factor of 100, a predicted no effect concentration (PNEC) of 61 μg/L was obtained.

With regard to chronic toxicity, the following reliable data were obtained: a 72-h NOEC of 577 μg/L for growth inhibition in the green alga *P. subcapitata*. Accordingly, based on this chronic toxicity value and an assessment factor of 100, a PNEC of 5.7 μg/L was obtained.

The value of 5.7 μg/L obtained from the chronic toxicity to the green alga was used as the PNEC for this substance

The PEC/PNEC ratio is less than 0.0004 for freshwater bodies. A concentration of less than 0.0021 μg/L was reported for a single seawater location. The ratio of this concentration to the PNEC is less than 0.0004; accordingly, further work is considered unnecessary at this time.

Hazard assessment (basis for PNEC)			Assessment coefficient	Predicted no effect concentration PNEC (μg/L)	Exposure assessment		PEC/ PNEC ratio	Assessment result
Species	Acute/ chronic	Endpoint			Water body	Predicted environmental concentration PEC (μg/L)		
Green algae	Chronic	NOEC Growth inhibition	100	5.7	Freshwater	<0.0021	<0.0004	○
					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	No need for further work.		○

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

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

（▲）: Further efforts to collect data required based on comprehensive review of existing relevant data

（■）: Candidate for further work based on comprehensive review of existing data