6	CAS No.: 119-93-7	Substance: 3,3'-Dimethylbenzidine

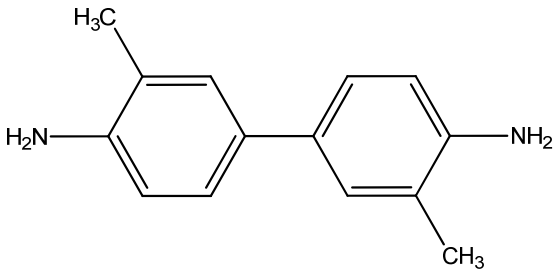
Chemical Substances Control Law Reference No.: 9-882

PRTR Law Cabinet Order No.: 1-231

Molecular Formula: $C_{14}H_{16}N_2$

Molecular Weight: 212.29

Structural Formula:



1.General information

The aqueous solubility of this substance is 1.3×10^3 mg/1,000 g (25°C), the partition coefficient (1-octanol/water) (log K_{ow}) is 2.34, and the vapor pressure is 2.1×10^{-5} mmHg(=2.8×10^{-3} Pa) (25°C, calculated value). The biodegradability (aerobic degradation) is characterized by a BOD degradation rate of 3%, and bioaccumulation is thought to be nonexistent or low. Further, the substance does not possess any hydrolyzable groups.

This substance is classified as a Class 1 Designated Chemical Substance under the PRTR Law. The main use of this substance are as a raw material for dyestuffs (Naphthol AS-G, Toluylene Orange R, Benzo Blue 3B, etc.) and for *o*-tolidine diisocyanate, which is a raw material for polyurethanes and gasket materials. The production and import quantity for fiscal 2016 was not disclosed because the number of reporting businesses was not more than two. The production and import quantity in fiscal 2016 was over 100 t.

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2. Exposure assessment

Total release to the environment in fiscal 2016 under the PRTR Law was 0.006 t; this quantity was estimated by government agencies because all releases were from sources not covered by mandatory reporting. In addition, 0.007 t was transferred to sewage and 0.069 t to waste. The chemical industry reported transfers. The largest releases to the environment including unreported releases were to water bodies. 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, based on general environmental atmospheric data, was around less than 0.000076 μg/m^3. There were no reported releases to the atmosphere in fiscal 2016 under the PRTR Law and accordingly, atmospheric concentrations were not estimated.

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 around less than 0.000064 μg/kg/day was obtained. However, while no releases to public freshwater bodies were reported in fiscal 2016 according to the PRTR Law, transfer to sewage was reported. Accordingly, when releases to public freshwater bodies estimated from the reported transfer to sewage 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 0.052 μg/L. Calculating oral exposure based on this gives 0.0021 μg/kg/day. The risk of exposure to this substance by intake from an environmental medium via food is considered slight, given its low bioaccumulation.

The predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, was reported to be around less than 0.0016 μg/L for public freshwater bodies and generally less than 0.0016 μg/L for seawater. No releases

to public freshwater bodies were reported in fiscal 2016 according to the PRTR Law, but transfer to sewage was reported. Accordingly, when releases to public freshwater bodies estimated from reported transfer to sewage 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 gives a maximum value of 0.052 μg/L.

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3. Initial assessment of health risk

This substance is irritating to the eyes and nose and may cause damages to the liver and kidneys.

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 to be necessary as well, and initial assessment was conducted for both non-carcinogenic and carcinogenic effects.

The non-carcinogenic LOAEL of 1.3 mg/kg/day for oral exposure (based on suppression of body weight gain, cellular degeneration and increased hematopoiesis in the liver and increased severity of nephropathy), determined from toxicity tests in rats, was divided by a factor of 10 to account for uncertainty in using a LOAEL. The calculated value of 0.13 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 16 $(mg/kg/day)^{-1}$ (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 0.000064 μg/kg/day, approximately. The MOE (Margin of Exposure) would exceed 41,000, when calculated from the predicted maximum exposure level and the 'non-toxic level*'of 0.13 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 1.0×10^{-6}, when calculated from the slope factor. No release of the substance to public freshwater bodies was reported in FY 2016 under the PRTR Law. However, when transfers to sewage are taken into consideration, the exposure level would be 0.0021 μg/kg/day. When calculated from this level, the MOE would be 1,200, and excess cancer incidence rate would be 3.4×10^{-5}, exceeding 10^{-6}. 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, collection of information would be required to assess the health risk of this substance via oral exposure, starting from data on concentrations in public freshwater bodies with consideration of transfers to sewage.

With regard to inhalation exposure, owing to the lack of identified 'non-toxic level*', the health risk could not be assessed. Assuming that 100% of the inhaled substance is absorbed, the 'non-toxic level*' for inhalation exposure, derived from the conversion of the 'non-toxic level*' for oral exposure, would be 0.43 mg/m^3. The MOE would exceed 110,000, when calculated from the predicted maximum exposure concentration in ambient air of less than 0.000076 $\mu g/m^3$, approximately, and the converted 'non-toxic level*' for inhalation exposure, 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 slope factor for inhalation exposure, derived from the conversion of the slope factor for oral exposure, would be 4.8×10^{-3} $(\mu g/m^3)^{-1}$. The excess cancer incidence rate corresponding to the predicted maximum exposure concentration would be less than 3.6×10^{-7}, when calculated from the converted slope factor above. Therefore, collection of further information would not be required to assess the health risk of the 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*'	0.13	mg/kg/day	Rats	Suppression of body weight gain, cellular degeneration in the liver, etc.	Drinking water	- μg/kg/day	MOE	-	(▲)
								Excess incidence rate	-	
	Slope factor	16	$(mg/kg/day)^{-1}$	Rats	Total tumors	Public freshwater bodies	<0.000064 μg/kg/day	MOE	>41,000	
								Excess incidence rate	$<1.0\times10^{-6}$	
Inhalation	'Non-toxic level*'	-	mg/m^3	-	-	Ambient air	<0.000076 $\mu g/m^3$	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 6,330 μg/L growth inhibition in the green alga *Pseudokirchneriella subcapitata*, a 48-h EC_{50} of 4,500 μg/L for swimming inhibition in the crustacean *Daphnia magna*, and a 96-h LC_{50} of 13,000 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 45 μg/L was obtained.

With regard to chronic toxicity, the following reliable data were obtained: a 72-h NOEC of 450 μg/L for growth inhibition in the green alga *P. subcapitata* and a 21-d NOEC of 160 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 1.6 μg/L was obtained.

The value of 1.6 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 0.001 for both freshwater bodies and seawater. Further, no releases to public freshwater bodies were reported in fiscal 2016 according to the PRTR Law, but transfer to sewage was reported. Accordingly, when releases to public freshwater bodies estimated from reported transfer to sewage 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 0.052 μg/L and the ratio of this value to the PNEC is 0.03; 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)		
Crustacean *Daphnia magna*	Chronic	NOEC reproductive inhibition	100	1.6	Freshwater	<0.0016	<0.001	○
					Seawater	<0.0016	<0.001	

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5. Conclusions

	Conclusions		Judgment
Health risk	Oral exposure	Further efforts to collect data required based on comprehensive review of existing relevant data.	(▲)
	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