4	CAS No.: 101-14-4	Substance: 3,3'-Dichloro-4,4'-diaminodiphenylmethane

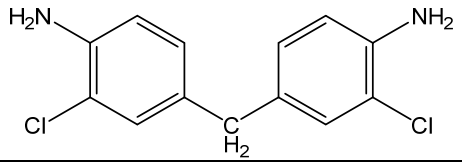
Chemical Substances Control Law Reference No.: 4-95

PRTR Law Cabinet Order No.: 1-160 (number after law revision*: 1-186)

Molecular Formula: $C_{13}H_{12}Cl_2N_2$

Molecular Weight: 267.15

Structural formula:



1. General information

The aqueous solubility of this substance is 13.9 mg/L (24°C), the partition coefficient (1-octanol/water) (log K_{ow}) is 3.91, and the vapor pressure is $<1.47\times10^{-3}$ Pa (20°C). The biodegradability (aerobic degradation) is characterized by a BOD degradation rate of 0%, and bioaccumulation is thought to be nonexistent or low. In addition, the half-life was >800 years (25°C, pH=7) for hydrolyzability.

This substance is classified as a Class 1 Designated Chemical Substance under the PRTR Law. The main use of this substance is as a curing agent for urethane resin used in applications such as waterproofing materials, flooring, and all-weather paving materials. The production and import quantity in fiscal 2020 was 1,755 t. The production and import category under the PRTR Law was more than 10 t.

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2. Exposure assessment

Total release to the environment in fiscal 2020 under the PRTR Law was approximately 0.019 t, and all releases were notified. The majority of notified releases to the atmosphere and public water bodies were to the atmosphere. In addition, approximately 8.1 t was transferred to waste. The main sources of notified releases were the rubber product manufacturing and chemical industries. 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 in general and the atmosphere in particular, the predicted portion distributed to soil was 91.0%.

The maximum expected concentration of exposure to humans via inhalation could not be defined because ambient atmospheric and indoor air quality data could not be obtained. Further, the mean annual value for atmospheric concentration in fiscal 2020 was calculated by use of a plume-puff model on the basis of releases to the atmosphere reported under the PRTR Law: this model predicts a maximum level of 0.0034 μg/m^3.

Data for potable water, groundwater, food, and soil to assess oral exposure could not be obtained. Thereupon, assuming ingestion solely from public freshwater bodies, a maximum predicted daily exposure of around less than 0.00030 μg/kg/day was obtained. Further, albeit based on data for a limited area, calculations using data measured for potable water gave a maximum daily exposure reference value of less than around 0.004 μg/kg/day. In addition, albeit using data measured for public freshwater bodies and older data measured for food, exposure values of less than around 0.00030 μg/kg/day and less than around 0.00060 μg/kg/day, respectively, were calculated. The reference maximum daily exposure value incorporating both of these values was less than around 0.00090 μg/kg/day.

As reference data for food, exposure values were also calculated from concentrations measured for fish and shellfish species. A maximum value between 0.00075 μg/kg/day and 0.00076 μg/kg/day was obtained from the sum of oral exposure from intake of fish species (0.00075 μg/kg/day) and shellfish species (less than 0.00001 μg/kg/day) estimated based on average daily intake values (fish: 61.3 g/capita/day (total); shellfish: 2.8 g/capita/day (total)) and maximum concentrations in fish (0.00061 μg/g) and shellfish (less than 0.00020 μg/g). Adding this to the oral exposure of less than 0.00030 μg/kg/day calculated from public freshwater body data gives a reference exposure of between 0.00075 μg/kg/day and 0.0011 μg/kg/day. However, no releases to public freshwater bodies were notified under the PRTR Law in fiscal 2020 and correspondingly, concentrations in public freshwater bodies are believed to be low.

The predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, was around less than

0.0080 μg/L for both public freshwater bodies and seawater.

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3. Initial assessment of health risk

Short-term exposure to this substance may cause effects on blood. The substance is suspected to cause genetic defects and may cause cancer and damage to blood. Ingestion will cause headache and dizziness. Inhalation will cause a cough in addition to the same symptoms as ingestion. Contact with the eyes will cause redness. The substance can be absorbed into the body through the skin.

This substance is classified as carcinogenic to humans, since there is evidence in experimental animals and in humans for its carcinogenicity. There is evidence for non-carcinogenic effects as well. Considering the above, the initial assessment was conducted for both non-carcinogenic and carcinogenic effects.

The NOAEL of 2 mg/kg/day for oral exposure (based on hemosiderin deposition in the spleen, the increased relative weight of kidneys, 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 0.2 mg/kg/day was deemed 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 1.5 $(mg/kg/day)^{-1}$, determined from carcinogenicity tests in dogs, was adopted assuming no threshold. Neither 'non-toxic level' nor unit risk could be identified for inhalation exposure.

Regarding oral exposure, assuming that the substance is absorbed via public freshwater bodies, the predicted maximum exposure level would be approximately less than 0.0003 μg/kg/day. The MOE (Margin of Exposure) would exceed 6,700 which is calculated from the predicted maximum exposure level and the 'non-toxic level' of 0.2 mg/kg/day, and subsequently divided by a factor of 10 to account for extrapolation from animals to humans, and by another factor of 10 to take into consideration the carcinogenicity. The excess cancer incidence rate corresponding to the predicted maximum exposure level assuming that the substance is absorbed via public freshwater bodies would be less than 4.5×10^{-7} which is calculated from the slope factor. These estimations would lead to the health risk judgment that no further work would be required at present. For reference, the MOE would exceed 500 which is calculated from the estimated maximum exposure level of approximately less than 0.004 μg/kg/day, according to the data in a certain area on drinking water, while the excess cancer incidence rate would be less than 6.0×10^{-6}. The exposure level via fish would be 0.00075 μg/kg/day which is calculated from the maximum concentration observed in seafood and the average daily consumption of fish, despite the lack of exposure level via food. Likewise, the exposure level via shellfish would be less than 0.00001 μg/kg/day which is calculated from the average daily consumption of shellfish. The MOE would be 1,800 to 2,700 and the excess cancer incidence rate would be 1.1×10^{-6} to 1.7×10^{-6} which are calculated from the exposure level of 0.00075 to 0.0011 μg/kg/day obtained as the sum of the predicted maximum exposure level via public freshwater bodies and the exposure levels via fish and shellfish. Therefore, as a comprehensive judgment, the collection of information would be required to assess the health risk of this substance via oral exposure, starting from the identification of the sources of production and emission to enhance the data on the substance level in fish.

Regarding inhalation exposure, due to the lack of identified 'non-toxic level', unit risk, and exposure concentration, the health risk could not be assessed. However, the tentative 'non-toxic level' of 0.67 mg/m^3 for inhalation exposure was derived from the conversion of the 'non-toxic level' for oral exposure, assuming that 100% of the inhaled substance is absorbed. The MOE for reference would be 2,000 which is calculated from the tentative 'non-toxic level' for inhalation exposure and the maximum concentration (annual mean) of 0.0034 $\mu g/m^3$ in ambient air near the operators that are releasing a large amount of the substance based on the releases to air reported in FY 2020 under the PRTR Law, and subsequently divided by a factor of 10 to account for extrapolation from animals to humans, and by another factor of 10 to take into consideration the carcinogenicity. The excess cancer incidence rate for reference, corresponding to the maximum concentration (annual mean) above would be 1.5×10^{-6} which is calculated from the tentative unit risk of 4.3×10^{-4} $(\mu g/m^3)^{-1}$ derived from the conversion of the slope factor for oral exposure. Therefore, as a comprehensive judgment, the collection of information

would be required to assess the health risk of this substance via inhalation in ambient air, starting from the data on the substance concentration in ambient air near the operators that are releasing a large amount of the substance.

Toxicity				Exposure assessment		MOE & Excess incidence rate		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*' 0.2 mg/kg/day	Rats	Hemosiderin deposition in the spleen, the increased relative weight of kidneys, etc.	Drinking water	- μg/kg/day	MOE	-	▲
						Excess incidence rate	-	
	Slope factor 1.5 $(mg/kg/day)^{-1}$	Dogs	Papillary transitional cell carcinomas of the urinary bladder	Freshwater	< 0.0003 μg/kg/day	MOE	>6,700	
						Excess incidence rate	$<4.5\times10^{-7}$	
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} exceeding 853 μg/L for growth inhibition in the green alga *Raphidocelis subcapitata*, a 48-h EC_{50} of 250 μg/L for swimming inhibition in the crustacean *Daphnia magna*, and a 96-h LC_{50} of 606 μg/L for the fish *Oryzias latipes* (medaka). Accordingly, based on this acute toxicity value and an assessment factor of 100, a predicted no effect concentration (PNEC) of 2.5 μg/L was obtained.

With regard to chronic toxicity, the following reliable data were obtained: a 72-h NOEC of 545 μg/L for growth inhibition in the green alga *R. subcapitata* and a 21-d NOEC of 9.5 μg/L for reproductive inhibition in the crustacean *D. magna*. Accordingly, based on this chronic toxicity value and an assessment factor of 100, a PNEC of 0.095 μg/L was obtained.

The value of 0.095 μg/L obtained from the chronic toxicity to the crustacean species was used as the PNEC for this substance.

The PEC/PNEC ratio was less than 0.08 for both freshwater bodies and seawater. Further work to assess the ecological risk of this substance is considered unnecessary at this time.

Considering trends in production and import quantities of this substance and releases to public water bodies, there is little need to collect further data at this time. Accordingly, based on a comprehensive review of the above findings, 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	Comprehensive judgment
Species	Acute/ chronic	Endpoint			Water body	Predicted environmental concentration PEC (μg/L)		
Crustacean *Daphnia magna*	Chronic	NOEC Reproductive inhibition	100	0.095	Freshwater	<0.0080	<0.08	○
					Seawater	<0.0080	<0.08	

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5. Conclusions

	Conclusions		Judgment
Health risk	Oral exposure	Requiring information collection.	▲
	Inhalation exposure	Requiring information collection.	▲
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

*Number after revision of law implemented on April 1, 2023