14	CAS No.: 101-77-9	Substance: 4,4'-Methylenedianiline

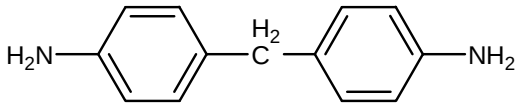
Chemical Substances Control Law Reference No.: 4-40

PRTR Law Cabinet Order No.*: 1-446

Molecular Formula: $C_{13}H_{14}N_2$

Molecular Weight: 198.26

Structural formula:



Note: No. in Revised Cabinet Order enacted on October 1, 2009

1. General information

The water solubility of this substance is 1.00×10^3 mg/L (25°C), the partition coefficient (1-octanol/water) (log K_{ow}) is 1.59, and the vapor pressure is 2.15×10^{-8} mmHg (=2.87×10^{-6} Pa) (25°C, extrapolated value). In the aerobic biodegradation test, BOD degradation rate was 0%. This substance is judged as a non- or low bioaccumulative. Furthermore, the substance does not have any hydrolyzable groups.

This substance is designated as a Priority Chemical Substance for Assessment under the Law Concerning the Examination and Regulation of Manufacture, etc. of Chemical Substances, and a Class 1 Designated Chemical Substance under the Law Concerning Reporting, etc. of Releases to the Environment of Specific Chemical Substances and Promoting Improvements in Their Management (PRTR Law). The main uses are as a raw material for diphenyl-methane-diisocyanate (MDI), which is itself a key raw material for synthetic resin (polyurethane), as a curing agent for epoxy resin, and as a raw material for chemical substances such as dyestuffs. The production and import quantity in FY 2009 was 1,121 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 FY 2009 under the PRTR Law was 0.68 t, and almost all releases were unreported. In addition, 7.9 t was transferred to waste materials. Because releases and transfer to sewage under the PRTR Law could not be obtained, predictions of distribution by medium using a Mackay-type level III fugacity model indicated that if equal quantities were released to the atmosphere, water bodies, and soil, the proportion distributed to soil would be greater.

The predicted maximum exposure to humans via inhalation, based on general environmental atmospheric data, was around less than 0.016 μg/m^3. The predicted maximum oral exposure was estimated to be around 0.00039 μg/kg/day to 0.0012 μg/kg/day based on calculations from data for public water bodies and food.

The predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, was around 0.0098 μg/L for public freshwater bodies and around 0.011 μg/L for seawater.

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3. Initial assessment of health risk

This substance may affect liver and cause damages on it. When inhaled, it will cause abdominal pain, nausea, vomiting, pyrexia and algor, and when orally taken, it may also cause jaundice. For mass food poisoning by bread produced by baking of wheat flour contaminated with this substance, abdominal pain, pyrexia and jaundice are major symptoms. Workers who had handled the substance often suffered from acute toxic hepatitis mainly with epigastric pain, hyperthermia, algor and jaundice, and this seemed to be attributed to its percutaneous absorption rather than its inhalation exposure.

Although some animal experiments have reported its carcinogenicity, its carcinogenicity for humans is yet to be studied, and an initial assessment was conducted on the basis of the information on its non-carcinogenic effects.

As for oral exposure to the substance, a LOAEL of 9 mg/kg/day (for symptoms such as fatty degeneration and swelling of liver) was obtained from mid- and long-term toxicity tests on rats. It was then divided by 10 as is always the case with LOAEL. Final outcome of 0.9 mg/kg/day was deemed to be the lowest reliable dose without any effect, and

this was identified as its 'non-toxic level*'. As for inhalation exposure to the substance, a LOAEL of 440 mg/m^3 (for symptoms such as degeneration of photoreceptor cells in eyes) was obtained from mid- and long-term toxicity tests on guinea pigs, and this was adjusted against exposure conditions to produce 52 mg/m^3. This 52 mg/m^3 was divided by 10 due to their short test periods and further divided by 10 as is always the case with LOAELs. Final outcome of 0.52 mg/m^3 was deemed to be the lowest reliable concentration without any effect, and this was identified as its 'non-toxic level*'.

As for its oral exposure, its mean exposure would be less than about 0.00085 μg/kg/day and its predicted maximum exposure would be no less than around 0.00039 μg/kg/day but less than about 0.0012 μg/kg/day, respectively, if its intakes through food and freshwater from public water bodies were assumed. The MOE would be from 15,000 to 46,000 when calculated from its 'non-toxic level*' of 0.9 mg/kg/day and the predicted maximum exposure, divided by 10 for conversion of the 'non-toxic level*' from animal experiments to an equivalent dose for humans, and further divided by 5 for consideration of its carcinogenicity. Therefore, the present exposure data suggest that no action is required at the moment to assess health risk from its oral exposure. Nevertheless, decomposition of other chemical substances in water may produce the present substance, so efforts should be made to collect more information on its exposure.

As for its inhalation exposure, its mean exposure concentration and the predicted maximum exposure concentration were both less than around 0.016 μg/m^3 when concentrations in the ambient air were considered. The MOE would be more than 650 when calculated from the 'non-toxic level*' of 0.52 mg/kg/day and the predicted maximum exposure concentration, divided by 10 for conversion of the 'non-toxic level*' from animal experiments to an equivalent concentration for humans, and further divided by 5 for consideration of its carcinogenicity. Therefore, further actions would not be required at the moment to assess health risk from inhalation exposure to this substance in the 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 * ' 0.9 mg/kg/day	Rats	Fatty degeneration or swelling of liver, etc	Drinking water/food	–	μg/kg/day	MOE	–	×	(▲)
				Freshwater/food	0.00039 to 0.0012	μg/kg/day	MOE	15,000 to 46,000	○	
Inhalation	Non-toxic level * ' 0.52 mg/m^3	Guinea pigs	Degeneration of photoreceptor cells in eyes, etc.	Ambient air	< 0.016	μg/m^3	MOE	> 650	○	○
				Indoor air	–	μg/m^3	MOE	–	×	×

Non-toxic level *

・When a LOAEL is available, it is divided by 10 to obtain a level equivalent to NOAEL.

・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 11,600 μg/L for growth inhibition in the green algae *Pseudokirchneriella subcapitata*; a 48-h EC_{50} of 2,470 μg/L for immobilization in the crustacean *Daphnia pulex*; and a 96-h LC_{50} of 20,600 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 25 μg/L was obtained.

With regard to chronic toxicity, the following reliable data were obtained: a 72-h NOEC of 1,830 μg/L for growth inhibition in the green algae *P. subcapitata*; and a 21-d NOEC of 5.25 μg/L for reproductive inhibition in the crustacean *Daphnia magna*. No value for fish species was obtained that could be used, but because the crustacean was considered to be the most sensitive organism, an assessment factor of 10 was applied and a predicted no effect concentration (PNEC) of 0.53 μg/L was obtained. This 0.53 μg/L obtained from the crustacean chronic toxicity was used as the PNEC

for this substance.

The PEC/PNEC ratio was 0.02 for both freshwater bodies and seawater. Accordingly, although further work is considered to be unnecessary at this time, improvement of exposure data is considered necessary given the perceived potential for other substances to break down in water to form this substance.

Hazard Assessment（Basis for PNEC）			Assessment factor	Predicted no effect concentration PNEC (μg/L)	Exposure Assessment		PEC/PNEC ratio	Judgment based on PEC/PNEC ratio	Assessment result
Species	Acute/ chronic	Endpoint			Water body	Predicted environmental concentration PEC (μg/L)			
Crustacean *Daphnia magna*	Chronic	NOEC reproductive inhibition	10	0.53	Freshwater	0.0098	0.02	○	▲
					Seawater	0.011	0.02		

5.Conclusions

	Conclusions		Judgment
Health risk	Oral exposure	Further information collection would be required for risk characterization.	（▲）
	Inhalation exposure	No need for further work.	○
Ecological risk	Improvement of exposure data considered necessary given perceived potential for other substances to break down in water to form this substance.		▲

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

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

（○）: Though a risk characterization cannot be determined, there would be little necessity of collecting information.

（▲）: Further information collection would be required for risk characterization.