1	CAS No.: 90-04-0	Substance: *o*-Anisidine

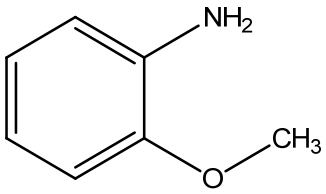
Chemical Substances Control Law Reference No.: 3-682 (Aminophenol alkyl (C=1–2) ether)

PRTR Law Cabinet Order No.: 1-17

Molecular Formula: C_7H_9NO

Molecular Weight: 123.15

Structural Formula:



1. General information

The aqueous solubility of this substance is 1.26×10^4 mg/1,000g (25°C), the partition coefficient (1-octanol/water) (log K_{ow}) is 1.18, and the vapor pressure is 0.098 mmHg (=13 Pa) (25°C). The biodegradability (aerobic degradation) is characterized by a BOD degradation rate of 54.6% and biodegradability is judged to be good. Further, hydrolysis does not occur under ambient environmental conditions.

This substances is classified as a Class 1 Designated Chemical Substance under the PRTR Law.

The main use of this substance is as a raw material for dyestuffs. The production and import quantity of aminophenol alkyl (C=1–2) ether in fiscal 2018 was less than 1,000 t. The production in fiscal 2018 of this substance was approximately 150 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 fiscal 2018 under the PRTR Law was 0.01 t, of which approximately 0.008 t or 79% of overall releases were reported. All reported releases were to the atmosphere. In addition, approximately 1.6 t was transferred to waste materials and 0.004 t was transferred to sewage. The chemical industry was the sole reporter of releases.

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 overall or the atmosphere in particular, the predicted proportion distributed to soil was 56.4% and that to the atmosphere was 26.9%. Where the largest quantity was estimated to have been released to public water bodies, the predicted proportion distributed to public water bodies was 98.1%.

The maximum expected concentration of exposure to humans via inhalation, based on ambient atmospheric data, was around less than 0.0016 μg/m^3. Further, the mean annual value for atmospheric concentration in fiscal 2018 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 0.0012 μg/m^3.

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 less than 0.00052 μg/kg/day was obtained. Further, albeit based on data for a limited area, calculations for potable water gave a daily exposure reference value of 0.004 μg/kg/day.

Food data is not available for these substances. For this reason, oral exposure reference values were estimated using concentrations in fish species and the average daily intake of fish and shellfish. Past data for fish species indicate measured values below the detection limit (less than 0.002 μg/g). Therefore, recent water quality data (less than around 0.013 μg/L) and a bioaccumulation factor (BCF: 2.8) were used to estimate the concentration in fish species and then 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 to be around less than 0.00005 μg/kg/day. Adding this to the oral exposure calculated from freshwater data gives around less than 0.0006 μg/kg/day. Further, no releases to public freshwater bodies were reported in fiscal 2018 under 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 0.028 μg/L, and the oral exposure calculated thereof is 0.0011 μg/kg/day.

The predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, was reported to be around less than 0.013 μg/L for public freshwater bodies, and around less than 0.013 μg/L for seawater. However, no releases to public freshwater bodies were reported in fiscal 2018 under the 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 0.028 μg/L.

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3. Initial assessment of health risk

This substance may cause effects on the blood, resulting in the formation of methemoglobin. This substance can be absorbed into the body by ingestion and inhalation as well as via skin, and causes symptoms including cyanosis to the lips, fingernails and skin, headache, dizziness and nausea. Contact to the eyes will cause redness and pain.

Though there is inadequate evidence in humans regarding the carcinogenicity, this substance is probably carcinogenic to the humans, due to the mechanisms of carcinogenesis. Considering the above, initial assessment was conducted for both non-carcinogenic and carcinogenic effects.

The non-carcinogenic NOAEL of 16 mg/kg/day for oral exposure (based on increased relative weight of liver, absolute weight of spleen, as well as the increased extramedullary hematopoiesis), determined from toxicity tests in rats, was divided by a factor of 10 to account for extrapolation to chronic exposure. The calculated value of 1.6 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 0.14 $(mg/kg/day)^{-1}$ (based on bladder tumors), determined from carcinogenicity tests in rats, was adopted assuming no threshold. Neither 'non-toxic level' nor unit risk could be identified for inhalation exposure.

Regarding the oral exposure, assuming that the substance is absorbed via public freshwater bodies, the predicted maximum exposure level would be less than 0.00052 μg/kg/day, approximately. The MOE (Margin of Exposure) would exceed 31,000, when calculated from the predicted maximum exposure level and the 'non-toxic level' of 1.6 mg/kg/day, and subsequently divided by a factor of 10 to account for extrapolation from animals to the 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 would be less than 7.3×10^{-8}, when 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 and the excess cancer incidence rate would be more than 4,000 and less than 5.6×10^{-7}, respectively, when calculated from the estimated maximum exposure level of less than 0.004 μg/kg/day, approximately, according to the data in a certain area on drinking water. When calculated from another estimation of the maximum exposure level of less than 0.0006 μg/kg/day, approximately, the MOE and the excess cancer incidence rate would be more than 27,000 and less than 8.4×10^{-8}, respectively. This maximum exposure level was estimated assuming that the substance is absorbed via fish and public freshwater bodies, due to the lack of exposure level via food. In addition, the MOE and the excess cancer incidence rate for reference would be 15,000 and 1.5×10^{-7}, respectively, when calculated from the estimated maximum exposure level of 0.0011 μg/kg/day. This maximum exposure level was estimated according to the concentration in effluents calculated from the transfers to the sewage system, reported in FY 2018 under the PRTR Law. Therefore, as a comprehensive judgment, no further work would be required at present.

Regarding the inhalation exposure, due to the lack of identified 'non-toxic level' and unit risk, the health risk could not be assessed. The tentative 'non-toxic level' for inhalation exposure would be 5.3 mg/m^3 derived from the conversion of the 'non-toxic level' for oral exposure, assuming that 100% of the inhaled substance is absorbed. However, to make conservative assessment, the LOAEL of 0.17 mg/m^3 for *p*-anisidine, determined from the effects observed in humans, would be used for assessment of the health risk via inhalation exposure. The MOE for reference would exceed 1,100, when calculated from the LOAEL for *p*-anisidine and the predicted maximum exposure concentration in ambient air of less than 0.0016 $\mu g/m^3$, and subsequently divided by a factor of 10 to account for uncertainty in using a LOAEL, and by

another factor of 10 to take into consideration the carcinogenicity. The excess cancer incidence rate corresponding to the predicted maximum exposure level would be less than 6.7×10^{-8}, when calculated from the tentative unit risk of 4.2×10^{-5} $(\mu g/m^3)^{-1}$, derived from the conversion of the slope factor for oral exposure. In addition, the MOE and the excess cancer incidence rate for reference would be 1,400 and 5.0×10^{-8}, respectively, when calculated from the concentration in ambient air of 0.0012 $\mu g/m^3$. This concentration was estimated as the maximum concentration (annual mean) in ambient air, near the operators that are releasing large amount of the substance, based on the releases to air reported in FY 2018 under the PRTR Law. 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 & 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' 1.6 mg/kg/day	Rats	Increased relative weight of liver, increased extramedullary hematopoiesis, etc.	Drinking water	- μg/kg/day	MOE	-	○
						Excess incidence rate	-	
				Public Freshwater bodies	<0.00052 μg/kg/day	MOE	>31,000	
	Slope factor 0.14 $(mg/kg/day)^{-1}$	Rats	Bladder tumors			Excess incidence rate	$<7.3\times10^{-8}$	
Inhalation	'Non-toxic level' - mg/m^3	-	-	Ambient air	<0.0016 $\mu g/m^3$	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 30,000 μg/L for growth inhibition in the alga *Raphidocelis subcapitata*, a 48-h EC_{50} of 2,180 μg/L for swimming inhibition in the crustacean *Daphnia magna*, and a 96-h LC_{50} exceeding 196,000 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 21 μg/L was obtained.

With regard to chronic toxicity, the following reliable data were obtained: a 72-h NOEC of 7,500 μg/L for growth inhibition in the alga *R. subcapitata* and a 21-d NOEC of 250 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 2.5 μg/L was obtained.

The value of 2.5 μg/L obtained from the chronic toxicity to the crustacean was used as the PNEC for this substance.

The PEC/PNEC ratio is less than 0.005 for freshwater bodies and seawater; accordingly, further work to evaluate the ecological risk is considered unnecessary at this time.

No releases to public freshwater bodies were reported in fiscal 2018 under the 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 0.028 μg/L. The ratio of this value to the PNEC is 0.01.

Accordingly, based on a comprehensive review of the above findings, there is little need to collect new data regarding this substance.

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	2.5	Freshwater	<0.013	<0.005	○
					Seawater	<0.013	<0.005	

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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