11	CAS No.: 120-71-8	Substance: 2-Methoxy-5-methylaniline

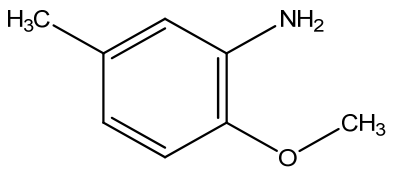
Chemical Substances Control Law Reference No.: 3-614 (Methoxytoluidine)

PRTR Law Cabinet Order No.:1-451

Molecular Formula: $C_8H_{11}NO$

Molecular Weight: 137.18

Structural Formula:



1.General information

The aqueous solubility of this substance is 3,000 mg/L (20°C, pH=7), the partition coefficient (1-octanol/water) (log K_{ow}) is 1.74, and the vapor pressure is 0.011 mmHg (=1.4 Pa) (25°C). The biodegradability (aerobic degradation) is characterized by a BOD degradation rate of 0.7%, and biodegradability is judged to be limited. In addition, the hydrolysis half-life is approximately 2.76 years (pH=7.01, water temperature = 25°C).

This substance 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 such as eosamine B, coccinine B, and diamino fast violet BBN. Further, the production and import quantity of methoxytoluidine in fiscal 2018 was not disclosed because the number of reporting businesses was less than two. The production and import category under the PRTR Law is from 1 t to less than 100 t.

2.Exposure assessment

Total release to the environment in fiscal 2018 under the PRTR Law was 0 t. 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 ambient atmospheric data, was around less than 0.0014 μg/m^3.

Data for potable water, ground water, public freshwater bodies, food, and soil to assess oral exposure could not be obtained. Further, albeit data for a limited area, calculations for potable water gave a daily exposure of around less than 0.004 μg/kg/day as a reference value. Furthermore, a value of generally 0.0021 μg/kg/day was obtained for maximum expected concentration of exposure based on data measured for public freshwater bodies. However, concentrations in public water bodies are not anticipated to be high given there was 0 kg of reported releases to public water bodies in fiscal 2018 under the PRTR Law.

The risk of exposure to this substance by intake from an environmental medium via food is considered slight, given the anticipated nonexistent or low bioaccumulation of the substance. Data for setting the predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, could not be obtained. Further, past data indicated values of around 0.052 μg/L for public freshwater bodies and around less than 0.032 μg/L for seawater. However, concentrations in public water bodies are not anticipated to be high given there was 0 kg of reported releases to public water bodies in fiscal 2018 under the PRTR Law.

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3. Initial assessment of health risk

Inhalation of this substance will cause a cough, and contact to the eyes will cause redness.

Since sufficient information on the carcinogenicity to the humans were not available, it could not be determined whether the substance is carcinogenic to humans or not. However, dose-dependent tumorigenesis in bladders was observed in all dose-groups of male and female rats and mice, in the carcinogenesis study by oral administration.

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 198 mg/kg/day for oral exposure (based on suppression of body weight gain and epithelial hyperplasia of the bladders) determined from long-term toxicity studies in rats, was divided by a factor of 10 to account for uncertainty in using a LOAEL. The calculated value of 20 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 0.15 $(mg/kg/day)^{-1}$ (based on bladder tumors), determined from carcinogenicity tests in mice, was adopted assuming no threshold. Neither 'non-toxic level' nor unit risk could be identified for inhalation exposure.

Regarding the oral exposure, due to the lack of identified exposure levels, the health risk could not be assessed. However, the maximum exposure level was estimated to be less than 0.004 μg/kg/day, approximately, based on data in a certain area on drinking water. The MOE (Margin of Exposure) for reference would exceed 100,000, when calculated from the estimated maximum exposure level and the 'non-toxic level' of 20 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 5 to take into consideration the carcinogenicity. The excess cancer incidence rate for reference would be less than 6.0×10^{-7}, when calculated from the estimated maximum exposure level and the cancer slope factor of 0.15 $(mg/kg/day)^{-1}$. In addition, the MOE and the excess cancer incidence rate would be 190,000 and 3.2×10^{-7}, respectively, when calculated from the exposure level of 0.0021 μg/kg/day derived from the past data on public freshwater bodies in 2005. Since exposure to the substance in environmental media via food is presumed to be limited despite the lack of exposure level via food, including it in the calculation would not change either MOE or excess cancer incidence rate significantly. Therefore, as a comprehensive judgment, collection of further information would not be required to assess the health risk of this substance via oral exposure.

Regarding the inhalation exposure, due to the lack of identified 'non-toxic level' and unit risk, the health risk could not be assessed. However, the tentative 'non-toxic level' for inhalation exposure, derived from the conversion of the 'non-toxic level' for oral exposure, would be 67 mg /m^3, assuming that 100% of the inhaled substance is absorbed. The tentative unit risk, derived from the conversion of the slope factor for oral exposure, would be 4.5×10^{-5} $(\mu g/m^3)^{-1}$. The MOE for reference would exceed 960,000, when calculated from the tentative 'non-toxic level' for inhalation exposure and the predicted maximum exposure concentration in ambient air of 0.0014 μg/m^3, and subsequently divided by a factor of 10 to account for extrapolation from animals to the humans and by another factor of 5 to take into consideration the carcinogenicity. The excess cancer incidence rate for reference corresponding to the predicted maximum exposure level would be less than 6.3×10^{-8}, when calculated from the tentative unit risk. 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	MOE & Excess incidence rate		
Oral	'Non-toxic level'	20 mg/kg/day	Rats	Suppression of body weight gain and epithelial hyperplasia of the bladders	Drinking water	- μg/kg/day	MOE	-	○
							Excess incidence rate	-	
	Slope factor	0.15 $(mg/kg/day)^{-1}$	Mice	Bladder tumors	Groundwater	- μg/kg/day	MOE	-	
							Excess incidence rate	-	
Inhalation	'Non-toxic level'	- mg/m^3	-	-	Ambient air	<0.0014 μg/m^3	MOE	-	○
							Excess incidence rate	-	
	Unit risk	- $(\mu g/m^3)^{-1}$	-	-	Indoor air	- μg/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.

4.Initial assessment of ecological risk

Reliable toxicity data for conducting an initial assessment of ecological risk could not be obtained for this substance, and the predicted no effect concentration (PNEC) could not be set.

The PNEC for this substance could not be derived and ecological risk could not be assessed because the PEC could not be set.

Toxicity data for algal, crustacean, and fish species that could be used in an initial assessment of this substance could not be obtained. Accordingly, toxicity was estimated for reference using QSARs for algal, crustacean, and fish species.

Of the values predicted by QSAR obtained from QSAR formulae with R^2 of 0.70 or higher and n of 5 or more, the lowest value for acute toxicity toward fish species was 31,436 μg/L. This value is similar to the lowest value of 12,270 μg/L measured for a fish species whose reliability could not be judged.

If an assessment factor of 1,000 (the same as that used for a reliable data measured for a single taxon) is tentatively applied to the value of 31,436 μg/L predicted using QSAR instead of the measured data, a PNEC value of 31 μg/L is obtained.

Next, for the toxicities toward algae (acute and chronic toxicities), crustaceans (acute and chronic toxicities) and fish (chronic toxicity) where QSAR formulae that satisfied the reference parameters could not be obtained, the similarity of reference substances that constituted each QSAR class and their toxicity data were used as a basis to make observations.

Among the reference substances that constituted QSAR classes for the three taxa, substances in which a primary amine ($-NH_2$) was directly bonded to a benzene ring were selected because of the high degree of similarity in chemical structure with methoxytoluidine and the fact that differences in log K_{ow} were less than 1. The reliability of toxicity data for all of these reference substances was not clear. For this reason, only toxicity values for which reliable initial assessments were conducted were used, and geometric mean values for the toxicities of similar substances were calculated while referencing the read-across method in the category approach. This gave acute toxicities towards algae and crustaceans of 7,263 and 1,225 μg/L, respectively, and chronic toxicities towards algae, crustaceans, and fish of 2,146, 22, and 201 μg/L, respectively. The lowest value was observed for the chronic toxicity towards crustacean species.

Dividing the geometric mean value for chronic toxicity towards the crustacean species of 22 μg/L using the same assessment factor of 10 that would be employed if reliable data could be obtained for this substance with regards to the three taxa gives 2.2 μg/L.

According to exposure assessments, total release to the environment in fiscal 2018 under the PRTR Law was 0 kg and concentrations in public water bodies are thus not anticipated to be high. Further, albeit past data, concentrations of generally 0.052 μg/L for public water bodies and generally less than 0.032 μg/L for seawater have been obtained.

The ratios of the 31 μg/L obtained by dividing the minimum value predicted by QSAR by the assessment factor and past environmental concentrations are 0.002 for freshwater and less than 0.001 for seawater.

In addition, the ratios of the 2.2 μg/L obtained by dividing the minimum geometric mean value of 22 μg/L for the chronic toxicity towards the crustacean species of similar substances constituting the QSAR class and past environmental concentrations are 0.02 for freshwater and less than 0.01 for seawater.

In summary, while calculations of the ratios of values predicted by QSARs and past environmental concentrations give values of less than 0.1, some of the similar substances used as references exhibit relatively high toxicities towards crustacean species in particular and it is difficult to categorically rule out the possibility that the PEC/PNEC may exceed 0.1 with a high degree of certainty based on existing information. For this reason, based on a comprehensive review of the above

findings, more work is considered necessary to collect data.

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)		
–	–	–	–	–	Freshwater	–	–	▲
					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	Requiring information collection.		▲

［Risk judgments］ ○: No need for further work ▲: Requiring information collection
■: Candidates for further work ×: Impossibility of risk characterization