5	CAS No. 657-24-9 (Metformin) 1115-70-4 (Metformin hydrochloride)	Substance: Metformin

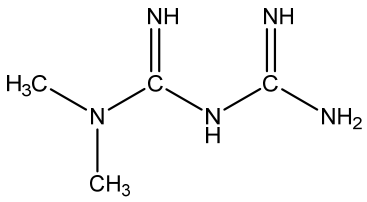
Chemical Substances Control Law Reference No.: 2-2883 (Metformin hydrochloride)

PRTR Law Cabinet Order No.:

Molecular Formula: $C_4H_{11}N_5$

Molecular Weight: 129.16

Structural formula:



1.General information

The aqueous solubility of this substance is 1×10^6 mg/L (estimated value), the partition coefficient (1-octanol/water) (log Kow) is -2.64 (estimated value), and the vapor pressure is 0.0101 Pa (25°C) (estimated value). Biodegradability (aerobic degradation) exceeded 95% for DOC (hydrochloride salt). The substance is hydrolytically stable (hydrochloride salt) (pH = 5, 7, 9, 50°C).

The primary use of metformin hydrochloride, the hydrochloride salt of this substance, is as a pharmaceutical (biguanide hypoglycemic agent). Furthermore, the production volume of metformin hydrochloride in fiscal 2022 was 766.0 t.

2.Exposure assessment

Because this substance is not classified as a Class 1 Designated Chemical Substance under the PRTR Law, release and transfer quantities could not be obtained. 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 predicted environmental concentration (PEC), which indicates exposure to aquatic organisms, was around 3.6 μg/L for public freshwater bodies, and around 0.75 μg/L for seawater.

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3. Initial assessment of ecological risk

With regard to acute toxicity, the following reliable data were obtained: a 7-d EC_{50} of 53,700 μg/L for growth inhibition in the aquatic plant *Lemna minor*, a 48-h EC_{50} of 14,300 μg/L for swimming inhibition in the crustacean *Daphnia similis*, a 96-h LC_{50} exceeding 766,000 μg/L for the fish *Lepomis macrochirus* (bluegill), and a 96-h LC_{50} of 3,918,000 μg/L for the freshwater hydrozoan *Hydra attenuata*. Accordingly, based on this acute toxicity value and an assessment factor of 100, a predicted no effect concentration (PNEC) of 140 μg/L was obtained.

With regard to chronic toxicity, the following reliable data were obtained: a 7-d NOEC of 16,700 μg/L for growth inhibition in the aquatic plant *L. minor*, a 14-d NOEC of 5000 μg/L for reproductive inhibition in the crustacean *D. similis*, 177-d NOEC of more than 322 μg/L for mortality of growth inhibition in the fish (embryo) *Pimephales promelas* (fathead minnow), and a 16-d NOEC of less than 25 μg/L for reproductive inhibition in the rotifers *Brachionus calyciflorus* and the *Plationus patulus*. Accordingly, based on this chronic toxicity value and an assessment factor of 10, a predicted no effect concentration (PNEC) of more than 32 μg/L was obtained. Note that if other organisms are used, the reference PNEC value based on chronic toxicity will be less than 2.5 μg/L.

The value of more than 32 μg/L obtained from the chronic toxicity to the fish was used as the PNEC for this substance.

The PEC/PNEC ratio is less than 0.11 for freshwater bodies and less than 0.02 for seawater. Accordingly, efforts to collect further data are considered necessary.

Concerns remain that this substance may have greater adverse effects on fish species in terms of its chronic toxicity.

Furthermore, when toxicity values for other organisms are used, the PNEC reference value is less than 2.5, and the ratio to the PEC exceeds 1.4 in freshwater environments.

Furthermore, the production and import volume of this substance has been increasing since around 2014 and has remained at a high level. Accordingly, based on a comprehensive review of the above findings, efforts to collect further data are considered necessary.

Trends in manufacturing and import volumes of this substance should continue to be monitored, as well as whether reports of high chronic toxicity in fish species.

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)		
Fish *Pimephales promela*	Chronic	NOEC Mortality / Growth inhibition	10	≧32	Freshwater	3.6	≦0.11	▲
					Seawater	0.75	≦0.02	

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4. Conclusions

	Conclusions	Judgment
Ecological risk	Requiring information collection.	▲

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