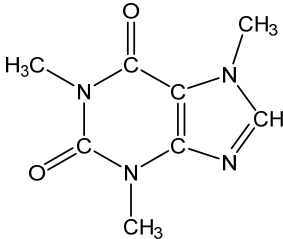| 2	CAS No. 58-08-2	Substance: Caffeine

Chemical Substances Control Law Reference No.: 9-419

PRTR Law Cabinet Order No.:

Molecular Formula: $C_8H_{10}N_4O_2$

Molecular Weight: 194.19

Structural Formula:

1.General information

The aqueous solubility of this substance is 2.17×10^4 mg/1,000 g (25°C), the partition coefficient (1-octanol/water) (log K_{ow}) is −0.07 (pH unknown), and the vapor pressure is 4.7×10^{-6} Pa (25°C). Biodegradability (aerobic degradation) is reported to be good. Further, degradability screening tests indicated a residual ratio of 108% after 5 days (initial concentration: 5.0 µg/mL, pH: 7) for hydrolyzability.

The main uses of this substance are as food additives (coffee beverages, coffee-containing beverages) and in pharmaceuticals. Caffeine is also used as a cosmetic ingredient(fragrances, skin conditioners (unclassified)). In pharmaceuticals, it is used as in xanthine-based central nervous system stimulants, cardiotonics, and diuretics, and its indications include drowsiness, fatigue, and vasodilatory and cerebral hypertensive headaches (migraines, hypertensive headaches, caffeine withdrawal headaches, etc.). In veterinary drugs, it is used as a blend with other drugs for the nervous system (antipyretic analgesic anti-inflammatory drugs) and metabolic drugs (allergy drugs (including non-specific immunogenics)). This substance is one of the food components naturally occurring in coffee beans, tea leaves including yerba mate, cacao beans, and guarana. Caffeine (extract) from coffee and tea leaves is used as a food additive in soft drinks and other beverages as a bittering agent. The export volume of caffeine and its salts in 2022 was 2.1 t, while the import volume was 432.7 t

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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 2.4 µg/L for public freshwater bodies, and about 0.13 µg/L for seawater. Further, albeit a survey of a limited area, a maximum of about 0.23 µg/L for seawater was reported.

3.Initial assessment of ecological risk

With regard to acute toxicity, the following reliable data were obtained: a 72-h EC_{50} exceeding 100,000 µg/L for growth inhibition in the green alga *Desmodesmus subspicatus*, a 24-h EC_{50} of 160,000 µg/L for swimming inhibition in the crustacean *Daphnia magna*, a 96-h LC_{50} of 151,000 µg/L for the fish *Pimephales promelas* (fathead minnow) and a 96-h LC_{50} exceeding 100,000 µg/L for the fresh-water polyp *Hydra attenuata*. Accordingly, based on the minimum acute toxicity value and an assessment factor of 100, a predicted no effect concentration (PNEC) exceeding 1,000 µg/L was obtained.

With regard to chronic toxicity, the following reliable data were obtained: 72-h NOEC of 6,250 µg/L for growth inhibition in the green alga *D. subspicatus*, an 8-d NOEC of 35,000 µg/L for reproductive inhibition on the crustacean *Ceriodaphnia dubia*, and a 96-h NOEC of 50,000 µg/L for the reproduction in the hydra *H. attenuata*. Accordingly, based on these chronic

toxicity values and an assessment factor of 100, a predicted no effect concentration (PNEC) of 62 µg/L was obtained.

The value of 62 g/L obtained from the chronic toxicity to the green alga was used as the PNEC for this substance.

The PEC/PNEC ratio is 0.04 for freshwater bodies and 0.002 for seawater. Accordingly, <u>efforts to collect data for determining ecological risk are considered unnecessary at this time.</u>

Albeit data for a limited area, a maximum value of about 0.23 µg/L was reported for seawater and the ratio of this concentration and the a predicted no effect concentration (PNEC) is 0.004. Accordingly, <u>based on a comprehensive review of the above findings efforts to collect data are considered unnecessary at this time.</u>

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)		
Green algae	Chronic	NOEC Growth inhibition	100	62	Freshwater	2.4	0.04	○
					Seawater	0.13	0.002	

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4. Conclusions

	Conclusions	Judgment
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