

| | | |
|---|------------------|----------------------|
| 5 | CAS No.: 57-41-0 | Substance: Phenytoin |
|---|------------------|----------------------|

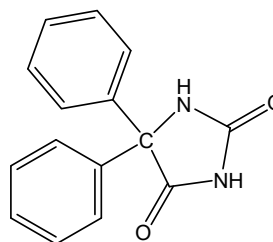
Chemical Substances Control Law Reference No.: 9-621

PRTR Law Cabinet Order No. (number after law revision*: 1-230)

Molecular Formula: C₁₅H₁₂N₂O₂

Molecular Weight: 252.27

Structural Formula:



1. General information

The aqueous solubility of this substance is 32.0 mg/L (22°C), the partition coefficient (1-octanol/water) (log K_{ow}) is 2.47, and the vapor pressure is 1.81×10⁻⁹ Pa (calculated value). The biodegradability (aerobic degradation) is characterized by a BOD degradation rate of 0.6%, biodegradability is judged to be limited, and the substance is not believed to be highly bioaccumulative. In addition, as this substance does not have any hydrolyzable groups, it does not hydrolyze in the environment.

This substance was formerly classified as a Class 2 Designated Chemical Substance under the PRTR Law, but after revision of the law in 2008 the substance was no longer classified as such. It is, however, scheduled to be classified as a Class 1 Designated Chemical Substance under the PRTR Law by the Cabinet Order partially revising the Enforcement Order for the Act on the Assessment of Releases of Specified Chemical Substances in the Environment and the Promotion of Management Improvement promulgated on October 20, 2021, that will come into force on April 1, 2023.

The main use of this substance is as a hydantoin anticonvulsant that is effective against epileptic convulsive seizures (tonic-clonic seizures, focal seizures), autonomic nervous attacks, and psychomotor seizures. In addition, the production quantity of this substance in 2013 was calculated to be 4.1 t based on drugs for human use.

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 less than 0.028 µg/L for public freshwater bodies and generally less than 0.0021 µg/L for seawater. Further, albeit past data, a maximum value of 0.0042 µg/L for public seawater bodies was reported.

3. Initial assessment of ecological risk

With regard to acute toxicity, the following reliable data were obtained: a 72-h IC₅₀ of 28,300 µg/L for growth inhibition in the green alga species *Raphidocelis subcapitata*, 96-h LC₅₀ exceeding 16,000 µg/L for the fish species *Oryzias latipes* (medaka), and a 24-h EC₅₀ of 9,081 µg/L for embryonic developmental abnormalities for the purple sea urchin *Arbacia punctulate*. Accordingly, based on these acute toxicity values and an assessment factor of 1,000, a PNEC of 28 µg/L was obtained. Further, adopting other organisms gave a reference value of 9.0 µg/L for PNEC.

With regard to chronic toxicity, the following reliable data were obtained: a 72-h NOEC of 1,630 µg/L for growth inhibition in the green alga species *R. subcapitata* and a 6–8-day NOEC of 3,120 µg/L for reproductive inhibition in the crustacean species *Ceriodaphnia dubia*. Accordingly, based on this chronic toxicity value and an assessment factor of 100, a PNEC of 16 µg/L was obtained

The value of 16 µg/L obtained from the chronic toxicity to the alga was used as the PNEC for this substance.

The PEC/PNEC ratio is 0.002 for freshwater bodies and less than 0.001 for seawater; accordingly, further work to assess the ecological risk of this substance is considered unnecessary at this time. Further, the ratio with PEC did not exceed 0.1 even if a

PNEC reference value derived from other organisms was used. In addition, albeit past data, a maximum concentration of 0.0042 µg/L for public seawater bodies was reported and the ratio of this value to PNEC is 0.0003, while the ratio to the PNEC reference value is 0.0005.

Accordingly, based on a comprehensive review of the above findings, the need to collect further data is considered to be minimal.

| 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 | 16 | Freshwater | 0.028 | 0.002 | ○ |
| | | | | | Seawater | <0.0021 | <0.0001 | |

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

*Note: Number after revision of law to be implemented on April 1, 2023