Wildlife Toxicity Assessment for Picric Acid (2,4,6-Trinitrophenol)

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INTRODUCTION

Picric acid (2,4,6-trinitrophenol, CAS No. 88-89-1) was once an extensively used for military applications as a high explosive and a component of rocket fuel.[1] It is used in research and industry as a sensitizer in photographic emulsions, a chemical intermediate in the production of picramic acid and chloropicrin, and a component of matches and batteries.[2] Picric acid is a severe explosion hazard due to its sensitivity to friction, heat, and shock.[1] Additionally, picric acid reacts vigorously with a variety of materials, and is toxic to humans through all exposure routes.[1] Given its historical and current widespread application, it is likely that the compound was released into the environment during the manufacture of explosives, and in load, assembly, and pack (LAP) activities at U.S. Army ammunition plants and other military installations.[2,3]

This report summarizes the current knowledge of potential impacts of picric acid on wildlife, emphasizing threshold doses for the onset of toxicological effects, as described in reports of experimental studies of the compound. Threshold dosimetry has led to the establishment of Toxicity Reference Values (TRVs), which are intended as protective exposure standards for wildlife ranging near affected or contaminated sites.

ENVIRONMENTAL FATE AND TRANSPORT

As summarized in the Hazardous Substance Data Bank (HSDB®), the wide-spread use of picric acid in explosives and other military applications has likely resulted in the compound's release into the environment in various waste streams.[1] The amount of picric acid in these waste streams has not been quantitated; however, certain aspects of the compound's likely disposition into the environment can be inferred from its physical and chemical characteristics. As shown in Table 1, the low vapor pressure of 7.5×10^{-7} millimeters of mercury (mm Hg) at 25°C suggests that picric acid may exist in both vapor and particulate phases in the ambient atmosphere.[1]

Atmospheric products of photolysis are possible since picric acid absorbs light at wavelengths greater than 290 nanometers (nm). Soil-borne picric acid may be expected to have high mobility due to the compound's high solubility in aqueous solution and estimated soil adsorption coefficient (K_{OC}) of 180. In fact, picric acid's low acid dissociation coefficient (pKa) of 0.42 also indicates that the compound will probably exist in the anionic form in soil and, therefore, display relatively limited mobility. With a Henry's law constant of 1.7×10^{-8} atm·m^3/mol, the compound's capacity to volatilize from moist soil surfaces is unlikely to be an important fate process. Among biotic processes, cultures of anaerobic *Pseudomonads*, such as *Pseudomonas aeroginosa*, can transform the compound to the degradation product, 2-amino-4,6-dinitrophenol.[1] In an *in vitro*

study, the concentration of picric acid was decreased by 22% during 30 days of incubation with *Pseudomonas aeruginosa*.[4] The authors attributed 1.7% of the decrease to conversion of picric acid to picramic acid; the remaining 20.3% decrease was attributed to adsorption onto bacterial surfaces, bacterial accumulation, and degradation into unidentifiable products.[4]

Table 1. Summary of the Physical-Chemical Properties of Picric Acid

CAS No.	88-89-1
Synonyms	2,4,6-trinitrophenol, 2-hydroxy-1,3,5-trinitrobenzene, melinite, picral, carbazotic acid
Molecular weight	229.10
Formula	$C_6H_3N_3O_7$
Color	Pale yellow
Physical state	Solid crystals
Density/Specific Gravity	1.763 g/cm^3
Melting point	122–123°C (251–253°F)
Boiling point	Explodes at 300°C (572°F)
Odor	Odorless
Solubility	Water 12.7 g/L) at 25°C; soluble in benzene, chloroform, ether, alcohol, ethanol, and acetone
Partition coefficients: Log K_{ow} Log K_{oc}	 K_{ow} = 1.44 K_{oc} = 0.42
Vapor pressure at 25°C	7.5 x 10^{-7} mm Hg
Henry's law constant at 25°C	1.7 x 10^{-8} atm·m^3/mol at 25°C
Vapor density	7.90 (air = 1)

Source: HSDB 2012[1]

SUMMARY OF MAMMALIAN TOXICITY

Mammalian Toxicity: Acute

There are very few data on the toxicity of picric acid in experimental studies; however, one study investigated its acute toxicity, cause of death, metabolites, and toxicokinetics in rats.[5] Oral lethal dose (LD_{50}) values of 290 ± 57.5 and 200 ± 42.9 milligrams per kilogram (mg/kg) were determined for male and female F344 rats, respectively,

receiving the compound via gavage.[5] Doses ranged from 50 to 800 mg/kg. Blood gas analysis was performed to determine the cause of death in a separate group of male rats administered between 100 and 400 mg/kg, and severe acidosis was found to be the most likely cause.

Additionally, Wyman *et al.*[5] identified metabolites via urine collection and analysis, and examined toxicokinetics and tissue distribution of picric acid. In the metabolite portion of the study, rats were administered 100 mg/kg picric acid. In addition to picric acid, N-acetylisopicramic acid, picramic acid, and N-acetylpicramic acid were found in the urine.

Rats used in the toxicokinetics portion were given either 100 mg/kg picric acid via gavage or 50 mg/kg via injection in the penile vein; radioactivity of all samples was assayed by liquid scintillation spectrometry. The urinary excretion rate was determined to be 60% at 24 hours post administration. For the tissue distribution component of this study, blood was determined to be the principal depot of picric acid, followed by the spleen, kidney, liver, lungs, and testes.[5] Other reported LD_{50} and lowest lethal dose (LD_{Lo}) values can be found in Table 2.

Table 2. LD_{50} and LD_{Lo} Values for the Class Mammalia

Species	Dose mg/kg	Value	Route	Additional Toxicity Information
Mouse	56.3	LD_{50}	Intraperitoneal	Convulsions or effect on seizure threshold
Cat	250	LD_{Lo}	Oral	na
Cat	500	LD_{50}	Oral	na
Guinea pig	100	LD_{50}	Oral	na
Rabbit	120	LD_{Lo}	Oral	Convulsions or effect on seizure threshold, diarrhea, body temperature increase
Rabbit	120	LD_{50}	Oral	
Dog	60	LD_{Lo}	Subcutaneous	na
Dog	60	LD_{Lo}	Unreported	Pulse rate and blood pressure decrease

Source: RTECS[6;] na = not available.

Mammalian Toxicity: Subacute

Takahashi *et al.*[7] reevaluated the toxicity of picric acid in young rats, and determined the toxicity in newborn rats for comparison. In the dose-finding study in newborn rats, four pups/sex/dose were given picric acid by gavage at 0, 16.3, 81.4, or 407 milligrams per kilograms per day (mg/kg/day) on postnatal days (PNDs) 4–17 (14 days), and euthanized on PND 18. Low body weight, behavioral changes, and death, were seen at 81.4 and 407 mg/kg/day in the dose-finding study.[7] Additionally, six pups/sex were given picric acid by gavage at 0, 4.1, 16.3, or 65.1 mg/kg/day on PNDs 4–21 (18 days) and euthanized after the last treatment. In the main study, no deaths were observed, but lower body weights were noted at 65.1 mg/kg. Because of this pattern of lower body weight, the no observed adverse effect level (NOAEL) for newborn rats was considered 16.3 mg/kg/day.

A dose-finding study and main study were then performed with young rats (5 weeks old). Initially, three rats/sex/dose were given picric acid by gavage at 0, 20, 100, or 500 mg/kg/day for 14 days. All males and one female rat given 500 mg/kg/day died by day 2 of the dosing period. In the main study, six rats/sex/dose received picric acid by gavage at 0, 4, 20, or 100 mg/kg/day for 28 days. No deaths were observed throughout the 28 day experimental period.[7] Significantly higher values of relative liver and spleen weights and hemolytic anemia were observed in the 100 mg/kg/day dose group. Hemolytic anemia was not seen in newborn rats receiving 81.4 mg/kg picric acid. Males in the 100 mg/kg/day dose group also had small testes at the end of the recovery period and lower values of relative epididymidis weights, indicating testicular toxicity.[7] The NOAEL for young rats was determined to be 20 mg/kg/day. Taken together, data from Takahashi *et al.* indicate that picric acid was more toxic to newborn rats, since newborns are at a sensitive life stage.

Mammalian Toxicity: Subchronic

No data available.

Mammalian Toxicity: Chronic

van Esch *et al.*[8] exposed groups of Wistar rats to 500 parts per millions (ppm) of picric acid, picramide, or hexanitrodiphenylamine in feed for up to 2.5 years. The main purpose of this study was to evaluate the carcinogenicity of hexanitrodiphenylamine; since the products of hydrolysis were picric acid and picramide, they were included in parallel. No chronic adverse effects of picric acid were reported.[8]

Studies Relevant for Mammalian TRV Development for Ingestion Exposures

No data available.

Mammalian Oral Toxicity: Other

No data available.

Mammalian Inhalation Toxicity

No data available.

Mammalian Dermal Toxicity

No data available.

SUMMARY OF AVIAN TOXICITY

An LD_{Lo} was reported for pigeons resulting from a single subcutaneous injection of 200 mg/kg.[6] No other data were available.

SUMMARY OF AMPHIBIAN TOXICITY

No data available.

SUMMARY OF REPTILIAN TOXICITY

No data available.

RECOMMENDED TOXICITY REFERENCE VALUES

TRVs for Mammals

TRVs for Ingestion Exposures for the Class Mammalia

Few relevant studies were conducted with picric acid. Acute data included four species from at least two orders. The LD_{50} values for male and female rats are 290 ± 57.5 and 200 ± 42.9 mg/kg, respectively.[5] Blood gas analysis suggests severe acidosis as the cause of death from these acute exposures. The approximation must be used since data are few. This method requires that uncertainty factors (100 for the female LD_{50} for

the NOAEL-based TRV and 20 for the LOAEL-based TRV) be applied to these acute data.[9] Therefore, the mammalian NOAEL-based TRV is 2 mg/kg/day and the LOAEL-based TRV is 10 mg/kg/day (Table 3). Both are given a low degree of confidence based on the scarcity of data for picric acid. These values are within similar ranges of nitroaromatics with structural similarities (e.g., 2,4,6-trinitrotoluene, 1,3,5-trinitrobenzene).

Table 3. Selected Ingestion TRVs of Picric Acid for the Class Mammalia

TRV	Dose mg/kg/day	Confidence Level
NOAEL-based	2	Low
LOAEL-based	10	Low

Source: Wyman *et al.* 1992[5]

TRVs for Ingestion Exposures for Mammalian Foraging Guilds

Existing toxicity data is representative of omnivorous rodents only; data for other species would be needed to derive values for other foraging guilds.

TRVs for Inhalation Exposures for the Class Mammalia

No data available.

TRVs for Dermal Exposures for the Class Mammalia

No data available.

TRVs for Birds

No data available.

TRVs for Amphibians

No data available.

TRVs for Reptiles

No data available.

IMPORTANT RESEARCH NEEDS

To develop useful TRVs, long-term exposure studies are needed for mammals and other vertebrates. The chemical/structural similarities between picric acid and other nitroaromatics may make using surrogates useful in the interim.

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