PICARIDIN
TECHNICAL FACT SHEET

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NPIC Technical Fact Sheets provide information that is complex and intended for individuals with a scientific background and/or familiarity with toxicology and risk assessment. This document is intended to promote informed decision-making. Please refer to the General Fact Sheet for less technical information.

Chemical Class and Type:

- Picaridin is an insect and acarid repellent in the piperidine chemical family.[1] The chemical name is 1-piperidinecarboxylic acid 2-(2-hydroxyethyl)-1-methylpropylester and its Chemical Abstracts Service (CAS) registry number is 119515-38-7.[2] The World Health Organization (WHO) refers to this chemical as icaridin. Other synonyms include pikaridin, propidine, hydroxyethyl isobutyl piperidine carboxylate (INCI), and the trade names Bayrepel™ and KBR 3023.[2,3]

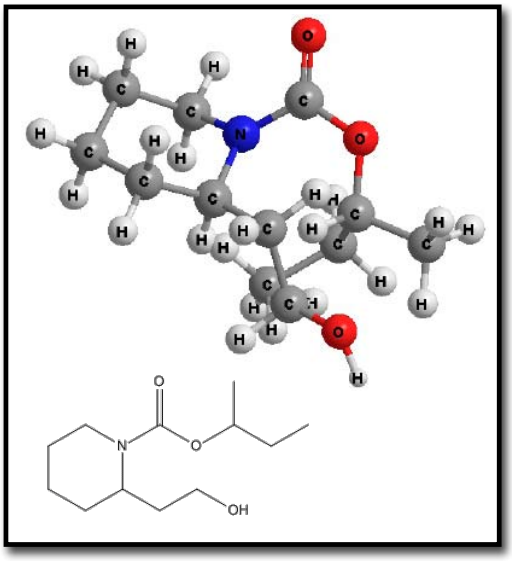
Laboratory Testing: Before pesticides are registered by the U.S. EPA, they must undergo laboratory testing for short-term (acute) and long-term (chronic) health effects. Laboratory animals are purposely given high enough doses to cause toxic effects. These tests help scientists judge how these chemicals might affect humans, domestic animals, and wildlife in cases of overexposure.

- Piperidine-based compounds such as picaridin are cyclic amines. Piperidines are structural components of piperine, the plant extract from the genus *Piper* that is also known as pepper.[3] Picaridin itself is a synthetic molecule developed by Bayer in the 1980s based on molecular modeling.[3]
- Picaridin was first registered for use by the United States Environmental Protection Agency (U.S. EPA) in 2001.[1] Picaridin has been registered for use in many countries world-wide but products containing picaridin first became available in the U.S. market in 2005.[4] It is widely used in Europe and Australia.[5] See the text box on **Laboratory Testing**.

Physical / Chemical Properties:

- Technical grade picaridin is a colorless liquid with little odor.[1] It is a racemic mixture of two diastereoisomers that occur in roughly equal proportions.[2]
- Vapor pressure[2]: 4.4 x 10^{-4} mmHg at 25 °C
- Octanol-Water Partition Coefficient (log K_{ow})[1]: 4.94; (log K_{ow})[2]: 2.23 at 20 °C and pH 4-9
- Henry's constant[6]: estimated as 3.0 x 10^{-11} atm·m^3/mol at 25 °C
- Molecular weight[1]: 229.3 g/mol
- Solubility (water)[1]: not soluble in water
- Soil Sorption Coefficient (K_{oc})[6]: estimated at 389

Molecular Structure - Picaridin



Uses:

- Picaridin is registered for use on the human body and clothing to repel biting flies, ticks, chiggers, fleas, and mosquitoes.[1,7] Product formulations include pump sprays, aerosols, and impregnated wipes.[7] Uses for individual picaridin products vary widely. Always read and follow the label directions when applying pesticide products.
- Signal words for products containing picaridin may range from Caution to Danger. The signal word reflects the combined toxicity of the active ingredient and other ingredients in the product. See the pesticide label on the product and refer to the NPIC fact sheets on ***Signal Words*** and ***Inert or "Other" Ingredients***.
- To find a list of products containing picaridin which are registered in your state, visit the website http://npic.orst.edu/reg/state_agencies.html and search by "active ingredient."

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Mode of Action:

Target Organisms

- Picaridin both repels and deters insects, so that insects move away from the chemical and do not feed if they encounter skin or clothing that has been treated.[8] Picaridin applied to cloth deterred insects from biting through the cloth to the skin.[8]
- Insects appear to detect the chemical through olfactory sensing.[8] Researchers studying the mosquito *Aedes aegypti* determined that picaridin stimulates sensory hairs on the mosquito's antennae, and this appears to prevent the mosquito from recognizing its host's cues.[9]
- Researchers have concluded that mosquito species differ in how they sense stimuli. The removal of maxillary bulbs in *Aedes aegypti* reduced the repellent effect of picaridin, whereas *Anopheles stephensi* appeared to sense both their prey and the repellents with different organs.[10]
- Exposure to picaridin did not kill *Aedes aegypti* mosquitoes or alter their behavior when the mosquitoes were kept in vials with filter paper that had been soaked with solutions of 2-7% of the repellent.[11]

Non-target Organisms

- No data were found regarding the mode of action of picaridin on non-target organisms.

Acute Toxicity:

Oral

- Picaridin is classified as slightly toxic if ingested.[1] WHO reported LD_{50} values of 2236 mg/kg and 4743 mg/kg in fasted and non-fasted male rats, respectively.[2] See the text boxes on **Toxicity Classification** and **LD_{50}/LC_{50}**.
- The NOEL for acute oral exposure was estimated at 100 mg/kg in both fasted and non-fasted rats.[2] See the text box on **NOAEL**, **NOEL**, **LOAEL**, and **LOEL** (page 3).

LD_{50}/LC_{50}: A common measure of acute toxicity is the lethal dose (LD_{50}) or lethal concentration (LC_{50}) that causes death (resulting from a single or limited exposure) in 50 percent of the treated animals. LD_{50} is generally expressed as the dose in milligrams (mg) of chemical per kilogram (kg) of body weight. LC_{50} is often expressed as mg of chemical per volume (e.g., liter (L)) of medium (i.e., air or water) the organism is exposed to. Chemicals are considered highly toxic when the LD_{50}/LC_{50} is small and practically non-toxic when the value is large. However, the LD_{50}/LC_{50} does not reflect any effects from long-term exposure (i.e., cancer, birth defects or reproductive toxicity) that may occur at levels below those that cause death.

Dermal

- Acute dermal LD_{50} values in rats were greater than 2000 mg/kg and 5000 mg/kg. No effects were seen at either the 2000 mg/kg or 5000 mg/kg dose level, so researchers estimated NOEL values of 2000 mg/kg and 5000 mg/kg, respectively for the two studies.[2]
- The U.S. EPA considered picaridin to be slightly toxic for acute dermal and ocular exposure.[1]
- Picaridin is not considered a skin irritant and is not a sensitizer, but it can cause slight to moderate eye irritation.[1,2]

Inhalation

- The LC_{50} over a 4-hour exposure period exceeded 4364 mg/m^3 in male rats, and the NOEL was determined to be 2153 mg/m^3.[2]
- The U.S. EPA considered picaridin to be practically non-toxic for inhalation exposure.[1]

Signs of Toxicity - Animals

- Rabbits showed no signs of dermal irritation following a single application of picaridin at a rate of 80 mg/cm^2 during a primary dermal irritation study.[12] No other reports of acute toxicity in animals were found.

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TOXICITY CLASSIFICATION - PICARIDIN

	High Toxicity	Moderate Toxicity	Low Toxicity	Very Low Toxicity
Acute Oral LD_{50}	Up to and including 50 mg/kg (≤ 50 mg/kg)	Greater than 50 through 500 mg/kg (> 50 – 500 mg/kg)	**Greater than 500 through 5000 mg/kg (> 500 – 5000 mg/kg)**	Greater than 5000 mg/kg (> 5000 mg/kg)
Inhalation LC_{50}	Up to and including 0.05 mg/L (≤ 0.05 mg/L)	Greater than 0.05 through 0.5 mg/L (>0.05 – 0.5 mg/L)	Greater than 0.5 through 2.0 mg/L (> 0.5 – 2.0 mg/L)	**Greater than 2.0 mg/L (> 2.0 mg/L)**
Dermal LD_{50}	Up to and including 200 mg/kg (≤ 200 mg/kg)	Greater than 200 through 2000 mg/kg (> 200 - 2000 mg/kg)	**Greater than 2000 through 5000 mg/kg (>2000 – 5000 mg/kg)**	Greater than 5000 mg/kg (> 5000 mg/kg)
Primary Eye Irritation	Corrosive (irreversible destruction of ocular tissue) or corneal involvement or irritation persisting for more than 21 days	Corneal involvement or other eye irritation clearing in 8 – 21 days	**Corneal involvement or other eye irritation clearing in 7 days or less**	Minimal effects clearing in less than 24 hours
Primary Skin Irritation	Corrosive (tissue destruction into the dermis and/or scarring)	Severe irritation at 72 hours (severe erythema or edema)	Moderate irritation at 72 hours (moderate erythema)	**Mild or slight irritation at 72 hours (no irritation or erythema)**

The highlighted boxes relfect the values in the "Acute Toxicity" section of this fact sheet. Modeled after the U.S. Environmental Protection Agency, Office of Pesticide Programs, Label Review Manual, Chapter 7: Precautionary Labeling. http://www.epa.gov/oppfead1/labeling/lrm/chap-07.pdf

Signs of Toxicity - Humans

- Researchers noted no dermal irritation on the backs of human subjects following the application of 20% picaridin aerosol, 20% picaridin lotion, or technical grade picaridin administered at the rate of 50 mg/cm^2. The substances were left in place for 48 hours. A total of 80 people participated, with 30 exposed to formulated products and 50 exposed to the technical grade picaridin. Subjects included individuals with skin conditions such as eczema, general sensitivity, and allergies.[12]
- A 39-year-old man developed allergic contact dermatitis several hours after using a repellent containing 10% picaridin and methylglucose dioleate. Patch tests suggested that the man had reacted to both the picaridin and the methylglucose dioleate in the product.[13]
- Always follow label instructions. If unintended exposures occur, be sure to follow the First Aid instructions on the product label carefully. For additional treatment advice, contact the Poison Control Center at 1-800-222-1222. If you wish to discuss an incident with the National Pesticide Information Center, please call 1-800-858-7378.

Chronic Toxicity:

Animals

- Subchronic oral exposure led to decreased body weights in both male and female rats when the rats consumed 1033 mg/kg/day.[1] In addition, the kidneys of the male rats increased in weight and there was evidence of protein droplet degenerative neuropathy.[1] Based on the doses in this study, researchers estimated the NOAEL to be 301 mg/kg/day, and the LOAEL to be 1033 mg/kg/day.[1] See the text box on **NOAEL**, **NOEL**, **LOAEL**, and **LOEL**.

NOAEL: No Observable Adverse Effect Level
NOEL: No Observed Effect Level
LOAEL: Lowest Observable Adverse Effect Level
LOEL: Lowest Observed Effect Level

- Subchronic dermal exposure in rats led to slight increases in liver size, chronic kidney inflammation, and hyalinosis in the kidneys at doses of 500 mg/kg/day for 90 days. Researchers set the LOAEL for systemic subchronic dermal effects at 500 mg/kg/day based on these effects, and the NOAEL was set at 200 mg/kg/day.[1,14]

- Researchers noted skin irritation including scabs and exfoliation at the site of application when rats were treated dermally with 80 mg/kg/day of picaridin for 90 days. This dose has been set as the LOAEL.[1] These changes were considered slight and of the magnitude expected when either water or medical grade petroleum was applied to skin on a daily basis.[14]
- Researchers placed technical grade picaridin at doses of 50, 100, or 200 mg/kg on the backs of beagle dogs every weekday for one year. The dogs demonstrated no adverse effects at any dose. The chronic dermal toxicity NOEL for both males and females was therefore estimated to be 200 mg/kg/day.[15]

Humans

- No human data were found on chronic effects of picaridin. See the text box on **Exposure**.

> **Exposure: Effects of picaridin on human health and the environment depend on how much picaridin is present and the length and frequency of exposure. Effects also depend on the health of a person and/or certain environmental factors.**

Endocrine Disruption:

- No evidence of endocrine disruption has been found for picaridin.[1]

Carcinogenicity:

Animals

- Researchers applied picaridin to the skin of rats at doses of 50, 100, or 200 mg/kg/day each weekday for two years. No increases in cancer occurrence following picaridin exposure were found.[14] Mice were treated dermally with picaridin at doses of 50, 100, or 200 mg/kg on weekdays for 18 months. Researchers did not observe any chemically-induced neoplasias in the mice. No changes in body weight or food consumption were noted in the living animals, and no gross changes or histopathological changes in the animals' organs were noted at their deaths.[16]

Humans

- The U.S. EPA classified picaridin as "not likely to be carcinogenic to humans" based on dermal exposure.[1] This determination was based on chronic dermal studies performed on rats and mice.[1] See the text box on **Cancer**.

> **Cancer: Government agencies in the United States and abroad have developed programs to evaluate the potential for a chemical to cause cancer. Testing guidelines and classification systems vary. To learn more about the meaning of various cancer classification descriptors listed in this fact sheet, please visit the appropriate reference, or call NPIC.**

- No human data were found on carcinogenic effects of picaridin.

Reproductive or Teratogenic Effects:

Animals

- Researchers conducted a two-generation reproductive study on rats, administering 50, 100, or 200 mg/kg picaridin to the rats' skin weekly beginning 10 weeks before mating and continuing through to weaning of the pups. The pups were treated from weaning through the weaning of their own pups. The rats did not show any effects of the treatment in terms of clinical signs or changes in body weight throughout the study, and no evidence of toxicity was found beyond acanthosis and hyperkeratosis in the skin at the application site. The researchers concluded that chronic picaridin exposure to the skin at doses as high as 200 mg/kg did not result in reproductive toxicity.[17]

- Rats and rabbits were treated daily with picaridin applied to their skin during gestation, and both the mothers and the fetuses were examined for effects. Researchers dosed rats daily with 50, 100, or 400 mg/kg picaridin and rabbits daily with 50, 100, or 200 mg/kg picaridin. Scaly or sloughing skin was observed at the application site in both species. In addition, researchers observed increases in the liver weights of the rats in the high dose group. No other effects were observed in the mothers, and no treatment-related malformations were observed in the fetuses.[18]
- Based on the aforementioned studies, the U.S. EPA reported a developmental NOAEL of 400 mg/kg/day. Maternal effects were noted at this dose including increased liver weights. A developmental NOAEL of greater than 200 mg/kg/day was reported for rabbits.[1]

Humans

- No human data were found on the teratogenic or reproductive effects of picaridin.

Fate in the Body:

Absorption

- A dermal metabolism study reported that 61-66% of radio-labeled picaridin was absorbed by skin dosed with 20 mg/kg while 40-55% was absorbed when researchers dosed skin at 200 mg/kg. The percentage absorbed was calculated from parent compound and metabolites measured in tissues including plasma and excreta.[14] No details on the origin of the skin or other experimental parameters were reported.
- Rats dosed with 20 mg/kg of radio-labeled picaridin applied to their skin absorbed approximately 60% of the dose, although this varied by gender and dose. In male rats, absorption half-lives ranged from 1.5 to 1.9 hours, whereas in females, values ranged from 0.8 hours for a single dose of 20 mg/kg picaridin, to 3.4 hours following a single dose of 200 mg/kg.[19]
- Researchers applied 14.7 or 15.0 mg of technical grade picaridin or a 15% wet weight preparation in ethanol to the skin of human volunteers and covered the application site with a protective wrap for eight hours. Less than 6% of the applied doses were absorbed after an 8-hour exposure.[20]

Distribution

- Rats were dosed with picaridin applied dermally at a rate of 20 mg/kg or 200 mg/kg. Maximal plasma concentrations occurred six to eight hours following dosing for all rats in all dose groups. Researchers measured plasma concentrations ranging from 0.5 µg/ml for males and 0.8-1.6 µg/ml for females in the 20 mg/kg dose groups. Following doses of 200 mg/kg, blood plasma concentrations of picaridin peaked at 4.48 and 1.70 µg/ml for male and female rats, respectively.[19]
- Picaridin applied to the arms of human volunteers was not found in blood plasma.[20]

Metabolism

- Rats excreted picaridin primarily through the urine following dermal exposure. Phase 1 metabolic reactions predominated, in which either the 2-methylpropyl side chain or the piperidine ring were hydroxylated. Researchers also noted that the hydroxyethyl sidechain was oxidized to produce a carbonyl group. There was very little Phase 2 metabolism of the picaridin.[19]
- No metabolites were noted in the bloodstream of either animals or humans, but data were limited.[19,20]

Excretion

- Urine was the primary route of excretion following dermal exposure in rats at a rate of 20 mg/kg, with 73-88% of the absorbed dose recovered in the urine. Male rats dosed with 200 mg/kg picaridin on their skin excreted 33% of the administered dose in the urine or feces, whereas females excreted 40% of the administered dose.[19]
- Excretion of radio-labeled picaridin applied to the arms of human volunteers was nearly complete in 24 hours.[20]

- No data were available on the composition of parent compound and metabolites in the urine of either animals or humans.[19,20]

Medical Tests and Monitoring:

- No information was located with respect to biomarkers of exposure to picaridin.

Environmental Fate:

Soil

- Picaridin is not expected to volatilize from wet or dry soil surfaces based on its Henry's Law constant and vapor pressure, respectively.[6]
- Picaridin is expected to be moderately mobile in soil based on its K_{oc} value.[6]
- No other data were found regarding the behavior or fate of picaridin in soil.

Water

- No information was available regarding the potential for picaridin to contaminate groundwater.
- The potential for picaridin to volatilize from water is low based on its Henry's Law constant.[6]
- Picaridin's K_{OC} value suggests that it will adsorb to sediments and suspended solids in the water column. Researchers estimated the bioconcentration factor (BCF) at 10.4, and do not expect picaridin to bioconcentrate in aquatic organisms.[6]
- German researchers detected picaridin at concentrations between 0.6 and 1.4 µg/L in wastewater treatment plant influent but no picaridin was detected in the effluent.[21] However, the researchers did detect the carboxylic acid derivative of picaridin in the effluent.[22]
- Picaridin is rapidly degraded by aerobic bacteria.[22] Although a number of possible metabolites have been proposed, only the carboxylic acid derivative appears to be stable in the environment.[22]
- Picaridin is stable to hydrolysis under environmentally relevant conditions.[1,2]

Air

- Picaridin has high potential for volatilization, and will primarily exist as a vapor in the atmosphere.[6]
- Although picaridin is not expected to be broken down directly by photolysis, photochemically produced hydroxyl radicals will degrade picaridin with an estimated half-life of 2.3 hours.[6] See the text box on **Half-life**.

Plants

- Researchers exposed the green alga, *Scenedesmus subspicatus,* to picaridin for 72 hours at six concentrations ranging from 5.6 mg/L to 100.0 mg/L. The alga exhibited reduced growth following exposure. The growth inhibition No Observed Effect Concentration (NOEC) for picaridin was determined to be 56 mg/L.[1] No information for terrestrial plants was found.

The "half-life" is the time required for half of the compound to break down in the environment.

1 half-life = 50% remaining
2 half-lives = 25% remaining
3 half-lives = 12% remaining
4 half-lives = 6% remaining
5 half-lives = 3% remaining

Half-lives can vary widely based on environmental factors. The amount of chemical remaining after a half-life will always depend on the amount of the chemical originally applied. It should be noted that some chemicals may degrade into compounds of toxicological significance.

Indoor

- No information was found regarding picaridin's behavior or fate in indoor environments, nor was information found regarding indoor residues.

Food Residue

- There are no tolerances for picaridin in food. Picaridin residues are not expected to occur in food due to picaridin's sole use as a topical repellent.[1] Neither the United States Department of Agriculture's (USDA) Pesticide Data Program (PDP) nor the United States Food and Drug Administration's (FDA) Center for Food Safety and Applied Nutrition Pesticide Program Residue Monitoring program analyzed food samples for picaridin.[23,24]

Ecotoxicity Studies:

Birds

- Researchers estimated a NOEC of greater than 5000 ppm picaridin in the diet of bobwhite quail. Based on this result, the U.S. EPA considers picaridin to be non-toxic to birds.[1]

Fish and Aquatic Life

- Researchers estimated the 96-hour LC_{50} in rainbow trout to be 173 mg/L and the NOEC to be 50.1 mg/L.[1,2] Based on this study, the U.S. EPA considers picaridin to be moderately toxic to fish.[1] Tests for bioaccumulation potential in the zebra danio fish indicated that there is no potential for bioaccumulation in fish through diet or other exposure routes.[2] Another study with the same fish species concluded that there was some potential for bioconcentration, or uptake through water alone.[2]
- *Daphnia magna* showed no signs of toxicity when exposed to concentrations ranging from 10 mg/L to 100 mg/L for 24 or 48 hours.[1]
- The Lowest Observed Effect Concentration (LOEC) for the green alga *Scenedesmus subspicatus* was estimated to be 56 mg/L based on 72-hour exposures to concentrations ranging from 5.6 to 100.0 mg/L.[1]

Terrestrial Invertebrates

- No data were found regarding the effects of picaridin on terrestrial invertebrates such as bees and earthworms.

Regulatory Guidelines:

- No RfD was found for picaridin. See the text box on **Reference Dose (RfD)**.
- The U.S. EPA has classified picaridin as "not likely to be carcinogenic to humans" by the dermal route of exposure.[1] See the text box on **Cancer** (page 4).

Reference Dose (RfD): The RfD is an estimate of the quantity of chemical that a person could be exposed to every day for the rest of their life with no appreciable risk of adverse health effects. The reference dose is typically measured in milligrams (mg) of chemical per kilogram (kg) of body weight per day.

U.S. Environmental Protection Agency, Technology Transfer Network, Air Toxics Health Effects Glossary, 2009. http://www.epa.gov/ttnatw01/hlthef/hapglossaryrev.html#RfD

- The U.S. EPA requires "clear, common sense use directions and restrictions" on labels of picaridin products, particularly application and reapplication instructions and directions for use on children.[1]

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