

PEER-REVIEWED

Moth repellent toxicosis

Camille DeClementi, VMD

Between 2002 and 2004, ASPCA Animal Poison Control Center (APCC) staff members consulted on 158 cases of moth repellent ingestion. In most instances, the exposure was oral, but dermal and inhalation exposures were also reported. Naphthalene was the active ingredient in 83% of the cases, and paradichlorobenzene was the active ingredient in 17%. Naphthalene, a bicyclic aromatic hydrocarbon, is a natural component of fossil fuels, such as petroleum and coal. It is also produced when wood and tobacco are burned.¹ Paradichlorobenzene, an organochlorine insecticide, is considered to be half as toxic as naphthalene.² Many moth repellent products contain nearly 100% naphthalene or paradichlorobenzene. The products can be formulated into balls, crystals, or flakes.

Pharmacokinetics

Naphthalene evaporates easily and has a strong odor that repels moths. People can detect it in the air at concentrations of 84 ppb.¹ Naphthalene can be inhaled, ingested, or absorbed transdermally. It is soluble in oils and fats, so dermal absorption is increased if oils have been previously applied to the skin. Similarly, oral absorption increases when naphthalene is coadministered with a fatty product such as corn oil.^{1,3}

Paradichlorobenzene also has a characteristic penetrating odor and is well-absorbed orally and by inhalation.⁴ As with naphthalene, drinking milk or eating a fatty meal after oral exposure to paradichlorobenzene increases its absorption.^{4,5} Mothballs of either type may take several days to dissolve in the gastrointestinal tract, so prolonged absorption is possible.²

Naphthalene is carried to other organs once it enters the bloodstream, regardless of the absorption route. After a single dose of naphthalene in pigs, the highest concentration of naphthalene was found in adipose tissue. The kidneys, liver, and lungs contained the next highest concentrations, respectively. But pigs given multiple doses of naphthalene had the highest concentrations in the lungs with little in adipose tissue.¹ The highest tissue concentrations of paradichlorobenzene are found in adipose tissue.⁴ Both naphthalene and paradichlorobenzene



are found in milk and are able to cross the placenta.^{3,5}

The metabolism of naphthalene is complex. The initial metabolite, a 1,2-oxide, is produced in the liver by the monooxygenase enzymes (P450). Naphthalene 1,2-oxide can then form epoxides or quinones that may cause cellular damage, or it can be conjugated with glutathione to nontoxic metabolites.⁶ Additionally, some metabolites are conjugated with sulfate or glucuronic or mercapturic acid.^{1,3} Paradichlorobenzene is oxidized to phenolic compounds and then undergoes rapid conjugation with sulfate and glucuronide.⁵ The metabolites of both naphthalene and paradichlorobenzene are excreted primarily through urine, but some metabolites are excreted in bile.^{1,3,5}

Toxicity

Paradichlorobenzene is considered less toxic than naphthalene. In rats, the oral LD₅₀ of naphthalene is 1.8 g/kg,⁷ whereas the oral LD₅₀ of paradichlorobenzene is 3.8 g/kg.⁵ Dogs ingesting 1.5 g/kg of paradichlorobenzene did not develop clinical signs of toxicosis,⁴ but hemolytic anemia was reported in a dog that received a single 1,525-mg/kg dose of naphthalene and in another dog that received about 263 mg/kg/day naphthalene for seven days.¹ One mothball of either type weighs about 5 g. Less than one naphthalene mothball may cause clinical signs of toxicosis in children, but accidentally ingesting up to one paradichlorobenzene mothball is generally well-tolerated.^{3,4}

Clinical signs of toxicosis

Naphthalene

Hematologic effects have been reported in dogs after naphthalene ingestion,^{1,8} and cataracts have developed in laboratory animals.¹ In the ASPCA APCC database, the most commonly reported clinical signs after ingesting naphthalene-containing moth repellent products were vomiting, lethargy,

"Toxicology Brief" was contributed by Camille DeClementi, VMD, ASPCA Animal Poison Control Center, 1717 S. Philo Road, Suite 36, Urbana, IL 61802. The department editor is Petra A. Volmer, DVM, MS, DABVT, DABT, College of Veterinary Medicine, University of Illinois, Urbana, IL 61802.

and anorexia (ASPCA APCC Database: Unpublished data, 2004). Seizures and methemoglobinemia were also reported.

In people, oral exposure to naphthalene can cause gastrointestinal signs, including vomiting, nausea, abdominal pain, and diarrhea. Hemolytic anemia and cataract formation have also been reported.¹ An association exists between glucose-6-phosphate dehydrogenase deficiency and the hematologic effects of naphthalene. Inhaling naphthalene can also cause hemolysis and gastrointestinal effects in people.¹

Paradichlorobenzene

In the ASPCA APCC database, the clinical signs reported after ingestion of paradichlorobenzene-containing moth repellent products were vomiting and trembling (ASPCA APCC Database: Unpublished data, 2004). A bird that had inhaled paradichlorobenzene showed depression, head bobbing, weakness, and anorexia. The bird recovered with symptomatic treatment including force-feeding, thermoregulation, and confinement. Long-term oral exposure in laboratory animals showed no hematologic or ocular effects with

paradichlorobenzene, but liver and renal changes were noted. Additionally, neurologic signs including weakness, ataxia, and tremors were noted in rats receiving doses between 770 and 1,200 mg/kg/day for at least five days.⁵

In people, paradichlorobenzene ingestion can cause nausea and vomiting. Hepatotoxicity is also possible but uncommon after large oral exposures. Paradichlorobenzene vapors are irritating to the nose and eyes, and central nervous system depression may occur at concentrations that are extremely objectionable. With dermal contact, the solid material produces a burning sensation but causes only slight skin irritation. Paradichlorobenzene has less potential for hematologic damage than naphthalene, but methemoglobinemia was seen in one pediatric patient, and anemia has been seen with long-term exposures. Paradichlorobenzene may cause cataract formation.⁴

Treatment

When treating moth repellent exposure, assess and stabilize the patient. If the patient is dyspneic, provide supplemental



Flavor Tablets

Tablet Summary:

Flavor tablets are available in 100 mg and 250 mg strengths.

Contraindications:

Do not use in dogs with a history of seizures or in the presence of a known seizure disorder.

Indications:

INTRECEPT® (methylene orange) Flavor Tabs® for dogs is indicated for use in the prevention of flea bite reactions caused by *Ctenocephalides felis*, the control of adult *Ancylostoma caninum* (hookworm), the control of adult *Trichostrongylus axei* (pinworm), and the control of adult *Ascaris suum* (roundworm) infections in dogs and in puppies four weeks of age to 12 weeks and two juvenile dogs weighing 12 pounds. They are also indicated for use in the prevention of flea bite reactions caused by *Ctenocephalides felis*, and the control of adult *Ancylostoma caninum* (hookworm) and *Trichostrongylus axei* (pinworm) in cats and for use in a series of ages to 12 weeks and 15 lbs body weight in puppies.

Dosage:

Give INTRECEPT Flavor Tabs one (1) mg daily, once a month, at the recommended minimum dosage rate of 300 mg methylene orange per pound of body weight (30 mg/kg).

Recommended Dosage Schedule for Dogs:

Body Weight	INTRECEPT
3-10 lbs.	One tablet (30 mg)
11-20 lbs.	Two tablets (60 mg)
21-50 lbs.	Three tablets (90 mg)
51-100 lbs.	Five tablets (150 mg)

Give one (1) mg once a month at the appropriate combination of tablets.

Give INTRECEPT Flavor Tabs for Cats as a chew tablet, once a month, at the recommended minimum dosage rate of 300 mg methylene orange per pound of body weight (30 mg/kg).

Recommended Dosage Schedule for Cats:

Body Weight	Flavor Tab
15 to 10 lbs.	One tablet (30 mg)
11-17 lbs.	Two tablets (60 mg)
18-25 lbs.	Three tablets (90 mg)

Give one (1) mg once a month at the appropriate combination of tablets.

Administration:

INTRECEPT Flavor Tabs are palatable and most of the taste will be covered by the dog or cat when administered by the owner. As an alternative, the dog or cat may be offered its food or administered with a small amount of water. Watch the dog or cat closely following dosing to be sure the entire dose has been consumed. If this is not readily consumed, induce vomit with 1% hydrogen peroxide as soon as possible.

INTRECEPT Flavor Tabs should be administered monthly, once a month, at the recommended dosage rate of 300 mg methylene orange per pound of body weight (30 mg/kg). Do not administer INTRECEPT Flavor Tabs to dogs or cats if they are currently receiving any other anthelmintic or flea control products.

INTRECEPT Flavor Tabs replace diethylcarbamazine (DEC) for flea control prevention. The first dose must be given within 30 days after the last dose of DEC.

Palatability:

Palatability trials conducted in 1994 demonstrate that 95% of dogs and 90% of cats accepted the first dose of INTRECEPT Flavor Tabs within 15 minutes of offering.

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Effectiveness:

INTRECEPT Flavor Tabs eliminate the flea stage of flea larvae from the adult stages of flea larvae (eggs, larvae, pupae, and adults) and the control of adult *Ancylostoma caninum* (hookworm) and *Trichostrongylus axei* (pinworm) infections when administered orally according to the recommended dosage schedule.

Give INTRECEPT Flavor Tabs for Cats alternate (1) to two (2) days of flea control for use and two (2) days of flea control (DEC) and roundworm (MORON) infections when administered orally according to the recommended dosage schedule.

Precautions:

Do not use in puppies less than four weeks of age and less than two (2) pounds of body weight. Prior to initiation of the INTRECEPT Flavor Tabs treatment program, dogs should be treated for existing hookworm infections (MORON), flea infestations (DEC) and other infections as indicated on labels for flea, roundworm, and pinworm. Do not use in dogs receiving any other anthelmintic or flea control products.

Cats: Do not use in kittens less than six weeks of age and less than 15 lbs. body weight. Its use in two (2) more puppies less than two (2) weeks of age is not recommended. Safety in breeding, pregnant, and lactating queens and nursing litters has not been established.

Adverse Reactions:

The following adverse reactions have been reported following the use of INTRECEPT in dogs: depression, lethargy, vomiting, anorexia, weakness, diarrhea, constipation, weakness and hyperaesthesia.

Safety:

In well-controlled clinical trials in 100 dogs and 141 cats completed treatment with methylene orange. Methylene orange was used to help in dogs and cats with dogs frequently used methylene orange such as seizures, arthralgia, myeloma, diabetes, thyroid, flea infestations, and dogs and cats receiving chemotherapy.

Studies in two (2) more selected dogs demonstrated mild, transient hyperaesthesia reactions in dogs at high methylene orange doses. Methylene orange is present in dogs given an unapproved dosage regimen, resulting in unacceptable concentrations of the drug in milk. Puppies nursing these females exhibit moderate hyperaesthesia during lactation demonstrating hyperaesthesia-related effects. It was determined that lactating dogs only have a mild hyperaesthesia reaction and demonstrated no effects on the progeny because of their ability to accept a daily dose of methylene orange once a month (1 mg/kg) once a month (1 mg/kg) at the time of an effect of hyperaesthesia is not expected in the puppy.

Some nursing puppies, at 2, 4, and 6 weeks of age, given growth-stimulated oral INTRECEPT doses (3.5 mg/kg - 100 mg/kg) did not gain weight by 12 weeks, diarrhea and anemia. These effects were all resolved and puppies returned to normal weight by 16 weeks. No effects were observed in puppies given the recommended dose of INTRECEPT (0.3 mg/kg). This product has not been tested in dogs less than 1 kg weight.

A study done in dogs only correlated in randomized clinical, randomized clinical studies consisting of adults, puppies and pinworm infestation, in cats of various ages treated with INTRECEPT at 17.5 mg/kg (300 mg monthly dose rate). No adverse reactions were observed in any of the cats treated with a 100 mg dose regimen (1 mg/kg) through the 100 mg/kg (300 mg monthly dose rate) dose.

Safety studies were conducted in young cats and kittens and doses of 15, 30, and 50 mg/kg minimum recommended dose of 300 mg/kg demonstrated no drug-related effects. Intolerance studies at unapproved doses of 300 mg/kg demonstrated no drug-related adverse effects in kittens and 30 mg/kg adult cats.

Use in Puppies:

INTRECEPT Flavor Tabs are indicated according to the weight of the dog or cat. Each tablet size is available in color-coded packaging of size and taste tablets match.

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oxygen and place an intravenous catheter. Initiate decontamination procedures if the patient is stabilized and provide supportive care. Fluid therapy is recommended in symptomatic animals. Induce emesis only in asymptomatic patients and only if ingestion occurred less than two hours before presentation and no contraindications to inducing emesis exist. Dogs, cats, ferrets, and potbellied pigs can vomit, but rodents, rabbits, birds, horses, and ruminants cannot. After the vomiting has subsided, administer activated charcoal (1 to 2 g/kg orally) and a saline cathartic (250 mg/kg magnesium sulfate or sodium sulfate orally).⁹ Administering activated charcoal with a cathartic may be beneficial up to 24 hours after mothball ingestion because mothballs dissolve slowly in the gastrointestinal tract.²

In general, naphthalene ingestion requires more aggressive treatment than paradichlorobenzene. If the type of mothball ingested is unknown and the owner has brought in a sample, perform the following test. Add three heaping tablespoons of table salt to tepid water, and mix vigorously until the salt will no longer dissolve. Place the mothball in the saturated salt water. Naphthalene mothballs float, and paradichlorobenzene mothballs sink.¹⁰

Obtain a baseline complete blood count and serum chemistry profile. Address any gastrointestinal signs. Vomiting may be controlled by administering metoclopramide hydrochloride (dogs and cats 0.2 to 0.5 mg/kg orally, intramuscularly, or subcutaneously t.i.d.¹¹) or another standard antiemetic. Sucralfate (1 g for large dogs, 0.5 g for small dogs orally t.i.d.; 0.25 g orally b.i.d. to t.i.d. for cats¹¹) can be used to relieve gastrointestinal irritation. Additionally, consider adding a medication to decrease gastric acid production, such as the H₂ antagonist famotidine (dogs and cats 0.5 to 1 mg/kg orally, subcutaneously, or intramuscularly once or twice a day¹¹) or proton-pump inhibitor omeprazole (dogs 0.5 to 1 mg/kg orally once a day; cats 0.7 mg/kg orally once a day¹¹). Seizures may be controlled with diazepam (dogs and cats 0.5 to 1 mg/kg intravenously to effect¹¹). Blood transfusions or polymerized bovine hemoglobin glutamer-200 (Oxyglobin—Biopure) (dogs single dose of 30 ml/kg intravenously at a rate of up to 10 ml/kg/hr; not labeled for use in cats¹¹) may be needed in patients with severe methemoglobinemia.

Methemoglobinemia occurs when oxidative injury to hemoglobin leads to conversion of the heme from the ferrous to the ferric state. Methemoglobin is incapable of carrying oxygen. The blood of patients with methemoglobinemia is a char-



acteristic chocolate-brown color, and their mucous membranes may appear brown. Methemoglobinemia is reversible, and the body has enzyme systems that reduce methemoglobin back to hemoglobin. Treatment is required when the body's enzyme systems become overloaded and clinical signs of hypoxia develop. Patients become symptomatic when 20% to 30% of their hemoglobin has been converted to methemoglobin.¹²

Methemoglobinemia has been treated in dogs and cats with ascorbic acid (20 mg/kg orally, intramuscularly, or subcutaneously up to every six hours^{10,13}) or methylene blue (1.5 mg/kg slowly intravenously as a 1% solution^{10,14}). Ascorbic acid is thought to reduce methemoglobin to hemoglobin by a nonenzymatic reserve mechanism that the body uses when the enzyme systems normally responsible for the reduction are overloaded.¹³ This conversion is relatively slow,¹⁰ so ascorbic acid may not be useful for seriously affected patients unless it is used in conjunction with other treatments. Methylene blue acts rapidly and works through its conversion to leucomethylene blue in the tissues. Leucomethylene blue acts as a reducing agent in the conversion of methemoglobin to hemoglobin. Because methylene blue is an oxidizing agent, increased methemoglobinemia is a possible adverse effect.¹¹ Cats are reported to be at an increased risk for this adverse effect because of their unusual hemoglobin structure, so methylene blue use in cats is considered controversial.^{11,12}

N-Acetylcysteine may also be helpful in treating naphthalene- or paradichlorobenzene-induced methemoglobinemia, but it has not been recommended in the literature for this purpose. Acetylcysteine is a precursor in the synthesis of glutathione, or it can be oxidized to organic sulfate that is used in the sulfate conjugation pathway. Acetylcysteine is regularly administered to patients with acetaminophen toxicosis to reduce methemoglobinemia by providing an alternative substrate for conjugation with the metabolites of acetaminophen and maintaining glutathione concentrations.^{11,15} Based on its mechanism of action, acetylcysteine may also help maintain glutathione and sulfate concentrations during naphthalene or paradichlorobenzene toxicosis. Acetylcysteine is available in 10% and 20% solutions; it should be diluted to a 5% solution, using 5% dextrose solution or sterile water, before use. Administer an initial loading dose of 140 mg/kg, followed by 70 mg/kg orally every six hours for seven treatments. When given orally, acetylcysteine may cause gastrointestinal upset.¹¹ Proper dilution can decrease the chances of gastrointestinal upset developing. Acetylcysteine is not labeled for intravenous use, but it

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Toxicology Brief

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can be given intravenously in severely affected patients or patients showing signs of gastrointestinal upset. Administer intravenous acetylcysteine slowly over 15 to 20 minutes through a bacteriostatic (0.2- μ) filter.¹⁰

Prognosis

The prognosis for patients exposed to naphthalene- or paradichlorobenzene-containing moth repellents is favorable if the clinical signs are treated and no underlying patient factors, such as liver disease or conditions causing anemia, are present. Therapy and monitoring should continue until the clinical signs have resolved and complete blood count and serum chemistry profile results have returned to normal.

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