● INSECTICIDE FACTSHEET

IMIDACLOPRID

Imidacloprid is a relatively new, systemic insecticide chemically related to the tobacco toxin nicotine. Like nicotine, it acts on the nervous system. Worldwide, it is considered to be one of the insecticides used in the largest volume. It has a wide diversity of uses: in agriculture, on turf, on pets, and for household pests.

Symptoms of exposure to imidacloprid include apathy, labored breathing, incoordination, emaciation, and convulsions. Longer-term exposures cause reduced ability to gain weight and thyroid lesions.

In studies of how imidacloprid affects reproduction, exposure of pregnant laboratory animals resulted in more frequent miscarriages and smaller offspring.

An agricultural imidacloprid product increased the incidence of a kind of genetic damage called DNA adducts.

Imidacloprid is acutely toxic to some bird species, including sparrows, quail, canaries, and pigeons. Partridges have been poisoned and killed by agricultural use of imidacloprid. It has also caused eggshell thinning.

The growth and size of shrimp are affected by imidacloprid concentrations of less than one part per billion (ppb). Shrimp and crustaceans are killed by concentration of less than 60 ppb.

Imidacloprid is persistent. In a field test in Minnesota, the concentration of imidacloprid did not decrease for a year following treatment. It is also mobile in soil, so is considered by the U.S. Environmental Protection Agency to be a potential water contaminant.

The development of resistance to imidacloprid by pest insects is a significant concern. In Michigan potato fields, the Colorado potato beetle developed resistance to imidacloprid after just two years of use.

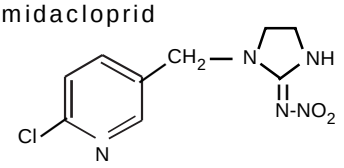
BY CAROLINE COX

Imidacloprid (see Figure 1) is a relatively new insecticide, first registered for use as a pesticide in the U.S. in 1994, and was the first insecticide in its chemical class to be developed for commercial use.[1] Imidacloprid is a systemic insecticide[1]; it moves through plants from the place where it was applied and kills insects when they feed. Its major manufacturer is Bayer Corporation that markets imidacloprid products with the brand names Merit, Admire, Premise, Pre-Empt, and Advantage, among others.[2-6]

Use

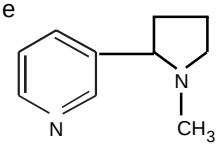
Although imidacloprid has not been in use for long relative to other common pesticides, according to University of Arizona entomologist George Ware "very possibly it is used in the greatest volume globally of all insecticides."[7] Imidacloprid has a wide variety of uses; it is used in agricultural products for use on cotton and vegetable crops,[3] in turfgrass and ornamental plant products,[2] in indoor and outdoor cockroach control products,[5] and in termite control products.[4] It is also used in products for pets, home, lawn, and garden use including some, like potting soil, that may not always be easily recognized as pesticides.[6,8-10]

Figure 1
Imidacloprid



1-((6-chloro-3-pyridinyl)methyl)-N-nitro-2-imidazolidinimine

Figure 2
Nicotine



Imidacloprid and nicotine have similar activity in the nervous system.

How Does Imidacloprid Kill Insects?

Imidacloprid, and other insecticides in the nicotinoid chemical family, are "similar to and modeled after the natural nicotine [a tobacco toxin]."[7] (See Figure 2.) Because of their molecular shape, size, and charge, nicotine and nicotinoids fit into receptor molecules in the nervous system that normally receive the molecule acetylcholine. Acetylcholine carries nerve impulses from one nerve cell to another, or from a nerve cell to the tissue that a

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nerve controls. Imidacloprid and other nicotinoids irreversibly block acetylcholine receptors.[7]

Why is imidacloprid less toxic to mammals' nervous systems than to insects'? Both insect and mammal nervous systems have acetylcholine receptors that are blocked by imidacloprid; most of the sensitive receptors are in the central nervous system of insects, but in nerves associated with muscles in mammals.[7] However, insect acetylcholine receptors are more sensitive to imidacloprid than are mammalian receptors,[11] although for some of imidacloprid's breakdown products this relationship is reversed.[12]

Inert Ingredients

Commercial imidacloprid insecticides, like nearly all pesticides, contain ingredients other than imidacloprid called "inert" or "other" ingredients. There is little publicly available information about the identity of these ingredients. Inerts that have been identified in imidacloprid products include the following:

Crystalline quartz silica (in Merit 0.5 G[13]) is classified by the International Agency for Research on Cancer as "carcinogenic to humans"[14] and as "known to be a human carcinogen"[15] by the National Toxicology Program because it causes lung cancer. It also causes emphysema and obstructive airway disease and has also caused genetic damage in exposed people and laboratory tests.[15]

Naphthalene (in Leverage 2.7[16]) has recently been classified by the National Toxicology Program as having "clear evidence of carcinogenic activity"[17] (through inhalation exposure) because it causes nasal cancers. It also caused two kinds of chromosome damage in laboratory tests.[17] Other symptoms of naphthalene exposure include anemia, liver damage, cataracts, and skin allergies.[18]

Whenever possible, the remaining sections of this article will specify whether tests were conducted with imidacloprid alone or with an imidacloprid-containing product (imidacloprid plus inerts).

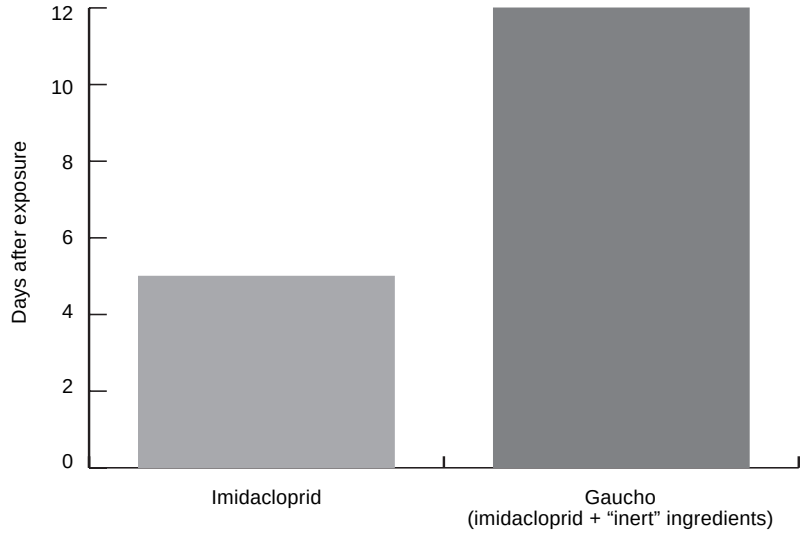
Toxicity of inerts to cats: An unidentified inert ingredient in Advantage, an imidacloprid flea insecticide applied as drops on the back of a pet's neck, can be toxic to kittens when applied above the label rate. In laboratory tests, death, coma, and incoordination were observed in kittens receiving five times the recommended dose of Advantage.[19] Further experiments showed that the toxicity was probably caused by the inert present in the largest amount.[20] No publicly available studies show the effects of smaller overdoses. Vomiting, salivation, and depression were also observed in cats fed Advantage or its inert ingredients.[21]

Acute Toxicity

In laboratory animals, symptoms of acute (short-term) oral exposure to imidacloprid included apathy, labored breathing, loss of the ability to move, staggering, trembling, and spasms. Some symptoms lasted for five days following exposure.[22] Symptoms following acute exposure to an agricultural imidacloprid product (imidacloprid plus "inerts") included reduced activity, incoordination, tremors, diarrhea, and emaciation. Some symptoms lasted 12 days after exposure,[23] twice as long as the symptoms of exposure to imidacloprid alone. (See Figure 3.) Symptoms following acute exposure to an imidacloprid flea control product included reduced activity, convulsions, and labored breathing.[24]

Also in laboratory animals, symptoms of breathing imidacloprid (for four hours) included difficult breathing, loss of the ability to move, and slight tremors. Symptoms of breathing two agricultural imidacloprid products were similar: incoordination, convulsions, reduced activity, tremors, and salivation. Some symptoms

Figure 3
Persistence of Acute Neurological Symptoms Caused by Imidacloprid and a Commercial Imidacloprid Product



Sources:
U.S. EPA. Office of Pesticides and Toxic Substances. 1992. Request for experimental use permit 00315-EUP-ENG and 003125 EUP-ENR for NTN 33893 (Imidacloprid-proposed) a crystalline end-use formulation containing 0.62% NTN 33893 active ingredient. Memo from M.S. Ottley, Health Effects Div., to D. Edwards, Registration Div. Washington, D.C., Mar. 24. (See attached Data Evaluation Report for MRID No. 420553-31.)

U.S. EPA. Office of Prevention, Pesticides and Toxic Substances. 1994. Imidacloprid. Evaluation of toxicity data submitted and identification of outstanding toxicology data requirements. Memo from M.S. Ottley, Health Effects Div., to P. Jenkins and D. Edwards, Registration Div. Washington, D.C., June 8. (See attached Data Evaluation Report for MRID No. 428557-02.

In laboratory tests, symptoms of exposure to a commercial imidacloprid product lasted over twice as long as symptoms of exposure to imidacloprid alone.

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persisted two days after exposure.[25]

Eye Irritation: Several imidacloprid products (Merit 0.5 G,[26] Merit 75 WP,[2] Premise 75,[4] Provado Solupak,[27] and Advantage[6]) cause eye irritation.

Subchronic Toxicity

Subchronic (medium-term; 10-day) exposure of rats to imidacloprid reduced weight gain at a dose of 10 mg/kg per day.[28]

There are no publicly available subchronic studies of commercial imidacloprid products.

Chronic Toxicity

Chronic (long-term; lifetime) feeding studies with rats showed that the thyroid is especially sensitive to imidacloprid. Thyroid lesions were caused by doses of 17 milligrams per kilogram (mg/kg) of body weight per day in males. Slightly higher doses (25 mg/kg per day) reduced weight gain in females.[29] At higher doses (100 mg/kg per day), effects included atrophy of the retina in females.[30]

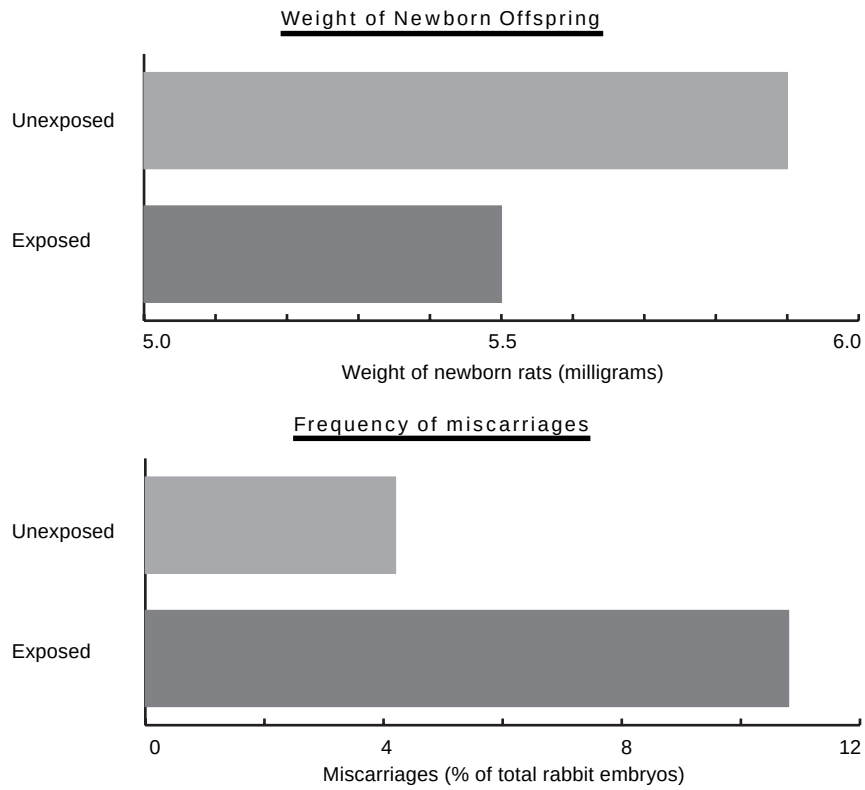
There are no publicly available chronic studies of commercial imidacloprid products.

Effects on Reproduction

Imidacloprid affects reproduction in a variety of ways. In pregnant rabbits, imidacloprid fed between the sixth and eighteenth days of pregnancy caused an increase in the frequency of miscarriages and an increase in the number of offspring with abnormal skeletons. These effects were observed at a dose of 72 mg/kg per day. In rats, a two generation feeding study found that rats fed imidacloprid gave birth to smaller offspring. Their weight was reduced at a dose of 19 mg/kg per day.[31] (See Figure 4.)

There are no publicly available studies of the effects of commercial imidacloprid products on reproduction.

Figure 4
Effects of Imidacloprid Exposure on Successful Pregnancy



Source:
U.S. EPA. Office of Prevention, Pesticides and Toxic Substances. 1993. Imidacloprid. Evaluation of toxicity data submitted and identification of outstanding toxicology data requirements. Memo from M.S. Ottley, Health Effects Div., to P. Jenkins and D. Edwards, Registration Div. Washington, D.C., Sept. 3. (See attached Data Evaluation Report for MRID Nos. 422563-40 and 422563-39.)

Imidacloprid exposure reduced birth weight 10 percent and doubled the number of miscarriages.

Mutagenicity

The tests of imidacloprid's ability to cause genetic damage that were submitted to the U.S. Environmental Protection Agency (EPA) as part of the registration process found no evidence of genetic damage, or evidence only at high exposures.[1] However, a new technique that looks at the ability of a chemical to cause genetic damage by chemically binding to DNA (the genetic material) found that the imidacloprid insecticide Admire increased the frequency of this kind of damage. DNA adducts (the binding of a chemical to DNA) were five times more common in calf thymus cells exposed to Admire than in unexposed cells.[32]

Toxicity of Imidacloprid's Metabolites

Several of imidacloprid's breakdown products (metabolites) can be toxic. One metabolite found in imidacloprid-treated plants, called the olefine metabolite, is more toxic to insects than imidacloprid itself.[33] Another metabolite, the desnitro metabolite, has very little nervous system toxicity to insects[33] but is more toxic than imidacloprid itself in mammals' nervous systems.[12] The soil metabolite 2-imidazolidone[34] (also known as ethyleneurea) induces tumors in combination with nitrate[35] and causes genetic damage.[36]

Effects on Birds

Imidacloprid's acute toxicity to birds varies widely among bird species. However, it is "highly toxic"[1] to certain species including house sparrow,[1] Japanese quail, canary, and pigeon.[37] The median lethal dose (LD_{50}; dose that kills half of a

test population) for all these species is less than 50 mg/kg.[1,37] Based on these tests, EPA's Ecological Effects Branch concluded that the agency's "levels of concern" were exceeded for both non-endangered and endangered songbirds.[38]

Imidacloprid causes abnormal behavior at doses less than 1/5 that which causes death. House sparrows fed a granular imidacloprid product showed symptoms of incoordination, lack of responsiveness, and inability to fly at doses of 6 mg/kg. At doses of 12 mg/kg diarrhea and immobility were added to the observed symptoms.[39] Even birds for whom imidacloprid is not highly toxic, mallard ducks for example, show these symptoms. Symptoms were observed in mallards at all imidacloprid doses used in tests submitted to EPA as part of the registration process.[40]

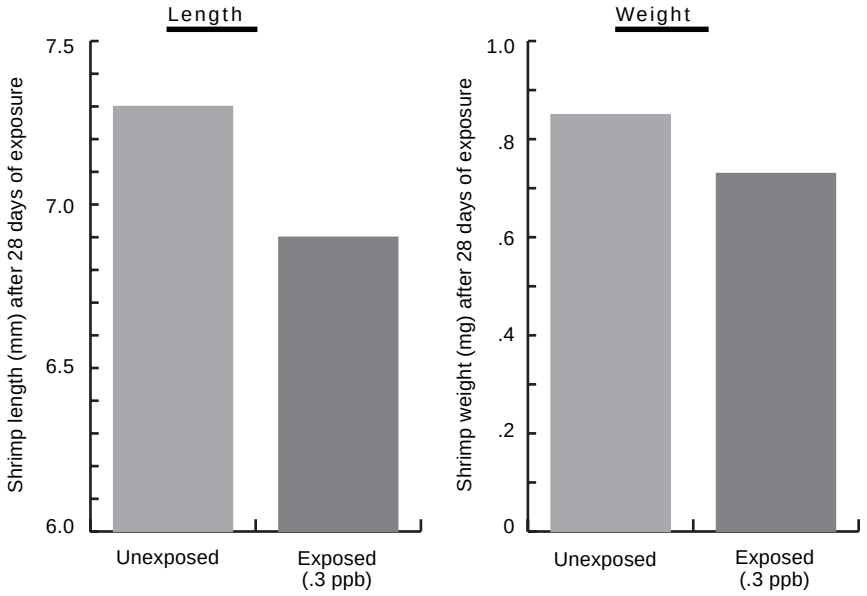
Other problems caused by imidacloprid in birds include eggshell thinning (at exposures of 61 mg/kg),[1] decreased weight (at exposures of 150 ppm in food),[41] and reduced egg production and hatching success (at exposures of 234 ppm in food).[42]

French veterinarians have found dead and poisoned partridges in agricultural fields following use of imidacloprid-treated seed and verified that the birds' symptoms matched those caused by imidacloprid. Imidacloprid residues were found in the crop, gizzard, and liver of these birds.[43]

Effects on Fish

Imidacloprid is acutely toxic to adult fish at relatively high concentrations (over 80 ppm). Juvenile fish, however are considerably more susceptible. Survival of rainbow trout fry, as well as their weight, was reduced at the lowest imidacloprid concentration tested (1.2 ppm). Therefore it was not possible to determine the lowest concentration that did not cause adverse effects.[44]

Figure 5
Effect of Low Concentrations of Imidacloprid on Shrimp



Source:
U.S. EPA. Office of Prevention and Toxic Substances. 1992. NTN 33893 ecological effects data, response to Miles Inc.'s request to upgrade four aquatic studies. Memo from D. Urban, Ecological Effects Branch, to D. Edwards, Registration Div. Washington, D.C., Aug. 25.

Imidacloprid concentrations of 0.3 ppb reduced growth of mysid shrimp, an important source of food for many saltwater fish species.

Effects on Other Aquatic Animals

Imidacloprid is toxic at extremely low concentrations to some species of aquatic animals. The following species have been studied as representatives of aquatic animals in general:

- The LC_{50} for the widespread freshwater crustacean *Hyalella azteca* is 55 ppb, classified by EPA as very highly toxic. Some mortality was recorded at a concentration of less than 1 ppb.[45]
- Imidacloprid's LC_{50} for the estuary crustacean *Mysidopsis bahia* is 37 ppb. Behavioral effects occurred in those animals that survived exposure: lethargy and loss of equilibrium.[46] The LC_{50} for an agricultural imidacloprid product was similar and EPA also classified it as very highly toxic.[47] Sublethal effects on mysid shrimp occurred at startling low concentrations: length, growth, and production of offspring were all reduced at concentrations less than 1 ppb.[48] (See Figure 5.) Mysid shrimp occupy "an important position in near shore food webs. They constitute a major source of food for many fish species…." In addition, "indirect effects to waterfowl may be expected if the mysid population, or similar organisms, is depleted."[49]
- A study of artificial ponds found that the number of invertebrate species and their abundance was reduced at concentrations of 5 ppb.[50]

Effects on Earthworms

Earthworms are an important part of the soil ecosystem. In a typical soil, about 80 percent of the animals, by weight, are earthworms. They make important contributions to soil fertility and the breakdown of organic material.[51]

Imidacloprid is acutely toxic to earthworms; for example, the LC_{50} of the species *Eisenia fetida* is between 2 and 4 ppm in soil.[51]

At lower concentrations, other effects occur. The activity of the enzyme cellulase, which is found in the earthworm's gut and allows it to break down plant

litter, is reduced by imidacloprid concentrations of 0.2 ppm.[52] The frequency of deformed sperm in earthworms was increased by a soil concentration of 0.2 ppm. (See Figure 6.) The frequency of damaged DNA (genetic material) in earthworms was increased by a concentration of 0.05 ppm.[51]

Effects on Beneficial Insects

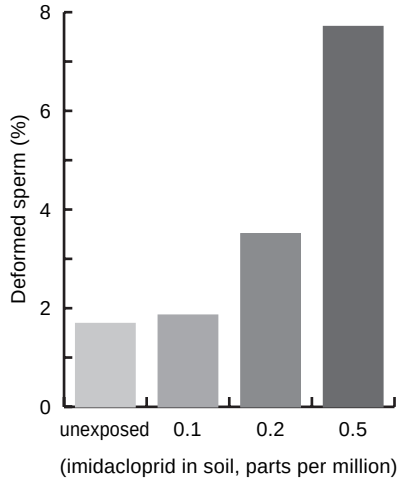
Since imidacloprid is an insecticide, it is not surprising that it is toxic to beneficial insects, those that provide an economic benefit to agriculture. Examples include the following:

- Imidacloprid is highly toxic to honey bees.[1]
- Lab tests indicated that no adults and only 10 percent of juvenile spiny soldier bugs (a predator of potato beetle, corn earworm, and other pests) would survive a typical application of imidacloprid.[53]
- Treatment of vegetable crops with the imidacloprid insecticide Provado reduced parasitoids of whiteflies between 35 and 50 percent.[54]
- Treatment of marigolds (with the imidacloprid insecticide Admire) or honeylocust trees (with the imidacloprid insecticide Merit) increased spider mite damage on both species because the insect natural enemies of the spider mites were killed by the imidacloprid.[55] A similar resurgence of spider mites occurred in eggplant treated with imidacloprid granules at planting.[56]
- Soil treatment of sunflowers, chrysanthemums, and dandelions with imidacloprid granules (Marathon) caused a decrease in the ability of lady beetles (predators) on the plants to move.[57]
- An imidacloprid insecticide was acutely toxic to a variety of predatory insects in laboratory tests: mirid bugs, lady beetles (adult and larvae), and lacewings.[58]

Effects on Cats

A British veterinarian reported that a cat (that was already ill with cancer) developed a severe skin rash following treatment with Advantage. The rash, centered at the spot where the imidacloprid was applied, caused intestinal problems and heart failure, leading to death.[59]

Figure 6
Imidacloprid and Sperm Deformities in Earthworms



Source:
Luo, Y. 1999. Toxicological study of two novel pesticides on earthworm, *Eisenia foetida. Chemosphere* 39:2347-2356.

Exposure to imidacloprid increases the frequency of deformed sperm in earthworms.

Effects on Plants

Although it is perhaps surprising for an insecticide, imidacloprid can be toxic to plants. For example, lemon seedlings growing in a greenhouse were damaged by trunk treatments with an imidacloprid insecticide,[60] and cauliflower seedlings were damaged by root drench and soil treatments.[61] In addition, a Polish researcher reported that treatment of peas with the imidacloprid insecticide Gaucho increased the incidence of *Fusarium* root rot.[62]

Also, an imidacloprid insecticide decreased growth of blue-green algae and diatoms at moderate concentrations (9–33 ppm).[63,64]

Food Contamination

Little monitoring of imidacloprid in food crops is publicly available. The U.S. Department of Agriculture and the Food and Drug Administration do not include imidacloprid in their food monitoring programs.[65,66] There are two published imidacloprid monitoring studies from Spain. One found imidacloprid residues in all samples of greenhouse vegetables tested one week after treatment.[67] The other found imidacloprid in tomatoes, peppers, potatoes, carrots, eggplant, pears, and melons; 21 percent of the samples were contaminated.[68]

Water Contamination

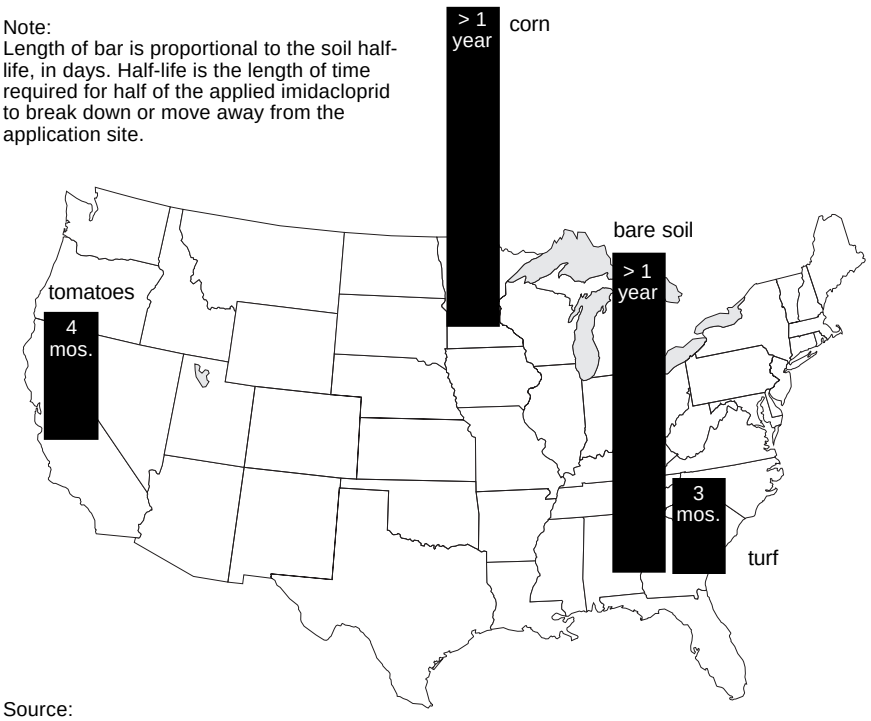
Imidacloprid, according to EPA, "has the potential to leach to ground water. In addition, high solubility and mobility are concerns for transport to surface water by dissolved runoff."[69] Details about these concerns include the following:

- Persistence of imidacloprid varies among sites in tests submitted as part of its registrations, but is always significant. The shortest half-life (the amount of time required for half of an applied pesticide to break down or move away from the test site) was 107 days in turf-covered soil in Georgia. The longest half-life was in Minnesota where the imidacloprid concentration in cornfield soil did not decline for one year after treatment.[70] (See Figure 7 for additional data.)
- Imidacloprid's ability to move in soil[69] has been demonstrated by a variety of studies. In a laboratory test, imidacloprid leached more quickly through soil columns than the other 11 pesticides tested.[71] Some of the other pesticides included in this study, diazinon, chlorpyrifos, and diuron, are widespread water contaminants.[72] EPA modeled the relative leaching potential of 14 turf insecticides; imidacloprid was in category I, pesticides with highest leaching potential.[73] When applied in a hop field drip irrigation system, imidacloprid moved to the maximum depth tested (105 cm) within 7 days after application.[74] (This represents a high-leaching scenario, as the soil was irrigated daily, but is a good example of imidacloprid's mobility in soil.)

Despite the concern raised by these studies that imidacloprid will contami-

FIgure 7
Persistence of Imidacloprid in Soil in Three States

Note:
Length of bar is proportional to the soil half-life, in days. Half-life is the length of time required for half of the applied imidacloprid to break down or move away from the application site.



Source:
U.S. EPA. Environmental Fate and Groundwater Branch. 1993. EFGWB review of imidacloprid. Washington, D.C., Jun 11. Pp. 5-6 and attached pesticide environmental fate one line summary.

Imidacloprid is persistent in soil. In some studies, over half of the applied imidacloprid is still present one year after application.

nate water, EPA did not classify imidacloprid as a restricted use product in order to protect water quality.[75] EPA explained their actions this way: "We are not recommending that the turf and ornamental products be classified as restricted use products due to ground water concerns for several reasons. First, several of the proposed NTN products contain directions for use around the home and a Restricted Use Classification would not allow sale of these products to the homeowner. Second, professional lawn care companies will be users of these products and they will not use a Restricted Use Product."[76] Thus, the decision was an economic one, not a scientific one.

Resistance

The development of resistance to imidacloprid in pest species appears to be a serious concern. In Michigan, imidacloprid resistance in the Colorado potato beetle was documented following two years of imidacloprid use on potatoes. (In both years, over 80 percent of the potato acreage was treated with imidacloprid.)[77] In laboratory experiments, thrips selected for their resistance to the organophosphate insecticide diazinon were also resistant to imidacloprid.[78] This situation, in which resistance to one insecticide confers resistance to another insecticide, is called cross-resistance and is "especially disconcerting"[78] to the University of Missouri researchers who conducted the study.

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