ChemicalWatch Factsheet

INDOXACARB

What is Indoxacarb?

Indoxacarb is a broad spectrum foliar insecticide used to initially control lepidopterous insects, like moths, in their larval stages. These include agricultural pests like the beet armyworm, cotton bollworm, the cabbage looper and leafhoppers. However, it also has broad spectrum activity on other pests, such as ants and cockroaches, and various plant bugs. It is manufactured by DuPont and was first conditionally registered in the U.S. in 2000.[1] Indoxacarb has several formulations, including tablet, broadcast granule, water dispersible, granule, and suspension concentrate, and it is currently marketed under the trade names, Steward,™ Advion, Avaunt,™ and Provaunt. It is registered to be used on various commodities, including apples, pears, lettuce, cabbage, corn, soybeans and cotton. Indoxacarb is also currently registered for residential and commercial sites for control of ants, cockroaches, wasps, centipedes, stinkbugs, and other household pests, including on cats and dogs for fleas.

Indoxacarb is typically a 75:25 mixture (DPX-MP062) of its two enantiomers (stereoisomers) – with one enantiomer responsible for the insecticidal activity. Indoxacarb is touted by industry as a "reduced-risk" pesticide and new organophosphate replacement. However, serious health effects have been observed to be associated with indoxacarb exposure in studies.

ChemicalWatch Stats

CAS Registry Number: 173584-44-6
Chemical Class: Oxadiazine
Use: Broad spectrum insecticide for chewing and suckling insects, fire ants.
Toxicity rating: Toxic
Signal Words: Caution
Health Effects: Neurotoxic and hematological effects, lung damage.
Environmental Effects: Toxic to honey bees and other beneficial insects, birds and fish. Generally persistent in soils.

Mode of Action

Indoxacarb is in a new class of chemistry with a new mode of action.[2] It belongs to the oxadiazine chemical family. Indoxacarb interferes with a group of ion channels by inhibiting the flow of sodium ions into nerve cells. This flow of sodium ions is essential to nervous system functioning. Disruption of these channels causes tremors, cessation of feeding, paralysis and death of insect pests. Lapeid, et al.[3] observed that indoxacarb acts in a manner distinct from other sodium channel modulators (e.g. pyrethroids), in that it acts to block voltage-dependent sodium channels. As a result of this mechanism, indoxacarb is considered a voltage-dependent sodium channel blocker.[4] Insects are exposed via ingestion of treated foliage/fruit and direct physical contact. It may take days for insects to die after exposure.

Acute Toxicity

Acute toxicity studies suggest that indoxacarb can cause skin sensitization. EPA has classified indoxacarb as a moderate dermal irritant (acute toxicity category III). Indoxacarb is moderately toxic to female rats via the oral route and is classified in toxicity category II for acute oral toxicity. It is readily absorbed after oral ingestion and extensively metabolized by the liver. No accumulation in tissues has been observed.[5,1] There is evidence of lung damage in the acute inhalation studies with both indoxacarb mixtures. "Lung noise" is observed and indicates the development of acute lung injury and high permeability pulmonary edema. This is attributed to an oxidant generated during indoxacarb metabolism.[6]

Indoxacarb shows some signs of neurotoxicity after acute exposures in rats. A decrease in motor activity occurs in females after a single dose of 100 milligrams per kilogram body weight (mg/kg). Other acute neurotoxicity studies find decreased forelimb grip strength and decreased foot splay at the high doses.[7] Indoxacarb causes some developmental effects in laboratory animals at doses that also cause maternal effects.[8]

Chronic Toxicity

The main adverse effect of indoxacarb after repeated ingestion

or application of a large quantity to the skin is a reduction in the number of red blood cells (anemia) observed in rats and dogs. There is depletion of blood-forming elements in the bone marrow and lymphoid organs in some studies with mice and rats. This reduction in the number of red blood cells is likely caused by the damaging effects of a metabolite. In oral toxicity studies in dogs, hemolytic anemia is observed as indicated by decreased red blood cells, increases in platelets, and secondary histopathologic findings indicative of blood breakdown.[9] Hemolytic effects are only observed in chronic studies with female rats. Subchronic (28 days) inhalation toxicity of indoxacarb in rats is characterized by increased spleen weights, increased pigmentation and hematopoiesis in the spleen, and hematological changes.[6]

There is no evidence that indoxacarb damages genetic material or leads to an increase in cancer. EPA classified indoxacarb as "not likely" to be carcinogenic to humans.[9] Studies have shown that there is a higher sensitivity of female rats to the toxic effects of indoxacarb.[6,10]

Developmental and Reproductive Effects

Indoxacarb causes some developmental toxicity in the offspring of pregnant rats and rabbits, at doses that also cause maternal toxicity. A decrease in fetal weights and the numbers of live fetuses per litter is seen at high doses, along with maternal toxicity effects (increased mortality, decreased mean body weights, body weight gain and food consumption). In a two-generation reproduction study in rats, no reproductive effects were observed at the highest dose tested, which was 6.4 mg/kg/day. However, maternal toxicity, characterized by reduced body weight gains, body weights, food consumption and increased spleen weights, occurs at a dose of 4.4 mg/kg/day.[7,9]

Neurotoxicity

Neurotoxicity is observed in several studies in both rats and mice. Symptoms are similar to acute exposures and are characterized by weakness, head tilting, and abnormal gait or mobility with inability to stand. Some of these signs occur at fatal doses. There is no evidence of susceptibility from either *in utero* or neonatal exposure to both rat and rabbit young. Clinical signs, (e.g. depression, salivation, abnormal gait and head tilt) are observed in chronic animal feeding studies with mice at 14 mg/kg/day and 20 mg/kg/day for males and females respectively.[7] Learning and memory parameters are affected in the pups in the developmental neurotoxicity study in rats.[6]

Volatility

Indoxacarb also has a low vapor pressure <1.0 X 10^{-7} mmHg, making it a relatively non-volatile rating.[5,11] However, scientists have found that temperature and humidity are significant factors influencing pesticide volatility. High temperature and low humidity increase volatility, and UV radiation and the types of microorganisms present affect how quickly a substance vaporizes and enters the air. Also, sealed buildings and air flow play a role in determining air quality and the levels of pesticide residues present indoors. Under any conditions, all substances will volatilize, albeit to different degrees.

Metabolites

Indoxacarb is extensively metabolized and the metabolites are eliminated in the urine, feces, and bile. The metabolite profile is dose-dependent and varies quantitatively between males and females. There are several metabolites associated with indoxacarb and they bear one of two ring structures; the indeno or trifluoromethoxyphenyl groups.[1] Of these, the trifluoromethoxyaniline (IN-P0036) metabolite has been identified as the likely metabolite causing oxidative damage to red blood cells in laboratory animals exhibiting hemolytic anemia after indoxacarb exposures.[10] The IN-JT333 metabolite is commonly observed in animal fat. Several metabolites result in the environment, including IN-JT333, IN-JU873, IN-KG433, IN-KT413, IN-MK638, IN-MK643, IN-ML438.[12] Some are more persistent and ecotoxic than others.

Ecological Effects

Indoxacarb is classified as moderately toxic to avian species on an acute dietary basis, especially to the bobwhite quail. The metabolite IN-JT333 is slightly toxic to birds on an acute oral basis. Indoxacarb and the metabolite IN-JT333 are highly toxic to rainbow trout and bluegill sunfish. A minor metabolite, IN-JU874, is slightly toxic to rainbow trout.[11] Indoxacarb and its metabolites are thus classified as moderately to highly acutely toxic to freshwater and estuarine/marine fish and moderately to very highly acutely toxic to freshwater and estuarine/marine invertebrates.[1] Indoxacarb and IN-JT333 are also slightly toxic to earthworms.[5] The metabolite IN-MP819 has been shown to exhibit greater toxicity to aquatic invertebrates than indoxacarb.[13]

Beneficial Insects

Honey Bees

Indoxacarb and its metabolites are considered to be highly toxic by contact, but practically non-toxic by dietary intake[1] to bees, based on laboratory studies. The insecticide was found to be moderately toxic to the honey bee when laboratory bees were given a honey solution containing 7.2ug a.i./bee.[5] However, the registrant, DuPont, contends that there is a low impact on honey bees after indoxacarb has dried. It is unknown what impacts to foraging bees would result from applications at the maximum proposed rate for indoxacarb.[5]

Other Non-target Insects

The Asian lady bettle's (*Harmonia axyridis*) survival, development, and reproduction rates are reduced even at reduced application rates of indoxacarb.[12] Various parasitic wasp species (*Aphidius colemani*; *Diaeretiella rapae*) experience increases in mortality after exposures to low doses of indoxacarb sprayed on plants. Other non-target species –pirate bugs, beetles and other arthropods– are also adversely impacted.[5]

Environmental Fate

Indoxacarb has an exceptionally complex degradation scheme, with the main breakdown products being IN-KT413 and IN-JT333. Indoxacarb undergoes rapid decomposition in terrestrial environments through microbial degradation, which is an important degradation pathway in soil. Under aerobic conditions, IN-JT333 is rapidly formed (after one day), followed by IN-KG433. Several other minor degradation products are also formed. Under anaerobic conditions, indoxacarb is more persistent, having a slower degradation rate. Indoxacarb has a moderately high soil sorption coefficient (Koc) of 2200- 8200, indicating a relatively low soil mobility and low probability of leaching into groundwater. However, as a result it is persistent in soil with aerobic half-lives ranging from 3 to 693 days.[1,5] The metabolite IN-JT333 has an even lower soil mobility and is thus more persistent in soil.

In water, indoxacarb degrades quickly –with a half-life of about 1 day at pH 9, but degrades slower at lower pHs (e.g. half-life ~500 days at pH 5). As a result, residues of this chemical in water resources can be expected.[1] The main breakdown product in water is IN-KT413. In sunlight, indoxacarb breaks down with half-lives of 3.2–4 days in water, but is very slow on soil with a half-life of 139 days.

Indoxacarb has no reported adverse effect on non-target terrestrial plants, and no phytotoxic effect on eight crops in field efficacy testing.[11]

Resistance

Indoxacarb has been advertised as an important new tool in resistance management programs due to its unique mode of action, not shared with other classes of pesticides to which certain pests have become resistant. However, in the relatively short time since it has been in use, a few cases of resistance have appeared. Resistance to indoxacarb has been documented in Hawaiian populations of the diamondback moth (*Plutella xylostella* (L).[12,14] The cotton bollworm (*Helicoverpa armigera*), a major pest in cotton and highly resistant to several conventional pesticides, is also found to have a three-fold tolerance to indoxacarb. The obliquebanded leafroller (*Choristoneura rosaceana*), on the other hand, has been found to be highly resistant to indoxacarb in the U.S., even before its field use.[12] One study in New York found that house flies exposed to indoxacarb produce a New York indoxacarb-resistant (NYINDR) strain, with more than 118-fold resistance after three generations.[15]

Regulation

DuPont was given a conditional registration for indoxacarb in October 2000 and was designated by the EPA to be a "reduced-risk" pesticide. The agency found that there was a potential for acute and chronic dietary exposure to indoxacarb and its isomer in drinking water, but concluded that the aggregate exposure and risk did not exceed any levels of concern. The agency also reduced the *Food Quality Production Act* (FQPA) safety factor to 1X, instead of the 10X safety factor used to protect children.[1] Tolerances for use on certain fruit, leafy greens, vegetables and corn are set.[6] Several data gaps exist for the environmental fate of indoxacarb's many degradation products.

A fully cited version of this factsheet can be found on Beyond Pesticides website at www.beyondpesticides.org/gateway.

Alternatives to Indoxacarb

For effective, long-term structural and agricultural control of insect pests, a sound, defined integrated pest management (IPM) plan should be implemented. This includes monitoring, sanitation, prevention, and use of least-toxic chemical alternatives as the last resort.

To manage pests:

- Caulk or repair any holes or openings around baseboards, water pipes, outlets, doors, windows and in walls and ensure doors are equipped with weather stripping.
- Practice good sanitation methods (e.g. keep areas free of clutter from papers and cardboard boxes). Store food in tightly sealed containers
- Secure and dispose of trash in containers with tight fitting lids

Use Least-Toxic Alternatives. If the problem persists after trying non-chemical interventions, apply least-toxic alternatives, such as non-volatile boric acid, diatomaceous earth or silica gel to cracks and crevices where pests hide: inside and behind cabinets and appliances, wall cavities and under sinks. [Boric acid/borates are widely available in various formulations like bait stations, powders, gels or pastes. To avoid exposure to boric acid dust, follow label directions and use caution when applying. Boric acid products should not be used anywhere children or pets can access.]

Endnotes

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