● INSECTICIDE FACTSHEET

DIAZINON: TOXICOLOGY

Diazinon is an organophosphate insecticide with agricultural, commercial, and household uses. Household uses predominate, with 75 million applications in the U.S. annually totalling over 5 million pounds.

Diazinon is toxic to the nervous system. Symptoms of acute diazinon poisoning include headache, nausea, dizziness, tearing, and sweating. Some symptoms, including blurred vision, headaches, and memory problems, can last for months or years.

In laboratory tests, feeding diazinon to pregnant animals has caused a decrease in the endurance, coordination, and growth of their offspring. In addition, the sexual development of offspring of both sexes was delayed.

Diazinon exposure has been associated with an increased risk of brain cancer in children and the cancer non-Hodgkin's lymphoma in farmers.

Infants are especially susceptible to diazinon. In addition, 9 - 16 percent of people have a slow form of an important detoxification enzyme and thus are particularly susceptible.

The U.S. Environmental Protection Agency estimated exposure to household residents following use of diazinon insecticide products and found that exposure following lawn care applications of liquid products and following indoor applications exceed the agency's "levels of concern."

BY CAROLINE COX

Diazinon (see Figure 1) is an organophosphate insecticide, chemically related to other common insecticides like malathion and chlorpyrifos.[1] It was first registered in the U.S. in 1956[2] and is sold under a variety of brand names, including DZN[3] and Knox Out 2FM.[4]

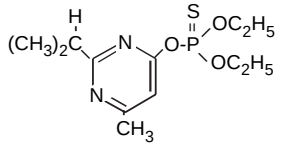
Use

Diazinon has agricultural, commercial, and household uses, but household uses predominate. Estimated agricultural use is 1.5 million pounds annually. Crops using the most diazinon are almonds, berries, pecans, and nectarines.[5] About 75 million household applications are made annually, 18 million indoors and 57 million outdoors.[6] Home, lawn, and garden use totals 5.5 million pounds per year.[5]

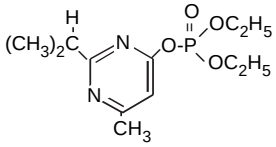
Mode of Action

Inside living things, diazinon is transformed into a molecule called diazoxon. (See Figure 1.) Diazinon, and the more potent diazoxon,[7] kill insects by interfering with nervous system function, as do all members of the organophosphate chemical family. Normally, impulses are transmitted chemically from the end of one nerve cell to the beginning of another; one of the chemical transmitters used in animal nervous systems is called acetylcholine. After transmitting the nerve impulse, acetylcholine is destroyed by an enzyme called acetylcholinesterase (AChE) in order to clear the way for another transmission. Organophosphates attach to AChE and prevent it from destroying acetylcholine, causing overstimulation of the nerves.[8]

Figure 1
Diazinon and Diazoxon



diazinon
(O,O-diethyl O-(2-isopropyl-6-methyl-4-pyrimidinyl)phosphorothioate)



diazoxon

Mammal and insect nervous systems are similar enough that effects of organophosphates are similar.[1]

It is worth noting that not all of diazinon's toxicological effects stem from its inhibition of AChE. Diazinon and other organophosphates inhibit numerous enzymes with molecular structures that are similar to AChE. For example, an enzyme involved in the metabolism of the amino acid tryptophan is strongly inhibited by diazinon and diazoxon.[9]

Inert Ingredients

Like most pesticide products, most commercial diazinon products contain ingredients other than diazinon that are misleadingly labelled as "inert." Public information about the identity of these inerts is scanty. See "Toxicology of Inert

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Ingredients," below, for information about inert ingredients that have been publicly identified.

Effects of Acute Exposure

Symptoms of acute (short-term) diazinon poisoning in people are similar to the symptoms of any organophosphate insecticide poisoning: headache, nausea, dizziness, tearing, sweating, salivation,[1] drowsiness, agitation, anxiety,[10] and influenza-like symptoms.[11] Symptoms of higher exposure include an abnormal heart rate (either too slow or too rapid),[12] muscle weakness, muscle twitching, pinpoint pupils,[1] lung congestion,[13] cardiac arrest,[14] and seizures.[15]

Other symptoms observed in laboratory animals after acute exposure include abnormal walking, reduced activity,[16] increased blood sugar levels,[17] low blood

TOXICOLOGY OF INERT INGREDIENTS

Ingredients in commercial diazinon products that have been publicly identified[1] include the following:

• 1,2-Benzisothiazolin-3-one is a preservative that has caused allergic skin reactions.[2]

• Calcium Silicate caused an increase in the frequency of abnormal chromosomes in a laboratory study using human blood cells. The incidence of a second kind of genetic damage, called sister chromatid exchanges, was also increased.[3]

• Cumene is a primary eye and skin irritant. It depresses the central nervous system. Symptoms of exposure include burning sensations, headache, dizziness, confusion, and drowsiness.[4]

• Diethylenetriamine is a potent skin irritant and also causes allergic skin sensitization. Other symptoms of exposure include irritation of the cornea and conjunctiva of the eye, asthmatic breathing, and nausea. In laboratory tests, it caused an increase in the incidence of a kind of genetic damage, sister chromatid exchanges.[5]

• Ethylbenzene can cause severe lung injury if inhaled. The offspring of rats who breathed ethylbenzene during their pregnancy had an increased incidence of birth defects. In laboratory animals who breathed ethylbenzene, the incidence of several cancers increased.[6]

• Isobutane depresses the central nervous system. It is also extremely flammable and can be an explosion hazard.[7]

• Polyvinyl Alcohol causes anemia in laboratory tests.[8]

• Propane is flammable and a severe explosion hazard.[9]

• Silica (crystalline) has been classified as "carcinogenic to humans" by the International Agency for Research on Cancer[10] and as "known to be a human carcinogen" by the National Toxicology Program.[11] It causes emphysema and obstructive airway disease and has also caused genetic damage in exposed people and laboratory tests.[11]

• Sodium sulfite. It may cause eye and skin irritation with vomiting and diarrhea[12] as well as skin allergies.[13] Exposure to small amounts can cause severe allergic reactions.[14]

•1,2,4-Trimethylbenzene damages the central nervous system and is irritating to eyes, skin, and the upper respiratory tract.[15]

• Xylenes are central nervous system depressants,[16] cause eye and skin irritation, headaches, nausea, and confusion. In laboratory tests they have caused kidney damage,[17] a reduction in fetal growth, an increase in fetal death, and an increase in the incidence of birth defects.[16]

1. Inert ingredients identified under the Freedom of Information Act (U.S. EPA. Office of Prevention, Pesticides, and Toxic Substances. 1999. Letter from Calvin Furlow to Marcy Trice, Aug. 5), and on material safety data sheets from www.cdms.net, www.ortho.com, and www.bonideproducts.con. For detailed information see NCAP's web page, www.pesticide.org.
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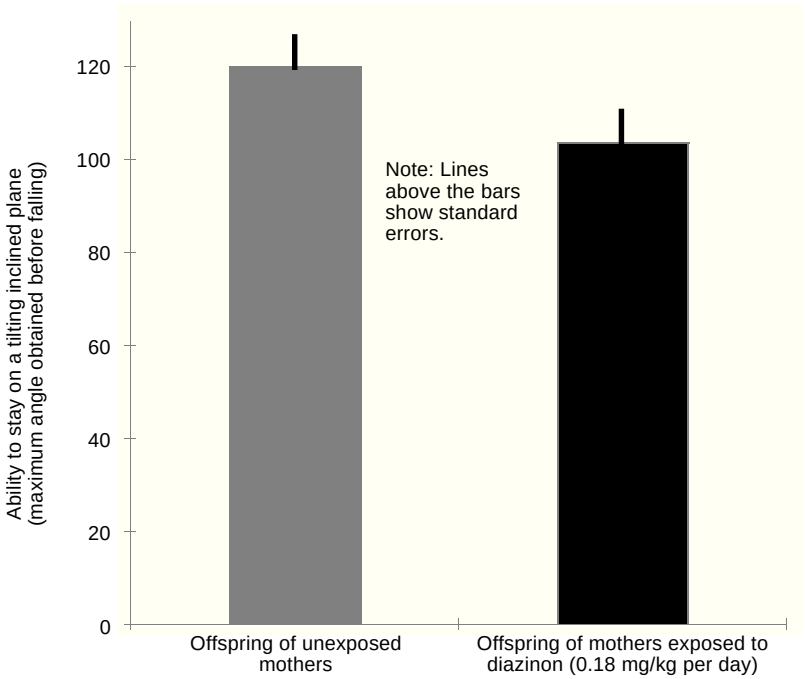
Figure 2
Developmental Effects of Diazinon: Endurance and Coordination



Source: Spyker, J.M. and D.L. Avery. 1977. Neurobehavioral effects of prenatal exposure to the organophosphate diazinon in mice. *J. Toxicol. Environ. Health* 3:989-1002.

Offspring of mice exposed to diazinon during pregnancy had less endurance and coordination than offspring of unexposed mothers.

pressure,[18] and inflammation of the pancreas.[19]

Physicians have reported that symptoms of acute diazinon exposure in children are different than those in adults. Tearing, sweating,[1] slow heart rate and muscle twitches,[20] common in adults, are infrequent in children. Seizures are much more common in children than in adults.[20] Inflammation of the pancreas is another symptom that is "not rare" in children with diazinon poisoning.[21]

Whether acute exposure to diazinon and other organophosphate insecticides can cause long-term health problems has been a controversial issue. Recently (1998), however, a U.S. Environmental Protection Agency (EPA) review found that "symptoms may persist for months or years after the initial exposure."[22] Persistent symptoms include blurred vision, headaches, muscle weakness, lethargy, short term memory impairment, inability to concentrate, confusion, lowered intelligence test scores, depression, and irritability.[23]

Skin Allergies

Both diazinon and the diazinon-containing insecticide Diazinon 4E caused allergic skin reactions in people. Although pesticides in general are tested on laboratory animals, diazinon and Diazinon 4E were tested on a group of 56 people. About 10 percent of them showed "positive dermal sensitization."[24] In this test, diazinon is applied to the skin of the subjects twice. If the reaction to the second exposure is greater than the reaction to the first exposure, the chemical causes sensitization.[25]

Effects of Subchronic and Chronic Exposure

Laboratory studies of subchronic (medium-term) and chronic (long-term) exposure typically expose animals by feeding them the test chemical over a period of several months, for subchronic tests, or over a one to two year period, for chronic tests. In subchronic and chronic tests with diazinon, the primary effect studied is inhibition of acetylcholinesterase (AChE), diazinon's target enzyme. In five studies (a six-week study of people; a one-year, a three-month, and a one-month study of dogs; and a one-month study of female rats) AChE inhibition occurred at strikingly low doses: the animals were fed less than 50 micrograms per kilogram of animal body weight per day.[26,27,28]

A study of rats who were exposed by breathing diazinon-contaminated air measured AChE inhibition at a similar level of exposure (26 micrograms per kilogram (µg/kg) of body weight per day).[29]

At somewhat higher feeding levels (500 µg/kg per day), other effects occur. Two studies from Simon Fraser University found that medium-term exposure caused reduced weight gain, liver injury, and reduced levels of four chemicals (other than acetylcholine) that are used to transmit nervous system impulses in the brain.[30,31]

For pets, one form of chronic exposure is from wearing flea collars. Several studies have shown that the activity of acetylcholinesterase was inhibited in dogs and cats wearing flea collars. Inhibition continued for the entire time the collar was worn, up to 315 days.[32]

Only four of the above studies, the tests of flea collars on pests and the one-month study of people, used commercial diazinon-containing products.

Effects on Reproduction

Diazinon exposure of pregnant animals in laboratory tests has demonstrated that this insecticide can cause a variety of reproductive problems, including damage to the developing nervous system, delays in sexual development, stillbirths, death of newborn offspring, and birth defects.

The effects on the developing nervous system are most significant. An EPA-funded study using mice exposed to low levels of diazinon in their food (0.18 mil-

ligrams per kilogram, mg/kg, per day) found that the endurance and coordination of the offspring was impaired. They were unable to remain on as steep of an inclined plane as mice born to unexposed mothers. (See Figure 2.) In addition, their ability to climb developed later than mice born to unexposed mothers.[33]

This study also showed that diazinon exposure of pregnant mice delayed the sexual development of their offspring. Sexual maturity (measured by the age when vaginal opening occurred in females and descent of the testes in males) was delayed about 6 percent in offspring of exposed mothers.[33]

A study of dogs that were fed diazinon (1 mg/kg per day) during pregnancy showed that their exposure increased the number of stillbirths. Less than 6 percent of the offspring of unexposed mothers were stillborn, while 15 percent of offspring of mothers fed diazinon were stillborn. The researchers who conducted this study, from the Food and Drug Administration, noted that diazinon made the mothers "extremely high strung"[34] resulting in stillbirths as the mothers "would not lay still while giving birth."[34]

These researchers also found that feeding diazinon (5 mg/kg per day) to pregnant pigs increased the incidence of skull deformities in the offspring.[34]

Finally, a study of pregnant rats fed diazinon (7 mg/kg per day) found that the number of offspring that died was greater in litters from exposed mothers than for litters from unexposed mothers. The offspring of exposed mothers also grew more slowly while they were nursing. This study was conducted by a diazinon manufacturer.[35]

Diazinon also has caused reproductive problems in male animals. Dogs fed diazinon (20 mg/kg per day) developed atrophied testicles.[36]

There is no publicly available information about the reproductive effects of commercial diazinon-containing products.

Endocrine Disruption

Problems caused by synthetic chemicals that disrupt the normal functioning of our hormone systems have been well publicized in the last decade. Of particular concern are chemicals that interfere with the activity of estrogen, often called the female sex hormone. Estrogen has recently been shown to affect the development and growth of cells in the lining of the colon. The result of abnormal growth of these cells is colon cancer. In tests with cultures of cells from a human colon, low concentrations of diazinon had growth-promoting effects, suggesting diazinon had interfered with the normal activity of estrogen.[37]

There is no publicly available information about the endocrine-disrupting effects of commercial diazinon-containing products.

Carcinogenicity

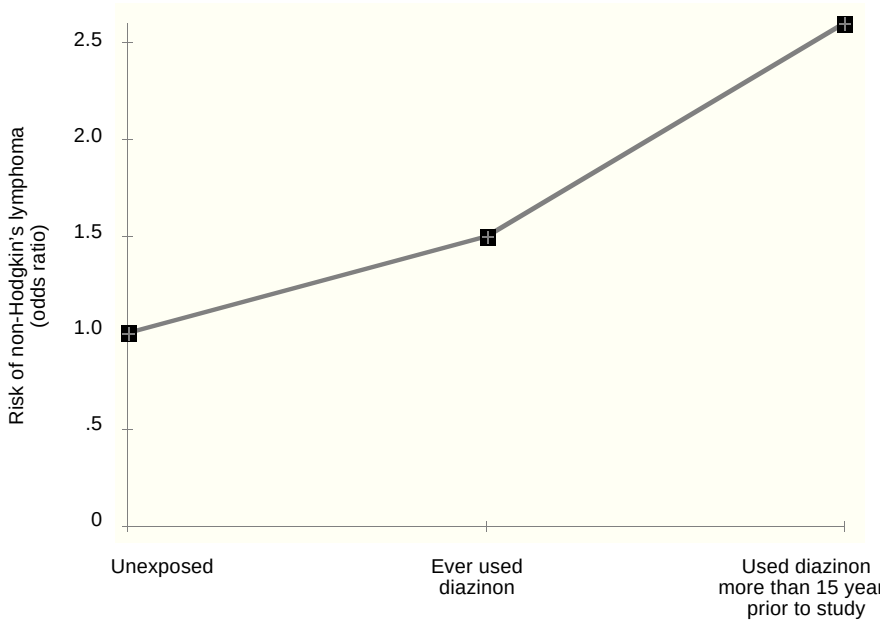
Diazinon's carcinogenicity (its ability to cause cancer) has been studied in laboratory animals with negative results; as a result it has been classified as "not likely" to be a carcinogen by EPA.[38]

Studies of people who have used diazinon, however, show just the opposite: there is an association between diazinon use and the risk of certain types of cancer. In a study of children in Missouri, garden diazinon use by the parents was associated with an increased risk of brain cancer in their children.[39] In a study of Iowa and Minnesota farmers conducted by the National Cancer Institute (NCI), use of diazinon was associated with an increased risk of non-Hodgkin's lymphoma.[40] (See Figure 3.) Similar results were found in an NCI study of Nebraska farmers.[41]

Mutagenicity

Diazinon's mutagenicity, its ability to cause genetic damage, is controversial. The World Health Organization, in its review of the effects of diazinon on hu-

Figure 3
Risk of Cancer in Farmers Using Diazinon



Source: Cantor, K.P. et al. 1992. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res.* 52:2447-2455.

Use of diazinon has been associated with an increased risk of cancer in several studies, including this National Cancer Institute study of farmers in Iowa and Minnesota.

man health and the environment, wrote that diazinon "gave no evidence of a mutagenic potential."[42]

However, a series of other studies show that diazinon in fact can damage genes in human blood cells, in cells from laboratory animals, and in bacteria.

A study conducted at by Italian cancer researchers used concentrations of diazinon equivalent to those found in an Italian food monitoring study. They found that this low level of exposure increased the occurrence in human blood cell cultures of a type of genetic damage called micronuclei.[43] Micronuclei are broken or separated chromosomes produced when a cell divides.[44] Micronuclei were about 50 percent more frequent in exposed cells than in unexposed cells.[43]

Two older studies of human blood cell cultures found that diazinon was mutagenic. Abnormal chromosomes were more frequent in human blood cell cultures exposed to diazinon than they were in unexposed cells,[45] as was a type of genetic damage called sister chromatid exchanges.[46] (Sister chromatid exchanges are exchanges of genetic material between parts of a duplicating chromosome.[47])

A fourth study, conducted by the National Institute of Hygenic Sciences in Japan, found that diazinon exposure increased the frequency of abnormal chromosomes in hamster lung cell cultures.[48]

Finally, a study of *Salmonella* bacteria found that diazinon was mutagenic to one of the four strains tested.[49]

There is no publicly available information about the mutagenicity of commercial diazinon-containing products.

Sensitive Populations

Physicians have long noted that infants appear to be particularly susceptible to diazinon poisoning. For example, in 1970, 3-week old twins were poisoned by a diazinon cockroach treatment in the other half of the duplex in which they lived. Both twins required five days of hospitalization, although none of the adults or older children living in either half of the duplex were ill.[50] In another example, a two-month old infant developed symptoms of cerebral palsy after a diazinon treatment of her home. Symptoms persisted for seven months, until her family moved out of the treated home.[51,52] One reason for infants' increased susceptibility is that newborns have low levels of the enzyme that usually breaks down diazoxon, the active form of diazinon.[53]

Individuals whose body chemistry is less efficient at breaking down diazoxon are also more sensitive to this insecticide. The enzyme that breaks down diazoxon is produced by a gene called PON1. Each person has two PON1 genes. One form of this gene, called the R form, produces an enzyme that is less efficient at breaking down diazoxon, so people with two R genes are most susceptible to diazinon. About 9 percent of people of northern European descent have two R genes, while about 16 percent of people of Hispanic origin have two R genes. This means that a substantial fraction of the population will be particularly sensitive to diazinon and suggests an additional hazard for farmworkers, since in the U.S. many farmworkers are of Hispanic origin.[54]

Another sensitive population may be those who are malnourished. Studies with laboratory animals have found that rats fed a protein deficient diet were almost twice as susceptible to diazinon as rats fed an adequate diet.[55,56]

Synergistic Effects

A wide variety of chemicals interact synergistically with diazinon, meaning that their toxicity together is greater than the sum of their individual toxicities. This synergism has been observed with compounds from strikingly different chemical families, including other pesticides, drugs, and nutrients. (See Table 1) The length of the list in Table 1 is sobering, since real-life exposures are often to multiple chemicals while most toxicological testing and most regulation of hazardous chemicals is based on single exposures.

Toxic Breakdown Products

If a diazinon-containing product is contaminated with a trace of water, some of the diazinon in the product breaks down into two chemicals that are extremely potent acetylcholinesterase inhibitors, monothiotepp and sulfotepp. Monothiotepp has been reported to be

Table 1
Synergistic Interactions with Diazinon

Other Pesticides	
clotrimazole (fungicide)	(1)
captan (fungicide)	(2)
dieldrin (insecticide)	(3)
carbaryl (insecticide)	(4)
atrazine (herbicide)	(5)
Drugs	
cimetidine (ulcer medication)	(6)
succinylcholine (anesthetic)	(7)
cocaine (narcotic)	(8)
Nutrients	
ascorbic acid (Vitamin C)	(9)
tryptophan (amino acid)	(10)

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14,000 times more toxic than diazinon itself. In the early 1990s, when several Australian dogs died after being washed with a diazinon product and some of their handlers became ill, regulatory authorities suspected monothiotepp or sulfotepp contamination and screened diazinon-containing products from pesticide retailers. They tested 169 products and found that about 5 percent were contaminated with the two breakdown products and traces of water.[57] The contamination of these products greatly increases their toxicity. NCAP located no similar studies of U.S. products.

Exposure

Exposure to diazinon is a complicated subject. "Organophosphates are efficiently absorbed by inhalation, ingestion, and skin penetration,"[1] according to EPA, and exposure by "multiple routes can lead to serious additive toxicity."[1] For exposures following residential applications, a single application can lead to exposure via all three routes.[58]

For example, researchers from British Columbia and from North Carolina State University studied broadcast applications to carpets and "crack and crevice" applications, thin streams of pesticide applied just to the kind of site usually inhabited by cockroaches. (Crack and crevice applications are an alternative to broadcast sprays and in general use a smaller amount of insecticide.) After application, diazinon was found both in the air of the treated rooms and on horizontal surfaces in the rooms.[59-61] Diazinon in air leads to inhalation exposure. Diazinon settling on horizontal surfaces leads to both exposure through the skin (if people contact the horizontal surfaces) and ingestion (if, for example, a hand contacts a contaminated surface and then is put in the mouth).

These exposures can be persistent. Air was contaminated for 21 days following crack and crevice application,[59] horizontal surfaces were contaminated for six weeks following application.[60] The British Columbia researchers recommended not entering any unventilated rooms for at least two days after treatment.[61]

EPA surveys of air inside houses, not specifically ones recently treated with diazinon, found that diazinon is surprisingly common in indoor air. In surveys in Florida,[62] Texas,[63] and Arizona,[64] between 53 and 100 percent of homes were contaminated with diazinon.

Outdoor applications also lead to exposure through inhalation (breathing of contaminated air), dermal (skin contact with treated turf), and ingestion (inadvertent hand-to-mouth transfers).[65]

EPA recently (April, 2000) estimated exposure via multiple routes following both lawn care and crack-and-crevice indoor applications. They found that exposures following lawn care applications of liquid diazinon products and following indoor crack and crevice treatments exceeded EPA's "level of concern" for both adults and children.[66]

Contaminated house dust has recently been studied and can also result in multiple routes of exposure. Skin can contact dust particles, the particles can be inhaled, and they can be ingested.[67] Dust is believed to be a particularly important source of exposure to children.[68]

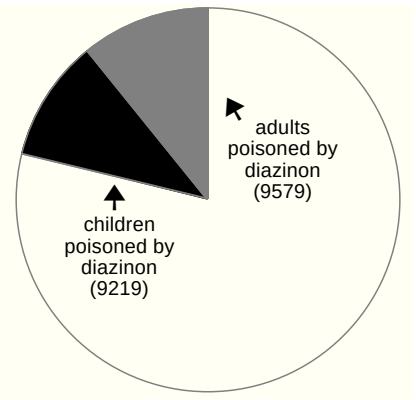
Diazinon-contaminated dust can be common. Surveys in Florida, New Jersey, California, Texas, and Arizona found diazinon in the dust from 53 to 80 percent of the houses tested.[63,64,68-70]

Farmworker children may be particularly at risk of exposure to diazinon via dust. The California study found higher and more frequent diazinon contamination in farmworker homes than in non-farmworker homes in the same town.[70]

Human Poisonings

Diazinon's frequent use and significant toxicity means that poisonings of people are frequent. EPA characterizes diazinon as "one of the leading causes of acute reactions to insecticide use reported as poisoning incidents in the United States."[71] A review of data collected by poison control centers nationwide between 1985 and 1992 showed that diazinon was the second most frequent cause of nonoccupational insecticide poisonings. Almost one-quarter of the insecticide poisonings reported to the centers were caused by diazinon. Nearly half of these poisonings involved children under six years of age.[72]

Figure 4
Diazinon Poisonings



Insecticide poisonings reported to poison control centers, 1985-1992.

Sources:
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U.S. EPA. Office of Prevention, Pesticides and Toxic Substances. 1994. Review of poison control center data call in. Memo from Blondell, J. Health Effects Div. to J. First, Special Review and Reregistration Div. Washington, D.C., Dec. 5. Pp. 11,32.

Diazinon is a leading cause of insecticide-related poisonings, responsible for 23 percent of reported incidents.

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