● HERBICIDE FACTSHEET

IMAZAPIC

Imazapic (Plateau, Cadre) is a relatively new herbicide classified as "reduced risk" by the U.S. Environmental Protection Agency. However, this does not mean that it is harmless to people and the environment.

Imazapic is in the imidazolinone herbicide family, "some of the most potent herbicides on the market." Imidazolinone herbicides have the same mode of action as another potent herbicide family, the sulfonylureas.

Toxicological problems caused by imazapic and imazapic-containing herbicides in laboratory studies include eye irritation, muscle degeneration, liver damage, anemia, increased blood levels of cholesterol, and a birth defect called rudimentary ribs.

An ingredient categorized as "inert" in two imazapic herbicide products is classified as a carcinogen by the International Agency for Research on Cancer.

Susceptible plant species are damaged by minute amounts of imazapic: 1/100 of an ounce per acre. There is little information about the susceptibility of native species to imazapic.

Imazapic is persistent, damaging crops up to 40 months after application, and has chemical properties that make it likely to contaminate water.

BY CAROLINE COX

Imazapic and its ammonium salt (see Figure 1) are herbicides that the U.S. Environmental Protection Agency (EPA) classifies as "reduced risk"[1] pesticides. This does not mean, however, that they do not pose hazards to human and environmental health. This article summarizes those hazards.

Imazapic is in the imidazolinone chemical family. Related herbicides include imazapyr, imazamethabenz-methyl, imazethapyr, imazaquin,[2] and imazamox.[3] Imidazolinones are used as selective herbicides[3]; alfalfa, clover, peanuts, certain trees and shrubs, and many grasses are not very susceptible to imazapic.[4]

According to American Cyanamid Company, the pesticide company that first commercialized imidazolinone herbicides, these chemicals are "some of the most potent herbicides on the market."[5] This is because they are rapidly taken up by plant roots and shoots, they are rapidly transferred to other parts of the plant, and they accumulate in actively growing plant tissues.[5] Imazapic is applied at rates of one to three ounces per acre.[4,6,7]

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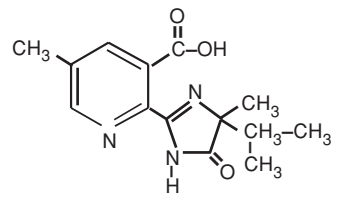
Figure 1
Imazapic



(±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-methyl-3-pyridinecarboxylic acid

Currently imazapic herbicides are marketed by BASF Corporation under the trade names Plateau,[6] Plateau DG,[4] and Cadre.[7]

Use

The imazapic-containing herbicide Cadre is used for weed control in peanuts.[7] Plateau and Plateau DG are used for weed control in grasslands, pastures, rangeland, and other noncrop areas.[4,6] There is no publicly available information about the amount of imazapic used in the U.S.[8]

Mode of Action

Imazapic, like other members of its chemical family, kills plants by inhibiting the activity of an enzyme called by two names, acetolactate synthase or acetohydroxyacid synthase.[9] This enzyme is essential for the production of certain amino acids, leucine, valine, and isoleucine. Proteins, essential components of living cells, are made of amino acids.[10] Lack of the three amino acids causes plant growth to stop. This leads to the death of the actively growing parts of the plant and eventually to the death of the whole plant.[5] Another family of herbicides, the sulfonylurea herbicides, has the same mode of action as imazapic.[9]

Mammals do not have the enzymes necessary to make these three amino acids; we obtain them in our food.[11]

Inert Ingredients

Like most pesticides, imazapic herbicides contain ingredients in addition to imazapic which, according to U.S. pesticide law, are called "inert."[12] In general, they are not identified and not included in most of the testing required in order to register these pes-

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ticides.[13] The only publicly identified inert ingredient in imazapic herbicides as of August, 2003, is crystalline silica in Cadre DG and Plateau DG.[14,15] See "Inert Ingredients," at right.

Toxicology Overview

Imazapic has damaged a variety of tissues and organs in laboratory tests (See Figure 2.) Details are summarized in the next four sections.

Acute Exposure Symptoms

Two imazapic-containing herbicides, Plateau DG and Cadre DG, cause "moderate eye irritation."[4,7]

Effects on Muscles

Imazapic can cause muscle deterioration. In a one-year study of dogs submitted to EPA by imazapic's manufacturer, degeneration of thigh and abdominal muscles, along with tissue death, occurred.[11,10] Although EPA calls these effects "minimal," they occurred at all dose levels tested in this study.[11]

There are no similar publicly available studies about imazapic-containing herbicide products.

Effects on Blood

Imazapic can cause anemia,[11] a deficiency of red blood cells.[10] In the study using dogs mentioned above, dogs exposed to imazapic had lower levels[11] of hemoglobin, the oxygen-carrying molecule in red blood cells,[10] than did unexposed dogs.[11] These effects occurred at the middle and high dose level tested in this study.[11]

Also, imazapic can increase blood levels of cholesterol.[11] In the study of dogs (above), this effect occurred at the middle dose level.[11] Cholesterol can cause arteriosclerosis, a thickening and hardening of artery walls.[10]

There are no similar publicly available studies about imazapic-containing herbicides.

Effects on the Liver

In the study mentioned above, dogs exposed to imazapic had larger livers than unexposed dogs. This effect occurred at the middle and high dose levels.[11] At the high dose level, exposed dogs had higher levels of two enzymes that are indicative of liver disease.[10,11]

"INERT" INGREDIENTS

Crystalline silica is associated with a variety of significant health hazards.

The International Agency for Research on Cancer classifies it as a carcinogen.[1] (See "Carcinogenicity," page 12.)

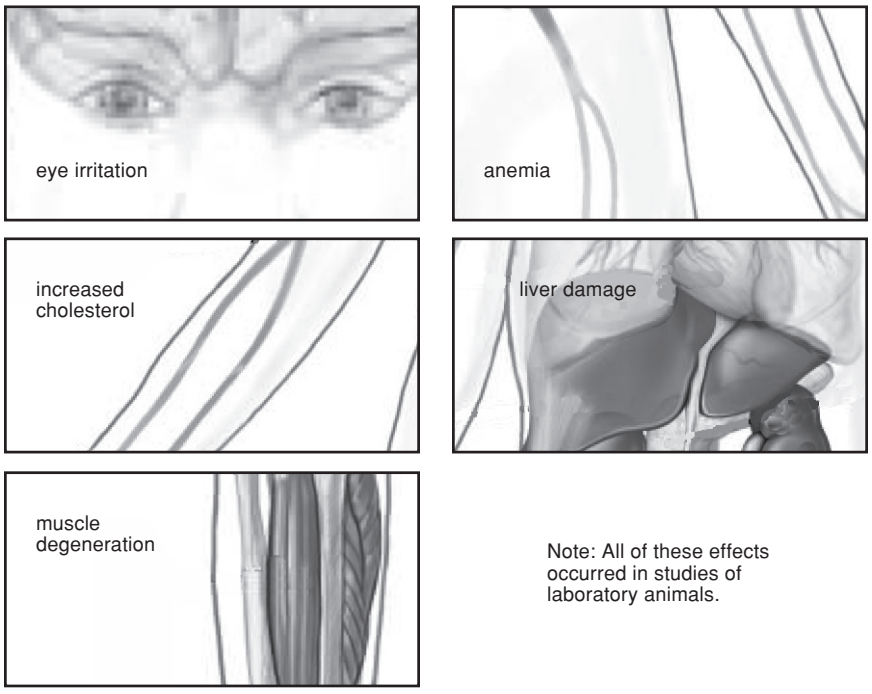
According to the National Institute for Occupational Safety and Health, multiple laboratory studies have shown that it causes cancer and genetic damage.[2] In these studies it caused liver cancer, lymphoma, lung cancer, and genetic damage in both hamster and human lung cells.

Other laboratory studies with crystalline silica showed that it decreased the ability of the immune system to respond to infection and also damaged the lungs.[2]

Occupational exposure to crystalline silica is associated with increased incidences of silicosis, chronic lung disease, tuberculosis, lung cancer, and rheumatoid arthritis.[3]

1. International Agency for Research on Cancer. 1997. Silica: crystalline silica—inhaled in the form of quartz or cristobalite from occupational sources (Group 1); amorphous silica (Group 3). IARC Monographs 68:41. http://www-cie.iarc.fr/htdocs/monographs/vol68/silica.ht.
2. National Institute for Occupational Safety and Health. 2002. The registry of toxic effects of chemical substances: Silica, crystalline—quartz. www.cdc.gov/niosh/rtecs/vv6fd8d0.html.
3. Calvert, G.M. et al. 2003. Occupational silica exposure and risk of various diseases: an analysis using death certificates from 27 states of the United States. *Occup. Environ. Med.* 60:122-129.

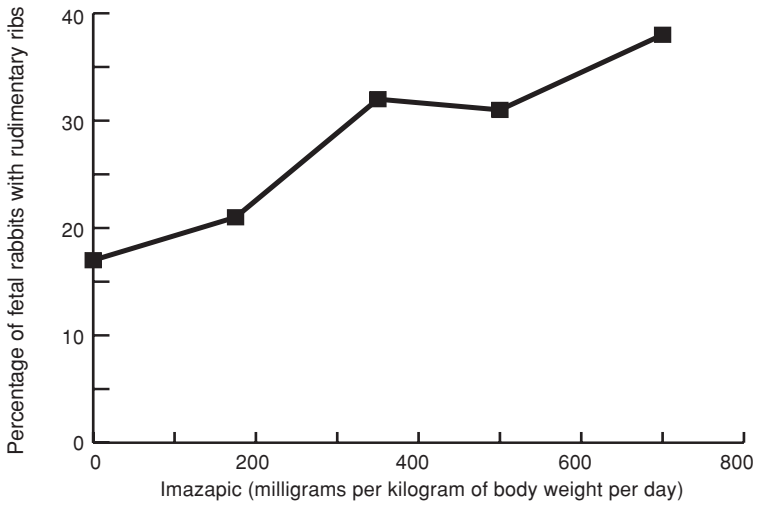
Figure 2
Imazapic Affects a Variety of Organs and Tissues



Sources: U.S. EPA. Health Effects Division. 2001. Imazapic -Report of the Hazard Identification Review Committee. Memo from W. Dykstra to W. Donovan. Washington D.C. and BASF Corp. 2000. Cadre DG and Plateau DG herbicide labels. www.cdms.net.

Tests submitted by imazapic's manufacturer to the U.S. Environmental Protection Agency show that imazapic and imazapic herbicide products can affect eyes, liver, blood, and muscles.

Figure 3
Imazapic Increases the Incidence of a Birth Defect in Rabbits



Source: U.S. EPA. Health Effects Division. 2001. Imazapic - Report of the Hazard Identification Review Committee. Memo from W. Dykstra to W. Donovan. Washington D.C., May 3.

In a laboratory study, imazapic increased the incidence of a skeletal abnormality.

There are no similar publicly available studies about imazapic-containing herbicides.

Effects on Reproduction

Imazapic can cause skeletal abnormalities in developing fetuses. In a study of pregnant rabbits submitted by imazapic's manufacturer to EPA, the incidence of an abnormality called rudimentary ribs in the offspring of rabbits that were exposed to imazapic during pregnancy was higher than in unexposed rabbits. (See Figure 3.) However, EPA concluded that "the increased occurrence of rudimentary ribs was not related to treatment"[11] because other studies from the same laboratory had found that rudimentary ribs were common in unexposed animals.[11]

There are no publicly available studies about effects on reproduction of imazapic-containing herbicides.

Carcinogenicity (Ability to Cause Cancer)

EPA has classified imazapic in Group E, meaning that tests on imazapic have demonstrated "evidence of non-carcinogenicity for humans."[16] EPA classified imazapic in Group E although a test submitted to EPA by an imazapic manufacturer showed that male rats exposed to imazapic developed thyroid tumors and cancers more often than unexposed rats.[11]

Crystalline silica, an inert ingredient in two imazapic herbicide products,[14,15] is classified by the International Agency for Research on Cancer as "carcinogenic to humans," when it is inhaled from occupational sources.[17] This classification is supported by a 2003 study from the National Institute for Occupational Safety and Health showing that occupational silica exposure is associated with an increased risk of death from lung cancer.[18]

There are no publicly available studies of the carcinogenicity of imazapic-containing herbicides.

Susceptibility of Nontarget Plants

Because they are "among the most potent herbicides on the market"[5] it is not surprising that imazapic-containing herbicides can damage plants other than the weeds that are the target of imazapic applications. The tiny amounts of these herbicides that can damage nontarget plants are startling. For example, in tests submitted to EPA by imazapic's manufacturer to support imazapic's registration, weight of the seedlings of one of the nontarget plants tested (cabbage) was reduced 25 percent by the equivalent of 0.007 ounce per acre.[19] (This is less than 1 percent of the lowest recommended application rate.[4,6,7,19]) Seedling weight was reduced 25 percent in other species (onions, tomato, cucumber, and ryegrass) by treatments equivalent to 2 or 3 percent of the lowest recommended application rate.[4,6,7,19] (See Figure 4.)

Imazapic is used in situations (grassland restoration, for example[8]) where nontarget plants are not crop species. However, the tests required for registration of imazapic use only crop plants[20,21] and there is not comprehensive information about exposure levels that damage native species.

Another indication of imazapic's significant potential to damage desirable plants is the label instructions for using Plateau and Plateau DG: "When making applications around desirable trees or ornamental plants, small areas should be tested to determine the tolerance of a particular species ...."[4,6]

Imazapic-containing herbicides are recommended for restoration of native prairie grasses and wildflowers.[4,6] However, even the product labels that make this recommendation warn that they should be used only if loss and injury can be tolerated.[4] Researchers at the University of Minnesota studying the effects of imazapic treatment on the establishment of five grass species and a prairie wildflower mix found that "injury [of the grass species] with imazapic was pronounced"[22] in one of the two years studied,[23] and that use of no herbicides "resulted in higher species diversity and increased stands of wildflowers" compared to most of the imazapic treatments tested.[22]

Aquatic Plants: Imazapic at low concentrations is toxic to aquatic plants. Duckweed, used by EPA as a representative aquatic plant species,[24] is damaged by concentrations of 4 parts per billion (ppb).[19]

Synergy: Imazapic-containing herbicides have a synergistic interaction with some insecticides. (This means that the total effect is greater than the sum of the individual effects.[10]) According to BASF Corporation, use of

these herbicides with organophosphates, a commonly used family of insecticides, can cause "severe injury"[6] to seedlings of desirable species. The Plateau DG label forbids use of organophosphate insecticides in the same year as Plateau DG.[4]

Effects on Plant Reproduction

Herbicides with the same mode of action as imazapic have an extraordinary ability to disrupt plant reproduction. EPA researchers have conducted a series of studies with chlorsulfuron (an herbicide that also inhibits the enzyme acetolactate synthase) that document how minute exposures reduce fruit or seed production.

In the first study, looking at cherry trees, spring applications of chlorsulfuron equivalent to 1/1000 of typical agricultural application rates reduced the amount of fruit produced. Fall applications at similar low levels caused fruit production to decline the following year. Neither fall nor spring applications caused visual damage to leaves, or branches.[25]

Subsequent studies looked at impacts on other plants: garden peas, canola, soybeans, sunflower, and smartweed. Results were similar.[26,27]

The first of these studies begins by pointing out that effects on plant reproduction can have a "devastating impact."[25] The researchers' conclusions are sobering: drift of these herbicides "may severely reduce both crop yields and fruit development on native plants, an important component of the habitat and foodweb for wildlife."[25]

There are no requirements for testing for effects on plant reproduction during the registration process[28] and imazapic has not been tested for these effects. However, they seem possible because imazapic has the same mode of action as chlorsulfuron, the herbicide used in the EPA studies above.

In addition there are two studies showing that imazapic has effects on seed/fruit production. One study, done by researchers at Florida State University, showed that imazapic caused citrus trees to drop fruit.[29] The second, done by researchers at Mississippi State University, showed that imazapic reduced seed production, germination, and the number of normal seedlings produced by sicklepod.[30]

Effects on Birds

Imazapic can reduce the ability of birds to successfully reproduce. A study of mallard ducks submitted to EPA by imazapic's manufacturer found that the survival of ducklings from mothers that were fed imazapic was less than that from unexposed mothers. The percentage of eggs that hatched was also reduced. These effects occurred at all but the lowest dose level tested in this study. In a similar study of quail, the number of live embryos was reduced at the highest dose level tested.[31,32]

Effects on Aquatic Animals

Imazapic can decrease the reproduction of aquatic animals. American Cyanamid Company, an imazapic manufacturer, reported that a concentration of 180 ppb reduced water flea reproduction.[33]

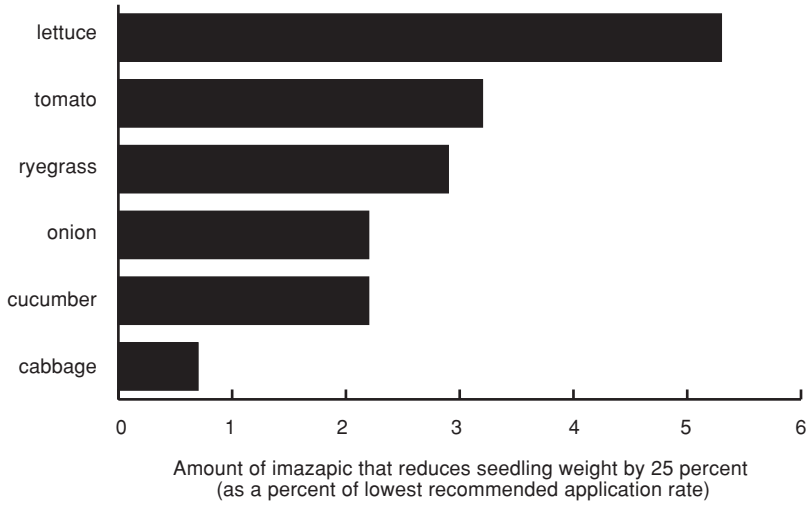
Water Contamination

Contamination of streams, wells, and lakes by imidazolinone herbicides, including imazapic, has not been well studied. According to the U.S. Geological Survey, "little is known about their occurrence, fate, or transport in surface water or ground water in the United States."[34] However, it is likely that imazapic can easily contaminate water for the following reasons:

• **Imazapic's chemical properties make it likely to contaminate water.** According to the Natural Resources Conservation Service, the potential of imazapic to move in surface runoff is "intermediate" and its potential to be leached by water below the root zone of plants is "high."[35,36] BASF Corporation, imazapic's manufacturer, reports that it "demonstrates the properties and characteristics associated with chemicals detected in groundwater"[4,6,7] and warns that Plateau "has a high potential for runoff for several months or more after application."[6]

• **Imazapic's chemical relatives contaminate water.** The U.S. Geological Survey recently found the imidazolinone herbicide imazethapyr in almost 70 percent of the streams, over 60 percent of the reservoirs, and over 15 percent of the wells the agency

Figure 4
Tiny Amounts of Imazapic Damage Seedlings



Source: U.S. EPA. Office of Prevention, Pesticides and Toxic Substances. 1995. The Ecological Effects Branch's (EEB) environmental risk assessment for the use of the imidazolinone type herbicide CADRE on peanuts. Memo from A. F. Maciorowski, Ecological Effects Branch, to R. Taylor, Registration Div. Washington, D.C., Aug. 25.

Seedlings of many plant species are highly susceptible to imazapic.

sampled in the Midwestern U.S. The agency also found that the other two imidazolinones that were part of its analytical protocol contaminated streams, wells, and reservoirs.[34]

Soil Persistence

According to the National Resources Conservation Service, imazapic has an average half-life (the time required for half of the amount of imazapic applied to break down or move away from the application site) of 232 days.[35,36] Half-lives vary 13-fold (31-410 days) according to tests submitted to EPA by imazapic's manufacturer.[37]

Using criteria established by Oregon State University, imazapic is a persistent herbicide, one that has an average half-life of over 100 days.[38]

Damage to crops planted after imazapic treatment also demonstrates its long persistence in soil. Researchers from Texas A&M University and American Cyanamid Company showed that about 65 percent of rice plants were injured when planted one year after an imazapic treatment of 1 ounce/acre. The treatment also reduced rice yield by about 25 percent.[39] The label for the imazapic-containing herbicides Cadre and Plateau DG requires an 18-month interval between imazapic treatment and planting of barley, oats, cotton, onions, sorghum, and corn. For canola, beets, and potatoes the label requires a 40-month interval.[4,7]

Resistance

Herbicide resistance, the inherited ability of a plant to survive and reproduce following exposure to an amount of an herbicide that would typically be lethal,[41] is common for herbicides with imazapic's mode of action.[40] There are more plant species (80) resistant to this kind of herbicide than any other.[41]

Cross-resistance to herbicides that share this mode of action is also common. In other words, plants that are resistant to one herbicide with this mode of action are often resistant to many similar herbicides.[42,43]

Resistance to imazapic can develop quickly. Palmer amaranth in Georgia developed resistance to imazapic in 2000,[41] only four years after this herbicide was first marketed.[44]

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