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GLYPHOSATE

In addition to the review that is presented below, a comprehensive review available from USDA Forest Service provides information that incorporates more recent studies and data. The US Forest Service risk assessment report is available at: http://www.fs.fed.us/foresthealth/pesticide/risk.shtml

Review conducted by MDAR and MassDEP for use in Sensitive Areas of Rights-of-Way in Massachusetts

Common Trade Name(s): Roundup, Glyphosate VMF Round Up Pro, Rodeo, Accord, Accord Concentrate,

Chemical Name: N—(phosphonomethyl)glycine—isopropylamine salt
CAS No.: 1071-83-6

GENERAL INFORMATION
Glyphosate, n-phosphonomethyl glycine, is a systemic, broad spectrum herbicide effective against most plant species, including deep rooted perennial species, annual and biennial species of grasses, sedges, and broadleafed weeds. The major pathway for uptake in plants is through the foliage, however, some root uptake may occur. The presence of surfactants and humidity increases the rate of absorption of glyphosate by plants (15).

Foliarly applied glyphosate is readily absorbed and translocated from treated areas to untreated shoot regions. The mechanism of herbicidal action for glyphosate is believed to be inhibition of amino acid biosynthesis resulting in a reduction of protein synthesis and inhibition of growth (10, 15, 101).

Glyphosate is generally formulated as the isopropylamine salt in aqueous solution (122). Of the three products containing glyphosate considered here, Roundup is sold with a surfactant and Rodeo and Accord are mixed with surfactants prior to use (15). Glyphosate has been reviewed by US Forest Service (15), FAO (122), and EPA 00W (51).

ENVIRONMENTAL FATE

Mobility
Glyphosate is relatively immobile in most soil environments as a result of its strong adsorption to soil particles. Adsorption to soil particles and organic matter begins almost immediately after application. Binding occurs with particular rapidity to clays and organic matter (l5). Clays and organic matter saturated with iron and aluminum (such as in the Northeast) tend to absorb more glyphosate than those saturated with sodium or calcium. The soil phosphate level is the main determinant of the amount of glyphosate adsorbed to soil particles. Soils which are low in phosphates will adsorb higher levels of glyphosate (14, 15).

Glyphosate is classified as immobile by the Helling and Turner classification system. In soil column leaching studies using aged (1 month) Glyphosate, leaching of glyphosate was said to be insignificant after 0.5 inches of water per day for 45 days (14).

Persistence

It has been reported that glyphosate dissipates relatively rapidly when applied to most soils (14). However, studies indicate that the soil half-life is variable and dependent upon soil factors. The half-life of glyphosate in greenhouse studies when applied to silty clay loam, silt loam, and sandy loam at rates of 4 and 8 ppm was 3, 27 and 130 days respectively, independent of application rate (14). An average half-life of 2 months has been reported in field studies for 11 soils (15).

Glyphosate is mainly degraded biologically by soil micro-organisms and has a minimal effect on soil microflora (15). In the soil environment, glyphosate is resistant to chemical degradation such as hydrolysis and is stable to sunlight (15). The primary metabolite of glyphosate is aminomethyl phosphonic acid (AMPA) which has a slower degradation rate than glyphosate (15). The persistence of AMPA is reported to be longer than glyphosate, possibly due to tighter binding to soil (14). No data are available on the toxicity of this compound.

Glyphosate degradation by microorganisms has been widely tested in a variety of field and laboratory studies. Soil characteristics used in these studies have included organic contents, soil types and pHs similar to those that occur in Massachusetts (117).

Glyphosate degradation rates vary considerably across a wide variety of soil types. The rate of degradation is correlated with microbial activity of the soils and does not appear to be largely dependent on soil pH or organic content (117). While degradation rates are likely temperature dependent, most reviews of studies do not report or discuss the dependence of degradation rate on temperature. Mueller et al. (1981 cited in 117) noted that glyphosate degraded in Finnish agricultural soils (loam and fine silt soils) over the winter months; a fact which indicates that degradation would likely take place in similar soils in the cool Massachusetts climate. Glyphosate halflives for laboratory experiments on sandy loam and loamy sand, which are common in Massachusetts, range up to 175 days (117). The generalizations noted for the body of available results are sufficiently robust to incorporate conditions and results applicable to glyphosate use in Massachusetts.

TOXICITY REVIEW

Acute (Mammalian)

Glyphosate has reported oral LD5Os of 4,320 and 5,600 mg/kg in male and female rats (15,4). The oral LD5Os of the two major glyphosate products Rodeo and Roundup are 5,000 and 5,400 mg/kg in the rat (15).

A dermal LD5O of 7,940 mg/kg has been determined in rabbits (15,4). There are reports of mild dermal irritation in rabbits (6), moderate eye irritation in rabbits (7), and possible phototoxicity in humans (9). The product involved in the phototoxicity study was Tumbleweed marketed by Murphys Limited UK (9). Maibach (1986) investigated the irritant and the photo irritant responses in individuals exposed to Roundup (41% glyphosate, water, and surfactant); Pinesol liquid, Johnson Baby Shampoo, and Ivory Liquid dishwashing detergent. The conclusion drawn was that glyphosate has less irritant potential than the Pinesol or the Ivory dishwashing liquid (120).

Metabolism

Elimination of glyphosate is rapid and very little of the material is metabolized (6,106).

Subchronic/Chronic Studies (Mammalian)

In subchronic tests, glyphosate was administered in the diet to dogs and rats at 200, 600, and 2,000 ppm for 90 days. A variety of toxicological endpoints were evaluated with no significant abnormalities reported (15,10).

In other subchronic tests, rats received 0, 1,000, 5,000, or 20,000 ppm (57, 286, 1143 mg/kg) in the diet for 3 months. The no observable adverse effect level (NOAEL) was 20,000 ppm (1,143 mg/kg) (115). In the one year oral dog study, dogs received 20, 100, and 500 mg/kg/day. The no observable effect level (NOEL) was 500 mg/kg (116).

Oncogenicity Studies
Several chronic carcinogenicity studies have been reported for glyphosate including an 18 month, mouse study; and a two year rat study. In the rat study, the animals received 0, 30, 100 or 300 ppm in their diet for 2 years. EPA has determined that the doses in the rat study do not reach the maximum tolerated dose (112) and replacement studies are underway with a high dose of 20,000 ppm (123). The mice received 1000, 5000 or 30,000 ppm for 18 months in their diets. These studies were non-positive (112,109). There was a non-statistically significant increase in a rare renal tumor (renal tubular adenoma (benign) in male mice (109). The rat chronic study needs to be redone with a high dose to fill a partial data gap (112). The EPA weight of evidence classification would be D: not classified (51).

Mutagenicity Testing
Glyphosate has been tested in many short term mutagenicity tests. These include 7 bacterial (including Salmonella typhimurim and B. subtilis) and 1 yeast strain Sacchomyces cerevisiae as well as a mouse dominant lethal test and sister chromatid exchange. The microbial tests were negative up to 2,000 mg/plate (15), as were the mouse dominant lethal and the Chinese hamster ovary cell tests. EPA considers the mutagenicity requirements for glyphosate to be complete in the Guidance for the Registration of Pesticide Products containing glyphosate (112).

The developmental studies that have been done using glyphosate include teratogenicity studies in the rat and rabbit, three generation reproduction studies in the rat, and a reproduction study in the deer mouse. (15)

Rats were exposed to levels of up to 3,500 mg/kg/d in one rat teratology study. There were no teratogenic effects at 3,500 mg/kg/d and the fetotoxicity NOEL was 1,000 mg/kg/d. In the rabbit study a fetotoxicity NOEL was determined at 175 mg/kg/d and no teratogenic effects were observed at 10 or 30 mg/kg/d in one study and 350 mg/kg/d in the other study (15). No effects were observed in the deer mouse collected from conifer forest sprayed at 2 lbs active ingredient per acre (15).

Tolerances & Guidelines
EPA has established tolerances for glyphosate residues in at least 75 agricultural products ranging from 0.1 ppm (most vegetables) to 200 ppm for animal feed commodities such as alfalfa (8).

U.S. EPA Office of Drinking Water has released draft Health Advisories for Glyphosate of 17.50 mg/L (ten day) and 0.70 mg/L (Lifetime)(51).

Avian
Two types of avian toxicity studies have been done with glyphosate: ingestion in adults and exposure of the eggs. The species used in the ingestion studies were the mallard duck, bobwhite quail, and the adult hen (chickens). The 8 day feeding LC5Os in the mallard and bobwhite are both greater than 4,640 ppm. In the hen study, 1,250 mg/kg was administered twice daily for 3 days resulting in a total dose of 15,000 mg/kg. No behavioral or microscopic changes were observed (15).

Invertebrates
A variety of invertebrates (mostly arthropods) and microorganisms from freshwater, marine, and terrestrial ecosystems have been studied for acute toxic effects of technical glyphosate as well as formulated Roundup. The increased toxicity of Roundup compared with technical glyphosate in some studies indicates that it is the surfactant (MONO 818) in Roundup that is the primary toxic agent (117). Acute toxicity information may be summarized as follows:

Glyphosate (technical): Acute toxicity ranges from a 48 hr EC5O for midge larvae of 55 mg/L to a 96 hr TL5O for the fiddler crab of 934 mg/L (15).

Roundup: Acute toxicity ranges from a 48 hr EC5O for Daphnia of 3 mg/L to a 95 hr LC5O for crayfish of 1000 mg/L (15).

Among the insects tested, the LD50 for honeybees was 100 mg/bee 48 hours after either ingestion, or topical application of technical glyphosate and Roundup. This level of experimental exposure is considerably in excess of exposure levels that would occur during normal field applications (15).

Aquatic Species (Fish) Technical glyphosate and the formulation Roundup have been tested on various fish species. Roundup is more toxic than glyphosate, and it is the surfactant that is considered to be the primary toxic agent in Roundup:

Glyphosate (technical):
Acute 96 hr LC5Os range from 24 mg/L for bluegill (Dynamic test) to 168 mg/L for the harlequin fish (15).

Roundup: Acute lethal toxicity values range from a 96 hr LC5O for the fathead minnow of 2.3 mg/L to a 96 hr TL5O for rainbow trout of 48 mg/L (15).

Tests with Roundup show that the egg stage is the least sensitive fish life stage. The toxicity increases as the fish enter the sac fry and early swim up stages.

Higher test temperatures increased the toxicity of Roundup to fish, as did higher pH (up to pH 7.5). Above pH 7.5, no change in toxicity is observed.

Glyphosate alone is considered to be only slightly acutely toxic to fish species (LC5Os greater than 10 mg/L), whereas Roundup is considered to be toxic to some species of fish, having LC5Os generally lower than 10 mg/L (15,118).

SUMMARY
Glyphosate when used as recommended by the manufacturer, is unlikely to enter watercourses through run-off or leaching following terrestrial application (117). Toxic levels are therefore unlikely to occur in water bodies with normal application rates and practices (118).

Glyphosate has oral LD5Os of 4,320 and 5,600 in male and female rats respectively. The elimination is rapid and very little of it is metabolized. The NOAEL in rats was 20,000 ppm and 500 mg/kg/d in dogs. No teratogenic effect was observed at doses up to 3,500 mg/kg/d and the fetotoxicity NOELS were 1,000 mg/kg/d in the rat and 175 mg/kg/d in the rabbit.

The evidence of oncogenicity in animals is judged as insufficient at this time to permit classification of the carcinogenic potential of glyphosate. The compound is not mutagenic.

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IMAZAPYR

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Review conducted by MDAR and MassDEP for use in Sensitive Areas of Rights-of-Way in Massachusetts

Common Trade Name(s): Arsenal

Chemical Name: Imazapyr!
2-(4-isopropyl-4-methyl--5-oxy-2-imidazolin-2-yl)
nicotinic acid with isopropyl amine (2)

CAS No.: 81510-83-0

GENERAL INFORMATION

Imazapyr is effective against and provides residual control of a wide variety of annual and perennial weeds, deciduous trees, vines and brambles in non—cropland situations. It also provides residual control and may be applied either pre or postemergence. Postemergence is the preferred method especially for the control of perennial species. Imazapyr is readily absorbed by the foliage and from soil by the root systems. Imazapyr kills plants by inhibiting the production of an enzyme, required in the biosynthesis of certain amino acids, which is unique to plants (10, 100).

ENVIRONMENTAL FATE

Mobility

There are few studies which have investigated the mobility of Imazapyr in soil, but available reports indicate that Imazapyr does not leach and is strongly absorbed to soil (100). Imazapyr has a high water solubility (1 — 1.5%) which could generally indicate a high leaching potential, but as with other organic acids Imazapyr is much less mobile than would normally be expected (100). No soil partition coefficients have been reported, but they may be expected to be quite high (100).

One field study investigated Imazapyr mobility in a sandy loam soil (0.9% organic matter, 8.0% clay; 38.8% silt). Imazapyr did not leach below the 18—21 inch layer after 634 days and 49.6 inches of rain. The levels found below the 12 inch layer were just above the 5 ppb detection limit. In addition, this study investigated the off—target mobility of Imazapyr and found no residues further than 3 inches from the sprayed area after 1 year (102).

Although low levels of Imazapyr did move to the 18 to 21 inch layer this was only after nearly 2 years and fifty inches of rain. This indicates that imazapyr is relatively non-mobile and does not leach through the soil profile. Imazapyr remains near the soil surface and heavy precipitation may cause some off target movement from surface erosion of treated soils.

Persistence

The main route of Imazapyr degradation is photolysis. In a study of photodegradation in water, the half—life of Imazapyr was calculated as 3.7, 5.3 and 2.5 days in distilled water, pH 5 and pH 9 buffers respectively (101). A soil photolysis study for Arsenal on sandy loam calculated a half—life of 149 days (101).

Studies have investigated the persistence of Imazapyr in soil under aerobic and anaerobic conditions. The half-life of Imazapyr in soil has been reported as varying from 3 months to 2 years (100). A laboratory study found the half-life to be 17 months (101). Detectable residues were found in a field study in all soil layers to 21 inches at 634 days (102). Vegetation was sprayed with radio-labelled Imazapyr at a rate of 1 lb. a.i./acre. The soil was a sandy loam (0.9% organic matter) which received 49.6 inches of rain during 634 days. The highest level of radioactivity (0.234 ppm Imazapyr) was found in the top 3 inches of soil at 231 days after application and there were detectable levels in the 9-12 inch layer. The concentrations in the top layer increased steadily from day 4 to 231 when they reached their maximum (0.234 ppm) and then declined. At day 634 the level in the top layer (0-3 inch) was 0.104 ppm (102). These data indicate that Imazapyr is persistent in soil and, most importantly, that Imazapyr is translocated within plants from the plant shoots back to the roots and released back into soil. Very little of the Imazapyr actually reached the soil during application. The soil residues may be due to the decay of plant material containing Imazapyr in the soil (102).

TOXICITY REVIEW

Acute (Mammalian)

The acute oral LD5O in both male and female rats was greater than 5000 mg/kg using technical Imazapyr. The acute dermal LD5O in male and female rabbits was greater than 2000 mg/kg. The compound was irritating to the rabbit eye but recovery was noted 7 days after application of 100 mg of the test substance. It was classified as mildly irritating to the rabbit skin following application of 0.5 grams of the material on abraded or intact skin (103).

Arsenal product formulation was tested in a similar battery of tests. The rat oral LD5O value was greater than 5000 mg/kg and the rabbit dermal LD5O was greater than 2148 mg/kg. The irritation was observed following installation of 0.5 ml of the test substance in the skin study and 0.1 ml in the eye study (104).

Technical Imazapyr was administered to rats as an aerosol for four hours at a concentration of 5.1 mg/L. There were ten rats per sex and the animals were observed for 14 days after treatment before they were sacrificed. Slight nasal discharge was seen in all rats on day one but disappeared on day two (105).

The inhalation LC5O is greater than 5.0 mg/L for both the formulation and the technical product (105,106). Technical Imazapyr was applied dermally at the following dosages: 0, 100, 200 and 400 mg/kg/day (109). Arsenal was used at 0, 25, 50 and 100% of the formulated solution in sterile saline. Each dose group consisted of 10 male and 10 female rabbits and the test substance was applied to either intact or abraded skin and occluded for 6 hours each day.

The result of the dermal studies with Imazapyr as well as Arsenal were non remarkable with regard to body weights, food consumption, hematology, serum chemistry, clinical observations, necropsy observations and histopathology. It was noted that Arsenal, undiluted, was locally irritating (109).

Subchronic and Chronic Studies (Mammalian)

In the subchronic tests a NOEL for systemic toxicity with dermal administration in rabbits was 400 mg/kg/d (2,109). After dietary administration for 13 weeks in the rat, there was no effect at 10,000 ppm (571. mg/kg/d) which was the highest dose tested (141).

A bioassay is currently underway to evaluate the potential oncogenicity of technical Imazapyr. Groups of 65 rats per sex per dose group have received 0, 1000, 5000 or 10,000 ppm in the diet. Hematology, clinical chemistry and urinalysis tests were conducted at 3, 6 and 12 months and will also be done at 18 months and at study termination. At the 12 month sacrifice the only effect noted was a slight increase in mean food consumption in all treated female groups. Most of the increases were statistically significant, but they did not always exhibit a dose response. The oncogenicity test is due to be submitted to the EPA in the spring of 1989 (115).

Oncogenicity Studies

Chronic bioassays as discussed in the subchronic/chronic section are underway.

Mutagenicity Testing

Five different bacterial strains of Salmonella typhimurium (TA1535, TA98, TAlOO, TA1537, and TA1538) and one of Escherichia coli (WP-2 uvrA-) were used to evaluate the mutagenicity of Imazapyr. It is unclear whether the compound used was technical or formulated Imazapyr. Dose levels up to 5000 micrograms/plate were used and each strain was evaluated both in the presence or absence of PCB—induced rat liver 5—9 microsomes. Negative results were noted in all assays. The six tester strains were designed to detect either base-pair substitutions or frameshift mutations (113).

Developmental Studies (Mammalian)

Two teratology studies have been done and both of these studies evaluated technical Imazapyr. One study used rats as the test species and the other utilized rabbits (111,112).

Pregnant rats received dosages of 0, 100, 300 or 1000 mg/kg/d of Imazapyr during days 6—15 of gestation. There were 22 rats in the control group and 24, 23 and 22 in the low, mid and high dose groups. All doses were administered orally by gavage. Salivation was noted only during the dosing period in 6 of the 22 females in the highest dose group (1000 mg/kg). No other adverse observations were noted in the treated dams (111). Fetal body weight and crown-rump length data for the treated groups were comparable to controls. Fetal development (external, skeletal and visceral) "revealed no aberrant structural changes which appeared to be the result of the exposure to Imazapyr" (111). The NOEL for maternal toxicity was 300 mg/kg and the NOEL for teratogenicity and fetoxicity was 1000 mg/kg (116).

Four groups of 18 pregnant rabbits were exposed on days 6-18 of gestation to doses of 0, 25, 100, 400 mg/kg/d Imazapyr. There was no statistically significant difference between control and treated groups at any dose (112).

Avian

Acute oral LD5Os of Imazapyr in bobwhite quail and mallard duck were 2150 mg/kg. The 8 day dietary LC5O in the bobwhite quail and mallard duck were greater than 5000 ppm (101).

Invertebrates

The dermal honey bee LD5O for Imazapyr is greater than 100 mg/bee (101). The LD5O (48 hr) was greater than 100 mg/L for the water flea (100).

Aquatic

The LC50s of Imazapyr in the rainbow trout, bluegill sunfish and channel catfish were greater than 100 mg/L (101).

SUMMARY

Imazapyr is a relatively immobile herbicide in the soil profile even when used in sandy and low organic content soils. It is also persistent in soils. The low mobility and persistence may result in off-target movement of Imazapyr from surface erosion of treated soils.

The atypical soil—plant flux characteristics of Imazapyr and delayed maximum soil concentrations indicate that repeated annual applications may result in build—up of Imazapyr in soil. Consequently, an interval is required to allow for the degradation of soil residues before a repeated application is made.

The oral LD5O of Imazapyr in rats is greater than 5000 mg/kg and the derrnal LD5O is greater than 2000 mg/kg in rabbits. The oncogenicity bioassay is currently underway and the only effect reported in the interim study was an increase in food consumption in the treated females. No mutagenic effects were observed.

The acute oral LD5Os of Imazapyr and the Arsenal formulation are greater than 5000 mg/kg. In the subchronic 13 week rat study there was no effect observed at the highest dose tested 10,000 ppm. The oncogenicity study is currently underway.

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METSULFURON METHYL

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Review conducted by MDAR and MassDEP for use in Sensitive Areas of Rights-of-Way in Massachusetts

Common Trade Names: Escort, Escort XP (2)

Chemical Name: Methyl 2 E[C[(4-Methoxy—6-methyl-l,3,5-Triazifl—
2-yl) aminolcarbonyl] amino] sulfonyl.]benzoate] (9)

CAS NO.: 74223-64-6

GENERAL INFORMATION

Metsulfuron methyl is a sulfonyl urea herbicide initially registered by E.I. DuPont in 1986. It is a foliar herbicide registered for use on wheat and barley and non-cropland sites such as Right of Way (9).

ENVIRONMENTAL FATE

Mobility

Metsulfuron methyl is a relatively new herbicide. The studies reviewed here have been provided by the registrant, EI DuPont.

The soil water partition coefficients (Kd) of Metsulfuron Methyl have been determined in four different soils: Cecil sand, Flanagan silt loam, Fallsington silt loam, and keyport silt loam. The Kd values range from 0.36 for Cecil sand to 1.40 for Flanagan silt loam, and Kom values ranged from 29 for Fallsington silt loam to 120 for Cecil sand (100). The values for Kd and Kom indicate that metsulfuron methyl is not adsorbed well to soil and that the organic content of the soil is not the only adsorption component. The silt and clay contents appear to influence adsorption, but there are probably other factors also involved.

The previous study also determined the Rf values for soil. Thin layer chromatography was performed on four soils for metsulfuron methyl. The Rf values ranged from 0.64 to 1.00; only one value was less than 0.90 (100). This result confirms the validity of the Kd values, indicating that metsulfuron methyl is mobiie and that the organic matter content of the Soil is a significant component of adsorption.

Metsulfuron methyl was applied to tops of 12 inch columns [containing four different soils], and eluted with 20 inches of water in 20 hours. Following the percolation of the total volume of water, 106% of the metsulfuron

methyl was eluted from the Fallsington sandy loam, 96% from the Flanagan silt loam, 81% for Keyport silt loam and 93% for Myakka sand (100). The breakthrough volumes for the Fallsington, Flangan, Keyport and Myakka soils were 6.5, 4.5, 6.9 and 5.8 inches of water respectively (101).

Metsulfuron methyl is relatively mobile in most soils, but will be retained longer in soils with higher percentages of organic matter.

Persistence

There are two studies which have reviewed the persistence of metsulfuron methyl in the soil. One study was conducted in the southern United States and the second was in the northern United States and Canada. The results of the studies indicate a somewhat contradictory picture of the persistence of metsulfuron methyl.

The soil half-lives in Delaware, North Carolina, Mississippi and Florida were 1 week, 4 weeks, 3 weeks and 1 week respectively following an application in mid to late summer (102). The results are varied and indicate that either climatic or soil factors determine the persistence. The climate is sufficiently similar to be able to discount that as a factor. However, both of the locations where the shortest half-lives were observed had the highest organic matter content in the soils. Furthermore, the half—lives correspond with the organic matter content.

The half—lives following spring applications were 4 and 56 weeks for two sites in Colorado, 6 weeks in North Dakota and 28 weeks in Idaho (103). In contrast to the southern United States study there does not appear to be any correlation with climatic or soil characteristics. There appears to be a slightly shorter half—life in acidic soils in the same location.

Metsulfuron methyl was also applied in the fall and the half-lives determined in two sites in Colorado, North Dakota and Idaho. These half—lives were 8 weeks, 12 weeks, 42 weeks and 28 weeks respectively. As was expected there were longer half—lives following fall applications in North Dakota (6 weeks vs. 42 weeks) however, in Idaho there was no change at all, which is unexpected.

In Canada following spring applications the reported half-lives were 10 weeks, 4 weeks, 4 weeks and 6 weeks for Alberta, 2 locations in Saskatchewan and Manitoba (103). One would expect longer half lives in Northern locations due to the effects of temperature on degradation rates. The results from Canada are generally shorter than those in the U.S. locations, which is unexpected.

Therefore, the half-life of Metsulfuron methyl in the soil is variable and dependent on the location. It is shorter when applied in the spring but appears independent of other environmental factors in most locations.

TOXICITY REVIEW

Acute (Mammalian)

The toxicology database for Metsulfuron methyl has been reviewed and accepted by the EPA (9). DuPont supplied excerpts from their monograph on Ally herbicide (112). Summaries of studies were supplied by DuPont for subchronic, chronic and reproductive studies.

Technical metsulfuron methyl has been tested in two acute oral LD50 studies in Crl:CD Rats. In the first study the LD5O was greater than 5,000 mg/kg and in the second it was greater than 25,000 mg/kg (the maximum feasible dose) (112). Clinical signs included salivation, chromodacryorrhea, stained face, stained perineal area and weight loss (112).

In a 10—dose subacute study using male rats, a single repeated dose of 3,400 mg/kg/day for 10 days over a 2 week period was administered. This was followed by a two week recovery period. No deaths occurred and slight weight loss was the only clinical sign observed. In addition, no gross or microscopic changes were observed (112). The dermal LD50 is greater than 2,000 mg/kg in male and female rabbits (112). Technical metsulfuron methyl caused mild erythema as a 40% solution in guinea pigs. There was no reaction observed at the 4% concentration. No response occurred when treated animals were challenged (112).

In rabbits, moderate areas of slight corneal clouding and severe to moderate conjunctivitis were observed in both washed and unwashed eyes following treatment with technical metsulfuron methyl. The unwashed eyes were

normal in 3 days and the washed eyes in 14 days (112).

Metabolism
Elimination of metsulfuron methyl in the rat is rapid, with 91% of a radioactive dose excreted over 96 hours (9). The routes of elimination were not specified within the report.

Subchronic/Chronic (Mammalian)
Ninety day feeding studies have been done with metsulfuron methyl in rats and mice. The rat study was done in conjunction with a one generation reproduction study (see Developmental Study Section). In this study rats received 0, 100, 1000, or 7500 ppm (0, 5.7, 57, 428 mg/kg/d) (a) in their diets. Effects observed at the high dose were: a decrease in body weight and an increase in total serum protein in the females, and a decrease in liver weight and a decrease in cytoplasmic clearing of hepatocytes in the males the NOEL in this study was 1000 ppm (104).

The 90 day mouse study was done in conjunction with the 18 month mouse study. Groups of 90 mice per sex per dose received 0, 5, 25, 500, 2500 or 5000 ppm (0, 0.66, 3.3, 66.6, 333.3, 666.6 mg/kg/d) in their diets. Clinical evaluations were made at 1, 2, 3, 6, 12 and 18 months. Ten animals per group were sacrificed at the 90 day time point for pathological evaluation. The 2500 ppm group was sacrificed at 12 months. Sporadic effects were observed on the body weight, food consumption, and organ weights. These were not dose related, resulting in a NOEL of 5000 ppm in diet for mice (111).

In the twenty-one day dermal rabbit study, the intact skin of male and female New Zealand White Rabbits received doses of 0, 125, 500 and 2,000 mg/kg for 6 hrs/day for 21 days. Clinical signs observed were sporadic weight loss and diarrhea in a few rabbits. These effects were not dose related. Non dose related histological effects were observed in male rabbits. This effect was characterized as mild testicular atrophy occurring sporadically at all doses (112, 108).

Feeding studies in dogs have been done with purebred beagles. The animals received metsulfuron methyl in diets at dose levels of 0, 50, 500 and 5000 ppm (0, 0.2, 2, 20 mg/kg/d) for one year. There was a decrease in food consumption in the high dose males. There was a decrease in serum lactate dehydrogenase in all groups of both sexes at two or more doses these values were within the historical controls. The NOEL was 500 ppm in the males and 5000 ppm in females (112).

In a chronic feeding study in rats, the animals received metsulfuron methyl at doses of 0, 5, 25, 500, 2500 or 5000 ppm (0, 0.28, 1.4, 28.6, 143 or 286 mg/kg/d. Interim sacrifices were done at 13 and 52 weeks (105).

At the 13 week sacrifice there was a decrease in body weight in the 2500 and 5000 ppm groups; there was a decrease in absolute liver weight at 2500 and 5000 ppm males. There was a decrease in the relative liver weights in the 2500 and 5000 ppm females.

(a) In these discussions the assumptions made for estimated conversion of ppm (diet) to mg/kg/D were:
Species Body weight (kg) Intake (kg)
Rat 0.35 0.020 Mouse 0.03 0.004 Dog 10 0.4
When data were presented as ppm, the dose was estimated in mg/kg and is presented in parenthesis.

Findings at the 52 week sacrifice included increase in kidney weight (2500 ppm males) and increased absolute brain weights (at doses of 25, 500, 2500 and 5000 ppm) in males and at doses of 2,500 and 5000 ppm in females. There was an increase in absolute heart weight at 2500 ppm in males and at 2500 and 5000 ppm in females. The absolute organ weights were back to normal at termination. Relative brain weights of the 2500 and 5000 ppm groups were increased (105)

Oncogenicity Studies
There were no gross or histopathological changes observed in mice receiving up to 5000 ppm metsulfuron methyl in their diets (112. 111). Similar results were obtained in the 104 week rat study; there were no histopathological changes observed which were attributable to metsulfuron methyl (105, 112). EPA concludes that there were no

oncogenic effects in rats or mice at the highest dose tested; 5000 ppm in both cases (9).

Mutagenicity Testing

Metsulfuron methyl was negative in the unscheduled DNA synthesis assay; in vivo bone marrow cytogenic assay in rats (doses were 500, 1,000, and 5,000 mglkg bw); CHO/HGPRT Assay; Salmonella typhimurium reverse mutation assay four strains with and without S9 metabolic activation; and also in the in vivo mouse micronucleus assay at doses of 166, 500, 1666, 3000 and 5000 mg/kg (112). 'T¶e only positive mutagenicity assay was in the in vitro assay for chromosome aberrations in Chinese Hamster Ovary at high doses (greater than 2.63 mM, 1.0 mg/mL)). In this assay no increases in structural aberrations were observed at 0.13 or 1.32 mM(0.05 or 0.5 mg/mL) (112).

Developmental Studies

Several studies have been done to investigate the effects of Metsulfuron methyl on reproduction and development in rats and rabbits.

Pregnant Cr1: COBS CD(SD) BR rats received metsulfuron methyl at doses of 0, 40, 250 or 1000 mg/kg by the oral route on days 5 to 14 of gestation. There were 25 rats per group. Maternal toxicity was observed at doses of 250 and 1000 mg/kg/d. The maternal toxicity NOEL was 40 mg/kg/d. There was no evidence of "teratogenic" response or embryo fetal toxicity (112).

In the rabbit study, New Zealand white rabbits received 0, 25, 100, 300 or 700 mg/kg/d on days 6 to 18 gestation. There was a dose related increase in maternal deaths; 1, 2 and 12 deaths at doses of 100, 300 and 700 mg/kg respectively. The maternal toxicity NOEL was 25 mg/kg/d and there was no evidence of teratogenic or embryolethal effects observed in this study (112).

Several multigenerational studies have been done with Metsulfuron methyl. A four litter reproduction study was done concurrently with the chronic bioassay. Rats from each treatment were separated from the main study and bred. The doses were 0, 5, 25, 500, 2500, and 5000 ppm (0, 0.28, 1.4, 28.6, 143 and 286 mg/kg/d). There was a dose dependent decrease in body weight in the parental (P1) generation at doses of 25 ppm and greater in males and females. This effect was not present in dams during gestation or lactation (106).

Overall fertility in the P1 and filial (Fl) matings was low in both control and treated groups with no apparent cause. There was a decrease in pup size in the Fla but not the Flb, F2a, or F2b litters. The gestation index was 100% for all groups in both filial generations with the exception of F2a when it was 90%. On the basis of the lower body weights and lower growth rates, the NOEL was 25 ppm for this study (106).

In a 90 day, 2 generation 4 litter protocol, rats received 0, 25, 500 or 5000 ppm (0, 1.4, 28.6, 286 mg/kg/d) Metsulfuron methyl in their diets for 90 days prior to mating. In this protocol the parental generation was bred twice first to produce the Fla and then the FiB. The FiB rats were then fed the appropridte diet for 90 days (after weaning). There was a decrease in litter size in the 5000 ppm group in the F2a generation, but not in any other generation. The NOEL for this study was 500 ppm (107).

In a 90 day feeding, one generation rat study, 16 male and 16 female rats received 0, 100, 1000 or 7500 ppm in their diet prior to mating. There were no differences observed in reproduction and lactation performance or litter survival among groups. There was an overall low fertility in the control and treated groups. This result made the effects of metsulfuron methyl on fertility difficult to assess from this study (104).

Tolerances and Guidelines

Tolerances have been set for metsulfuron methyl in barley wheat (from 0.05 to 20 ppm, depending on the commodity) and in meat and meat byproducts (0.1 ppm). The tolerance in milk is 0.05 ppm (8, 9). The acceptable daily intake is 0.0125 mg/kg/d based on a one year dog NOEL of 1.25 mg/kg/d using a safety factor of 100 (9).

Avian

Metsulfuron methyl has been tested in two species of birds, the mallard duck and the bobwhite quail. The acute oral LD5O is greater than 2150 mg/kg in the duck. Two, 8 day dietary studies have been done. The 8 day LC5O is greater than 5620 ppm in both the duck and the quail (9).

Invertebrates

The 48 hour LC5O for Daphnia is greater than 150 ppm and the acute toxicity in the honeybee is greater than 25 mg/bee (9).

Aquatic

Metsulfuron methyl has acute LC5O of greater than 150 ppm in both the rainbow trout and the bluegill sunfish (9).

Summary

Metsulfuron methyl has a moderate to high mobility in the soil profile and is relatively persistent in the environment, especially when applied in the fall. These factors would be of concern under most circumstances. However, metsulfuron methyl is applied at very low rates (3-4 ozs./A) and therefore the amounts which reach the soil are quite low. Consequently, Metsulfuron methyl should not impact groundwater as a result of leaching or migrate from the target area. Metsulfuron methyl has low toxicity (EPA Toxicity Category III) for acute dermal exposure and primary eye irritation and is category IV for all other acute exposures. The chronic studies indicate no oncogenicity response and the systemic NOEL's are 500 ppm in rats and 5000 ppm in mice. There was no evidence of teratological effects in the rat or the rabbit at the highest dose tested in both species. While there was evidence of maternal toxicity at 40 mg/kg/d in the rat and 100 mg/kg/d in the rabbits.

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SULFOMETURON METHYL

In addition to the review that is presented below, a comprehensive review available from USDA Forest Service provides information that incorporates more recent studies and data. The US Forest Service risk assessment report is available at: http://www.fs.fed.us/foresthealth/pesticide/risk.shtml

Review conducted by MDAR and MassDEP for use in Sensitive Areas of Rights-of-Way in Massachusetts

COMMON TRADE NAME(S): Oust

CHEMICAL NAME : N-[4,6-dimethylpyrimidin-2-yI) amino-carbonyl -2-methoxycarbonylbenzenesulfonaflhide

CAS NO: 74222-97-2

GENERAL INFORMATION

Sulfometuron methyl, the active ingredient in the herbicide Oust, is a member of the group of sulfonylurea herbicides. Sulfometuron Methyl is a broad-spectrum selective weed control agent used in non-crop areas. Oust is applied pre- or post-emergence which provides control against many broad-leaf weeds and grasses through contact and residual activity. (15)

ENVIRONMENTAL FATE

Mobility

The mobility of sulfometuron methyl has been reported in literature and the database available is complete. Sulfometuron methyl is a weak acid (pKa 5.2) and consequently, adsorption coefficients were calculated for various soils at pH values of 5, 6, and 7. In a low organic matter I soil (1%) the adsorption coefficients were 2.0, 0.8 and 0.3 at the respective pH values. This study indicates that sulfometuron methyl is more strongly adsorbed to soil as the pH decreased, and as organic matter increases. (15)

Soil thin layer chromatography and adsorption coefficients were performed and calculated for four standard soils. Kd values ranged from 0.71 to 2.85 and Rf values ranged from 0.33 to 0.85 indicated a moderate mobility. In addition, soil column studies using the same four soils indicate a moderate to moderately high mobility pesticide. Koc values calculated from the soil Kd values range from 61 to 122 which is lower than the EPA guideline of 400. (101)

In a field mobility study, sulfometuron methyl was applied to soil tubes in five locations (Delaware, North Carolina, Oregon, Colorado, and Saskatchewan, Canada) at a rate of 1 lb a.i./Acre. There was no report of rainfall at these sites. Each application was made at a different time making it difficult to compare results. Samples were taken for a minimum of a year and at some for two years, and at 8 cm (3 in) intervals to 32 cm (12 inches). Results indicate that sulfometuron methyl is moderately mobile under most conditions. One surprising fact is that immediately after application, all locations had detectable residues in a layer below the top layer of soil, and in two locations (Colorado and Oregon) in the deepest layer sampled. All locations except Delaware also had detectable residues at the 24-32 cm layer at other times during the study. There are also indications that sulfometuron methyl would leach further than the deepest soil layer which was sampled. (102)

Persistence

Sulfometuron methyl is degraded by microbial action, photo-decomposition and by hydrolysis at acidic pH's. The photolysis half-life on soil is between 1 to 2 weeks and in distilled water, approximately 160 hours. The hydrolysis half-life at pH 2 and 5 is 100 and 475 hours respectively. At neutral or basic pH's, sulfometuron methyl is stable to hydrolysis. (15,100, 101)

Reports indicate that the overall rate of sulfometuron methyl degradation in soil depends on pH and soil moisture content. Half-lives of one week were reported under laboratory conditions, but field studies at neutral pH revealed greater persistence. Increased soil moisture content resulted in increased degradation rates, but only approximately 10%. (15, 101)

The soil half-life is reported as four weeks with longer times in colder conditions. A review of available studies, however reveals that the shortest half-life was six weeks in Delaware. In the same study the half-life ranged from six weeks to one year in Oregon. (15, 102)

The reported half-life of four weeks is relatively short and would not be cause for concern. However, it seems evident that in most circumstances it may be significantly longer. In all cases reported in this study, the half-life was six weeks or longer and a more realistic estimate may be closer to two months. Another point discussed in the literature is the lack of any significant degradation during the cold periods of the year. Applications in the late fall could lead to longer half-lives and thereby more potential for increased leaching.

The field study discusses the faster degradation rates of sulfometuron methyl in the east as possibly attributable to the more acidic and moister soils in the east. This is certainly true and may in fact have contributed to shorter half-lives, but a point which is not discussed was the timing of the applications. The two western sites were treated in early to mid-July, whereas the western sites were treated in the fall. Saskatchewan was treated in late July, but the climate at that location is cooler and becomes much colder.

TOXICITY REVIEW

Five animals per sex per group were gavaged with sulfometuron methyl suspended in corn oil at a dosage of 5,000 mg/kg. Gross pathological examination revealed slight weight increase in the lungs that were pale red with grey foci in males and similar lung effects in one female. In addition, four females had a pink thymus and one had a slight liver weight. The oral LD50 in male and female ChR-CD rats was determined to be greater than 5,000 mg/kg. (110)

The inhalation LC5O was tested in groups of five male and five female Crl:CD rats. Rats were exposed to control air or test concentrations of either 6.4 or 11 mg/L. There were no clinical or pathological differences between controls or test groups. The inhalation LC5O was greater than 5.0 mg/L (111) while sulfometuron methyl was tested at 6.4 and 11 mg/L. The EPA cutoff for LC5O concentration is 5 mg/L.

Acute skin absorption LD5O tests were performed on five male and five female New Zealand white rabbits. Doses of 2,000 mg/kg of pesticide were applied to abraded skin on the back of the rabbit. Clinical signs in males were sporadic weight loss, slight erythema 1 to 2 days after treatment and diarrhea at 11 days. Gross pathological examination showed no changes due to the test material. The dermal LD5O in rabbits was greater than 2,000

mg/kg. (112)

In a separate acute dermal LD5O test, four groups of five adult male and one group of five adult female New Zealand rabbits were used. Groups of males were dosed at the following levels: 1,500 mg/kg, 2,000 mg/kg, and 8,000 mg/kg and the females were dosed at 2,000 mg/kg. Clinical signs in all the groups of males were moderate to mild redness and sporadic weight loss. The animals in the two highest dose experienced mild swelling, the 2,000 mg/kg group showed moderate swelling while the 1,500 mg/kg group had slight swelling. Clinical signs in the females were severe to mild redness, severe to slight swelling and sporadic weight loss. There were no compound related pathological observations. There was one death in the male 2,000 kg/mg group, but it was not believed to be related to the compound. The LD5O for the acute skin absorption in rabbits was greater than 2,000 mg/kg. (116)

Eye irritation studies were performed by placing 10 mg of solid test material in the conjunctival ac of each of two albino rabbits. There were no corneal or iritic effect. However, there was redness (1 hour to 1 day; not washed eyes and mild for 1 hour unwashed eyes); swelling (1 to 4 hours unwashed eyes) and no discharge was observed. Both washed and unwashed eyes were normal within 1 to 2 days. (113)

In guinea pigs, both primary skin irritation and sensitization tests were run. Ten animals per group were exposed to 0.05 ml of either a 50% or a 5% suspension of sulfometuron methyl. The 50% suspension showed mild to no skin irritation response in 24 hours and no irritation at 48 hours. The 5% suspension reproduced no skin irritation. There was no sensitization response. (114)

The oral LD5O test was conducted with the formulation using young male and female adult Crl:CD rats, five rats per group. 5,000 mg/kg was administered by gavage in a 25% suspension in corn oil. The only clinical finding was alopecia in males. Gross pathological examination showed in both males and females slightly heavy lungs that were pale to pale red with red to dark red foci and white mottling in 1 to 3 animals. The LD5O is greater than 5,000 mg/kg. Additionally in a range finding study, no mortalities were seen in doses from up to 7,500 mg/kg. (115)

Nine male albino rabbits were tested for eye irritation studies. The right eyes were treated with 0.1 ml (61.8 mg) of test material. The left eyes served as untreated controls. Results indicated a transient localized area of slight corneal cloudiness in 2 of the 6 unwashed eyes. The eyes returned to normal in 2 to 3 days. Two of the three eyes treated and washed showed a transient localized area slight corneal cloudiness and mild conjunctivitis with no iritic effects. The washed eyes returned to normal within 3 to 4 days. This compound was considered a slight to mild irritant. (117)

Skin irritation tests were conducted on six male albino rabbits. Doses of 0.5 g of solid pesticide (moistened with saline) were applied to two intact and two abraded skin areas on each rabbit. Each rabbit serves as its own control; treated areas were compared to adjacent untreated areas. Observations and scoring were done by the method of Draize (118) and at 24 and 72 hours after exposure. The compound was not found to be a primary irritant on either intact or abraded skin of rabbits. (119)

Primary skin irritation tests were performed on ten guinea pigs. The procedure was the same as used in testing the technical sulfometuron methyl. Doses of 0.05 ml of a 50% suspension of the pesticide in dimethyl phthalate were used. The 50% suspension caused mild to no irritation in five of the animals. No irritation was caused by the 5% suspension. No sensitization response was observed. (120)

Subchronic and Chronic Studies (Mammalian)

Male and female CD-i mice were fed diets to which had been added 0, 100, 1,000, or 7,500 ppm (0, 13.3, 133, or 997 mg/kg) (a) sulfometuron methyl for 90 days. Hematological evaluations were conducted on all mice (tail cut bleeding at approximately 1, 2 and 3 months after study initiation. All mice were sacrificed and necropsied at 90 days. Organs were weighed and examined histologically. Male mice fed the diet containing 7,500 ppm pesticide showed reduced mean body weights and weight gains. Growth of the 100 and 1,000 ppm groups of males and all treated females was the same as that in the control group. No mortalities occurred. (121)

Hemolytic effects were seen as a result of dietary exposure to sulfometuron methyl in all groups. Significant increases in leukocyte count were found in the 7,500 ppm (997 mg/kg) males. There were statistically significant changes in other blood parameters that were not dose related. Mean absolute and relative liver weights were elevated in all male treatment groups. Histological examination revealed bile stasis in five of ten males in the 7,500 ppm group. In the females, a slight increase in relative liver weight and increased hepatocellular cytoplasmic granularity was observed. Decreases in both mean and relative thymus weights were observed in all treated male groups. Thymic cortical atrophy occurred in three males in the 7,500 ppm group and one male in the 100 ppm group. Because of low frequency of occurrence 7,500 and 100 ppm and absence in the 1,000 ppm group, the thymic cortical atrophy is not considered to be related to the decreased thymus wrights. Based on the observed hemolytic effect, there was no NOEL from this study.

In a second mouse study, five groups of 80 males and 80 female Crl:CD-1 (1 CR)BR mice were fed diets containing one of the following concentrations of sulfometuron methyl: 0. 5, 20, 100, or 1,000 ppm (0, 0.66, 2.66, 13.3,133 mg/kg) for 18 months. Food consumption was monitored throughout the study, mice were weighted and hematological evaluations were performed at regular intervals. At 18 months, mice were sacrificed and necropsied. Mean body weights and mean body weight gains in all treatment groups except for the 1,000 ppm female group were comparable to control groups. Sporadic changes in weight gain were observed in that group.

(a) In these discussions the assumptions made for conversion of ppm (diet) to mg/kg/D were:

SPECIES BODYWEIGHT (kg) INTAKE ((kg)
Rat 0.35 0.020 Mouse 0.03 0.004 Dog 10 0.4
(133)
When data was presented as ppm the does was estimated in mg/kg and is presented in parenthesis.

Mild anemia was observed in the female 1,000 ppm group as evidenced by statistically significant decreases in erythrocyte count, hemoglobin concentration and hematocrit. There was also a significant increase in mean corpuscular volume and platelet count. While the hematological results appear to differ from those in the 90 day mouse study, the data indicate that there were several statistically significant changes in some blood parameters at the three month (90 day) sampling time which were not apparent at other sampling times. However, although reticulocyte smears were made, they were not evaluated and it cannot be ascertained that a response to a hemolytic effect actually occurred. If it did, a NOEL in this strain of mice for a hemolytic effect at 90 days in the 18 month study would be 5 ppm. There was a non-dose related but, statistically significant increase in the incidence of amyloidosis in the female 1,000 ppm groups, but no specific target organ was identified. The overall NOEL for dietary intake of sulfometuron methyl for male and female mice was 1,000 ppm (133 mg/kg) and 100 ppm (13.3 mg/kg) respectively under the conditions of this study based on body weight, body weight gain, clinical pathology and pathological findings. (124)

Groups of 16 male and 16 female CD rats were fed diets containing 0, 100, 1,000, 5,000 ppm (0, 5.7 57, 285 mg/kg) sulfometuron methyl. At 1, 2 and 3 months after the study initiation, hematological, urological and clinical chemistry evaluations were performed. At the end of the study, ten rats from each group were sacrificed and evaluated pathologically. There were no differences between treatments and controls in body weight, weight gain, food consumption and food efficiency. There were no mortalities. The only clinical sign observed was alopecia in three males in the 100 ppm group. The male 5,000 ppm treatment group showed slightly elevated mean leukocyte counts, increased mean relative number of lymphocytes and decreased mean relative number of neutrophils. Due to the effects of white blood cells in male 5,000 ppm group, the NOEL dietary concentration i this study was 1,000 ppm (56 mg/kg/D). (122)

Four groups of five male and five female New Zealand white rabbits were dermally exposed to either 1, 125, 500, or 2,000 mg/kg, six hours per day for 21 consecutive days. After the exposure period, three male and three female rabbits per group were sacrificed for pathological evaluation. The remaining two males and two females from each group were sacrificed and evaluated pathologically following a two week recovery period. Clinical signs observed in rabbits from all test groups including controls were sporadic weight loss and diarrhea. Histopathological and clinical pathological examination showed no compound-related effects. One rabbit did after the eighth dose from

causes not related to the test substance. (123)

Groups of 80 male and 80 female Crl:CD (SD) BR rates were fed diets containing 0, 50, 500 or 5,000 ppm (0, .8, 28.5, or 285 mg/kg) sulfometuron methyl for approximately two years. Hematological, clinical chemistry and urological testing was conducted a 3, 6, 9,12,18, and 24 months. After 12 months, ten male and ten female rats per group were randomly selected, sacrificed and pathologically examined. At 24 months, all surviving rats were sacrificed, necropsied, and examined pathologically.

In the female 5,000 ppm group, food consumption throughout the study was slightly depressed and overall mean weight gain during the first year and mean body weights during the second year were significantly depressed. There were no abnormalities in appearance or behavior observed during the study.

Decreased erythrocyte count and hematocrit in the male 500 and 5,000 ppm groups were observed at the 24 month clinical evaluation suggesting a minimal dose-related hemolytic effect. There were no other compound related hematological, clinical chemistry or urological abnormalities observed. Mean absolute brain weights were significantly lower in the male 5,000 ppm group at both one and two sacrifice times. However, no abnormal gross or histological observation were noted. Mean relative and absolute thymus weight of the 500 and 5,000 ppm males was decreased compared to controls at terminal sacrifice. Mean testes weights of rats in the 5600 and 5,000 ppm groups were less than controls.

Histological examinations revealed dose-dependent increases in the incidence of bile duct hyperplasia and fibrosis in the female 500 and 5,000 ppm groups at the two year sacrifice. Severity of the lesions were minimal to mild, suggesting a slightly toxic effect of sulfometuron methyl on the livers of these female rats.

The NOEL in this strain of rat under these study conditions was 50 ppm (2.8 mg/kg/D). (125)

Oncogenicity Studies

Oncogenic endpoints were evaluated in the chronic mouse and rat studies for sulfometuron methyl. Cr1: CD-i (1 CR) BR mice received 0, 5, 20, 100, or 1,000 ppm sulfometuron in the diet of 18 months. There were no compound related increases in tumor incidence (124). CRL:CD (SD) BR rats received 0, 50, 500, or 5,000 ppm sulfometuron in the diet for two years. There was no increase in frequency of occurrence of tumors in these rats (125). Sulfometuron methyl is not carcinogenic in rats and mice under these conditions.

Mutagenicity Testing

The Ames Salmonella/microsome assay tested the ability of Sulfometuron methyl to revert four strains of Salmonella typhimurium from histidine dependence to histidine independence. The assay was performed both with and without a rat liver homogenate (S-9) activation system. The test substance was found not to be mutagenic for these strains of bacteria under the test conditions at doses from 2.5 to 1,000 mg/plate. (129)

Frequency of chromosome aberrations was tested in CHO cells both with and without metabolic activation (S-9). The doses tested ranged from 300 ug/mI to 10 ng/ml in a half log series. No increase in chromosome aberrations was observed in culture exposed under the test conditions to these concentrations of the test material. (130)

The CHO cell line was used to test mutations in the gene coding for the enzyme hypoxanthineguanine phosphoribosyl transferase (HGPRT) both in the presence and absence of an activation (S-9) system. Concentration of the test material ranged from 0 to .1 mM. No mutagenic activity was detected. (131)

The ability of sulfometuron methyl to induce unscheduled DNA (UDS) synthesis in freshly isolated rat hepatocytes was tested. Concentrations of test material ranged for 1 X 10 -5 to 1.0 mM in half log increments. Under these test conditions, no induction of UDS was detected. (132)

Developmental Studies

Groups of 17 female artificially inseminated rabbits wee gavaged with test material on days 6 to 18 of gestation. Dosage levels were 0, 30, 100, and 300 mg/kg suspended in 0.5% methylcellulose in water. Animals were sacrificed on day 29 of gestation and fetuses wee removed by cesarean section. No treatment-related effects were observed in the maternal clinical observations or gross pathology. There were no statistically significant differences between control and treatment groups in any of the other parameters measured (maternal body weight changes, clinical observations, survival, gross pathology pregnancy rates, numbers and percentages of corpora lutea, implantations, resorptions in each maternal animal, fetal sex, viability and development). Under the conditions of this study, sulfometuron methyl was not considered to be teratogenic in New Zealand white rabbits. (127)

A teratology study was conducted using female Crl:CD (SR) BR rats which were fed a diet containing sulfometuron methyl. Concentrations of 0, 50, 1,000, and 5,000 ppm were used. Thirty-five rats were used as controls, 25 rats were assigned to the 50 and 1,000 ppm group and 15 rats were assigned to the 5,000 ppm group. Rats were fed the test diet on days 6 to 15 of gestation and sacrificed on day 21 of gestation for gross and histological examination. (128)

Rats on the highest dose level gained significantly less weight and ate significantly less feed than controls. The fetuses of this exposure group weighted significantly less than those of the control dams. No other adverse effects were noted in the lower exposure groups. No teratogenicity was demonstrated in this study. The minimum effect level of maternal toxicity and embryofetal toxicity was 5,000 ppm (286 mg/kg) and the NOEL under these study conditions was 1,000 ppm (57 mg/kg). (128) Reproductive studies were performed in conjunction with the 90 day feeding study in rats and the two year feeding study in rats.

In the 90 day feeding study (122), six male and six female rats which had been fed diets obtaining 0,100,1,000, and 5,000 ppm of sulfometuron methyl (for 90 days) were mated and delivered litters. No adverse effects were observed as indicated by fertility, gestation, viability and lactation indies. In addition, there wee no differences between treatment and controls in the mean body weights and survival of weaning pups.

In the two year feeding study (125), 20 rats per group were used in a two generation, four litter reproduction study, initiated 90 days after the start of the long-term feeding study. Fo rats were mated. Females were allowed to give birth and Fla pups wee followed until weaning (21 days) at which time they were sacrificed. Fo females wee again mated, but to different Fo males. Fib pups were delivered and observed. At weaning, 20 males and 20 females were selected from each dietary level (0, 50, 500, and 5,000 ppm) and continued on the treatment for 90 days. Fib rats were bred twice within their respective group, producing F2a and F2b litters. Ten males and ten females from the F2b litters were sacrificed and examined histologically. (125)

During the 90 day feeding period for Fl b rats, body weight and diet consumption were decreased in the female 5,000 ppm group. The number of pus born and the number of pups born alive to the 5,000 ppm groups was consistently lower in both the Fl and F2 generations and was statistically significant for F2b litters. Decreased pup counts may reflect the general health status of the mother as evidenced by decreased body weight and diet consumption of the Fl b 5,000 ppm group. No gross or histopathological changes or effects on organ weights were observed in the weaned F2b rats. The NOEL established, based on this sub-study was 500 ppm (28 mg/kg). (125)

Avian Toxicity

Sulfometuron methyl has been tested in the bobwhite quail and the mallard duck. The **8** day dietary LC5O's were greater than 5,620 and 5,000 ppm respectively. The acute oral LD5O in the mallard duck was greater than 5,000 mg/kg. (101)

Invertebrate Toxicity

The aquatic invertebrate, Daphnia magna was tested and the 48 hour LOSO was greater than 12.5 ppm sulfometuron methyl. (15)

Aquatic Toxicity

Species tested on the aquatic toxicity studies include bluegill sunfish (96 hour) and rainbow trout (96 hour). In both cases the LC5O was greater than 12.5 ppm.

A life stage study was done using the fathead minnow. There were no effects observed on embryo hatch, larval survival or growth at concentrations of 1.2 mg/L or less. (15)

SUMMARY

Sulfometuron methyl is a material both moderately mobile and moderately persistent. A closer look at the material however, reveals that the Oust is applied at the average rate of five ounces of product (3.75 oz a.i.)/acre or 106 grams per acre. These studies were conducted with applications of 1 lb a.i./acre. The lower application rates both minimize the persistence of sulfometuron methyl in soil and thereby diminish the amount of material which is available to leach through the soil. Therefore, sulfometuron may be used if the application rates are kept sufficiently low. This is because the soil organic material and soil microorganisms are able to absorb and degrade lower rates of pesticides.

The oral LD50 in rats for sulfometuron methyl is greater than 5,000 mg/kg and the dermal LD5O is greater than 2,000 mg/kg in rabbits.

The sub-chronic and chronic NOELS are 50 ppm (2.8 mg/kg/D) in rates; 200 ppm (i mg/kg/D) in dogs; and 5 ppm (0.66 mg/kg/D) at 90 days for the reversible hemolytic effect and 100 ppm (13.3 mg/kg/D) at two years in the mouse. This makes the mouse at 90 days the most sensitive species with a transient hemolytic effect, to sulfometuron methyl exposure.

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FOSAMINE AMMONIUM

Common Trade Name: Krenite, Krenite UT

Chemical Name: Ammonium ethyl carbamoylphosphate

CAS No.: 25954—13—6

GENERAL INFORMATION

Fosamine ammonium is usually applied to plants in the late summer and early fall. It is systemically absorbed by buds, stems and foliage. In most plants, effects of herbicide treatment are not evident until the following spring when buds fail to develop, or develop into miniature spindly leaves that do not provide adequate photosynthesis. The plant consequently dies. Although it is translocated within plants, effective treatment requires the complete coverage of all parts of woody plants. In some species of non-deciduous plants, such as pines and bindweed, leaves may turn brown immediately after application.

ENVIRONMENTAL FATE

Mobility

Fosamine ammonium is a low mobility herbicide and is not readily leached from soil. Soil adsorption coefficients (Kd) for Fosamine ammonium are reported as ranging from 0.22 (low organic sandy barns) to 350 (silt barns) (103). The organic matter adsorption coefficients are more variable and range from 20 to 62, with one adsorption coefficient reported at 7400 (103). There does not appear to be a good correlation between the soil adsorption coefficents and organic matter, clay or silt content of the soil.

In a study using soil thin layer plates to assess mobility, the Rf values (ratio of the compound mobility versus the leading edge of the water movement) for Fosamine ammonium ranged from 0.92 to 0.98 on the four soils tested (103). These Rf values indicate a high mobility pesticide, in contrast to the soil adsorption coefficients and leaching studies which indicate low mobility. This information may reflect the solubility of fosamine ammonium and not its mobility characteristics.

Fosamine arnmonium is strongly adsorbed to soil particles and it is not carried away in precipitation, in spite of its high water solubility. In a laboratory study using inclined soil flats (Fallingston sandy loam), Fosamine ammonium was applied at the rate of 15 lbs a.i/acre followed by simulated rainfall. The Fosamine ammonium remained near the surface of the soil and in the upper part of the flat, thus indicating no appreciable downward or lateral mobility (105). Field studies conducted in Florida, Delaware and Illinois have confirmed the laboratory results and indicate very little or no downward movement in soil of the herbicide or its degradation products (15, 104, 105).

Field studies indicate that Fosamine ammonium has low vertical mobility but, soils with higher adsorption capacities will tend to retard movement more than soil with lower adsorption capacities (15). However, Fosamine ammonium may move with the soil during erosion (14). Due to strong adsorption of fosamine ammonium to soil particles, there is little tendency for ground water contamination or for surface waters to become contaminated

without direct application of the material (14, 15).

In the field studies, the Delaware soil (Keyport silt loam) was the most representative soil of Massachusetts conditions. However, the Fallsington sandy loam which was used in the greenhouse studies represents a close approximation to Massachusetts soils. In these studies Fosamine ammonium exhibited slight tendency to leach in both those soils. Consequently, it is expected that fosamine ammonium will exhibit slight leaching in Massachusetts soils.

Persistence

The major route of Fosamine ammonium degradation is metabolism by soil microorganisms. Fosamine ammonium is stable to degradation by hydrolysis at pH values 5, 7, and 9; it is also stable to photodegradation (10, 14, 101, 102).

Fosamine ammonium is not considered a persistent compound in soils. Under field conditions in Florida, Delaware and Illinois, the half-life of Fosamine ammonium in soils was approximately one week following the application of 10 lbs/acre (104).

In the field, the metabolite carbamoylphosphonic acid (CPA) was found several days after initial soil treatment. All Fosamine ammonium and CPA had disappeared completely by 3 to 6 months (14, 15).

Greenhouse soil studies indicate a half-life of about 10 days, which is in close agreement with the field study half—life (15,104). In the field, Fosamine ammonium was metabolized to CPA more quickly in fine sand than in two silt barns (14, 104).

There is little persistence information in the literature for Fosamine ammonium and the only reported field degradation rates are from one study. This might be a cause for concern were it not for the close agreement in soil half-lives reported, not withstanding the varied location and soils used in the field stu-dies. Moreover, the greenhouse degradation study was also in close agreement with the reported field half-life.

It is assumed that the half-lives reported in the previous study have been obtained in spring to summer conditions, since they were not stated. The degradation of fosamine ammonium was investigated for a one year period in the previous study but, because of the short half-life complete degradation had occurred before the winter. It is expected that fosamine ammonium will be applied in summer or fall only since it must be applied to full foliage for control. Consequently, the lack of winter degradation rates is not a major concern.

With most herbicides soil characteristics and local climatic factors have a pronounced effect on soil half—life. This study suggest that degradation of Fosamine ammonium by soil microorganisms is not influenced by soil characteristics or local climate to any appreciable extent.

Due to the similar persistence of Fosamine ammonium in all locations and soils there is no most representative location. In this case, all sites represent expected persistence. Therefore, the half-life of Fosamine ammonium under Massachusetts condition is expected to be approximately one week.

TOXICITY REVIEW

Acute (Mammalian)

The oral LD5Os have been determined for both the formulated product and the formulated product plus surfactant (41.1 to 42% active ingredient (ai) in both cases). The LD5Os in the male rat were 24,400 mg (ai) (formulated product)/kg and 7,295 mg (ai) (formulated product with surfactant)/kg. Female rats had an LD50 of 5,000 (ai) mg (formulated product with surfactant)/kg. The formulated product has an LD50 of 7,380 mg(ai)/kg (formulated product) in male guinea pigs (107).

Fosamine ammonium was tested in an acute dermal study. 10 ml of the formulated product at a dose of 1,683 mg(ai)/kg resulted in no mortalities and no clinical signs of toxicity (107). The formulation plus surfactant was tested in rabbits and was not a primary eye irritant. There was mild transient erythema in tested skin. No sensitization was found in Guinea pigs (107).

The formulation plus surfactant (0.1 ml) produced transient mild corneal opacity and transient conjunctual irritation. The formulation without the surfactant was not an irritant (107).

Metabolism

The metabolism of Fosamine ammonium in the rat is rapid with 86% in feces and 11% in urine after 48 hrs (103,15). Compounds identified in the feces included 14C radiolabelled fosamine ammonium (86%) and 14C Carbamoylphosphonic Acid (CPA) diammonium salt (14%). The compnunds identified in the urine were also fosamine ammonium and CPA (103).

Subchronic and chronic feeding studies have been performed using several species, for various time periods.

The No Observable Effect Level (NOEL) for Fosamine Ammonium in diet studies for rats (90 day), dog (6 month), and sheep (90 day) were: 5,000/10,000 ppm, (286/572 mg/kg); 1,000 ppm (40 mg/kg) and 2,000/2,500 ppm highest dose tested (HDT) respectively (107). In the feeding studies the dose was increased after a certain time point when effects were not observed at the lower dose. These dose groups are written first dose/increased dose. In the six month dog study, the female dogs receiving 5000/7500/10000 ppm had increased stomach weights (107).

Oncogenicity Studies

Long term carcinogenicity studies are not available. These studies have not been required by EPA as there are no food uses proposed for Krenite.

Mutagenicity Studies

Mutagenicity testing has been done using Fosamine Ammonium formulated product. It was negative in 5 strains of the Ames assay, and negative both with and without activation in Chinese Hamster ovary point mutation assay. Chromosome damage was produced in the in vitro cytogenetic assay using Chinese Hamster ovary cells at 1.6% and 3.2 formulation (nonactivated) and 1.4, 2.8 and 5.7% formulation (activated) (107). There were no compound related increases in chromosomal aberrations in an in vivo bone marrow study and no changes in unscheduled DNA synthesis in rat hepatocytes (107).

Developmental Studies

The developmental studies that have been performed using fosamine ammonium include a one generation/two litter rat study and a rat oral teratogenicity study. The doses in the 90 day reproduction study were 0, 200, 1,000 and 5,000/10,000 ppm (0, 11, 57 and 285/570 mg/kg/d). There were no effects observed on reproduction and lactation in the reproduction study (NOEL = 5,000/10,000 ppm HOT). The doses in the teratogenicity study were 0, 200, 1,000 and 5,000/10,000 ppm (0, 11, 57 and 285/570 mg/kg/d). There were no effects observed on teratogenicity and fetoxicity at the 1,000 ppm dose level(107).

(a) In these discussions the assumptions made for conversion of ppm (diet) to mg/kg/D were:
Species Body weight (kg) Intake (kg)
Rat 0.35 0.020 Mouse 0.03 0.004 Dog 10 0.4

Avian

Unformulated Fosamine ammonium was administered to Mallard ducks and bobwhite quail by intubation in acute toxicity studies. Five birds per species-sex group received doses of 0, 312.5, 625, 1,250, 2,500, and 5,000 mg/kg. The LD50 was greater than 5,000 mg/kg in both the ducks and quail (15, 107).

Ducks and quail were also used in subacute dietary studies at doses of 0, 625, 1,250, 2,500, 5,000 and 10,000 ppm in the diet for 5 days. Basal diet was given for the last three days of the 8 day exposure. The 8 day LC50 in the diet was greater than 10,000 ppm. There was no increase in duck mortality: food consumption was depressed but body weight gain was normal. There was variable quail mortality and food consumption and body weight were decreased as compared with control (15, 107).

Invertebrates:

Fosamine ammonium toxicity has been determined for only a very few microorganisms and invertebrates. The available studies indicate that Fosamine ammonium has a very low acute toxicity to those organisms tested (15):

Fosamine ammonium salt (42% formulation): 48 hr LC5Os range from 1,524 mg/L for Daphnia to 10,000 mg/L for bees sprayed with the herbicide.

Aquatic Species (fish):

Fosamine ammonium has a very low toxicity to those fish species tested.
Fosamine ammonium salt (42% formulation): 96 hr LC5Os range from 670 mg/L for bluegill sunfish to 8,290 mg/L for coho salmon (15).

Except for the LC5O of 670 mg/L for the bluegill sunfish, reported adult fish LC5Os are all in excess of 1000 mg/L. (15) The yolk-sac fry stage in salmonids was the most sensitive to Fosamine ammonium.

Threshold-effect concentrations of Krenite for salmonids in partial life-cycle studies are less than 75 times the maximum theoretical concentration of Krenite that would be found in shallow waters due to direct overhead spray application (15).

SUMMARY

Fosamine ammonium is not persistent in the environment and is a low mobility herbicide in soil. Fosamine ammonium has a low potential to leach to groundwater or to reach surface waters from surface runoff. With acute oral LD5Os in rats of greater than 5,000 mg/kg, Fosamine ammonium is considered to be of low acute and subchronic mammalian toxicity. Subchronic exposures to Fosamine ammonium resulted in NOELS of greater than 1,000 ppm in a 6 month dog study. Mutagenicity test were negative in all but one case and there are no carcinogenicity data for this active ingredient. Fosamine ammonium is also considered to have very low aquatic and invertebrate acute toxicity.

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TRICLOPYR

In addition to the review that is presented below, a comprehensive review available from USDA Forest Service provides information that incorporates more recent studies and data. The US Forest Service risk assessment report is available at: http://www.fs.fed.us/foresthealth/pesticide/risk.shtml

Review conducted by MDAR and MassDEP for use in Sensitive Areas of Rights-of-Way in Massachusetts

Common Trade Name(s): Garlon 3A, Garlon 4

Chemical Name: Triclopyr [(3 ,5,6-Trichloro-2-pyridinyl) oxy] acetic acid

CAS No: 55335—06—3

GENERAL INFORMATION

Triclopyr is a picolinic acid derivative and is marketed as Garlon 3A the triethylamine (TEA) salt (CAS #057213-69-1) and Garlon 4 the butoxyethyl ester ***(CAS#*** 008008-20-6).

Triclopyr is effective against a wide variety of woody plants as a foliar spray, basal spray and when applied to cut surfaces. Triclopyr is absorbed by both plant leaves and roots and is readily translocated throughout the plant. It produces an auxin-type response in growing plants in that it appears to interfere with normal growth processes. Thus, maximal plant response occurs when applications are made soon after full leaf development and when there is sufficient soil moisture for plant growth.

ENVIRONMENTAL FATE

Mobility

Most laboratory and field studies indicate that Triclopyr is a relatively mobile herbicide under most conditions. Soil organic carbon partition coefficients K(oc) were determined for the TEA salt in 12 soils which ranged from 0.081% to 21.7% organic carbon. The K(oc) values range from 12 to 78 (14), indicating that Triclopyr should be mobile in most soils. In the same study the K(oc) values of trichloropyridinol, the major metabolite, were reported to range from 114 to 156 in three soils which were not identified. This indicates that trichloropyridinol is less mobile than Triclopyr and should have moderate mobility in soil(14).

In a laboratory study using sandy loam soil with a low organic matter content (0.62%), 75-80% of the applied Triclopyr leached through a 12 inch soil column between days 11 and 15. Water was applied at the rate of 0.5 inches/day for 45 days. The major degradation product, tricloropyridinol required 13 inches of applied water to elute, nearly twice as much (7.5 inches) as Triclopyr(14).

In a field study, Garlon 3A was applied at the rate of 3 gallons/ acre (9 lbs/acre) to six soils ranging from clays to loamy sands in six states. Rainfall was reported to be normal, but not given. Small amounts of Triclopyr and its metabolites were found in the 6—12 inch and 12-18 inch layers of soil 28 to 56 days after application (14,15). Although an application rate of 9 lbs per acre is rather high, the presence of Triclopyr at those depths should be noted especially since there is a correlation with the previous laboratory studies.

In other studies, Triclopyr exhibited significantly lower mobility than had been previously reported. In a field study conducted in Massachusetts, Triclopyr was applied to sandy loam soil at a rate of 0.6 lb/acre. Rainfall was reported as normal, but not given. Triclopyr was never detected below the top ten inch layer of soil at any time during the three month study (100). As part of the same study, Triclopyr was applied to soil columns containing the same soil as in the field study at the rate of 0.6 and 6.0 lbs/acre. Simulated rainfall was applied to the soil columns at a rate of 1 inch per week for a total of 5 inches. Triclopyr was not detected below the top 4 inch layer of soil (100). These results indicate lower mobility than previously reported, but they may reflect the short persistence of Triclopyr in soil rather than its mobility through the soil profile.

Persistence

Soil

Microbial degradation is the primary mechanism by which Triclopyr is degraded in soils to two metabolites (15). Degradation under anaerobic conditions (i.e. saturated soils) is reported to be 5 to 8 times slower than under aerobic conditions (14). Triclopyr in soils is not thought to be degraded to any appreciable extent by chemical hydrolysis and, due to its low volatility, is not thought to volatilize from soil to any great extent (15).

A review by TRW states that Triclopyr "is not considered to be a persistent compound in soils" (95). Studies indicate that under certain conditions the half-life of Triclopyr can be relatively short. The Dow Chemical Company has reported a half-life of 10 days in silty clay loam (96). In a small West Virginia watershed the half-life was estimated as between 14 and 16 days (15). Triclopyr was applied aerially at the rate of 10 lbs/acre, but much of the Triclopyr was intercepted by foliage. Average Triclopyr residues in soil from the treated area of this study, measured on the day of the treatment, were non—detectable in densely wooded areas, 4.4 ppm in lightly wooded areas, and 18 ppm in open areas (15). In a Massachusetts field study, the half—life of Triclopyr was reported as 10 days after the applications of 0.6 and 6.0 lbs/acre Triclopyr to non-target vegetation (100).

Most other studies suggest a much longer persistence for Triclopyr in soil. In a laboratory study, Dow reported a half-life of 46 days for Triclopyr in loam. The loam was maintained in the laboratory at **95 deg** F with moisture at field capacity for the duration of the study (96). A **95 deg** soil temperature and moisture at field capacity are both quite high and indicate that the persistence at less than ideal conditions would be longer. Dow also reports the average half-life of Triclopyr in soil to be 30 days (101). An average half-life of 46 days is reported in the Herbicide Handbook (10) and by Ghassemi et al. (95). In addition, other investigators have reported a half—life in soil of "less than 50 days" at temperatures between 25-35 deg C, and between 79 and 156 days at 15deg C (14). In a field study conducted in Sweden, Garlon 3A was applied at the rate of 2 lbs (a.i.)/acre to eight different forest soils. Residues of Triclopyr persisted for 1 to 2 years, and in some cases in excess of 2 years, at levels approximately 10 percent or less of initial soil residue levels (15). It must be noted that soil temperature levels never exceeded 14deg C (57 deg F) and these temperatures are not favorable to microbial degradation (15). These low maximum temperatures are not typical of year round Massachusetts temperatures, but indicate the increased persistence that may occur when applications are made in the fall and are followed by cold weather.

The variable half-lives reported for Triclopyr indicate that soil half-life may be dependent on the soil and climatic conditions. As in most situations of microbial degradation; cold and, dry or saturated soils decrease the decomposition rate, while warm moist soils increase it.

Aquatic

The fate of the butoxyethyl ester of Triclopyr (TBEE) in water is summarized in Figure 1. This diagram shows the major degradation pathways for the ester in water, but does not include processes such as sediment and particulate adsorption. The fate of the ester in water has also been simulated with a modelling technique by McCall et al., 1988 (115). A recent study by Woodburn (116) with the triethylamine salt of Triclopyr experimentally applied to a lake in Florida also provides useful comparative data on the persistence of Triclopyr degradation products. The degradation path is believed to be TBEE to Triclopyr acid to 3,5,6—trichloro-2-pyridinol (TCP) to non-halogenated organic acids.

TBEE degrades quite rapidly in water to Triclopyr acid. Laboratory studies indicate that photolysis is the principal degradation pathway with hydrolysis also contributing (117, 118). Several studies indicate that the half-life of the ester in water can range from 1.5—2 days as a result of photolysis (117, 119). Hydrolysis half—lives are dependent upon water pH and temperature and range from 0.06 d to 208 d in natural waters. They decrease with increasing temperature and increasing pH. Acidic conditions increase the persistence of the ester substantially. The 208 d half—life was observed in natural unbuffered water at pH 5 and 15 ^{o}C. Waters with this pH level occur in Massachusetts. One laboratory study has produced contradictory results where the ester was stable to hydrolysis, and little photodegradation of the ester occurred over 9 months (120). This study however was performed with buffered, sterile water. Modelling results for the dissipation of the ester indicate that decay should be fairly rapid with a half-life of 12-18 hours (115).

The acid is short-lived in the aquatic environment with reported half—lives of from 2.1 hours at the water's surface in summer at **40deg** N latitude to 14 hr at 1m water depth in winter (117). The principal decay product of the acid is 3,5,6-trichloro-2-pyridinol (TCP), a transient metabolite in water with half—lives ranging from minutes to one day (121). TCP rapidly degrades into nonhalagenated, low molecular weight organic acids (116,121), with phototransformation playing a larger role than hydrolysis in this process.

Salomon et al. (118) demonstrated a half—life of 3.8-4.3 days at l6-17 deg C for the ester to TCP step in an Ontario Lake. Woodburn (116) added Triclopyr salt to a Florida lake and determined a half—life of 0.5—3.6 d at 300 C for the salt to organic acid step. The time scales of both of these studies are in general agreement with the other data on the time course of breakdown for the ester (or salt) to organic acids. With the exceptions of the Hamaker (120) study and a slow breakdown at pH 5, most studies indicate that TBEE in water is degraded relatively rapidly.

TOXICITY REVIEW

Acute (Mammalian)

The Triclopyr toxicity database has been reviewed in several places including the GEIR on the Control of Vegetation on Utility and Railroad Rights-of-Way in Massachusetts (14), Herbicide Handbook Weed Science Society of America (10), and by the U.S. Forest Service (15). Several Dow Publications review the Triclopyr information (101) and Garlon products (102 and 103).

The oral LD5O for Triclopyr in rats is 729 mg/kg in males and 630 mg/kg in females (15, 101). The rat oral LD5O for combined sexes has been reported as 713 mg/kg (10, 14). Rabbits and guinea pigs are more susceptible to oral administration of Triclopyr with LDSOs of 550 and 310 mg/kg respectively (14, 15, 10). The Garlon products have oral LD5Os of greater than 2000 mg/kg (10, 14, 15, 101, 103, 103).

The dermal LD5Os are greater than 2000 mg/kg in rabbits (Triclopyr), and greater than 3980 mg/kg in rabbits for Garlon 4 and Garlon 3A (101, 102, 103)

The effects of Triclopyr on the eye are dependent on the chemical derivative involved: the butoxyethyl ester found in Garlon 4 is essentially non—irritating (102, 15, 14, and 101), while the triethylamine salt is not only an irritant but can cause serious injury (101, 14, 15). These eye injuries include conjunctival irritation, moderate internal redness and moderate to severe corneal damage which may be permanent (14). An inhalation study showed that 100% of the test rats survived a 1 hour exposure to 3 to 20 dilutions of Garlon 3A in air. Transitory nasal irritation to rats was noted after a 4 hour exposure to Garlon 4 aerosol (14).

Metabolism

Two studies, one dermal and one oral have been done in humans to determine pharmacokinetic and metabolic profiles. Five mg/kg acid equivalent (ae) was applied to the forearm of 5 volunteers in the dermal study. One point five eight percent to 1.11% of the applied dose was absorbed and the percutaneous absorption half -life was 16.8 hours (108). In the oral study, 6 volunteers received 0.1 or 0.5 mg/kg Triclopyr (acid equivalent) in apple juice. The excretion half—life is 5 hours and 80% of the dose is recovered as unchanged Triclopyr in the urine (109). The 20% which was unaccounted for could be attributed to one of several explanations including incomplete collections of urine, incomplete absorption of material or metabolism to an unknown metabolite.

Subchronic/Chronic Studies (Mammalian)

Long—term bioassays have been done using Triclopyr in rats (107) and mice (106). Summaries of these studies, provided by Dow Chemical Company have been reviewed for this discussion.

Fischer 344 rats received 5, 20, 50 or 250 mg/kg/d in a preliminary 13 week study. There was a decrease in body weight gain at 50 and 250 mg/kg/d and kidney effects were observed in both sexes at doses of 20 mg/kg or greater (107). In the full two year study, the doses were 0, 3, 12 and 36 mg/kg/d. The dose related effects in the males were increased body weight at 12 and 36 mg/kg/d, and in females there was an increase in pigmentation in the proximal tubules at 3, 12 and 36 mg/kg/d. Neither the weight increase in the males nor the increased pigmentation in the females were accompanied by morphological, histological or functional changes. The NOAEL for males and females was reported to be 3 mg/kg/d (107).

In the mouse bioassay, ICR mice received Triclopyr in their diets for twenty-two months. The doses were 0, 50, 250, 1250 ppm (0, 5, 55, 28.6 and 143 mg/kg/d in males and 0, 5.09, 26.5 and 135 mg/kg/d in females). The range finding study included doses of 0, 200, 400, 800, 1600 or 3200 ppm. At the high dose there were decreases in body weight, anemia, changes in urine, increase in cholesterol levels and multiple changes in liver functions. Some of the liver changes were also observed in the 1600 and 800 ppm groups. There were decreases in body weights, changes in kidney and urine (at various doses and points in time) and liver effects at the 1250 ppm dose. At 250 ppm there were mild kidney effects and the NOEL was reported as 50 ppm (5.55 and 5.09 mg/kg/d for males and females respectively) (106).

In subchronic studies, the 90 day dietary NOELs were 30 mg/kg/d and 20 mg/kg/d for rats and mice, respectively. Dogs were more sensitive to dietary administration of Triclopyr, with kidney effects (decrease in excretion) at 2.5 mg/kg/d (14, 101). Dogs refused to eat food that would result in doses of 30 and 100 mg/kg (104). In a one year study, dogs received doses of 0. 0.5, 2.5 or 5.0 mg/kg/d. Minimal kidney effects were observed at 2.5 and 5.0 mg/kg/d. These findings were considered non—adverse by Dow making the NOAEL 5.0 mg/kg/d and the NOEL 0.5 mg/kg/d (105).

Two monkey studies were done to investigate kidney effects in primates. In one study, the monkeys received 0, 10, 20 or 30 mg/kg/d in diet for 28 days. There was no effect on urinary excretion or other responses observed (101, 104). In a second study, 4 monkeys received Triclopyr at 5 mg/kg/d for 28 days, the dose was then increased to 20 mg/kg/d for 102 days. The effects observed in this study were stool softening and diarrhea (104).

Oncocrenicitv Studies

There have been two chronic bioassays done for Triclopyr. Rats received 0, 3, 12 or 36 mg/kg/d and mice received 0, 50, 250 or 1250 ppm (0, 5.55, 28.6, 143 mg/kg/d for males and 0, 5.09, 26.5 and 135 mg/kg/d for females). The only positive result was an increase in combined incidence of mammary adenomas and adenocarcinomas in the female rats at the high dose. There was no evidence of multiple tumors and the effect was not dose related (107, 106).

Mutagenicitv Testing

Triclopyr has been tested for mutagenicity in a variety of test systems and found to be weakly positive in one, the dominant lethal study in rats. Triclopyr was non-mutagenic in bacterial assay systems, cytogenic assays, and mouse dominant lethal studies (15).

Developmental Studies

The teratology of Triclopyr was investigated using the rabbit model. Doses in the range finding study were 0, 25, 50, 100 and 200 mg/kg. There was 50% and 71% mortality in the 100 and 200 mg/kg groups respectively. The doses used in the full study were 0, 10, 25 and 75 mg/kg/d for days 6 to 18 of gestation. There were 16 rabbits per dose group. One dam in the 25 mg/kg/d group aborted and one dam in the 75 mg/kg/d group died. In the 25 mg/kg group one fetus had hyperplasia of the aortic arch with pulmonary arterial semilunar valve stenosis. Another fetus had a missing gall bladder. There was a statistically significant but non-dose related increase in resorptions at 10 mg/kg/d. This increase was within historical control variability. The developmental NOEL was reported as 75 mg/kg/d with a slight increase in maternal mortality
(110)

Tolerances and Other Guidelines

Tolerances are set for Triclopyr on 5 raw agricultural commodities:
grasses, forage (500 ppm); grasses, forage, hay (500 ppm); milk (0.01 ppm); meat, fat and meat by products (except liver and kidney) of cattle, goats, hogs, horses, and sheep (0.05 ppm); and liver and kidney of cattle, goats, hogs, horses, and sheep (0.5) ppm (8).

The Dow internal guideline for inhalation exposure to Triclopyr is 10 milligrams/cubic meter (102, 103).

Avian

The toxic effects of Triclopyr on birds have been investigated in a small number of studies conducted by the Dow Chemical Company. For mallard ducks, acute oral LCSOs are reported at 1,698 mg/kg for unformulated Triclopyr, 3,176 mg/kg for Garlon 3A, and 4,640 mg/kg for Garlon 4. Eight day subchronic oral LC5Os are reported as follows for the various triclopyr formulations:

Triclopyr	
	mallard duck LC50 = 5,000 ppm
	bobwhite quail LC50 = 2,935 ppm
	Japanese quail LC50 = 3,278 ppm
Garlon 3A	mallard duck LC50=10,000 ppm
	bobwhite quail LC50=11,622 ppm
Garlon 4	mallar d duck LC50=l0,000 ppm
	bobwhite quail LC50=9,026 ppm

Source: (15)

The data summarized above indicate low acute and subchronic toxicity to the bird species tested. No field studies on the toxic effects of Triclopyr or its formulations in birds have been reported (15).

Invertebrates

Very little data were available on the invertebrate and microorganism toxicity of Triclopyr. The data reported are primarily for the triethylamine salt (Garlon 3A) and were generated by the Dow Chemical Company.

The data indicate low acute lethal toxicity* to organisms tested, with a 96 hr LC5O of 895 ppm in shrimp, 96 hr LC5O greater than 1000 ppm in crabs, and 48 hr LC5Os ranging between 56 and 87 ppm in oysters (15). The 48 hr LC5O for Daphnia is reported as 1,170 ppm (15). After 72 hours of incubation with 500 ppm of Triclopyr, no apparent effects on growth were observed in six soil microorganisms when compared to a control (15).

No information was obtained on the invertebrate toxicity of Garlon 4, the butoxyethyl ester of Triclopyr.

Aquatic

The available information on Triclopyr toxicity to fish indicate a wide response of fish to the two formulations of Triclopyr and to unformulated Triclopyr. The butoxyethyl ester of Triclopyr (Garlon 4) is "highly toxic to fish", based upon the Clarke et al. criteria. The 96 hour LC5O values for rainbow trout and bluegill sunfish are 0.74 and 0.87 ppm respectively (15). The corresponding value for juvenile Coho salmon is 1.3 ppm (122).

The triethylamine salt formulation (Garlon 3A) is "slightly toxic" to fish with 96 hour LC5Os of 552 and 891 ppm for rainbow trout and bluegills respectively. The corresponding values for unformulated Triclopyr are 117 ppm for rainbow trout and 148 ppm for bluegill. Both fish species were less sensitive to Garlon 3A than to the active ingredient (15).

No fish toxicity data are available for 3,5,6—trichloro—2—pyridinol (TCP), the intermediate breakdown product from the Triclopyr acid to the non—halogenated organic acid end product.

Dow Chemical Company reports that in natural soil and aquatic environments, both amine and ester formulations rapidly convert (photodegrade) to Triclopyr acid, which in turn is neutralized to a salt at normal environment pH (5.5-6.5)(15). No information is provided with any of the fish toxicity data on the actual form of Triclopyr present in the test water. The persistence data summarized in a previous section and the simulation results of McCall et al. (115), however provide a description of the probable fate of Triclopyr in the toxicity test tanks. The majority of the fish mortalities during the toxicity tests with bluegill sunfish and rainbow trout exposed to the ester occurred during the first 24 hours of the test: a pattern consistent with the change of the toxic ester form to less toxic breakdown products during this period (124).

EXPOSURE ASSESSMENT

For the exposure assessment, we have chosen to analyze the fate of the butoxyethyl ester form of Triclopyr (Garlon 4) in water because of its reported high aquatic toxicity in laboratory studies. Garlon 4 would be applied basally at an average application rate of 0.5 pints per acre for the proposed utility program.

In aquatic organisms, LC5Os greater than 10 ppm are considered to be indicative of only slight toxicity and LC5Os less than 1 ppm are considered to reflect high acute toxicity (Clarke et al., 1970 as referenced in [15]).

Since Garlon 4 contains 61.6% of the active ingredient, this application could distribute 37 mg Triclopyr BEE/m^2. The requested maximum application rate is 2 pints per acre.

Two aquatic exposure scenarios have been constructed to evaluate the potential contamination of non-target surface waters with Garlon 4 from a typical land application. The first, most extreme, and very unlikely scenario is for the case of a static stream traversing a treated acre with a percentage of all of the herbicide applied to the acre running into the water. The second represents a more shallow, static stream or standing water body of much less volume with runoff from a portion of the bordering land.

SCENARIO (1)

ASSUMPTIONS:

Application rate = 0.5 pint/acre
0.47 L/pint
61.6% active ingredient
20% of herbicide applied to acre runs off
density of applied herbicide = 1.0 g/ml

RUNOFF:

0.20 x 0.5 pt/acre x 0.47 L/pt x 0.616 = 0.03 L/acre

RECEIVING WATER:

Static stream crossing a treated acre

Dimension: 0.3 x 1.22 x 64 m = 23.4 **in^3** (volume)

DILUTION:

0.03L into 23.4 m = 1.3 mL/m^3

1.3 mL/m^3 x 1 m^3 /10^3 L = 1.3 x 10 mL/L

1.3 x $l0^{-3}$ mL/L x 1 g/ml x $l0^3$ mg/g = 1.3 mg TBEE/L

SCENARIO (2)

ASSUMPTIONS:

Application Rate = 0.5 pt/acre
0.47 L/pt
61.6% active ingredient **2**

20% of herbicide applied to 3m^2 runs off
density of applied herbicide = 1.0 g/ml

RUNOFF:

0.2 x 0.5 pt/acre x 0.47 L/pt x 0.616 x 2.47
x 10^{-4} acre/m^2 x 10 mL/L x 3 m^2 = 0.02 mL

RECEIVING WATER:

Static stream,

Dimensions: 0.15 x 1 x 5 m = 0.75 **m^3** (volume)

DILUTION:

0.02 mL into 0.75 m3 = 0.03 mL/m^3

0.03 mL/ m^3 x 10^{-3} m /L x 10^3 mg/g x 1 g/ml = <u>0.03 mg/L</u>

The calculations presented above illustrate that the probable immediate post—runoff concentrations of TBEE in static water bodies will be in the sub-parts per million range. At maximum application rates (2 pts/acre), these concentrations would range from about 0.1 to 5.2 mg/L. The concentrations for the worst exposure scenario (#1) are greater than (7x) the 96 hour LC5O concentrations for freshwater fish; those

for the other scenario are almost an order of magnitude less. The no effect level for TBEE with juvenile Coho salmon is ≤1.0 mg/L (122). Therefore, under the worst exposure scenario with the maximum application rate of herbicide, the 96 hour LC5O could be exceeded. Under other, less extreme conditions at average application rates, predicted concentrations of the active ingredient would be substantially less than the reported no effect level in Coho salmon. The persistence characteristics of TBEE are such that the ester form of Triclopyr would not likely persist in surface waters for longer than a couple of days, except in those waters in Massachusetts which are acidic where the ester may persist for up to several months. It is also very unlikely that rainbow trout would be impacted at application rates of 0.5 pts/acre based on the reasonable scenario (#2) which predicts water concentrations of Garlon 4 less than toxic concentrations.

The following factors would also tend to reduce the exposure concentrations that fish would experience: flowing waters would provide greater dilution than assumed for static conditions; the Massachusetts Right-of-Way Management Act mandates an application setback of 10 feet from standing or flowing waters or from wetlands (33 CMR 1l.04:(l) and (4) (a)); and actual runoff of the applied herbicide would probably be less than used for these sample calculations. Scenario 1 represents an extremely unlikely event where 20% of all the herbicide applied to an acre runs off into a small water course. The conditions which would foster this type of runoff across setbacks (i.e. heavy rains) would tend to turn static stream systems into flowing water courses and hence increase dilution.

The application rate used in the previous non—target species assessment (June 23, 1990) was 0.5 pints per acre applied basally. The utilities involved in managing rights-of-way and the manufacturer of Garlon 4 have since indicated that the required application rate may range as high as 2-3 quarts of Garlon 4 per acre for effective control of vegetation. The following addition to the exposure assessment examines the resultant changes in the predicted exposure concentrations that might occur in freshwater fish habitats when Garlon 4 is applied at the 2-3 quarts /acre rate.

The change in the application rate will result in the following differences in predicted exposure concentrations from those originally predicted for 0.5 pts/acre:

2 at/acre x 2pt/ qt = x 8 0.5 pt/acre

3at/acre x 2pt/qt = x 12 0.5 pt/acre

Application rates will therefore be 8-12 times greater than for the 0.5 pts/acre case. The probable concentrations in water after runoff as previously predicted were 1.3 (Scenario 1) and 0.03 mg/L (Scenario 2) ing butoxyethyl ester of Triclopyr / L. These concentrations would therefore range from 0.24 — 15.6 ing/L for application rates between two and six quarts.

These predicted concentrations encompass and substantially exceed the reported LCSO concentrations for fish (in range of 0.7 - 1.3 mg/L and the NOEL of 1 mg/L for juvenile Coho salmon. The more realistic exposure scenario (#2) predicts exposure concentrations of the same order of magnitude as the LC5O values.

Given that the higher application rates required for vegetation control in some areas have the potential to produce potentially lethal concentrations of the butoxyethyl ester of Triclopyr to fish in water as a result of runoff, a setback greater than the mandated 10 feet from standing or flowing waters (333 CMR 11.04: (1) and (4) (a)) will provide an additional level of protection when application rates exceed 0.5 pts/acre.

SUMMARY

Triclopyr exhibits moderate mobility in most of the soils tested. Soils with higher organic carbon content would be expected to retard the mobility of Triclopyr. Trichloropyridinol, the major breakdown product, is less mobile than Triclopyr.

Microbial degradation is the primary mechanism by which Triclopyr is degraded in soils. Degradation rates are variable and appear to be dependent on the soil and climatic conditions. In Massachusetts conditions, Triclopyr can be expected to have moderate persistence when applied in warm weather (late spring —early fall), and slightly longer persistence in colder weather.713 mg/kg. Rabbits and guinea pigs have oral LDSOs of 550 and 310 mg/kg respectively. The target organ for Triclopyr is in the liver. The only positive result in the oncogenicity studies was an increase in the combined incidence of mammary adenomas and adenocarcinoinas in the female rats at the high dose. Mutagenicity tests were negative. The developmental NOEL was reported as 75 mg/kg/d with a slight increase in maternal mortality. Using EPA's carcinogen classification scheme, Triclopyr may be considered a group C carcinogen (possible human carcinogen: limited animal evidence).

RECOMMENDATION

The herbicide Garlon 4, containing the butoxyethyl ester of Triclopyr (EPA Reg. No. 464-554), is recommended for use in sensitive areas only at application rates of 0.5 pt/acre pursuant to 333 CMR 11.00. Applications at rates up to three quarts per acre are permitted with a setback of 50 feet from standing or flowing waters suitable for fish habitat. The set back restriction may be waived upon demonstration to both the Departments of Food and Agriculture and Environmental Protection that runoff concentrations from applications of Garlon 4 with setbacks less than 50 feet do not pose a threat to fish.

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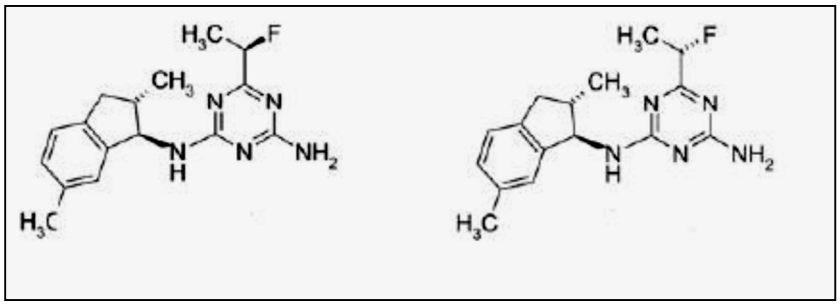
Review of Indaziflam for Application to Sensitive Areas of Rights-of-Way

This document summarizes the environmental fate and transport, as well as toxicological and ecological effects of the herbicide indaziflam. The information summarized in this review was considered in the evaluation of indaziflam for use in Sensitive Areas of Rights-of-Ways in Massachusetts. This review was jointly conducted by the Massachusetts Department of Environmental Protection (MassDEP) Office of Research and Standards (ORS) and the Massachusetts Department of Agricultural Resources (MDAR) in accordance with the cooperative agreement issued between the two agencies in 1987 and updated in 2011 pursuant to the provisions of Section 4(1)(E) of 333 CMR 11.00 Rights-of-Way Management Regulations.

Much of the information used to conduct this review is from the US Environmental Protection Agency (US EPA), including the Pesticide Fact Sheet for Indaziflam (US EPA 2010a), as well as information from several supporting documents available in the US EPA docket no. EPA-HQ-OPP-2009-0636. This information was supplemented by additional, more recent information on ecological risk from Bayer CropScience, reviews of indaziflam conducted by the New York State Department of Environmental Conservation, Health Canada and the Australian Pesticides and Veterinary Medicines Authority, as well as fate and transport studies obtained from the literature.

Indaziflam (N-[(1R, 2S)-2,3-dihydro-2,6-dimethyl-1H-inden-1-yl]-6-[(1RS)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine) is an alkylazine herbicide manufactured by Bayer used for preemergent control of annual grasses and broadleaf weeds. It is an active ingredient contained in several herbicide products manufactured by Bayer. The active ingredient indaziflam was initially registered by the US EPA in 2010 for non-crop use and then in 2011 for food crop (such as citrus, stone and pome fruit, and grapes) uses. Technical grade indaziflam is a mixture of two isomers, including 95-100% of isomer A and 0-5% of isomer B (NYSDEC, 2012)).

Figure 1. Indaziflam Isomer Structures



Isomer A Isomer B

At the time of this active ingredient review by MDAR and MassDEP, Esplanade 200 SC (EPA Reg. No. 432-1516), an end-use product manufactured by Bayer Environmental Science, was submitted for review. Additional details on the evaluation of this product can be found in a separate review document.[1]

Herbicidal Mode of Action:

Indaziflam is a cellulose biosynthesis inhibitor. It prevents the deposition of cellulose into the plant cell wall, thus severely affecting cell wall formation, cell division and cell elongation. It interferes with synthesis of the cell wall in actively growing parts of the plant, where cellulose synthesis is occurring, such as in actively growing meristematic tissues, dividing cells, expanding cells and growing roots. It targets seed growth prior to germination and during root development. Indaziflam has little to no effect on fully developed leaves and plant tissues in which cellulose synthesis is not taking place. Thus, its main use is in targeting pre-emergent weeds (US EPA, 2010a,b; APVMA, 2015; HC, 2011).

Indaziflam Fate and Transport:

Indaziflam applied to soil is moderately mobile, with reported K_{oc} values ranging from 396 to 789 L/kg (APVMA, 2015, HC, 2011). It is moderately persistent in aerobic soils, with reported half-lives of greater than 150 days, and persistent (stable) in anaerobic soils and sediments. Photolysis is not a major degradation pathway of indaziflam in soil. Indaziflam dissipates mainly through biotic degradation and leaching.

In water, indaziflam is a weak acid and has low solubility. In clear, shallow waters, it degrades fairly rapidly by photolysis, with a half-life of about 3.7 days though is stable to hydrolysis. It readily partitions to sediment in 0-3 days, where it is persistent.

The major environmental metabolites of indaziflam (see Figure 2.) include triazine-indanone, indaziflam carboxylic acid, indaziflam-hydroxyethyl, indaziflam-olefin, diaminotriazine and dihydrotriazine (APVMA, 2015). The degradates of indaziflam are more mobile than the parent indaziflam and were detected at the deepest depths sampled (i.e., up to 120 cm). Of the three major metabolites identified in soil (i.e., triazine-indanone, indaziflam carboxylic acid and diaminotriazine), diaminotriazine is also more persistent as well as being mobile to highly mobile and thus has the potential to leach to groundwater (APVMA, 2015, USEPA, 2010a).

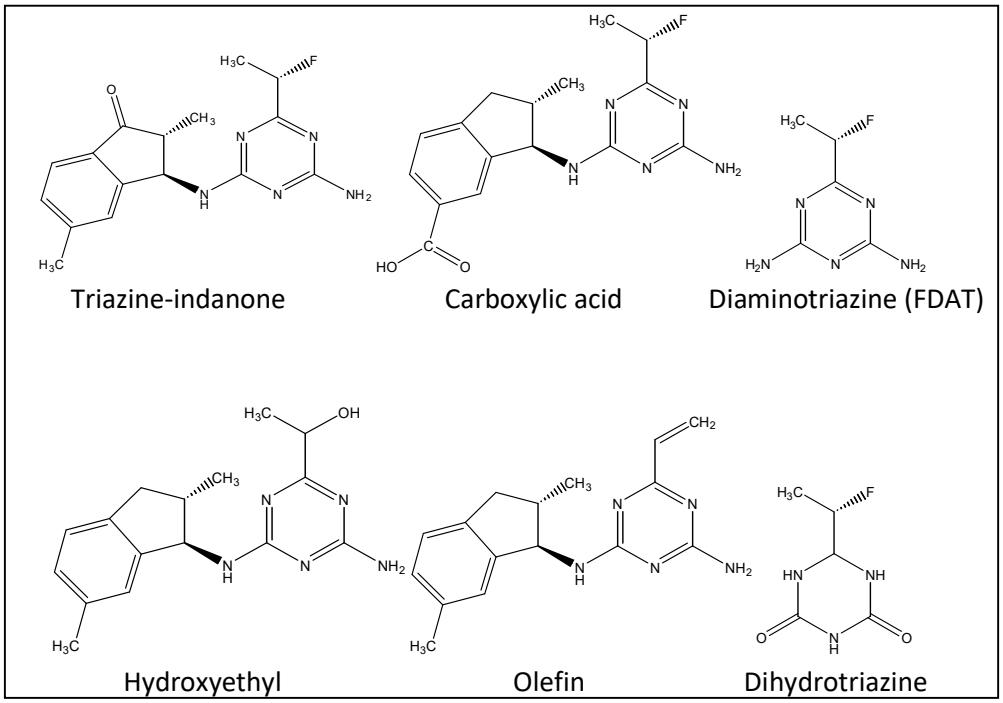
Environmental modeling conducted by several of the secondary sources cited above and confirmed by MDAR however, indicate that predicted concentrations of indaziflam in groundwater are low.

Based on the GUS or Groundwater Ubiquity Score[2], indaziflam has moderate potential to move toward

[1] Product Review of Esplanade Herbicide For Addition to the Sensitive Area Materials List in Massachusetts
[2] Groundwater Ubiquity Score (GUS) (orst.edu)

groundwater and ranks lower in such potential compared to several other herbicides on the Sensitive Area Materials List.[3]

Figure 2. Indaziflam Major Environmental Metabolites



(HC, 2015)

<u>Human Toxicity</u>:

Once ingested, indaziflam is rapidly and completely absorbed. In animal studies, it was also metabolized and excreted rapidly mainly in the feces and urine, with elimination of the administered dose complete by 48 hours. Thus, the potential for indaziflam to bioaccumulate is low. About 40% of the parent indaziflam was excreted unchanged. The major metabolite is an oxidized carboxylic acid form of indaziflam. Dermal absorption of indaziflam is low.

Technical indaziflam has low acute toxicity in rats by the dermal, inhalation and ingestion exposure routes. It was non-irritating to the eyes and skin of rabbits and not a skin sensitizer in guinea pigs. In subchronic and chronic studies in rats and dogs, the nervous system is the major target organ. There are species differences in toxicity, with the dog being the most sensitive, greater than ten times more sensitive than the rat. Other organs affected by indaziflam in rodent studies include the kidney, liver, thyroid, stomach, seminal vesicles, and ovaries.

[3] Sensitive Area Materials List: Rights of Way Sensitive Area Materials List | Mass.gov; GUS values for individual herbicides can be found in the Pesticide Properties Database (https://sitem.herts.ac.uk/aeru/ppdb/)

There is no evidence of carcinogenicity in long-term studies with mice and rats. Neither indaziflam, nor two of its metabolites (i.e., diaminotriazine and indaziflam carboxylic acid) were found to be mutagenic in a battery of genotoxicity tests. Based on the results of these tests, the US EPA classified indaziflam as, "not likely to be carcinogenic to humans".

Indaziflam caused some developmental effects in the offspring of rats, but not rabbits, at doses that also caused maternal toxicity. The US EPA concluded that there is evidence of increased quantitative susceptibility to rat fetuses exposed *in utero* to indaziflam.
Because indaziflam and its metabolite, (fluoroethyl) diaminotriazine (FDAT), both contain a triazine ring (i.e., a six-membered benzene-like ring that includes three nitrogens), the possibility that this structure is associated with toxicity endpoints similar to several other triazine herbicides (i.e., atrazine, simazine, propazine) and their metabolites (desethyl-s-atrazine (DEA), deisopropyl-s-atrazine (DIA), and diaminochlorotriazine (DACT)) has been considered by US EPA and others. These other analogous compounds have been designated as a group by US EPA, known as the "triazine common mechanism group" (TCMG). The TCMG chemicals have a common mechanism of toxicity on the endocrine system, producing effects on the reproductive system in female rats, including a decrease in the luteinizing hormone surge, altered pregnancy outcome and delayed preputial separation, in addition to an increase in the incidence of mammary gland tumors. However, US EPA concluded that, despite the structural similarities, indaziflam and its metabolite did not meet the criteria for inclusion in the TCMG group based on both structural and toxicological reasons. Indaziflam and FDAT contain a fluoroethyl group in their triazine rings whereas the TCMG chemicals contain a chlorine. In addition, the same types of toxicological responses noted above were not seen in an Indaziflam reproduction and fertility study in rats, other than delayed sexual maturation at the highest dose, but at a much higher dose as compared to DACT. Therefore, US EPA does not assume that indaziflam and its metabolite have a common method of toxicity and thus does not include them in a cumulative risk approach as it does for the TCMG chemicals (US EPA, 2010a).

Due to the structural similarity of indaziflam to its metabolites, US EPA assumes that all of the metabolites of indaziflam have comparable toxicity to the parent compound. Diaminotriazine, a single-ring metabolite, is not expected to be more toxic than indaziflam based on its non-neurotoxic mode of action.

The US EPA developed a chronic Population Adjusted Dose (cPAD) for indaziflam of 0.02 mg/kg/day based on the most sensitive effect in the most sensitive species in the indaziflam database. This value, which is similar to a US EPA Reference Dose (RfD) was identified as the No Observed Adverse Effect Level (NOAEL) of 2.0 mg/kg/day from a chronic toxicity study in dogs, to which was applied an uncertainty factor of 100. In this study, degeneration of nerve fibers occurred in the brain, spinal cord and sciatic nerve at the Low Observed Adverse Effect Level (LOAEL) of 6 mg/kg/day and 7 mg/kg/day in males and females, respectively (US EPA, 2010a).

For short- and intermediate-term incidental oral, dermal and inhalation exposure, the US EPA developed a short-term acute Population Adjusted Dose (aPAD) level of 0.075 mg/kg/day based on a NOAEL of 7.5 mg/kg body weight/day from a subchronic toxicity study in dogs, to which an uncertainty factor of 100 was applied. The same effect (i.e., degeneration of nerve fibers in the brain, spinal cord and sciatic nerve) was seen at the NOAEL of 7.5 as in the chronic study. This short-term value is also adopted as relevant for acute exposure. Though an acute exposure study in rats was available and was the basis of a previous short-term level developed by US EPA in 2010, the US EPA observed that the dog is much more sensitive (i.e., greater than the ten-fold factor for inter-species differences that is part of the 100-fold uncertainty factor used to derive this value) than the rat, and though generally, use of a subchronic endpoint as the basis of an acute value is conservative, given the severity of observed neurotoxic effects in the dog as compared to the rat and the absence of a neurotoxicity study in dogs, US EPA concluded that this conservative approach was prudent (US EPA, 2010a,b; APVMA, 2015; HC, 2011).

In its review of the active ingredient, indaziflam, US EPA calculated aggregate exposure estimates for indaziflam from food, water and residential exposures, including via ingestion, inhalation and dermal exposure, compared these to the appropriate points of departure (i.e., the aPAD and cPAD) to determine whether acute and chronic dietary pesticide exposures are safe, and concluded that there is a reasonable certainty that no harm will result to the general population or to infants and children from these exposures. Though agriculturally related or residential exposures are not relevant to exposures expected in the ROW application scenario, ingestion of surface water and/or groundwater is identified as a relevant dietary pathway for the general public.

Since the potential for several metabolites of indaziflam to contaminate groundwater is high, due to its high mobility and propensity to leach, the US EPA used water exposure models that estimate, based on their physical, chemical and fate/transport characteristics, surface water and groundwater concentrations of indaziflam and its metabolites following indaziflam application at label rates. Total toxic residue concentrations in water were conservatively calculated for indaziflam, the four major indaziflam metabolites that maintain the dual ring structure of the parent indaziflam, and the two single-ring metabolites. As discussed above, all metabolites are assumed to be of comparable toxicity to the parent.

US EPA compared these modeled concentrations to acute one-day (500 ug/L) and chronic (100 ug/L) drinking water benchmark concentrations, known as US EPA Human Health Benchmarks for Pesticides (HHBP) (derived by the US EPA based on the aPAD and cPAD information discussed above) and demonstrated that the predicted concentrations of these compounds are well below the HHBP values and thus have low, potential toxicity to humans.

EPA also examined potential ingestion of indaziflam in surface water by conducting a similar conservative evaluation considering the potential for both indaziflam and its metabolites to enter surface water and demonstrated that expected concentrations of indaziflam and its metabolites following indaziflam application in accordance with label instructions, would be well below the HHBP benchmark concentrations. Given that ROW areas in Massachusetts must observe setbacks from

streams and waterbodies, the concern that high concentrations of Indaziflam will enter surface waters is even less likely.

The groundwater and surface water conclusions reached by the US EPA and others were also confirmed in a modeling evaluation conducted by MDAR (2020). MDAR modeled a very conservative scenario, in which indaziflam was applied annually for thirty years at the maximum concentration to a watershed with sandy soils (to simulate soils in areas such as southeastern Massachusetts and Cape Cod) at the maximum label rate use. The model results assume application to 100% of the area whereas in a ROW area, only fractions of a given area receive pesticide applications, plus there is a 100 foot setback requirement from surface drinking water supplies. Peak, modeled concentrations for this worst-case scenario were well below both acute and chronic HHBP levels. See MDAR (2020) for additional details (USEPA, 2010c; MDAR, 2020).

Ecotoxicity

Indaziflam has low toxicity to wild mammals, upon both acute as well as chronic exposure. Toxicity to most birds was also low, though there was an outstanding question regarding potential reproductive effects in mallards. At the request of the US EPA, the manufacturer conducted an additional mallard reproductive study, in which several female birds were found with regressed ovaries. However, no statistically significant differences were found in adult body weight effects, or mortality, egg or embryo reproductive effects, or hatchling effects and body weight. US EPA identified a LOAEL of 720 ppm in this study, which corresponds to a daily dietary dose of 89 mg/kg/day of the active ingredient. EPA protocol for evaluating toxicity to reptiles uses data for birds as a surrogate and, as such, toxicity to reptiles is assumed by EPA to be low.

Indaziflam has low toxicity to honeybees, non-target arthropods, and earthworms. It is not toxic to freshwater and sediment-dwelling invertebrates. It is acutely highly toxic to fish, both freshwater and marine/estuarine, moderately to highly toxic to estuarine invertebrates, and slightly toxic to moderately toxic to freshwater invertebrates. Toxicity to amphibians was evaluated using data on the most sensitive fish species as a surrogate. Thus, indaziflam is assumed to be toxic to amphibians as well.

Almost all of the fish and aquatic toxicity tests were classified by the US EPA as supplemental because test solutions were not centrifuged to accurately determine how much of the indaziflam was actually in solution (NYSDEC, 2012). However, according to Bayer, their procedure is to evaluate the solubility of the test material in water prior to testing with aquatic animals to determine the limits of solubility in the test system—and they only centrifuge or filter the test solutions prior to chemical analysis if they observe precipitate in the test solutions. They state that they are confident that the analytical measurements are valid and adequately reflect the dissolved concentrations—and that the fact that US EPA did not request them to repeat the aquatic studies indicates that the information is of sufficient quality to be used in a risk assessment (US EPA, 2010a).

Despite the high toxicity of indaziflam to aquatic organisms, application rates of indaziflam are low—and thus environmental concentrations of indaziflam in ROWs predicted using modeling are low. This is confirmed by the results of surface water exposure modeling for ecological risk assessment conducted by the US EPA and repeated by DAR (using conservative assumptions as well as land, soil and weather modeling data that are more representative of Massachusetts ROW areas).

This modeling conservatively does not account for the fact that in Massachusetts ROW areas, application of herbicides must observe setbacks from streams and waterbodies, which would likely further decrease predicted concentrations of indaziflam in surface water to negligible concentrations. The EPA acknowledges that toxicity to aquatic organisms is high and requires label language to help mitigate these risks and keep the herbicide on the intended treatment area. Thus, concern that high concentrations of Indaziflam will enter surface waters is low if indaziflam applications are made as specified in the product label.

According to the US EPA, based on the most sensitive ecological taxa tested, indaziflam-olefin and indaziflam-hydroxyethyl, are similar in toxicity to the parent compound, while the rest of the environmental degradates demonstrate a toxicity about 2-7 times less than the parent compound. Thus, none of the degradates are any more toxic than the parent compound (US EPA, 2010).

Plant Toxicity

Given indaziflam's mode of action, which is specific to plant cell wall biology, it is not surprising that non-target nonvascular and vascular aquatic plants, as well as both monocot and dicot terrestrial plants, are sensitive to it. These non-target sensitive plants include a number of plants listed under the Endangered Species Act. In addition, effects on non-target plants that might not be endangered species but which might serve as a food source for endangered animal species would be of concern (US EPA 2010a).

Similar to the strategy used for aquatic life, the US EPA mitigates potential risks to plants by requiring label language intended to keep the herbicide on the intended treatment area (US EPA, 2010a).

Conclusions

Review of secondary documents from both US EPA and other agencies consistently present the same profile and conclusions on the toxicity, fate and transport of this herbicide. This information, supplemented by additional MDAR predictive modeling of indaziflam concentrations in groundwater and surface water following its application as per label instructions in ROW area in Massachusetts, indicate that exposures to indaziflam residues by human and ecological receptors should not be of toxicological concern.

While indaziflam and its metabolites do have the potential to leach to groundwater especially in looser soils, predicted concentrations of these compounds in groundwater used as drinking water following indaziflam application at label rates are well below toxicity benchmarks for humans.

Indaziflam in surface water quickly partitions to sediment, and it dissipates quickly via photolysis in shallow water. The probability that high concentrations of indaziflam will enter surface water is very low, especially since herbicide application in Massachusetts ROW's must observe a 100-foot setback from surface water bodies used as a source of public water. Modeling conducted by the US EPA and MDAR confirm this. Thus, concentrations of indaziflam in surface water used as drinking water following application of indaziflam as per label instructions are also expected to be well below toxicity benchmarks for human exposure.

Indaziflam is absorbed completely and metabolized fairly quickly so the potential for it to bioaccumulate in ecological receptors is low. While it is toxic to mammals, especially dogs, at doses administered in laboratory studies, exposure concentrations of indaziflam associated with herbicide applications are well below concentrations of concern for these receptors.

Although Indaziflam is highly toxic to freshwater and marine/estuarine fish, moderately toxic to freshwater invertebrates, highly toxic to marine/estuarine invertebrates and assumed to be toxic to amphibians, application rates of indaziflam are low and modeling based on these applications predict low exposures to ecological receptors. However, impacts to amphibians and reptiles are based on surrogate toxicity information for fish and birds respectively, and as such have additional uncertainty. Therefore, additional precautions should be taken as warranted to identify potentially significant amphibian and reptilian habitat prior to application.

Sensitive non-target plant species have been identified as organisms of concern. Given that herbicides are designed to control plants, this is not surprising. This information, coupled with the fact that indaziflam is moderately mobile and some of its metabolites are highly mobile strongly indicates that application of indaziflam should be targeted as much as possible to avoid impacts on non-target plants. Measures that minimize drift should be used in applying this product. In addition, as with any application, a preliminary field survey should be conducted prior to application to identify any plants on the endangered species list and/or any other plant species that are important to that ecosystem.

Based upon the available database for indaziflam, use of this herbicide in sensitive areas of rights-of-ways should be acceptable if it is applied in a manner that is consistent with the product label, the above recommendations and the Massachusetts Sensitive Areas of Rights-of-Way Regulations.

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