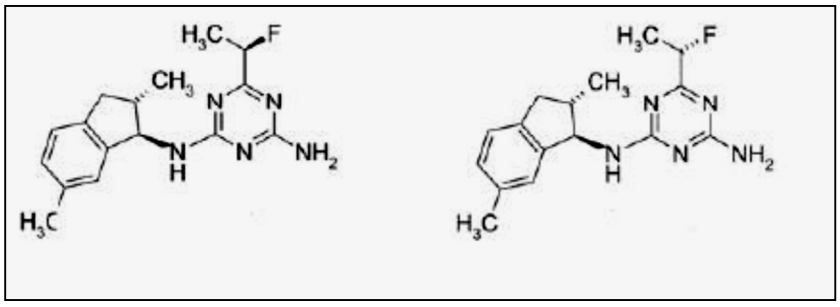
Review of Indaziflam for Application to Sensitive Areas of Rights-of-Way

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).

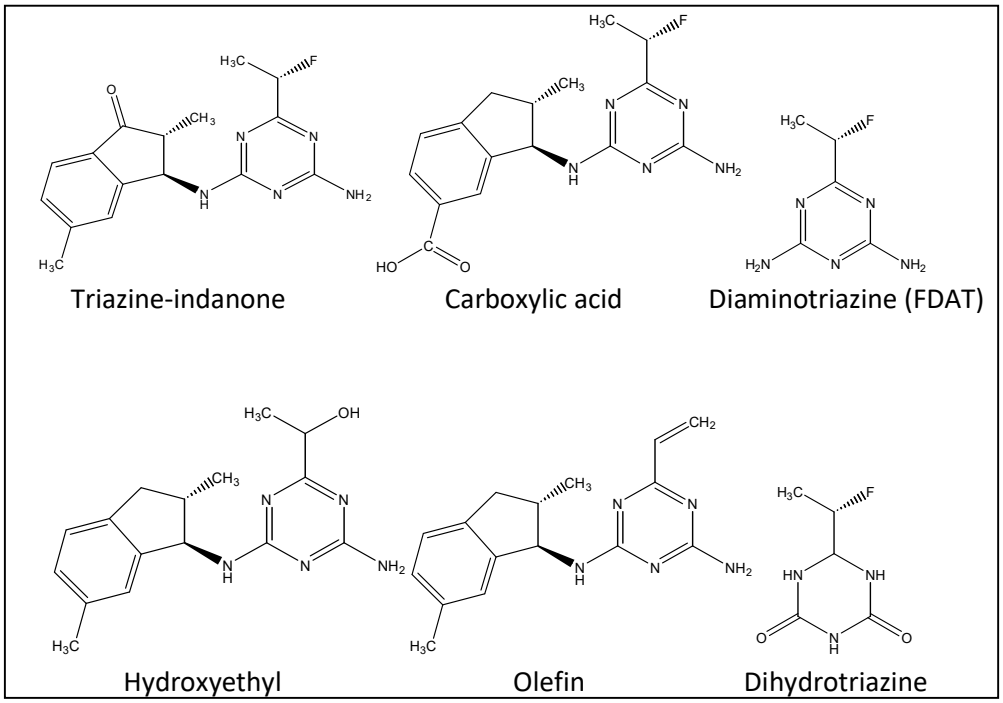
Environmental modeling conducted by several of the secondary sources cited above and confirmed by MDAR however, indicate that predicted concentrations of indaziflam in groundwater are low.

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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