UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: **September 27, 2013**

SUBJECT: **Indaziflam.** Human Health Risk Assessment to Support Proposed New Import Tolerances (Without a U.S. Registration) on Banana, Coffee, and Palm Oil.

PC Code: 080818
Decision No.: 472679
Petition No.: 2E8125

Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D408033
Registration No.: 264-1129
Regulatory Action: Tolerance Without US Registration
Case No.: NA
CAS No.: 730979-19-8
40 CFR: 180.653

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TO: Maggie Ruddick/Kable Davis, RM Team 25
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The Registration Division (RD) requested that the Health Effects Division (HED) conduct a risk assessment for the active ingredient indaziflam to estimate the risk to human health that will result from the proposed new import tolerances on banana, coffee, and palm oil.

The attached human health risk assessment addresses exposure and risk associated with the proposed tolerances, as well as the existing agricultural and residential uses. The exposures assessed include dietary (food and water), residential exposure durations and scenarios involving incidental oral, dermal and inhalation exposure, and aggregate exposure and risk for residential handlers resulting from use on turf. There were no risks of concern identified for any route or duration of exposure.

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1.0 Executive Summary

The Agency has received a petition from the registrant, Bayer CropScience, for import tolerances associated with the use of the herbicide indaziflam {1,3,5-triazine-2,4-diamine, N-[(1*R*,2*S*)-2,3-dihydro-2,6-dimethyl-1H-inden-1-yl]-6-[(1*S*,1*R*)-fluoroethyl)-} outside the U.S. on coffee, banana, and palm oil. The end use product used in the submitted crop field trials and processing studies is the currently registered Indaziflam 500 SC formulation, a suspension concentrate formulation of indaziflam, containing 500 g active ingredient (a.i.)/L (4.16 lb a.i./gallon).

Indaziflam is registered for control of many annual grasses and broadleaf weeds in lawns, golf course/turf, sod farms, recreational turf, ornamentals, non-crop areas, Christmas tree farms and forested areas. It is also registered for use as a pre-emergent herbicide for weed control in parks, railroads, utility, industrial and municipal sites. Registered agricultural use sites for pre-emergent control of annual grasses and broadleaf weeds include citrus, stone, and pome fruits, grapes, tree nuts (including pistachio), and olives, with permanent tolerances established under 40 CFR §180.653 ranging from 0.01 ppm to 0.15 ppm in plant commodities. The residue definition for both tolerance enforcement and risk assessment for crops is indaziflam and the fluoroethyl diaminotriazine metabolite, FDAT. Acceptable analytical methods are available to enforce tolerances for residues of indaziflam in plant and livestock commodities.

The toxicology database is considered adequate for conducting a human health risk assessment in accordance with the Food Quality Protection Act (FQPA). The scientific quality is relatively high, and the toxicity is well-characterized for all types of effects, including potential developmental, reproductive, immunologic and neurologic toxicity. The nervous system is a target for indaziflam and neurotoxic effects are being used to assess risks from indaziflam exposure. Indaziflam is classified as "Not likely to be carcinogenic to humans," and, therefore, is not a concern for cancer effects. HED has evaluated the available data with respect to the Food Quality Protection Act (FQPA) safety factor and has reduced the required 10X FQPA safety factor to 1X, based on the following considerations: the toxicity data base is complete; there was no evidence of increased susceptibility (qualitative or quantitative) for pre- and/or postnatal effects in developmental toxicity studies in the rat and rabbit, the rat developmental neurotoxicity study or the rat two-generation reproductive toxicity study; the endpoints selected for risk assessment are protective of the observed neurotoxicity; and the residential and dietary exposure estimates are considered to be upper bound and will not underestimate exposure.

The residue chemistry database is complete and there are no residue chemistry issues that would preclude granting the requested registrations and establishing permanent import tolerances. Adequate crop field trials and processing studies have been conducted to support import tolerances in plant commodities (coffee, banana, and palm oil). HED is recommending for the establishment of permanent import tolerances (without U.S. registrations) for all of the requested crops.

HED used modeling to assess acute and chronic dietary exposure to indaziflam. In combination with an extensive database of food consumption patterns for the U.S. population and population subgroups, this modeling used conservative upper-bound assumptions regarding residues of indaziflam and its breakdown products in food and drinking water. Specifically, the dietary

assessments included tolerance-level residues from the existing and proposed uses, the assumption of 100% crop treated (CT) for all crops, and drinking water residues derived from modeling the maximum application rate in vulnerable areas. The highest potential drinking water exposure is from surface water sources. The acute and chronic dietary exposure and risk estimates are below HED's level of concern (LOC) of 100% of the acute population adjusted dose (aPAD) or chronic population adjusted dose (cPAD) for the general U.S. population and all population subgroups, including those of infants and children. The highest exposed population subgroup was infants <1 year old, with dietary risk estimates of 19% aPAD and 8% cPAD; all other population subgroups had lower risk estimates, including the general U.S. population at 6% aPAD and 3% cPAD.

There are no new indaziflam residential uses associated with this regulatory action. However, there are existing residential uses - home lawn/turf and gardens/trees uses – that have been reassessed to reflect updates to HED's 2012 Residential SOPs[1] along with policy changes for body weight assumptions. Short-term dermal and inhalation handler exposures are expected for those making applications at their homes and short-term dermal, inhalation, and incidental oral exposures are expected via contact with residues following applications in outdoor home environments. No risks of concern were identified for any scenario – all MOEs were greater than 100.

In accordance with the FQPA, in evaluating human health risks from exposure to pesticides, HED aggregates exposure from various routes, i.e., residential exposure is added to dietary exposure from food and drinking water. For adults, the highest residential exposure estimate was from dermal high-contact (playing) with treated turf, and it was combined with the chronic dietary exposure from the mostly highly exposed adult (General U.S. Population) sub-population to determine aggregate exposure and risk. For children, the highest post-application dermal and incidental oral risk estimates on turf associated with children 1<2 years old were combined with the chronic dietary exposure for the most highly exposed child (Infants <1 year old), to determine aggregate exposure and risk. The resulting aggregate MOEs for both adults and children are above the LOC of 100, and therefore the aggregate risk estimates are not of concern.

As there are no occupational exposures associated with the proposed import tolerances, a new occupational exposure assessment was not conducted for this risk assessment. Occupational exposures from the existing registered uses of indaziflam were previously assessed and no risks of concern were identified.

Indaziflam contains a symmetrical triazine moiety. Based on a comparative review of its structure and toxicological profile, HED previously determined that indaziflam does not belong in the triazine cumulative assessment group (E. Scollon, D371661, 04/21/2010).

The risk assessment is based, in part, on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies are compliant with applicable ethical requirements (refer to Appendix C).

[1] Available: http://www.epa.gov/pesticides/science/residential-exposure-sop.html

2.0 HED Recommendations

HED recommends in favor of the proposed import tolerances (i.e., without a U.S. registration) for indaziflam on banana, coffee, and palm oil as summarized in **Table 2.2.3**.

2.1 Data Deficiencies/Conditions of Registration

None.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Approved tolerance enforcement methods for crops are available for indaziflam using high performance liquid chromatography with tandem mass spectrometry detection (LC/MS/MS; Method DH-003-P07-02) for fruit and tree nut matrices. The method has been sufficiently validated and is suitable as an enforcement method for crops. The method is able to determine, separately, residues of indaziflam and FDAT. The method has been adequately radiovalidated using samples from the apple and grape metabolism studies. Use of the proper stable- isotope-labeled internal standards is critical to the methods accuracy and effectiveness.
This LC/MS/MS method uses extraction, by blending with a mixture of acetonitrile and water. The limit of quantitation (LOQ) for vegetables and non-citrus fruits is 0.01 ppm. The method was validated to a limit of quantitation (LOQ) of 0.005 ppm in fruit and tree nut crop matrices. These data support a total method LOQ of 0.01 ppm in all fruit and tree nut matrices [combined residues of parent (0.005 ppm) and FDAT metabolite (0.005 ppm)].

2.2.2 International Harmonization

There are currently no established Codex, Canadian, or Mexican maximum residue limits (MRLs) for indaziflam on banana, coffee, or palm oil; therefore, there are no issues of harmonization. Codex has no tolerances established for indaziflam on any commodity, whereas Canada has established tolerances for indaziflam on other commodities not currently under review. For existing uses of indaziflam, tolerances are harmonized for all commodities where both the U.S. and Canada have established tolerances.

2.2.3 Recommended Tolerances

Table 2.2.3. Tolerance Summary for Indaziflam.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
Banana	0.01	0.01	Tolerance without a corresponding U.S. registration
Coffee	0.01	0.01	Tolerance without a corresponding U.S. registration
Palm oil	0.03	0.03	*Palm, oil*; Tolerance without a corresponding U.S. registration

2.2.4 Revisions to Petitioned-For Tolerances

With the exception of revising the palm oil commodity listing as given in Table 2.2.3 above, there are no revisions to the petitioned-for tolerances.

2.3 Label Recommendations From Residue Review

None.

3.0 Introduction

3.1 Chemical Identity

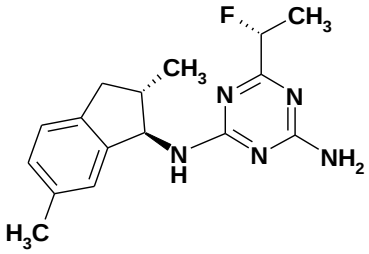
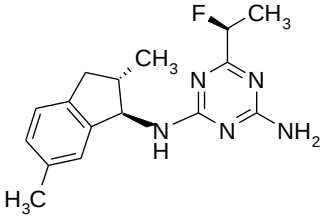
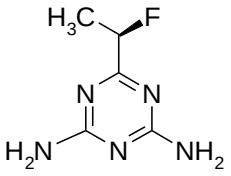
Table 3.1. Nomenclature.	
Compound AE 1170437 Isomer A	
Common name	Indaziflam
Company experimental name	AE 1170437
IUPAC name	*N*-[(1*R*,2*S*)-2,6-Dimethyl-2,3-dihydro-1*H*-inden-1-yl]-6-[(1*R*)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine
CAS name	1,3,5-triazine-2,4-diamine, *N*-[(1*R*,2*S*)-2,3-dihydro-2,6-dimethyl-1*H*-inden-1-yl]-6-[(1*R*)-1-fluoroethyl]-
CAS #	730979-19-8
Compound AE 1170438 Isomer B	
Common name	Indaziflam
Company experimental name	AE 1170438
IUPAC name	*N*-[(1*R*,2*S*)-2,6-Dimethyl-2,3-dihydro-1*H*-inden-1-yl]-6-[(1*S*)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine
CAS name	1,3,5-triazine-2,4-diamine, *N*-[(1*R*,2*S*)-2,3-dihydro-2,6-dimethyl-1*H*-inden-1-yl]-6-[(1*S*)-1-fluoroethyl]-
CAS #	730979-32-5

Table 3.1. Nomenclature.	
Compound 1-Fluoroethyl diaminotriazine (FDAT)	
Common name	Indaziflam-diaminotriazine
Company experimental name	AE 1170437-diaminotriazine
IUPAC name	6-[(1*R*)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine
CAS name	6-[(1*R*)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine
CAS #	Unavailable

Due to the presence of three chiral carbons in the indaziflam structure, there are eight possible isomers for this herbicide. Based on the product chemistry review of the manufacturing use product (MUP) by the Registration Division (RD, H. Mukhoty, 12/1/2008, D356393), the registrant is declaring the active ingredient to consist of only isomers "A" (AE 1170437) and "B" (AE 1170438) with concentrations of about 92% and 3%, respectively. Two later RD reviews (S. Malak, 9/22/09, D367608 and 3/18/10, D372513) report additional statements of formula with similar levels of isomer A (92-93%) and isomer B (2.4-2.9%). The first chemical name appearing above in Table 3.1 (N-[(1R,2S).]-6-[(1R) diamine) represents that of the A isomer. The second name is for isomer B and is identical to A with the exception of the stereochemistry at the fluorine-bearing carbon (i.e., 6-[(1S) diamine). The remaining six isomers are present at significantly lower levels and are considered to be impurities. The batches used for dosing in the toxicology studies had >90% isomer A, about 1-3% isomer B, and negligible (<1%) levels of the remaining six isomers. These isomer contents are appropriate for the above described composition of indaziflam.

3.2 Physical/Chemical Characteristics

The information regarding physical chemical characteristics of indaziflam does not indicate that there are any special concerns in terms of bioaccumulation, exposure or other risk assessment considerations. A table of physical and chemical properties for indaziflam is included in Appendix B.

3.3 Pesticide Use Pattern

Indaziflam is an alkylazine herbicide registered for non-selective pre-emergent and early post-emergent control of annual grass and dicot species in trees, nuts, vines, and turf. This herbicide is a cellulose biosynthesis inhibitor and is active at rates of 50 to 100 g ai/ha. The technical-grade a.i. (TGAI) is made up of at least 95% of the 1*R*-fluorethyl isomer and no more than 5% of the 1*S*-fluoroethyl isomer. Although the company name AE 1170437 refers specifically to the 1*R*-fluoroethyl isomer, it has been used interchangeably with the technical grade active ingredient (TGAI). Both isomers have equal herbicidal activity.

Currently registered end use products include Indaziflam 200 SC and Indaziflam 500 SC, which are suspension concentrate formulations of indaziflam, containing 200 and 500 g active ingredient (a.i.)/L (1.67 lb a.i./gallon and 4.16 lb a.i./gallon), respectively. The products are registered for use in ground-directed application for pre-emergent weed control in orchards of pome fruits, stone fruits, citrus, tree nuts (including pistachios), grapes, and olives. Use rates for both formulations are dependent, to some extent, on the soil type within the use area. For existing uses, seasonal maximum application rates are 0.089 lb a.i./A for grapes and 0.134 lb a.i./A for all other crops. Indaziflam is not to be applied through any type of irrigation system or by aerial equipment for the registered uses. However, aerial applications are permitted on the overseas labels associated with the import tolerances.

The pre-harvest intervals (PHIs) on the labels associated with the import tolerances are 0 days for banana, 0-30 days for palm oil, and 19-20 days for coffee. All of the submitted crop field trials and processing studies used the 500 SC formulation. For the proposed uses on various labels in other countries, the use rates range from 0.049 to 0.098 lb ai/A on palm oil, 0.079 lb ai/A on banana, and from 0.088 to 0.098 lb ai/A on coffee.

Table 3.3 provides a summary of the labels supporting the proposed import tolerances**.**

Table 3.3. Summary of Directions for Use of Indaziflam (On Proposed Labels for Registration Outside the U.S.).[a]

Applic. Timing, Type, and Equip.	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Banana (Non-Domestic Use)					
Broadcast spray, pre- or post-crop emergence, pre-emergence for weeds; ground or aerial equipment	0.079 lb a.i./A (80 g a.i./ha)	1	0.079 lb a.i./A (80 g a.i./ha)	0	None that are relevant.
Coffee (Non-Domestic Use)					
Broadcast spray, pre- or post-crop emergence, pre-emergence for weeds; ground or aerial equipment	0.088-0.098 lb a.i./A (90-100 g a.i./ha)[b]	1	0.088-0.098 lb a.i./A (90-100 g a.i./ha)	19-20	None that are relevant.
Palm Oil (Non-Domestic Use)					
Broadcast spray, pre- or post-crop emergence, pre-emergence for weeds; ground or aerial equipment	0.049-0.098 lb ai/A (50-100 g a.i./ha)[c]	1	0.049-0.098 lb ai/A (50-100 g a.i./ha)	0-30	None that are relevant.

[a] All submitted crop field trials and processing studies were conducted using the Indaziflam 500 SC Herbicide (Soluble Concentrate, 45.05% a.i.) formulation.

[b] The proposed label (Alion 50SC) is proposed for use on coffee at 90 g a.i./ha in Belize, Cuba, Dominican Republic, El Salvador, Guatemala, Honduras, Jamaica, Nicaragua, and Panama. The proposed label (Alion) is proposed for us at 100 g a.i./ha in Brazil.

[c] Multiple proposed labels for use on oil palm at a maximum single application rate at 50, 60, 75, 80, and 100 g a.i./ha in various countries, with the maximum application rate varying by country. The low value of 50 g a.i./ha is for the proposed Alion 50 SC label for use in Thailand, with the high value of 100 g a.i./ha coming from the proposed Alion 500 SC label in Peru.

3.4 Anticipated Exposure Pathways

As a result of the registered and proposed uses of the insecticide indaziflam, humans may be exposed through food and drinking water, since the chemical may be applied directly to growing crops and may reach surface and ground water sources of drinking water. In an occupational setting, applicators may be exposed while handling the pesticide prior to application (i.e., mixing/loading), as well as during application. There is also potential for post-application exposure for workers re-entering treated fields.

Since indaziflam is also registered for use on lawns/turf and gardens/tree uses, there is likely to be exposure in residential and non-occupational settings. Short-term dermal and inhalation handler exposures are expected for those making applications at their homes and short-term dermal, inhalation, and incidental oral exposures are expected via contact with residues following applications in outdoor home environments.

This risk assessment considers all of the relevant exposure pathways, combining them as appropriate, to estimate overall exposure and risk.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf. As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture under the National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA). These food consumption patterns are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for children, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

Indaziflam is a broad-spectrum, pre- and/or post-emergent herbicide of the fluoroalkyltriazine class. It affects germination of seeds of grasses and broadleaf weeds by inhibiting cell wall biosynthesis and affecting meristematic stem growth. The exact mode of toxic action in mammals is unknown.

4.1 Toxicology Studies Available for Analysis

The toxicology data for indaziflam are sufficient and are of good quality for selecting toxicity endpoints and points of departure for risk assessment. The available toxicology studies include: (1) subchronic oral toxicity studies in rats, mice and dogs; (2) a 28 day dermal toxicity study in rats; (3) developmental toxicity studies in rats and rabbits; (4) a 2-generation reproduction study in rats; (5) chronic toxicity studies in rats and dogs; (6) carcinogenicity studies in mice and rats; (7) a battery of genotoxicity studies; (8) two metabolism studies in rats; (9) a dermal penetration study in rats; (10) acute, subchronic and developmental neurotoxicity studies in rats; and (11) an immunotoxicity study in mice. The requirement of the subchronic inhalation toxicity study has been waived by HED's Hazard and Science Policy Council (HASPOC, Rury, K. 3/20/2013, TXR 0056608).

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

The metabolism of indaziflam has been evaluated in the rat. Indaziflam is rapidly and completely absorbed. Radioactivity was detected in the blood within 5 minutes of dosing with peak blood concentrations between 40-60 minutes. Absorption was estimated at 90% or greater of administered dose, based on bile cannulation experiments. Absorption was slightly more rapid in females than males. Indaziflam was distributed to multiple tissues with the highest levels found in the gastrointestinal tract, liver, skin and thyroid. Radioactivity was not retained at significant levels in the tissues by 3 days' post dosing (less than 0.2 to 0.3% of dose). Metabolism was extensive with only 2-16% of the dose excreted in feces as unchanged parent, and occurred primarily via oxidative processes. The major metabolite in the rat was the carboxylic acid metabolite of indaziflam (37-39% AD in bile cannulated rats and 63-67% AD in non-cannulated rats), which was largely excreted in the bile but also found in urine and feces. Other compounds that were identified as major metabolites (>5% AD) in combined excreta in one or more groups were 3-hydroxyindane acid (11-12% AD), 3-hydroxyindane acid epimer (11% AD), dihydroxy (6-13% AD), hydroxy glucuronic acid (11-13% AD), 3-ketoindane acid (5-6% AD), and hydroxyethyl acid metabolite (5% AD). Metabolite profiles in males and females were comparable, with some minor qualitative differences, but females excreted significantly less unchanged parent compound. Radioactivity was rapidly excreted (approximately 90% of dose by 24 hrs postdosing). Excretion was predominantly fecal at the high dose (1:10 urine:feces). However, at the low dose, urinary excretion was also prominent (1:1 to 1:2 urine:feces), indicating absorption from the gastrointestinal tract was overwhelmed at the higher oral doses.

4.2.1 Dermal Absorption

An *in vivo* dermal absorption study in the rat and *in vitro* dermal absorption study in rat and human were submitted. The data demonstrated an inverse relationship between dosing concentration and percent absorption. Based on *in vivo* dermal absorption observed in the rat and *in vitro* comparative rat:human absorption data, an estimated human dermal absorption factor (DAF) of 7.3% was obtained.

The human DAF was calculated as follows (all absorption values adjusted for recovery): (1) in the rat *in vivo* dermal absorption study, a dermal absorption of 27.39% (directly absorbed plus absorbable) was found at 24 hrs post-exposure (actual exposure time 8 hrs) using an application of 0.05 mg/cm^2; (2) *in vitro* exposure of microtomed rat skin under the same exposure and assessment conditions gave a dermal absorption of 22.40% (directly absorbed plus absorbable); (3) the ratio of the *in vitro* to the *in vivo* absorption is 0.82 (22.4/27.39) and therefore, is close to 1, indicating that the *in vitro* data is predictive of *in vivo* absorption; (4) based on this ratio, a DAF for humans may be calculated using *in vitro* human dermal absorption (5.975%, adjusted for recovery) observed under the same exposure conditions. The DAF for humans is therefore 5.975%/0.82 = 7.3%.

4.3 Toxicological Effects

The nervous system is the major target for toxicity in rats and dogs. Evidence of neurotoxicity (e.g., decreased motor activity, clinical signs, and/or neuropathology) was observed in both species throughout the database, which included the dog subchronic and chronic toxicity studies, the rat acute, subchronic, and developmental neurotoxicity studies, the rat two-generation reproduction study, the rat chronic toxicity study, and the rat combined carcinogenicity/chronic toxicity study. In repeated-dose studies, the dog was the more sensitive species, showing the lowest NOAELs and LOAELs among all available studies, based on neuropathology (degenerative nerve fibers in the brain, spinal cord and sciatic nerve). At higher doses, three dogs in the subchronic study were prematurely terminated due to excessive clinical signs including ataxia, tremors, decreased pupil response, seizures and other findings.

In the rat, a marginal decrease in motor/locomotor activity was observed in females in the acute neurotoxicity study. Decreases in motor/locomotor activity were also seen in the subchronic neurotoxicity study in females and in the developmental neurotoxicity study in male offspring at PND 21. Clinical signs of neurotoxicity were observed in the acute, subchronic, and developmental neurotoxicity studies and consisted primarily of tremors, changes in activity and reactivity, repetitive chewing, dilated pupils, and oral, perianal, and nasal staining. Similar clinical signs of neurotoxicity were observed in the 2-generation reproduction study, the rat chronic toxicity study, and the combined rat carcinogenicity/chronic toxicity study. Neuropathology findings were also observed in the rat manifested as focal/multifocal vacuolation of the median eminence of the brain and the pituitary *pars nervosa* and degenerative nerve fibers in the gasserian ganglion, sciatic nerve, and tibial nerve. Evidence of neurotoxicity was not seen in the mouse.

Other organs affected by indaziflam in mice and rats included the kidney, liver, thyroid, stomach,

seminal vesicles and ovaries. Effects on the kidney were observed following chronic exposure in rats and mice while effects on the liver were observed following chronic exposure in the rat. Effects on the thyroid were only observed in multiple dose rat studies. Chronic exposures also lead to atrophied or small seminal vesicles in male rats and glandular erosion/necrosis in the stomach and blood-filled ovarian cysts/follicles in female mice. However, these effects occurred at higher doses than those at which neurotoxicity was observed in the dog. In rats, effects observed on the liver, thyroid, kidney, and seminal vesicles occurred at doses that were similar to those that produced neurotoxicity. Decreased body weight gain was also observed in most studies following exposure to indaziflam. There was no evidence of immunotoxicity in the available studies, which included a guideline immunotoxicity study in the rat. No systemic effects were observed in the rat following a 28-day dermal exposure period.

No evidence of increased quantitative or qualitative susceptibility was seen in developmental toxicity studies in rats and rabbits or in a reproduction study in rats. In the rat developmental toxicity study, decreased fetal weight was observed in the presence of maternal effects that included decreased body weight gain and food consumption. No developmental effects were observed in rabbits up to maternally toxic dose levels. Decreased pup weight and delays in sexual maturation (preputial separation in males and vaginal patency in females) were observed in the rat two-generation reproductive toxicity study, along with clinical signs of toxicity, at a dose causing parental toxicity that included coarse tremors, renal toxicity and decreased weight gain. In the developmental neurotoxicity study, transiently decreased motor activity (PND 21 only) in male offspring was observed and was considered a potential neurotoxic effect. It was observed at a dose that also caused clinical signs of neurotoxicity along with decreased body weight in maternal animals.

Indaziflam showed no evidence of carcinogenicity in the two-year dietary rat and mouse bioassays. All genotoxicity studies that were conducted on indaziflam were negative.

Testing in acute lethality studies with indaziflam resulted in low toxicity via the oral (Category III), dermal (Category III), and inhalation (Category IV) routes of exposure. Indaziflam was not an irritant to eyes (Toxicity Category IV) or skin (Toxicity Category IV) and was not a skin sensitizer.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

The toxicology and the exposure databases support a reduction of the required 10X FQPA safety factor to 1X for the following reasons, based on the following considerations: The toxicology data based is complete; there is no evidence of qualitative or quantitative susceptibility; the endpoints selected for risk assessment are based on and protective of the neurotoxic effects seen in the guideline studies; and exposure will not be underestimated because the assessment was based on tolerance-level residues in food, upper-bound estimates of potential residues in drinking water, the updated Residential SOPs, and chemical-specific data for post-application exposure.

4.4.1 Completeness of the Toxicology Database

The toxicology database is considered complete and is adequate for the purpose of assessing pre- and postnatal susceptibility. Acceptable/guideline developmental toxicity studies in rats and rabbits and a reproduction study in rats, as well as acute, subchronic, and developmental neurotoxicity studies in rats were available for FQPA assessment. There is no concern for increased susceptibility in the developing young.

4.4.2 Evidence of Neurotoxicity

Evidence of neurotoxicity was observed in dogs and rats throughout the database, which included the dog subchronic toxicity study, the rat subchronic toxicity, the rat acute, subchronic, and developmental neurotoxicity screening batteries, the rat two-generation reproduction study, the rat chronic toxicity study, and the rat combined carcinogenicity/chronic toxicity study. Evidence of neurotoxicity was manifested as neuropathology in dogs and as decreased motor activity and clinical signs (e.g., tremors) in rats. Evidence of neurotoxicity was the most consistent effect (seen in dogs and rats), the most sensitive toxicological finding (based on neuropathology in dogs), and the basis for the risk assessment.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

No developmental effects were observed in rabbits up to maternally toxic dose levels. Offspring effects in the developmental toxicity study in rats, DNT, and multigeneration toxicity studies only occurred in the presence of maternal toxicity and were not considered more severe than the parental effects. In addition, clear NOAELs/LOAELs were identified for these studies. Therefore, HED concluded that there is no evidence of increased quantitative or qualitative susceptibility to rat or rabbit fetuses exposed *in utero* and/or post-natally to indaziflam.

4.4.4 Residual Uncertainty in the Exposure Database

There is no residual uncertainty in the exposure database. There are no exposure data gaps and the current dietary assessment is based on high-end assumptions such as tolerance-level residue values, 100% crop treated, and modeled estimates of drinking water residues. New 2012 Residential SOPs and chemical-specific data were used to assess post-application exposure to children including incidental oral exposure. The residential post-application assessment assumes that maximum application rates are applied and that hand-to-mouth activities occur on the day of application. All of the exposure estimates are based on conservative, health-protective assumptions and are not likely to underestimate risk.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

The toxicity endpoints and points of departure are presented in Table 4.5.4.1 and Table 4.5.4.2, and the details for selecting toxicity endpoints and points of departure for various exposure scenarios are presented in Appendix A.

A comprehensive risk assessment for indaziflam was conducted in 2010 (Collantes, M. 16 September 2010, D367451). In the last risk assessment the point of departure (POD) for acute dietary exposure was chosen from the acute neurotoxicity study in the rat, based on a NOAEL of 50 mg/kg. In this study, evidence of neurotoxicity in females (marginal decreases in motor and locomotor activity) was seen within the first hour following dosing at the LOAEL of 100 mg/kg. However, following subchronic and chronic exposures, the dog was the most sensitive species with the lowest NOAELs among all of the available studies. The apparent increased sensitivity of the dog is still present following allometric scaling using the ¾ power of body weight. While the greater sensitivity of dogs compared to rats is based on subchronic and chronic exposures and may not apply to acute exposure, increased sensitivity cannot be ruled out due to the absence of data for acute exposures in dogs. The magnitude of sensitivity is greater than the 10x interspecies uncertainty factor used in the previous risk assessment for calculation of the aRfD. Thus, there is a concern that using the NOAEL from the rat acute neurotoxicity battery may be under protective despite being from a study of the appropriate route and duration.

In addition to a potential sensitivity issue between rats and dogs, there is evidence that supports that the effects observed in the subchronic oral study in dogs could have been the result of a single dose. In the acute neurotoxicity (ACN) study in rats, nerve fiber degeneration of the gasserian ganglion, sciatic nerve, and the tibial nerve, were observed following a single exposure to indaziflam at the limit dose (neuropathology examination was conducted 14 days after exposure, at the end of the study). Similar effects (axonal nerve fiber degeneration in the brain, spinal cord, and sciatic nerve) were observed following treatment of dogs with indaziflam for 90 days. Since nerve degeneration was only visible following sacrifice of the animals at the end of the study, it is impossible to determine if nerve fiber degeneration was present following a single dose in the subchronic dog study as was the case in the rat ACN.

Following the observation of seizures and clinical signs of neurotoxicity in two dogs of the high dose group (30 mg/kg/day) of the subchronic oral study in dogs (study days 15 and 22), the study investigators attempted to split the dose into two 15 mg/kg/day doses 7-8 hours apart to determine if lowering the C_{max} would prevent further seizures. This dosing regimen was instituted following a two day break from the 30 mg/kg/day dosing regimen and was followed for ten days before seizures and clinical signs of neurotoxicity were observed in another female dog (study day 35). Based on the description of the dosing, there were 16 hours between the second dose on a given study day and the first dose on the next day. Metabolism data in rats indicate that indaziflam is excreted rapidly. It is estimated that >90% of the administered dose is excreted after 24 hours in male bile cannulated rats dosed with 13.35 or 14.00 mg/kg indaziflam with the majority (~76%) of the excretion in bile and urine occurring within 12 hours. Although metabolism data in dogs are not available, the rat metabolism data support the concept that a large portion of the absorbed dose is likely eliminated within the 16 hours between doses. Furthermore, the seizures and clinical signs of neurotoxicity observed following the conversion to the split dosing occurred ~2 hours after the first dose in the morning. This is similar to the estimated time of peak of effect in the rat acute neurotoxicity battery (~50 mins) and the time to peak plasma concentration in the rat metabolism study (~40-60 mins). The study did not indicate how long after dosing the seizures and clinical signs of neurotoxicity were observed in the two dogs that received the single 30 mg/kg/day dose of indaziflam and had seizures on study days 15 and 22.

In addition, in a range-finding study (MRID 49073701) for the subchronic oral study in dogs, seizures in three dogs were observed on day 0-1 following exposure to indaziflam in the diet at 50 (two dogs) or 200 (one dog) mg/kg/day indicating that neurotoxicity in dogs could occur from an acute exposure. The NOAEL for this study was 15 mg/kg/day and the LOAEL was 50 mg/kg/day based on seizures. While the 90-day range finding study supports the conclusion that seizures in dogs could result from a single dose, the 90-day range finding study itself with a NOAEL of 15 mg/kg/day was not considered appropriate for selection of an acute endpoint and dose for risk assessment due to the limited number of dogs used (n=2/dose group) and because no neuropathology was conducted. However, HED considers it likely that nerve degeneration occurred in these animals because neuropathology was seen at a dose (15 mg/kg/day) that was below the dose (30 mg/kg/day) that caused seizures in the subchronic oral study in dogs and nerve degeneration was found in rats following a single dose in the rat acute neurotoxicity study. A summary of all seizures observed in the multiple dose dog studies is provided in appendix A (Table A.3).

Based on a weight of evidence approach, HED has concluded that the subchronic oral toxicity study in dogs should be used as basis for endpoint and dose selection for the acute dietary exposure scenario. While the rat acute neurotoxicity study is of the appropriate duration, the increased sensitivity of the dog following subchronic and chronic exposure to indaziflam suggests that the rat acute neurotoxicity study may be under protective of risk from an acute exposure. Furthermore, the observation of similar effects in the acute neurotoxicity study at higher doses, the rapid excretion of indaziflam in rat metabolism studies, and the timing of the observation of seizures and clinical signs of neurotoxicity in the subchronic oral toxicity study and the range-finding study in dogs suggest that signs of neurotoxicity could result from a single dose in dogs. Similar neuropathology (axonal nerve fiber degeneration in the brain, spinal cord, and sciatic nerve) was also observed in the chronic oral study in dogs, which could have been the result of an acute exposure. Although a lower NOAEL (2 mg/kg/day) and LOAEL (6 mg/kg/day) were identified in the chronic oral study in dogs, it was not selected for the acute dietary risk assessment since a clear NOAEL of 7.5 mg/kg/day was identified in the subchronic toxicity study in dogs which is a more appropriate duration for the acute dietary exposure scenario. HED acknowledges that selecting an endpoint from the subchronic toxicity study in dogs is likely conservative. However, given the severity of observed effects in the dog, the apparent increased sensitivity of dogs to the neurotoxic effects of indaziflam relative to rats, and absence of an acute neurotoxicity study in dogs, the Agency concluded that it was prudent to adopt this conservative approach.

The POD for chronic dietary exposure was chosen from the chronic study in dogs, based on a NOAEL of 2 mg/kg/day with axonal degeneration of nerve fibers in the brain, spinal cord and sciatic nerve at the LOAEL of 6 and 7 mg/kg/day in males and females, respectively, in the dog chronic dietary study. This provided the most sensitive endpoint available for chronic dietary exposure since rat and mouse chronic NOAELs were ≥12 mg/kg/day.

For short- and intermediate-term residential and occupational exposure scenarios involving incidental oral and inhalation exposure, the NOAEL of 7.5 mg/kg/day from the dog oral subchronic toxicity study was selected. The LOAEL of 15 mg/kg/day was based on axonal

degeneration of nerve fibers in the brain, spinal cord and sciatic nerve. Developmental toxicity studies in the rat and rabbit were also available for short-term exposure, but had higher NOAELs (25 mg/kg/day) and therefore were not considered protective of potential neurotoxicity. The rat subchronic neurotoxicity study also had a significantly higher NOAEL (244 mg/kg/day), as did the developmental neurotoxicity study (maternal and developmental 84 mg/kg/day). The chronic dog study was considered for intermediate-term exposure due to greater incidence and severity of lesions at lower doses with continued exposure, but was not selected because, at one year, the neuropathology at the LOAEL was minimal. Furthermore, based on the proposed use patterns, continuous daily exposures occurring for more than 90 days are not expected.

Although a 28-day dermal toxicity study in the rat was available and showed no toxicity up to the limit dose, including neuropathology or clinical signs, it was not selected for dermal risk assessment because the dog showed considerably greater sensitivity for neuropathology than the rat in the oral studies. The NOAEL from the subchronic dog study was therefore selected to be protective of potential neurotoxicity, but is considered a conservative endpoint due to the bolus (gavage) dosing method employed in the dog subchronic study.

Long-term dermal and inhalation exposures are not expected; therefore, endpoints were not selected.

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

For short- and intermediate-term aggregate risk assessments, incidental oral, dermal and inhalation routes can be combined due to the selection of a common toxicological endpoint of concern (axonal nerve degeneration). Long-term dermal and inhalation exposure are not expected for the currently registered uses of indaziflam.

4.5.3 Cancer Classification and Risk Assessment Recommendation

Increased tumor incidence was not seen in acceptable carcinogenicity studies in rats and mice, and indaziflam is classified as “Not likely to be Carcinogenic to Humans.” Cancer risk is not an issue for the chemical.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Use in Indaziflam Dietary and Non-Occupational Human Health Risk Assessments.

Exposure Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General population, including Infants and Children and females 13-49)	NOAEL = 7.5 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Acute RfD = 0.075 mg/kg/day aPAD = 0.075mg/kg/day	Subchronic Gavage Toxicity Study in Dogs LOAEL = 15 mg/kg/day, based on axonal degenerative microscopic findings in the brain, spinal cord and sciatic nerve.
Chronic Dietary (All populations)	NOAEL = 2 mg/kg/day	UF_A=10X UF_H=10X FQPA SF = 1X	Chronic RfD = 0.02 mg/kg/day cPAD = 0.02 mg/kg/day	Chronic Dietary Toxicity Study in Dogs LOAEL = 6/7 mg/kg/day M/F, based on nerve fiber degenerative lesions in the brain, spinal cord and sciatic nerve.
Incidental Oral, Short-term (1 to 30 days) and Intermediate-term (1 to 6 months)	NOAEL = 7.5 mg/kg/day	UF_A=10X UF_H=10X FQPA SF = 1X	Residential LOC for MOE = 100	Subchronic Gavage Toxicity Study in Dogs LOAEL = 15 mg/kg/day, based on axonal degenerative microscopic findings in the brain, spinal cord and sciatic nerve.
Dermal, Short-term (1 to 30 days) and Intermediate-term (1 to 6 months)	NOAEL = 7.5 mg/kg/day DAF = 7.3%	UF_A=10X UF_H=10X FQPA SF = 1X	Residential LOC for MOE = 100	Subchronic Gavage Toxicity Study in Dogs LOAEL = 15 mg/kg/day, based on axonal degenerative microscopic findings in the brain, spinal cord and sciatic nerve.
Inhalation, Short-term (1 to 30 days) and Intermediate-term (1 to 6 months)	NOAEL = 7.5 mg/kg/day	UF_A=10X UF_H=10X FQPA SF = 1X	Residential LOC for MOE = 100	Subchronic Gavage Toxicity Study in Dogs LOAEL = 15 mg/kg/day, based on axonal degenerative microscopic findings in the brain, spinal cord and sciatic nerve.
Cancer (oral, dermal, inhalation)	No Evidence of Carcinogenicity. Classified as "Not Likely to be Carcinogenic to Humans."			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF =

uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. N/A = not applicable.

Table 4.5.4.2. Summary of Toxicological Doses and Endpoints for Use in Indaziflam Occupational Human Health Risk Assessments.

Exposure Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term (1 - 30 days) and Intermediate-Term (1-6 months)	NOAEL = 7.5 mg/kg/day	UF_A=10X UF_H=10X	Occupational LOC for MOE = 100	Subchronic Gavage Toxicity Study in Dogs LOAEL = 15 mg/kg/day, based on axonal degenerative microscopic findings in the brain, spinal cord and sciatic nerve.
Inhalation Short-Term (1 - 30 days) and Intermediate-Term (1-6 months)	NOAEL = 7.5 mg/kg/day	UF_A=10X UF_H=10X	Occupational LOC for MOE = 100	Subchronic Gavage Toxicity Study in Dogs LOAEL = 15 mg/kg/day, based on axonal degenerative microscopic findings in the brain, spinal cord and sciatic nerve.
Cancer (oral, dermal, inhalation)	No Evidence of Carcinogenicity. Classified as "Not Likely to be Carcinogenic to Humans."			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern.

5.0 Dietary Exposure and Risk Assessment

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

The nature of the residue for indaziflam is considered to be adequately understood for registered and proposed crops and appropriate livestock (ruminant only).

Plant and livestock metabolism data were reviewed in greater detail in a recent chemistry summary document (D383415, E. Holman, 2/28/11). Radiolabeled metabolism studies are available for apple, sugarcane, grape, lactating goat, and rat. In plants, the metabolism of indaziflam is relatively uncomplicated. The only identified terminal residues in any of the plant studies were parent indaziflam and the FDAT metabolite. The metabolism data are sufficient to support the requested import tolerances; however, if uses in other crops are sought in the future,

additional studies depicting the nature of the residue may be necessary (e.g., root/tuber vegetables, small grain).

Based on the available information, indaziflam appears to undergo significant oxidative metabolism in ruminants. The metabolic pathways observed in these studies were similar, with the exception of the label specific diaminotriazine metabolite found in the triazine label study. The same was true for the [^{14}C]-AE 1170437 rat metabolism study (MRID 47443312, 47743418) with only minor differences (two additional metabolites, AE 1170437-4-hydroxy-hydroxymethyl and AE 1170437-3-keto-4-hydroxy, were found in the goat metabolism studies).

5.1.2 Summary of Environmental Degradation

Memo, K. Milians, Ph.D., Chemist, 8/17/2011, D388876

Field and laboratory data indicate that indaziflam and its degradates have a potential to leach to ground water, particularly FDAT. Indaziflam is classified as moderately mobile; however, transformation products of indaziflam are mobile to highly mobile and were detected in field studies at depth. Further, data show that indaziflam is persistent in anaerobic soil and anaerobic aquatic systems. There are no data available on the anaerobic degradation of the transformation products of indaziflam. Key lines of evidence show that residues of indaziflam, and degradate products (e.g., FDAT) are a concern for exposure via ground water. A prospective ground water study could help reduce the uncertainty regarding the exposure via ground water.

5.1.3 Comparison of Metabolic Pathways

The metabolism of indaziflam is complex, with a few major metabolites (fluoroethyl diaminotriazine = FDAT, and indaziflam carboxylic acid) found in plants, goat, rat, soil and water and numerous minor metabolites.

The metabolism of indaziflam has been evaluated in the rat using indaziflam labeled with ^{14}C at either the indane or the triazine ring. Indaziflam is rapidly and completely absorbed. Radioactivity was rapidly excreted (approximately 90% of dose by 24 hrs postdosing). Metabolism was extensive with only 2-12% of the dose excreted in feces as unchanged parent, and occurred primarily via oxidative processes. The major metabolite in the rat was the carboxylic acid metabolite of indaziflam, which was largely excreted in the bile but also found in urine. Other compounds that were identified as major metabolites in combined excreta in one or more groups were 3-hydroxyindane acid, 3-hydroxyindane acid epimer, dihydroxy, hydroxy glucuronic acid, 3-ketoindane acid, and hydroxyethyl acid metabolites. The fluoroethyl diaminotriazine (FDAT) metabolite was identified at low levels (1.18 to 1.69% of administered dose) in the triazine-labeled groups.

5.1.4 Residues of Concern Summary and Rationale

D371659 – Report of the Residues of Concern Knowledgebase Subcommittee. G. Kramer. 18 February 2010

With the exception of FDAT and dihydroamino triazine, all of the major metabolites are

assumed to have comparable toxicity to the parent due to structural similarity (i.e., both rings intact). FDAT is not expected to be more toxic than the parent indaziflam based on FDAT's non-neurotoxic mode of action (E. Scollon, D371661, April 21, 2010). Therefore, the neurotoxic endpoints selected for this risk assessment will be protective of potential FDAT toxicity. Dihydroamino triazine (ROI1) is assumed to have comparable toxicity to FDAT.

Conclusions regarding residues of concern for metabolites in proposed crops and livestock are that while the residue profile in crops is comprised of indaziflam and FDAT being the only indentified compounds, in the goat indaziflam appears to undergo significant oxidative metabolism. There are a number of significant (> 10% TRR) metabolites, depending on the commodity (i.e., milk, liver, muscle, fat) being examined, with most consisting of some level of increased hydroxylation relative to the parent compound.

Several environmental degradates are of concern for drinking water risk assessment. Drinking water residues of concern for this purpose include triazine indanone, indaziflam carboxylic acid, FDAT, dihydroamino triazine, indaziflam hydroxyethyl, and indaziflam olefin.

The toxicological and residue chemistry databases for indaziflam have been examined to determine residue definitions for the purposes of setting tolerances and risk assessments. The residue definitions are summarized in **Table 5.1.4**.

Table 5.1.4. Compounds to be Included in the Risk Assessment and Tolerance Expression.

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression for Compliance Monitoring
Plants	Primary Crop	Indaziflam + Fluoroethyl Diaminotriazine (FDAT)	Indaziflam + FDAT
	Rotational Crop	Not applicable at this time (no data available)	Not applicable at this time (no data available)
Livestock	Ruminant	Indaziflam + FDAT + Indaziflam-3-ketohydroxymethyl + Indaziflam carboxylic acid + Indaziflam-3-hydroxyindane	Indaziflam + FDAT + Indaziflam-3-ketohydroxymethyl + Indaziflam carboxylic acid + Indaziflam-3-hydroxyindane*
	Poultry	Not applicable at this time** (no data available)	Not applicable at this time (no data available)
Drinking Water		Indaziflam + FDAT + Triazine indanone + Indaziflam carboxylic acid + Indaziflam hydroxyethyl + Indaziflam olefin	Not Applicable

Indaziflam = *N*-[(1*R*,2*S*)-2,3-dihydro-2,6-dimethyl-1*H*-inden-1-yl]-6-(1-fluoroethyl)-1,3,5-triazine-2,4-diamine (CAS)
FDAT = 6-[(1*R*)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine
Indaziflam carboxylic acid = (2*S*,3*R*)-3-[[4-amino-6-[(1*R*)-1-fluoroethyl]-1,3,5-triazin-2-yl]amino)-2,3-dihydro-2-methyl-1*H*-indene-5-carboxylic acid
Indaziflam-3-ketohydroxymethyl = (2*S*,3*R*)-3-[[4-amino-6-[(1*R*)-1-fluoroethyl]-1,3,5-triazin-2-yl]amino)-5-hydroxymethyl-2-methylindane-1-one
Indaziflam-3-hydroxyindane = (2*R*,3*R*)-3-({4-amino-6-[(1*R*)-1-fluoroethyl]-1,3,5-triazin-2-yl}amino)-2-methylindan-1-ol-5-carboxylic acid
Triazine indanone = *N*-[(1*R*,2*S*)-2,3-Dihydro-2,6-dimethyl-3-oxo-1*H*-inden-1-yl]-6-[(1*R*)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine
Indaziflam hydroxyethyl = 1-{4-Amino-6-[(1R,2S)-2,6-dimethyl-2,3-dihydro-1*H*-inden-1-ylamino]-1,3,5-triazin-2-yl}ethanol
Indaziflam olefin = *N*-[(1*R*,2*S*)-2,6-dimethyl-2,3-dihydro-1*H*-inden-1-yl]-6-vinyl-1,3,5-triazine-2,4-diamine

* tentative, these residues should be included in the feeding study (if required).
**None of the target crop commodities are used in poultry feeds to any significant degree.

5.2 Food Residue Profile

Memo, E. Holman, 09/26/2013, D408151

Acceptable crop field trial data are available to support import tolerances on banana, coffee, and palm oil, and to establish tolerances for residues in the associated commodities. No quantifiable residues were observed in/on all crop commodities. Due to the unquantifiable residues at each sampling interval, residue decline could not be evaluated; however, because no individual value approached the LOQ for either analyte in/on any sample, there was no evidence that residues increase over time. The available data are adequate for risk assessment and tolerance assessment. The results from these field trials are summarized in **Table 5.2**.

Because there are no processed commodities for bananas, processing studies were not required for this raw agricultural commodity (RAC). The coffee processing study demonstrated that residues of concern were below the limit of quantitation at exaggerated rates appropriate for waiving analysis of the processed foods and feeds (*i.e.*, residues were < LOQ at 5X exaggerated application rates). The submitted palm oil processing study is adequate, supporting a palm oil tolerance of 0.03 ppm.

The available storage stability data are adequate, and support the storage conditions and durations for samples from the submitted banana, coffee, and palm oil field trials, and the palm oil processing study.

Using information in the goat metabolism studies, residues of indaziflam (as defined by the livestock residue definition) are expected to be below the limit of quantitation of the livestock analytical method. Hence a 40 CFR 180.6(a)(3) situation (i.e., no reasonable expectation of finite residues) exists. Furthermore, none of the proposed import tolerances have associated livestock commodities. Neither feeding studies nor tolerances for livestock commodities are required at this time. Feeding studies and analytical methods may be required to support future uses of indaziflam that involve significant livestock feed items.

Table 5.2. Summary of Residue Data from Crop Field Trials with Indaziflam.											
Commodity	Total Applic. Rate (lb ai/A) [kg ai/ha]	PHI (days)	Analyte	Residue Levels[1] (ppm)							
				n	Sample Min.	Sample Max.	LAFT[2]	HAFT[2]	Median	Mean	Std. Dev.
Banana (proposed use = 0.079 lb ai/A total application rate, 0-day PHI)											
Banana whole fruit (bagged)	0.086-0.095 [0.096-0.107]	0	Indaziflam	14	<0.005	<0.005	<0.005	<0.005	0.005	0.005	N/A
			AE 1170437-diaminotriazine	14	<0.005	<0.005	<0.005	<0.005	0.005	0.005	N/A
			Combined	14	<0.010	<0.010	<0.010	<0.010	0.010	0.010	N/A
Banana whole fruit (unbagged)	0.086-0.095 [0.096-0.107]	0	Indaziflam	14	<0.005	<0.005	<0.005	<0.005	0.005	0.005	N/A
			AE 1170437-diaminotriazine	14	<0.005	<0.005	<0.005	<0.005	0.005	0.005	N/A
			Combined	14	<0.010	<0.010	<0.010	<0.010	0.010	0.010	N/A
Coffee (proposed use = 0.098 lb ai/A maximum total application rate, 19-20 day PHI)											
Coffee bean, green	0.087-0.099 [0.098-0.111]	18-20	Indaziflam	7	<0.005	<0.005	<0.005	<0.005	0.005	0.005	N/A
			AE 1170437-diaminotriazine	7	<0.005	<0.005	<0.005	<0.005	0.005	0.005	N/A
			Combined	7	<0.010	<0.010	<0.010	<0.010	0.010	0.010	N/A
Oil Palm Fruit (proposed use = 0.098 lb ai/A maximum total application rate, 0-30 day PHI)											
Oil palm fruit	0.067-0.072 [0.075-0.080]	0	Indaziflam	3	<0.005	<0.005	<0.005	<0.005	0.005	0.005	N/A
			AE 1170437-diaminotriazine	3	<0.005	<0.005	<0.005	<0.005	0.005	0.005	N/A
			Combined	3	<0.010	<0.010	<0.010	<0.010	0.010	0.010	N/A

[1] Except for sample min/max, values reflect per trial averages; n = no. of field trials. For calculation of median, mean, and standard deviation, the LOQ (0.005 ppm for each analyte and 0.010 ppm for combined residues) was used for results reported as nondetectable in Table 7. N/A = Not Applicable.
[2] LAFT = lowest average field trial; HAFT = highest average field trial.

5.3 Water Residue Profile

Tier 2 Drinking Water Exposure Assessment for the Section 3 New Chemical Registration of Indaziflam; R. Baris, D356141; February 2, 2010

Based on a review of the available environmental fate data, the ROCKS determined that the four major transformation products that maintain the dual ring structure of indaziflam should be included in the drinking water exposure assessment since they may be of toxicological concern (i.e., they are assumed to be of equal or lower toxicity to the parent in the absence of toxicological data). These transformation products include: triazine indanone, indaziflam-carboxylic acid, indaziflam-olefin, and indaziflam-hydroxyethyl. In order to account for residues of these transformation products, the Environmental Fate and Effects Division (EFED) calculated drinking water concentrations for total indaziflam residues which included indaziflam and similarly structured degradates. EFED also calculated separate concentration estimates for FDAT plus dihydroamino triazine (ROI1; a degradate of FDAT). Drinking water concentrations were based on the maximum seasonal application rate for citrus (0.134 lb ai/A), which is higher than the turf application rate (0.094 lb ai./A) and thus is protective of all other drinking water scenarios. As noted above, HED has included the residue estimates for FDAT and ROI1 directly in the indaziflam assessment due to the available toxicity data indicating the neurotoxic endpoints for indaziflam are protective of toxicity from these degradates. The drinking water

concentrations used to estimate exposure via drinking water have not changed since the last risk assessment, and are included in **Table 5.3**.

Table 5.3. Summary of Estimated Surface Water and Groundwater Concentrations for Indaziflam.

Exposure Duration	Indaziflam		FDAT + ROI1		Combined*	
	Surface, ppb [a]	Ground, ppb [b]	Surface, ppb [a]	Ground, ppb [b]	Surface, ppb	Ground, ppb
Acute	48	1.6	19	1.1	84	3.7
Chronic (non-cancer)	14	1.6	6	1.1	26	3.7

* Residue estimates for FDAT and ROI1 have been converted to indaziflam equivalents (molecular weight ratio = 301÷157 = 1.92) and included directly in the indaziflam concentration estimates.
[a] From the PRZM and EXAMS assuming a maximum seasonal use rate of 0.134 lb ai/A for citrus.
[b] From the SCI-GROW model assuming a maximum seasonal use rate of 0.134 lb ai/A for citrus.

5.4 Dietary Risk Assessment

Memo, E. Holman, 09/2013, D408152

5.4.1 Description of Residue Data Used in Dietary Assessment

For this analysis existing and recommended tolerance levels were used, as well as 100% CT assumptions for all commodities. DEEM (Version 7.81) default processing factors were used for most processed commodities that do not have individual tolerances, except in cases where available processing data indicate that no concentration of residues occurs in processed commodities. In these cases where no concentration occurred, the processing factor was reduced to 1.

HED has selected the most conservative drinking water residue estimates in order to be protective of all possible exposures through drinking water. The above residue estimates for FDAT and ROI1 were stoichiometrically converted to indaziflam equivalents and included directly in the indaziflam concentration estimates (Table 5.3). Thus, following this stoichiometric conversion, the combined maximum surface water concentration was 84 ppb for the acute analysis and 26 ppb for the chronic analysis. These values were used in the acute and chronic dietary analyses, respectively.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The acute and chronic dietary exposure assessments, based on food and drinking water, include the assumption of 100% CT for all existing and proposed uses.

5.4.3 Acute Dietary Risk Assessment

An unrefined acute dietary analysis for indaziflam was conducted using tolerance level residues and 100% CT for all existing and proposed primary crop import uses. The DEEM-FCID™ analyses estimate the dietary exposure of the U.S. population and various population subgroups. The results reported in Table 5.4.4 are for the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, females 13-49, adults 20-49, and adults 50-99 years. The acute results summarized in Table 5.4.4 are for the 95th percentile of exposure.

Based on highly conservative assumptions, acute dietary (food and water) risk estimates at the 95th percentile of exposure are less than or equal to 19% of the acute population-adjusted dose (aPAD) for all population subgroups. Generally, HED is concerned when risk estimates exceed 100% of the PAD; therefore, all acute dietary risk estimates are below HED's level of concern (LOC). The most highly exposed population subgroup is all infants <1 year old.

The results of the acute dietary exposure analysis are reported in the Summary **Table 5.4.4**.

5.4.4 Chronic Dietary Risk Assessment

An unrefined chronic dietary analysis for indaziflam was conducted using tolerance level residues and 100% CT for all existing and proposed primary crop import uses. Indaziflam chronic dietary (food + drinking water) exposure estimates using the DEEM-FCID™ software are below HED's level of concern for the U.S. population and each of the population subgroups. Chronic dietary exposure was 3% of the cPAD for the U.S. population. The chronic dietary exposure for the highest reported exposed population subgroup, Infants <1 year old, was 8% of the cPAD. The results of the analysis indicate that chronic risk from the dietary (food + drinking water) exposure to indaziflam will not exceed HED's LOC for the general U.S. population, nor any other population subgroups. Based on the very conservative assumptions used, actual dietary exposure to indaziflam from food and drinking water is expected to be significantly lower than the exposures presented in Table 5.4.4.

The results of the chronic dietary exposure analysis are reported in the Summary **Table 5.4.4**.

Table 5.4.4. Summary of Dietary Exposure and Risk for Indaziflam.[1]

	Acute Dietary (95th percentile)		Chronic Dietary		Cancer	
Population Subgroup*	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	0.004648	6	0.000586	3	N/A	N/A
All Infants (< 1 year old)	**0.014510**	**19**	**0.001545**	**8**		
Children 1-2 years old	0.007509	10	0.001014	5		
Children 3-5 years old	0.005873	8	0.000807	4		
Children 6-12 years old	0.004480	6	0.000540	3		
Youth 13-19 years old	0.003838	5	0.000425	2		
Adults 20-49 years old	0.004526	6	0.000568	3		
Adults 50+ years old	0.004056	5	0.000565	3		
Females 13-49 years old	0.004615	6	0.000567	3		

[1]The value for the highest exposed population in the acute and chronic risk assessment is bolded.

5.4.5 Cancer Dietary Risk Assessment

HED classified indaziflam as "not likely to be carcinogenetic to humans" and, therefore, cancer risk is not of concern for indaziflam.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Memo, Z. Figueroa 09/2013; D415431

There are no new indaziflam residential uses associated with this regulatory action. However, there are existing residential uses - home lawn/turf and gardens/trees uses – that have been reassessed to reflect updates to HED's 2012 Residential SOPs[2] along with policy changes for body weight assumptions. In order to incorporate residential exposure into the short-term aggregate risk assessment, a summary of the residential exposure and risk estimates resulting from the residential use of indaziflam is provided below.

6.1 Residential Handler Exposure

The existing residential uses include a liquid concentrate for use on home lawn/turf and gardens/trees (Reg. No. 72155-89) and a granule for use on home lawn/turf (Reg. No. 72155-91). The following use scenarios and sources of unit exposures were used to assess residential handler exposures:

- Mixing/Loading/Applying for Sprays Using Manually-pressurized Handwand,
- Mixing/Loading/Applying for Sprays with Backpack Sprayer,
- Mixing/Loading/Applying for Sprays with Hose-end Sprayer,
- Mixing/Loading/Applying for Granule with Rotary/push-type Spreader, and
- Mixing/Loading/Applying for Granule Belly Grinder.

HED's LOC is a MOE greater than or equal to 100 for residential exposure. Handler MOEs from either inhalation or dermal exposure were significantly greater than 100 (ranging from 13,000 to 71,000,000) and are not of concern. Although a point of departure from an oral study was used to assess the handler inhalation risks, the calculated MOEs are all ≥570,000, thus providing an ample margin of safety to account for any uncertainties in route-to-route extrapolation. Combined inhalation and dermal MOEs ranged from 12,000 to 440,000 and are also not of concern. Handler exposure and risk estimates are summarized in Table 6.1.

Table 6.1. Residential Handler Non-cancer Exposure and Risk Estimates for Existing Residential Uses of Indaziflam.

Scenario	Formulation	Equipment	Dose (mg/kg/day)		MOE		
			Dermal	Inhalation	Dermal	Inhalation	Combined
Lawns/Turf	Liquid	Manually-pressurized Handwand	0.00016	0.00000062	47,000	12,000,000	47,000
		Backpack	0.00033	0.0000048	23,000	1,600,000	23,000

[2] Available: http://www.epa.gov/pesticides/science/residential-exposure-sop.html

Table 6.1. Residential Handler Non-cancer Exposure and Risk Estimates for Existing Residential Uses of Indaziflam.							
Scenario	**Formulation**	**Equipment**	**Dose (mg/kg/day)**		**MOE**		
			Dermal	**Inhalation**	**Dermal**	**Inhalation**	**Combined**
		Hose-end Sprayer	0.00059	0.000013	13,000	570,000	12,000
	Granule	Rotary/push-type Spreader	0.00002	0.0000007	460,000	10,000,000	440,000
		Belly Grinder	0.00039	0.0000006	19,000	13,000,000	19,000
Gardens/Trees	Liquid	Manually-pressurized Handwand	0.00016	0.00000062	47,000	12,000,000	47,000
		Hose-end Sprayer	0.00032	0.00000011	23,000	71,000,000	23,000
		Backpack	0.00033	0.0000048	23,000	1,600,000	23,000

6.2 Dermal Post-application Exposure

An existing indaziflam TTR study ("*Determination of Transferable Residues from Turf*", D. Fisher, EPA MRID 47443316) was used to assess post-application exposures from treated turf. The study was first reviewed by HED in 2010 (M. Collantes; D372538; 04/21/2010). Based on current practices and updated policies, HED assumed first-order dissipation kinetics to generate dissipation curves for indaziflam. HED conducted linear regression analyses for each state evaluated in the TTR study using the natural logarithm of the individual turf residue values collected immediately after the application through the last day of sampling. Based on linear regression of the natural log transformed data, the calculated half-lives for indaziflam dislodged from treated turf were 1.2 days ($R^2 = 0.848$) for the Florida site, 9.6 days ($R^2 = 0.710$) for the Kansas site, and 2.6 days ($R^2 = 0.846$) for the California site. The predicted day 0 residue value of 0.019 ug/cm^2 from the Florida site (reflecting an adjustment for the maximum application rate of 0.096 lb ai/A) was used in this assessment to estimate residential post-application exposure and risk. A complete summary of the study is presented in Memo, Z. Figueroa 09/26/2013; D415431.

For post-application exposures from treated turf, both registered formulations (liquid vs. granular) were assessed; however, only the exposure scenarios with the highest risk estimates were presented below. Risks from liquid spray applications are considered protective of granule formulation uses which would result in lower exposures. Since there is an acute dietary endpoint, a post-application episodic incidental ingestion of granules/pellets assessment for children was also conducted.

Table 6.2 summarizes the post-application risk estimates for the existing residential uses of indaziflam. No risks of concern were identified.

Table 6.2. Post-application Non-cancer Exposure and Risk Estimates for Existing Residential Uses of Indaziflam.							
Use/Target	**Lifestage**	**Post-application Exposure Scenario**		**Dose (mg/kg/day)**	**MOE**	**Combined Routes (X indicates included in Combined MOE)**	**Combined MOE**
Turf (Spray Application)[1]	Adult	Dermal	High-contact (playing)	0.00468	1,600	--	NA
			Mowing	0.00010	77,000	--	
			Golfing	0.00037	20,000	--	
	Child 11<16 yrs	Dermal	Mowing	0.00011	68,000		NA
			Golfing	0.00043	18,000	--	

Table 6.2. Post-application Non-cancer Exposure and Risk Estimates for Existing Residential Uses of Indaziflam.						
Use/Target	**Lifestage**	**Post-application Exposure Scenario**	**Dose (mg/kg/day)**	**MOE**	**Combined Routes (X indicates included in Combined MOE)**	**Combined MOE**
	Child 6<11 yrs	Dermal Golfing	0.00050	15,000	--	NA
	Child 1<2 yrs	Dermal (High-contact; playing)	0.00927	810	X	630
		Hand to Mouth	0.00260	2,900	X	
		Object to Mouth	0.00008	95,000	--	
		Incidental Soil Ingestion	0.0000032	2,300,000	--	
Turf (Granules)	Child 1<2 yrs	Incidental Ingestion of Granules/Pellets	0.01	550	--	NA
Gardens/Trees	Adult	Dermal	0.00459	1,700	--	NA
	Child 6<11 yrs	Dermal	0.00308	2,400	--	NA

[1] Risk estimates are based on the predicted day-of-application residue value from a submitted turf transferable residue study (MRID 47443316). Risks from liquid spray applications are presented above and are considered health-protective of granule formulation uses for the following reasons: 1) the AR for the liquid formulation is higher than the AR for the granular formulation, therefore, the liquid TTR data is a conservative representation of granular TTR data (with a lower AR); and 2) granular formulations have lower transferability when compare to liquid formulations.

6.3 Residential Bystander Post-Application Inhalation Exposure

Based on the Agency's current practices, a quantitative post-application inhalation exposure assessment was not performed at this time for the agricultural indaziflam uses primarily because of the low acute inhalation toxicity (Toxicity Category IV) and low vapor pressure (5.1×10^{-10} mmHg at 25°). However, volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[3]. The Agency is in the process of evaluating the SAP report and may, as appropriate, develop policies and procedures to identify the need for and, subsequently, the way to incorporate post-application inhalation exposure into the Agency's risk assessments. If new policies or procedures are developed, the Agency may revisit the need for a quantitative post-application inhalation exposure assessment for the existing uses of indaziflam.

6.5 Spray Drift

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast) employed for indaziflam. The Agency has been working with the Spray Drift Task Force (a task force composed of various registrants which was developed as a result of a Data Call-In issued by EPA), EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the Agency's Spray Drift website for more information). The Agency is also taking means to qualitatively and qualitatively address spray drift as a potential source of exposure in risk assessments for pesticides through existing programs such as Ag Drift and chemical specific properties of

[3] Available: http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html

pesticides. The potential for spray drift will be quantitatively evaluated for each pesticide during the Registration Review process which ensures that all uses for that pesticide will be considered concurrently.

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. In the case of indaziflam, acute and chronic aggregate risks result from exposure through food and water only. For short-term risk, adult and child post-application exposure was combined with background exposure from food and water.

7.1 Acute Aggregate Risk

Other than dietary exposure, there are no other sources of exposure that constitute an acute exposure scenario; therefore, acute aggregate exposure and risk estimates are equivalent to the acute dietary exposure and risk estimates summarized in Table 5.4.4 and are below HED's level of concern.

7.2 Short-Term Aggregate Risk

When estimating adult residential exposure, HED does not generally combine handler and dermal post-application exposure as it would result in an overestimate of exposure. For adults, the highest post-application exposure from high-contact (playing) on turf where indaziflam was applied (Table 6.2) was combined with the chronic dietary exposure from the mostly highly exposed adult (General U.S. Population) sub-population, to determine aggregate exposure and risk as shown in Table 7.2. For children, the highest post-application dermal and oral exposure risk estimates on turf associated with children 1-2 years old (Table 6.2) were combined with the chronic dietary exposure for the most highly exposed children's sub-population (Infants <1 year old), to determine aggregate exposure and risk as shown in Table 7.2. The aggregate MOEs are above the LOC of 100, and therefore aggregate risk estimates are not of concern.

Table 7.2. Short-Term Aggregate Risk Calculations for Indaziflam.

Population	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food and Water Exposure mg/kg/day	Residential Exposure mg/kg/day[3]	Total Exposure mg/kg/day[4]	Aggregate MOE (food, water, and residential)[5]
Adult (Post-application)	7.5	100	0.075	0.000586	0.00468	0.005266	1400
Child (Post-application)	7.5	100	0.075	0.001545	0.01187	0.013415	560

[1] The LOC is based on the standard inter- and intra- species uncertainty factors totaling 100. The FQPA Safety Factor has been reduced to 1X.

[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC.
[3] Residential Exposure (Adult Post-application) = Turf High-contact (Playing, Table 6.2). Residential Exposure (Child Post-Application) = Combined Dermal and Oral Exposure from Turf Spray Application for Child 1<2 Years Old.
[4] Total Exposure = (Avg. Food & Water Exposure + Residential Exposure).
[5] Aggregate MOE = [NOAEL 7.5mg/kg/day/Total Exposure mg/kg/day].

7.3 Chronic Aggregate Risk

Chronic aggregate risk is equivalent to chronic dietary exposure and risk, which is not of concern. Refer to Section 5.4.4.

8.0 Cumulative Exposure/Risk Characterization

Several triazine herbicides were determined to have a common mechanism of toxicity based on their ability to disrupt the hypothalamic-pituitary-gonadal axis (US EPA, 2002). The triazine common mechanism group (TCMG) includes atrazine, simazine, propazine, and the metabolites desethyl-s-atrazine (DEA), deisopropyl-s-atrazine (DIA), and diaminochlorotriazine (DACT). Indaziflam and its metabolite FDAT were considered for incorporation into the TCMG by the HED ToxSAC committee based on structure; indaziflam, FDAT, and the TCMG members contain a common triazine moiety (E. Scollon, D371661, April 21, 2010). However, HED determined that it would not be appropriate to include indaziflam and FDAT in the TCMG for the following reasons: 1) The structures of indaziflam and FDAT are unique in that they contain a fluoroethyl group at the 2-position of the triazine ring; whereas, the TCMG members contain a chlorine substituent at the 2-position of the triazine ring and; 2) Indaziflam and FDAT do not elicit the same toxicological responses shared by the TCMG members. The TCMG members cause an increase in mammary gland tumors in rats and multiple developmental effects such as attenuation of the luteinizing hormone surge, altered pregnancy outcome, and delayed preputial separation. None of these effects were observed in the carcinogenicity or developmental guideline studies for indaziflam. Delayed maturation was observed in the rat reproduction study, however, the effect occurred at the highest dose and was attributed to significant clinical toxicity rather than a perturbation of the hypothalamic-pituitary-gonadal axis. In a non-guideline study, FDAT delayed vaginal potency in a dose dependent manner. However, none of the other characteristic developmental effects of the TCMG members were observed.

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for indaziflam or its metabolite FDAT and any other substances, and indaziflam does not appear to produce a toxic metabolite produced by other substances. Therefore, for the purposes of this risk assessment, EPA has not assumed that indaziflam or its metabolite FDAT has a common mechanism of toxicity with other substances.

For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Characterization

As there are no occupational exposures associated with the proposed import tolerances, a new occupational exposure assessment was not conducted for this import tolerance petition on banana, coffee, and palm oil. Occupational exposures from the existing registered uses of indaziflam were previously assessed and no risks of concern were identified.

10.0 References

Indaziflam: Occupational/Residential Exposure Assessment for Use of Indaziflam on Turf, Golf Courses, Sod Farms, Christmas Tree Farms, Non-Crop Areas and Forestry (M.Collantes, D372538; April 2010)

Indaziflam: Revised Residential Exposure Assessment to Support Import Tolerances for Banana, Coffee, and Palm Oil. (Z. Figueroa, D415431, 09/26/2013)

Tier 2 Drinking Water Assessment for the Section 3 New Chemical Registration of Indaziflam; Rueben Baris; D356141; and D367447; February 2, 2010.

Indaziflam. Petition for the Establishment of Import Tolerance Use on Banana, Coffee, and Palm Oil. Summary of Analytical Chemistry and Residue Data. (E. Holman, D408151; 09/26/2013)

Indaziflam: Acute and Chronic Aggregate Dietary Exposure (Food and Drinking Water) and Risk Assessment for the Section 3 Registration (Import Use Only) on Banana, Coffee, and Palm Oil. (E. Holman, D408152; 09/26/2013)

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The toxicology data requirements (40 CFR 158.340) for indaziflam food and turf uses are presented below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test	Technical Indaziflam	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21/28-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	-
870.3465 90-Day Inhalation	no	-
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes[1]
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5550 Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotoxicity (hen)	no	--
870.6100b 90-Day Neurotoxicity (hen)	no	--
870.6200a Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b 90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300 Developmental Neurotoxicity	yes	yes
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	yes	yes
870.7800 Immunotoxicity	yes	yes
Special Studies for Ocular Effects		
Acute Oral (rat)	no	--
Subchronic Oral (rat)	no	--
Six-month Oral (dog)	no	--

1 Satisfied by 870.4300.

A.2 Toxicity Profiles

Table A.2.1 Acute Toxicity Profile - Indaziflam technical

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral - rat	47443281	LD_{50} > 2000 mg/kg (both sexes)	III
870.1200	Acute dermal - rabbit	47443282	LD_{50} > 2000 mg/kg (both sexes)	III
870.1300	Acute inhalation - rat	47443283	LC_{50} > 2.3 mg/L (both sexes)	IV
870.2400	Acute eye irritation - rabbit	47443284	Non-irritant	IV
870.2500	Acute dermal irritation - rabbit	47443285	Non-irritant	IV
870.2600	Skin sensitization - guinea pig	47443286	Not a sensitizer (Buehler method)	N/A

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Indaziflam technical			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (rat)	47443287 (2005) Acceptable/Guideline 0, 200, 5000 or 10,000 ppm in diet for 13 weeks M: 0, 14, 338 or 689 mg/kg/day F: 0, 16, 410 or 806 mg/kg/day 98.7% a.i.	NOAEL = 14/410 mg/kg/day M/F LOAEL = 338/806 mg/kg/day M/F, based on: in males at 338 mg/kg/day, increased TSH at Week 3 and diffuse thyroid follicular cell hypertrophy at Week 13; in females at 806 mg/kg/day, mortality (one female, sacrificed *in extremis* with clinical signs, decreased motor activity and gastric red foci), marginally decreased body weights and decreased food consumption.
870.3100	90-Day oral toxicity (mouse)	47443288 (2005) Acceptable/Guideline 0, 100, 500 or 1200 ppm in diet for 13 weeks M: 0, 19, 91 or 218 mg/kg/day; F: 0, 23, 118 or 256 mg/kg/day 96.5% a.i.	NOAEL = 91/118 mg/kg/day M/F LOAEL = 218/256 mg/kg/day M/F, based on increased mortality and wasted appearance (females), hunched posture in males and females, decreased body weight/weight gain and food consumption in males and females.
870.3150	90-Day oral toxicity (dog)	47443289 (2008) Acceptable/Guideline 0, 7.5, 15 or 30 mg/kg/day by gavage 94.5-99.4% a.i.	NOAEL = 7.5 mg/kg/day M/F LOAEL = 15 mg/kg/day, based on axonal degeneration in the brain, spinal cord and sciatic nerve in males and females. At 30 mg/kg/day, 3 animals were sacrificed with seizures by Day 30; all remaining group animals were sacrificed on Day 36. Decreased body weight gain and neuropathology were observed.
870.3200	28-Day dermal toxicity (rat)	47443290 (2006) Acceptable/Guideline 0, 40, 200 or 1000 mg/kg/day applied to skin 5 days/week for 4 weeks (22/23 total applications in M/F) 90.32% a.i.	**Systemic** NOAEL = 1000 mg/kg/day LOAEL = not determined (>1000 mg/kg/day) **Local dermal** NOAEL = 1000 mg/kg/day LOAEL = not determined (>1000 mg/kg/day). Some indication of local dermal irritation was observed at all doses but the findings were transient and observed only in females, and therefore were not considered adverse.
870.3700a	Prenatal developmental in (rat)	47443291 (2006) Acceptable/Guideline 0, 10, 25 or 200 mg/kg/day by gavage in 0.5% aqueous methylcellulose, GD 6 through 20	**Maternal** NOAEL = 25 mg/kg/day LOAEL = 200 mg/kg/day based on decreased body weight gain and food consumption. **Developmental** NOAEL = 25 mg/kg/day LOAEL = 200 mg/kg/day based on decreased fetal body weights.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Indaziflam technical			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
		94.5% a.i.	
870.3700b	Prenatal developmental in (rabbit)	47443292 (2008) Acceptable/Guideline 0, 10, 25 or 60 mg/kg/day by gavage in 0.5% aqueous methylcellulose, GD 6 through 28 93.14% a.i.	**Maternal** NOAEL = 25 mg/kg/day LOAEL = 60 mg/kg/day based on decreased maternal body weight gain and food consumption and macroscopic changes in the liver in one doe. **Developmental** NOAEL = 60 mg/kg/day LOAEL = not established (>60 mg/kg/day).
870.3800	Reproduction and fertility effects (rat)	47443293 (2008) Acceptable/Guideline 0, 150, 1000 or 8000 ppm in the diet; F1 high dose reduced to 4000 ppm at 5-17 days' postweaning Average P/F_1 consumption (note: high dose not averaged due to F1 dose reduction) M: 0, 10.4, 69.3 or 560.1 mg/kg/day (P males) and 317.6 mg/kg/day (F_1 males, due to reduction in dietary dose) F: 0, 12.9, 85.2 or 656.2 mg/kg/day (P females) and 355.2 mg/kg/day (F_1 females, due to reduction in dietary dose) 93.14-94.5% a.i.	**Parental** NOAEL = 69.3/85.2 mg/kg/day M/F LOAEL = 560.1/656.2 mg/kg/day M/F, based on coarse tremors in females from Weeks 6-17 and in gestation and lactation, decreased body weight/weight gain and food consumption and renal toxicity (tubular degeneration/ regeneration and increased weight) in males. **Offspring** NOAEL = 69.3/85.2 mg/kg/day M/F LOAEL = 317.6/355.2 mg/kg/day M/F, based on clinical signs (perianal, urine or nasal staining, diarrhea or soft stool, distended abdomen, weakness, tremors, myoclonus, increased activity and reactivity) and decreased pup body weights throughout postnatal period. **Reproductive** NOAEL = 69.3/85.2 mg/kg/day M/F (based on F1 intakes) LOAEL = 317.6/355.2 mg/kg/day M/F, based on delayed sexual maturation in males and females (% pups reaching criterion unaffected).
870.4100a	Chronic toxicity (rat)	47443296 (2007) Acceptable/Guideline 0, 300, 3000 or 10,000 ppm in the diet (6000 in females after Day 280) equivalent to average daily intake of M: 0, 14, 136 or 474 mg/kg/day; F: 0, 19, 185 or 589 mg/kg/day 93.14% a.i.	NOAEL = 19 mg/kg/day F, 136 mg/kg/day M; LOAEL = 185 mg/kg/day F, based on increased mortality, clinical signs of toxicity, mydriasis and absence of papillary reflex; 474 mg/kg/day M, based on decreased body weight/weight gain and food consumption.
870.4100b	Chronic toxicity (dog)	47443294 (2008; main study);47443295 (2007; dietary stability)	NOAEL = 2.0 mg/kg/day LOAEL = 6/7 mg/kg/day M/F, based on axonal degeneration of nerve fibers in the brain, spinal

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Indaziflam technical			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
		Acceptable/Guideline 0, 60, 225 or 450 ppm in the diet M: 0, 2, 6 or 12 mg/kg/day; F: 0, 2, 7 or 11 mg/kg/day 93.16% a.i.	cord and sciatic nerve in males and females. Marginal body weight decreases early in study seen at 12/11 mg/kg/day M/F.
870.4200a	Carcinogenicity (rat)	See 870.4300, below	
870.4200b	Carcinogenicity (mouse)	47743416 (2008) Acceptable/Guideline 0, 50, 250 or 1000 ppm in diet M: 0, 6.8, 34 or 142 mg/kg/day; F: 0, 8.4, 42 or 168 mg/kg/day 93.14% a.i.	NOAEL = 34/42 mg/kg/day M/F LOAEL = 142/168 mg/kg/day M/F, based on decreased body weight/weight gain and food consumption, M/F; renal and hepatotoxicity in males; stomach and ovarian toxicity in females. **No evidence of carcinogenicity**
870.4300	Combined carcinogenicity/ chronic toxicity (rat)	47743417 (2009) Acceptable/Guideline 0, 300, 3000 or 10,000 ppm in the diet M: 0, 12, 118 or 414 mg/kg/day; F: 0, 17, 167 or 452 mg/kg/day 93.14% a.i.	NOAEL = 12/17 mg/kg/day M/F LOAEL = 118/167 mg/kg/day M/F, based on decreased body weight/weight gain, signs of neurotoxicity (various symptoms, including dilated pupils, tremors, limb/movement effects, reduced activity/alertness) and renal toxicity in females, liver toxicity in males and females and atrophic seminal vesicles and increased TSH (Week 3 only) and thyroid colloid alteration in males. Thyroid alterations in males appeared to be secondary to liver effects. Decreased survival was observed at 452 mg/kg/day in females and both males and females showed more pronounced clinical signs of toxicity. **No evidence of carcinogenicity**
Gene Mutation 870.5100	Bacterial reverse gene mutation assay (*S. typhimurium*)	47443297 (2006) Acceptable/Guideline 0, 16, 50, 158, 500, 1581 or 5000 µg/plate in presence or absence of S9 activation. Trial 1 – plate incorporation method and Trial 2, pre-incubation method	**Negative** +/-S9 activation in *S. typhimurium* strains TA98, TA100, TA 102, TA1535, TA1537 for increased frequency of revertant colonies up to cytotoxic (500 µg/plate) and precipitating concentrations (5000 µg/plate).

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Indaziflam technical			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
		90.32% a.i.	
Gene Mutation 870.5100	Bacterial reverse gene mutation assay (*S. typhimurium*)	47443301 (2007) Acceptable/Guideline Trial 1: 0, 15, 50, 158, 500, 1502 or 5000 µg/plate in the presence or absence of S9 activation, plate-incorporation method Trial 2: 0, 100, 200, 400, 800, 1600 or 3200 µg/plate in the presence or absence of S9 activation, pre-incubation method 95.7% a.i.	**Negative** +/-S9 activation in *S. typhimurium* strains TA98, TA100, TA102, TA1535, TA1537 for increased frequency of revertant colonies up to cytotoxic (≥800 µg/plate) and precipitating (3200 µg/plate) concentrations.
Gene Mutation 870.5300	Mammalian cell *in vitro* forward gene mutation (cultured V79 cells, HGPRT locus)	47443302 (2006) Acceptable/Guideline 0, 10, 100 or 1000 µg/mL in presence or absence of S9 activation 90.32% a.i.	**Negative** for increased frequency of mutation in CHO cells (not cytotoxic).
Cytogenetics 870.5375	Mammalian *in vitro* cytogenetic assay (Chinese hamster V79 lung cells)	47443305 (2006) Acceptable/Guideline 4 hr exposure, 14 hr recovery period: 0, 15, 30, 60, 90 or 120 µg/mL in the absence of S9 activation; 0, 50, 100, 160, 200 and 240 µg/mL in the presence of S9 activation. 4 hr exposure, 26 hr recovery period: 0, 60, 90 and 120 in the absence of S9 activation; 0, 160, 200 and 240 µg/mL 18 hr exposure, no recovery period in the absence of S9 activation: 0, 4, 8, 16, 20 and 24 µg/mL 90.32% a.i.	**Negative** for induction of chromosomal aberrations above background in the presence or absence of S9 metabolic activation. Tested up to the limit of solubility (160 µg/mL, -S9)
Cytogenetics 870.5395	Mammalian *in vivo* micronucleus	47443308 (2006)	**Negative** for induction of increased frequency of micronucleated polychromatic erythrocytes

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Indaziflam technical			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
	assay (mouse)	Acceptable/Guideline Two doses of 0, 10, 20 or 40 mg/kg by IP injection in 0.5% aqueous Cremaphor vehicle administered 24 hrs apart; harvested 24 hrs after second dose 90.32% a.i.	in bone marrow at any treatment time.
870.6200a	Acute neurotoxicity screening battery (rat)	47443310 (2008) Acceptable/Guideline 0, 50, 100 or 2000 mg/kg by gavage in corn oil. Time of peak effect estimated at 50 min postdosing. 93.14% a.i.	NOAEL = 50 mg/kg LOAEL = 100 mg/kg based on decreased motor and locomotor activity in females (threshold effect level).
870.6200b	Subchronic neurotoxicity screening battery (rat)	47443309 (2008) Acceptable/Guideline 0, 200, 4000 or 8000/10,000 ppm (M/F) equivalent to average daily intake in the diet of M: 0, 12.2, 243.6 or 585.7 mg/kg/day F: 0, 15.1, 306.9 or 580.9 mg/kg/day 93.14% a.i.	NOAEL = 243.6/306.9 mg/kg/day M/F LOAEL = 585.7/580.9 mg/kg/day M/F, based on decreased total session motor and locomotor activity in females, an increased incidence of minimal spinal nerve degeneration, clinical signs/FOB effects in males and females (tremors, repetitive chewing motion and perianal and lacrimal staining), decreased body weights (females) and cumulative body weight gain in males and females.
870.6300	Developmental neurotoxicity (rat)	47443311 (2008) Acceptable/Nonguideline 0, 150, 1000 or 7000 ppm in the diet (high dose reduced to 4000 ppm on LD4) equivalent to average daily intake in the diet of 0, 13, 83.8 or 432 mg/kg/day 93.14% a.i.	**Maternal** NOAEL = 83.8 mg/kg/day LOAEL = 432 mg/kg/day, based on clinical signs at daily observation and FOB assessment (coarse tremors, dilated pupils and dilated pupils unresponsive to penlight, nasal staining, repetitive chewing movements), decreased body weights/weight gain and reduced number of litters (-17%). **Offspring** NOAEL = 83.8 mg/kg/day LOAEL = 432 mg/kg/day, based on decreased body weight through PND 21 in males and females. Males postweaning had slightly decreased body weights. Decreased motor activity (-29%) on PND 21 in males was considered treatment-related, but was not seen at other measurement times nor in females.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Indaziflam technical			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485	Metabolism and pharmacokinetics (rat) – tier 1	47443312 (2008) Acceptable/Guideline Male rats given single gavage dose of either ^{14}C-indane labeled or -triazine labeled indaziflam at 11.5-14.98 mg/kg. Mass balance groups – excreta collected for 3 days postdosing. Bile-duct cannulated groups – bile and excreta collected for 2 days postdosing. 99-100% radiochemical purity	Absorption was complete (>90% bioavailability) and rapid, with radioactivity found in bile by 1 hr postdosing and most radioactivity (generally around 90%) excreted by 24 hrs. Tissue levels of radioactivity were low (0.2% of administered dose by 3 days) with highest levels observed in the GIT, liver, kidney, skin and thyroid. In the bile duct-cannulated animals, tissue levels were about 2-4 times greater in the triazine-labeled group than the indane-labeled group but levels in other groups were similar. Excretion was largely fecal (62-70%), with significant biliary excretion observed. CO_2 exhalation was negligible. Parent compound was identified at between 2-16% of dose in urine and feces. Major routes of metabolism were oxidative pathways; glucuronide conjugation also observed. Major metabolite was carboxylic acid, found in urine, bile and feces. Numerous other metabolites identified or characterized; profile varied among dose groups. Other metabolites identified at low levels included the 3-hydroxyindane acid epimer, diaminotriazine and 3-ketohydroxymethyl metabolites.
870.7485	Metabolism and pharmacokinetics (rat) – tier 2	47743418 (2009) Acceptable/Guideline Single gavage doses as follows: (1) low dose mass balance studies in females given ^{14}C-indane-labelled indaziflam at 4.8 mg/kg or ^{14}-triazine-labelled indaziflam at 8.8 mg/kg; (2) high dose mass balance studies in males given ^{14}C-indane-labelled indaziflam at 559 mg/kg or ^{14}-triazine-labelled indaziflam at 723 mg/kg; (3) plasma pharmacokinetic experiments with indane-label at 2.9 mg/kg (females) or 13.7 mg/kg (males) or triazine-label at 13.2 mg/kg (females) or 16.3 mg/kg (males). Radiochemical purity	Absorption was rapid (radioactivity detected in blood by 5 minutes and peak blood concentrations observed between 40-60-minutes postdosing; rapidly decreasing thereafter) Females showed slightly higher absorption than males. Excretion was rapid (>87% by 24 hrs) and was equally distributed between urine and feces in females but was greater in feces in males (10:1). CO_2 excretion was negligible. Radioactivity was not retained at significant levels in tissues; the GIT, liver and skin showed the highest residues. The carboxylic acid metabolite was the major metabolite in both high dose males and low dose females, which was found in urine and feces. Additional metabolites present at >5% of dose included 3-hydroxyindane acid metabolite in low dose females, dihydroxy metabolite in low dose females and hydroxyethyl acid metabolite in the high dose males (indane-label).

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Indaziflam technical			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
		99%	
870.7600	Dermal absorption, *in vivo* (rat)	47743420 (2008) Acceptable/Guideline 0.5, 2 or 5000 µg ai/ cm^2 on 12 cm^2 skin for 8 hrs to male rats; absorption evaluated after 8, 24, 72 and 168 hr postdosing Radiochemical purity >98%	Absorption was inversely proportional to dose, indicating saturation of skin penetration with increasing dose. Between 0.4-20.4% of the applied dose was recovered in combined residual carcass, excreta, blood and non-treated skin. Based on decreased radioactivity at the application site, the most conservative value for risk assessment is a dermal absorption of 42.7% observed at 0.5 µg ai/ cm^2 at 8 hr postapplication.
870.7800	Immunotoxicity - rat	47443313 (2008) Acceptable/Guideline 0, 300, 3000 or 6000 (females) or 10,000/6000 (males) ppm in the diet equivalent to average daily intake in the diet of M: 0, 27.7, 258 or 528 mg/kg/day F; 0, 31, 334.2 or 737.9 mg/kg/day 93.12% a.i.	**Systemic** NOAEL = 258.8/334.2 mg/kg/day M/F LOAEL = 528/737.9 mg/kg/day M/F, based on mortality (one male sacrificed *in extremis)*, clinical signs of toxicity in males and females (including tremor, abnormal gait, pallor, hunched back), decreased food and water consumption in males and decreased body weight/weight gain in males and females. **Immunotoxicity** NOAEL = 528/737.9 mg/kg/day M/F LOAEL = not established (>528/737.9 mg/kg/day M/F)
Non-guideline	*In vitro* dermal absorption – rat and human skin	47743419 (2007) Acceptable/Nonguideline Application of a 10µL/ volume of concentrated 500 mg/mL formulation and representative spray dilutions of 0.5, 0.2 or 1.0 mg/mL to excised human and rat dermatomed skin. Exposure duration was 24 hr. Radiochemical purity >98%	Total absorbed dose decreased with increasing concentration, indicating saturation of skin penetration with increasing dose. Rat skin was 3.8 to 10.7 times more permeable than human skin over 24 hr at the concentrations tested.

A.3 Hazard Identification and Endpoint Selection

A.3.1 Acute Reference Dose (aRfD) - General Population including females age 13-49

Study Selected: Subchronic gavage toxicity study in dogs.

MRID No: 47443289

EXECUTIVE SUMMARY: In a subchronic oral toxicity study in dogs (MRID 47443289), BCS-AA10717 (AE 1170437, indaziflam tech.; 94.5-99.4% a.i.; Batch Nos. EFIM000511 and NLL 7482-5A, respectively) in 0.5% aqueous methyl cellulose was administered via daily oral gavage in a dose volume of 1 or 5 mL/kg to four beagle dogs/sex/dose group at doses of 0, 7.5 15 or 30 mg/kg/day for at least 90 days. On Day 23, dosing was halted in the 30 mg/kg/day group due to a seizure in one female, and resumed on Day 25 at 15 mg/kg given twice daily approximately 7-8 hours apart. The 30 mg/kg/day animals were terminated on Day 36 due to seizures.

No adverse, treatment-related effects were observed on food consumption, ophthalmoscopic examinations, hematology, clinical chemistry, urinalysis, organ weights, or gross pathology.

At 15 mg/kg/day, treatment-related histopathological findings were observed in the nervous system (brain, spinal cord, sciatic nerve). In the males, slight multifocal axonal degeneration of the sciatic nerve was observed in 1/4 dogs, and minimal multifocal axonal degeneration of the spinal cord was noted in 1/4 dogs, both compared to 0 controls. In the females, minimal multifocal axonal degeneration was observed in the brain in 1/4 dogs, minimal focal/multifocal axonal degeneration was observed in the sciatic nerve in 2/4 dogs, and minimal to moderate multifocal axonal degeneration of the spinal cord was noted in 2/4 dogs, all compared to 0 controls. No clinical signs of toxicity were observed.

At 30 mg/kg/day, three dogs presented with seizures on Days 15, 22, and 35, respectively, and were killed on the day the seizures were observed. Treatment-related clinical findings observed in these dogs included the following: seizures in the male; aggressive, tremors, ataxia (unsteady), labored breathing, pupil no reaction to light or sluggish, decreased activity, circling, seizures, and sores due to seizures in the females. Due to the seizures, dosing of the 30 mg/kg/day group was halted on Day 35, and the surviving dogs of this group were euthanized on Day 36 for humane reasons. Additionally at this dose, male dogs displayed decreased body weight gains for Days 0-35 compared to all other groups, while females lost weight during this period compared to the other groups. Treatment-related histopathologic findings were observed in the nervous system (brain, spinal cord and sciatic nerve). In the males, slight multifocal axonal degeneration of the sciatic nerve was observed in 1/4 dogs, and minimal to moderate multifocal axonal degeneration of the spinal cord was noted in 4/4 dogs (mean severity 1.8), both compared to 0 controls. In the females, minimal to slight multifocal axonal degeneration was observed in the brain in 2/4 dogs, minimal to slight focal/multifocal axonal degeneration was observed in the sciatic nerve in 2/4 dogs, and minimal to moderate multifocal axonal degeneration of the spinal cord was noted in 4/4 dogs (mean severity 2.3), all compared to 0 controls. Although the dogs affected by seizures all showed neurohistopathology, there did not appear to be an association with the severity of these findings.

The LOAEL is 15 mg/kg/day, based on axonal degeneration in the nervous system of both sexes. The NOAEL is 7.5 mg/kg/day.

This study is classified **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3150; OECD 409) for a subchronic oral toxicity study in dogs.

Dose and Endpoint for Risk Assessment: NOAEL= 7.5 mg/kg/day

Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

$$\textbf{Acute RfD} = \frac{7.5 mg/kg/day}{100\,(UF)} = \textbf{0.075 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor:
The results of the subchronic toxicity study in dogs were used to select the dose and endpoints for establishing the aRfD of 0.075 mg/kg for the general population based on axonal nerve fiber degeneration seen at the LOAEL of 15 mg/kg. The nerve fiber degeneration is considered a potential single-dose effect because similar nerve fiber degeneration was seen in the acute neurotoxicity study in rats following a single dose, the majority (~90%) of indaziflam is excreted within 24 hours in rat metabolism studies, the timing of the observation of seizures (occurring on day 0 at 50 mg/kg/day in 2 dogs in a range finding subchronic dog study), and clinical signs of neurotoxicity in the subchronic dog study were observed ~2 hours following dosing of indaziflam. While there was an acute neurotoxicity study in rats available, this study had a much higher LOAEL of 586/581 mg/kg (M/F). Based on the 39-fold increased sensitivity of the dog compared to the rat for subchronic exposure, the acute neurotoxicity study was determined to likely be under protective of potential neurotoxicity. The 90-day range-finding study (with seizures occurring at day 0 at 50 mg/kg/day) with a NOAEL of 15 mg/kg/day, however, was not considered appropriate for acute endpoint and dose selection due to the limited number of dogs used (n=2/dose group) and because no neuropathology was conducted in that study. In combination with the potential of the effects observed in the subchronic toxicity study in dogs to be a single dose effect, the subchronic dog study was chosen in the absence of an acute study in dogs. The endpoint is protective of the decreases in maternal body weight gains seen within the first three days of exposure in the developmental rat (25/200 mg/kg/day, NOAEL/LOAEL) and rabbit (25/60 mg/kg/day, NOAEL/LOAEL) toxicity studies. The endpoint is also protective of potential developmental effects, based on the lack of observed increased pre- and/or postnatal susceptibility and higher LOAELs observed in developmental, reproductive, neurotoxicity, developmental neurotoxicity and immunotoxicity studies.

A.3.2 Chronic Reference Dose (cRfD)

Study Selected: Chronic dietary toxicity study in dogs.

MRID No: 47443294

EXECUTIVE SUMMARY: In a chronic oral toxicity study (MRID 47443294), BCS-AA10717 technical (AE 1170437; Indaziflam; 94.5% a.i.; Batch No. EFIM000511) was administered to four beagle dogs/sex/dose group in the diet at doses of 0, 60, 225 or 450 ppm

(equivalent to 0/0, 2/2, 6/7 or 12/11 mg/kg/day in males/females) for at least 12 months. In addition to evaluation of standard chronic toxicity study parameters, a neurological examination was performed monthly from months 7 through 11 and just prior to termination.

No adverse, treatment-related effects were observed on mortality, clinical signs of toxicity, neurological or ophthalmoscopic examinations, hematology, clinical chemistry, urinalysis, organ weights or gross pathology. One high dose male was sacrificed on Day 190 due to seizures that were not considered treatment-related: this animal had dilatation of the lateral ventricles and no seizures were observed in the subchronic dog study with bolus dosing at 15 mg/kg/day.

Although body weights of the 450 ppm group were not significantly different from controls, body weight gains (calculated by reviewers) were decreased by treatment in the early months of the study. Male dogs lost 1.7 g during Days 0-91 compared to a gain of 534.5 g in the controls, and female dogs body weight gains were decreased by 66% compared to controls during this period. Overall (Day 0-364) body weight gains were decreased by 12% in the males and by 21% in the females. Additionally at 450 ppm, decreased food consumption was generally observed in both males and females throughout the study (Days 1-368), resulting in an overall mean decrease of 20% in both sexes (calculated by reviewers). Although these decreases infrequently attained statistical significance, the magnitude was generally greater than 10%, and correlated with the decreased body weight gains observed in this group.

Treatment-related microscopic findings were primarily observed within the dorsal funiculi (primarily the funiculus cuneatus) of the spinal cord at 225 and 450 ppm. The lesion was characterized by axonal degeneration of individual nerve fibers, consisting of fragmented and lysed axonal fibers, sometimes associated with phagocytic macrophages forming a digestion chamber. Secondary subtle demyelination was also noted. At 225 ppm, multifocal axonal degeneration was observed in the spinal cord of 3/4 males (minimal) and 1/4 females (slight), both compared to 0 controls. At 450 ppm in the males: minimal axonal degeneration was observed in the brain of 1/4 dogs; minimal perivascular multifocal lymphocytic inflammation was noted in the brain of 1/4 dogs; minimal multifocal axonal degeneration of the sciatic nerve was observed in 1/4 dogs; and minimal to moderate multifocal axonal degeneration of the spinal cord was noted in 3/4 dogs, all compared to 0 controls. In the females, minimal axonal degeneration was observed in the brain of 1/4 dogs, minimal to moderate multifocal axonal degeneration of the spinal cord was observed in 4/4 dogs ($p \leq 0.05$), all compared to 0 controls and minimal multifocal axonal degeneration of the sciatic nerve was observed in 1/4 females.

The LOAEL is 225 ppm (equivalent to 6/7 mg/kg/day in males/females), based on microscopic lesions of the nervous system of both sexes as described above. The NOAEL is 60 ppm (equivalent to 2/2 mg/kg/day in males/females).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4100b; OECD 452) for a chronic oral toxicity study in dogs.

Dose and Endpoint for Risk Assessment: NOAEL= 2.0 mg/kg/day

Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

$$\textbf{Chronic RfD} = \frac{2.0 mg/kg/day}{100\,(UF)} = \textbf{0.02 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor:
The NOAEL selected for this risk assessment represents the lowest available NOAEL for effects of indaziflam following long-term dietary administration. The RfD is protective of potential developmental effects, based on the lack of observed increased pre- and/or postnatal susceptibility and significantly higher NOAELs observed in developmental, reproductive, neurotoxicity, developmental neurotoxicity and immunotoxicity studies.

A.3.3 Incidental Oral Exposure (Short- and Intermediate-Term)

Study Selected: Subchronic gavage toxicity study in dogs.

MRID No: 47443289

Dose and Endpoint for Risk Assessment: NOAEL= 7.5 mg/kg/day

Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

Comments about Study/Endpoint/Uncertainty Factors: The selected endpoint is the most sensitive NOAEL available from an oral study of appropriate exposure duration (90-days) for short-term (up to 30 days) and intermediate-term (up to 6 months) exposure via the oral route. The selected endpoint is protective of potential postnatal developmental toxicity, based on the lack of observed postnatal susceptibility and significantly higher NOAELs for postnatal toxicity in the developmental neurotoxicity and the two-generation reproductive toxicity studies.

A.3.4 Dermal Absorption

In addition to a 28-day study evaluating dermal toxicity in the rat, an *in vivo* dermal absorption study in the rat and *in vitro* dermal absorption studies in the rat and human were submitted. The data demonstrated an inverse relationship between dosing concentration and percent absorption. Based on *in vivo* dermal absorption observed in the rat and *in vitro* comparative rat:human absorption data, an estimated human dermal absorption factor (DAF) of 7.3% was obtained.

The human DAF was calculated as follows (all absorption values adjusted for recovery): (1) in the rat *in vivo* dermal absorption study, 27.39% of the applied dose was absorbed at 24 hrs postexposure (actual exposure time 8 hrs) using an application of 0.0005 mg/cm^2; (2) *in vitro* exposure of microtomed rat skin under the same exposure and assessment conditions gave a dermal absorption of 22.40%; (3) the ratio of the *in vitro* to the *in vivo* absorption is 0.82 (22.4/27.39) and therefore is close to 1, indicating that the *in vitro* data is predictive of *in vivo* absorption; (4) based on this ratio, a DAF for humans may be calculated using *in vitro* human dermal absorption (5.975%, adjusted for recovery) observed *in vitro* under the same exposure conditions. The DAF for humans is therefore 5.975%/0.82 = 7.3%.

A.3.5 Dermal Exposure (Short-and Intermediate-Term)

Study Selected: Subchronic gavage toxicity study in dogs.

MRID No: 47443289

Dose and Endpoint for Risk Assessment: NOAEL= 7.5 mg/kg/day

Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

Comments about Study/Endpoint/Uncertainty Factors: The selected endpoint is the most sensitive NOAEL available from a study of appropriate exposure duration (90 days) for short- and intermediate-term exposure. The subchronic oral dog study was selected over other studies because the dog was the most sensitive species for neurotoxicity and had the lowest overall NOAEL. Although a 28-day dermal toxicity study in the rat showed no effects at the limit dose (including neuropathology), it was not selected as an endpoint for this exposure scenario due to the significantly greater sensitivity for neurotoxicity seen in the dog relative to the rat. Neurotoxic effects in the dog were identified at doses that were 10-20 times lower than in the rat. The endpoint is nonetheless considered conservative because the effects in the dog were observed following gavage dosing, in contrast to a relatively slower dermal absorption rate. For route-to-route extrapolation, dermal absorption of 7.3% relative to oral absorption was used, estimated from human and rat *in vitro* and rat *in vivo* dermal absorption.

A.3.6 Inhalation Exposure (Short-and Intermediate-Term)

Study Selected: Subchronic gavage toxicity study in dogs.

MRID No: 47443289

Dose and Endpoint for Risk Assessment: NOAEL= 7.5 mg/kg/day

Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

Comments about Study/Endpoint/Uncertainty Factors: The selected endpoint is the most sensitive NOAEL available from a study of appropriate exposure duration (90-days) for short- and intermediate-term exposure. The subchronic oral dog study was selected over other studies because the dog was the most sensitive species for neurotoxicity and overall lowest NOAEL. For route-to-route extrapolation, inhalation absorption of 100% is assumed relative to oral absorption because there are no data on inhalation absorption and a route-specific inhalation study is not available.

A.3 Summary table for the observation of seizures in dog toxicity studies.

Study	# of animals with finding	Day of observation (dose in mg/kg/day and sex)	Timing after dose
Subchronic oral (gavage)-dog (MRID	3	15 (30, M), 22 (30, F), and 35 (15x2[a], F)	~2 hours after dosing with 15

Study	# of animals with finding	Day of observation (dose in mg/kg/day and sex)	Timing after dose
47443289)			mg/kg/day for the day 35 dog, timing was not reported for the other dogs.
Chronic oral (diet)-dog (MRID 47443289)	1	190 (12, M)	Timing not reported.
Subchronic oral (gavage) range-finding study (MRID 49073701)	8	0 (50, 1M and 1F), 1 (200, 2M[b]), 2 (100, M[c]), 3 (100, F[b]), 7 (100, M), and 9 (100, F)	Timing not reported.
Subchronic range-finding study (not submitted)[d]	2	5 (600, F and 800, M)	24 hours for the female and 1-1.5 hours for the male.
Subchronic range-finding study (not submitted)[d]	1	5 (400, F)	Timing not reported.

[a] After the observation of seizures in the two animals dosed with 30 mg/kg/day, the dosing was stopped for two days and then started again as two 15 mg/kg/day doses given 7-8 hours apart.
[b] Described as "vibratory shake of the head and shoulders".
[c] This dog also had a "seizure" on day 9.
[d] This study was referenced in the subchronic oral (gavage) range finding study (MRID 49073701).

Appendix B. Physical/Chemical Properties.

Physicochemical Properties of the Technical Grade AE 1170437 (Indaziflam)			
Parameter	Value		Reference
Molecular weight	301.37		
Melting point/range	183 -184 °C AE 1170437 pure substance		H. Mukhoty, 1 Dec 2008, D356393.
pH (23 °C)	pH = 6.5 AE 1170437 pure substance pH = 5.1 AE 1170437 technical substance		
Density (g/mL at 20 °C) (relative density compared to water at 4 °C, D_4^{20})	1.23 AE 1170437 pure substance 1.23 AE 1170437 technical grade active ingredient		
Water solubility (at 20 °C)	pH 4: 4.4 mg/L, pH 9: 2.8 mg/L, Distilled water (pH 6.6-6.9): 2.8 mg/L		
Solvent solubility (g/L at 20 °C)	Acetone: Acetonitrile: Dichloromethane: Dimethyl sulfoxide: Ethanol: Ethyl acetate: Heptane: Toluene:	55 g/L 7.6 g/L 150 g/L >250 g/L 13.0 g/L 47 g/L 0.032 g/L 4.3 g/L	
Vapor pressure	2.5×10^{-8} PA at 20 °C 6.8×10^{-8} PA at 25 °C 6.9×10^{-6} PA at 50 °C		
Henry's law constant	2.69 x 10E-6 [Pa x m³/mol] at 20 °C		
Dissociation constant (pK_a)	3.5		
Octanol/water partition coefficient Log (K_{OW})	pH 2: 2.0 pH4, pH7 and pH9: 2.8		
UV/visible absorption spectrum methanol (nm)	λ_{max1} = 213 nm / A = 1.428 λ_{max2} = 268 nm / A = 0.197 λ_{max3} = 291 nm / A = 0.019		

Appendix C. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; and the Outdoor Residential Exposure Task Force (ORETF) database; are subject to ethics review pursuant to 40 CFR 26, have received that review, and are compliant with applicable ethics requirements. For certain studies that review may have included review by the Human Studies Review Board. Descriptions of data sources as well as guidance on their use can be found at http://www.epa.gov/pesticides/science/handler-exposure-data.html and http://www.epa.gov/pesticides/science/post-app-exposure-data.html.