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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: June 22, 2017

SUBJECT: **Indoxacarb:** Human Health Draft Risk Assessment for Indoxacarb to Support Registration Review and the Proposed New Use for Controlling Ants at Ornamental Nurseries, Sod Farms, and Livestock Corrals of non-Food Bearing Animals.

PC Code: 067710
Decision No.: 526245 & 520173
Petition No.: NA

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

DP Barcode: D438155 & D435483
Registration No.: 100-1481
Regulatory Action: Registration Review & New Use Outdoor, non-Food (R230)
Case No.: 7472
CAS No.: 173584-44-6
40 CFR: §180.564

FROM: Peter Savoia, Chemist, Risk Assessor
Ume Hassan, Biologist
John Liccione, Toxicologist
David Nardrchal, Chemist
Risk Assessment Branches V and VII (RAB V/VII)
Health Effects Division (HED; 7509P)

THROUGH: Risk Assessment Review Committee (RARC)
RARC Detail Reviewers:
Matthew Crowley, Biologist (CEB/HED)
Julie L. Van Alstine, MPH, Chemist (RAB VI/HED)
And
Michael S. Metzger, Chief
Risk Assessment Branches V and VII (RAB V/VII)
Health Effects Division (HED; 7509P)

TO: Moana Appleyard, Risk Manager Reviewer, and
Jill Bloom, Team Leader
Risk Management and Implementation Branch 5 (RMIB 5)
Pesticide Re-Evaluation Division (7508P)
And
Eric Bohnenblust, Ph.D., Risk Manager Reviewer
Invertebrate-Vertebrate Branch 2
Registration Division (7505P)

Table of Contents

1.0 Executive Summary

This assessment is conducted to satisfy the requirement for a Draft Risk Assessment (DRA) to support the Registration Review of the insecticide indoxacarb for the Pesticide Re-evaluation Division (PRD). It is also being conducted to support the requested new use the Registration Division (RD) received for controlling ants at ornamental nurseries, sod farms, and livestock corrals of non-food bearing animals. For these actions, HED has evaluated the hazard and exposure data and conducted dietary, occupational, and residential exposure assessments, as needed, to estimate the risk to human health that will result from the registered and proposed new uses of indoxacarb.

Background

Indoxacarb is an oxadiazine class insecticide registered for use in both agricultural and residential sites. Blockage of the neuronal sodium channel produces the insecticidal mode of action of indoxacarb. Permanent tolerances are established on a number of plant and livestock commodities under 40 CFR §180.564(a) to support its many registered agricultural uses. Its residential uses include spot-on treatments of cats and dogs, indoor and outdoor spot and crack and crevice uses, and uses on lawns/turf. The end-use products of indoxacarb include granules, water dispersible granules, emulsifiable and soluble concentrates, and ready-to-use (RTU) products. The International Organization for Standardization (ISO) defines indoxacarb to be the insecticidal active S-enantiomer. Indoxacarb products are produced as the insecticidally active S-enantiomer or a mixture of the S-enantiomer and the insecticidally inactive R-enantiomer. The percent active ingredient and application rates listed on indoxacarb product labels reflect the S-enantiomer; labels do not reflect the amount of R-enantiomer in the mixtures. Toxicological equivalency has been established for the formulated indoxacarb products. In this risk assessment the term indoxacarb refers to the S-enantiomer but does consider both enantiomers because the analytical method does not distinguish between them.

Exposure Profile

Based on the proposed uses of indoxacarb, the durations of exposure are expected to be both short- (1 to 30 days) and intermediate-term (1 to 6 months) for agricultural occupational handlers and post-application workers. Based on the proposed uses of indoxacarb, additional residential handler exposures are not expected because there are no proposed residential uses associated with indoxacarb; however, there are currently registered residential uses. Residential post-application exposures including incidental oral exposures to indoxacarb are expected to be short-term. Personal protective equipment (PPE) on the proposed label requires occupational handlers to wear baseline clothing (long-sleeved shirt, long pants, shoes plus socks) and gloves. A restricted entry interval (REI) of 4 hours is listed on the proposed label.

Based on the registered uses of indoxacarb, exposure to indoxacarb may occur from ingestion of residues in/on foods and in drinking water, and via the dermal and inhalation routes for adults using indoxacarb products in occupational and residential settings. In addition, both adults and children may be exposed dermally in post-application scenarios on golf courses, lawns, and in homes; children may also be exposed orally in post-application scenarios on pets, lawns, and in homes. There is a potential for post-application dermal exposure for workers re-entering treated fields. However, dermal exposures were not assessed, due to the lack of a dermal endpoint.

Hazard Assessment

The database for indoxacarb is complete and is sufficient for characterizing toxicity. Toxicology studies have been performed using either MP062 or JW062 (S-enantiomer and R-enantiomer mixtures) or the KN128 (S-enantiomer only). The toxicity profiles for KN128, MP062 and JW062 in rats, mice and dogs with both subchronic and chronic oral exposures were similar. The endpoints that most frequently defined the lowest-observed-adverse-effect-level (LOAEL) were non-specific, and included decreases in body weight, food consumption, and food efficiency. These compounds also affected the hematopoietic system by decreasing the red blood cell count, hemoglobin, and hematocrit in rats, dogs, and mice.

There was no evidence of reproductive effects in the two-generation reproduction study in rats. There was no evidence of increased susceptibility in developing fetuses or in the offspring following prenatal and/or postnatal exposure to indoxacarb in the rat and rabbit developmental toxicity studies and the two-generation rat reproduction study. There was no evidence of increased susceptibility in the young in the developmental neurotoxicity study in rats. Neurotoxicity was seen in animal studies in rats and mice, but at doses much higher than those selected for points of departure (which are based on changes in body weight, food consumption and changes in hematology) for the current risk assessment. There is no evidence of teratogenicity, mutagenicity, or immunotoxicity in the indoxacarb studies.

Indoxacarb did not show evidence of carcinogenicity in either the rat or mouse studies, nor was there any evidence of mutagenicity; therefore, a cancer risk assessment was not conducted.

The FQPA safety factor for indoxacarb is reduced to 1X based on: 1) the hazard and exposure databases are complete; 2) there is no susceptibility in fetuses or offspring in any of the in utero or postnatal toxicity studies; 3) there are no residual uncertainties with regard to pre- and/or postnatal toxicity; 4) the acute neurotoxicity, subchronic neurotoxicity, and developmental neurotoxicity studies are available and all endpoints used in this risk assessment are protective of neurotoxic effects; and 5) exposures estimates will not underestimate actual exposures.

The no-observed-adverse-effect-level (NOAEL) of 12 mg/kg/day from the acute oral neurotoxicity study in the rat was selected for the acute dietary PoD. Uncertainty factors for interspecies extrapolation (UF_A =10x) and intraspecies variation (UF_H=10x) were applied to the PoD to calculate an acute dietary reference dose (aRfD) of 0.12 mg/kg/day. The FQPA SF was 1x. The chronic RfD (cRfD) of 0.02 mg/kg/day was derived from a weight-of-evidence approach of 3 studies (90-day subchronic rat, rat subchronic neurotoxicity, and a rat chronic/carcinogenicity). The standard 100 UF was applied to account for interspecies extrapolation and intra-species variation. The FQPA SF was reduced to 1x for chronic dietary risk assessment. The short, intermediate and long-term endpoints were selected from the same studies utilized for derivation of the chronic RfD. The level of concern is for a margin of exposure (MOE) less than 100. A quantitative dermal assessment is not required for indoxacarb, since the calculated human dermal LOAEL based on results of the dermal triple pack exceeds the limit dose of 1000 mg/kg/day. Short-term and intermediate-term inhalation endpoints for risk assessment were selected from the route-specific 28-day inhalation toxicity study in rats with a LOAEL of 0.29 mg/L/day and a NOAEL of 0.023 mg/L/day. Human equivalent doses were calculated from the human equivalent concentrations for residential and occupational handler scenarios. The total LOC is 30.

Residue Chemistry and Dietary Exposure and Risk

The indoxacarb residue chemistry database is complete. The residues of concern for tolerance enforcement in both plants and livestock is indoxacarb and its R-enantiomer, except for tolerances on poultry commodities which also include several quantifiable indoxacarb metabolites of structural similarity. For risk assessment, the residues of concern in plants and ruminant tissues is indoxacarb and its R-enantiomer. Various metabolites and degradates of indoxacarb are also included for risk assessment in milk, poultry commodities, and drinking water. Permanent tolerances are established under 40 CFR §180.564(a) for indoxacarb and its R-enantiomer on a number of plant and livestock commodities. Adequate methods are available for the enforcement of the established indoxacarb tolerances. The proposed new use of indoxacarb for controlling ants at ornamental nurseries, sod farms, and livestock corrals of non-food bearing animals will not yield residues in food. No tolerances are therefore needed as this requested registration is regarded as a non-food use. Revised dietary exposure and risk assessments which used anticipated residue values and the latest percent crop treated data available for refinement were conducted to support the Registration Review of indoxacarb. These dietary analyses include the updated commodities contained in the crop group conversions which are recommended for implementation. Updated drinking water assessments were provided by the Environmental Fate and Effects Division (EFED). These assessments concluded that the new and continued use of indoxacarb will not result in higher estimated drinking water concentrations (EDWCs) than were previously determined. The refined acute and chronic dietary risk estimates were below the level of concern for the general U.S. population and all population subgroups (acute population adjusted dose (aPAD) or chronic population adjusted dose (cPAD) <100%).

Residential (Non-Occupational) Exposure and Risk

No new residential uses are being requested with the petition received for treating ornamental nurseries, sod farms, and livestock corrals of non-food bearing animals with indoxacarb to control ants. The proposed new uses are not expected to result in residential exposure. However, the existing uses are expected to result in residential handler dermal and inhalation exposures and residential post-application dermal and incidental oral exposure. Residential handler dermal exposures were not assessed, due to the lack of toxicity via the dermal route. Only inhalation exposures were assessed for residential handlers. Residential post-application incidental oral exposures were assessed for children 1 to < 2 years old. Indoxacarb may be used by residential handlers on lawns and turf; around perimeters of homes; around ornamental plants; around home gardens; on pets; indoor applications (broadcast and spot and crack and crevice); and on sidewalks, patios, and driveways. Indoxacarb is also registered for use as a residential ant mound treatment. Spot and crack and crevice exposures and risks for gels and bait stations were not quantified due to formulation type, which minimize the potential for handler and post-application exposures, and are expected to be negligible.

All residential handler scenarios for the registered uses of indoxacarb resulted in inhalation MOEs greater than the level of concern (LOC) (inhalation MOE = 30) and are not of concern. The MOEs range from 92 to 5,500,000.

All residential incidental oral post-application risk estimates for registered uses were not of concern, with MOEs > LOC, (LOC = 100). MOEs ranged from 170 to 100,000.

Non-Occupational Spray Drift

Since risks of concern were not identified for turf uses, a quantitative spray drift assessment for indoxacarb is not required because the maximum application rate to a crop/target site multiplied by the adjustment factor for drift of 0.26 is less than the maximum direct spray residential turf application rate (0.225 lb ai/A) for any indoxacarb products. The turf post-application MOEs have been previously assessed and are based on the revised SOPs for Residential Exposure Assessment (see Section 6.2).

Volatilization/Residential Bystander

For agricultural/commercial outdoor uses, 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 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for indoxacarb.

Aggregate

Based on the existing and newly proposed uses of indoxacarb, exposures can occur both from dietary sources (food and water) and in residential settings. For aggregate risk assessment, risk estimates resulting from food, drinking water, and residential uses are combined. Acute, short-and intermediate-term, and long-term (chronic) aggregate assessments were performed for indoxacarb. The scenarios resulting in the highest non-dietary exposures are selected as protective scenarios for the aggregate assessments – these were lawn applications for handlers and post-application exposure to spot-treatment of pets (cats). There are no acute, short-term, intermediate-term, or long-term (chronic) aggregate risk estimates of concern for adult or child aggregate exposure to indoxacarb as a result of current and proposed uses (short-term aggregate MOE = 120, long-term aggregate MOE = 260).

Occupational Exposure and Risk

An occupational handler and post-application dermal assessment was not conducted, due to the lack of a dermal endpoint.

All occupational handler inhalation risk estimates for the proposed uses of indoxacarb were not of concern, MOEs > LOC (LOC = 30). MOEs ranged from 55,000 to 3,700,000 with baseline attire.

All occupational handler inhalation risk estimates for registered uses of indoxacarb were not of concern, with MOEs > LOC, (LOC=30), except mixing/loading water dispersible granule (WDG) formulations for aerial application to high acreage field crops (MOE = 19). The addition of a PF5 respirator would result in risk estimates not of concern, with MOE = 95, (LOC = 30). MOEs with baseline PPE (i.e. no respirator) ranged from 19 to 960,000.

Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for indoxacarb at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for indoxacarb.

Human Studies Review

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) and the Agricultural Handler Exposure Task Force (AHETF) database and the Residential SOPs, 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 the Agency website[1].

2.0 HED Recommendations

2.1 Data Deficiencies

There are no data deficiencies for the registered or proposed new uses of indoxacarb in regards to the toxicology, occupational and residential exposure, and residue chemistry databases.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

A number of adequate methods are available for enforcing indoxacarb tolerances on both plant and livestock commodities. These protocols are all common moiety methods which work to provide a total measure of indoxacarb concentration. For the enforcement of tolerances established on crops, two High Performance Liquid Chromatograph/Ultraviolet Detection (HPLC/UV) methods, DuPont protocols AMR 2712-93 and DuPont-11978, are available for use. The limits of quantitation (LOQs) for these methods range from 0.01 to 0.05 ppm for a variety of plant commodities. A third Gas Chromatograph/Mass-Selective Detection (GC/MSD) procedure, DuPont method AMR 3493-95 Supplement No. 4, is also available for the confirmation of residues in plants. For the enforcement of livestock tolerances, an HPLC/column switching/UV Method (AMR 3337-95) is capable of determining the parent compound as well as the metabolite IN-JT333. This method has been demonstrated to provide an LOQ of 0.01 ppm with a reported limit of detection (LOD) of 0.002-0.003 ppm. For poultry commodity analyses, a Liquid Chromatograph/Mass Spectrometer/Mass Spectrometer (LC/MS/MS) method, AMR 12739, was developed by DuPont for use. This method has been successfully validated using hen muscle, liver, skin, and fat as well as, whole egg, egg yolk, and egg white samples.

[1] http://www.epa.gov/sites/production/files2016-11/documents/handler-exposure-table-2016.pdf and http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

2.2.2 Recommended and Established Tolerances

Because the new application of indoxacarb for controlling ants is a non-food use, no tolerances are required for this requested registration.

As noted below in section 2.2.3, the U.S. tolerances for alfalfa hay, cattle fat, cattle meat byproducts, sweet corn stover, cotton gin byproducts, stone fruit, goat fat, goat meat byproducts, hog fat, hog meat byproducts, horse fat, horse meat byproducts, peanut, peanut hay, peppermint tops, sheep fat, sheep meat byproducts, spearmint tops, and the subgroup 1-C tuberous and corm vegetables may be increased for harmonization with the maximum residue limits (MRLs) set by Codex on these commodities. The crop groupings have been updated for fruiting vegetable group 8, pome fruit group 11 except pear, and stone fruit group 12. The listings for these crop groupings can be amended in the federal register to specify the current established crop grouping nomenclature. The established tolerances for the group 4 leafy vegetables except *Brassica*, and the group 5 leafy *Brassica* vegetables can also be converted to the new crop groupings for these commodities. Following the conversion plan for implementation, these crop groups can be deleted from the federal register and replaced with the establishment of leafy greens subgroup 4-16A at 14 ppm, Brassica leafy greens subgroup 4-16B at 12 ppm, vegetable head and stem Brassica group 5-16B at 12 ppm, leaf petiole vegetable subgroup 22B at 14 ppm, celtuce at 14 ppm, fennel florence at 14 ppm, and kohlrabi at 12 ppm. In addition, further review of the established indoxacarb tolerances have shown that the limits for bean dry seed, succulent beans, low growing berries, and small vine climbing fruit also require revision to express the appropriate number of significant figures. See table 2.2.2 below for summaries of the revisions recommended for the established indoxacarb §180.564(a) tolerances:

Table 2.2.2. Tolerance Revision Summary for Indoxacarb, §180.564(a).

Commodity	Established Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Alfalfa, hay	50	60	
Bean, dry, seed	0.2	0.20	
Bean, succulent	0.9	0.90	
Berry, low growing, except strawberry, subgroup 13-07H	1	1.0	
Brassica leafy greens subgroup 4-16B	--	12	*Updated crop group conversion*
Cattle, fat	1.5	2.0	
Cattle, meat byproducts	0.03	0.05	
Celtuce	--	14	*Commodity displaced by the crop group conversion*
Corn, sweet, stover	15	25	
Cotton, gin byproducts	15	20	
Fennel, florence	--	14	*Commodity displaced by the crop group conversion* *Fennel, florence, fresh leaves and stalk*
Fruit, small vine climbing, except fuzzy kiwifruit, subgroup 13-07F	2	2.0	
Fruit, pome, except pear, group 11-10	1.0	1.0	*Updated crop group conversion*

Table 2.2.2. Tolerance Revision Summary for Indoxacarb, §180.564(a).			
Commodity	Established Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Fruit, stone, group 12-12	0.90	1.0	*Updated crop group conversion*
Goat, fat	1.5	2.0	
Goat, meat byproducts	0.03	0.05	
Hog, fat	1.5	2.0	
Hog, meat byproducts	0.03	0.05	
Horse, fat	1.5	2.0	
Horse, meat byproducts	0.03	0.05	
Kohlrabi	--	12	*Commodity displaced by the crop group conversion*
Leaf petiole vegetable subgroup 22B	--	14	*Updated crop group conversion*
Leafy greens subgroup 4-16A	--	14	*Updated crop group conversion*
Peanut	0.01	0.02	
Peanut, hay	40	50	
Peppermint, tops	11	15	
Sheep, fat	1.5	2.0	
Sheep, meat byproducts	0.03	0.05	
Spearmint, tops	11	15	
Vegetable, fruiting, group 8-10	0.50	0.50	*Updated crop group conversion*
Vegetable, head and stem Brassica, group 5-16B	--	12	*Updated crop group conversion*
Vegetable, tuberous and corm, subgroup 1-C	0.01	0.02	

2.2.3 International Harmonization

Permanent tolerances are established under 40 CFR §180.564(a) for indoxacarb on a number of plant and livestock commodities. Tolerances on poultry commodities also include several quantifiable indoxacarb metabolites of structural similarity. Mexico and Canada do not have MRLs established for indoxacarb. There are Codex MRLs established for indoxacarb also expressed as both enantiomers. Most of the U.S. tolerance levels are harmonized with the MRLs established by Codex; however, there are several tolerances not harmonized with the Codex values. There are tolerances set higher than the Codex MRLs on cotton undelinted seed, pome fruit, soybean seed, leafy *B*rassica group 5 vegetables, cucurbit group 9 vegetables, and leafy *B*rassica group 4 vegetables. These tolerances cannot be harmonized with the Codex MRLs because higher residues are incurred in the U.S. for these crops. There are tolerances set lower than the Codex MRLs on alfalfa hay, livestock commodities (fat, meat, and meat byproducts), sweet corn stover, cotton gin byproducts, stone fruit, peanut, peanut hay, peppermint tops, spearmint tops, and the subgroup 1-C tuberous and corm vegetables. Increasing these tolerances is acceptable for harmonization with the respective Codex MRLs since these limits are protective of any residues incurred in the U.S. A summary of the U.S. tolerances and Codex MRLs is presented in Appendix D.

2.3 Label Recommendations

2.3.1 Recommendations from Residue Reviews

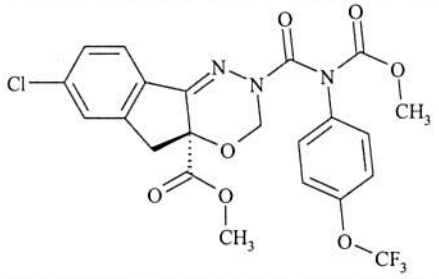
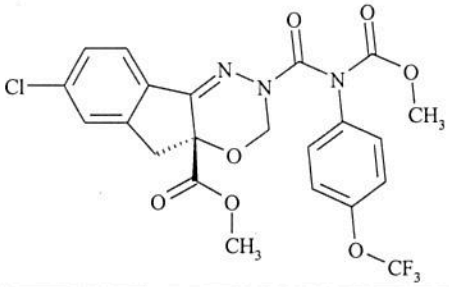
None

2.3.2 Recommendations from Occupational/Residential Assessment

Although no specific recommendations are being made, one scenario is of concern for occupational handlers and requires additional PPE (respirator) to be not of concern.

3.0 Introduction

3.1 Chemical Identity

Table 3.1. Indoxacarb Nomenclature.	
Compound	
Common name	Indoxacarb S-enantiomer
Company experimental name	DPX-KN128 (pesticidally active)
IUPAC name	(S)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-e][1,3,4]oxadiazine-4a(3*H*)-carboxylate
CAS name	methyl (4aS)-7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-e][1,3,4]oxadiazine-4a(3H)-carboxylate
CAS registry number	173584-44-6
End-use product (EP) for the proposed use	30% WDG DuPont™ Avaunt® eVo (EPA Reg. No. 352-906) formulated solely with the 98% ai (DPX-KN128; aka KN128) technical substance.
Compound	
Common name	Indoxacarb R-enantiomer
Company name	IN-KN127 (pesticidally inactive)

3.2 Physical/Chemical Characteristics

The physical and chemical properties of indoxacarb are detailed in Appendix B.

Indoxacarb is an oxadiazine pesticide developed by DuPont which is formed as a white granule. Indoxacarb has a very low vapor pressure of $1.9x10^{-10}$ mm Hg at 25 °C; volatilization is not expected to be a significant route of dissipation for this pesticide. The octanol water partition coefficient (Kow = 44000) suggests that it is lipophilic. Indoxacarb is slightly soluble in water (0.8 mg/L at pH 7 at 20°C). Indoxacarb is considered to be moderately persistent with aerobic half-lives ranging from 3 to 693 days and anaerobic range from 147 to 233 days. It is considered to be immobile with K_{ocs} ranging from 3300 to 9600 ml/g.

3.3 Pesticide Use Pattern

Indoxacarb is formulated as granules, water dispersible granules, emulsifiable and soluble concentrates, and RTU products. Indoxacarb products are produced as the insecticidally active S-enantiomer or a mixture of the S-enantiomer and the insecticidally inactive R-enantiomer. The percent active ingredient and application rates listed on indoxacarb product labels reflect the S-enantiomer; labels do not reflect the amount of R-enantiomer in the mixtures. In this risk assessment the term indoxacarb refers only to the S-enantiomer. Formulated products may appear as 1) isomer enriched DPX-MP062 (also referred to as MP062) which is a mixture containing the S-enantiomer and its R-enantiomer at approximately a 75:25 ratio, 2) racemic mixture DPX-JW062 (also referred to as JW062) which is a mixture of the enantiomers at a 50:50 ratio, or 3) DPX-KN128 formulations (S-enantiomer only; no R-enantiomer). The R-enantiomer is also referred to as IN-KN127 or KN127. A summary of the proposed and registered uses are included in Appendix F below.

3.4 Anticipated Exposure Pathways

These uses include registration on numerous agricultural crops as well as on pets, turf, and inside homes. The registered uses of indoxacarb may expose humans to this pesticide active ingredient in food and drinking water, since it is applied directly to growing crops. Exposure to indoxacarb may also occur from the dermal and inhalation routes for adults using indoxacarb products in occupational and residential settings. In addition, both adults and children may be exposed dermally in post-application scenarios on golf courses, lawns, and in homes; children may also be exposed orally in post-application scenarios on pets, lawns, and in homes. There is a potential for post-application dermal exposure for workers re-entering treated fields. There is potential for non-occupational exposure via spray drift.

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.archives.gov/federal-register/executive-orders/pdf/12898.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's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and 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 are evaluated, based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application. 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

Indoxacarb is a oxadiazine insecticide and used for the control of lepidopterous pests in the larval stages. Insecticidal activity occurs via blockage of the sodium channels in the insect nervous system. Indoxacarb products contain the enantiomeric compounds indoxacarb (S-enantiomer; DPX-KN128) and its R-enantiomer (IN-KN127). Only the S-enantiomer has insecticidal activity. DPX-MP062 (also referred to as MP062) is a mixture containing the S-enantiomer and its R-enantiomer at approximately a 75:25 ratio. DPX-JW062 (also referred to as JW062) is the racemic mixture of the enantiomers. Many of the toxicity studies were conducted with JW062 (50:50). HED's Hazard Identification Assessment Review Committee (HIARC; HED Doc No. 013528) determined that it is appropriate to use data from DPX-JW062 (50:50) to satisfy the requirements for dietary subchronic, chronic, oncogenicity and reproductive studies. The HIARC also concluded the bridging of toxicological data from DPX-JW062 and DPX-MP062 to register DPX-KN128 formulations is acceptable (S-enantiomer only; no R-enantiomer).

4.1 Toxicology Studies Available for Analysis

The toxicological database for indoxacarb is complete and adequate for hazard characterization, toxicity endpoint selection, and FQPA SF evaluation.

It is recognized that the NOAELs and LOAELs from some of the studies, including those used for endpoint selection, in the indoxacarb database have not been updated to reflect current practices in hazard evaluation and may be considered conservative. The currently selected points of departure are protective of the effects observed in the indoxacarb database and any updates to these studies would not impact the overall findings of the risk assessment (i.e., would result in higher/lower NOAEL/LOAEL values).

4.2 Absorption, Distribution, Metabolism, and Excretion (ADME)

Both DPX-JW062 and DPX-MP062 were rapidly absorbed and eliminated following oral administration. For DPX-JW062, peak time (tC_{max}) in plasma were similar for males (6.8 hr) and females (5.3 hr). This parameter was also similar in males (8 hr) and females (7.3 hr) dosed with DPX-MP062. Both DPX-JW062 and DPX-MP062 were widely distributed following oral administration (single low dose), but deposition in tissues was limited to only 3.4-12.9% of the administered dose. Fat tissue contained the greatest level of radioactivity (1.76-8.76% of the

administered dose) and, for both compounds, was greater in female rats. Remaining tissue generally contained <1% of the administered radioactivity. Urine and feces represented major routes of excretion for both DPX-JW062 and DPX-MP062. The metabolites of DPX-MP062 and DPX-JW062 were eliminated in the urine, feces, and bile.

4.2.1 Dermal Absorption

An *in vivo* dermal-penetration study in rats (MRID 45911402) and *in vitro* dermal-penetration studies using rat and human skin (MRID Nos. 45911401 and 45911403) are available for indoxacarb. In the *in vivo* study, a dermal absorption factor (DAF) of 4.91% (for the aqueous dilution) after 6 hours of exposure was calculated at the lowest dose tested (13.3 $\mu g/cm^2$) based on total absorbable dose, which was the sum of the absorbed dose (urine, feces, cage wash, residual food, non-dosed skin, whole blood, red blood cells, plasma) and radioactivity in the tape-stripped skin) at the 162-hour post-exposure time point.

In the *in vitro* studies, the total absorbed dose (calculated as the sum of the absorbed dose plus the dose associated with the skin) at 13.3 $\mu g/cm^2$ was estimated as 0.87% and 15.2% of the administered dose in human and rat skin, respectively, at the 18 hour post-exposure time point. These results demonstrated that absorption was higher for rat skin than human skin. Although tape strips (except 1 and 2) are typically included in the dermal absorption factor (DAF) calculation, in the case of indoxacarb the tape strips were not included since the amount associated with tape strips did not change over time. The physicochemical properties of indoxacarb (log Kow = 4.65, molecular weight = 528) also support relatively low permeability. Furthermore, the CDC finite skin permeation calculator also indicates that indoxacarb would have low absorption through human skin (<1%). The National Institute for Occupational Health and Safety (NIOSH) finite dose skin permeation calculator (http://www.cdc.gov/niosh/topics/skin/finiteSkinPermCalc.html) and the physical chemical properties of thiamethoxam (see appendix for a full list), no dermal absorption (0%) was predicted over an 8 hour period with a dermal load of 3 $\mu g/cm^2$. The Finite Dose Skin Permeation Calculator was developed through support of a Center of Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH) grant, and provides an estimation of fluxes, skin concentrations, and amounts absorbed from any size dose applied to partially or fully hydrated skin, using the physicochemical properties of the test compound and defined exposure parameters.

4.3 Toxicological Effects

The toxicity profiles for KN128, MP062, and JW062 in rats, mice and dogs with both subchronic and chronic oral exposures were similar. Dermal subchronic exposure in the rat also resulted in a similar profile. The toxic signs occurred at similar doses and with a similar magnitude of response, with females generally being more sensitive than males. The endpoints that most frequently defined the LOAEL were non-specific, and included decreases in body weight, weight gain, food consumption and food efficiency. These compounds also affected the hematopoietic system by decreasing the red blood cell count, hemoglobin and hematocrit in rats, dogs and mice. It was frequently accompanied by an increase in reticulocytes in all three species and an increase in Heinz bodies (dogs and mice only). None of these signs of toxicity appeared to get worse over time. In one subchronic rat study,

the parameters appeared to return to normal levels following a four-week recovery period. High doses in the rats and mice also sometimes caused mortality.

Neurotoxicity was observed in rats and mice, but at higher doses (>100 mg/kg/day) than the hematologic effects (3.3 mg/kg/day) which were used as the basis for the risk assessment endpoints and points of departure. Neurotoxicity was characterized by one or more of the following symptoms in both male and female rats and mice: weakness, head tilting, and abnormal gait or mobility with inability to stand, ataxia. There was possible evidence of lung damage in the acute inhalation studies with both MP062 and JW062. Subchronic (28 days) inhalation toxicity on indoxacarb in rats was characterized by increased spleen weights, increased pigmentation and hematopoiesis in the spleen, and hematological changes. Decreased body weights were the primary maternal and offspring effects observed in the developmental and reproductive toxicity studies with indoxacarb products.

There was no evidence of carcinogenicity in either the rat or mouse in acceptable studies on indoxacarb. Indoxacarb is classified as "not likely" to be carcinogenic in humans by all relevant routes of exposure (TXR 0052478).

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)[2]

The following factors support reduction of the FQPA safety factor (SF) to 1X: 1) the hazard and exposure databases are complete; 2) there is no susceptibility in fetuses or offspring in any of the in utero or postnatal toxicity studies; 3) there are no residual uncertainties with regard to pre- and/or postnatal toxicity; 4) the acute neurotoxicity, subchronic neurotoxicity, and developmental neurotoxicity studies are available and all endpoints used in this risk assessment are protective of neurotoxic effects; and 5) exposures estimates will not underestimate actual exposures.

4.4.1 Completeness of the Toxicology Database

The existing toxicological database is complete and adequate for characterizing indoxacarb toxicity and quantifying hazard for dietary, residential, and occupational exposures. The developmental toxicity studies in rats and rabbits, two-generation reproduction toxicity study in rats, and neurotoxicity studies in rats (acute, subchronic, and developmental neurotoxicity) are available to assess potential fetal/offspring sensitivity.

4.4.2 Evidence of Neurotoxicity

Although neurotoxic effects were observed across studies on indoxacarb (see section 4.3), concern is low since the selected PODs are protective of observed neurotoxic effects.

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

There was no evidence of increased susceptibility in the rat and rabbit developmental toxicity studies, the two-generation rat reproduction study, or the developmental neurotoxicity study in rats.

[2] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (http://www.epa.gov/children/epas-policy-evaluating-risk-children)

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the indoxacarb exposure database. While some refinements were incorporated into the dietary exposure calculations, EPA is confident that the aggregate risk from exposure to indoxacarb in food, drinking water, and residential pathways will not be underestimated. The acute dietary (food) exposure assessment utilized conservative upper-bound inputs including assuming 100% of the registered crops treated, and tolerance-level residues for all existing and proposed commodities, except citrus fruits where the highest field trial residue was used as a refinement. The chronic dietary exposure assessment was partially refined, and used tolerance-level residues for all commodities and % CT estimates when available (Screening Level Usage Analysis (SLUA), 10/14/14). Although the acute and chronic assessments included minor refinements, the use of field trial estimates ensures that actual exposures/risks from residues in food will not be underestimated. The drinking water assessment utilized water concentration values generated by models and associated modeling parameters which are designed to produce conservative, health protective, high-end estimates of water concentrations which are not likely to be exceeded. The dietary (food and drinking water) exposure assessment does not underestimate the potential exposure for infants, children, or women of child bearing age.

In addition, the residential exposure assessments are based on the 2012 Residential SOPs employing surrogate study data, including conservative exposure assumptions based on Day 0 dermal/oral contact to turf and surfaces treated at the maximum application rate. These data are not expected to underestimate risks to adults or children. The Residential SOPs are based upon reasonable "worst-case" assumptions are not expected to underestimate risk.

4.5 Toxicity Endpoint and Point of Departure Selections for Indoxacarb

Acute dietary (all populations): In the 2016 risk assessment (D428812), an acute reference dose (aRfD) of 0.12 mg/kg was established for all populations. It was based on an acute oral neurotoxicity study in the rat. A NOAEL of 12 mg/kg was based on decreased body weight, body-weight gain, and food consumption in females observed at the LOAEL of 50 mg/kg. The NOAEL is based on a 7% body weight decrease (in females only on day 8, but no significant differences were noted for days 1, 2 or 15). Currently, a 10% decrease in adult body weight is the threshold for an adverse effect, thus this study NOAEL was considered in the 2016 risk assessment to be **very conservative**. In addition, the current 2017 indoxacarb risk assessment team notes that the slight (22%↓) statistically significant decrease in food consumption (during test days 1 and 2 only) noted in the 50 mg/kg females was not seen at the high dose (100 mg/kg) females and may not be a single-dose effect. The team also notes that during the first 10-minute interval of motor activity evaluations on days 1 and 8, high-dose females exhibited significantly ($p<0.05$) decreased duration of movements (37% and 21%, respectively). Motor activity was not significantly affected at day 15. The effect on motor activity may potentially be a more robust single-dose effect, although the statistical analyses of the motor activity was limited and did not include the best analyses for repeated measures. Therefore, the indoxacarb risk assessment team considers the acute dietary endpoint based on body weight and food consumption decrements at the NOAEL of 12 mg/kg to be **highly conservative**. The standard 100 UF was applied to account for interspecies extrapolation and intraspecies variation. The FQPA SF can be reduced to 1x for acute dietary risk assessment. Thus, the acute population-adjusted dose (aPAD) is equivalent to the aRfD of 0.12 mg/kg.

Chronic dietary (all populations): The chronic RfD (cRfD) of 0.02 mg/kg/day was based on the: 1) rat 90-day subchronic toxicity study; 2) rat subchronic neurotoxicity study; and 3) rat chronic/carcinogenicity study. The LOAELs for the three co-critical studies were: 1) 3.8 mg/kg/day; 2) 3.3 mg/kg/day; and; 3) 3.6 mg/kg/day. These were based on decreased body weight, alopecia, body-weight gain, food consumption and food efficiency in females. In addition, the rat chronic/carcinogenicity study also had decreased hematocrit, hemoglobin and red blood cells only at 6 months in females. Using a weight-of-evidence approach, the NOAEL for use in establishing the cRfD was 2.0 mg/kg/day. This NOAEL was also supported by the developmental neurotoxicity study in which the systemic toxicity NOAEL was 1.5 mg/kg/day. The standard 100 UF was applied to account for interspecies extrapolation and intra-species variation. The FQPA SF may be reduced to 1x for chronic dietary risk assessment. Thus, the chronic population-adjusted dose (cPAD) is equivalent to the cRfD of 0.02 mg/kg.

Short-, intermediate, and long-term incidental oral: The short, intermediate and long-term endpoints were selected from the studies mentioned in the chronic dietary section (see above), using the NOAEL of 2 mg/kg/day. The co-critical studies are protective of all effects following subchronic exposure. A target margin of exposure (MOE) of 100 is considered adequate for incidental oral exposure risk assessment.

Short- and intermediate-term dermal: A quantitative dermal assessment is not required for indoxacarb, since the calculated human dermal LOAEL exceeds the limit dose of 1000 mg/kg/day. The rat *in vivo* dermal absorption was 4.91%, with results from an acceptable guideline study. In comparison, the ratio of the LOAELs from the rat developmental oral study and the rat 28-day dermal study of similar durations estimates the rat dermal absorption to be a much lower value of 0.8% (i.e. 100 x 4 mg/kg/day/500 mg/kg/day). Based on the *in vitro* dermal absorption data on indoxacarb for human skin and rat skin, the rat dermal absorption was 17.5X higher than human dermal absorption. Specifically, for indoxacarb, the rat *in vitro* absorption was 15.2% and human *in vitro* absorption was 0.87%. Therefore, the dermal triple pack data was utilized to refine the dermal POD from the rat sub-chronic dermal study. Using the NOAEL value of 50 mg/kg/day from the route-specific 28-day dermal study in rats and the 17.5x ratio of human skin to rat skin absorption, the equivalent human dermal NOAEL is 875 mg/kg/day for indoxacarb (mixed isomers, 50 mg/kg/day x 15.2%/0.87%). The corresponding human dermal LOAEL value is calculated to be 8750 mg/kg/day (exceeding the limit dose); thus a dermal assessment is not required for indoxacarb. Additionally, utilizing the 4.91% rat dermal absorption and the rat:human dermal absorption ratio of 17.5X, the human equivalent dermal absorption is estimated to be very low, at 0.28%, using the parallelogram method.

Short- and intermediate-term inhalation: Short-term and intermediate-term inhalation endpoints for risk assessment were selected from the route-specific 28-day inhalation toxicity study in rats with a LOAEL of 0.29 mg/L/day and a NOAEL of 0.023 mg/L/day. Effects observed at the LOAEL included increased spleen weights, pigmentation and hematopoiesis in the spleen, hematological changes, mortality (females), and nasal ulceration and inflammation. Human Equivalent Concentrations (HEC)/Human Equivalent Doses (HED) for residential and occupational scenarios were calculated on the basis of these effects (i.e., systemic and portal of entry). The HECs for nasal effects (portal of entry) were the lowest values. The HEC/HEDs were derived using the NOAEL and the regional deposited-dose ratio (RDDR). The RDDR accounts for the particulate diameter [mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD)] and estimates the different dose fractions deposited along the respiratory tract. The

RDDR also accounts for interspecies differences in ventilation and respiratory tract surface areas. For the subchronic inhalation toxicity study with indoxacarb, an RDDR was estimated at 0.169 based on the extrathoracic effects seen at the NOAEL of 23 µg/L/day, with a MMAD of 1.25 µm and GSD of 2.3.

Human equivalent doses were subsequently calculated from the human equivalent concentrations (based on portal of entry effects) for residential and occupational handler scenarios. The resulting human equivalent doses ranged from 0.07-0.28 mg/kg/day, depending on the exposure scenario. Human equivalent concentration and dose calculations are summarized in Table 4.5.3.3.

A 3X uncertainty factor was applied to account for inter-species variability (to account for the PD differences), and a 10X uncertainty factor was applied to account for intra-species variability. The usual 10X interspecies uncertainty factor was reduced to 3X because the human equivalent concentration (HEC) methodology was used to reduce the uncertainty of certain physiological differences between humans and the mammalian test species. The total LOC is 30.

4.5.1 Recommendation for Combining Routes of Exposures for Risk Assessment

Inhalation exposures cannot be combined with incidental oral exposures because different toxic effects were observed for oral exposure.

4.5.2 Cancer Classification and Risk Assessment Recommendation

Indoxacarb is classified as "not likely" to be carcinogenic to humans via relevant routes of exposure (TXR 0052478). Therefore, a quantitative cancer risk assessment is not required.

4.5.3 Summary of Points of Departure and Toxicity Endpoints Used in Human Health Risk Assessment for Indoxacarb

Table 4.5.3.1 Points of Departure and Toxicological Endpoints Selected for Indoxacarb for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure Scenario	Dose for Use in Risk Assessment, UF	FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary all populations	NOAEL= 12 mg/kg UF = 100 **Acute RfD** = 0.12 mg/kg	UF_A= 10x UF_H=10x FQPA SF = 1x **aPAD** = = 0.12 mg/kg	Acute oral rat neurotoxicity study. MRID 44477127 LOAEL = 50 mg/kg based on decreased body weight and body-weight gain in females (MP062).

Table 4.5.3.1 Points of Departure and Toxicological Endpoints Selected for Indoxacarb for Use in Dietary and Non-Occupational Human Health Risk Assessments			
Exposure Scenario	**Dose for Use in Risk Assessment, UF**	**FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Chronic Dietary all populations	NOAEL= 2.0 mg/kg/day UF = 100 **Chronic RfD** = 0.02 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF = 1x **cPAD** = = 0.02 mg/kg/day	Weight of evidence approach was used from four studies: 1) Subchronic toxicity study- rat (MP062). MRID 44477129 2) Subchronic neurotoxicity study - rat (MP062). MRID 44477135 3) Chronic/carcinogenicity study - rat (JW062). MRID 44477145 4) Two generation rat reproduction study (JW062). MRID 44477144 LOAEL = 3.3 mg/kg/day based on decreased body weight, body-weight gain, food consumption and food efficiency; decreased hematocrit, hemoglobin and red blood cells only at 6 months.
Short -Term Incidental Oral	Oral NOAEL= 2.0 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF = 1x Residential LOC for MOE = 100	Weight of evidence approach was used from four studies: 1) Subchronic toxicity study- rat (MP062). 2) Subchronic neurotoxicity study - rat (MP062). 3) Chronic/carcinogenicity study - rat (JW062). 4) Two generation rat reproduction study (JW062). LOAEL = 3.3 mg/kg/day based on decreased body weight, body-weight gain, food consumption and food efficiency; decreased hematocrit, hemoglobin and red blood cells only at 6 months.
Short-Term Inhalation (**1 to 30 days**) Intermediate-Term Inhalation (1 - 6 months)	Inhalation NOAEL= 23 µg/L/day	UF_A= 3x UF_H=10x FQPA SF = 1x Residential LOC for MOE = 30	28-day rat inhalation toxicity study (MP062). MRID 45870001 The LOAEL of 290 µg/L/day mg/kg/day) is based on increased spleen weights, pigmentation and hematopoiesis in the spleen, hematological changes, mortality (females), and nasal ulceration and inflammation. Note: The HEC used for the endpoint was based on the nasal effects. This HEC was lower than the systemic effects.
Cancer (oral, dermal, inhalation)	"Not likely" to be carcinogenic to humans since no evidence of carcinogenicity in either the rat or mouse studies, and no evidence of mutagenicity.		

Table 4.5.3.2 Points of Departure and Toxicological Endpoints Selected for INDOXACARB for Use in Occupational Human Health Risk Assessments			
Exposure Scenario	**Dose for Use in Risk Assessment, UF**	**FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Short-Term Dermal (**1 to 30 days**) Intermediate-Term Dermal (1 - 6 months)	A quantitative dermal assessment is not required for indoxacarb, since the calculated human dermal LOAEL exceeds the limit dose of 1000 mg/kg/day.		
Short-Term Inhalation (**1 to 30 days**) Intermediate-Term Inhalation (1 - 6 months)	Inhalation NOAEL= 23 µg/L/day	UF_A= 3x UF_H=10x FQPA SF = 1x Occupational LOC for MOE = 30	28-day rat inhalation toxicity study (MP062). The LOAEL of 290 µg/L/day mg/kg/day) is based on increased spleen weights, pigmentation and hematopoiesis in the spleen, hematological changes, mortality (females), and nasal ulceration and inflammation. Note: The HEC used for the endpoint was based on the nasal effects. This HEC was lower than the systemic effects.
Cancer (oral, dermal, inhalation)	"Not likely" to be carcinogenic to humans since no evidence of carcinogenicity in either the rat or mouse studies, and no evidence of mutagenicity.		

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. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 4.5.3.3. Calculated Inhalation Human Equivalent Concentrations and Doses for Indoxacarb.						
Population	Scenario	Duration Adjustment		Human Equivalent Concentration		Human Equivalent Dose (mg/kg/day)
		hours/day	days/week	mg/L	mg/m3	
Occupational	Handler	8	5	0.003	2.915	0.28
Residential	Handler	NA	NA	0.004	3.887	0.09
	Indoor Post-application	NA	7	0.003	2.776	0.07

4.6 Endocrine Disruption

As required by the Federal insecticide, Fungicide, and Rodenticide Act (FIFRA) and the United States Federal Food, Drug, and Cosmetic Act (FFDCA), EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision for indoxacarb, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), indoxacarb is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[3] and includes some pesticides scheduled for Registration Review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[4]

5.0 Dietary Exposure and Risk Assessment

5.1 Metabolite/Degradate Residue Profile

[3] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.

[4] http://www.epa.gov/endo/

5.1.1 Summary of Plant and Animal Metabolism Studies

Adequate metabolism studies on cotton, lettuce, and tomatoes were previously reviewed with earlier indoxacarb petitions. A confined rotational crop study is available which is adequate in supporting a 30-day plant-back interval for all non-labeled crops. Adequate ruminant and poultry metabolism studies have also been reviewed with earlier indoxacarb petitions. Based on these studies, the HED Metabolism Assessment Review Committee (MARC) concluded indoxacarb and its R-enantiomer to be the residue of concern for both tolerance expression and risk assessment in plants and ruminant commodities (D263986, S. Levy, 07/10/2000). The MARC also determined the metabolite IN-MP819 along with indoxacarb and its R-enantiomer to be the residues of concern for risk assessment in milk.

For poultry, the MARC determined that there was a reasonable expectation for finite residues to occur in these commodities (Category 2 of 40 CFR §180.6a). However, because it was not possible to establish with certainty whether finite residues would be incurred in these commodities based only on the metabolism data, a poultry feeding study was requested. The MARC further recommended that the requested feeding study include in these analyses the determination of indoxacarb, IN-JT333, IN-KG433, 5-HO-IN-JT333, IN-KB687, and Metabolite F (D263986, S. Levy, 07/10/2000). Through the submission of a subsequent feeding study (MRID No. 46114302), adequate data were provided and the relevant residues of concern for tolerance enforcement and risk assessment were established in poultry (D297936, S. Levy, 09/22/2004). The tolerance expression for poultry commodities was concluded to be indoxacarb, its R-enantiomer, and the metabolites IN-JT333, IN-JU873, IN-KB687, IN-KG433, and IN-KT319. For risk assessment, the residues of concern for poultry were concluded to be indoxacarb, its R-enantiomer, and the metabolites IN-JT333, IN-JU873, IN-KB687, IN-KG433, IN-KT319, 5-HO-IN-JT333, and Metabolite F.

5.1.2 Summary of Environmental Degradation

Indoxacarb was found to be immobile and persistent in soil. The major routes of degradation of indoxacarb include alkaline-catalyzed hydrolysis, photodegradation in water, and microbial-mediated degradation. The environmental fate and transport of indoxacarb included the degradation products IN-JT333, IN-KG433, IN-KT413, and IN-ML437-0H. Indoxacarb was characterized to have a rapid initial rate of degradation followed by a much slower degradation rate. The degradation pathway of indoxacarb generally proceeds as oxidative mineralization to CO_2 and residue incorporation into non-extractable soil organic matter.

5.1.3 Comparison of Metabolic Pathways

There are several minor differences in the metabolic pathways of indoxacarb found in the rat and plants and livestock. These studies show that the breakdown of indoxacarb is initially the same in the rat, as well as in plants and livestock, but then slight differences do appear as metabolism proceeds. In plants, indoxacarb is fairly stable, even at 90-days, and what does break-down went to CO_2. The IN-MP819 metabolite formed in livestock (ruminants and poultry) does not appear in the rat, or as an intermediate in its metabolic pathway. Furthermore, it appears that the amine group in indoxacarb can be cleaved in the metabolic pathway of rotated crops (to a limited extent as it is not a residue of concern), but not in the rat. In poultry, a number of quantifiable metabolites structurally similar to the parent were identified and concluded to be residues of concern.

5.1.4 Residues of Concern Summary and Rationale

The indoxacarb residues of concern concluded for plants, livestock, and drinking water are shown below in Table 5.1.4. The chemical name and structure of the indoxacarb residues of concern are provided in Appendix E.

Table 5.1.4. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression[1]

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Indoxacarb and its R-enantiomer	Indoxacarb and its R-enantiomer
	Rotational Crop	Indoxacarb and its R-enantiomer	Indoxacarb and its R-enantiomer
Livestock	Ruminant	Indoxacarb and its R-enantiomer (for all) Metabolite IN-MP819 (for milk only)	Indoxacarb and its R-enantiomer
	Poultry	Indoxacarb, its R-enantiomer, and the metabolites IN-JT333, IN-JU873, IN-KB687, IN-KG433, IN-KT319, 5-HO-IN-JT333, and Metabolite F	Indoxacarb , its R-enantiomer, and the metabolites IN-JT333, IN-JU873, IN-KB687, IN-KG433, and IN-KT319
Drinking Water		Indoxacarb, its R-enantiomer, and the degradation products IN-JT333, IN-KG433, IN- KT413, and IN-ML437-0H	NA

[1] Adapted from: S. Levy, D325479, 03/09/2007; and D402100, Christopher M. Koper, 11/06/2012.

5.2 Food Residue Profile

The proposed new application of indoxacarb for controlling ants is a non-food use, and tolerances are not required for this requested registration. In regard to Registration Review, the residue chemistry database for indoxacarb is complete in supporting all established uses. The nature of the residue is adequately understood with indoxacarb and its R-enantiomer having been concluded to be the residue of concern for tolerance expression and risk assessment in plants and ruminants (metabolite IN-MP819 is included in milk only for risk assessment). For poultry commodities, indoxacarb and its R-enantiomer along with several structurally similar metabolites are included in the tolerance expression and for risk assessment. Field trial data have been evaluated for determining the magnitude of indoxacarb residues of concern in/on all registered food and feed crops. Residues are quantifiable in food and feed crops, and tend to decline with increasing pre-harvest intervals (PHIs). Adequate storage stability data show that residues are relatively stable in frozen storage on a wide variety of plant commodities for up to 19-23 months as shown in corn forage, stover and ears. Empirical processing data for wet apple pomace, and grape raisins indicate that the residues of indoxacarb concentrate in these processed commodities. There are tolerances required for livestock commodities because finite residues can occur in the edible tissues of meat, milk, poultry, and eggs. Data for confined rotational crops demonstrate that a 30-day plant-back interval is appropriate for non-labeled crops. Adequate residue data have been submitted in order to set tolerances and support all registered uses. No additional residue chemistry data are required.

5.3 Water Residue Profile

Drinking water exposure is possible, since indoxacarb is used outdoors to treat crops. The drinking water residues for dietary assessment attributed to the proposed new use for controlling ants was evaluated by EFED in the memorandum: *Indoxacarb: Drinking Water Exposure Assessment for Proposed New Uses to Control a Variety of Ants on Commercial Nurseries, Sod Farms, and Pastures for Grazing Companion Animals* (D436386, C. Koper, 02/13/2017). A subsequent drinking water assessment was also conducted by EFED for the purpose of Registration Review and to support a proposed new use on field corn in the memorandum: *Indoxacarb: Drinking Water Assessment to Support Registration Review and a Proposed New Use on Corn* (D439057, C. Koper, 04/03/2017). A human health risk assessment for the proposed new use on field corn is forthcoming and not addressed herein.

For the assessment of drinking water residues, EFED used a total residue modeling approach to account for the environmental fate and transport of indoxacarb plus its degradation products of concern which were determined by the HED MARC. Both updated EFED memorandums report that the exposure estimates generated in the 2015 drinking water assessment will remain current for dietary assessment (D430585, C. Koper, 12/18/2015). For surface water, the EDWCs generated for the proposed new uses did not exceed the previous EDWCs for use on cranberry. For groundwater, a pesticide root zone model-groundwater (PRZM-GW) simulation was executed for leafy green vegetables, which has the highest annual use rate of all registered crops as well as for the proposed new uses. With a rate revision on the proposed label, the previous SCI-GROW peak (acute) concentration of 0.33 µg/L and chronic concentration of 0.33 µg/L were revised using PRZM-GW modeling to estimate the current acute concentration of **131 µg/L** and chronic concentration of **123 µg/L** which represents leafy green vegetables (4 seasons). These EDWCs reported in Table 5.3 below remain recommended for dietary assessment. These models and their descriptions are available at the EPA internet site: http://www.epa.gov/oppefed1/models/water/.

Table 5.3. Recommended Indoxacarb Estimated Drinking Water Concentrations (EDWCs)[1] for Surface Water and Ground Water

Model	Scenario[1]	Method[2]	Maximum Application Rate (interval between applications; # seasons)	1-in-10 year acute (µg/L)	1-in-10 year chronic (µg/L)	30- year average (µg/L)
Surface Water						
SWCC	Leafy Green Veggies (CA Lettuce)	A	16 app @ 0.11 lb a.i./acre (3 days; 4 seasons)	39	16	11
Ground Water						
PRZM-GW	WI Sands	--	16 app @ 0.11 lb a.i./acre (4 seasons)	**131**	**123[3]**	

[1] For surface water (SWCC), EDWC values are adjusted with a Percent Cropped Area (PCA) factor of 1.0
[2] A = aerial application
[3] For PRZM-GW, the chronic value is represented by the post-breakthrough average concentration.
Bold values denote recommended EDWCs

5.4 Dietary Risk Assessment

5.4.1 Overview of Residue Data Used

Because the proposed new application of indoxacarb for controlling ants is a non-food use, there is no dietary contribution of additional food residues to consider for this requested registration. Refined acute probabilistic and chronic dietary exposure assessments were conducted for all established uses of indoxacarb and drinking water to support Registration Review (D438790, D. Nadrchal, 5/3/2017). These dietary analyses include the updated commodities contained in the crop group conversions which are recommended for implementation. Model-derived EDWCs of 131 ppb for the acute concentration and 123 ppb for the chronic concentration were provided by EFED for these analyses. For all food commodities, residue-distribution files (RDFs) to simulate point estimates for probabilistic determination were used for acute dietary assessment and anticipated residues (ARs) to estimate average concentrations were used for chronic screening level usage analysis (SLUA). December 5, 2016, Reporting Years: 2005-2015 were used for refinement of this dietary assessment. For the acute dietary risk assessment, the following maximum percent crop treated estimates were used: apples: 10%; apricots: 15%; blueberries: 5%; broccoli: 70%, cabbage: 35%; cantaloupe: 10%; cauliflower: 60%; celery: 5%; cherries: 2.5%; cotton: 2.5%; cucumbers: 10%; grapes: 5%; lettuce: 15%; nectarines: 15%; peaches: 10%; peanuts: 10%; pears: 2.5%; peppers: 30%; plumes/prunes: 5%; potatoes: 2.5%; soybeans: 2.5%; spinach: 5%; squash: 5%; sweet corn: 10%; and tomatoes: 40%.

For the chronic dietary assessment, the following average percent crop treated estimates were used: apples: 5%; apricots: 5%; blueberries: 5% broccoli: 45%, cabbage: 20%; cantaloupe: 5%; cauliflower: 35%; celery: 5%; cherries: 2.5%; cotton: 2.5%; cucumbers: 2.5%; grapes: 2.5%; lettuce: 5%; nectarines: 15%; peaches: 2.5%; peanuts: 5%; pears: 1%; peppers: 15%; plumes/prunes: 5%; potatoes: 2.5%; soybeans: 1%; spinach: 2.5%; squash: 2.5%; sweet corn: 2.5%; and tomatoes: 20%.

For all other crop commodities with indoxacarb uses, 100% of the crop treated was assumed.

5.4.3 Acute Dietary Risk Assessment

The acute risk estimates determined for indoxacarb were found to be below the Agency's level of concern at the 99.9th exposure percentile for the general U.S. population and all population subgroups (i.e., <100% of the acute population adjusted dose (aPAD)). The most highly exposed population subgroup is children ages 1-2 with an estimate for indoxacarb for food and water of 47% of the aPAD with an exposure of 0.056707 mg/kg/day at the 99.9th percentile.

5.4.4 Chronic Dietary Risk Assessment

The chronic risk estimates determined for indoxacarb were found to be below the Agency's level of concern for the general U.S. population and all population subgroups (i.e., <100% of the chronic population adjusted dose (cPAD)). The most highly exposed population subgroup is all infants with an estimate for indoxacarb for food and water of 36% of the cPAD with an exposure of 0.007154 mg/kg/day.

5.4.5 Cancer Dietary Risk Assessment

A cancer dietary exposure and risk assessment was not conducted since indoxacarb is not likely to be carcinogenic to humans.

5.4.6. Dietary Assessment Summary Tables

The results of the acute and chronic dietary exposure analyses are reported in Table 5.4.6. Risks are below the level of concern of (< 100%) of the PAD.

Table 5.4.6. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Indoxacarb

Population Subgroup	Acute Dietary[1] (99.9th Percentile)		Chronic Dietary[2]	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.034679	29	0.003125	16
All Infants (< 1 year old)	0.053645	45	**0.007154**	**36**
Children 1-2 years old	**0.056707**	**47**	0.004891	24
Children 3-5 years old	0.050904	42	0.004079	20
Children 6-12 years old	0.034701	29	0.002872	14
Youth 13-19 years old	0.027210	23	0.002262	11
Adults 20-49 years old	0.025581	21	0.003043	15
Adults 50-99 years old	0.031981	27	0.003120	16
Females 13-49 years old	0.026226	22	0.003029	15

[1] Acute dietary analysis derived from a 0.12 mg/kg/day aPAD.
[2] Chronic dietary analysis derived fom a 0.02 mg/kg/day cPAD.
[3] Highest exposures found for eachassessment are noted in bold.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are no proposed new residential uses at this time. However, indoxacarb is currently registered on a number of residential use sites and on pets. The indoor uses include spot, and crack and crevice applications. Outdoor applications in residential use sites include broadcast (i.e., turf), perimeter and foundations, spot (i.e., direct mound applications for fire ants), and crack and crevice applications. Indoxacarb products for residential use sites are formulated as RTU bait stations, granules, gels, WDG, and RTU spot-ons. There are a number of products without PPE that are intended for use by residential handlers and have been assessed for both handler and post-application exposures. However, the following labels: EPA Reg. Nos. 100-1481, 100-1487, 100-1501, 352-597, 352-598, 352-638, and 352-906 require PPE to be worn by handlers. These labels were not considered to be marketed for residential handlers and have been considered only for residential post-application exposures. Turf transferable residue (TTR) studies (MRID 4679820) and pet spot-on data (MRIDs 47834502; 48010801) were submitted for indoxacarb, reviewed and determined to be acceptable for use in risk assessment.

6.1 Residential Handler Exposure

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are addressed

somewhat differently by HED as homeowners are assumed to complete all elements of an application without use of any protective equipment.

There are registered indoxacarb product labels with residential use sites (e.g., around perimeters of homes, around ornamental plants, around home gardens, outdoor applications on sidewalks, turf, patios, and driveways; and pet treatments) that do not require specific clothing (e.g., long sleeve shirt/long pants) and/or PPE, and these labels have been considered in the residential handler assessment for indoxacarb.

Residential handler inhalation exposure is considered negligible for applying RTU pet spot-ons. Residential handler dermal exposures are expected for RTU pet spot-ons, however were not assessed due to the lack of a dermal endpoint. Residential handler inhalation and dermal exposures are considered negligible for applying RTU arenas (i.e., baits or stations)

Spot and crack and crevice exposures were not assessed due to formulation types that minimize the potential for handler and post-application exposures (i.e., gels or bait stations). Risks from spot and crack and crevice were not assessed since exposures from these formulation types are expected to be negligible.

A dermal assessment was not conducted, due to the lack of a dermal endpoint.
The quantitative exposure/risk assessment developed for residential handlers is based on the following scenarios:

- Outdoor Area Treatments (e.g., lawns, around residential structures, around home gardens, around ornamentals, and around perimeters of homes)
    - Applying granules via push-type rotary spreader,
    - Applying granules via belly grinder, and
    - Applying granules via spoon.

Residential Handler Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the residential handler risk assessments. Each assumption and factor is detailed below.

Application Rate:
Application rates and use pattern are summarized in Appendix F.

Unit Exposures and Area Treated or Amount Handled:
Unit exposure values and estimates for area treated or amount handled were taken from HED's 2012 Residential SOPs[5].

Exposure Duration:
Residential handler exposure is expected to be short-term in duration. Intermediate-term exposures are not likely because of the intermittent nature of applications by homeowners.

[5] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Residential Handler Non-Cancer Exposure and Risk Estimate Equations

The algorithms used to estimate exposure and dose for residential handlers can be found in the 2012 Residential SOPs[6].

Combining Exposures/Risk Estimates:

A quantitative dermal assessment is not required for indoxacarb; therefore, only residential handler inhalation exposures are quantitatively assessed.

Summary of Residential Handler Non-Cancer Exposure and Risk Estimates

The proposed new uses are not expected to result in residential exposure.

All residential handler scenarios for registered uses resulted in inhalation risk estimates greater than the LOC (inhalation MOE ≥ 30) and are not of concern. The MOEs range from 92 to 5,500,000.

Table 6.1.1. Residential Handler Non-cancer Exposure and Risk Estimates for Indoxacarb.

Exposure Scenario	Level of Concern	Inhalation Unit Exposure (mg/lb ai)	Maximum Application Rate[1]	Area Treated or Amount Handled Daily[2]	Inhalation	
					Dose (mg/kg/day)[3]	MOE (LOC = 30)[4]
Gardens/trees via push-type rotary spreader	30	0.0026	0.00075lb ai/ft^2	1200 ft^2	0.000029	3,100
Lawns/turf via push-type rotary spreader	30	0.0026	0.0039 lb ai/A	0.5 acres	0.000000063	1,400,000
Lawns/turf via belly grinder	30	0.039	0.00075 lb ai/ft^2	1200 ft^2	0.00044	210
Gardens/trees via spoon	30	0.087	0.00075 lb ai/ft^2	1200 ft^2	0.00098	92
Lawns/turf via spoon	30	0.087	0.00075 lb ai/ft^2	100 ft^2	0.000082	1,100
Gardens/trees via shaker can	30	0.013	0.00075 lb ai/ft^2	1200 ft^2	0.00015	620
Mound treatment via shaker can	30	0.013	0.00002 lb ai/mound	5 mounds/day	0.000000016	5,500,000

1 Based on registered labels (See).
2 Based on HED's 2012 Residential SOPs (http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre, ft^2 or mound) × Area Treated (A, ft^2 or mounds/day) ÷ BW (80 kg).
4 Inhalation MOE = Inhalation HED (0.092 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

6.2 Residential Post-Application Exposure

Post-application exposure to the RTU bait arenas/station and gel registered end-use products is expected to be negligible, given that the use directions specify the products are only to be applied in areas not accessible to children or animals, and when used indoors, the products are in tamper- and child- resistant packaging. There is potential for post-application exposure for other registered uses for individuals exposed as a result of being in an environment that has been previously treated with indoxacarb. Indoxacarb can be used in areas frequented by the general population including residences, golf courses, and indoor premises such as schools, hotels, and hospitals. The quantitative

[6] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

exposure/risk assessment for residential post-application exposures is based on the following scenarios:

- Children (1 to <2 years old) incidental oral exposure to treated turf,
- Children (1 to <2 years old) incidental oral exposure to treated pets,
- Children (1 to <2 years old) episodic granular ingestion,
- Adult inhalation exposures to spot and crack and crevice applications, and
- Children (1 to <2 years old) incidental oral exposures to spot and crack and crevice applications.

Post-application assessments were not conducted for the ant mound uses, since these are considered perimeter/spot uses; residential exposure is expected to be negligible. Spot and crack and crevice exposures were not assessed for gels or bait stations; exposure is considered negligible. A golfer assessment was not conducted, due to the lack of a dermal endpoint.

Post-application inhalation exposure is generally not assessed following application to pets and turf. The combination of low vapor pressure ($1.9x10^{-10}$ mm Hg at 25 °C for indoxacarb) for chemicals typically used as active ingredients in pet and turf pesticide products, and the small amounts of pesticide applied to pets is expected to result in only negligible inhalation exposure.

Ingestion of granules is considered an episodic event and not a routine behavior. Because HED does not believe that this would occur on a regular basis, our concern for human health is related to acute poisoning rather than short-term exposure. Therefore, an acute dietary endpoint and point of departure are used to estimate exposure and risk resulting from episodic ingestion of granules applied to turf.

Hand-to-mouth (HTM) exposures are protective of object-to-mouth (OTM) exposures.

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[7]. While not the only lifestage potentially exposed for these post-application scenarios, the lifestage that is included in the quantitative assessment is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

Residential Post-application Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Each assumption and factor is detailed in the 2012 Residential SOPs[7].

Lawn/Turf Scenarios

Indoxacarb liquid, granular, and water dispersible granular formulations are registered for use in residential lawns, recreational areas and golf courses. Residential exposure and risk estimates were conducted for residential post-application activities associated with these turf uses.

- The exposure and risk estimates for the residential exposure scenarios are assessed for the day of application (day "0") because it is assumed that adults and children could contact the lawn immediately after application.

[7] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

A chemical-specific (indoxacarb) turf transferable residue (TTR) study (MRID 46798201, D363731) was used to estimate post-application exposure to children (1 to < 2 years old) for the turf exposures scenarios. Data were collected at three sites with the application of a soluble concentrate/liquid formulation in the TTR study including New York, California, and North Carolina at a rate of 0.22 lb ai/A. The data from this study were used to assess incidental oral ingestion exposure on turf. The average highest predicted Day 0 residue data from the three sites was used in this assessment (*i.e.* TTR= 0.023 $\mu g/cm^2$). TTRs were adjusted to account for differences in application rates. The liquid formulation scenario was assessed at a maximum application rate of 0.225 lb/A (0.0675 lb total active isomer/A) or 0.5 fl. oz/1,000 ft^2 (0.0065 lb total isomer/1000 ft^2 or per gallon) for registered broadcast uses on turf grass, which represents a 30% active S-enantiomer labeled rate. The default predicted Day 0 TTR value of 0.031 $\mu g/cm^2$ was used for the liquid formulation assessment. The occupational and residential exposure assessment (U. Hassan, D438791, 6/22/2017) provides summaries of the study.

Treated Pets Scenarios

Post-application incidental oral exposures from spot-on treatments of liquid formulations of indoxacarb on dogs and cats were assessed previously (Rivera-Lupianez, A., D411342; 5/1/2013). Post-application inhalation exposures are not expected from treated pets.

- Application rates: 0.00044 lb ai/pet (medium sized cat spot-on treatments: EPA Reg. No.773-93); 0.002 lb ai/pet (extra-extra-large dog spot-on treatments: EPA Reg. No.773-94); and 0.017 lb ai/pet (extra-extra-large dog spot-on treatments: EPA Reg No. 773-95). These are worst-case estimates for each cat and dog based on application rate and pet surface area (SA).
- Short-, intermediate- and long-term post-application incidental oral exposure risk estimates are presented. The post-application exposure estimated doses are based on day of application residues (*i.e.,* Day 0). Due to temperate climates in some parts of the country, the potential exists for pet pest pressures and resulting treatment to extend beyond a short-term duration (*i.e.,* intermediate- and long-term).
- Two indoxacarb dislodgeable residue studies: the "Dislodgeable Residue Study of SCH 783460 from Spot-On Treated Beagle Dogs" (MRID 47834502), and the "One-Month Dislodgeable Residue Study of SCH 783460 from Spot-On Treated Cats" (MRID 48010801) were used to estimate the fraction of the application rate available as transferable residue (F_{AR}) from indoxacarb pet treatments. The post-application studies were conducted to measure the transferability of the test substance SCH 783460, a spot-on formulation of indoxacarb, over time from the hair coat of treated pets to a gloved mannequin hand. In each study the test substance, SCH 783460, was administered to 10 pets (10 beagle dogs for the dog study and 10 cats for the cat study), by topical application to the back using plastic syringes. Indoxacarb residues were measured on treated pets after stroking the pets three times per simulation, for 10 simulations (30 strokes total) with a mannequin hand fitted with two cotton gloves over top of a nitrile glove. The cotton and nitrile glove samples were analyzed for indoxacarb (SCH 783460) and the active metabolite JT333. The residue levels of indoxacarb in each glove were reported and used for calculating the percent of dislodgeable residues. Residues were calculated in µg/glove, $\mu g/cm^2$ of dog/cat surface area, and percent of applied dose transferred. For the dog study, indoxacarb average residues from all three gloves combined increased from 4,037 µg/glove (1.78% of applied dose and 0.65 $\mu g/cm^2$) at 4 hours after application to a maximum of 5,690 µg/glove (2.55% of applied dose and 0.926 $\mu g/cm^2$) at 1 day after application. Residues then declined to 177 µg/glove (0.078% of applied dose and 0.028 $\mu g/cm^2$) by Day 28 after application. For the cat study,

indoxacarb average residues from all three gloves combined decreased from 1,941 µg/glove (1.24% of applied dose and 0.56 µg/cm^2) at 4 hours after application to 227 µg/glove (0.141% of applied dose and 0.064 µg/cm^2) by Day 28 after application. Time weighted average (TWA) values of .0276 and 0.012 were used to assess short-term exposure and 0.0276 and 0.0062 were used to assess intermediate- and long-term exposures from spot on treatments on dogs and cats respectively, in lieu of the Agency's default value for transfer, 2% (*i.e.*, F_{AR}=0.020). The occupational and residential exposure assessment (U. Hassan, D438791, 6/22/2017) provides summaries of the studies and references for Agency reviews.

For surface area estimates, because registered weight ranges do not correspond with those recommended by the Treated Pet SOP [i.e., dogs - small (3000 cm^2), medium (7000 cm^2) and large (11,000 cm^2); cats - small (1500 cm^2), medium (2500 cm^2) and large (4000 cm^2)], the following algorithm recommended by the Treated Pet SOP was used to determine the dog and cat surface areas: (12.3*((animal body weight (lbs)*454)^0.65)). In order to be most conservative, HED selected the low end weight of each dog and cat weight range for surface area calculation. The resulting dog and cat surface areas are as follows: dogs – small (4 lb), 1616 cm^2; medium (14 lb), 3647 cm^2; large (22 lb), 4893 cm^2; extra-large (44 lb), 7678 cm^2; and extra-extra-large (88 lb), 12048 cm^2; cats – small (2 lb), 1030 cm^2; and medium (9 lb) 2737 cm^2.

Residential Post-application Non-Cancer Exposure and Risk Equations

The algorithms used to estimate residential post-application exposure and dose can be found in the 2012 Residential SOPs[8].

Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates

All residential post-application MOEs are greater than the LOC of 100, and are therefore not of concern (Table 5.2.1). MOEs ranged from 470 to 16,000.

Table 6.2.1. Residential Post-application Non-cancer Exposure and Risk Estimates for Indoxacarb

Lifestage	Post-application Exposure Scenario		Application Rate/Residue/% Active Ingredient[1]	Dose (mg/kg/day)[2,3]	MOEs[4] LOC = 100
	Use Site	Route of Exposure			
Child (1 <2 years)	Lawns/Turf	HTM)	0.031 µg/cm^2	0.00424	470
Child (1 <2 years)	Treated Pets (Dogs)	HTM	600 mg ai/pet	0.00275	730 (short-term)
				0.00275	730 (intermediate- and long-term)
	Treated Pets (Cats)	HTM	100 mg ai/pet	0.00153	1,300 (short-term)
				0.00075	2,700 (intermediate- and long-term)

[8] http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Table 6.2.1. Residential Post-application Non-cancer Exposure and Risk Estimates for Indoxacarb					
Lifestage	**Post-application Exposure Scenario**		**Application Rate/Residue/% Active Ingredient[1]**	**Dose (mg/kg/day)[2,3]**	**MOEs[4] LOC = 100**
	Use Site	**Route of Exposure**			
Child (1 <2 years)	Lawns/Turf	Episodic Granule Ingestion	0.045%	0.01	980
Adult	Spot and Crack and Crevice	Inhalation	0.008 lb ai/gal	0.00000069	100,000
Child (1<2 years)		Inhalation	0.008 lb ai/gal	0.0000029	24,000
Child (1<2 years)	Spot (Coarse) Carpet	HTM	0.000008 lb ai/ft^2	0.011559023	170
	Spot (Coarse) Hard Surfaces		0.000008 lb ai/ft^2	0.003853008	520
Child (1<2 years)	Spot (Pin Stream) Carpet	HTM	0.000008 lb ai/ft^2	0.011559023	170
	Spot (Pin Stream) Hard Surfaces		0.000008 lb ai/ft^2	0.003853008	520
Child (1<2 years)	Crack and Crevice Carpet	HTM	0.000008 lb ai/ft^2	0.002298509	870
	Crack and Crevice Hard Surfaces		0.000008 lb ai/ft^2	0.00076617	2600

1 Based on application rates (AR) from labels that led to highest exposure: Actyvil Liquid RTU Formulation for spot-on treatments on cats (EPA Reg. No. 773-93) and dogs (EPA Reg. No 773-94; 773-95)

2 *Fraction Application Rate* (F_{ar}) = Peak amount of indoxacarb removed as a fraction of dose applied from MRIDs: 48135325 and 48010801; Far = 0.0255 (dogs); 0.0124 (cats).

3 *Hand-to-Mouth Dose* (mg/kg/day) = [(Hand Residue Loading (mg/cm^2) × Fraction of Hand Mouthed × Surface Area of 1 Hand (150 cm^2) × Exposure Time (1.5 hrs/day) × # of Replenishment Intervals/hr (4 int/hr) × (1-((1-Saliva Extraction Factor (0.5))^(Number of Hand-to-Mouth Events per Hour (13.9 events/hr))÷ (# of Replenishment Intervals/hr))] / Body Weight (11 kg child 1 < 2 years old)]

4 Incidental Oral MOE = NOAEL (2 mg/kg/day; KN128)/ Incidental Oral Dose (mg/kg/day). Episodic Granule Ingestion MOE = NOAEL (12 mg/kg/day) / Episodic granule ingestion dose (mg/kg/day).
lb ai to mg ai: 1 lb = 453,592 mg

6.3 Residential Risk Estimates for Use in Aggregate Assessment

Table 6.3.1 reflects the residential risk estimates that are recommended for use in the aggregate assessment for indoxacarb. Ingestion of granules is considered an episodic event and not a routine behavior. Because HED does not believe that this would occur on a regular basis, our concern for human health is related to acute poisoning rather than short-term residue exposure. For these reasons, the episodic ingestion scenario is not recommended for inclusion in the aggregate assessment. The only residential route of exposure for inclusion in the adult aggregate assessment is inhalation. However, inhalation exposures cannot be aggregated with background dietary exposures since the toxicity endpoints for the inhalation and short-term oral routes are different. Therefore, only residential exposures for children are presented below.

- The recommended residential exposure for use in the children 1 to <2 years old short-term aggregate assessment reflects hand-to-mouth exposures from post-application exposure to spot treatment on carpets (coarse and pin stream).
- The recommended residential exposure for use in the children 1 to <2 years old intermediate- and long-term aggregate assessment reflects exposures from treated pets (cats).

Table 6.3.1. Recommendations for the Residential Exposures for the Indoxacarb Aggregate Assessment.

Lifestage	Exposure Scenario	Dose (mg/kg/day)[1]				MOE[2]			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Short-Term									
Child	Spot (Coarse and Pin Stream) Carpet	N/A	N/A	0.011559023	0.011559023	N/A	N/A	470	**170**
Intermediate- and Long-Term									
Child	Treated Pets (Dogs)	N/A	N/A	0.00242	**0.00275**	N/A	N/A	730	**730**

1 Dose = the highest dose for each applicable lifestage of all residential scenarios assessed. Total = dermal + inhalation + incidental oral (where applicable).
2 MOE = the MOEs associated with the highest residential doses.

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.

Based on the existing and newly proposed uses of indoxacarb, exposures can occur both from dietary sources (food and water) and in residential settings. Residential uses of indoxacarb resulting in the highest estimated exposures include spot-treatment of companion animals (cats) and uses on turf (lawns).

The aggregate risk assessments are intended to be representative of exposures that are likely to co-occur. The scenarios expected to result in the highest exposures are used as representative scenarios for the

aggregate assessment and are considered protective of other scenarios. The lifestages selected for the aggregate assessments represent the population subgroups expected to be the most highly exposed for each scenario. For more information on the residential exposure scenarios selected for aggregate assessment, see Section 6.3 above.

7.1 Acute Aggregate Risk

Typically, HED does not consider residential exposures when assessing acute aggregate risk unless such exposures can be characterized as a series of single-day exposures, which is not the case for indoxacarb. Therefore, acute aggregate risk estimates for indoxacarb are equivalent to the acute dietary (food and drinking water) risk estimates (Section 5.4) and are below HED's level of concern.

7.2 Short-Term Aggregate Risk

The short-term aggregate risk for indoxacarb includes background contribution from dietary (food and drinking water) exposure plus the short-term residential exposures from post-application exposure to lawns/turf. The short-term aggregate risk estimate for children post-application exposure to lawns/turf is not of concern (Table 7.2.1). For adults, since residential exposures cannot be aggregated because of different effects, the short-term aggregate risk assessment for indoxacarb is equivalent to chronic dietary risk assessment conducted in Section 5.4 of this document and is not of concern.

Table 7.2.1 Short-Term Aggregate Risk Calculations

Population	Short- Term Scenario				
	LOC for Aggregate Risk[1]	Dietary MOE[2]	MOE Oral Residential Exposure[3]	MOE Inhalation Residential Exposure[4]	Aggregate MOE (food, water, and residential)[5]
Child (1<2 yrs)	100	410[2]	170	NA	120

[1] LOC=100 (10x inter- and 10x intra- species uncertainty factors)
[2] MOE dietary = [(short-term oral NOAEL)/(chronic dietary exposure)]. Oral NOAEL= 2 mg/kg/day. Chronic dietary exposure values from Table 5.4.6 (0.004891 mg/kg/day for children 1-2 years old).
[3] MOE oral = [(short-term oral NOAEL)/(hand-to-mouth residential exposure)]. Oral NOAEL= 2 mg/kg/day. Oral exposure value from Table 6.3.1 (Spot/Carpet – coarse and pin stream).
[4] Not applicable. Inhalation exposures not combined due to differences in effects.
[5]MOE Aggregate = 1/[(1/MOE dietary) + (1/MOE oral)]

For indoxacarb, the child lifestage with the highest dietary exposure (all infants <1 year old) does not match the child lifestage with the highest residential exposure (children 1 to <2 years old). The lifestages selected for each residential post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[1]. This analysis provides a quantitative and qualitative basis for why children 1 to <2 years old are the representative lifestage for most residential post-application scenarios involving young children, as well as reasons why a residential assessment is not conducted for infants. For children, therefore, the indoxacarb aggregate assessment only combines the residential exposure estimates for children 1 to <2 years old with the dietary exposure estimates for that same lifestage, children 1-2 years old.

7.3 Intermediate-/Long-Term (Chronic) Aggregate Risk

The intermediate-/long-term (or chronic) aggregate risk for indoxacarb includes contribution from dietary (food and drinking water) exposure plus the intermediate-/long-term post-application exposure to treated pets. The intermediate-/long-term aggregate risk estimate for children post-application exposure is not of concern (Table 7.3.1). For adults, since residential exposures cannot be aggregated because of different toxic effects observed from oral vs. inhalation exposure, the intermediate-/long-term aggregate risk assessment for indoxacarb is equivalent to chronic dietary risk assessment conducted in Section 5.4 of this document and is not of concern.

Table 7.3.1 Long- Term Aggregate Risk Calculations. ***Post-Application Treated Pets (KN128)***

Population	Long-Term Scenario				
	LOC for Aggregate Risk[1]	Dietary MOE[2]	MOE Oral Residential Exposure[3]	MOE Inhalation Residential Exposure[4]	Aggregate MOE (food, water, and residential)[5]
Child (1<2 yrs)	100	410	730	NA	260

[1] LOC=100 (10x inter- and 10x intra- species uncertainty factors)
[2] MOE dietary = [(intermediate- and long-term oral NOAEL)/(chronic dietary exposure)]. Oral NOAEL= 2 mg/kg/day. Chronic dietary exposure values from Table 5.4.6 (0.004891 mg/kg/day for children 1-2 years old).
[3] MOE oral = [(intermediate-/long-term oral NOAEL)/(hand-to-mouth residential exposure)]. Oral NOAEL= 2 mg/kg/day. Residential exposure value from Table 6.3.1 (Treated Pets - dogs).
[4] Not applicable. Inhalation exposures not combined due to differences in effects.
[5]MOE Aggregate = 1/[(1/MOE dietary) + (1/MOE oral]

7.4 Cancer Aggregate Risk

Indoxacarb is classified as "Not Likely to be Carcinogenic to Humans;" therefore, cancer risk is not a concern and cancer risks are not quantified.

8.0 Residential Bystander Post-application Inhalation Exposure

For agricultural/commercial outdoor uses, 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 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for indoxacarb.

9.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with

residues can eventually lead to indirect exposures (e.g., children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them. Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

Several indoxacarb products have existing labels for use on turf, thus it was considered whether the risk assessment for that use may be considered protective of any type of exposure that would be associated with spray drift. It should be noted that the registered residential uses on turf result in exposure greater than potential exposure from spray drift; therefore, no new residential assessment needs to be completed. If the maximum application rate on crops adjusted by the amount of drift expected is less than or equal to existing turf application rates, the existing turf assessment is considered protective of spray drift exposure. Note that this assumes similar formulations are being applied to the agricultural crops and the residential turf (i.e., if a granular product is registered for use on residential turf, the scenarios assessed for that use may not be protective of liquid applications made to agricultural crops). The currently registered maximum single application rate of indoxacarb for various crops is 0.11 lb ai/A. The highest degree of spray drift noted for any application method immediately adjacent to a treated field (Tier 1 output from the aerial application using fine to medium spray quality) results in a deposition fraction of 0.26 of the application rate. A quantitative spray drift assessment for indoxacarb is not required because the maximum application rate to a crop/target site multiplied by the adjustment factor for drift of 0.26 (0.0286 lb ai/A) is less than the maximum direct spray residential turf application rate (0.225 lb ai/A) for any indoxacarb products and resulted in no risk estimates of concern. The turf post-application MOEs have been previously assessed and are based on the revised SOPs for Residential Exposure Assessment (i.e., see above in Section 6.2).

10.0 Cumulative Exposure/Risk Characterization

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 as to indoxacarb and any other substances and indoxacarb does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that indoxacarb has a common mechanism of toxicity with other substances. In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[1] and conducting

cumulative risk assessments (CRA)[1]. During Registration Review, the Agency will utilize this framework to determine if the available toxicological data for indoxacarb suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

11.0 Occupational Exposure/Risk Characterization

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Occupational handler inhalation exposure is considered negligible for applying RTU spot-on pet treatments. Dermal exposure was not assessed for treated pets, due to the lack of a dermal endpoint. Spot and crack and crevice exposures were not assessed due to formulation type (gels or bait stations); exposure is considered negligible.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed and registered uses. The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

Proposed New Uses:

- Outdoor Area Treatments - Control of fire ants in commercial nurseries, sod farms, and grazed pastures
    - Mixing/loading granules via aerial application,
    - Mixing/loading granules via tractor-drawn spreader,
    - Applying granules via aerial application,
    - Applying granules via tractor drawn spreader,
    - Flagging for granular aerial application,
    - Loading/applying granules via spoon, and
    - Loading/applying granules via belly grinder.

Registered Uses:
(e.g., *Brassica* Cole leafy vegetables, alfalfa, bushberries, commercial facilities, cucurbit vegetables, dried beans, fruiting vegetables and okra, garden beet, grape, industrial facilities, institutional facilities, peanuts, residential buildings, schools, small fruit vine climbing subgroup except fuzzy kiwi fruit, soybeans, succulent beans, sweet corn, succulent beans, soybeans, sweet corn, residential lawns, golf courses, and athletic fields). The scenarios assessed are listed below:

- Mixing/loading WDG via aerial application,
- Mixing/loading WDG via backpack,
- Mixing/loading WDG via mechanically pressurized handguns,
- Mixing/loading granules via aerial application,
- Mixing/loading granules via tractor-drawn spreader,

- Mixing/loading WDG via chemigation,
- Mixing/loading WDG via groundboom application,
- Mixing/loading WDG via airblast equipment,
- Applying sprays via aerial application,
- Appling sprays via groundboom application,
- Applying sprays via airblast equipment,
- Applying granules via tractor-drawn spreader,
- Appling sprays via mechanically pressurized handgun,
- Applying granules via aerial applications,
- Flagging for aerial application,
- Flagging for granular aerial application,
- Mixing/loading/applying WDG via backpack,
- Mixing/loading/applying WDG via manually pressurized handwand,
- Mixing/loading/applying WDG via mechanically pressurized handgun,
- Loading/applying granules via backpack,
- Loading/applying granules via belly grinder,
- Loading/applying granules via rotary spreader,
- Loading/applying granules via spoon,
- Loading/applying WDG via backpack,
- Loading/applying granules via belly grinder, and
- Loading/applying granules via rotary spreader.

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis.

Application Rate:
Application rates and use pattern information are provided in Appendix F.

Unit Exposures: It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, and the Outdoor Residential Exposure Task Force (ORETF) database. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[9]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[10].

Unit exposure values for granular formulations via backpack, mechanically-pressurized handgun, aerial, and tractor-drawn spreader for rights of way uses are based off of the unit exposures for liquid application via the above methods. The EPA does not currently have data available for granular applications to rights

[9] Available: http://www.epa.gov/sites/production/files/2016-11/documents/handler-exposure-table-2016.pdf
[10] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

of way. The liquid formulation unit exposure values would be considered protective of the granular formulations.

Area Treated or Amount Handled:
The area treated/amount handled estimates can be found in ExpoSAC Policy 9.1.

Exposure Duration:
HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many things, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. For most agricultural uses, it is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region).

For indoxacarb, based on the proposed and registered uses, short- and intermediate-term exposures are expected. However, the inhalation POD selected is applicable to both short- and intermediate-term exposures; therefore, the short-term exposure assessment is protective of both durations.

Mitigation/Personal Protective Equipment: Estimates of inhalation exposure were calculated for various levels of personal protective equipment (PPE). Results are presented for "baseline," defined as a single layer of clothing consisting of a long-sleeved shirt, long pants, shoes plus socks, no protective gloves, and no respirator, as well as baseline with various levels of PPE as necessary (e.g., gloves, respirator, etc.). All indoxacarb product labels direct mixers, loaders, applicators and other handlers to wear baseline attire (long sleeved shirt, long pants, shoes, and socks). Some labels require the addition of waterproof or chemical resistant gloves.

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations
The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in the occupational and residential exposure assessment for indoxacarb (U. Hassan, D438791, 6/22/2017).

Combining Exposures/Risk Estimates:
A quantitative dermal assessment is not required for indoxacarb; therefore, only occupational handler inhalation exposures are quantitatively assessed.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates
All occupational handler inhalation risk estimates for the proposed uses of indoxacarb were not of concern, MOEs > LOC (LOC = 30). MOEs ranged from 55,000 to 3,700,000.

All occupational handler inhalation risk estimates for registered uses of indoxacarb were not of concern, with MOEs > LOC, (LOC=30), except mixing/loading water dispersible granule (WDG) formulations for aerial application to high acreage field crops (MOE = 19). The addition of a PF5 respirator results in risk estimates not of concern, with MOE = 95, (LOC = 30). MOEs with baseline PPE (i.e., no respirator) ranged from 19 to 960,000.

The Agency matches quantitative occupational exposure assessment with appropriate characterization of exposure potential. While HED presents quantitative risk estimates for human flaggers where

appropriate, agricultural aviation has changed dramatically over the past two decades. According the 2012 National Agricultural Aviation Association (NAAA) survey of their membership, the use of GPS for swath guidance in agricultural aviation has grown steadily from the mid 1990's. Over the same time period, the use of human flaggers for aerial pesticide applications has decreased steadily from ~15% in the late 1990's to only 1% in the most recent (2012) NAAA survey. The Agency will continue to monitor all available information sources to best assess and characterize the exposure potential for human flaggers in agricultural aerial applications.

HED has no data to assess exposures to pilots using open cockpits. The only data available is for exposure to pilots in enclosed cockpits. Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeved shirt, long pants, shoes, and socks); per the Agency's Worker Protection Standard stipulations for engineering controls, pilots are not required to wear protective gloves for the duration of the application. With this level of protection, there are no risk estimates of concern for applicators.

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Indoxacarb.

Exposure Scenario	Crop or Target	Level of Concern	Inhalation Unit Exposure (µg/lb ai)[1]	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Inhalation	
			Baseline			Dose (mg/kg/day)[4]	MOE[5] LOC = 30
Proposed New Use							
Mixer/Loader							
Granular Formulation via Aerial	Sod	30	1.7	0.00068 lb ai/A	350 acres	0.00000506	55,000
Granular Formulation via Aerial	Nursery (ornamentals, trees)	30	1.7	0.00068 lb ai/A	60 acres	0.000000868	320,000
Granular Formulation via Tractor-Drawn Spreader	Sod	30	1.7	0.00068 lb ai/A	80 acres	0.00000116	240,000
Granular Formulation via Tractor-Drawn Spreader	Nursery (ornamentals, trees)	30	1.7	0.00068 lb ai/A	60 acres	0.000000868	320,000
Applicator							
Granular Formulation via Aerial	Sod	30	1.3 (EC)	0.00068 lb ai/A	350 acres	0.00000386	73,000
Granular Formulation via Aerial	Nursery (ornamentals, trees)	30	1.3 (EC)	0.00068 lb ai/A	60 acres	0.000000663	420,000
Granular Formulation via Tractor-Drawn Spreader	Sod	30	1.2	0.00068 lb ai/A	80 acres	0.000000816	340,000
Granular Formulation via Tractor-Drawn Spreader	Nursery (ornamentals, trees)	30	1.2	0.00068 lb ai/A	60 acres	0.000000613	460,000
Flagger							
Granular Formulation via Aerial	Nursery (ornamentals, trees)	30	0.15	0.00068 lb ai/A	60 acres	0.0000000765	3,700,000
Granular Formulation via Aerial	Sod	30	0.15	0.00068 lb ai/A	350 acres	0.000000446	630,000
Loader/Applicator							
Granular Formulation via Belly Grinder	Nursery (ornamentals, trees)	30	62	0.00068 lb ai/A	1 acre	0.000000528	530,000
Granular Formulation via Spoon	Mounds/nest	30	121	0.000014 lb ai/mound	100 mounds	0.00000211	130,000

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Indoxacarb.

Exposure Scenario	Crop or Target	Level of Concern	Inhalation Unit Exposure (µg/lb ai)[1]	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Inhalation	
			Baseline			Dose (mg/kg/day)[4]	MOE[5] LOC = 30
Registered Uses							
Mixer/Loader							
WDG Formulation via Aerial	Orchard/vineyard[6]	30	8.96	0.11 lb ai/A	350 acres	0.00431	65
	Field crop, typical[7]	30	8.96	0.11 lb ai/A	350 acres	0.00431	65
	Field crop, high-acreage[8]	30	8.96	0.11 lb ai/A	1200 acres	0.0148	**19** 95 (PF5)
WDG Formulation via Backpack	Rights-of-way	30	8.96	0.005 lb ai/gallon	1000 gallons	0.00056	500
WDG Formulation via Mechanically-pressurized Handgun	Rights-of-way	30	8.96	0.005 lb ai/gallon	1000 gallons	0.00056	500
Granular Formulation via Aerial	Rights-of-way	30	1.7	0.0039 lb ai/A	350 acres	0.0000813	3,400
Granular Formulation via Tractor-drawn Spreader	Rights-of-way	30	1.7	0.0039 lb ai/A	80 acres	0.000106	2,600
WDG Formulation via Chemigation	Orchard/vineyard[6]	30	8.96	0.11 lb ai/A	350 acres	0.00431	65
	Field crop, typical[7]	30	8.96	0.11 lb ai/A	350 acres	0.00431	65
	Field crop, high-acreage[8]	30	8.96	0.11 lb ai/A	1200 acres	0.00431	65
WDG Formulation via Groundboom	Golf course (greens and tees only)	30	8.96	0.225 lb ai/A	5 acres	0.000126	2,200
	Golf course (fairways, tees, greens)	30	8.96	0.225 lb ai/A	40 acres	0.00101	280
	Orchard/vineyard[6]	30	8.96	0.11 lb ai/A	40 acres	0.000493	570
	Field crop, typical[7]	30	8.96	0.11 lb ai/A	80 acres	0.000985	280
	Field crop, high-acreage[8]	30	8.96	0.11 lb ai/A	200 acres	0.00246	110
WDG Formulation via Airblast	Orchard/vineyard[6]	30	8.96	0.11 lb ai/A	40 acres	0.000493	570
Granular Formulation via Tractor-drawn Spreader	Golf course (greens and tees only)	30	1.7	0.00068 lb ai/A	40 acres	0.00000331	85,000
	Golf course (fairways, tees, greens)	30	1.7	0.00068 lb ai/A	5 acres	0.000000415	670,000
Applicator							
Spray (all starting formulations) via Aerial	Orchard/vineyard[6]	30	0.0049 (EC)	0.11 lb ai/A	350 acres	0.00000236	120,000
	Field crop, typical[7]	30	0.0049 (EC)	0.11 lb ai/A	350 acres	0.00000236	120,000
	Field crop, high-acreage[8]	30	0.0049 (EC)	0.11 lb ai/A	1200 acres	0.00000809	35,000
Spray (all starting formulations) via Groundboom	Golf course (greens and tees only)	30	0.34	0.225 lb ai/A	5 acres	0.00000479	58,000
	Golf courses (fairways, tees, greens)	30	0.34	0.225 lb ai/A	40 acres	0.0000383	7,300
	Orchard/vineyard[6]	30	0.34	0.11 lb ai/A	40 acres	0.0000188	15,000
	Field crop, typical[7]	30	0.34	0.11 lb ai/A	80 acres	0.0000374	7,500
	Field crop, high-acreage[8]	30	0.34	0.11 lb ai/A	200 acres	0.0000935	3,000
Spray (all starting formulations) via Airblast	Orchard/vineyard[6]	30	4.71	0.11 lb ai/A	40 acres	0.000259	1,100

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Indoxacarb.							
Exposure Scenario	**Crop or Target**	**Level of Concern**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Inhalation**	
			Baseline			**Dose (mg/kg/day)[4]**	**MOE[5] LOC = 30**
Granular Formulation via Tractor-drawn Spreader	Golf course (greens and tees only)	30	1.2	0.0039 lb ai/A	40 acres	0.00000234	120,000
	Golf course (fairways, tees, greens)	30	1.2	0.0039 lb ai/A	5 acres	0.000000293	960,000
Spray (all starting formulations) via Mechanically-pressurized Handgun	Rights-of-way	30	8.68	0.005 lb ai/gallon	1000 gallons	0.000543	520
Granular Formulation via Aerial	Rights-of-way	30	1.3 (EC)	0.0039 lb ai/A	350 acres	0.0000221	13,000
Granular Formulation via Tractor-drawn Spreader	Rights-of-way	30	1.2	0.0039 lb ai/A	80 acres	0.00000468	60000
Flagger							
Spray (all starting formulations) via Aerial	Orchard/vineyard[6]	30	0.35	0.11 lb ai/A	350 acres	0.000169	1,700
	Field crop, typical[7]	30	0.35	0.11 lb ai/A	350 acres	0.000169	1,700
	Field crop, high-acreage[8]	30	0.35	0.11 lb ai/A	350 acres	0.000169	1,700
Granular Formulation via Aerial	Rights-of-way	30	0.15	0.0039 lb ai/A	350 acres	0.00000256	110,000
Mixer/Loader/Applicator							
WDG Formulation via Backpack	Orchard/vineyard[6]	30	2.58	0.09 lb ai/gal	40 gallons	0.00116	2,400
	Landscaping, trees/shrubs/bushes	30	69.1	0.005 lb ai/gal	40 gallons	0.000173	1,600
	Landscaping, plants/flowers	30	69.1	0.005 lb ai/gal	40 gallons	0.000173	1,600
	Landscaping, turf (lawns, athletic fields, parks, etc.)	30	69.1	0.005 lb ai/gal	40 gallons	0.000173	1,600
	Landscaping, turf (lawns, athletic fields, parks, etc.)	30	2.58	0.005 lb ai/gal	40 gallons	0.00000645	43,000
	Industrial/commercial (tires, railyards, junk yards, etc.)	30	30	0.005 lb ai/gal	40 gallons	0.00012	2,300
	Foundations/perimeter	30	2.58	0.008 lb ai/gal	40 gallons	0.0000103	27,000
WDG Formulation via Manually-Pressurized Handwand	Landscaping, trees/shrubs/bushes	30	30	0.005 lb ai/gal	40 gallons	0.000075	3,700
	Landscaping, plants/flowers	30	30	0.005 lb ai/gal	40 gallons	0.000075	3,700
	Landscaping, turf (lawns, athletic fields, parks, etc.)	30	30	0.005 lb ai/gal	40 gallons	0.000075	3,700
	Industrial/commercial	30	30	0.008 lb ai/gal	40 gallons	0.000868	320
	Food handling establishment	30	1100	0.008 lb ai/gal	40 gallons	0.0044	64
	Warehouse	30	1100	0.008 lb ai/gal	40 gallons	0.0044	64
	Foundations/perimeter	30	30	0.008 lb ai/gal	40 gallons	0.00012	2,300

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Indoxacarb.

Exposure Scenario	Crop or Target	Level of Concern	Inhalation Unit Exposure (µg/lb ai)[1]	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Inhalation	
			Baseline			Dose (mg/kg/day)[4]	MOE[5] LOC = 30
	Mounds	30	30	0.008 lb ai/gal	40 gallons	0.00012	2,300
	Residential living spaces (homes, apartments)	30	1100	0.008 lb ai/gal	40 gallons	0.0044	64
	Childcare centers/schools/institutions	30	1100	0.008 lb ai/gal	40 gallons	0.0044	64
WDG Formulation via Mechanically Pressurized Handgun	Orchard/Vineyard[6]	30	8.68	0.011 lb ai/gal	1000 gallons	0.00119	240
	Golf course (tees and greens only)	30	42	0.225 lb ai/A	5 acres	0.000591	470
	Golf course (fairways, tees, greens)	30	42	0.225 lb ai/A	5 acres	0.000591	470
	Landscaping, trees/shrubs/bushes	30	8.68	0.005 lb ai/gal	1000 gallons	0.000543	520
	Landscaping, turf (lawns, athletic fields, parks, etc.)	30	42	0.225 lb ai/A	5 acres	0.000591	470
	Industrial/commercial	30	8.68	0.008 lb ai/gal	1000 gallons	0.000868	320
	Field crop, typical[7]	30	8.68	0.011 lb ai/gal	1000 gallons	0.00119	240
Loader/Applicator							
Granular Formulation via Backpack	Industrial/commercial	30	23.8	0.0039 lb ai/A	1 acre	0.00000116	240,000
Granular Formulation via Belly Grinder	Nursery (ornamentals, trees); landscaping, turf (lawns, athletic fields, parks, etc.); industrial/commercial; foundations/perimeter	30	62	0.0039 lb ai/A	1 acre	0.00000303	92,000
Granular Formulation via Rotary Spreader	Golf course (fairways, tees, and greens); industrial/commercial; landscaping, turf (lawns, athletic fields, parks, etc.)	30	10	0.0039 lb ai/A	5 acres	0.00000244	110,000
Granular Formulation via Spoon	Mounds	30	121	0.00002 lb ai/mound	100 mounds	0.00000303	92,000
WDG Formulation via Backpack	Rights-of-Way	30	69.1	0.005 lb ai/gallon	40 gallons	0.000173	1,600
Granular Formulation via Belly Grinder	Rights-of-Way	30	62	0.0039 lb ai/A	1 acre	0.00000303	92,000
Granular Formulation via Rotary Spreader	Rights-of-Way	30	10	0.0039 lb ai/A	1 acre	0.000000488	570,000

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (November 2016); Level of mitigation: Baseline, PPE, Eng. Controls.
2 Based on registered or proposed label (See Appendix F).
3 Exposure Science Advisory Council Policy #9.1.
4 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (80 kg).
5 Inhalation MOE = Inhalation HED (0.28 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
6 Orchard/Vineyard crops include: grapes and bushberries
7 Field crop, typical crops include: beets, sweet corn, low growing berries, *Brassica* cole leafy vegetables, cucurbit vegetables, and okra
8 Field-crop, high-acreage crops include: dried beans, succulent beans, alfalfa, peanuts, soybeans, and cotton

11.2 Short- and Intermediate-Term Post-Application Risk

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

11.2.1 Dermal Post-Application Risk

There is no potential hazard via the dermal route for indoxacarb; therefore, a quantitative occupational post-application dermal risk assessment was not completed.

Restricted Entry Interval

Based on the acute toxicity categories for indoxacarb, the Worker Protection Standard (WPS) Interim Restricted Entry Interval (REI) for indoxacarb is 12-hours.

Proposed New Use
The proposed new use label recommends a REI of 4 hours. REIs may be further reduced if certain criteria are met in accordance with the Pesticide Registration (PR) Notice 95-3 [Reduction of WPS Interim REIs for Certain Low Risk Pesticides][11]. In PR Notice 95-3, there are a set of criteria listed for the active ingredient that must be met for chemicals to be eligible for a reduced REI. These criteria include:

1. The active ingredient is in Toxicity category III or IV based upon data for acute dermal toxicity, acute inhalation toxicity, primary skin irritation, and primary eye irritation. Acute oral toxicity data were used if no acute dermal data were available. If EPA lacked data on primary skin irritation, acute inhalation, or primary eye irritation of the active ingredient, the Agency reviewed data on that end-point for similar active ingredients (analogs), and excluded such active ingredients from consideration for the reduced REI, if the analog is in Toxicity Category I or II for that endpoint.
2. The active ingredient is not a dermal sensitizer (or in the case of biochemical and microbial active ingredients, no known reports of hypersensitivity exist).
3. The active ingredient is not a cholinesterase inhibitor (NMethyl carbamate and Organophosphate) as these chemicals are known to cause large numbers of pesticide poisonings and have the potential for serious neurological effects.
4. No known reproductive, developmental, carcinogenic, or neurotoxic effects have been associated with the active ingredient. If active ingredients did not have data available for these chronic health effects, EPA considered data on appropriate chemical and biological analogs.

[11] Available: https://www.epa.gov/pesticide-registration/prn-95-3-reduction-worker-protection-standard-wps-interim-restricted-entry

Active ingredients that have been classified as carcinogenic in Category B (probable human carcinogen) or Category C with a potency factor, Q* (possible human carcinogen, for which quantification of potential risk is considered appropriate), or are scheduled for the Health Effects Division's Cancer Peer Review process, were omitted from consideration.

5. EPA does not possess incident information (illness or injury reports) that are ``definitely'' or "probably" related to post-application exposures to the active ingredient.

Upon review of the criteria for the active ingredient only, it appears that the proposed new use of indoxacarb for controlling ants is consistent with the criteria in PRN 95-3 that allow for a 4-hour REI. Note: The PR Notice also includes similar criteria for the end-use product. These criteria have not been evaluated by HED. Based solely on the active ingredient criteria, a 4-day REI is acceptable for indoxacarb.

Registered Uses

For the registered uses, indoxacarb has a low order of acute toxicity via the dermal and inhalation routes (Toxicity Category IV) of exposures and has a moderate acute toxicity via the oral route (Category II). It is neither an eye nor skin irritant, nor is it a dermal sensitizer. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 12 hours is adequate to protect agricultural workers from post-application exposures to indoxacarb. HED would recommend a REI of 12 hours. This is the REI listed on the registered agricultural labels, and is considered protective of post-application exposure.

11.2.2 Inhalation Post-Application Risk

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. 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 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for indoxacarb.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments.

Commercial applicators do not typically return to the treated areas after an indoor commercial pesticide application (sites such as warehouses, food handling establishments, and hotels, etc.) and thus an occupational post-application inhalation exposure assessment was not performed for commercial applicators.

12.0 Human Incidents

Indoxacarb incidents were previously reviewed in 2013 (D409841, E. Evans and S. Recore, 03/13/2013). A current incident analyses was subsequently conducted from January 1, 2013 to April 25, 2017, through a review of the Main IDS and SENSOR-Pesticides databases (Personal Communication, E. Evans, 05/09/2017). Based on the continued low frequency and severity of indoxacarb incidents reported to both IDS and SENSOR-Pesticides, there does not appear to be a concern at this time. The Agency will continue to monitor the incident data and if a concern is triggered, additional analysis will be conducted.

13.0 References

Rivera-Lupianez, A. (2013). D411342, Indoxacarb: Occupational and Residential Risk Assessment to Support Request for Section 3 Registrations on Bean (dry), Bean (snap), Bean (forage), and Small Fruit Vine Climbing Subgroup 13-07F and Low-Growing Berry Subgroup 13-07H.

Hassan, U. (2017). D438791, Indoxacarb: Occupational and Residential Risk Assessment to Support Registration Review and its Proposed New Use for Controlling Ants at Ornamental Nurseries, Sod Farms, and Livestock Corrals of non-Food Bearing Animals.

Negrón-Encarnación, I. (2016). D428812, Indoxacarb. Human Health Risk Assessment for the Amended Registration of DuPont Avaunt eVo Formulated with 98% S-enantiomer of Indoxacarb for use on Several Crops.

Levy, S. (2000). D263986, Results of HED Metabolism Assessment Review Committee (MARC) Meeting of 6/12/00.

46114302 McLean, C., Swain, R. (2003) Magnitude of Residues of Indoxacarb (As DPX-MP062) in Laying Hen Tissue and Eggs: A Feeding Study Conducted to EPA Guidelines. Lab Project Number: DuPont-8305; Inveresk #200491. Unpublished study prepared by Inveresk Research, PTRL Europe GmbH, and Du Pont. 844 p.

Levy, S. (2004). D297936, Indoxacarb. Review of Amendment Submitted in Response to HED's Memorandum of 19-JAN-2000.

Levy, S. (2007). D325479, Indoxacarb. Petitions for Tolerances on Vegetable, Leafy, Except *Brassica* (Group 4), Pome Fruits (Group 11, except pear), Tuberous and Corm Vegetables (Subgroup 1C), Cucurbit Vegetables (Group 9), Stone Fruits (Group 12), Cranberry, Mint, Okra, and Southern Pea. Summary of Analytical Chemistry and Residue Data.

Koper, C. (2012). D402100, Tier II Drinking Water Assessment for the New Use Registration of Indoxacarb on Dry Beans, Snap Beans, Small Fruit Vine Climbing Subgroup 13-07F and Low-Growing Berry Subgroup 13-07H.

Koper, C. (2017). D436386, Indoxacarb: Drinking Water Exposure Assessment for Proposed New Uses to Control a Variety of Ants on Commercial Nurseries, Sod Farms, and Pastures for Grazing Companion Animals.

Koper, C. (2017). D439057, Indoxacarb: Drinking Water Assessment to Support Registration Review and a Proposed New Use on Corn.

Koper, C. (2015). D430585, Indoxacarb: Tier II Drinking Water Exposure Assessment for a Label Amendment (change in crop season and application number) on Previously Registered Crops.

Nadrchal, D. (2017). D438790, Indoxacarb. Acute and Chronic Dietary Exposure Assessments of Food and Drinking Water for Indoxacarb to Support Registration for New Uses on Ornamentals.

Sahafeyan, M. (2007). D339398, Indoxacarb: Acute and Chronic Dietary Exposure and Risk Assessments for the Proposed Section 3 Registrations and Petitions for Tolerances on Grapes; Vegetable, *Brassica*, Leafy, Group 5; Turnip Greens; Vegetable, Leafy, Except *Brassica* (Group 4); Pome Fruits (Group 11, except pear); Tuberous and Corm Vegetables (Subgroup 1C); Cucurbit Vegetables (Group 9); Stone Fruits (Group 12); Cranberry; Mint; Okra; and Southern Pea.

Shah, A. (2016). DP No. None, Screening Level Usage Analysis for Indoxacarb (PC Code # 067710).

Evans, E. and Recore, S. (2013). D409841. Indoxacarb: Review of Human Incidents.

Evans, E. (2017). Personal Communication. Email Update Review of Human Incidents for Indoxacarb Draft Risk Assessment.

Appendix A. Toxicology Profile and Executive Summaries

Table A.1 Toxicology Requirements for Indoxacarb

Guideline Number and Toxicity Study		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 Sub-chronic (Rodent)	yes	yes
870.3150	Oral Sub-chronic (Non-Rodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	CR	--
870.3465	90/28-Day Inhalation	CR	yes
870.3700	Developmental Toxicity (Rodent)	yes	yes
870.3700	Developmental Toxicity (Non-rodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100	Chronic Toxicity (Rodent)	yes	yes
870.4100	Chronic Toxicity (Non-rodent)	no	yes
870.4200	Oncogenicity (Rat)	yes	yes
870.4200	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
870.5395	Mutagenicity: Cytogenetics	yes	yes
870.5500	Mutagenicity: Other Genotoxic Effects	yes	yes
870.6100	Acute Delayed Neurotoxicity (Hen)	no	-
870.6100	90-Day Neurotoxicity (Hen)	no	-
870.6200	Acute Neurotoxicity Screening Battery (Rat)	yes	yes
870.6200	90-Day Neurotoxicity. Screening Battery (Rat)	yes	yes
870.6300	Developmental Neurotoxicity	CR	yes
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	yes
870.7800	Immunotoxicity	yes	yes

A.2 Toxicity Profiles

Table A.2.1 Acute Toxicity Data on Indoxacarb (DPX-KN128)			
Guideline No./Study Type	**MRID #**	**Results**	**Toxicity Category**
870.1100 Acute oral toxicity	44477115	LD50 = 179 (F) and 843 (M) mg/kg (rat)	II
870.1200 Acute dermal toxicity	46240001	LD_{50} > 5000 mg/kg (rat)	IV
870.1300 Acute inhalation toxicity	N/A	N/A	IV
870.2400 Primary eye irritation	46240002	Not a eye irritant (rabbit)	IV
870.2500 Primary dermal irritant	46240003	Not a dermal irritant (rabbit)	IV
870.2600 Skin sensitization	46240004	Is a dermal sensitizer (Guinea Pig)	NA

Table A.2.2 Acute Toxicity Data on DPX-MP062 Technical (94.5%;) 80% DPX KN128, 20% IN KN127			
Study Type	**MRID #**	**Results**	**Toxicity Category**
870.1100 Acute oral toxicity	44477113	LD_{50} = 1730mg/kg males 268 mg/kg females <1000 mg/kg combined (rat)	II
870.1200 Acute dermal toxicity	44477118	LD_{50} >5000mg/kg (limit test) (rat)	IV
870.1300 Acute inhalation toxicity	70%MUP 44477120	LC_{50} > 5.5 mg/L males, females and combined	IV
870.2400 Primary eye irritation	44477122	Moderate eye irritant (rabbit)	III
870.2500 Primary dermal irritant	44477125	Not a dermal irritant (rabbit)	IV
870.2600 Skin sensitization	44477126	Magnusson-Kligman Maximization test, Is a dermal sensitizer (Guinea Pig)	NA

Table A.2.3 Acute Toxicity Data on DPX-JW062 (50% DPX KN128,50% IN KN127)			
Guideline No./ Study Type	**MRID No.**	**Results**	**Toxicity Category**
870.1100 Acute oral toxicity	44701601	LD_{50} > 5000 mg/kg (males, females, combined) (in corn oil)	IV
870.1200 Acute dermal toxicity	44477119	LD_{50} > 2000 mg/kg (males, females, combined) (rabbit)	III

870.1300 Acute inhalation toxicity	44477121	LC_{50} > 5.4 mg/L males LC_{50} = 4.2 mg/L females (rat)	IV
870.2400 Primary eye irritation	44701602	Slight eye irritant (rabbit)	IV
870.2500 Primary dermal irritation	44701603	Slight dermal irritation (rabbit)	IV
870.2600 Skin sensitization	44701604	Is not a dermal sensitizer Magnusson-Kligman Maximization test, (Guinea Pig)	NA

Table A.2.4 Sub-Chronic, Chronic, and Other Toxicity Data on Indoxacarb (DPX-KN128)

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	
870.3700a Prenatal developmental in rodents - rat	46240005(2004) Acceptable/guideline 0, 0.5, 1.0, 2.0, or 3.5 mg/kg/day	**Maternal** NOAEL = 2.0 mg/kg/day LOAEL = 3.5 mg/kg/day, based on decrease in maternal overall body-weight gain and adjusted body-weight gain. **Developmental** NOAEL = 2.0 mg/kg/day LOAEL = 3.5 mg/kg/day, based on decreased mean fetal weight.
Gene Mutation 870.5100	46240006 (2004) Acceptable/guideline	Strains TA98, TA100, TA1535 and TA1537 of S. typhimurium and strain WP2(uvrA) of E. coli were negative for mutagenic activity both with and without S9 activation for the concentration range 2.5-5000 µg/plate
Gene Mutation 870.5300	46240007 (2003) Acceptable/guideline	Negative for mutagenic activity for the following concentration range 5-50 µg/mL (±S9)
Cytogenetics 870.5375	46240008 (2003) Acceptable/guideline	No evidence of chromosomal aberrations induced by the test article over background for the following concentration ranges: 1.25-100 µg/mL (±S9)
870.6300 Developmental neurotoxicity - rat	46749002 (2006) 46749003 (2006) Acceptable/non-guideline 0, 0.5, 1.0, 1.5, or 3.0 mg/kg/day	**Maternal systemic/neurotoxicity** NOAEL = 1.5 mg/kg/day LOAEL = 3.0 mg/kg/day, based on the adverse clinical signs observed, decreased body-weight gain and food consumption and mortality. **Offspring systemic/neurotoxicity** NOAEL= 1.5 mg/kg/day LOAEL = 3.0 mg/kg/day, based on an increased incidence of stillbirths, decreased mean pup body weight at birth and increased pup mortality during PND 1-4 in males and females, and increase in number of learning trials to reach criterion and increased latency in males.
870.7800 Immunotoxicity	48478002 (2011) Acceptable/guideline	Immunotoxicity NOAEL=23 mg/kg/day HDT Systemic NOAEL=23 mg/kg/day HDT Systemic LOAEL was not established (>23 mg/kg/day).

Table A.2.5 Sub-Chronic, Chronic, and Other Toxicity Data on Indoxacarb (DPX-MP062) 80% DPX KN128, 20% IN KN127		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90-Day oral toxicity rodents	44477129 (1997) Acceptable/guideline M: 0, 10, 50, 100, 200 ppm M: 0, 0.6, 3.1, 6.0, 15 mg/kg/day F: 0, 10, 25, 50, 100 ppm, F: 0, 0.76, 2.1, 3.8, 8.9 mg/kg/day	NOAEL = 3.1 (M), 2.1 (F) mg/kg/day LOAEL = 6.0 (M), 3.8 (F) mg/kg/day based on decreased body weight, body-weight gain, food consumption and food efficiency.
870.3200 28-Day dermal toxicity	44477134 (1997) acceptable (guideline) 0, 50, 500, 1000, 2000 mg/kg/day	NOAEL = 2000 mg/kg/day LOAEL = >2000 mg/kg/day in rats.
870.3200 28-Day dermal toxicity	44983901 (1999) acceptable/guideline 0, 50, 500, 1000, 2000 mg/kg/day	NOAEL = 50 mg/kg/day LOAEL = 500 mg/kg/day based on decreased body weights, body-weight gains, food consumption, and food efficiency in F, and changes in hematology parameters (incr. reticulocytes), the spleen (incr. abs. and rel. weight–M only, gross discoloration), clinical signs of toxicity in both sexes in rats. [Based on the *in vitro* dermal absorption data from rat skin and human skin (i.e. 15.2% and 0.87%, respectively), the human equivalent NOAEL is 875 mg/kg/day (i.e. 50 x 15.2%/0.87%). Thus, the calculated human dermal LOAEL of 8750 mg/kg/day exceeds the dermal limit dose of 1000 mg/kg/day. See MRIDs 45911401, 45911402, 45911403]
870.3465 28-Day inhalation toxicity	45870001 (2003) Acceptable/non-guideline 0, 4.6, 23, 290 µg/L/day	NOAEL = 23 µg/L/day LOAEL = 290 µg/L/day (75.69 mg/kg/day), based on increased absolute and relative spleen weights, pigmentation and hematopoiesis in the spleen, and hematological changes.
870.3700a Prenatal developmental in rodents - rat	44477138, 44477142 (1997) Acceptable (guideline) 0.0, 0.5, 1.0, 2.0, or 4.0 mg/kg/day (in PEG)	**Maternal** NOAEL = 2.0 mg/kg/day LOAEL = 4.0 mg/kg/day based on decreased mean body weights, body-weight gains, food consumption. **Developmental** NOAEL = 2.0 mg/kg/day LOAEL = 4.0 mg/kg/day based on decreased fetal weights.
Gene Mutation 870.5100	44477149 (1997) acceptable/guideline	Negative: strains TA97a, TA98, TA100 and TA1535 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* were negative for mutagenic activity both with and without S9 activation for the concentration range 10-5000 µg/plate
Gene Mutation 870.5300	44477147 (1997) acceptable/guideline	Negative: negative for mutagenic activity for the following concentration ranges: 3.1-250 µg/mL (-S9); 3.1-250 µg/mL (+S9)
Cytogenetics 870.5375	44477146 (1996) acceptable/guideline	Negative: no evidence of chromosomal aberrations induced by the test article over background for the following concentration ranges: 15.7-1000 µg/mL (±S9)
Cytogenetics	44477148 (1997)	Negative: no evidence of mutagenicity for the following dose ranges: 3000-4000 mg/kg - males; 1000-2000 mg/kg - females

Table A.2.5 Sub-Chronic, Chronic, and Other Toxicity Data on Indoxacarb (DPX-MP062) 80% DPX KN128, 20% IN KN127		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.5395	acceptable/guideline	
Other Effects 870.5550	44477151 (1997) acceptable/guideline	Negative: no evidence of mutagenic activity at the following concentration range: 1.56-200 µg/mL; cytotoxicity was seen at concentrations of ≥100 µg/mL
870.6200a Acute neurotoxicity screening battery	44477127 (1997) acceptable/guideline M: 0, 25, 100, 200 mg/kg F: 0, 12.5, 50, 100 mg/kg	NOAEL = 100 mg/kg (M), 12.5 mg/kg (F) LOAEL = 200 mg/kg (M) based on decreased body-weight gain, decreased food consumption, decreased forelimb grip strength, and decreased foot splay. 50 mg/kg (F) based on decreased body weight and body-weight gain
870.6200b Subchronic neurotoxicity screening battery	44477135 (1997) acceptable/guideline M: 0, 10, 100, 200 ppm 0.57, 5.6, 12 mg/kg/d, F: 0, 10, 50, 100 ppm 0.68, 3.3, 6.1 mg/kg/d	NOAEL =0.57 (M), 0.68 (F) mg/kg/day LOAEL = 5.6 (M), 3.3 (F) mg/kg/day based on decreased body weight and alopecia.
870.7600 Dermal penetration (Triple pack study)	45911401 (2002) 45911402 (2002) 45911403 (2002) Acceptable/guideline 0, 13.3, 2000 µg/cm2 for 6 hours	Dermal absorption ranged from 0.41% to 0.94% following 6 hours exposure in rats. Following a 162 hours post dosing, the absorption in rats ranged from 0.88% to 4.91% depending upon the dose/dilution. The in vitro dermal absorption for rat skin was 15.2% and the in vitro dermal absorption in human skin was 0.87%, or 17.5X lower. The equivalent dermal absorption in humans was calculated to be 0.28%.

Table A.2.6 Sub-Chronic, Chronic, and Other Toxicity Data on Indoxacarb (DPX-JW062) (50% DPX KN128, 50% IN KN127)		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.3700a Prenatal developmental in rodents - rat	44477140, 44477143 (1997) acceptable/guideline 0, 10, 100, 500, 1000 mg/kg/day (in methyl cellulose)	**Maternal** NOAEL = 10 mg/kg/day LOAEL = 100 mg/kg/day based on mortality, clinical signs, and decreased mean body weights, body-weight gains, and food consumption. **Developmental** NOAEL = 10 mg/kg/day LOAEL = 100 mg/kg/day based on decreased numbers of live fetuses/litter.
870.3700a Prenatal developmental in rodents - rat	44477139 (1997) acceptable/guideline 0, 20, 40, 80, or 120 ppm 1.11, 2.2, 4.1, 5.7 mg/kg/day	**Maternal** NOAEL = 1.1 mg/kg/day LOAEL = 2.2 mg/kg/day based on decreased mean body weights, body-weight gains, food consumption, and food efficiency. **Developmental** NOAEL = 2.2 mg/kg/day

		LOAEL = 4.1 mg/kg/day based on decreased fetal body weights.
870.3700b Prenatal developmental in nonrodents - rabbit	44477141 (1995) acceptable/guideline 0, 250, 500, or 1000 mg/kg/day in methyl cellulose	**Maternal** NOAEL = 500 mg/kg/day LOAEL = 1000 mg/kg/day based on slight decreases in maternal body-weight gain and food consumption. **Developmental** NOAEL = 500 mg/kg/day LOAEL = 1000 mg/kg/day based on decreased fetal body-weights and reduced ossification of the sternebrae.
870.3800 Reproduction and fertility effects	44477144 (1997) acceptable/guideline 0, 20, 60, 100 ppm M: 0, 1.3, 3.9, 6.4 mg/kg/d F: 0, 1.5, 4.4, 6.9 mg/kg/d	**Parental/Systemic** NOAEL = 1.5 mg/kg/day LOAEL = 4.4 mg/kg/day based on decreased body weights, body-weight gains, and food consumption of F_0 females, and incr. spleen weights in the F_0 and F_1 females. **Reproductive** NOAEL = 6.4 mg/kg/day LOAEL > 6.4 mg/kg/day. **Offspring** NOAEL = 1.5 mg/kg/day LOAEL = 4.4 mg/kg/day based on decrease in the body weights of the F_1 pups during lactation.
870.4100a Chronic toxicity rodents - rat	44477145 (1997) acceptable/guideline 0, 20, 40, 60, 125, 250 ppm M: 0, 0.80, 1.6, 2.4, 5.0, 10 mg/kg/day F: 0, 10, 20, 40, 60, 125 ppm 0, 0.55, 1.0, 2.1, 3.6, 7.8 mg/kg/day	NOAEL = 5 (M), 2.1 (F) mg/kg/day LOAEL = 10 (M), 3.6 (F) mg/kg/day based on decreased body weight, body-weight gain, and food consumption and food efficiency; decreased HCT, HGB and RBC at 6 months in F only. **No evidence of carcinogenic potential.**
870.4100b Chronic toxicity dogs	44477136 (1997) acceptable/guideline 0, 40, 80, 640, 280 ppm M: 0, 1.1, 2.3, 18, 34 mg/kg/day F: 0, 1.3, 2.4, 19, 36 mg/kg/day	NOAEL = 2.3 (M), 2.4 (F) mg/kg/day LOAEL = 18 (M), 19 (F) mg/kg/day based on decreased HCT, HGB and RBC; incr. Heinz bodies and reticulocytes and assoc. secondary microscopic changes in the liver, kidneys, spleen, and bone marrow; incr. abs. and rel. liver weights.
870.4200 Carcinogenicity rats	see 870.4100a	see 870.4100a **No evidence of carcinogenicity.**
870.4300 Carcinogenicity mice	44477137 (1997) 0, 20, 100, 200/150/125 ppm M: 2.6, 14, 22 mg/kg/day F: 4.0, 20, 31 mg/kg/day	NOAEL = 2.6 (M), 4.0 (F) mg/kg/day LOAEL = 14 (M), 20 (F) mg/kg/day based on decreased body weight, body-weight gain, and food efficiency and clinical signs indicative of neurotoxicity. **No evidence of carcinogenicity.**
Gene Mutation 870.5100	44701606 (1995) acceptable/guideline	Negative: strains TA97a, TA98, TA100 and TA1535 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* were negative for mutagenic activity both with and without S9 activation for the concentration range 10-5000 µg/plate.
Gene Mutation 870.5300	44701607 (1995) acceptable/guideline	Negative for mutagenic activity for the following concentration ranges: Negative;100-1000 µg/mL (-S9); 100-1000 µg/mL (+S9), precipitate ≥1000 µg/mL

Cytogenetics 870.5375	44701608 (1995) acceptable/guideline	Negative: No evidence of chromosomal aberrations induced by the test article over background for the following concentration ranges: 19-300 µg/mL (-S9), 19-150 µg/mL (+S9); partial insoluble & cytotoxicity ≥ 150 µg/mL
Cytogenetics 870.5395	44701610 (1995)	Negative: No evidence of mutagenicity at 2500 or 5000 mg/kg
Other Effects 870.5550	44701609 (1995) acceptable/guideline	Negative: No evidence of mutagenic activity at the following concentration range: 0.1-50 µg/mL, cytotoxicity observed at ≥50 µg/mL
870.6200a Acute neurotoxicity screening battery	44477128 (1996) acceptable/guideline 0, 500, 1000, 2000 mg/kg	NOAEL >= 2000 mg/kg (M) = < 500 mg/kg (F) LOAEL > 2000 mg/kg (M) < 500 mg/kg (F) based on clinical signs, decreased body-weight gains and food consumption, and FOB effects
870.7485 Metabolism and pharmacokinetic	44477152, 44477153 (1997) acceptable/guideline	Both **indoxacarb** and **JW062** were extensively metabolized and the metabolites were eliminated in urine, feces, and bile. The metabolite profile for **JW062** was dose dependent and varied quantitatively between males and females. Differences in metabolite profiles were also observed for the different label positions (indanone and trifluoromethoxyphenyl rings). All biliary metabolites undergo further biotransformation in the gut. The proposed metabolic pathway for both **indoxacarb** and **JW062** has multiple metabolites bearing one of the two ring structures.

Table A.2.7 Toxicity Data on Indoxacarb (DPX-KN128) EC Formulation

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3050 28-Day oral toxicity rodents DPX-KN128 EC (15% ai)	48799001 (2012) Acceptable/guideline 0, 2.45, 4.18, 6.35 or 7.32 mg/kg/day (corrected for ai)	NOAEL = 2.45 mg/kg/day LOAEL = 4.18 mg/kg/day based on hematological effects, decreased body weights, food consumption and efficiency, increased spleen weight and histological effects of the spleen.
870.3050 28-Day oral toxicity rodents DPX-KN128 EC (30.5% ai)	48889101 (2012) Acceptable/guideline 0, 2.14, 4.71, 7.11 or 8.08 mg/kg/day (corrected for ai)	NOAEL = 2.14 mg/kg/day LOAEL = 4.71 mg/kg/day based on hematological effects, increased weight and histology of the spleen.
870.3100 90-Day oral toxicity rodents DPX-KN128 EC (30.5% ai)	49004301 (2012) Acceptable/guideline 0, 1.17, 2.28, or 4.21mg/kg/day (corrected for ai)	NOAEL = 2.45 mg/kg/day LOAEL = 4.21 mg/kg/day based on hematological effects, decreased body weights, food consumption and efficiency, increased weight and histology of the spleen.

Appendix B. Physical/Chemical Properties

Table B.1 Physicochemical Properties of Indoxacarb		
Parameter	Value	Reference
Melting point/range	140-141°C	DP# D244253, S. Levy, 1/19/2000
pH	5.32 at 25°C	
Density	1.34 at 20°C	
0Water solubility	15.4 ± 2.3 ppb in pH 5 buffer 800 ppb at pH 7 (20°C)[1]	
Solvent solubility	1.72 g/L in n-heptane; 14.5 g/L in 1-octanol; 103 g/L in methanol; 117 g/L in o-xylene; 139 g/L in acetonitrile; 160 g/L in ethyl acetate; and >250 g/kg in methylene chloride, acetone, and dimethyl-formamide	
Vapor pressure (25°C)	2.5×10^{-8} Pa (1.9×10^{-10} mmHg)	
Dissociation constant, pK_a	Does not dissociate at pHs of 2.42-11.36	
Octanol/water partition coefficient, $Log(K_{OW})$	4.65 at pH 5	
UV/visible absorption spectrum	Molar absorptivities at three maxima were affected by pH, but not over wavelengths of environmental significance.	

[1] EFED memo D402100, 11/6/12

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 Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; the ARTF database; and the Outdoor Residential Exposure Task Force (ORETF) database, are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics 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 the Agency website[12].

[12] http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

Appendix D. International Residue Limits

Table D. Summary of US and International Tolerances and Maximum Residue Limits for Indoxacarb				
(a) General. (1) Residue Definition:				
US		Canada	Mexico[2]	Codex[3]
40 CFR 180.564 (a) (1): Indoxacarb, (S)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-e][1,3,4][oxadiazine-4a(3H)-carboxylate, and its R-enantiomer, (R)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-e][1,3,4][oxadiazine-4a(3H)-carboxylate		None		Sum of indoxacarb and its R enantiomer. The residue is fat soluble.
Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[1]	Codex[2]
Apple, wet pomace	3.0			
Alfalfa, forage	10			
Alfalfa, hay	50			60 alfalfa fodder
Bean, dry, seed	0.20			0.2 chick-pea (dry), 0.2 mung bean (dry) 0.1 cowpea (dry)
Bean, succulent	0.90			
Beet, garden, roots	0.30			
Beet, garden, tops	6.0			
Berry, low growing, except strawberry, subgroup13-07H	1.0			1 cranberry
Brassica leafy greens, subgroup 4-16B	12			
Bushberry subgroup 13-07B	1.5			
Cattle, fat	1.5			2 (fat) meat from mammals other than marine mammals)
Cattle, meat	0.05			
Cattle, meat byproducts	0.03			0.05 Edible offal (mammalian)
Celtuce	14			
Corn, sweet, forage	10			
Corn, sweet, kernel plus cob with husk removed	0.02			0.02 sweet corn (corn-on-the-cob)
Corn, sweet, stover	15			25 maize fodder dry
Cotton, gin byproducts	15			20 cotton fodder, dry
Cotton, undelinted seed	2.0			1 cotton seed
Cowpea, forage	50			
Cowpea, hay	100			
Fennel, florence	14			
Fruit, pome, except pear, group 11-10	1.0			0.5 apple 0.2 pear
Fruit, small vine climbing, except fuzzy kiwifruit, subgroup, 13-07F	2.0			2 grape
Fruit, stone, group 12-12	0.90			1 3 prunes
Goat, fat	1.5			2 (fat) meat from mammals other than marine mammals)
Goat, meat	0.05			
Goat, meat byproducts	0.03			0.05 Edible offal (mammalian)
Grain, aspirated fractions	45			

Table D. Summary of US and International Tolerances and Maximum Residue Limits for Indoxacarb				
(a) General. (1) Residue Definition:				
US		Canada	Mexico[2]	Codex[3]
Grape, raisin	5.0			5 dried grapes (=currants, raisins and sultanas)
Hog, fat	1.5			2 (fat) meat from mammals other than marine mammals)
Hog, meat	0.05			
Hog, meat byproducts	0.03			0.05 Edible offal (mammalian)
Horse, fat	1.5			2 (fat) meat from mammals other than marine mammals)
Horse, meat	0.05			
Horse, meat byproducts	0.03			0.05 Edible offal (mammalian)
Kohlrabi	12			
Leaf petiole vegetable, group 22B	14			
Leafy greens, subgroup 4-16A	12			7 head lettuce 3 leaf lettuce
Milk	0.15			0.1
Milk, fat	4.0			2
Okra	0.50			
Pea, southern, seed	0.10			
Peanut	0.01			0.02 (*)
Peanut, hay	40			50 peanut fodder
Pear	0.20			0.2
Pear, oriental	0.20			
Peppermint, tops	11			15 mints
Sheep, fat	1.5			2 (fat) meat from mammals other than marine mammals)
Sheep, meat	0.05			
Sheep, meat byproducts	0.03			0.05 Edible offal (mammalian)
Soybean, hulls	4.0			
Soybean, seed	0.80			0.5 soya bean (dry)
Spearmint, tops	11			15 mints
Turnip, greens	12			
Vegetable, cucurbit, group 9	0.60			0.5 Fruiting vegetables, cucurbits
Vegetable, fruiting, group 8-10	0.50			0.5 eggplant 0.3 peppers 0.5 tomato
Vegetable, head and stem *Brassica*, group 5-16	12			0.2 broccoli, cauliflower 3 cabbages, head
Vegetable, tuberous and corm, subgroup 1-C	0.01			0.02 potato

Table D. Summary of US and International Tolerances and Maximum Residue Limits for Indoxacarb				
(a) General. (2) Residue Definition:				
40 CFR 180.564 (a) (2): Poultry: (2) sum of indoxacarb, (S)-methyl-7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy)-phenyl]amino]carbonyl]indeno[1,2e] [1,3,4]oxadiazine-4a(3 H)-carboxylate, its R-enantiomer, (R)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy) phenyl]amino]carbonyl]indeno [1,2-e] [1,3,4] oxadiazine-4a(3 H)-carboxylate, and the metabolites: IN-JT333, methyl 7-chloro-2,5-dihydro-2-[[[4-(trifluoromethoxy)phenyl]-amino]carbonyl]indeno[1,2-e][1,3,4]oxadiazine-4a(3 H)-carboxylate; IN-KT319, (E)-methyl 5-chloro-2,3,-dihydro-2-hydroxy-1-[[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]-carbonyl]hydrazono]-1 H -indene-2-carboxylate; IN-JU873, methyl 5-chloro-2,3-dihydro-2-hydroxy-1-[[[[4-(triflurormethoxy)-phenyl]amino]carbonyl]hydrazono]-1 H -indene-2-carboxylate; IN-KG433, methyl 5-chloro-2,3,-dihydro-2-hydroxy-1-[[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]carbonyl]-hydrazono]-1 H -indene-2-carboxylate; and IN-KB687, methyl [4-(trifluoromethoxy)phenyl]carbamate, calculated as the stoichiometric equivalent of indoxacarb	None		Plant/Livestock commodities: sum of indoxacarb and its R enantiomer. The residue is fat-soluble.	

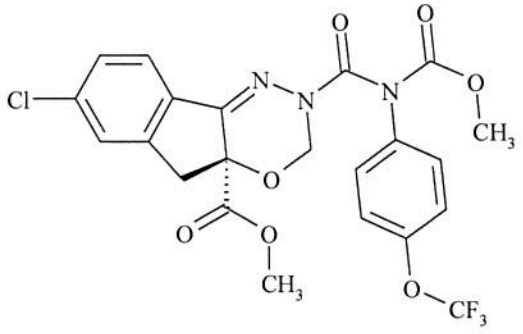
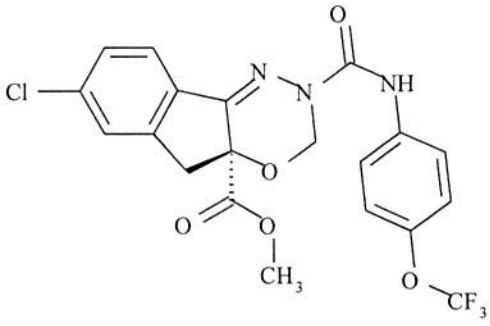
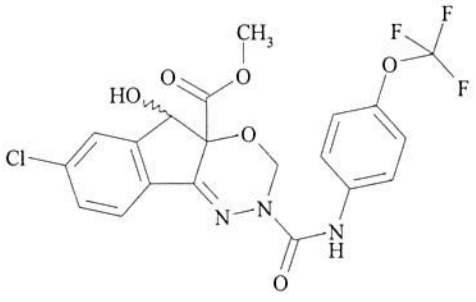
Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[2]	Codex[3]
Egg	0.20			0.02
Poultry, fat	0.20			
Poultry, meat	0.06			0.01 (*) (fat)
Poultry, meat byproducts	0.06			0.01 (*) poultry edible offal of
Completed: P. Savoia; 04/19/2017				

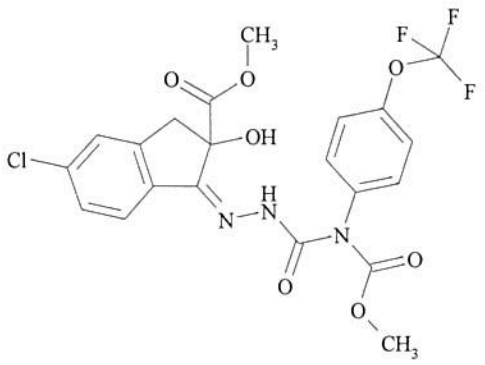
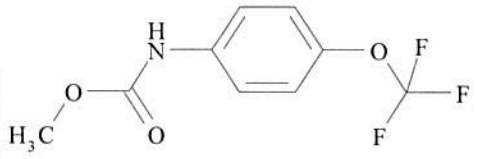
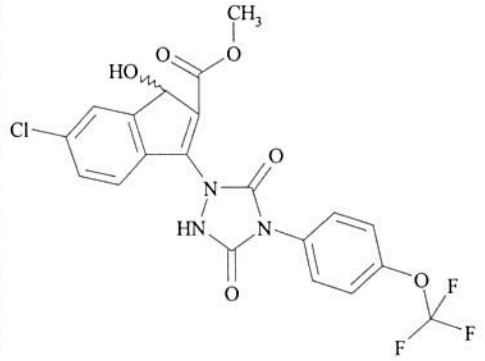
[1]* = absent at the limit of quantitation; Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample. MRLs indicated as proposed have not been finalized by the CCPR and the CAC.

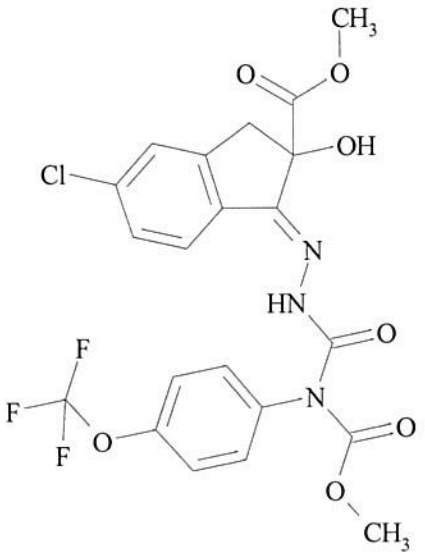
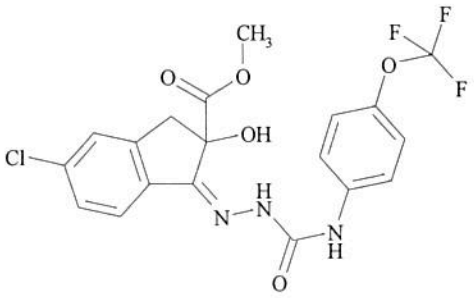
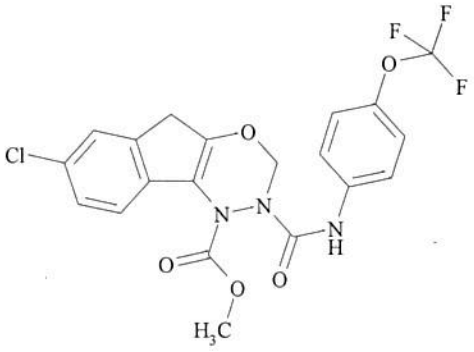
[2]Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

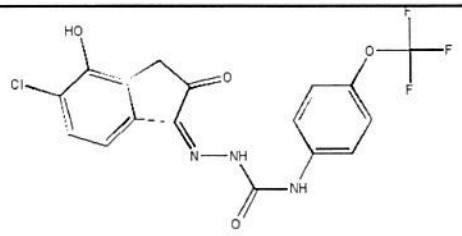
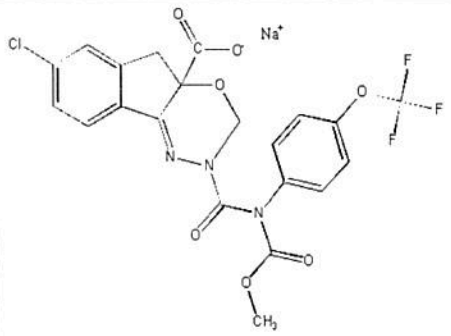
[3]Note: Indoxacarb is a fat-soluble compound. Previously, the milk MRL would have been marked with an "F" to indicate a procedure for calculating "MRLs" for processed dairy products.
Currently, indoxacarb MRLs for milk and milk fat are available to support "MRLs" for processed dairy products (2005).

Appendix E: Metabolism Assessment

Chemical name and structure of Indoxacarb and its metabolites.	
Chemical name	**Chemical structure**
Indoxacarb/R-indoxacarb CAS Name: (R,S)-Methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]-carbonyl]indeno[1,2-e] [1,3,4]-oxadiazine-4a(3*H*)-carboxylate	
IN-JT333 CAS Name: Methyl 7-chloro-2,5-dihydro-2-[[[4-(trifluoromethoxy)-phenyl]amino]carbonyl]indeno-[1,2-e][1,3,4]oxadiazine-4a(3*H*)-carboxylate CAS Inverted Name: Indeno-[1,2-e][1,3,4]oxadiazine-4a(3*H*)-carboxylic acid, 7-chloro-2,5-dihydro-2-[[[4-(trifluoromethoxy)-phenyl]amino]carbonyl]-, methyl ester	
5-HO-IN-JT333 CAS Name: Methyl 7-chloro-2,5-dihydro-5-hydroxy-2-[[[4-(trifluoromethoxy)phenyl]-amino]carbonyl]indeno[1,2-e]-[1,3,4]oxadiazine-4a(3*H*)-carboxylate	

IN-KG433 CAS Name: Methyl 5-chloro-2,3-dihydro-2-hydroxy-1-[[[(methoxycarbonyl)[4-trifluoromethoxy) phenyl]amino]carbonyl]hydrazono]-1H-indene-2-carboxylate CAS Inverted Name: 1H-indene-2-carboxylic acid, 5-chloro-2,3-dihydro-2-hydroxy-1-[[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]-carbonyl] hydrazono]-, methyl ester (Z)	
IN-KB687 CAS Inverted Name: Methyl [4-(trifluoro-methoxy)phenyl]-carbamate	
Metabolite F Characterized as the product of dehydration and rehydration of IN-KG433.	

IN-KT319 Note: IN-KT319 is a geometrical isomer of IN-KG433. CAS Name: (E)-methyl 5-chloro-2,3-dihydro-2-hydroxy-1-[[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]-carbonyl]hydrazono]-1*H*-indene-2-carboxylate	
IN-JU873 CAS Name: Methyl 5-chloro-2,3-dihydro-2-hydroxy-1-[[[[4-(trifluoromethoxy)phenyl]amino]-carbonyl]hydrazono]-1*H*-indene-2-carboxylate	
IN-MP819 CAS Inverted Name: Indeno-[1,2-e][1,3,4]oxadiazine-1(2H)-carboxylic acid, 7-chloro-3,5-dihydro-2-[[[4-(trifluoromethoxy)-phenyl]amino]carbonyl]-, methyl ester	

IN-ML437-OH CAS Name: none reported	
IN-KT413 CAS Name: sodium 7-chloro-2,5,-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-e][l,3,4]oxadiazine-4a(3H)-carboxylic acid	

Appendix F: Use Profile Table

Appendix F. Summary of Directions for Use of Indoxacarb						
Equipment	**Formulation [EPA Reg. No.]**	**Applic. Rate**	**Max. No. Applic. per Year**	**Max. Yearly Applic. Rate**	**REI**	**Use Directions and Limitations**
Proposed New Uses						
Commercial Nurseries, Sod Farms, and Livestock Corrals of non-Food Bearing Animals						
Aerial, Tractor-Drawn Spreader, Belly Grinder, & Spoon	Granule 100-1481 0.045% ai	0.00068 lb ai/A 0.000014 lb[a] ai/mound	4	0.0027 lb ai/A	4 hours	Broadcast Treatment: Make application with broadcast equipment capable of applying 1.5 lb product/A. Individual Mount Treatment: Uniformly distribute the product 3-4 feet around the mound. Do not disturb the mound. Do not apply to tops of mound. Do not allow livestock or domestic animals to consume the bait. Do not apply this product through any type of irrigation system. Apply at the first sign of imported fire ant, bigheaded ant, and pavement ant or turfgrass ant activity. Applications may be made at any time of the day, but are more effective when ants are actively foraging, usually when the soil surface temperature is above 60° F. Up to 4 applications may be applied per year,

Appendix F. Summary of Directions for Use of Indoxacarb						
Equipment	**Formulation [EPA Reg. No.]**	**Applic. Rate**	**Max. No. Applic. per Year**	**Max. Yearly Applic. Rate**	**REI**	**Use Directions and Limitations**
						generally at 12-16 week intervals. PPE: long-sleeved shirt and long pants, shoes plus socks, and gloves
Registered Uses						
Occupational, Residential, Institutional, Commercial, and Industrial Areas (Outdoor)						
Backpack, manually-pressurized handwand, mechanically pressurized handgun, tractor drawn spreader, belly grinder, rotary spreader, & Spoon	Granule 100-1482 12455-107 0.008% ai	0.0035 lb ai/A[b] 0.00000004 lb ai/ft^{2}[c] 0.00001 lb[d] ai/mound	N/A	0.0035 lb ai/A 0.00001 lb ai/mound	N/A	Broadcast Application: use hand held or rotary broadcast spreader. Mound Treatment: Sprinkle bait evenly around each mound in a 4-foot diameter circle.
Backpack, manually-pressurized handwand, mechanically pressurized handgun, tractor drawn spreader, belly grinder, rotary spreader, & Spoon	Granule 9688-217 0.016%	0.00000006 lb ai/ft^{2} [c] 0.0035 lb ai/A[e] 0.00002 lb ai/mound[f]	N/A	0.0035 lb ai/A 0.00002 lb ai/mound	N/A	Broadcast Application: use hand held or rotary broadcast spreader Mound Treatment: Sprinkle bait evenly around each mound in a 4-foot diameter circle.
Backpack, manually-pressurized handwand, mechanically pressurized handgun, tractor drawn spreader, belly grinder, rotary spreader, & Spoon	Granule 352-753 0.012%	0.0039 lb ai/A[g] 0.00075 lb ai/ft^{2} [h] 0.000015 lb ai/mound[i]	N/A	0.0039 lb ai/A 0.000015 lb ai/mound	N/A	Do not water-in bait. Do not water within 6 hours of a mound or 24 hours of a broadcast application. Do not use kitchen utensils for measuring.
Spoon	Granule 9688-235 0.032% ai	0.00002 lb ai/mound[j]	N/A	0.00002 lb ai/mound	N/A	Do not water in. Do not apply if rain expected in 4-6 hours.

Appendix F. Summary of Directions for Use of Indoxacarb						
Equipment	**Formulation [EPA Reg. No.]**	**Applic. Rate**	**Max. No. Applic. per Year**	**Max. Yearly Applic. Rate**	**REI**	**Use Directions and Limitations**
						Do not water or mow treated areas for 24 hours after application.
Spoon	Granule 100-1488 0.008%	0.00001 lb ai/mound[k]	N/A	0.00001 lb ai/mound	N/A	Do not water in. Do not apply if rain expected in 4-6 hours. Do not water or mow treated areas for 24 hours after application.
Occupational, Residential, Institutional, Commercial, and Industrial Areas (Indoor)						
RTU	RTU Gel 100-1483 100-1484 0.6% ai 100-1504 4822-595 0.3%	5 spots or 2.5 g/10 linear ft	N/A	5 spots/10 linear ft	N/A	Do not apply where food/feed, utensils/ surfaces may come in contact. Do not apply to areas routinely washed. Do not apply areas with high temperatures. Crack and crevice use. Spots must equal 0.5 g (1/4" diameter) Lines must be less than 1/8" wide and 2" long.
RTU	RTU Bait 100-1485 0.1%	4 ant bait arenas/stations	6	24 ant bait arenas/stations	N/A	Arenas/stations placed in areas where ants are foraging. Arenas/stations in child resistant packaging. Do not place bait arenas/stations in areas treated with other pest control products.
RTU	RTU Bait 100-1486 0.5%	10 bait arenas (stations)/100 linear ft	4	40 bait arenas/ stations/100 linear feet	N/A	Inspect area to determine placements of arenas/stations.

Appendix F. Summary of Directions for Use of Indoxacarb						
Equipment	**Formulation [EPA Reg. No.]**	**Applic. Rate**	**Max. No. Applic. per Year**	**Max. Yearly Applic. Rate**	**REI**	**Use Directions and Limitations**
						Do not place bait arenas/stations in areas treated with other pest control products.
RTU	RTU Bait 9688-193 0.10%	24 baits	2	24 baits	N/A	Indoor Residential Use Only Child-resistant bait stations. Do not use sprays around baits.
RTU	RTU Bait 9688-214 0.05% 9688-221 0.04%	12 baits	4	12 baits	N/A	Break bait stations apart and place along ant trail. Do not allow children or pets to play with bait stations.
RTU	RTU Gel 100-1498 0.05% 100-1502 12455-118 0.03%	1.0 g spots	N/A	N/A	N/A	No not apply to surfaces that food contact or allow open foods to contact gel material. Inspect applications periodically. Avoid treating surfaces previously treated with sprays. Spots must equal 0.1-1.0 g spots (1/4" diameter) Lines must be at 1/8" wide and 2-3" long.
Occupational and Residential: Golf Course, Turf Grass, and Ornamentals						
Broadcast	Water Dispersible Granule 100-1487 30%	0.225 lb ai/A 0.005 lb ai/gal[l] 0.00092 lb ai/gal (ornamentals)	N/S	0.45 lb ai/A (turfgrass)	N/S	Do not use on plants being grown for sale or for commercial seed production. Do not formulate into other end-use products.

Appendix F. Summary of Directions for Use of Indoxacarb						
Equipment	**Formulation [EPA Reg. No.]**	**Applic. Rate**	**Max. No. Applic. per Year**	**Max. Yearly Applic. Rate**	**REI**	**Use Directions and Limitations**
						Do not apply through irrigation system. Do not apply in commercial nurseries, greenhouses, or on sod farms. RTI(Re-treatment interval): 7 days PPE: long-sleeved shirt, long pants, chemical resistant gloves, and shoes plus socks.
Occupational and Residential: Residential Buildings, Schools, Institutional, Commercial, and Industrial Facilities (Outdoor & Indoor)						
Manually Pressurized Handwand & Crack and Crevice/Spot Equipment	Water Dispersible Granule 100-1501 20%	0.008 lb ai/gal[m]	N/S	0.008 lb ai/gal	N/S	Do not formulate into other end-use products. Do not apply through irrigation system. Do not apply in commercial nurseries, greenhouses, or on sod farms. Do not apply broadcast to interior surfaces of residential and commercial structures. Do not apply to pets or crops. Do not apply in rooms of elderly and infirm. Do not apply in institutions when in use. PPE: shirt and long pants, water proof gloves, and shoes plus socks
Occupational: Agricultural Crops						

Appendix F. Summary of Directions for Use of Indoxacarb						
Equipment	**Formulation [EPA Reg. No.]**	**Applic. Rate**	**Max. No. Applic. per Year**	**Max. Yearly Applic. Rate**	**REI**	**Use Directions and Limitations**
Aerial, Chemigation, Groundboom, Mechanically-pressurized Handgun	Water Dispersible Granules 352-597+ 30%	0.11 lb ai/A (dried beans except soybeans)	4	1.32 lb ai/A	12 hours or 14 days for hand harvesting (sweet corn)	Use only in commercial and farm plantings. Not for use in home plantings. Do not apply through irrigation systems except cranberries, mint, potatoes, and sweet corn. PPE: Long-sleeved shirt and long pants, chemical resistant gloves, and shoes plus socks.
		0.11 lb ai/A (succulent beans except soybeans)		1.04 lb ai/A		
		0.11 lb ai/gal (bushberries)		0.44 lb ai/A		
		0.11 lb ai/A (sweet corn)		0.78 lb ai/A		
		0.11 lb ai/A (low growing berry subgroup)	3	0.44 lb ai/A		
		0.11 lb ai/A (cucurbit vegetables)	4	1.32 lb ai/A		
		0.065 lb ai/A (fruiting vegetables and okra)		0.78 lb ai/A		
		0.11 lb ai/A (garden beet)		1.76 lb ai/A		
		0.11 lb ai/A (grape)	2	0.22 lb ai/A		
		0.11 lb ai/A (small fruit vine climbing subgroup [except fuzzy kiwifruit])		0.22 lb ai/ A		
		0.11 lb ai/A (leafy green vegetables [except spinach and spinach varieties])	4	1.76 lb ai/A		

Appendix F. Summary of Directions for Use of Indoxacarb						
Equipment	**Formulation [EPA Reg. No.]**	**Applic. Rate**	**Max. No. Applic. per Year**	**Max. Yearly Applic. Rate**	**REI**	**Use Directions and Limitations**
		0.065 lb ai/A (leafy petioles)		1.04 lb ai/A		
		0.065 lb ai/A (mint)		0.26 lb ai/A		
		0.11 lb ai/A (pear)		0.44 lb ai/A		
		0.11 lb ai/A (pome fruit [except pear])		0.44 lb ai/A		
		0.065 lb ai/A (spinach)		1.04 lb ai/A		
		0.11 lb ai/A (stone fruit)		0.44 lb ai/A		
		0.11 lb ai/A (tuberous and corm vegetables)		1.76 lb ai/A		
		0.065 lb ai/A (*Brassica* (cole) leafy vegetables)		1.04 lb ai/A		
Aerial, Groundboom, Mechanically-pressurized Handgun	Liquid 352-598 14.5%	0.11 lb ai/A (alfalfa, peanut, and soybean (except California))	4	0.44 lb ai/A	12 hours	PPE: Long-sleeved shirt and long pants, chemical resistant gloves, and shoes plus socks.
Aerial, Chemigation, Groundboom, Mechanically-pressurized Handgun	Liquid 352-638 15.84%	0.11 lb ai/A (alfalfa)	4	0.44 lb ai/A	12 hours	Do not use in greenhouses. Not for residential use, commercial use only. Not for use on ornamental plants. Do not apply through irrigation except for alfalfa,
		0.11 lb ai/A (dried bean (except soybeans))		1.32 lb ai/A		
		0.11 lb ai/A (cotton)		0.44 lb ai/A		

Appendix F. Summary of Directions for Use of Indoxacarb						
Equipment	**Formulation [EPA Reg. No.]**	**Applic. Rate**	**Max. No. Applic. per Year**	**Max. Yearly Applic. Rate**	**REI**	**Use Directions and Limitations**
		0.11 lb ai/A (peanut)				cotton, and peanut. PPE: Long-sleeved shirt and long pants, chemical resistant gloves, and shoes plus socks.
		0.11 lb ai/A (soybeans (except California))				
Aerial, Airblast, Chemigation, Groundboom, Mechanically-pressurized Handgun	Water Dispersible Granules 352-906[+] 30%	0.11 lb ai/ (dried beans except soybeans)	4	1.32 lb ai/A	12 hours	Use only in commercial and farm plantings. Not for use in home plantings. Do not apply through irrigation systems except cranberries, mint, potatoes, and sweet corn. PPE: Long-sleeved shirt and long pants, chemical resistant gloves, and shoes plus socks.
		0.11 lb ai/A (succulent beans except soybeans)				
		0.09 lb ai/gal (bushberries)		0.44 lb ai/A		
		0.065 lb ai/A (sweet corn)		0.78 lb ai/A		
		0.11 lb ai/A (low growing berry subgroup)		0.44 lb ai/A		
		0.065 lb ai/A (*Brassica* (cole) leafy vegetables)		1.04 lb ai/A		
		0.11 lb ai/A (cucurbit vegetables)		1.32 lb ai/A		
		0.11 lb ai/A (fruiting vegetables and okra)				
		0.11 lb ai/A (garden beet)				
		0.09 lb ai/gal (grape)	2	0.22 lb ai/A		
		0.11 lb ai/A (small fruit vine climbing subgroup (except fuzzy kiwifruit))				
		0.11 lb ai/A (leafy green vegetables [except spinach	4	1.32 lb ai/A		

Appendix F. Summary of Directions for Use of Indoxacarb						
Equipment	**Formulation [EPA Reg. No.]**	**Applic. Rate**	**Max. No. Applic. per Year**	**Max. Yearly Applic. Rate**	**REI**	**Use Directions and Limitations**
		and spinach varieties])				
		0.11 lb ai/A (leafy petioles)	3	1.32 lb ai/A		
		0.065 lb ai/A (mint)	4	0.26 lb ai/A		
		0.11 lb ai/A (pear)		0.44 lb ai/A		
		0.11 lb ai/A (pome fruit [except pear])		0.44 lb ai/A		
		0.065 lb ai/A (spinach)		1.04 lb ai/A		
		0.11 lb ai/A (stone fruit)		0.44 lb ai/A		
		0.11 lb ai/A (tuberous and corm vegetables)		1.32 lb ai/A		
Pets						
RTU	RTU Spot On 773-93 19.53%	0.00022 lb ai/cat 100 mg ai/pet (small)[n] 0.000044 lb ai/cat 200 mg ai/pet (medium)[o]	N/A	0.00038 lb ai/pet	N/A	Do not use on cats or kittens under 8 weeks of age and weighing less than 2 lb. Do not use on cats intended for breeding, or that are pregnant or nursing. Do not use more than once a month.
RTU	RTU Spot On 773-94 19.53%	0.00022 lb ai/dog 100 mg ai/pet (small)[n] 0.00033 lb ai/dog 150 mg ai/pet (medium)[o] 0.00066 lb ai/dog 300 mg ai/pet (large)[p] 0.0015 lb ai/dog	N/A	0.00204 lb ai/pet 900 mg ai/pet	N/A	Do not used on dogs and puppies under 8 weeks of age and weighing less than 4 lb. Do not use on cats. Keep cats away from treated dogs for 24 hours.

Appendix F. Summary of Directions for Use of Indoxacarb						
Equipment	**Formulation [EPA Reg. No.]**	**Applic. Rate**	**Max. No. Applic. per Year**	**Max. Yearly Applic. Rate**	**REI**	**Use Directions and Limitations**
		600 mg ai/pet (extra-large)[q] 0.002 lb ai/dog 900 mg ai/pet (extra-extra-large)[r]				
RTU	RTU Spot On 773-95 13.01%	0.00014 lb ai/dog 100 mg ai/pet (small)[s] 0.00029 lb ai/dog 150 mg ai/pet (medium)[t] 0.00057 lb ai/dog 300 mg ai/pet (large)[u] 0.0011 lb ai/dog 600 mg ai/pet (extra-large)[v] 0.017 lb ai/dog 900 mg ai/pet (extra-extra-large)[w]	N/A	0.00169 lb ai/pet 600 mg ai/pet	N/A	Do not used on dogs and puppies under 8 weeks of age and weighing less than 4 lb. Do not use on cats. Keep cats away from dogs.

a. 0.5 oz/mound * 1 lb /16 oz * 0.045% ai = 0.000014 lb ai/mound
b. (1 lb/1000 ft^2) * (43,560 sq ft/1 A) * (0.00008) = 0.0035 lb ai/A
c. (0.5 lb/1000 ft^2) * (0.00008) = 0.00000004 lb ai /ft^2
d. (4 tbls/mound) * (0.5 oz/4 tbls) * (1 lb/16 oz) * 0.00008 = 0.0000025 lb ai/mound
e. (0.5 lb/1000 ft^2) * (43,560 ft^2 /1 A) * (0.00016) = 0.0035 lb ai/A
f. (4 tbls/mound) * (0.5 oz/1 tbls) * (1 lb/16 oz) * 0.00016 = 0.00002 lb ai/mound
g. (0.75 lb/1000 ft^2) * (43560 ft^2/1 A) * (0.00012) = 0.0039 lb ai/A
h. (0.75 lb/1000 ft^2) * (0.00008) = 0.00000006 lb ai/ft^2
i. (4 tbls/mound) * (0.5 oz/1 tbls) * (1 lb/16 oz) * 0.00012 = 0.000015 lb ai/mound
j. (2 tbls/mound) * (0.5 oz/1 tbls) * (1 lb/16 oz) * 0.00032 = 0.00002 lb ai/mound
k. (4 tbls/mound) * (0.5 oz/1 tbls) * (1 lb/16 oz) * 0.00008 = 0.00001 lb ai/mound
l. (0.275 oz/1000 ft^2) * (1000 ft^2/gal) * (1 lb/16 oz) * 0.3 = 0.005 lb ai/gal (0.66 fl oz/1 gal) * (1 lb/16 oz) * (0.2 lb ai/lb product) = 0.00825 lb ai/gal
m. 0.51 mL = [based on the density of water] = 0.51 g * (1lb/453g) * 0.1953 = 0.00022 lb ai/pet
n. 1.03 mL = [based on the density of water] = 1.03 g * (1lb/453g) * 0.1953 = 0.00044 lb ai/pet
o. 0.77 mL = [based on the density of water] = 0.77 g * (1lb/453g) * 0.1953 = 0.00033 lb ai/pet
p. 1.54 mL = [based on the density of water] = 1.54 g * (1lb/453g) * 0.1953 = 0.00066 lb ai/pet
q. 3.08 mL = [based on the density of water] = 3.08 g * (1lb/453g) * 0.1953 = 0.0015 lb ai/pet
r. 4.62 mL = [based on the density of water] = 4.62 g * (1lb/453g) * 0.1953 = 0.002 lb ai/pet
s. 0.05 mL = [based on the density of water] = 0.05 g * (1lb/453g) * 0.1301 = 0.00014 lb ai/pet
t. 1.0 mL = [based on the density of water] = 1.0 g * (1lb/453g) * 0.1301 = 0.00029 lb ai/pet
u. 2.0 mL = [based on the density of water] = 2.0 g * (1lb/453g) * 0.1301 = 0.00057 lb ai/pet
v. 4.0 mL = [based on the density of water] = 4.0 g * (1lb/453g) * 0.1301 = 0.0011 lb ai/pet
w. 6.0 mL = [based on the density of water] = 6.0 g * (1lb/453g) * 0.1301 = 0.017 lb ai/pet
\+ Mechanically pressurized handgun and manually pressurized hand wands have dilution rates lower than other application equipment and therefore the current application rates are considered protective.
* Application rate may not equal max yearly application rate due to differences in crop cycles.