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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 23-MAY-2007

SUBJECT: PP#s: 2E6482, 3F6576, 5E6911, 5E6926, and 5E6991. **Indoxacarb. Health Effects Division (HED) Risk Assessment for 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; Southern Pea; and Fire Ant Bait.** PC Code: 067710. DP#s: 324855, 324862, 324893, 339668, and 339669. Decision#s: 355154, 356203, 360904, 306007, and 332867.

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The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The OPP RD has requested that HED evaluate hazard and exposure data and conduct dietary, occupational/residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed and registered uses of indoxacarb.

A summary of the findings and an assessment of human risk resulting from the proposed uses of indoxacarb is provided in this document. The risk assessment and residue chemistry data review were provided by Sarah Levy of RAB1, the dietary exposure risk assessment was provided by Mohsen Sahafeyan and Sarah Levy of RAB1; the hazard characterization by Guruva Reddy of RAB1, the occupational and residential exposure and risk assessment by Kelly Lowe and Yudith Tesfaye of RAB1, and the water exposure assessment by Jim Hetrick of the Environmental Fate & Effects Division (EFED).

NOTE: The most recent Section 3 indoxacarb risk assessment that HED completed was for new uses on alfalfa, lettuce, peanut, potato, and soybean (Memo, S. Levy, *et al.*, 23-MAY-2002; DP#: 276567). The current risk assessment document contains those aspects of the risk assessment which are affected by the new toxicological studies and the addition of proposed uses of indoxacarb on grapes, *Brassica* leafy vegetables, 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, as well as a residential use as a fire ant bait.

TABLE OF CONENTS

1.0. EXECUTIVE SUMMARY

DuPont™ and Interregional Research Project No. 4 (IR-4) have submitted petitions (PP#s: 2E6482, 3F6576, 5E6911, 5E6926, and 5E6991) proposing to amend the label for DuPont™'s 30% water-dispersible granule (WDG) to include new uses on grapes, *Brassica* leafy vegetables, turnip greens, cranberry, cucurbit vegetables (group 9), leafy vegetables except *Brassica*, mint, okra, pome fruits (group 11, except pear), southern peas, stone fruits (group 12), and tuberous and corm vegetables (subgroup 1C). Furthermore, the occupational/residential use of indoxacarb as a fire ant bait (DuPont™, Advion®; 0.045% (granular formulation, EPA Reg. No. 352-627)) is assessed as well. In conjunction with these new uses, the petitioners proposed the following indoxacarb tolerances:

Grape	2.0	ppm
Raisin	6.0	ppm
Vegetable, brassica, leafy, group 5	12	ppm
Turnip greens	12	ppm
Cranberry	1	ppm
Fruit, pome, except pear, group 11	1.0	ppm
Fruit, stone, group 12	1	ppm
Leafy vegetables except *Brassica*	14	ppm
Mint	10	ppm
Okra	0.5	ppm
Pea (southern)	0.1	ppm
Vegetable, cucurbit, group 9	0.5	ppm
Vegetable, tuberous and corm, subgroup 1C	0.01	ppm

An alternative to organophosphate (OP) insecticides, indoxacarb is an oxadiazine class insecticide that is used primarily for the control of lepidopteran pests in the larval stages on a variety of fruit, vegetable and field crops. Insecticidal activity occurs via blockage of the sodium channels in the insect nervous system and mode of entry is via stomach and contact routes. Indoxacarb is a reduced-risk insecticide. There are currently two end-use products of indoxacarb with food/feed uses registered to DuPont™: a 30% WDG formulation (DuPont™ Avaunt® Insecticide, EPA Reg. No. 352-597) and a 1.25 lb/gal (15%) suspension-concentrate (SC) formulation (DuPont™ Steward® Insecticide, EPA Reg. No. 352-598). Also, as stated above, there is one indoxacarb product for use as a fire ant bait (DuPont™, Advion®; 0.045% (granular formulation, EPA Reg. No. 352-627)). These formulations contain an isometric mixture of indoxacarb (insecticidally active S-enantiomer; DPX-KN128) and the R-enantiomer (insecticidally inactive; IN-KN127). The percentage of active ingredient (a.i.) listed on each label and the labeled use rates for each crop are based only on the amount of indoxacarb.

Permanent tolerances are established for the combined residues of indoxacarb, (*S*)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoro methoxy)phenyl]amino] carbonyl] indeno[1,2-*e*][1,3,4]oxadiazine-4a(3*H*)-carboxylate, and its inactive R-enantiomer in/on various plant commodities at levels ranging from 0.01 ppm in/on peanuts and potatoes to 50 ppm in/on alfalfa hay [40 CFR §180.564(a)]. Tolerances are established for the combined residues of indoxacarb + its R-enantiomer in livestock commodities at levels ranging from 0.03 ppm in

livestock meat byproducts to 4.0 ppm in milk fat. Time-limited tolerances are also established for the combined residues of indoxacarb + its R-enantiomer, in connection with use under FIFRA Section 5 experimental-use permit (EUP) on sweet and tart cherries (set to expire 21-MAY-2007) and peaches (expired 15-MAY-2006). Lastly, time-limited tolerances are established for the combined residues of indoxacarb + its R-enantiomer, in connection with use under Section 18 Emergency Exemptions on collards (expired 30-JUN-2006) and cranberries (set to expire 31-DEC-2007).

Hazard Assessment

DPX-MP062 is an enantiomeric mixture containing indoxacarb, the S-enantiomer (DPX-KN128, the insecticidally active component) and its R-enantiomer (DPX-KN127, the insecticidally inactive component,) at approximately a 75:25 ratio. However, many of the toxicity studies for this registration request were conducted with DPX-JW062, the racemic mixture of the enantiomers at a 50:50 ratio. HED's Hazard Identification Assessment Review Committee (HIARC; HED Doc No. 013528) determined that it is appropriate to use data from DPX-JW062 to satisfy the requirements for dietary subchronic, chronic, oncogenicity and reproductive studies. Based on previous conclusions by the HIARC, HED also accepted the same rationale for bridging the data from DPX-JW062 and DPX-MP062 to register DPX-KN128 (100% insecticidally active isomer).

DPX-KN128, DPX-MP062 and DPX-JW062 appear to be of similar toxicity acutely. DPX-KN128 and DPX-MP062 were moderately acutely toxic by the oral route (toxicity category II) while DPX-JW062 was practically non-toxic (toxicity category IV) due to its poor solubility in the corn oil vehicle. However, it was as toxic as indoxacarb orally, when tested using a solvent where it had a higher solubility, such as polyethylene glycol (PEG). By the dermal route, they had low toxicity (toxicity category III and IV). No acute inhalation toxicity study is available for DPX-KN128; however, a waiver was requested for this study based on the data from other two entantiomers. DPX-MP062 and DPX-JW062 had low acute inhalation toxicity (IV). DPX-MP062 and DPX-JW062 had moderate to low ocular irritant properties (III and IV), while DPX-KN128 was practically non-irritant to the rabbit's eyes. By the maximization test, DPX-KN128 and DPX-MP062 were considered dermal sensitizers, while DPX-JW062 was not a sensitizer.

There was possible evidence of lung damage in the acute inhalation studies with both DPX-MP062 and DPX-JW062. "Lung noise," observed with JW062 may indicate the development of acute lung injury and high permeability pulmonary edema. This was not unexpected since an oxidant was generated during indoxacarb metabolism. "Hunched over back and gasping" were also present and suggested arterial hypoxemia that accompanies alveolar flooding. The acute inhalation study report with indoxacarb 70% manufacturing use product, noted that a "red nasal discharge" was detected for 2 days after exposure. This may be indicative of a lung exudate, a sign of lung injury. 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.

The toxicity profiles for DPX-KN128, DPX-MP062 and DPX-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 lowest-observed-adverse-effect-level (LOAEL) were non-specific, and included decreased 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.

There was no evidence of susceptibility from either *in utero* or neonatal exposure to both rat and rabbit young with either DPX-MP062 or DPX-JW062. There was no evidence of susceptibility from *in utero* exposure in rats with DPX-KN128. There was no evidence of increased susceptibility in the developmental neurotoxicity study in rats with DPX-KN128. No evidence of teratogenicity was observed in rats and rabbits with DPX-MP062 or DPX-JW062. No evidence of teratogenicity was observed in rats with DPX-KN128. There was no evidence of reproductive effects in the 2-generation reproduction study in rats.

Neurotoxicity was present in both rats and mice; however, it did not occur in the absence of other signs of toxicity. 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. Acute and subchronic neurotoxicity screening batteries were performed using DPX-MP062 in rats. Neurotoxicity was characterized by clinical signs (depression, abnormal gait, head shake, salivation) and functional-observation battery (FOB) (circling behavior, incoordination, slow righting reflex, decreased forelimb grip strength, decreased foot splay, decreased motor activity). However, there was no evidence of neurohistopathology in any study. Learning and memory parameters were affected in the pups in the developmental neurotoxicity study in rats with DPX-KN128.

There was no evidence of carcinogenicity in either the rat or mouse in acceptable studies (using DPX-JW062). DPX-JW062 was not mutagenic in a complete battery of mutagenicity studies. There was also no evidence of mutagenicity with either DPX-KN128, or DPX-MP062. Therefore, DPX-KN128, DPX-MP062 were classified as “not likely” to be carcinogenic in humans by all relevant routes of exposure.

Both DPX-JW062 and DPX-MP062 were rapidly absorbed and eliminated following oral administration. The absorption of DPX-JW062 was dose dependent and appeared be saturated at the high dose. Overall absorption of [indanone-1-14C]DPX-JW062 was approximately 69-81% in the low dose group and 8-14% in the high-dose group. Plasma $t_{1/2}$ values were notably shorter for male rats than for female rats. Both urine and feces represented major routes of excretion (35-45% and 33-47%, respectively). The distribution pattern did not vary with dosing regimen and overall tissue burden was limited to only 3.4-12.9% of the administered dose. The red blood cells of rats dosed with the trifluoromethoxyphenyl label consistently contained much greater levels of radioactivity than did plasma. 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. The

finding also demonstrates a greater propensity for accumulation by female rats than by male rats. Both DPX-MP062 and DPX-JW062 were extensively metabolized and that the metabolites were eliminated in the urine, feces, and bile. With the exception of parent compound (DPX-JW062, which accounted for 19.2% of a single low dose in the feces of female rats), none of the metabolites from any source represented more than 12.3% of the administered dose. The metabolite profile for DPX-JW062 was dose dependent and varied quantitatively between males and females. Differences in metabolite profiles were also observed for the different label positions. All of the biliary metabolites appear to undergo further biotransformation in the gut.

Dose Response Assessment

On 06-JUN-2000, HIARC reviewed the recommendations of the toxicology reviewer for DPX-MP062 with regard to the acute and chronic reference doses (RfDs) and the toxicological endpoint selection for use, as appropriate, in occupational/residential exposure risk assessments. HIARC also determined that toxicity data from DPX-JW062 (the racemic mixture) could be used to support DPX-MP062 (HED Doc. No. 014241, 17-JUL-2000). On 02-MAR-2004, the HED HIARC met to re-evaluate the potential for increased susceptibility of infants and children from exposure to indoxacarb as required by the Food Quality Protection Act (FQPA) of 1996 according to the FEB-2002 OPP 10x Guidance Document and to re-evaluate the inhalation endpoints based on the submission of a 28-day inhalation toxicity study (HED Doc. 0052478). HED concluded that the endpoints previously selected by the HIARC should be adjusted to 100% insecticidally active isomer (DPX-KN128), since the registrant requested the registration of DPX-KN128 (25-AUG-2004; DP#: 307220). RAB1 toxicologists re-evaluated the endpoints due to submission of a developmental neurotoxicity study (DNT). RAB1 toxicologists concluded that the database uncertainty factor (UF) due to lack of the DNT study should be removed and the results of the DNT study did not impact previously selected endpoints by the HIARC (HED Doc. No. 0052478). The FQPA Safety Factor (SF) Committee met on 19-JUN-2000 to evaluate the hazard and exposure data for DPX-MP062 and recommended that the 10x safety factor to account for enhanced sensitivity of infants and children *be reduced* (1x) for the general U.S. population and all population subgroups and scenarios (HED Document Number 014226, B. Tarplee, 03-JUL-2000). RAB1 toxicologists re-evaluated FQPA assessment in light of the DNT study and concluded that the hazard-based FQPA factor be reduced.

Acute Dietary Endpoints: An acute RfD (aRfD) of 0.09 mg/kg was established for the general U.S. population (including infants and children). It was based on an acute oral neurotoxicity study in the rat with DPX-MP062. The no-observable-adverse-effect-level (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 of 12 mg/kg was adjusted to 9.0 mg/kg based on DPX-KN128. The standard 100 UF was applied to account for interspecies extrapolation and intraspecies variation. The FQPA SFC determined that a FQPA SF of 1x is applicable for acute dietary risk assessment. Thus, the acute population-adjusted dose (aPAD) is equivalent to the aRfD of 0.09 mg/kg. An endpoint of concern attributable to a single dose for females 13-49 was not identified in the database.

Chronic Dietary Endpoint: The chronic RfD (cRfD) of 0.015 mg/kg/day was based on the: 1) rat 90-day subchronic toxicity study with DPX-MP062; 2) rat subchronic neurotoxicity study

with DPX-MP062; and 3) rat chronic/ carcinogenicity study with DPX-JW062. The selected NOAEL was 2.0 mg/kg/day. The LOAELs for the 3 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, study #3 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. Studies #1, #2 and #3 are all co-critical. There appeared to be little difference in toxicity between DPX-MP062 (90-day studies, #1 and #2) and DPX-JW062 (2-year study, #3), regardless of study duration. In addition, the low NOAEL (0.57 mg/kg/day) for study #2 was due solely to the dose selection and was not used to establish the chronic RfD since the LOAEL was approximately the same as for studies #1 and #3. Studies #1 and #2 were first since they were conducted on DPX-MP062, the formulation being registered. The NOAEL of 2 mg/kg was adjusted to 1.5 mg/kg based on DPX-KN128. This NOAEL was also supported by the newly-submitted DNT study conducted with DPX-KN128 in which the systemic toxicity NOAEL was 1.5 mg/kg/day. The standard 100 UF was applied to account for interspecies extrapolation and intraspecies variation. The FQPA SFC determined that a FQPA SF of 1x is applicable for chronic dietary risk assessment. Thus, the chronic population-adjusted dose (cPAD) is equivalent to the cRfD of 0.015 mg/kg.

Carcinogenicity: HIARC recommended that DPX-MP062 be classified as "not likely" to be carcinogenic to humans via relevant routes of exposure using the Guidelines for Carcinogen Risk Assessment. This was based on no evidence of carcinogenicity in either the rat or mouse in acceptable studies for DPX-JW062 and no evidence of mutagenicity for DPX-MP062 or DPX-JW062. DPX-KN128 was also non-mutagenic in various assays. Therefore, DPX-KN128 is not expected to be carcinogenic to humans via relevant routes of exposure. Therefore, a cancer risk assessment is not required.

Incidental Oral: The short- and intermediate-term endpoints were selected from the studies mentioned in the chronic dietary endpoint (see above). The NOAEL of 2 mg/kg was adjusted to 1.5 mg/kg based on DPX-KN128. A margin of exposure (MOE) of 100 is considered adequate for incidental oral exposure risk assessment.

Short- and Intermediate-Term Dermal Endpoints: The short-, and intermediate-term dermal endpoints were selected from a rat 28-day dermal toxicity study with DPX-MP062. The NOAEL of 50 mg/kg/day was based on decreased body weights, body-weight gains, food consumption, and food efficiency in females, and changes in hematology parameters (increased reticulocytes), the spleen (increased absolute and relative weight–males only, gross discoloration), and clinical signs of toxicity in both sexes occurring at the LOAEL of 500 mg/kg/day. The NOAEL of 50 mg/kg/day was adjusted to 38 mg/kg/day based on DPX-KN128. There was little evidence (based on comparing oral subchronic and chronic NOAEL/LOAELs and toxicity profiles) to indicate that studies of longer duration would have a significantly more severe response. Since dermal studies were used for estimating dermal risks, no adjustment for dermal absorption is required. MOEs of 100 are considered adequate for dermal exposure risk assessment.

Short- and Intermediate-Term Inhalation Endpoints: The short-, intermediate-, and long-term

inhalation endpoints were selected from a 28-day inhalation toxicity study in rats with DPX-MP062. The systemic toxicity no-observed-adverse-concentration (NOEC) of 23 µg/L/day (equivalent to 6 mg/kg/day) was based on increased spleen weights, pigmentation and hematopoiesis in the spleen, hematological changes and mortality (females) seen at the LOAEL of 290 µg/L/day (equivalent to 75.69 mg/kg/day). Since the NOAEL was from a DPX-MP062 study, it was adjusted to 4.5 mg/kg/day based on DPX-KN128. The effects do not seem to be progressing as study duration increases from subchronic to chronic since the NOAELs of oral subchronic and chronic studies are similar. Therefore, use of the 28-day inhalation study is also appropriate for the long-term exposure scenario. MOEs of 100 are considered adequate for inhalation exposure risk assessment.

FQPA Decisions

The indoxacarb risk assessment team recommends that the FQPA SF be reduced to 1X for dietary, occupational, and residential exposure assessments. This recommendation by the indoxacarb risk assessment team is based on 1) the hazard and exposure databases are considered complete, 2) there are no concerns for pre- and/or postnatal toxicity, 3) there are no residual uncertainties with regard to pre- and/or postnatal toxicity, and 4) there are no neurotoxic concerns.

MOE for Occupational/Residential Risk Assessments

A MOE of $\geq$100 is not of concern for HED's dermal or inhalation occupational exposure risk assessment. Based on the use patterns, there are no anticipated long-term exposures to indoxacarb.

Residential Exposure Estimates

Currently, there is one registered use of indoxacarb that would result in residential exposures. Indoxacarb is registered for use as a fire ant bait (0.045%), which may be applied as a mound treatment or as a broadcast application by "residential" (*i.e.*, private persons) applicators as well as by commercial handlers such as professional lawn care operators (PCOs).

Occupational Exposure and Risk Estimates

Based on the proposed use patterns, commercial and private (*i.e.*, grower) pesticide handlers are expected to have short-term (1-30 days) exposures. While it is possible for handlers to experience intermediate-term exposures (1-6 months), HED believes it is highly unlikely. Since the short- and intermediate-term dermal and inhalation toxicity endpoints are the same; however, the short-term assessment is considered protective of intermediate-term exposures.

Several pesticide handler activities are likely, including mixing/loading of water-dispersible granules, application by air and ground (groundboom, airblast, tractor-drawn spreader), and commercial and residential mixer/loader/applicators applying granular fire ant bait. The most highly exposed handlers are expected to be mixer/loaders supporting aerial operations,

applicators using airblast equipment, applicators using tractor-drawn spreader equipment, mixer/loader/applicators using a scoop/spoon, and mixer/loader/applicators using a push-type spreader. No chemical-specific handler exposure data were available with which to estimate handler exposure and risk; therefore, surrogate data from the Pesticide Handler's Exposure Database (PHED) Surrogate Guide (AUG-1998) were used to estimate the exposures and risk to pesticide handlers. This assessment indicates there are no risks of concern to pesticide handlers (*i.e.,* MOEs >100) who use a single layer of work clothing (long pants, long-sleeved shirt, shoes plus socks) and protective gloves.

Agricultural workers may have post-application exposures that occur during the course of normal agricultural activities. For several of the proposed crop uses, mechanical harvesting is utilized, thereby minimizing post-application exposure. However, there are activities that occur prior to harvest that may result in post-application exposure. For those activities, exposures were calculated using dermal transfer coefficients (TCs) from the Science Advisory Council for Exposure (ExpoSAC) Policy Number 3.1: Agricultural TCs (AUG-2000). For all crops, except grapes, there were no risks of concern to post-application workers (*i.e.*, MOEs >100). The restricted-entry interval (REI) is 24-hours.

For grapes, the registrant provided compound-specific dislodgeable-foliar residue (DFR) data for indoxacarb. In this study, two applications were made, 5 days apart. Since the revised label indicates a 21-day interval for grape application, HED utilizes the study data taken after the first application. The MOE calculated using the maximum DFR is of concern. Since the highest DFR value reported results in a MOE of concern, HED used the study results for all three study sites and the associated MOEs for the DFR values reported for each day, post-application.

For table and raisin grapes, where the post-application activities are cane tying and turning, the MOE is not of concern on the day of application at the California and New York sites and on Day 1 post-application at the Washington site. For wine and juice grapes, use of the maximum reported DFR value and a TC of 5,000 cm^2/hr results in a MOE >100, which is not of concern.

For the turf uses, TCs were taken from a post-application exposure study on golf course maintenance (MRID 46734001). For transplanting sod, the TC (6800 cm^2/hr) was taken from MRID 45432303. HED assumes 5% of the application rate is available as DFR on day zero after application for turf. The MOEs calculated for post-application to turf are >100; therefore, the estimated risks do not exceed HED's level of concern.

Although the interim Worker Protection Standard (WPS) REI of 12 hours is adequate to protect agricultural workers from most post-application exposures to indoxacarb, **a 24-hour REI is recommended** to be protective of post-application activities in table and raisin grapes.

Dietary Risk Estimates (Food + Water)

Partially-refined acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which uses food consumption data from the U.S. Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The exposure assessments were conducted for all existing and proposed new food uses of indoxacarb. Anticipated residues (ARs) for all registered and proposed food commodities were based on field trial data. ARs for all current uses were further refined using percent crop treated (%CT) data (Memo, A. Halvorson, 05-APR-2007; DP#: 338731, and electronic communication, A. Halvorson to M. Sahafeyan, 12-APR-2007, and A. Halvorson to S. Levy, 10-MAY-2007), following the guidance provided in HED Standard Operating Procedure (SOP) 99.6 (*Classification of Food Forms with Respect to level of Blending*; 20-AUG-1999). 100% CT was assumed for the remaining new uses. Available processing data for indoxacarb were used to refine ARs for apples/pears (juice), potato (dry, chips), cotton (oil), tomato (paste and puree), peanut (oil), soybean (oil), grapes (raisin and juice), prunes (dried), and mint (oil), and other commodities where translation was applicable. For all other processed commodities, DEEM-FCID™ (ver. 7.81) default processing factors were assumed.

Estimated drinking water concentrations (EDWCs) were provided by EFED (Memo, J. Hetrick, 01-FEB-2007; DP#: 293793) and incorporated directly into the acute and chronic DEEM-FCID™ analyses. Both the acute and chronic analyses were conducted using estimated surface water residues generated using the Pesticide Root Zone/Exposure Analysis Modeling System (PRZM/EXAMS). EFED provided modeling results for several crop scenarios. The scenarios resulting in the highest EDWCs (cotton in Mississippi) were used in this assessment. For the acute and chronic assessment, the estimated 1-in-10 year annual peak and 1-in-10 year annual mean residue in surface water respectively were used as point estimates in the DEEM-FCID™ analysis.

Estimated acute dietary exposure to indoxacarb from food and drinking water are not of concern to HED for any population subgroup. Combined dietary exposure from food and drinking water at the 99.9th percentile of exposure is estimated to be 0.034881 mg/kg/day for the overall U.S. population, equivalent to 39% of the aPAD. The population subgroup with the highest estimated acute dietary exposure to indoxacarb is children, 3 to 5 years old, with an estimated exposure at the 99.9th percentile of 0.075914 mg/kg/day, equivalent to 84% of the aPAD. Estimated chronic dietary exposure to indoxacarb from food and drinking water are not of concern to HED for any population subgroup. Combined dietary exposure from food and drinking water is estimated at 0.002411 mg/kg/day for the general U.S. population (16% of the cPAD) and 0.007940 mg/kg/day (53% of the cPAD) for children, 1 to 2 years old, the population subgroup with the highest estimated chronic dietary exposure to indoxacarb.

Aggregate-Risk Estimates

Aggregate exposure risk assessments were performed for the following: acute aggregate exposure (food + drinking water exposure), short- and intermediate-term aggregate exposure (food + drinking water + residential exposure), and chronic aggregate exposure (food + drinking water exposure). The acute and chronic dietary exposure estimates mentioned above are equivalent to the acute and chronic aggregate exposures. A cancer aggregate risk assessment was *not* performed because HIARC determined that cancer dietary risk concerns due to long-term consumption of indoxacarb residues are adequately addressed by the chronic exposure assessment. Short- and intermediate-term aggregate exposures and risk estimates were calculated for toddlers and adults. The aggregate MOEs are ≥100; and, therefore are not of concern to HED.

Recommendations for Tolerances/Registration

Pending submission of revised Sections B and F, there are no residue chemistry, toxicology, or occupational/residential issues that would preclude granting an unconditional registration for the requested uses of indoxacarb. The proposed uses and the submitted data support the following permanent tolerances for the combined residues of indoxacarb + its R-enantiomer in/on the following raw agricultural commodities (RACs):

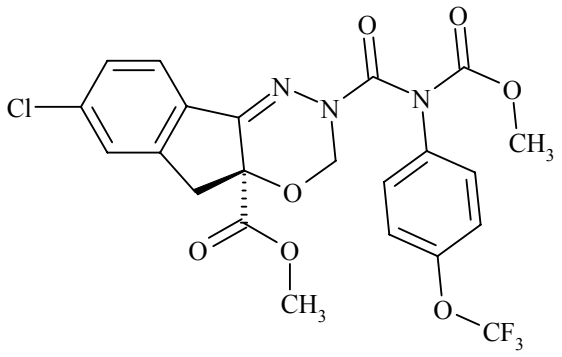
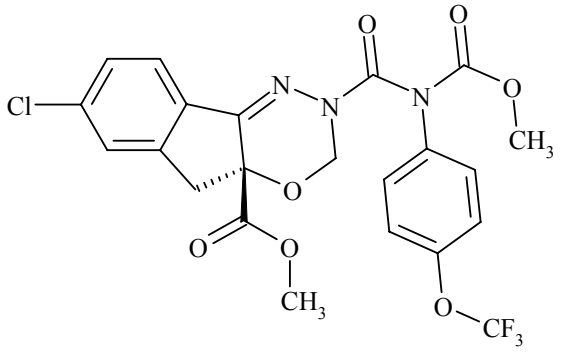
Grape	2.0	ppm
Grape, raisin	5.0	ppm
Vegetable, *Brassica,* leafy, group 5	12	ppm
Turnip greens	12	ppm
Cranberry	0.90	ppm
Fruit, pome, except pear, group 11	1.0	ppm
Fruit, stone, group 12	0.90	ppm
Vegetable, leafy, except *Brassica*, group 4	14	ppm
Peppermint, tops	11	ppm
Spearmint, tops	11	ppm
Okra	0.50	ppm
Pea, southern, seed	0.10	ppm
Vegetable, cucurbit, group 9	0.60	ppm
Vegetable, tuberous and corm, subgroup 1C	0.01	ppm
Pear, oriental	0.20	ppm

[Note to RD: in the current 2006 40 CFR §180.564 tolerance definition, the word "enantimomer" is misspelled, the correct spelling is "enantiomer." Furthermore, in 2004, HED recommended for poultry tolerances which have not been established (Memo, S. Levy, 22-SEP-2004; DP#: 297936).]

2.0. PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1. Identification of Active Ingredient

Table 2.1.1. Indoxacarb Nomenclature.

Compound	
Common name	Indoxacarb
Company experimental name	DPX-KN128
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 (4a*S*)-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 registry number	173584-44-6
End-use product (EP)	30% WDG (DuPont™ Avaunt® Insecticide; EPA Reg. No. 352-597)
Regulated Enantiomer	
Company experimental name	IN-KN127 (inactive R-enantiomer)

2.2. Physical and Chemical Properties

TABLE 2.2.1. Physicochemical Properties of Technical Grade Indoxacarb.

Parameter	Value	Reference
Melting range	140-141ºC	Memo, S. Levy, 19-JAN-2000; DP#: 244253
pH	5.32 at 25ºC	
Relative Density	1.34 at 20ºC	
Water solubility (25°C)	15.4 ± 2.3 ppb in pH 5 buffer	
Solvent solubility(25°C)	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 (25ºC)[1]	2.5 x 10^{-8} Pa	
Dissociation constant, pK_a[1]	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 (λmax, nm)[1]	Molar absorptivities at 3 maxima were affected by pH, but not over wavelengths of environmental significance.	

[1] Properties are for pure active ingredient. These properties were not reported for technical grade indoxacarb.

3.0. HAZARD CHARACTERIZATION

A complete hazard characterization is presented in the Section 3 indoxacarb risk assessment conducted in the year 2000 (Memo, Levy *et al.*, 22-AUG-2000; DP#: 267325). Since this assessment, new toxicological data were submitted. The toxicological profile and endpoints table are revised and incorporated in this risk assessment. For purposes of clarity, a brief summary of health hazard characterization and dose response assessment are summarized below.

3.1. Hazard Profile

On 06-JUN-2000, HIARC reviewed the recommendations of the toxicology reviewer for DPX-MP062 with regard to the acute and chronic RfDs and the toxicological endpoint selection for use, as appropriate, in occupational/residential exposure risk assessments. HIARC also determined that toxicity data from DPX-JW062 (the racemic mixture) could be used to support DPX-MP062 (HED Doc. No. 014241, 17-JUL-2000). On 02-MAR-2004, the HED HIARC met to re-evaluate the potential for increased susceptibility of infants and children from exposure to indoxacarb as required by FQPA of 1996 according to the FEB-2002 OPP 10x Guidance Document and to re-evaluate the inhalation endpoints based on the submission of a 28-day inhalation toxicity study (HED Doc. 0052478). HED concluded that the endpoints previously selected by the HIARC should be adjusted to 100% insecticidally active isomer DPX-KN128), since the registrant requested the registration of DPX-KN128 (25-AUG-2004; DP#: 307220). RAB1 toxicologists re-evaluated the endpoints due to submission of a DNT study. RAB1

toxicologists concluded that the database UF due to lack of the DNT study should be removed as the results of the DNT study did not impact previously selected endpoints by the HIARC (HED Doc. No. 0052478). The FQPA SFC met on 19-JUN-2000 to evaluate the hazard and exposure data for DPX-MP062 and recommended that the 10x SF to account for enhanced sensitivity of infants and children *be reduced* (1x) for the general U.S. population and all population subgroups and scenarios (HED Document Number 014226, B. Tarplee, 03-JUL-2000). RAB1 toxicologists re-evaluated FQPA assessment in light of the DNT study and concluded that the hazard-based FQPA SF should be reduced.

Acute Dietary Endpoints: An aRfD of 0.09 mg/kg was established for the general U.S. population (including infants and children). It was based on an acute oral neurotoxicity study in the rat with DPX-MP062. The 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 of 12 mg/kg was adjusted to 9.0 mg/kg based on DPX-KN128. The standard 100 UF was applied to account for interspecies extrapolation and intraspecies variation. The FQPA SFC determined that a FQPA SF of 1x is applicable for acute dietary risk assessment. Thus, the aPAD is equivalent to the aRfD of 0.09 mg/kg. An endpoint of concern attributable to a single dose for females 13-49 was not identified in the database.

Chronic Dietary Endpoint: The cRfD of 0.015 mg/kg/day was based on the: 1) rat 90-day subchronic toxicity study with DPX-MP062; 2) rat subchronic neurotoxicity study with DPX-MP062; and 3) rat chronic/carcinogenicity study with DPX-JW062. The selected NOAEL was 2.0 mg/kg/day. The LOAELs for the 3 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 study #3 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. Studies #1, #2 and #3 are all co-critical. There appeared to be little difference in toxicity between DPX-MP062 (90-day studies, #1 and #2) and DPX-JW062 (2 year study, #3), regardless of study duration. In addition, the low NOAEL (0.57 mg/kg/day) for study #2 was due solely to the dose selection and was not used to establish the chronic RfD since the LOAEL was approximately the same as for studies #1 and #3. Studies #1 and #2 were first since they were conducted on DPX-MP062, the formulation being registered. The NOAEL of 2 mg/kg was adjusted to 1.5 mg/kg based on DPX-KN128. The standard 100 UF was applied to account for interspecies extrapolation and intraspecies variation. The FQPA SFC determined that a FQPA SF of 1x is applicable for chronic dietary risk assessment. Thus, the cPAD is equivalent to the cRfD of 0.015 mg/kg.

Carcinogenicity: HIARC recommended that DPX-MP062 be classified as "not likely" to be carcinogenic to humans via relevant routes of exposure using the Guidelines for Carcinogen Risk Assessment. This was based on no evidence of carcinogenicity in either the rat or mouse in acceptable studies for DPX-JW062 and no evidence of mutagenicity for DPX-MP062 or DPX-JW062. DPX-KN128 was also non-mutagenic in various assays. Therefore, DPX-KN128 is not expected to be carcinogenic to humans via relevant routes of exposure. Therefore, a cancer risk assessment is not required.

Incidental Oral: The short- and intermediate-term endpoints were selected from the studies mentioned in the chronic dietary endpoint (see above). The NOAEL of 2 mg/kg was adjusted to 1.5 mg/kg based on DPX-KN128. The MOEs of 100 are considered adequate for incidental oral exposure risk assessment.

Short- and Intermediate-Term Dermal Endpoints: The short-, and intermediate-term dermal endpoints were selected from a rat 28-day dermal toxicity study with DPX-MP062. The NOAEL of 50 mg/kg/day was based on decreased body weights, body-weight gains, food consumption, and food efficiency in females, and changes in hematology parameters (increased reticulocytes), the spleen (increased absolute and relative weight–males only, gross discoloration), and clinical signs of toxicity in both sexes occurring at the LOAEL of 500 mg/kg/day. The NOAEL of 50 mg/kg/day was adjusted to 38 mg/kg/day based on DPX-KN128. There was little evidence (based on comparing oral subchronic and chronic NOAEL/LOAELs and toxicity profiles) to indicate that studies of longer duration would have a significantly more severe response. Since dermal studies were used for estimating dermal risks, no adjustment for dermal absorption is required. The MOEs of 100 are considered adequate for dermal exposure risk assessment.

Short- and Intermediate-Term Inhalation Endpoints: The short-, intermediate-, and long-term inhalation endpoint were selected from a 28-day inhalation toxicity study in rats with DPX-MP062. The systemic toxicity NOEC of 23 µg/L/day (equivalent to 6 mg/kg/day) was based on increased spleen weights, pigmentation and hematopoiesis in the spleen, hematological changes and mortality (females) seen at the LOAEL of 290 µg/L/day (equivalent to 75.69 mg/kg/day). Since the NOAEL was from DPX-MP062 study, it was adjusted to 4.5 mg/kg/day based on DPX-KN128. The effects do not seem to be progressing as study duration increases from subchronic to chronic since the NOAELs of oral subchronic and chronic studies are similar. Therefore, use of the 28-day inhalation study is also appropriate for the long-term exposure scenario. The MOEs of 100 are considered adequate for inhalation exposure risk assessment.

MOE for Occupational/Residential Risk Assessments: A MOE of $\geq$100 is not of concern to HED for dermal or inhalation and occupational/residential exposure risk assessment. Based on the use patterns, there are no anticipated long-term exposures to indoxacarb.

Table 3.1.1. 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 3.1.2. DPX-MP062 technical - Toxicity Categories.

Study type	DPX-MP062 Technical (94.5%;) 80% DPX KN128, 20% DPX KN127	
81-1	MRID 44477113	LD_{50} = 1730mg/kg males 268 mg/kg females , Toxicity Category II (in corn oil) <1000 mg/kg combined (rat)
81-2	MRID 44477118	LD_{50} >5000mg/kg (limit test) (rat), Toxicity Category IV
81-3	**70%MUP** MRID 44477120	LC_{50} > 5.5 mg/L males, females and combined , Toxicity Category IV
81-4	MRID 44477122	Moderate eye irritant (rabbit), Toxicity Category III
81-5	MRID 44477125	Not a dermal irritant (rabbit), Toxicity Category IV
81-6	MRID 44477126:	Magnusson-Kligman Maximization test, Is a dermal sensitizer (Guinea Pig)

Table 3.1.3. Acute Toxicity Data on DPX-JW062 (50% DPX KN128,50% DPX 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 3.1.4. Subchronic, Chronic, and Other Toxicity Data on Indoxacarb (DPX-KN128).

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
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.

Table 3.1.5. Subchronic, Chronic, and Other Toxicity Data on Indoxacarb (DPX-MP062).

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 = M 3.1 mg/kg/day F 2.1 mg/kg/day LOAEL = M 6.0 mg/kg/day, F 3.8 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.
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	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 for mutagenic activitity for the following concentration ranges: 3.1-250 µg/mL (-S9); 3.1-250 µg/mL (+S9)
Cytogenetics 870.5375	44477146 (1996) acceptable/guideline	no evidence of chromosomal aberrations induced by the test article over background for the following concentration ranges: 15.7-1000 µg/mL (±S9)
Cytogenetics 870.5395	44477148 (1997) acceptable/guideline	no evidence of mutagenicity for the following dose ranges: 3000-4000 mg/kg - males; 1000-2000 mg/kg - females
Other Effects 870.5550	44477151 (1997) acceptable/guideline	no evidence of mutagenic activity at the following concentration range: 1.56-200 µg/mL; cytotoxicity was seen

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
		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	study NOAEL = M 100, F 12.5 mg/kg LOAEL = M 200 mg/kg based on decreased body-weight gain, decreased food consumption, decreased forelimb grip strength, and decreased foot splay. F 50 mg/kg 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	study NOAEL = M 0.57, F 0.68 mg/kg/day LOAEL = M 5.6, F 3.3 mg/kg/day based on decreased body weight and alopecia.
870.7600 Dermal penetration	45911401 (2002) 45911402 (2002) 45911403 (2002) Acceptable/guideline 0, 13.3, 2000 µg/cm2 for 6 hours	Absorption ranged from 0.41% to 0.94% following 6 hours exposure. Following a 162 hours post dosing, the absorption ranged from 0.88% to 4.91% depending upon the dose/dilution.

Table 3.1.6. Subchronic, Chronic, and Other Toxicity Data on Indoxacarb (DPX-JW062).

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 (rounded to 2 sig. fig.)	**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 = 1.1 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 = M 5, F 2.1 mg/kg/day LOAEL = M 10, F 3.6 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 = M 2.3, F 2.4 mg/kg/day LOAEL = M 18, F 19 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 (rounded to 2 sig. fig.)	NOAEL = M 2.6, F4.0 mg/kg/day LOAEL = M 14, F 20 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	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 $\geq$1000 µg/mL
Cytogenetics 870.5375	44701608 (1995) acceptable/guideline	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 $\geq$ 150 µg/mL

Cytogenetics 870.5395	44701610 (1995)	No evidence of mutagenicity at 2500 or 5000 mg/kg
Other Effects 870.5550	44701609 (1995) acceptable/guideline	No evidence of mutagenic activity at the following concentration range: 0.1-50 µg/mL, cytotoxicity observed at $\geq$50 µg/mL
870.6200a Acute neurotoxicity screening battery	44477128 (1996) acceptable/guideline 0, 500, 1000, 2000 mg/kg	study NOAEL >= M 2000 mg/kg = F < 500 mg/kg LOAEL > M 2000 mg/kg F < 500 mg/kg 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.

SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Table 3.1.7. Doses and Toxicological Endpoints Selected for INDOXACARB for Various Exposure Scenarios.

Exposure Scenario	Dose Used in Risk Assessment, UF		FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
	Study NOAEL	Adjusted to KN128		
Acute Dietary females 13-49 years of age	An endpoint of concern attributable to a single dose was not identified. An acute RfD was not established.			
Acute Dietary general population including infants and children	NOAEL= 12 mg/kg UF = 100 **Acute RfD** = 0.12 mg/kg	NOAEL= 9 mg/kg UF = 100 **Acute RfD** = 0.09 mg/kg	FQPA SF = 1x **aPAD** = 0.09 mg/kg (aRfD) / 1x (FQPA SF) = 0.09 mg/kg	acute oral rat neurotoxicity study. LOAEL = 50 mg/kg based on decreased body weight and body-weight gain in females.
Chronic Dietary all populations	NOAEL= 2.0 mg/kg/day UF = 100 **Chronic RfD** = 0.02 mg/kg/day	NOAEL= 1.5 mg/kg/day UF = 100 **Chronic RfD** = 0.015 mg/kg/day	FQPA SF = 1x **cPAD** = 0.015mg/kg (cRfD) / 1x (FQPA SF) = 0.015 mg/kg/day	Weight of evidence approach was used from four studies: 1) Subchronic toxicity study-rat (INDOXACARB) 2) Subchronic neurotoxicity study - rat (INDOXACARB) 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 Incidental Oral (**1 to 30 days**)	Oral NOAEL= 2.0 mg/kg/day	Oral NOAEL= 1.5 mg/kg/day	Residential **LOC for MOE** = 100 Occupational **LOC for MOE** = 100	Weight of evidence approach was used from four studies: 1) Subchronic toxicity study-rat (INDOXACARB) 2) Subchronic neurotoxicity study - rat (INDOXACARB) 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.

Intermediate-Term Incidental Oral (1- 6 months)	oral NOAEL= 2.0 mg/kg/day	oral NOAEL= 1.5 mg/kg/day	Residential **LOC for MOE** = 100 Occupational **LOC for MOE = 100**	Weight of evidence approach was used from four studies: 1) Subchronic toxicity study-rat (INDOXACARB) 2) Subchronic neurotoxicity study - rat (INDOXACARB) 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 Dermal (**1 to 30 days**) Intermediate-Term Dermal (1 - 6 months) Long-Term Dermal (**> 6 Months**)	Dermal NOAEL= 50 mg/kg/day	Dermal NOAEL= 38 mg/kg/day	Residential **LOC for MOE** = 100 Occupational **LOC for MOE** = 100	28-day rat dermal toxicity study. LOAEL = 500 mg/kg/day based on decreased body weights, body-weight gains, food consumption, and food efficiency in females, and changes in hematology parameters (increased reticulocytes), the spleen (increased absolute and relative weight–males only, gross discoloration), and clinical signs of toxicity in both sexes.
Short-Term Inhalation (**1 to 30 days**) Intermediate-Term Inhalation (1 - 6 months) Long-Term Inhalation (**> 6 Months**)	Inhalation NOAEL= 23 µg/L/day (6 mg/kg/day)	Inhalation NOAEL= 17 µg/L/day (4.5 mg/kg/day)	Residential **LOC for MOE** = 100 Occupational **LOC for MOE** = 100	28-day rat inhalation toxicity study. The LOAEL of **290 µg/L/day (75.69 mg/kg/day)**. is based on increased spleen weights, pigmentation and hematopoiesis in the spleen, hematological changes and mortality (females).
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.			

[1] UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no-observable-adverse-effect-level, LOAEL = lowest-observable-adverse-effect-level, PAD = population-adjusted dose (a = acute, c = chronic) RfD = reference dose, LOC = level of concern, MOE = margin of exposure.

3.2. FQPA Considerations

3.2.1. Pre-and/or Postnatal Toxicity

3.2.1.1. Determination of Susceptibility

There was no evidence of increased susceptibility in the two developmental toxicity studies in rats with DPX-JW062, one developmental toxicity study in rats with DPX-MP062 and DPX-KN128, one developmental toxicity study in rabbits with DPX-JW062, one 2-generation reproduction studies in rats with DPX-JW062 and a DNT study in rats with DPX-KN128. In these studies, developmental toxicity was observed in the presence of maternal toxicity.

3.2.1.2. Degree of Concern Analysis and Residual Uncertainties

HED concluded that there is no increased susceptibility following pre-natal or post-natal exposure to indoxacarb. In these studies there are well defined NOAELs/LOAELs; therefore, there are no residual uncertainties with regard to pre- and/or post-natal susceptibility.

3.2.2. Recommendation for a DNT Study

The DNT study is available with DPX-KN128.

3.3. FQPA SF

After evaluating the toxicological database, the indoxacarb risk assessment team has identified the following factors supporting reduction of the FQPA SF to 1X: 1) the hazard and exposure databases are complete; 2) there are no concerns for pre- and/or postnatal toxicity; 3) there are no residual uncertainties with regard to pre- and/or postnatal toxicity; and 4) there are no neurotoxic concerns.

3.3.1. Adequacy of the Exposure Database

Exposure pathways resulting from the use of indoxacarb are dietary (food and drinking water), occupational, and residential. The chronic dietary analysis incorporated field trial data, %CT estimates provided by OPP's Biological and Economic Analysis Division (BEAD), and processing factors. The database is considered adequate to characterize the risks (including aggregate) associated with potential exposure to indoxacarb in all three exposure pathways.

3.3.2. FQPA SF Conclusion

Based on above discussion, the indoxacarb risk assessment team recommends that the FQPA SF be reduced to 1X for dietary, occupational and residential exposure risk assessments.

3.4. Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, indoxacarb may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0. EXPOSURE ASSESSMENT

4.1. Summary of Proposed Food Uses

Proposed Food Uses: DuPont™ and IR-4 have proposed amending the label for DuPont™ Avaunt® Insecticide (EPA Reg. No. 352-597) to include new uses on grapes, *Brassica* leafy vegetables, turnip greens, cranberry, cucurbit vegetables (group 9), leafy vegetables except *Brassica* (group 4), pome fruits (group 11, except pear), tuberous and corm vegetables (subgroup 1C), mint, okra, southern peas, and stone fruits (group 12). The petitioners have submitted new field trial data to support these uses and/or they have proposed using existing field trial data on apples, lettuce, peppers, and potatoes to support expanding the uses on the 30% WDG to cover pome fruits (expect pear), leafy vegetables except *Brassica*, okra, and tuberous and corm vegetables. The petitioners provided both a summary of the proposed uses and example labels containing the use directions. The proposed use directions are summarized below in Table 4.1.1.

Table 4.1.1. Summary of Proposed Food Use Directions for Indoxacarb.

Applic. Timing, Type, and Equip.[1]	Formulation [EPA Reg. No.]	Applic. Rate (lb a.i./A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb a.i./A)	Pre-harvest interval (PHI) (days)	Use Directions and Limitations[2]
Grape						
Broadcast foliar applications using ground or aerial equipment	30% WDG [352-597]	0.065-0.11	NS = not specified	0.44	7	The proposed label specifies a minimum retreatment interval (RTI) of 5 days and a maximum seasonal use rate of 0.44 lb a.i./A. Mix with water for application to obtain thorough, uniform coverage. For aerial application, a minimum of 5 GPA are required.
***Brassica* Leafy Vegetables and Turnip Greens**						
Broadcast foliar applications using ground or aerial equipment	30% WDG [352-597]	0.045-0.065	NS	0.26	3	The proposed label specifies a minimum RTI of 3 days and a maximum seasonal use rate of 0.26 lb a.i./A. Mix with water for application to obtain thorough, uniform coverage. For aerial application, a minimum of 5 GPA are required.
Cranberry						
Broadcast foliar applications using ground or aerial equipment	30% WDG [352-597]	0.11	4	0.44	30	Minimum RTI is 7 days. Do not apply to flow through bogs or allow release of irrigation water from bogs for at least 1 day following application.
Cucurbit Vegetables						
Broadcast foliar applications using ground or aerial equipment	30% WDG [352-597]	0.045-0.11	4	0.44	3	Minimum RTI is 5 days. Make uniform application of insecticide in 10-50 GPA of water. For ground application, apply using a minimum of 10 GPA of water.
Leafy Green Vegetables, except spinach						
Broadcast foliar applications using ground or aerial equipment	30% WDG [352-597]	0.045-0.11	4	0.44	3	Minimum RTI is 3 days.
Leaf Petiole Vegetables						
Broadcast foliar applications using ground or aerial equipment	30% WDG [352-597]	0.065	4	0.26	3	Minimum RTI is 3 days.
Mint						
Broadcast foliar applications using ground or aerial equipment	30% WDG [352-597]	0.065	4	0.26	7	Minimum RTI is 3 days. Use a minimum of 20 GPA of water for ground applications.
Okra						
Broadcast foliar applications using ground or aerial equipment	30% WDG [352-597]	0.065	4	0.26	3	Minimum RTI is 5 days.

Pome Fruits, except pears						
Foliar applications using Ground or aerial equipment	30% WDG [352-597]	0.056-0.11	4	0.44	14	Minimum RTI is 7 days. For best results, apply a uniform application of insecticide in 50-150 GPA of water. Do not apply in a dilute application of more than 200 GPA of water.
Southern Pea						
Broadcast foliar applications using ground or aerial equipment	30% WDG [352-597]	0.065	4	0.26	7	Minimum RTI is 3 days. Make a uniform application in approximately 20-100 GPA of water.
Spinach						
Broadcast foliar applications using ground or aerial equipment	30% WDG [352-597]	0.065	4	0.26	3	Minimum RTI is 3 days.
Stone Fruits						
Foliar applications using ground or aerial equipment	30% WDG [352-597]	0.09-0.11	4	0.44	14	Minimum RTI is 7 days. For best results, apply a uniform application of insecticide in 50-150 GPA of water. Do not apply in a dilute application of more than 200 GPA of water.
Tuberous and Corm Vegetables						
Broadcast foliar applications using ground or aerial equipment	30% WDG [352-597]	0.045-0.11	4	0.44	7	Minimum RTI is 5 days. For aerial application, use a minimum of 5 GPA of water.

[1] Do not apply through any type of irrigation equipment, except as allowed by supplemental labels.

[2] The label currently specifies a minimum REI of 12 hours and a rotation crop restriction of 30 days for food/feed crops not registered for use with indoxacarb. Unless otherwise specified, apply aerial applications in a minimum of 5 gallons per acre (GPA) or 10 GPA for tree and orchard crops.

RTI = retreatment interval.

Conclusions. The proposed use directions adequately reflect the use patterns used in the new or previously reviewed field trials, with the exceptions of southern peas and turnip greens. Based on the available southern pea field trial data, it is unclear whether the petitioner is pursuing a use on succulent or dry southern peas. The proposed label directions for southern peas should be amended to allow applications only to varieties used to produce dry seed. If the petitioner intends to support a generalized use on southern peas, field trials will be required for the succulent variety as well. In addition, the use directions for southern peas should prohibit applications to varieties grown for livestock feed. For turnip greens, a restriction should be placed on the label to prohibit use on dual purpose turnip cultivars or varieties which produce a harvestable root. **Revised Section B's should be submitted.**

4.2. Dietary Exposure

The residue chemistry data submitted in support of the proposed petitions were evaluated by HED on 18-FEB-2005 (Memo, S. Levy; DP#: 290126) and 09-MAR-2007 (Memo, S. Levy; DP#: 325479). The drinking water assessment was completed by EFED (Memo, J. Hetrick *et al.*, 01-FEB-2007; DP#: 293793). The dietary exposure assessment was completed by HED

(Memo, M. Sahafeyan, *et al.*, 23-MAY-2007; DP#: 339398).

4.2.1. Residue Profile

Because the insecticidal efficacy of the end use products are based on the concentration of indoxacarb, the petitioner normalized the application rates for the submitted studies on an indoxacarb basis. The residue analytical methods proposed for enforcement, as well as those used for data collection, do not distinguish between the enantiomers; therefore, residues are reported as the sum of indoxacarb + its R-enantiomer.

Background

Data for indoxacarb were originally reviewed by HED under a petition (PP# 8F04948) for use on *Brassica*, sweet corn, cotton, fruiting vegetables, lettuce (head and leaf), and pome fruit (Memo, S. Levy, *et al.*, 22-AUG-2000; DP#: 267325). Tolerances for indoxacarb residues have since been established in 40 CFR 180.564 in/on various RACs and meat and milk products. HED also recommended (Memo, S. Levy, 22-SEP-2004; DP#: 297936) that tolerances be established for the combined residues of indoxacarb + its R-enantiomer, IN-JT333, IN-KT319, IN-JU873, IN-KG433, and IN-KB687 in/on egg, and poultry meat, fat, and meat byproducts. (Note to RD: these tolerances were recommended for by HED, but have not been established in the 40 CFR 180.564.)

DuPont™ and IR-4 have submitted five petitions (PP#s: 2E6482, 3F6576 5E6911, 5E6926, and 5E6991) proposing new uses of indoxacarb, formulated as a 30% WDG (DuPont™ Avaunt® Insecticide; EPA Reg. No. 352-597), on the following crops or crop groups: grapes, *Brassica* leafy vegetables (group 5), turnip greens, cranberry, cucurbit vegetables (group 9), mint, southern pea and stone fruits (group 12). Under these petitions, IR-4 has also proposed expanding existing uses and tolerances on apples, lettuce, peppers and potatoes to cover pome fruits (except pear, group 11), leafy vegetables except *Brassica* (group 4), okra, and tuberous and corm vegetables (subgroup 1C).

The proposed uses on *Brassica* leafy vegetables, turnip greens, leaf petiole vegetables, mint, okra, and southern pea are for up to four broadcast foliar applications at 0.065 lb a.i./A, at minimum RTIs of 3-5 days, for a total application rate of 0.26 lb a.i./A/crop. The proposed uses on grapes, cranberry, leafy green vegetables (except spinach), pome fruits, stone fruits, and tuberous and corm vegetables are for up to four broadcast foliar applications at 0.11 lb a.i./A, at minimum RTIs of 3-7 days, for a total application rate of 0.44 lb a.i./A/crop. All uses allow applications using either ground or aerial equipment, and the proposed PHIs range from 3 days (for *Brassica* leafy vegetables, turnip greens, cucurbits, okra, and leafy vegetables, except *Brassica*, group 4) to 30 days (for cranberries). In conjunction with these uses, the petitioners have proposed permanent tolerances for combined indoxacarb residues at the following levels:

Grape	2.0	ppm
Raisin	6.0	ppm
Vegetable, brassica, leafy, group 5	12	ppm
Turnip greens	12	ppm
Cranberry	0.90	ppm
Fruit, pome, except pear, group 11	1.0	ppm
Fruit, stone, group 12	0.90	ppm
Vegetable, leafy, except Brassica, group 4	14	ppm
Peppermint	11	ppm
Spearmint	11	ppm
Okra	0.50	ppm
Pea, southern, seed	0.10	ppm
Vegetable, cucurbit, group 9	0.60	ppm
Vegetable, tuberous and corm, subgroup 1C	0.01	ppm

Nature of the Residue – Plants/Livestock

Adequate metabolism studies on cotton, lettuce, and tomatoes were reviewed in conjunction with an earlier petition (Memo, S. Levy, 19-JAN-2000; DP#: 244253). The nature of the residue in plants is adequately understood based on these studies. The HED Metabolism Assessment Review Committee (MARC) determined that the residue of concern in plants is indoxacarb + its R-enantiomer (Memo, S. Levy, 10-JUL-2000; DP#: 263986).

Adequate ruminant and poultry metabolism studies were reviewed in conjunction with an earlier petition (Memo, S. Levy, 19-JAN-2000; DP#: 244253). Based on these studies, the MARC has determined that the tolerance expression for milk and ruminant commodities will include indoxacarb + its R-enantiomer (Memo, S. Levy, 10-JUL-2000; DP#: 263986). However, for purposes of risk assessment, the metabolite IN-MP819 should also be considered in milk. For poultry commodities, HED has recommended that tolerances be established for the combined residues of indoxacarb + its R-enantiomer, IN-JT333, IN-KT319, IN-JU873, IN-KG433, and IN-KB687 (Memo, S. Levy, 22-SEP-2004; DP#: 297936). For purposes of risk assessment, residues of concern in poultry commodities also include 5-OH-IN-JT333 and Metabolite F (Memo, S. Levy, 04-OCT-2001; DP#: 277922).

Analytical Methods

For PP#s: 5E6911, 5E6926 and 5E6991: 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: Two high-performance liquid chromatography (HPLC)/column switching/ultraviolet (UV) methods (AMR 2712-93 and DuPont-11978) are available for enforcing indoxacarb tolerances on plant commodities, and a third gas chromatography (GC)/mass-selective detector (MSD) method (AMR 3493-95, Supplement No. 4) is available for confirmation of residues in plants. The limits of quantitation (LOQs) for the HPLC methods are 0.01-0.05 ppm for a variety of plant commodities, and the limits of detection (LODs) are 0.0025-0.006 ppm. For the GC/MSD method, the LOQs range from 0.2 to 1.0 ppm depending on the

matrix, and the LODs are 0.0008-0.21 ppm. Each of these methods determines both indoxacarb + its R-enantiomer as a single component. Another HPLC/column switching/UV Method (AMR 3337-95) is also available for enforcing the current tolerances on livestock commodities. The LOQ for this method is 0.01 ppm and the LOD is 0.002-0.003 ppm.

For PP#s: 3F6576 and 2E6482: Grapes, *Brassica* Leafy Vegetables, and Turnip Greens. The petitioner submitted a method that combines the extraction procedure from one previously-validated method (Method AMR 3493-95, Supplement No. 1) with the cleanup and analysis procedures from another previously-validated method (Method AMR 2712-93). Therefore, only a limited verification of the combined method was made. An independent laboratory validation (ILV) of this method was conducted (MRID 45900304) and observations from the ILV work concerning the method were incorporated into this method revision. A petition method validation (PMV) is not necessary for this method; however, this method will be sent to the U.S. Food and Drug Administration (FDA) for inclusion in the Pesticide Analytical Manual, Volume II (PAM, Vol. II). There is adequate methodology for monitoring and confirming indoxacarb tolerance-level residues. Tolerances can be monitored by method AMR 2712-93 with confirmation/specificity provided by method AMR 3493-95, Supplement 4.

Multiresidue Method

Acceptable data are available depicting the recovery of indoxacarb + its R-enantiomer using FDA multiresidue method protocols (PAM, Vol. I) C, D, and E. Indoxacarb + its R-enantiomer were not evaluated through Protocol A because it does not possess an N-methylcarbamate structure. It was not tested through Protocol B because it does not possess a carboxylic acid or phenolic moiety. It was not tested through Protocol F because indoxacarb + its R-enantiomer are not recoverable from Florisil at a level ≥30%. Indoxacarb + its R-enantiomer are completely recovered through Protocol D; however, matrix enhancement effects were seen in certain matrices. The results of multiresidue testing were forwarded to FDA for review (Memo, S. Levy, 03-NOV-1999; DP#: 260955).

Meat, Milk, Poultry, and Eggs

The only livestock feed items associated with the proposed uses are wet apple pomace and potato culls and processed waste, which are covered under the proposed uses for pome fruits and tuberous and corm vegetables. The effects of indoxacarb residues in these commodities on livestock diets were previously addressed under earlier petitions supporting uses on apples and potatoes (Memos, S. Levy, 19-JAN-2000; DP#: 244253 and 30-MAY-2002; DP#: 276516). As the proposed uses will not alter the dietary exposure of livestock, data requirements pertaining to meat, milk, poultry, and eggs will not be further addressed under the current petitions. Note that new poultry and livestock diets were constructed based on current guidelines ("reasonably-balanced diet" guidelines, J. Stokes, Revisions of Livestock Diets Percents) for purposes of assessing dietary risk from exposure to consuming livestock RACs (see Memo, M. Sahafeyan, *et al.*, 23-MAY-2007; DP#: 339398 for details).

Magnitude of the Residue

To support the proposed new uses of indoxacarb (30% WDG), crop field trials on grapes, cherries, plums, peaches, cucumbers, summer squash, cantaloupes, mint, cranberry, and southern peas were submitted. To support the purposed uses on pome fruits (group 11, except pear), leafy vegetables except *Brassica* (group 4), and tuberous and corm vegetables (subgroup 1C), IR-4 cited the existing tolerances and field trial data on apples, leaf and head lettuce, and potatoes. IR-4 also submitted new field trial data on mustard greens, and spinach and celery to support the crop group tolerance on *Brassica* leafy vegetables (group 5), and leafy vegetables except *Brassica* (group 4), respectively. Furthermore, IR-4 requested that the existing tolerance and residue data on peppers be translated to support the proposed use on okra. The results from these studies are discussed below and summarized in Table 4.2.1.1.

Table 4.2.1.1. Summary of Residue Data from Field Trials on Grapes, Mustard Greens, Spinach, Celery, Cucurbit Vegetables, Southern Pea, Stone Fruits, Cranberry, and Mint Following Application of Indoxacarb (30% WDG).

Commodity	Total Applic. Rate (lb a.i./A)	PHI (days)	Residue Levels (ppm)[1]						
			n	Min.	Max.	HAFT[2]	Median	Mean	Std. Dev.
Grapes (proposed maximum application rate: 0.44 lb a.i./A; PHI: 7 days)									
Fruit	0.438-0.507	7	26	0.089	1.72	1.52		0.487	0.450
***Brassica* leafy vegetables, group 5** (proposed maximum application rate: 0.26 lb a.i./A; PHI: 3 days)									
Mustard Greens	0.265 - 0.268	3	10	1.2	10	9.8		5.63	3.61
Leafy Vegetables except *Brassica*, group 4 (proposed maximum application rate: 0.26 lb a.i./A; PHI: 3 days)									
Spinach	0.268	3	16	2.2	13.0	10.5	4.45	5.27	2.59
		7	16	0.49	6.1	5.20	2.90	3.16	1.44
		14	14	0.29	2.5	2.35	1.90	1.69	0.70
Celery Untrimmed Stalks (RAC)	0.268	7	12	0.32	1.80	1.70	1.20	1.07	0.62
		14	12	0.12	1.00	0.99	0.37	0.51	0.36
		21	12	0.11	0.77	0.50	0.21	0.27	0.18
Celery Trimmed Stalks	0.268	3	12	0.31	1.90	1.75	0.54	0.82	0.55
		7	12	0.21	0.65	0.62	0.37	0.38	0.13
		14	12	0.12	0.53	0.38	0.19	0.24	0.13
Southern Peas (proposed maximum application rate: 0.26 lb a.i./A; PHI: 7 days)									
Mature Seed[3]	0.255-0.266	6-7	14	<0.01	0.067	0.065	0.014	0.021	0.021
Cucurbit Vegetables (proposed maximum application rate: 0.44 lb a.i./A; PHI: 3 days)									
Cantaloupe	0.437-0.475	3-4	22	0.018	0.393	0.312	0.064	0.102	0.095
Cucumber	0.414-0.463	3	20	<0.01	0.069	0.055	0.020	0.022	0.014
Summer Squash	0.423-0.459	2-4	22	<0.01	0.120	0.102	0.024	0.032	0.033
Stone Fruits (proposed maximum application rate: 0.44 lb a.i./A; PHI: 14 days)									
Cherry	0.437-0.468	12-14[4]	32	0.07	0.64	0.63	0.20	0.25	0.16
Peach	0.420-0.449	13-14[4]	30	0.03	0.59	0.59	0.10	0.16	0.14
Plum	0.431-0.448	13-15	22	<0.01	0.19	0.185	0.020	0.045	0.050
Cranberry (proposed maximum application rate: 0.44 lb a.i./A; PHI: 30 days)									
Cranberry	0.438-0.451	13-15	12	0.11	0.39	0.32	0.22	0.23	0.09
		28-30	12	0.086	0.69	0.63	0.15	0.22	0.20
Mint (proposed maximum application rate: 0.26 lb a.i./A; PHI: 7 days)									
Mint Tops	0.260-0.270	7-8	12	2.10	6.84	6.37	3.06	3.87	1.83

[1] The validated LOQ is 0.01 ppm for cantaloupes, cucumbers, squash, southern peas, peaches and plums; 0.02 ppm for spinach, celery and cherries; and 0.05 ppm for cranberries and mint. For samples having residues <LOQ, ½ LOQ was used for calculating of the median, mean and standard deviation.

[2] HAFT = Highest-Average Field Trial.

[3] Samples were only identified as "mature seed" and did not specify whether samples were dry seed or succulent seed.

[4] Includes samples from one cherry trial collected at 5 days after the last application (DALA) and one peach trial at 7 DALA. Residues in/on

samples from these earlier intervals were similar to residues in/on samples collected at ~14 DALA.

The submitted field trial data on spinach, cantaloupes, cucumbers, summer squash, cherries, peaches, plums, cranberries, mint, grape, and mustard greens are adequate and support the proposed use patterns for indoxacarb (30% WDG) on these crops or crop groups. The number and geographic distribution of the field trials are adequate, and the appropriate samples were collected at the proposed PHIs. The samples were analyzed using adequate analytical methods and the sample storage intervals are supported by the available storage stability data.

The available field trial data on celery (the representative crop for subgroup 4B) would not be adequate to support a subgroup tolerance, as only six field trials were conducted using the WDG formulation, rather than the required eight field trials, but are adequate to support a crop group tolerance for the crop group vegetable, leafy, except *Brassica* (group 4).

The southern pea field trial data are also adequate; however, the petitioner did not specify if they wanted succulent or dry. The field trial data submitted were for dry peas. The proposed label directions for southern peas should be amended to allow for applications only to varieties used to produce dry seed. If the petitioner intends to support a generalized use on southern peas, then field trials will be required for succulent varieties as well. Furthermore, the use directions for southern peas should prohibit applications to varieties grown for livestock feed.

Storage Stability

Adequate storage stability data have been previously reviewed indicating that indoxacarb residues are stable in frozen storage for up to 6-23 months in a wide variety of plant commodities. In addition, adequate storage stability data were provided with the new field trials and processing studies. These data also indicate that indoxacarb is stable in frozen storage for at least 1.5 months in cranberries, 5-8 months in peaches, plums, prunes, and mint tops and oil, 10-12 months in peas, celery, spinach, cantaloupes, and squash, 15 months in cherries, and 24 months in cucumbers. These data support the sample storage intervals and conditions used in the submitted field trials and processing studies. The submitted grape and mustard green field trials and grape processing study are supported by the previously-submitted storage stability data.

Processed Food/Feed

To support the proposed new uses of indoxacarb (30% WDG), adequate processing studies were conducted on grapes, mint and plums. For **grapes**, a separate tolerance is not required for juice as residues were reduced on average by 0.007x for grape juice. However, residue concentrations were observed in raisins (2.7x). Based on the observed 2.7x processing factor for raisins and HAFT residues of 1.52 ppm from the grape field trials, the maximum expected indoxacarb residues in raisins would be 4.1 ppm. These data support a tolerance of 5.0 ppm for residues in/on "grape, raisin." **A revised Section F should be submitted.**

For **mint**, a separate tolerance is not required for oil as residues were reduced on average by 0.028x in mint oil. For **plums**, although residues were shown to concentrate by 4x in prunes, a separate tolerance is not required for prunes. Based on the highest-average field trial (HAFT)

residues for plums (0.185 ppm) and the above processing factor, the maximum expected residues in prunes would be 0.74 ppm, which is below the recommended tolerance for stone fruits (0.90 ppm). Processing studies on apples and potatoes were previously considered under earlier petitions. Based on these petitions, no tolerances were required for potato processed products and a 3.0 ppm tolerance was established for wet apple pomace.

Confined/Field Accumulation in Rotational Crops

An adequate confined rotational crop study, conducted at a rate of 0.268 lb a.i./A (1x the proposed application rate for proposed crops), was reviewed in conjunction with an earlier petition (Memo, S. Levy, 19-JAN-2000; D244253). The residues of concern in rotated crops include indoxacarb + its R-enantiomer (Memo, S. Levy, 10-JUL-2000; D263986). HED has also concluded that the available data support a 30-day plant-back interval (PBI) for all non-labeled crops (Memo, S. Levy, 07-SEP-2000; D256351). As the maximum rate conducted in the confined accumulation study does not exceed the proposed application rate for the proposed crops, the study conclusions support the proposed uses in the subject petition.

Other Considerations

There are no established or proposed Codex or Canadian maximum residue limits (MRLs) for indoxacarb. However, Mexico has established MRLs for indoxacarb on several crops at levels ranging from 0.5 mg/kg on tomatoes and pepper to 10 mg/kg on corn. None of the proposed crops currently have equivalent Mexican MRLs; therefore, there are no international harmonization issues associated with these petitions.

Proposed/Recommended Tolerances

For PP#s: 5E6911, 5E6926 and 5E6991: 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: The tolerances proposed by the petitioners are listed below in Table 4.2.1.2, along with the HED's recommended tolerance levels. The recommended tolerance levels for each RAC or crop group in the current petitions were determined using recent Agency Guidance (*Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP). For southern peas, the recommended tolerance was based on the observed maximum residue value.

For purposes of determining tolerances, adequate field trial data are available to set individual tolerances on southern peas, cranberries, and mint. In addition, the available data on cantaloupes, cucumbers, and squash will support a crop group tolerance on cucurbit vegetables, and the available data on cherries, peaches and plums will support a crop group tolerance on stone fruits. As residues were highest in cantaloupes and cherries, these data were used to set tolerances for their respective crop groups.

Based on previously reviewed field trial data supporting the existing tolerances on leaf and head lettuce (10 and 5.0 ppm, respectively) and the currently-submitted spinach and celery data, a new crop group tolerance can be established at 14 ppm for "vegetable, leafy, except *Brassica*, group 4." As residues were highest in spinach, these data were used to set the crop group tolerance.

Based on previously reviewed field trial data supporting the existing tolerances on potatoes and apples, new tolerances can be established at the same levels on tuberous and corm vegetables (subgroup 1C) and pome fruit (group 11, except pear). The existing pear tolerance (0.20 ppm) can be translated to pear, oriental. In addition, the residue data on fruiting vegetables can be translated to support the same use pattern for indoxacarb (WDG) on okra, as okra is now considered part of the "vegetable, fruiting, group 8" crop group.

Based on the mint and plum processing studies, separate tolerances are not required for either mint oil or prunes.

For PP#s: 3F6576 and 2E6482: Grapes, *Brassica* Leafy Vegetables, and Turnip Greens. DuPont™ and IR-4 proposed tolerances for indoxacarb of 2.0 ppm in/on grape and 6.0 ppm in/on raisins and 12 ppm in/on Vegetable, brassica, leafy, group 5 and turnip greens, respectively. Furthermore, IR-4 requests that the established 5.0 ppm tolerance for residues in/on *Brassica*, head and stem, subgroup be revoked. HED concludes that the proposed tolerances for grape, vegetable, *Brassica*, leafy, group 5, and turnip greens are adequate. However, the proposed raisin tolerance should be lowered to 5.0 ppm and the correct commodity definition is "grape, raisin."

The petitioner has requested a tolerance be set for residues in/on turnip greens at 12 ppm. Turnip greens is not officially classified under 40 CFR 180.41 as a part of group 5; however, a turnip green tolerance can be requested when submitting mustard greens data for a tolerance (Memo, B. Schneider, 10-FEB-2000). Thus, the residue chemistry database also supports a 12 ppm tolerance for turnip greens.

Table 4.2.1.2. Tolerance Summary for Indoxacarb.

Crop Commodity	Proposed or Existing Tolerance (ppm)	Recommended Tolerance (ppm)	Comments *(Corrected commodity definition)*
Cranberry	1	0.90[1]	Adequate residue data are available.
Fruit, pome, except pear, group 11	1.0	1.0[2]	The existing residue data on apples are adequate and will support an expanded use and a tolerance on *Fruit, pome, group 11, except pear*.
Pear, oriental	--	0.20[2]	The existing pear tolerance is adequate to cover a separate *Pear, oriental* tolerance.
Apple	1.0	Delete	Once the tolerance is established on group 11, the separate tolerance on apple should be deleted.
Fruit, stone group 12	1	0.90[1]	Adequate residue data are available on cherries, plums and peaches. The group tolerance is based on residue data from cherries. *Fruit, stone, group 12*
Leafy vegetables except *Brassica*	14	14[1]	The existing residue data on leaf and head lettuce are adequate, as well as the currently- submitted spinach and celery data will support a crop group tolerance for *Vegetable, Leafy, Except* Brassica, *Group 4*.
Lettuce, head	5.0	Delete	Once the tolerance is established on Vegetable, Leafy, except *Brassica*, Group 4, the separate tolerances on leaf and head lettuce should be deleted.
Lettuce, Leaf	10.0		
Mint	10	11[1]	Adequate residue data are available. Separate tolerances should be established for *Peppermint, tops* and *Spearmint, tops*.
Okra	0.5	0.50[2]	The existing residue data on tomatoes and peppers will be translated to support the same use pattern and tolerance on okra, as okra is now considered part of the "vegetable, fruiting, group 8" crop group.
Pea (southern)	0.1	0.10[1]	Adequate residue data are available for dried pea only. *Pea, southern, seed*
Vegetable, cucurbit, group 9	0.5	0.60[1]	Adequate residue data are available on cucumbers, squash, and cantaloupes. The tolerance is based on residue data from cantaloupes.
Vegetable, tuberous and corm, subgroup 1C	0.01	0.01[2]	The existing residue data on potatoes are adequate and will support an expanded use and a tolerance on *Vegetable, tuberous and corm, subgroup 1C*.
Potato	0.01	Delete	Once the tolerance is established on

			subgroup 1C, the separate tolerance on potato should be deleted.
Grape	2.0	2.0	Adequate residue data are available.
Raisin	6.0	5.0	*Grape, raisin*
Vegetable, brassica, leafy, group 5	12	12	Adequate residue data are available.
Brassica, head and stem, subgroup 5A	5.0	Delete	Once the tolerance is established on crop group 5, the separate "*Brassica*, head and stem, subgroup 5A" should be revoked.
Turnip Greens	12	12	Adequate residue data are available.

[1] Tolerance was determined using tolerance calculating spread sheet.
[2] Tolerance is based on translation of existing residue data.

4.2.2. Dietary Exposure Analyses

Indoxacarb acute and chronic dietary exposure assessments were conducted using the DEEM-FCID™, Version 2.03, which incorporates consumption data from USDA's CSFII, 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups, but for acute exposure assessment are retained as individual consumption events. Based on analysis of the 1994-96, 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old.

For chronic dietary exposure assessments, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form to produce a residue intake estimate. The resulting residue intake estimate for each food/food form is summed with the residue intake estimates for all other food/food forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (*i.e.*, only those who reported eating relevant commodities/food forms) and a per-capita (*i.e.*, those who reported eating the relevant commodities as well as those who did not) basis. In accordance with HED policy, per capita

exposure and risk are reported for all tiers of analysis. However, for Tiers 1 and 2, any significant differences in user vs. per capita exposure and risk are specifically identified and noted in the risk assessment.

Partially-refined acute probabilistic and chronic dietary exposure assessments were conducted for all existing and proposed new food uses of indoxacarb. A cancer dietary exposure assessment was not conducted for indoxacarb, because indoxacarb has been classified as "not likely to be carcinogenic." ARs for all registered and proposed food commodities were based on field trial data. ARs for all current uses were further refined using %CT data (Memo, A. Halvorson, 05-APR-2007; DP#: 338731, and electronic communication, A. Halvorson to M. Sahafeyan, 12-APR-2007, and A. Halvorson to S. Levy, 10-MAY-2007), following the guidance provided in HED SOP 99.6 (*Classification of Food Forms with Respect to level of Blending*; 20-AUG-1999). 100% CT was assumed for the remaining new uses. Available processing data for indoxacarb were used to refine ARs for apples/pears (juice), potato (dry, chips), cotton (oil), tomato (paste and puree), peanut (oil), soybean (oil), grapes (raisin and juice), prunes (dried), and mint (oil), and other commodities where translation was applicable. For all other processed commodities, DEEM-FCID™ (ver. 7.81) default processing factors were assumed.

EDWCs were provided by EFED (Memo, J. Hetrick, 01-FEB-2007; DP#: 293793) and incorporated directly into the DEEM-FCID™ analyses. Both the acute and chronic analyses were conducted using estimated surface water residues generated using PRZM/EXAMS. EFED provided modeling results for several crop scenarios. The scenarios resulting in the highest EDWCs (cotton in Mississippi) were used. For the acute and chronic assessments, the estimated 1-in-10 year annual peak and 1-in-10 year annual mean residue in surface water, respectively, were used as point estimates in the DEEM-FCID™ analysis.

4.2.2.1. Acute Dietary Exposure Analysis

Indoxacarb acute dietary (food + water) exposure estimates using the DEEM-FCID™ software are below HED's level of concern for the U.S. population and each of the population subgroups. Combined dietary exposure from food and drinking water at the 99.9th percentile of exposure is estimated to be 0.034881 mg/kg/day for the overall U.S. population, equivalent to 39% of the aPAD. The population subgroup with the highest estimated acute dietary exposure to indoxacarb is children, 3 to 5 years old, with an estimated exposure at the 99.9th percentile of 0.075914 mg/kg/day, equivalent to 84% of the aPAD. The estimated exposures/risks from food and water are summarized in Table 4.2.2.1.1 for all populations.

Table 4.2.2.1.1. Summary of Acute Dietary (Food + Drinking Water) Exposure and Risk for Indoxacarb.

Population Subgroup	aPAD (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.09	0.007763	8.6	0.015056	17	0.034881	39
All Infants (< 1 year old)		0.011092	12	0.021882	24	0.039554	44
Children 1-2 years old		0.018245	20	0.027641	31	0.070299	78
Children 3-5 years old[1]		0.013500	15	0.021957	24	0.075914	**84**
Children 6-12 years old		0.008839	9.8	0.013521	15	0.029817	33
Youth 13-19 years old		0.005670	6.3	0.011517	13	0.039626	44
Adults 20-49 years old		0.004719	5.2	0.008655	9.6	0.027228	30
Adults 50+ years old		0.004489	5.0	0.012210	14	0.031662	35

[1] The population subgroup with the highest estimated acute dietary (food + drinking water) exposure and risk is indicated by bold text.

4.2.2.2. Chronic Dietary Exposure Analysis

Indoxacarb chronic dietary (food + water) exposure estimates using the DEEM-FCID™ software are below HED's level of concern for the U.S. population and each of the population subgroups. Estimated chronic dietary exposure to indoxacarb from food and drinking water is below HED's level of concern. Combined dietary exposure from food and drinking water is estimated at 0.002411 mg/kg/day for the general U.S. population (16% of the cPAD) and 0.007940 mg/kg/day (53% of the cPAD) for children, 1 to 2 years old, the population subgroup with the highest estimated chronic dietary exposure to indoxacarb.

Table 4.2.2.2.1. Summary of Chronic Dietary (Food + Drinking Water) Exposure and Risk for Indoxacarb.

Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.015	0.002411	16
All Infants (< 1 year old)		0.002574	17

Children 1-2 years old[1]		**0.007940**	**53**
Children 3-5 years old		0.006068	41
Children 6-12 years old		0.003701	25
Youth 13-19 years old		0.002197	15
Adults 20-49 years old		0.001764	12
Adults 50+ years old		0.001747	12
Females 13-49 years old		0.001693	11

[1]The population subgroup with the highest estimated chronic dietary (food + drinking water) exposure and risk is indicated by bold text.

4.2.2.3. Cancer Dietary Exposure Analysis

Indoxacarb has been classified as "not likely to be carcinogenic in humans" by HIARC; therefore, no carcinogenic dietary risk analysis was performed.

4.3. Water Exposure/Risk Pathway

The drinking water assessment was revised (original drinking water assessment dated on 08-JUN-2004) to clarify and correct application rates and model output for current and proposed uses of indoxacarb. The highest indoxacarb concentrations in surface and ground source water are associated with cotton. This use pattern has a maximum label rate of 0.11 lbs a.i.[1]/A (0.15 lbs KN128+KN127/A). Similar use rates are recommended for apples, potatoes, and grapes (Draft Label for DuPont™ Avaunt®). Tier II surface water modeling for cotton using the index reservoir with the default percent cropped area (PCA=0.87) predicts the 1-in-10 year peak (acute) concentration of DPX-JW062 residues of 25.1 µg/L. The 1-in-10 year annual average concentration (non-cancer chronic) and 30-year annual average concentration (cancer) of DPX-JW062 residues are not likely to exceed 5.37 and 2.78 µg/L, respectively. SCI-GROW modeling indicates concentrations of DPX-JW062 are not expected to exceed 0.21 µg/L. The highest indoxacarb residue concentrations are associated with the Mississippi cotton scenario (Table 4.3.1).

For acute and chronic dietary risk assessments, the 1-in-10 year peak (25.1 ppb) and the 1-in-10 year annual average, (5.37 ppb) indoxacarb residues of concern in water from cotton scenario were used.

Table 4.3.1. Default PCA Corrected PRZM/EXAMS Indoxacarb Residue Concentrations (µg/L).

[1] ai = active ingredient is defined as the S isomer of indoxacarb (KN128). The R isomer (KN127) is an inactive isomer.

Scenario	1-in-10 year peak	1-in-10 year annual average	30-year annual average
Cotton (MS)	25.068	5.373	2.782
Turf (FL)[1]	0.05	0.014	0.008
Apples (NC)	18.093	4.738	2.560
Cabbage (FL)	8.275	1.940	1.185
Potato (ME)	11.083	5.346	3.961
Swiss Chard (CA) Aerial Application	9.220	3.788	2.643
Swiss Chard (CA) Ground Application	9.173	3.564	2.379

1- The default PCA correction (0.87) was not used for turf because this use pattern was not considered in development of PCAs.

4.4. Residential Exposure/Risk Pathway

Residential exposure/risk assessments for indoxacarb were provided by M. Dow (Memo, 25-AUG-2004; DP#: 289892).

Residential Handlers

Indoxacarb is registered for use as a fire ant bait (DuPont™ Indoxacarb 0.045% fire ant bait), which may be applied as a mound treatment or as a broadcast application by "residential" (*i.e.*, private persons) applicators as well as by commercial handlers such as PCOs. The broadcast treatment results in a higher exposure than the mound treatment and, therefore, is the scenario assessed here.

A residential (homeowner) applicator using a push-type spreader to apply granules is assessed using HED's SOPs for Residential Exposure Assessments (DEC-1997) in conjunction with unit exposures developed by the Outdoor Residential Exposure Task Force (ORETF) and cited as ExpoSAC standard operating procedure in a memorandum by G. Bangs (Memo, G. Bangs, 30-APRIL-2001; MRID 44972201). The dermal unit exposure for an applicator wearing short pants and short sleeved shirt plus shoes and socks is 0.68 mg a.i./lb handled. The inhalation unit exposure is 0.00091 mg a.i./lb handled. The rate of application is taken from the proposed label for indoxacarb fire ant bait 0.045%.

Dose (mg/kg/day) = Unit exposure (mg/lb a.i. handled) * Application rate (lb a.i./A) * Amount handled (A/day) ÷ Body weight (kg)

Dermal dose = 0.68 mg a.i./lb handled * 0.000675 lb handled/A * 0.5 A/day ÷ 70 kg bw = 0.0000033 mg a.i./kg/day

Inhalation dose = 0.00091 mg a.i./lb handled * 0.000675 lb handled/A * 0.5 A/day ÷ 70 kg bw = 4.38×10^{-9} mg a.i./kg/day

Dermal MOE = NOAEL/Dose = 38 mg a.i./kg/day ÷ 0.0000033 mg a.i./kg/day = 11,500,000.

Inhalation MOE = NOAEL/Dose = 4.5 mg a.i./kg/day ÷ 4.38 x 10^{-9} mg a.i./kg/day = 1,030,000,000.

Residential Post-application Exposure

There is the potential for postapplication exposure to adults and children from entering areas previously treated with indoxacarb (*i.e.*, turf treated for fire ants). The postapplication scenarios assessed from exposure to treated turf include:

- Dermal exposure from treated lawns due to high contact lawn activities (adult and toddler);
- Dermal exposure from treated turf due to golfing (adults and youths);
- Hand-to-mouth transfer of pesticide residues on lawns (toddler);
- Incidental ingestion of granules from pesticide-treated residential areas (toddler); and
- Incidental ingestion of soil from pesticide-treated residential areas (toddler).

Exposures were calculated by considering the potential sources of exposure, then calculating dermal and incidental oral exposures.

A summary of the residential exposures and risks are provided in Table 4.4.1. Residential post-application MOEs ranged from 1,000 for a toddler ingesting pesticide granules to 45 million for toddler incidental oral ingestion of treated soil. Therefore, the fire ant bait residential use is not of concern to HED (*i.e.*, MOEs >100).

Table 4.4.1. Summary Residential Post-Application Exposures and Risks.

Activity	Exposure (Dose) mg a.i./kg bw/day	MOE[3]
Adult dermal post application turf contact	0.000156	244,000
Toddler dermal post app turf contact	0.00026	146,000
Adult golfer post app turf contact	0.0000108	3,520,000
Child golfer post app turf contact	0.0000184	2,070,000
Toddler oral hand to mouth from contacting treated turf	0.00001	150,000
Toddler oral - ingestion of granules	0.009	1,000
Toddler incidental oral ingestion of treated soil	3.33×10^{-8}	45,000,000
Combined Exposures		
Adult combined dermal exposure = application + post-application[1]	dermal application -- 0.000003 dermal post-application -- 0.000156 total adult dermal exposure -- 0.000159	239,000
Toddler combined exposure[2]	oral hand to mouth treated turf -- 1×10^{-5} oral ingestion treated soil -- 3.33×10^{-8} dermal post application -- 2.6×10^{-4} total toddler dermal + oral exposure -- 2.7×10^{-4}	74,000[4]

1. For the combined adult exposure (i.e., from application and from post-application exposure) HED only sums the dermal fractions. Post-application inhalation exposure is considered negligible since the material is a granule and is not volatile. As can be seen above (under "Resident Applicator"), the inhalation fraction of exposure to the resident applicator is so small (4.38×10^{-9} mg a.i./kg bw/day) it would not materially change the summed dermal exposures (application + post-application). The resulting inhalation MOE is $> 1.0 \times 10^{9}$ for the resident applicator.
2. For combined exposure to a toddler, since the oral and dermal toxicological effects are similar, HED sums exposures from 1) oral hand to mouth from treated turf, 2) oral ingestion of treated soil and 3) dermal post-application exposure. Ingestion of treated granules is considered to be an episodic, "one-time" occurrence and is therefore not summed (combined) with other toddler exposures.
3. MOE = Margin of Exposure = NOAEL (mg a.i./kg bw/day) ÷ Dose (mg a.i./kg bw/day).
4. MOEs for two or more routes of exposure can be combined (Memo, J. Whalen & H. Pettigrew, "Inhalation Risk Characterization and the Aggregate Risk Index [ARI]", 25 NOV. 1998) to derive an MOE_T provided the MOEs are based on studies of similar duration and exhibit the same toxicological effects and are compared against the same UF (100 in this case). The MOEs are combined with the following convention:
$MOE_T = 1 / ((1/MOE_{o\ turf}) + (1/MOE_{o\ soil}) + (1/MOE_{d\ post\text{-}applic}))$
$MOE_T = 1 / ((1/150,000) + (1/45,000,000) + (1/146,000) = 74,000$

Spray Drift

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from groundboom application methods. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT® computer model to its risk assessments for pesticides applied by air, orchard airblast, and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

5.0. AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

Aggregate exposure risk assessments were performed for the following: acute aggregate exposure (food + drinking water exposure), short- and intermediate-term aggregate exposure (food + drinking water + residential exposure), and chronic aggregate exposure (food + drinking water exposure). The acute and chronic dietary exposure estimates provided in Sections 4.2.2.2 and 4.2.2.3, respectively, of this document represent acute and chronic aggregate exposure. A cancer aggregate risk assessment was *not* performed because HIARC determined that cancer dietary risk concerns due to long-term consumption of indoxacarb residues are adequately addressed by the chronic exposure assessment.

5.1. Short- and Intermediate-Term Aggregate Risk (food + drinking water + residential exposure)

Short- and intermediate-term exposures exist for adults and children from the registered turf (fire ant bait) application use. For both short- and intermediate-term exposures, incidental oral and dermal exposure risk assessments are appropriate to aggregate due to the same target organ toxicity (endpoints of concern) identified in both oral and dermal studies used for risk assessment. The short- and intermediate-term incidental oral and dermal exposures are combined with chronic dietary (food and water) exposure for determination of aggregate short- and intermediate-term exposures. HED uses chronic dietary exposure when conducting short- and intermediate-term aggregate assessments as they have been determined that these will more accurately reflect exposure from food over the HED defined short-term interval (1-30 days) than will acute exposure. When different endpoints and dose levels have been identified for dermal, incidental oral, dietary and inhalation routes of exposure, but the LOCs are the same, the "1/MOE" approach is used to aggregate exposure.

For adults, there is no significant incidental oral exposure; therefore, only dermal exposure (application + post-application) was appropriate to aggregate with dietary (food) and water. For young children, due primarily to their hand-to-mouth activities, potential for post-application exposure to children was assessed. Since there is both short- and intermediate-term post-application, (non-dietary) oral and dermal exposures, for children, it is appropriate to aggregate these exposures with dietary (food) and water. Children can be exposed to the following three post-application scenarios: 1) post-application exposure from the incidental ingestion (hand-to-mouth) from contacting treated turf; 2) post-application exposure from incidental ingestion of treated soil (soil ingestion); and 3) post-application dermal exposure from contact with treated turf. 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, HED's concern for human health is related to acute poisoning rather than short or intermediate-term residue exposure and therefore was not aggregated into the total oral exposure in determining aggregate risk.

Tables 5.1.1 and 5.1.2 are summaries of the short- and intermediate-term aggregate exposures and risk estimates for toddlers and adults, respectively. Since the aggregate MOEs are ≥100, short- and intermediate-term aggregate exposures to indoxacarb is not of concern to HED.

Table 5.1.1. Short/Intermediate-Term Aggregate Risk Calculations for Toddlers.

Population	Target MOE	Chronic Food + Water		Residential Oral		Residential Dermal		Aggregate MOE[6] (food + water + residential)
		Exposure (mg/kg/day)	MOE[1]	Exposure[2] (mg/kg/day)	MOE[3]	Exposure[4] (mg/kg/day)	MOE[5]	
Children (1-2 years old)	100	0.007940	190	$0.00001+3.3x10^{-8}$	150,000	0.00026	146,000	190

[1] MOE = NOAEL (1.5 mg/kg/day) ÷ (chronic food + water exposure)
[2] Residential oral = sum of oral (hand-to-mouth from contacting treated turf and ingestion of treated soil).
[3] MOE = NOAEL (1.5 mg/kg/day) ÷ (sum of residential oral exposure)
[4] Residential dermal = post-application turf contact
[5] MOE = NOAEL (38 mg/kg/day) ÷ (residential dermal exposure)
[6] Aggregate MOE = 1/[(1/191) + (1/150,000) + (1/146,000)]

Table 5.1.2. Short/Intermediate-Term Aggregate Risk Calculations for Adults.

Population[1]	Target MOE	Chronic Food + Water		Residential Dermal		Aggregate MOE[5] (food + water + residential)
		Exposure (mg/kg/day)	MOE[2]	Exposure[3] (mg/kg/day)	MOE[4]	
U.S. Population	100	0.002411	620	0.000159	239,000	620

[1] Adult population with highest chronic food and water exposure value was used.
[2] MOE = NOAEL (1.5 mg/kg/day) ÷ (chronic food + water exposure)
[3] Residential dermal = combined application (0.000003) + post-application (0.000156)
[4] MOE = NOAEL (38 mg/kg/day) ÷ (residential dermal exposure)
[5] Aggregate MOE = 1/[(1/620) + (1/239,000)]

6.0. CUMULATIVE RISK

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether indoxacarb has a common mechanism of toxicity with other substances. 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. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

7.0. OCCUPATIONAL EXPOSURE

7.1. Occupational Handler Exposure

Occupational exposure/risk assessments for indoxacarb were provided by M. Dow (Memo, 22-FEB-2002; DP#: 325480; Memo, 26-MAR-2006; DP#:326515; Memo, 25-AUG-2004, DP#: 289892) and K. Lowe/Y. Tesfaye (Memo, 15-FEB-2007; DP#: 335921).

DuPont™ has submitted an application to register the compound indoxacarb for new uses on leafy green vegetables, leaf petiole vegetables, okra, pome fruit (except pear), spinach, tuberous and corm vegetables, southern pea, mint, stone fruit, cucurbit vegetable crop group, cranberry, swiss chard, *Brassica* leafy vegetables, turnip greens, grape, and as a fire ant bait. HED has conducted an estimate of exposure and risk to pesticide handlers from mixing, loading and applying the material and to agricultural workers from post-application re-entry exposures.

The products proposed for use are DuPont™ Avaunt® insecticide (EPA Reg. No. 352-597) and DuPont™ Advion®; 0.045% fire ant bait (EPA Reg. No. 352-627). Avaunt® is a 30% by weight, a.i., WDG formulation. DuPont™ Indoxacarb 0.045% fire ant bait is a granular formulation. Table 7.1.1 provides a summary of the proposed use patterns.

Table 7.1.1. Summary of Proposed New Uses of Indoxacarb.

Formulation	DuPont™ Avaunt® insecticide; 30% a.i. WDG; EPA Reg. No. 352-597 DuPont™ Advion®; 0.045% fire ant bait, EPA Reg. No. 352-627
Methods of Application	aerial, groundboom, airblast as broadcast or mound treatment for fire ants using drop or broadcast spreaders or "scoop"/spoon for mound treatment
Use Sites	Leafy green vegetables, leafy petiole vegetables, okra, pome fruit (except pear), spinach, tuberous & corm vegetables Southern pea, mint, stone fruit, cucurbit vegetables and cranberry Swiss chard *Brassica* leafy vegetables, turnip greens, grapes, fire ant bait
Maximum Rates of Application	Leafy greens: 0.11 lb a.i./A; 0.44 lb a.i./A/crop Leafy petioles: 0.065 lb a.i./A; 0.26 lb a.i./A/crop Okra: 0.065 lb a.i./A; 0.26 lb a.i./A/crop Pome fruit: 0.11 lb a.i./A; 0.44 lb a.i./A/crop Spinach: 0.065 lb a.i./A; 0.26 lb a.i./A/crop Tubers & corms: 0.11 lb a.i./A; 0.44 lb a.i./A/crop Southern pea & mint: 0.065 lb a.i./A; 0.26 lb a.i./A/yr Cucurbit vegetables, stone fruit, cranberry: 0.11 lb a.i./A; 0.44 lb a.i./A/crop Swiss chard: 0.11 lb a.i./A; 0.263 lb a.i./A/crop *Brassica* leafy vegetables: 0.065 lb a.i./A; 0.26 lb a.i./A/crop Turnip greens: 0.065 lb a.i./A; 0.26 lb a.i./A/crop Grapes: 0.11 lb a.i./A; 0.44 lb a.i./A/crop Fire ant bait: 0.000675 lb a.i./A; 0.00135 lb a.i./A/year
Frequency of Application	4 per crop at the highest rates, except for swiss chard: 2 per crop at the highest rate

Table 7.1.1. Summary of Proposed New Uses of Indoxacarb.

PHI	Leafy greens and Okra - 3 days Tubers & corms - 7 days Leafy petioles, pome fruit and spinach - 14 days Southern pea and mint - 7 days Stone fruit - 14 days Cucurbit vegetable - 3 days Cranberry - 30 days Swiss chard - 3 days *Brassica* leafy vegetables – 3 days Turnip greens – 3 days Grapes – 7 days
REI	12 hours
Manufacturer	E. I. du Pont de Nemours and Company (DuPont™)

The proposed Avaunt® product may be applied by air, groundboom, or airblast. The label directs applicators and other handlers to wear the following personal-protective equipment (PPE): long-sleeved shirt, long pants, shoes plus socks and chemical resistant gloves.

The 0.045% fire ant bait may be applied as a mound treatment or as a broadcast application. It may be applied by "residential" (*i.e.*, homeowner) applicators as well as by commercial handlers such as PCOs. The fire ant bait use does not fall under the purview of the WPS because it is a nonagricultural use and, therefore, there is no restricted REI. However, the label does direct: "Do not allow unprotected workers or other persons or pets in treated area during application." The label also directs applicators and other handlers "must wear: Long-sleeved shirt and long pants. Shoes plus socks."

7.1. Handler

Based on the proposed use patterns, commercial and private (*i.e.*, grower) pesticide handlers are expected to have short-term (1-30 days) exposures. While it is possible for handlers to experience intermediate-term exposures (1-6 months), HED believes it is highly unlikely. Since the short- and intermediate-term dermal and inhalation toxicity endpoints are the same, however, the short-term assessment is considered protective of intermediate-term exposures.

The labels indicate several probable pesticide handler activities, including mixing/loading of water dispersible granules, application by air and ground (groundboom, airblast, and tractor-drawn spreader), and commercial and residential mixer/loader/applicators applying granular fire ant bait. HED expects the most highly exposed occupational pesticide handlers are likely to be involved in: 1) mixing/loading dry flowables for aerial applications, 2) applying sprays via groundboom equipment, 3) applying sprays via airblast equipment, 4) applying granules via tractor-drawn spreader, 5) mixing/loading/applying granules with a scoop/spoon, and 6) mixing/loading/applying granules with a push-type spreader.

No chemical-specific data are available with which to assess potential exposure to pesticide handlers. The estimates of exposure in this document are based upon study data available in the

PHED Surrogate Guide (AUG-1998). For pesticide handlers, it is HED policy to present estimates of dermal exposure with a single layer of work clothing (*i.e.*, long pants, long-sleeved shirt and shoes plus socks) and either with or without gloves. Table 7.1.1 provides a summary of estimates of pesticide handler exposure and risk.

Table 7.1.1. Estimated Handler Exposure and Risk from the Use of Indoxacarb.

Unit Exposure[1] mg a.i./lb handled	Application Rate[2] lb a.i./A	Units Treated[3] Per Day	Average Daily Dose[4] mg a.i./kg bw/day	MOE[5]
Mixing/Loading Dry Flowables for Aerial Application				
Dermal: No Glove 0.066 LC With Glove 0.066 HC Inhal 0.00077 HC	0.11 1b a.i./A	350A	Dermal: No Glove 0.036 With Glove 0.036 Inhal 0.00049	Dermal: No Glove 1,000 With Glove 1,000 Inhal 9,100
Applying Sprays via Groundboom Equipment				
Dermal: No Glove 0.014 HC With Glove 0.014 MC Inhal 0.00074 HC	0.11 lb a.i./A	200A	Dermal: No Glove 0.0044 With Glove 0.0044 Inhal 0.00027	Dermal: No Glove 8,600 With Glove 8,600 Inhal 17,000
Applying Sprays via Airblast Equipment				
Dermal: No Glove 0.36 HC With Glove 0.24 HC Inhal 0.0045 HC	0.11 lb a.i./A	40 A	Dermal: No Glove 0.023 With Glove 0.015 Inhal 0.00033	Dermal: No Glove 1,700 With Glove 2,500 Inhal 14,000
Applying Granules via Tractor-drawn Broadcast Spreader				
Dermal: No Glove 0.0099 LC With Glove 0.0069 LC Inhal 0.0012 LC	0.000675 lb a.i./A	80	Dermal: No Glove 7.6×10^{-6} With Glove 5.3×10^{-6} Inhal 9.3×10^{-7}	Dermal: No Glove 5×10^{6} With Glove 7.2×10^{6} Inhal 4.8×10^{6}
Mixer/Loader/Applicator - Scoop/Spoon (Granular bait dispersed by hand)				
Dermal: No Glove no data With Glove 71.0 MC Inhal 0.47 MC	2.35×10^{-7} lb a.i./mound	2.35×10^{-7} a.i./mound 40 mounds/A @ 5A/day 200 mounds/day = 0.000047 lb a.i./day	Dermal: No Glove no data With Glove 4.8×10^{-5} Inhal 3.2×10^{-7}	Dermal: No Glove no data With Glove 792,000 Inhal 1.4×10^{7}
Mixer/Loader/Applicator - Push spreader				
Dermal: No Glove 0.35 HC With Glove 0.22 HC Inhal 0.0075 HC	0.000675	5 A	Dermal: No Glove 1.7×10^{-5} With Glove 1.1×10^{-5} Inhal 3.6×10^{-7}	Dermal: No Glove 2.2×10^{6} With Glove 3.5×10^{6} Inhal 1.3×10^{7}

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database, August 1998. Dermal No Glove = Dermal Unit Exposure with a Single Layer Work Clothing and **No** Gloves; Dermal With Glove = Dermal Unit Exposure with a Single Layer Work Clothing **With** Gloves; Inhal. = Inhalation. Units = mg a.i./pound of a.i. handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence.
2. Application Rate. = Maximum rate of application listed on the proposed label.
3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture"; Policy No. 9. Expo SAC; Revised 05-JUL-2000.
4. Average Daily Dose = Unit Exposure * Applic. Rate * Units Treated ÷ Body Weight (70 kg for short- and intermediate-term dermal and 60 kg for short and intermediate inhalation). Inhalation absorption assumes 100% absorption. Dermal exposures not adjusted for percent dermal

absorption as NOAELs were derived from 28-day rat dermal toxicity study.
5. MOE = Margin of Exposure = No-Observable-Adverse-Effect-Level (NOAEL) ÷ ADD. Short- and intermediate-term dermal NOAEL = 38 mg a.i./kg/day. Short- and intermediate-term inhalation NOAEL = 4.5 mg a.i./kg/day.

HED's level of concern is for MOEs <100. HED did not identify any risks of concern since the estimated MOEs ≥100.

7.2. Post-Application

Estimates of re-entry exposure are based upon ExpoSAC No. 3.1 (AUG-2000) and conventional HED methodology for assessing re-entry exposure.

All Crops except Grapes
Agricultural workers may have post-application exposures that occur during the course of normal agricultural activities. For several of the proposed crop uses, mechanical harvesting is utilized, thereby minimizing post-application exposure. However, there are activities that occur prior to harvest that may result in post-application exposure (e.g., irrigation, scouting, pruning, thinning). For those activities, exposures were calculated using dermal TCs from the ExpoSAC Policy Number 3.1: Agricultural TCs (AUG-2000). Among the crops considered here with the highest application rates, the most conservative (protective) TC is 3,000 cm²/hr for thinning pome fruit, and this value was used in the assessment.

Post-application agricultural worker exposure is estimated using an HED procedure that assumes 20% of the application rate is available as DFR on the day of treatment. HED does not expect post-application exposures to exceed short-term exposure. Therefore, only short-term exposures are assessed. However, since the toxicological endpoints are the same for short-term and intermediate-term exposures, the risks from short- or intermediate-term exposures would also be the same. The following convention is used to estimate post-application agricultural worker exposure:

$$PDR_t = DFR_t * CF1 * TC * ET$$

where:

PDR_t	=	potential dose rate on day "t" (mg/day);
DFR_t	=	DFR on day "t" (µg/cm^2);
CF1	=	weight unit conversion factor to convert µg units in DFR value to mg for the daily dose (0.001 mg/µg);
TC	=	transfer coefficient (cm^2/hr) (In this case 3,000 cm^2/hr; ExpoSAC Policy 003.1 Rev. 07-AUG-2000); and
ET	=	Exposure Time (8 hrs).

and

$$DFR_t = AR * F * (1-D)^t * CF2 * CF3$$

where:

AR	=	application rate (0.11 lb a.i./A);
F	=	fraction of a.i. retained on foliage (20%);
D	=	fraction of residue that dissipates daily (10%);

t = post-application day on which exposure is being assessed;
CF2 = weight unit conversion factor to convert the lbs a.i. in the application rate to µg for the DFR value (4.54E8 µg/lb); and
CF3 = area unit conversion factor to convert the surface area units in the application rate to cm^2 for the DFR value (2.47E-8 acre/cm^2).

∴ DFR = 0.11 lb a.i./A * 0.20 * $(1-0)^0$ * 4.54 x 10^8 µg/lb * 2.47 x10^{-8} A/cm² = 0.25 µg/cm^2

PDR = (0.25 µg/cm^2 * 0.001 mg/µg * 5,000 cm^2/hr * 8 hr/day) / 70 kg = 0.143 mg/kg/day.

MOE = NOAEL ÷ PDR
∴ 38 mg a.i./kg/day ÷ 0.086 mg a.i./kg/day = 450

HED's level of concern is for MOEs <100. In this case the estimated MOE is >100 and, therefore, not of concern to HED.

Grapes
The registrant has presented compound specific DFR data for indoxacarb on grapes (MRID 45900302; Memo, M. Dow, 10-MAR-2004; DP#: 299249). In this study, two applications were made, 5 days apart. Since the revised label indicates a 21-day interval for grape application, HED utilizes the study data taken after the first application. The maximum DFR reported after the first application was from the Washington site (0.532 µg/cm²).

TC = 10,000 cm^2/hr Grapes (table/raisin)

0.532 µg/cm^2 * 10,000 cm^2/hr * 8 hr/day * 0.001 mg/µg * 1/70 kg bw = 0.608 mg/kg bw/day.

MOE = NOAEL ÷ ADD then 50 mg/kg bw/day ÷ 0.608 mg/kg bw/day = 82.

For grapes, the unadjusted NOAEL (50 mg/kg/day) has been used since the formulation measured in the DFR study is the same as that measured in the toxicity studies. An MOE < 100 is of concern to HED. Since the highest DFR value reported results in a MOE of concern, HED presents the summary study results for all three study sites and the associated MOE's for the DFR values reported for each day, post-application.

Table 7.2.1. Indoxacarb DFR Data for Grape Vines in California.

Sampling Interval (days after treatment)	Corrected DFR level[1] (µg/cm^2)			
	Replicate 1	Replicate 2	Replicate 3	Arithmetic Mean (µg/cm^2)
0.083	0.174	0.179	0.186	0.180
1	0.180	0.177	0.151	0.169
3	0.116	0.196	0.136	0.150
5	0.097	0.120	0.139	0.118

[1] Raw residue data corrected for overall average field fortification recovery of 84.3%.

Table 7.2.2. Indoxacarb DFR Data for Grape Vines in New York.

Sampling Interval (days after treatment)	Corrected DFR level[1] ($\mu g/cm^2$)			
	Replicate 1	Replicate 2	Replicate 3	Arithmetic Mean ($\mu g/cm^2$)
0.083	0.450	0.328	0.380	0.386
1	0.368	0.241	0.288	0.299
3	0.259	0.284	0.245	0.263
5	0.166	0.150	0.188	0.168

[1] Raw residue data corrected for overall average field fortification recovery of 87.3%

Table 7.2.3. Indoxacarb DFR Data for Grape Vines in Washington.

Sampling Interval (days after treatment)	Corrected DFR level[1] ($\mu g/cm^2$)			
	Replicate 1	Replicate 2	Replicate 3	Arithmetic Mean ($\mu g/cm^2$)
0.083	0.466	0.543	0.585	0.532
1	0.436	0.415	0.464	0.438
3	0.426	0.432	0.413	0.424
5	0.348	0.382	0.426	0.385

[1] Raw residue data corrected for overall average field fortification recovery of 85.4%

To reiterate, ADD (mg a.i./kg bw/day) = DFR µg/cm^2 * TC cm^2/hr * hr/day * 0.001 mg/µg * 1/70 kg bw where TC is 10,000 cm²/hr for 8 hr/day and

MOE = NOAEL (50 mg a.i./kg bw/day) ÷ ADD (mg a.i./kg bw/day)

Table 7.2.4. Summary of MOEs Associated with DFR for Table/Raisin Grapes with a TC of 10,000 cm²/hr for Three Treatment Sites (CA, NY and WA).

Post-application day	DFR µg/cm²	ADD	MOE
California			
Day 0 (12 hours)	0.180	0.210	240
Day 1	0.169	0.190	260
Day 3	0.150	0.170	290
Day 5	0.118	0.130	370
New York			
Day 0 (12 hours)	0.386	0.440	110
Day 1	0.299	0.340	150
Day 3	0.263	0.300	170
Day 5	0.168	0.190	260
Washington			
Day 0 (12 hours)	0.532	0.610	**82**

Table 7.2.4. Summary of MOEs Associated with DFR for Table/Raisin Grapes with a TC of 10,000 cm²/hr for Three Treatment Sites (CA, NY and WA).

Post-application day	DFR µg/cm²	ADD	MOE
Day 1	0.438	0.500	100
Day 3	0.424	0.480	100
Day 5	0.385	0.440	110

Sample calculation:

0.180 µg/cm² ***** 10,000 cm^2/hr * 8 hr/day * 0.001 mg/µg * 1/70 kg bw = 0.210 mg/kg bw/day.

MOE = NOAEL ÷ ADD then 50 mg/kg bw/day ÷ 0.210 mg a.i./kg bw/day = 240

For table and raisin grapes, where the post-application activities are cane tying and turning, the MOE is not of concern to HED on the day of application at the California and New York sites and on Day 1 post-application at the Washington site.

For wine and juice grapes, use of the maximum reported DFR value and a TC of 5,000 cm²/hr results in a MOE >100 on the day of application, which is not of concern to HED.

TC = 5,000/Grapes (wine/juice)

0.532 µg/cm^2 * 5,000 cm^2/hr * 8 hr/day * 0.001 mg/µg * 1/70 kg bw = 0.304 mg/kg bw/day.

MOE = NOAEL ÷ ADD then 50 mg/kg bw/day ÷ 0.304 mg/kg bw/day = 164.

Turf Uses

For the turf uses, TCs were taken from a post-application exposure study on golf course maintenance (MRID 46734001). It should be noted that a previous study on golf course maintenance (MRID 45530101) had been submitted, but had been determined to be unacceptable. Data from MRID 46734001 are believed to be more appropriate for this use. For transplanting sod, the TC (6800 cm^2/hr) was taken from MRID 45432303. The TCs used are conservative, and were used here per ExpoSAC recommendation.

Compound-specific data were not available for the proposed new crop uses. Therefore, HED assumes 5% of the application rate is available as turf transferable residue on day zero after application. This is adapted from the ExpoSAC SOP No. 003 (07-MAY-1998 - Revised 07-AUG-2000). HED considers this practice to be conservative, that is to say, protective.

TC = 6,800/Turf harvest

0.000675 lb a.i./A * 0.05 * $(1-0)^0$ * 4.54 x 10^8 µg/lb * 2.47 x10^{-8} A/cm² = 0.000378 µg/cm^2 , therefore,

0.000378 µg/cm^2 * 6,800 cm^2/hr * 8 hr/day * 0.001 mg/µg * 1/70 kg bw = 0.00029 mg/kg bw/day.

MOE = NOAEL ÷ ADD then 38 mg/kg bw/day ÷ 0.00029 mg/kg bw/day = 130,000.

TC = 3,400/Turf Golf Course maintenance

0.000675 lb a.i./A * 0.05 * $(1-0)^0$ * 4.54 x 10^8 µg/lb * 2.47 x10^{-8} A/cm² = 0.000378 µg/cm^2 , therefore,

0.000378 µg/cm^2 * 3,400 cm^2/hr * 8 hr/day * 0.001 mg/µg * 1/70 kg bw = 0.00015 mg/kg bw/day.

MOE = NOAEL ÷ ADD then 38 mg/kg bw/day ÷ 0.00015 mg/kg bw/day = 260,000.

A MOE of 100 is adequate to protect agricultural workers from post-application exposures to indoxacarb. **Except as reported earlier for table and raisin grapes,** the MOEs are > 100, and the estimated risks are not of concern to HED.

REI

Indoxacarb is in Acute Toxicity Category IV for acute dermal, III for primary eye irritation, IV for primary skin irritation and it is not a dermal sensitizer. Although the interim WPS REI of 12 hours is adequate to protect agricultural workers from most post-application exposures to indoxacarb, **a 24-hour REI is recommended** to be protective of post-application activities in table and raisin grapes.

7.3. Incidents

The OPP's Incident Data System (25-MAR-2002) indicates there are no incidents reported for the compound indoxacarb.

8.0. DATA NEEDS/LABEL REQUIREMENTS

8.1. Toxicology

- None.

8.2. Chemistry

- **Revised Section B.** Based on the available southern pea field trial data, it is unclear whether the petitioner is pursuing a use on succulent or dry southern peas. The proposed label directions for southern peas should be amended to allow applications only to varieties used to produce dry seed. If the petitioner intends to support a generalized use on southern peas, field trials will be required for the succulent variety as well. In addition, the use directions for southern peas should prohibit applications to varieties grown for livestock feed. For turnip greens, a restriction should be placed on the label to prohibit use on dual purpose turnip cultivars or varieties which produce a harvestable root.

- **Revised Section F.** The petitioner should submit a revised Section F reflecting the HED-recommended tolerance levels and correct commodity definitions as specified in Table 4.2.1.2.

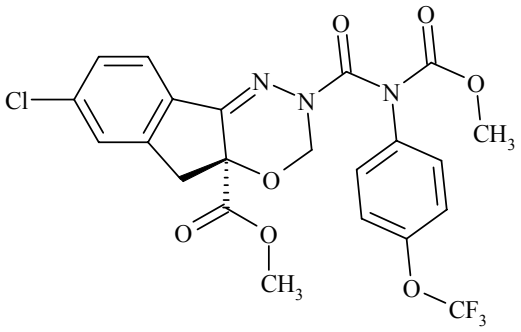
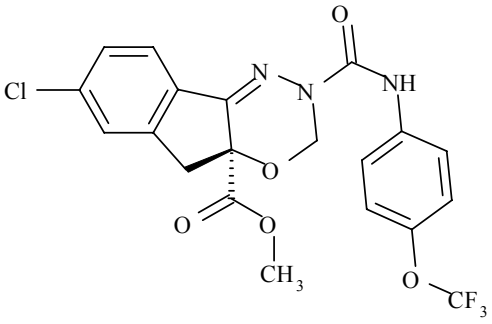
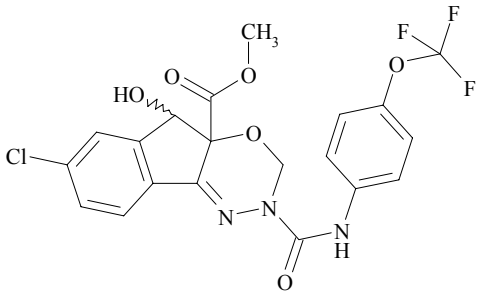
8.3. Occupational/Residential Exposure

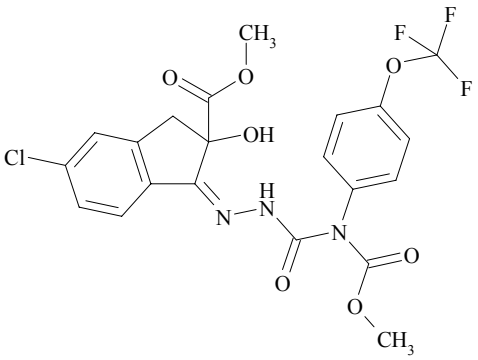
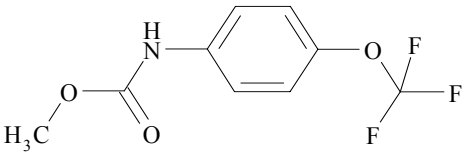
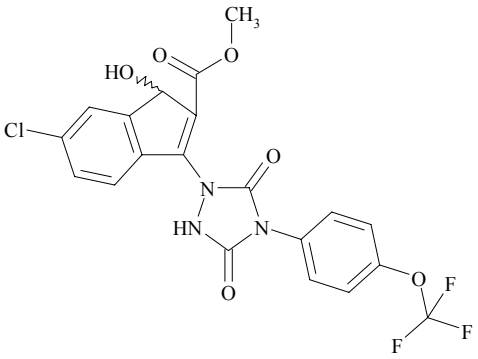
- **Revised Section B.** The label should be revised to indicate a 24-hour REI for postapplication activities.

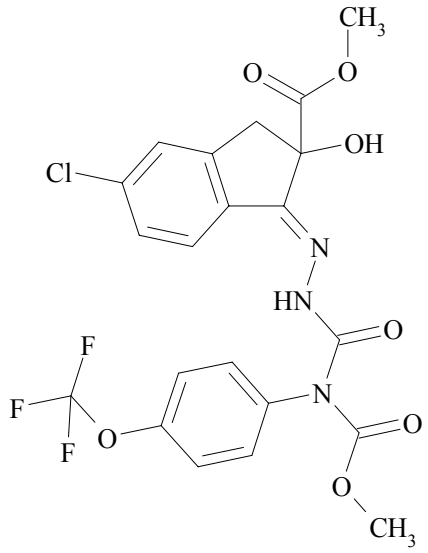
Attachments
Attachment 1: Chemical Structures

cc: S. Levy (RAB1/HED-7509P)
RDI: PV Shah (16-MAY-2007); RAB1 (16-MAY-2007)
S. Levy:S-10953:PY1:(703)305-0783:7509P:RAB1

Attachment 1: Chemical Structures

Common Name Chemical Name	**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]-I*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