United States Environmental Protection Agency

Office of Prevention, Pesticides and Toxic Substances (7505C)

Pesticide Fact Sheet

Name of Chemical: Indoxacarb
Reason for Issuance: Conditional Registration
Date Issued: October 30, 2000

I. DESCRIPTION OF CHEMICAL

Generic 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

Common Name: Indoxacarb Structural Formula:

Other Name: DPX-KN128

Trade Name: Indoxacarb Technical™ Insecticide
STEWARD™ Insecticide
AVAUNT™ Insecticide

EPA Pesticide Chemical Code: 067710

Chemical Abstracts Service (CAS) No.: 173584-44-6

Year of Initial Registration: 2000

Pesticide Type: Insecticide

Chemical Family: oxadiazines

U.S. Producer: E. I. du Pont de Nemours and Company (DuPont), Wilmington, DE.

II. OVERVIEW at the Time of Registration

Indoxacarb is a new insecticide produced by DuPont and marketed in the U.S. as Steward™ , Avaunt™ and Technical Indoxacarb™. At the time of initial registration (10/2000) Indoxacarb was formulated as a 30% a.i. water dispersible granule (WG) proposed for use on apples, pears, *Brassica*, sweet corn, lettuce and fruiting vegetables at a maximum of 4 applications at 3 to 7 day intervals. It was also formulated as a 15% a.i. suspension concentrate (SC) liquid for use on cotton only. Indoxacarb is used for the control of certain lepidopteran pests including the beet armyworm. There were no international registrations at the time of initial registration.

Indoxacarb is designated by the EPA to be a "reduced-risk" pesticide and is considered an organophosphate (OP) replacement. It has moderate to low acute and chronic toxicity and does not cause mutagenic, carcinogenic, developmental, or reproductive effects. Some neurotoxicity was present, but often at fatal doses. Based on the lack of evidence of increased susceptibility of infants and children, the Agency reduced the FQPA safety factor to 1X.

At the time of registration based on the uses noted above, the acute dietary exposure from food to indoxacarb and its R-enantiomer occupied 33% of the acute Population Adjusted Dose (aPAD) for the most sensitive population subgroup, females 13-50 years of years. The acute dietary risk was fairly conservative in that 100% crop treated was assumed as well as anticipated residues and processing factors. The chronic dietary exposure occupied 73% of the chronic PAD for children (ages 1-6) which was a conservative estimate based on 100% crop treated and tolerance level residues. In addition, there was a potential for acute and chronic dietary exposure to indoxacarb and it R-enantiomer in drinking water. After calculating Drinking Water Levels of Concern (DWLOCs) and comparing them to the Estimated Environmental Concentrations (EECs) for surface and ground water, the aggregate exposure and risk did not exceed any of the Agency's levels of concern for the U. S. population and any of the population subgroups, in particular children and infants on a chronic or acute basis.

Occupational exposure as a result of mixer, loader, flagger and applicator activities were expected; however, the scenarios at the time of registration did not exceed the EPA's level of concern when characterized.

The environmental fate data to support the registration of indoxacarb and its R-enantiomer were complete and adequately characterized indoxacarb, its R-enantiomer and a few of the degradates. Due to the exceptionally complex degradation scheme, the registration is conditional upon receiving further elucidation and characterization of some additional degradates. The environmental fate profile indicates no major issues in the areas of soil persistence, mobility, and fish bioaccumulation for indoxacarb and its R-enantiomer. The risk posed to non-target organisms, including endangered species, were based on the conservative Tier I terrestrial assessment. Several levels of concern resulted, in marginal exceedences that, with further refinements, would fall within the Agency's levels of concern. In addition, these risk values are very low when compared to those of the alternative chemicals.

III. USE PATTERNS, FORMULATIONS, AND MODE OF ACTION

Conditionally Registered Products:

1. Indoxacarb Technical ™ (EPA Reg. No. 352-694)
2. STEWARD™ Insecticide (EPA Reg. No. 352-598)
3. AVAUNT™ Insecticide (EPA Reg. No. 352-597)

Table 1. Application Rates, Restrictions[1] & Tolerances:

Commodity	Tolerance (ppm) [2]	Maximum Number Applications /Season	Maximum Application Rate (lb. a.i./A)		PHI (days)	REI
			per application	per season		
Apple	1.0	3	0.11	0.44	12	12 hrs
Apple, wet pomace	3.0	NA				
Pear	0.20	3	0.11	0.44	12	12 hrs
Brassica, head and stem, subgroup	5.0	4	0.0669	0.268	3	12 hrs
Cotton, undelinted seed	2.0	4	0.11	0.44	14	12 hrs
Cotton gin byproducts	15	NA				
Lettuce, leaf	10	4	0.0669	0.268	3	12 hrs
Lettuce, head	4.0	4	0.0669	0.268	3	12 hrs
Vegetables, fruiting, group (except Cucurbits)	0.50	4	0.0669	0.268	3	12 hrs
Corn, sweet, kernel plus cob with husk removed	0.02	4	0.0669	0.268	3	**
Corn, sweet, forage	10	4	0.0669	0.268	3	**
Corn, sweet, stover	15	4	0.0669	0.268	35 fodder, stover	**
Meat [3]	0.03	NA	NA	NA	NA	NA
Fat [3]	0.75					
Mbyp [3]	0.02					
Milk fat	3.0					
Milk	0.10					

NA = Not Applicable

**** 12 hrs, 14 days for hand harvest.**

[1] **Environmental Hazards**: "This pesticide is toxic to mammals, birds, fish, and aquatic invertebrates. Do not apply directly to water or to areas where surface water is present or to intertidal areas below the mean high water mark. Runoff from treated areas may be hazardous to aquatic organisms in neighboring areas. Cover, incorporate, or clean up granules that are spilled. Do not contaminate water when disposing of equipment wash water or rinsate."

[1] **Crop Rotation Restrictions:** "Crops that are on this label and cotton may be planted immediately following harvest. Do not plant for food or feed any other crops not registered for use with indoxacarb for 30 days after last use."

[2] For crops, meat, and milk, the tolerance expression is indoxacarb + its R-enantiomer.

[3] of cattle, goats, hogs, horses, and sheep.

Mechanism of Pesticidal Action

The insecticide belongs to the oxadiazine chemical family and is being registered for the control of lepidopterous pests in the larval stages. Insecticidal activity occurs via blockage of the sodium channels in the insect nervous system and the mode of entry is via the stomach and contact routes.

IV. SCIENCE FINDINGS

A. Chemical Characteristics

Empirical Formula: $C_{22}H_{17}ClF_3N_3O_7$

Molecular Weight: 527.8 g/mole

Melting Point: 88.1 C (99% indoxacarb PAI)

Vapor Pressure: 7.3×10^{-11} torr at 20° C (9.8×10^{-9} Pa)
1.9×10^{-10} torr at 25° C (2.5×10^{-8} Pa)
Henry's Law Constant at 25° C = 6×10^{-5} Pa m^3/mol
(99% indoxacarb PAI; Knudsen-Effusion apparatus)

Solubility:

99% Indoxacarb TGAI at 25° C
1.72 mg/mL in n-heptane
14.5 mg/mL in 1-octanol
103 mg/mL in methanol
117 mg/mL in o-xylene
139 mg/mL in acetonitrile
160 mg/mL in ethyl acetate
>250 g/kg in dichloromethane, acetone, and dimethyl-formamide

99% indoxacarb PAI (25° C)
0.20 ppm in distilled water (generator column)
9.49 mg/mL in n-octanol (shake-flask method)

Partition Coefficient: $\log K_{ow} = 4.65$

B. Toxicology Characteristics

The nature of the toxic effects caused by indoxacarb and its R-enantiomer are discussed in the following Tables 2-5 as well as the no observed adverse effect level (NOAEL) and the lowest observed adverse effect level (LOAEL) from the toxicity studies reviewed. DPX-MP062 is a 75:25 mixture of the two enantiomers: indoxacarb which is insecticidally active, and its R-enantiomer, which is insecticidally inactive, respectively. DPX-JW062 is a mixture of these same two enantiomers; however, they are in a 50:50 ratio. Toxicology data submitted on DPX-JW062 were considered relevant and included in the evaluation.

1. Acute Toxicity

Table 2. Acute Toxicity Data on Technical DPX-MP062 ™ Insecticide (EPA Reg No. 352-597)).

Guideline No./ Study Type	MRID No.	Results	Toxicity Category
870.1100 Acute oral toxicity	44477113	LD_{50}=1730 mg/kg (male) = 268 mg/kg (females) <1000 mg/kg (combined) (rat)	II
870.1200 Acute dermal toxicity	44477118	LD_{50} > 5000 mg/kg (rat)	IV
870.1300 Acute inhalation toxicity	44477120 (70% MUP)	LC_{50} > 5.5mg/L (males, females, combined) (rat)	IV
870.2400 Primary eye irritation	44477122	Moderate eye irritant (rabbit)	III
870.2500 Primary dermal irrit.	44477125	Not a dermal irritant (rabbit)	IV
870.2600 Skin sensitization	44477126	Is a dermal sensitizer (Guinea Pig)	NA

Table 3. Acute Toxicity Data on DPX-MP062 MUP (67.8%;) (50.6% indoxacarb, 17.2% R-enantiomer).

Guideline No./ Study Type	MRID No.	Results	Toxicity Category
870.1100 Acute oral toxicity	44477114	LD_{50} = 1070mg/kg males 407 mg/kg females <750 mg/kg combined (rat)	II
870.1200 Acute dermal toxicity	no test		
870.1300 Acute inhalation toxicity	44477120	LC_{50} > 5.5 mg/L males, females and combined (rat)	IV
870.2400 Primary eye irritation	44477123	Mild eye irritant (rabbit)	III
870.2500 Primary dermal irritat.	no test		
870.2600 Skin sensitization	no test		

Table 4. Acute Toxicity Data on STEWARD™ Insecticide (EPA File Symbol 352-598) (14.7% indoxacarb, 4.3% R-enantiomer).

Guideline No./ Study Type	MRID No.	Results	Toxicity Category
870.1100 Acute oral toxicity	44482003 in corn oil	LD_{50} = 3619 mg/kg males 751 mg/kg females 1818 mg/kg combined (rat)	III
870.1200 Acute dermal toxicity	44482004	LD_{50} > 5000 mg/kg males, females, combined (rat)	IV
870.1300 Acute inhalation toxicity	44482005	LC_{50} > 2.7 mg/L males, females and combined (rat)	IV
870.2400 Primary eye irritation	44482006	Mild eye irritant (rabbit)	III
870.2500 Primary dermal irritation	44482007	Moderate dermal irritant (rabbit)	III
870.2600 Skin sensitization	44482008	Is a dermal sensitizer (Guinea Pig) with the Magnusson-Kligman Maximization test	NA

2. Subchronic, Chronic, Carcinogenicity, Developmental, Reproductive, and Mutagenic Toxicity

Indoxacarb has been classified as a "not likely" human carcinogen. Neurotoxicity was observed in several studies in both rats and mice. It is characterized by weakness, head tilting, and abnormal gait or mobility with inability to stand. Some of these signs occurred at fatal doses. There was no evidence of susceptibility from either in utero or neonatal exposure to both rat and rabbit young. A developmental study was used to determined the acute dietary endpoint for females 13 - 50 years of age based on decreased fetal body weight. The compound is negative for mutagenicity. The compound(s) was extensively metabolized and the metabolites were eliminated in the urine, feces and bile in rats. The metabolite profile was dose dependent and varied quantitatively between males and females. The metabolic pathway proposed yielded multiple metabolites bearing one of the two ring structures, the indeno or trifluoromethoxyphenyl groups. Additional details are provided in Table 5. A summary of the toxicological endpoints used for risk assessment are provided in Table 6.

Table 5.--Subchronic, Chronic and Other Toxicity

Guideline No./ Study Type	Test material / Results
870.3100 90-Day oral toxicity rodents - rats	**DPX-MP062 (75% indoxacarb / 25% enantiomer)** NOAEL = Male (M) 3.1 mg/kg/day, Female (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.
870.3100 90-Day oral toxicity rodents - rats	**DPX-JW062** (50% indoxacarb / 50% enantiomer) / NOAEL = M 8.0, F 4.6 mg/kg/day LOAEL = M 16, F 9.5 mg/kg/day based on mortality (F only), decreased. body weight, body weight gain, food consumption and food efficiency in rats.
870.3100 90-Day oral toxicity rodents - rats	**DPX-JW062** / NOAEL = M 3.7, F 4.9 mg/kg/day LOAEL = M 7.5, F 12 mg/kg/day based on decreased in absolute body weight, body weight gain and food efficiency in rats.

Guideline No./ Study Type	Test material / Results
870.3100 90-Day oral toxicity rodents - mice	**DPX-JW062 /** NOAEL = M23, F 16 mg/kg/day LOAEL = M 44, F 30 mg/kg/day based on mortality (M only); increased reticulocytes and Heinz bodies and decreased body weight, weight gain, food consumption, food efficiency; and increased clinical signs (leaning to one side and/or with abnormal gait or mobility) (F only) in mice.
870.3150 90-Day oral toxicity in nonrodents - dogs	**DPX-JW062** / NOAEL = 5.0 mg/kg/day LOAEL = 19 mg/kg/day based on hemolytic anemia, as indicated by decreased in HGB, RBCs; increases in platelets, increased reticulocytes; and secondary histopathologic findings indicative of blood breakdown (pigment in Kupffer cells, renal tubular epithelium, and spleen and bone marrow macrophages); increased in splenic EMH; and RBC hyperplasia in bone marrow in dogs.
870.3200 28-Day dermal toxicity - rats	**DPX-MP062** NOAEL = 2000 mg/kg/day LOAEL = >2000 mg/kg/day in rats.
870.3200 28-Day dermal toxicity - rats	**DPX-MP062** / 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 (increased reticulocytes), the spleen (increased absolute and relative weight–M only, gross discoloration), clinical signs of toxicity in both sexes in rats.
870.3700a Prenatal developmental in rodents - rats	**DPX-MP062** **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.
870.3700a Prenatal developmental in rodents - rats	**DPX-JW062** **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 - rats	**DPX-JW062** **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 = 2.2 mg/kg/day based on decreased fetal body weights.
870.3700b Prenatal developmental in nonrodents - rabbits	**DPX-JW062** **Materna**l NOAEL = 500 mg/kg/day LOAEL = 1000 mg/kg/day based on slight decreases in maternal body weight gain and food consumption. **Developmenta**l NOAEL = 500 mg/kg/day LOAEL = 1000 mg/kg/day based on decr. fetal body weights and reduced ossification of the sternebrae.

Guideline No./ Study Type	Test material / Results
870.3800 Reproduction and fertility effects - rats	**DPX-JW062** **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 increased 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 decreased in the body weights of the F_1 pups during lactation.
870.4100a Chronic toxicity rodents - rats	**DPX-JW062 /** 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	**DPX-JW062 /** 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; increased Heinz bodies and reticulocytes and associated secondary microscopic changes in the liver, kidneys, spleen, and bone marrow; increased absolute and relative liver weights.
870.4200 Carcinogenicity - rats	**DPX-JW062** / see 870.4100a **no evidence of carcinogenicity**
870.4300 Carcinogenicity - mice	**DPX-JW062 /** 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**
870.5100 Gene Mutation	**DPX-MP062** / 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
870.5100 Gene Mutation	**DPX-JW062 /** 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.
870.5300 Gene Mutation	**DPX-MP062** / negative for mutagenic activity for the following concentration ranges: 3.1-250 µg/mL (-S9); 3.1-250 µg/mL (+S9)
870.5300 Gene Mutation	**DPX-JW062** / negative for mutagenic activity for the following concentration ranges: Negative;100-1000 µg/mL (-S9); 100-1000 µg/mL (+S9), precipitate $\geq$1000 µg/mL
870.5375 Cytogenetics	**DPX-MP062** / no evidence of chromosomal aberrations induced by the test article over background for the following concentration ranges: 15.7-1000 µg/mL ($\pm$S9)
870.5375 Cytogenetics	**DPX-JW062 /** 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
870.5395 Cytogenetics	**DPX-MP062** / no evidence of mutagenicity for the following dose ranges: 3000-4000 mg/kg - males; 1000-2000 mg/kg - females
870.5395 Cytogenetics	**DPX-JW062** / no evidence of mutagenicity at 2500 or 5000 mg/kg

Guideline No./ Study Type	Test material / Results
870.5550 Other Effects	**DPX-MP062** / no evidence of mutagenic activity at the following concentration range: 1.56-200 µg/mL; cytotoxicity was seen at concentrations of ≥100 µg/mL
870.5550 Other Effects	**DPX-JW062 /** No evidence of mutagenic activity at the following concentration range: 0.1-50 µg/mL, cytotoxicity observed at ≥50 µg/mL
870.6200a Acute neurotoxicity screening battery - rat	**DPX-MP062** / 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, body weight gain, and food consumption
870.6200a Acute neurotoxicity screening battery -rats	**DPX-JW062** / 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
870.6200b Subchronic neurotoxicity screening battery - rats	**DPX-MP062** / 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.
870.7485 Metabolism and pharmacokinetic - rats	Both **DPX-MP062** and **DPX-JW062** were extensively metabolized and the metabolites were eliminated in urine, feces, and bile. 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 (indanone and trifluoromethoxyphenyl rings). All biliary metabolites undergo further biotransformation in the gut. The proposed metabolic pathway for both DPX-MP062 and DPX-JW062 has multiple metabolites bearing one of the two ring structures.

C. Toxicological Endpoints and Exposure Doses

Based on the review of the toxicological data submitted and summarized in Table 5, the Agency selected specific studies, end points (adverse biological effects), a Lowest Observed Adverse Effect Level (LOAEL), and several No Observed Adverse Effect Levels (NOAELs), and modified by several safety (SF) or uncertainty factors (UF), to derive acceptable exposure doses in mg/kg/day for use in acute and chronic risk assessments. Table 6 lists the studies, endpoints, exposure doses, uncertainty/safety factors, and exposure profiles that the Agency used in these risk assessments.

The FQPA safety factor is 1x. EPA determined that the 10X safety factor to protect infants and children should be removed because:

1) there is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure;

2) the requirement of a developmental neurotoxicity study is not based on the criteria reflecting special concern for the developing fetuses or young which are generally used for requiring a developmental neurotoxicity study - *and* a safety factor (e.g.: neuropathy in adult animals; central nervous system malformations following prenatal exposure; brain weight or sexual maturation changes in offspring; and/or functional changes in offspring) - and therefore does not warrant an FQPA Safety Factor;

3) the dietary (food and drinking water) exposure assessments will not underestimate the potential exposures for infants and children; and

4) there are no registered residential uses at the current time.

Table 6.--Summary of Toxicological Dose and Endpoints for Indoxacarb and its R-enantiomer for Use in Human Risk Assessment.*

Exposure Scenario	Dose Used in Risk Assessment, Uncertainty Factor (UF)	FQPA Safety Factor (SF)** and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary females 13-50 years of age	NOAEL = 2.0 mg/kg/day UF = 100 **Acute RfD** = 0.02 mg/kg	FQPA SF = 1 **aPAD** = acute RfD / FQPA SF = 0.02 mg/kg/day	developmental rat toxicity study. developmental LOAEL = 4.0 mg/kg/day based on decreased fetal body weight.
Acute Dietary general population including infants and children	NOAEL= 12.5 mg/kg UF = 100 **Acute RfD** = 0.12 mg/kg	FQPA SF = 1 **aPAD** = acute RfD / FQPA SF = 0.12 mg/kg/day	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	FQPA SF = 1 **cPAD** = chr RfD / FQPA SF = 0.02 mg/kg/day	90-day rat subchronic toxicity study, 90-day rat neurotoxicity study, chronic/carcinogenicity rat study. LOAEL = 3.3 mg/kg/day based on decreased body weight, alopecia, body weight gain, food consumption and food efficiency; decreased hematocrit, hemoglobin and red blood cells only at 6 months. 3.3 mg/kg/day is the lowest NOAEL of the 3 studies.
Short-Term Oral (1-7 days) (Residential)	oral study NOAEL= 2.0 mg/kg/day	**LOC for MOE** = 100 (Residential, includes the FQPA SF)	developmental rat toxicity study. maternal LOAEL = 4.0 mg/kg/day based on decreased mean maternal body weights, body weight gains, and food consumption.
Intermediate-Term Oral (1 week - several months) (Residential)	oral study NOAEL= 2.0 mg/kg/day	**LOC for MOE** = 100 (Residential, includes the FQPA SF)	90-day rat subchronic toxicity study. LOAEL = 3.8 mg/kg/day based on decreased body weight, body weight gain, food consumption and food efficiency.
Short- (1-7 days), Intermediate- (1 week - several months), and Long- (several months - lifetime) Term Dermal (Occupational/ Residential)	dermal study NOAEL= 50 mg/kg/day	**LOC for MOE** = 100 (Occupational) **LOC for MOE** = 100 (Residential, includes the FQPA SF)	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.

Table 6.--Summary of Toxicological Dose and Endpoints for Indoxacarb and its R-enantiomer for Use in Human Risk Assessment.*

Exposure Scenario	Dose Used in Risk Assessment, Uncertainty Factor (UF)	FQPA Safety Factor (SF)** and Endpoint for Risk Assessment	Study and Toxicological Effects
Short-Term Inhalation (1-7 days) (Occupational/ Residential)	oral study NOAEL= 2.0 mg/kg/day (inhalation absorption rate = 100%)	**LOC for MOE** = 100 (Occupational) **LOC for MOE** = 100 (Residential, includes the FQPA SF)	rat developmental toxicity study. maternal LOAEL = 4.0 mg/kg/day based on decreased mean maternal body weights, body weight gains, and food consumption.
Intermediate-Term Inhalation (1 week - several months) (Occupational/ Residential)	oral study NOAEL= 2.0 mg/kg/day (inhalation absorption rate = 100%)	**LOC for MOE** = 100 (Occupational) **LOC for MOE** = 100 (Residential, includes the FQPA SF)	90-day rat subchronic toxicity study. LOAEL = 3.8 mg/kg/day based on decreased body weight, body weight gain, food consumption and food efficiency.
Long-Term Inhalation (several months - lifetime) (Occupational/ Residential)	oral study NOAEL= 2.0 mg/kg/day (inhalation absorption rate =100%)	**LOC for MOE** = 100 (Occupational) **LOC for MOE** = 100 (Residential, includes the FQPA SF)	90-day rat subchronic toxicity study, 90-day rat neurotoxicity study, chronic/carcinogenicity rat study. 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.
Cancer (oral, dermal, inhalation)	"not likely" to be carcinogenic to humans	N/A	no evidence of carcinogenicity in either the rat or mouse in acceptable carcinogenicity studies and no evidence of mutagenicity.

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

** The reference to the FQPA Safety Factor refers to any additional safety factor retained due to concerns unique to the FQPA.

E. Residue Chemistry

Tolerances are established for the combined residues of the insecticide indoxacarb [(S)-methyl 7-chloro-2,5-dihydro-2-[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-e][1,3,4]oxadiazine-4a(3H)-carboxylate] and its R-enantimomer[(R)-methyl7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-e] [1,3,4]oxadiazine-4a(3H)-carboxylate] in or on the following raw agricultural commodities:

apple	1.0 ppm
apple, wet pomace	3.0 ppm
Brassica, head and stem, subgroup	5.0 ppm

cattle, goat, horse, sheep and hog fat	0.75 ppm
cattle, goat, horse, sheep and hog meat	0.03 ppm
cattle, goat, horse, sheep and hog meat byproducts	0.02 ppm
corn, sweet, forage	10 ppm
corn, sweet, kernel plus cob with husk removed	0.02 ppm
corn, sweet, stover	15 ppm
cotton gin byproducts	15 ppm
cotton, undelinted seed	2.0 ppm
lettuce, head	4.0 ppm
lettuce, leaf	10 ppm
milk	0.10 ppm
milk fat	3.0 ppm
pear	0.20 ppm
vegetables, fruiting, group	0.50 ppm

- The metabolism of indoxacarb in plants and animals is understood.
- The enforcement methodologies for indoxacarb residues are adequate.

F. Occupational and Residential Exposure and Risk:

1. Handlers. The worker exposure and risk assessment presented in this document are based on the Pesticide Handler Exposure Database Version 1.1 (PHED, Surrogate Exposure Guide, August 1998) unit exposure estimates for workers wearing long pants, long sleeves, gloves, and using open cab ground equipment. The worker exposure and risk assessment was conducted using the maximum application rate, the crop with the highest average farm size (cotton), and the unit exposure estimates for liquid formulations representing the worst case scenario among the proposed uses.

Based on the use patterns, only short- and intermediate- term exposures resulting from the proposed uses are expected. Short-term exposures are expected for the private applicator (farmers treating their own fields). Both short- and intermediate-term exposures are expected for the commercial handler (mixer/loaders and applicators for groundboom and aerial applications). Since the maximum application rate, the crop with the highest average farm size (cotton), and the unit exposure estimates for liquid formulations were used to assess exposures from dry flowable and suspension concentrate formulations, the estimates of risk are considered conservative. The potential risks for occupational workers from short- and intermediate- term exposures from the proposed uses of indoxacarb do not exceed HED's level of concern.

2. Post application. The post-application exposure and risk assessments are based on chemical specific data on apples, tomatoes, and broccoli. Since lettuce, sweet corn, and cotton were not included in the

studies, the highest average residue of the submitted data were used to determine the potential risks from post-application activities associated with the proposed Section 3 uses of indoxacarb for these crops. There is potential for post-application exposures to workers entering treated areas for routine crop maintenance tasks and harvesting of the subject crops. The risk estimate for post-application exposures for the use of indoxacarb on broccoli, cabbage, cauliflower, and lettuce do not exceed Agency's level of concern after four applications of DPX-MP062. The risk estimates for post-application exposures from the uses of indoxacarb do not exceed Agency's level of concern for hand harvesting sweet corn with a 14 day restricted entry interval. Because of the post-application exposures and risk estimates for thinning/hand harvesting of apples and pears, the applications were reduced from 4 to 3 resulting in a marginal exceedence. Further refinements would likely lower the risk estimate to the point there is no exceedence of the Agency's level of concern.

3. Residential. There are no registered residential uses for indoxacarb at this time.

G. Human Risk Assessments

1. Acute Dietary and Aggregate Risk. There is a reasonable certainty of no harm resulting from aggregate acute dietary exposure to indoxacarb and its R-enantiomer. The Acute Population Adjusted Dose (aPAD) is less than 100% for all population groups including infants and children based on conservative assumptions (100% crop treated, anticipated residues, processing factors). The EECs in surface (3.81 ppb) and ground (0.02 ppb) water are less than the Drinking Water Levels of Concern (DWLOCs). No residential non-food exposures are expected.

Acute Dietary Risk:	Females 13-50 years old	= 33% aPAD
	Children 1-6 years old	= 10% aPAD
	All other groups	= $\leq$ 10 % aPAD

Acute DWLOC:	Females 13-50 years old	= 3400 ppb
	Children 1-6 years old	= 1100 ppb
	All other groups	= > 3400 ppb

2. Chronic Dietary and Aggregate Risk. There is reasonable certainty of no harm resulting from aggregate chronic dietary exposure to indoxacarb and its R-enantiomer. The chronic population adjusted dose (cPAD) is less than 100% for all population groups including infants and children based on very conservative assumptions (tolerance level residues and 100% crop treated). The EECs in surface (0.56 ppb) and ground (0.02 ppb) water are less than the drinking water levels of concern (DWLOCs).

Chronic Dietary Risk:	Females 13-50 years old	= 22% cPAD
	Children 1-6 years old	= 73% cPAD
	All other groups	= $\leq$ 40 % cPAD

Chronic DWLOC:	Females 13-50 years old	= 540 ppb
	Children 1-6 years old	= 53 ppb
	All other groups	= >120 ppb

3. Short-term risk. Short-term aggregate exposure takes into account residential exposure plus chronic exposure to food and water (considered to be a background exposure level). Indoxacarb and its R-enantiomer is not registered for use on any sites that would result in residential exposure at this time. Therefore, the aggregate risk is the sum of the risk from food and water which does not exceed the Agency's level of concern.

4. Intermediate-term risk. Intermediate-term aggregate exposure takes into account residential exposure plus chronic exposure to food and water (considered to be a background exposure level). Indoxacarb and its R-enantiomer are not registered for use on any sites that would result in residential exposure. Therefore, the aggregate risk is the sum of the risk from food and water, which does not exceed the Agency's level of concern.

5. Determination of safety. Based on these risk assessments, EPA concludes that there is a reasonable certainty that no harm will result to the general population, and to infants and children from aggregate exposure to indoxacarb and its R-enantiomer residues.

H. Ecological Effects

1. Hazard

Toxicity to Birds - Indoxacarb and its R-enantiomer are "moderately toxic" to avian species on an acute oral basis and subacute dietary basis. The lowest LC_{50} is 808 mg/kg-diet for bobwhite quail. The metabolite JT333 is "slightly toxic" to avian species on an acute oral basis (LC_{50} 1618 mg/kg).

Toxicity to Bees - Indoxacarb and its R-enantiomer is "practically non-toxic" by dietary intake and "highly toxic" by contact.

Toxicity to Mammals - Mammalian toxicity studies were extrapolated from laboratory studies in rats. The acute LD_{50} was determined to 179 mg/kg-bw. A chronic No Observable Effect Concentration (NOEC) of 40 mg/kg diet was determined for developmental and reproductive effects. Additionally, a subchronic/chronic toxicity value was determined which yields a NOEC of 8 mg/kg diet. However, the importance of the endpoint (hemolysis) to the effect on wildlife populations was not certain.

Toxicity to Aquatic Animals - Indoxacarb, its R-enantiomer and degradates are "moderately to very highly toxic" to freshwater and estuarine/marine fish on an acute basis with LC_{50}s ranging from 0.024 to > 1.3 mg/L. These same compounds are "moderately toxic" to "very highly toxic" freshwater and estuarine/marine invertebrates on an acute basis with EC_{50}s ranging from 0.029 to 2.94 mg/L. Chronic toxicities range from 0.0006 to 0.0184 mg/L for estuarine fish and invertebrates and from 0.004 to 0.15 mg/L for freshwater fish and invertebrates.

I. Environmental Fate Characteristics

The environmental fate data base submitted to support the registration of indoxacarb and its R-enantiomer is complete and adequately characterizes indoxacarb, its R-enantiomer and a few of the degradates. However, due to the exceptionally complex degradation scheme, the registration is conditional upon receiving further elucidation and characterization of some additional degradates.

- Indoxacarb is considered to be moderately persistent with aerobic half lives ranging from 3 to 693 days and anaerobic range from 147 to 233 days. It is considered to be immobile with K_{ocs} ranging from 3300 to 9600 ml/g.

- The environmental fate profile indicates no major issues in the areas of soil persistence, mobility, and fish bioaccumulation for the indoxacarb and its R-enantiomer.

- Minimal environmental residues of this chemical in water resources are expected; only the risks associated with indoxacarb and its R-enantiomer were included in the water assessment.

J. Environmental Exposure

Terrestrial exposure was evaluated using estimated environmental concentrations generated from a spreadsheet-based model that calculates the decay of a indoxacarb and its R-enantiomer applied to foliar surfaces for a single or multiple applications. The Tier I terrestrial exposure assessment is based on the methods of Hoerger and Kenaga as modified by Fletcher et al. Overall, the terrestrial exposure is considered low for indoxacarb and its R-enantiomer. There was no compensation to the exposure assessment to include the numerous degradates.

Using the Tier II PRZM/Exams index reservoir model, EFED estimated environmental concentrations (EECs) in surface water resulting from the application of indoxacarb, its R-enantiomer and a limited number of degradates to cotton over a 36 year period. The model predicted the peak and average concentrations using the percent cropped area for cotton in surface water were not likely to exceed 3.81 ppb and 0.56 ppb on an acute and chronic basis respectively. A Tier I SCI-GROW groundwater modeling predicted the acute and chronic concentration of indoxacarb, its R-enantiomer and a limited number of degradates in shallow groundwater is not likely to exceed 0.02 ppb. An uncertainty in these assessments is the lack of environmental fate data for the unknown transformation products of indoxacarb.

Several levels of concern are exceeded for indoxacarb, its R-enantiomer and a limited number of degradates. However, the risk determination was based on the Tier I terrestrial assessments and maximum application rates resulting, in many cases, in only slight exceedences. Further refinements would likely lower the value to the point where there is no exceedence. In addition, these risk values are very low when compared to those of the alternative chemicals.

Aquatic Organisms - The acute restricted use level of concern (0.1) was only marginally exceeded for for one scenario (estuarine/marine invertebrates) for indoxacarb, its R-enantiomer and one degradate (JT333).

Birds - The acute restricted risk levels of concern (0.1) were only marginally exceeded for two avian scenarios and one avian food item (short grass) as a result of multiple applications of indoxacarb and it R-enantiomer.

Mammals - Several subchronic/chronic levels of concern for small mammals (1.0) were exceeded for several food items; however, these risks are based on conservative assumptions (potentially reversible hemolytic effects) and the importance of these toxic effects on survival of wildlife is uncertain.

Bees - Risks to bees via the dietary route were considered minimal; however, high toxicities were noted by the contact routes.

Endangered Species - The level of concerns for endangered species (0.05) were only marginally exceeded for one scenario (estuarine/marine invertebrates) for indoxacarb, its R-enantiomer and one degradate (JT333). The level of concerns for endangered species were exceed for two avian scenarios and one avian food item as a result of multiple applications of indoxacarb and its R-enantiomer. The risk quotients (RQs) are likely fall below the levels of concern upon refinement.

V. SUMMARY OF REGULATORY POSITION AND RATIONALE

The Agency has established permanent tolerances for use on apples, pears, cotton, sweet corn, *Brassica*, lettuce and fruiting vegetables in a Final Rule published in the Federal Register on September 29, 2000 (65 FR 58415-24). As part of the labeling for crop uses, EPA, in some cases reduced the number of applications and required a pre-harvest intervals (PHI), crop rotation restrictions, environmental hazard information, and various restricted re-entry intervals for indoxacarb (**see Table 1**). Available data provided adequate information to

support the conditional registrations of Indoxacarb technical, STEWARD™ Insecticide on cotton, and AVAUNT™ Insecticide on fruiting vegetables, head and leaf lettuce, broccoli, cabbage, cauliflower, apples, pears, and sweet corn

VI. SUMMARY OF DATA GAPS

Product Chemistry Data: The basic data requirements have been met; however, additional clarification or supplementation data and/or information is required for these guideline studies.

- 830.1550 - product identity and composition
  - 830.1600 - description of materials used to produce the product
  - 830.1620 - description of production process
  - 830.1650 - description of formulation process
  - 830.1670 - discussion of formation of impurities
  - 830.6313 - stability to normal, elevated temperatures, metal ions, metals

Residue Chemistry Data: The basic data requirements have been met; however, additional clarification or supplementation data and/or information is required for these guidelines.

- revised Section B's and Section F's
- 860.1480 - poultry feeding study
- 860.1340 - confirmatory method for plants
- 860-1340 - specificity testing for analytical methods for plants
- 860.1380 - storage stability data reflecting the maximum frozen storage intervals of cotton processed samples.
- receipt of analytical methodology standards to EPA repository (awaiting confirmation for shipment of Sept. 13, 2000.)

Toxicology Data: These data are not part of the core requirements for registration.

- 870.6300 - developmental neurotoxicity study in the rat (due to neurotoxicity concerns, not developmental concerns)
- 870.3465 - 90-day inhalation toxicity study in the rat

Specially recommended study conditions are:

(1) HED is in the process of determining whether it wants lungs for histopathology (from inhalation studies) to be fixed by immersion in the fixative, or by intra-tracheal instillation of the fixation. Lungs fixed by intra-tracheal instillation may show artifacts, such as pre-bronchial and peri-vascular cuffing, and widening of interstitial spaces, making it difficult to diagnose actual toxicity effects. Therefore, it is recommended that the Registrant contact OPP/HED prior to initiating the study; (2) In addition to H&E staining of lung tissue, another set of slides should be stained with fibrin-specific stain in order to be able to detect the possible presence of organized fibrin in the lung following the multiple exposure (90-days).

Environmental Fate Data: The basic data requirements have been satisfied for these guideline studies; however, additional elucidation of the degrates are necessary which are not part of the core requirements.

- hydrolysis
- photodegradation in water
- aerobic soil metabolism
- anaerobic aquatic metabolism
- aerobic aquatic metabolism
- leaching-adsorption/desorption
- terrestrial field dissipation

- accumulation in fish

VI. CONTACT PERSON AND MAILING ADDRESS AT EPA

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