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MEMORANDUM

DATE: 3/11/2010

SUBJECT: **Occupational and Residential Exposure Assessment for Proposed Section 3 Registration of Indoxacarb for Use on Dogs.**

PC Code: 067710
MRID No.: 478345-02
Petition No.: NA
Assessment Type: NA
TXR No.: NA

DP Barcode: D362329
Registration No.: 773-OU
Regulatory Action: Section 3 Registration
Reregistration Case No.: NA
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Schering-Plough Animal Health Corporation has requested a registration of the active ingredient (ai) indoxacarb for use on dogs. This document contains an occupational and residential exposure/risk assessment for the requested use.

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Executive Summary

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, a reduced risk pesticide, is an oxadiazine class insecticide active ingredient (ai). Indoxacarb is proposed for use on dogs (registration number 773-OU) and is currently registered for use as a fire ant and mole cricket bait, and for control of lepidopteran larvae on turf and/or ornamentals. The proposed product is formulated as a spot-on for flea control. Indoxacarb can be used by homeowners and by commercial applicators.

Hazard Identification

Indoxacarb is an isomeric compound containing an S-enantiomer (DPX-KN128) and R-enantiomer (DPX-KN127). DPX-MP062 (also referred to as MP062) is an enantiomeric mixture containing the S-enantiomer and its R-enantiomer at approximately a 75:25 ratio. DPX-JW062 (also referred to as JW062) is the racemic mixture of the enantiomers at a 50:50 ratio. Many of the toxicity studies for this registration request were conducted with JW062 (50:50). HED's Hazard Identification Assessment Review Committee (HIARC; HED Doc No. 013528) determined that it is appropriate to use data from DPX-JW062 (50:50) to satisfy the requirements for dietary subchronic, chronic, oncogenicity and reproductive studies. 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 for which registration is requested).

The toxicity profiles for KN128, MP062 and JW062 in rats, mice and dogs with both subchronic and chronic oral exposures were qualitatively 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 decreases in body weight, weight gain, food consumption and food efficiency. These compounds also affected the hematopoietic system by decreasing the red blood cell count, hemoglobin and hematocrit in rats, dogs and mice. It was frequently accompanied by an increase in reticulocytes in all three species and an increase in Heinz bodies (dogs and mice only). None of these signs of toxicity appeared to get worse over time. In one subchronic rat study, the parameters appeared to return to normal levels following a four-week recovery period. High doses in the rats and mice also sometimes caused mortality.

Short- and intermediate-term dermal endpoints were selected from a rat 28-day dermal toxicity study with MP062 (75:25). 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 (based on 75% KN128 test material) was adjusted to 38 mg/kg/day (based on 100% KN128 in the proposed new product). 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.

The incidental oral endpoint was selected based on: 1) rat 90-day subchronic toxicity study with MP062; 2) rat subchronic neurotoxicity study with MP062; and 3) rat chronic/ carcinogenicity study with 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. The NOAEL of 2 mg/kg was adjusted to 1.5 mg/kg based on KN128 (100% active). This NOAEL was also supported by the developmental neurotoxicity (DNT) study conducted with KN128 in which the systemic toxicity NOAEL was 1.5 mg/kg/day.

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

FQPA Safety Factor

After evaluating the toxicological database, the indoxacarb risk assessment team has identified the following factors supporting reduction of the FQPA safety factor (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.

Occupational Handler Exposure/Risks

HED determined there is a potential for short- and intermediate-term exposure in occupational settings during the application of products containing indoxacarb. Proposed domestic pet spot-on use of indoxacarb could be performed by professional animal care workers; however, exposure/risk from application to dogs was not assessed because handler contact is expected to be negligible. The spot-on product is designed to be self-contained as it is applied directly from the tube to the pet with the tip of the applicator used to part the pet's hair.

Occupational Post-application Exposure/Risks

To develop a post-application assessment, HED considers the types of tasks and activities that individuals are likely to be doing in areas recently treated with a pesticide. For indoxacarb, post-application activities are either not expected to occur or are expected to be significantly less than residential post-application exposures (i.e., minimal involvement by a professional animal care worker with the animal is assumed to occur after such treatment occurs). EPA believes that the residential post-application exposure/risk assessment (Section 4.2) is a reasonable worst-case surrogate for occupational post-application exposures/risks.

Residential Handler Exposure/Risks

Indoxacarb is proposed for residential use in the control of fleas on domestic pets; however, exposure/risk from indoxacarb application to domestic pets was not assessed because residential handler contact is expected to be negligible. EPA believes that the residential post-application exposure and risk assessment is a reasonable worst-case surrogate for both occupational and residential handler exposures/risks.

Residential Post-application Exposure/risks

HED has determined that exposure to indoxacarb is likely following residential use on dogs. Individuals of varying ages can potentially be exposed when they have contact with pets treated with the spot-on product. It is assumed that most residential uses of indoxacarb will result in short- and intermediate-term post-application dermal (adults and children 3 to < 6 years old) and oral/hand-to-mouth (children 3 to < 6 years old) exposures.

Adult and child 3 to < 6 years old dermal post-application exposure to dogs treated with the proposed indoxacarb spot-on product result in an estimated MOE > 100 and, therefore, are not of concern to HED. Child 3 to < 6 years old oral (hand-to-mouth) exposure to treated dogs is also not of concern to the Agency. Since a common toxicological endpoint exists for the dermal and incidental oral routes of exposure, these routes of exposure were combined for children 3 to < 6 years old. Combined child 3 to < 6 years old dermal and oral exposure is not of concern to the Agency.

1.0 Hazard and Toxicity Profile

Short- and Intermediate-Term Dermal

The short- and intermediate-term dermal endpoints were selected from a rat 28-day dermal toxicity study with 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 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 (i.e., are not of concern to HED).

The proposed product is derived from a technical formulation which is ≤ 1 % of KN127; therefore, short- and intermediate-term dermal exposure was assessed using the point of departure based on KN128 (i.e., a NOAEL of 38 mg/kg/day). The endpoint selection for indoxacarb is presented in Table 3.

Short- and Intermediate-Term Incidental Oral

The incidental oral endpoint was selected based on: 1) rat 90-day subchronic toxicity study with MP062; 2) rat subchronic neurotoxicity study with MP062; and 3) rat chronic/ carcinogenicity study with 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. The NOAEL of 2 mg/kg was adjusted to 1.5 mg/kg based on KN128 (100% active). This NOAEL was also supported by the developmental neurotoxicity (DNT) study conducted with 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, therefore, a margin of exposure (MOE) of 100 is considered adequate for incidental oral exposure risk assessment. The endpoint selection for indoxacarb is presented in Table 3.

Non-Cancer Level of Concern (LOC)

HED's level of concern (LOC) for indoxacarb dermal and oral exposures is 100 (i.e., an MOE less than 100 exceeds HED's level of concern) for residential scenarios. The level of concern is based on 10X to account for interspecies extrapolation (differences between humans and animals) to humans from the animal test species, and 10X to account for intraspecies sensitivity (differences among humans).

Acute Toxicity

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 equally toxic 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). 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-irritating 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 MP062 and JW062. Subchronic (28 days) inhalation toxicity on indoxacarb in rats was characterized by increased spleen weights, increased pigmentation and hematopoiesis in the spleen, and hematological changes.

Acute toxicity data for indoxacarb DPX-KN128 and DPX-JW062 are presented below in Table 1 and 2, respectively.

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.

Body Weight: The adverse effects for the short- and intermediate-term dermal endpoints are based on studies where the effects were observed in males and females, therefore, the body weight of an average adult (i.e. 70 kg) was used to estimate occupational and residential exposures. The body weight of the average child 3 to < 6 years old (15 kg) was used to estimate residential post-application exposure.

Table 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 2. Acute Toxicity Data on Indoxacarb (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. Doses and Toxicological Endpoints Selected for Indoxacarb for Dermal and Incidental Oral 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 (100% active)		
Short- (1 to 30 days) and Intermediate-Term (1- 6 months) Incidental Oral	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 (MP062) 2) Subchronic neurotoxicity study - rat (MP062) 3) Chronic/carcinogenicity study - rat (JW062) 4) Two generation rat reproduction study (JW062). LOAEL = 3.3 mg/kg/day based on decreased body weight, body-weight gain, food consumption and food efficiency; decreased hematocrit, hemoglobin and red blood cells only at 6 months.

Table 3. Doses and Toxicological Endpoints Selected for Indoxacarb for Dermal and Incidental Oral 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 (100% active)**		
Short- (1 to 30 days) and Intermediate-Term Dermal (1 - 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 (MP062). 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.
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.			

2.0 Use Profile

Indoxacarb is proposed for use on dogs and is currently registered for use as a fire ant and mole cricket bait, and for control of lepidopteran larvae on turf and/or ornamentals. The proposed product is formulated as a spot-on for flea control. Indoxacarb can be used by homeowners and by commercial applicators. Table 4 presents the proposed spot-on use as labeled for application to dogs.

Table 4. Summary of Proposed Spot-On Product Containing Indoxacarb (19.5% ai)		
EPA Reg. No.	**Use Site**	**Application Rate**
773-OU	Dogs (8 weeks and older)	Dogs ≤ 14 pounds (0.02 fluid ozs): 115 mg ai/ treatment Dogs 15 – 22 pounds (0.03 fluid ozs): 171 mg ai/ treatment Dogs 23 – 44 pounds (0.05 fluid ozs): 285 mg ai/ treatment Dogs 45 – 88 pounds (0.10 fluid ozs): 570 mg ai/ treatment Dogs 89 -132 pounds (0.16 fluid ozs): 912 mg ai/ treatment

3.0 Occupational Exposure/Risk

HED has considered the potential for short- and intermediate-term dermal exposure in occupational settings during the application of products containing indoxacarb.

3.1 Occupational Handler

The Agency uses the term "handlers" to describe those individuals who are involved in the pesticide application process. The anticipated use patterns and current labeling indicate occupational exposure scenarios based on the types of equipment and techniques that can potentially be used for indoxacarb applications.

Indoxacarb is proposed for use as spot-on application to dogs with occupational use likely occurring in a veterinary or professional pet grooming setting; however, exposure/risk from application to domestic pets was not assessed because handler contact is expected to be negligible. The spot-on product is designed to be self-contained as it is applied directly from the tube to the pet with the tip of the applicator used to part the pet's hair.

3.2 Occupational Post-application

Occupational post-application exposure to treated animals is not expected. Domestic pets are expected to be treated and immediately returned to their owners such that post-application contact will be negligible. EPA believes that the residential post-application exposure/risk assessment (Section 4.2) is a worst case surrogate for any potential occupational post-application exposures.

4.0 Residential (Non-Occupational) Exposure/Risk

HED has considered the potential for short- and intermediate-term dermal (adults and children 3 to < 6 years old) and oral/hand-to-mouth exposures (children 3 to < 6 years old) in residential settings resulting from homeowner use of the proposed products containing indoxacarb.

4.1 Residential Handler Exposure/Risk

The Agency uses the term "handlers" to describe those individuals who are involved in the pesticide application process. The Agency believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task as was described above for occupational handlers. Residential handlers are addressed differently by the Agency as homeowners are assumed to complete all elements of an application with little use of any protective equipment.

Indoxacarb is formulated for residential use for the control of fleas on dogs. Exposure/risk from indoxacarb application to domestic pets was not assessed because handler contact is expected to be negligible. The spot-on product is designed to be self-

contained as it is applied directly from the tube to the pet with the tip of the applicator used to part the pet's hair.

4.2 Residential Post-application Exposure/Risk

The proposed use of indoxacarb on dogs can result in a wide array of individuals of varying ages potentially being exposed when they have contact with treated animals. There is potential for dermal exposure to adults and children 3 to < 6 years old and hand-to-mouth exposure to children 3 to < 6 years old following contact with a treated dog.

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

(1) Dermal exposure to adults and children from contact with a treated companion animal (hug)
(2) Hand-to-mouth exposure to children from contact with a treated companion animal

4.2.1 Data and Assumptions for Residential Post-application Exposure Scenarios

The series of assumptions and exposure factors which serve as the basis for estimating the dermal and incidental oral (hand-to-mouth) exposures are derived from the "HED Standard Operating Procedures (SOPs) for Residential Exposure Assessments (December 19, 1997)" and the 1999 Draft Policy 13, "Post-application Exposure Assessment for Children from Treated Pets." The residential SOPs are currently undergoing further revision, but are not sufficiently developed for use in this assessment.

HED's default assumption for the transferability of residues from pet fur to humans is 20%. The registrant, Schering-Plough Animal Health Corporation, submitted an indoxacarb-specific exposure study (MRID 478345-02) related to this route of exposure for use of the product on dogs. The study was reviewed by the Agency and used in this assessment to inform the transferability measure. A citation and summary of the exposure study is presented below.

- Study: Dislodgeable Residue Study of SCH 783460 from Spot-On Treated Beagle Dogs. Wrzesinski, C. (2009). EPA MRID 478345-02. Unpublished study prepared by Schering-Plough Animal Health Corporation.
- Review: Indoxacarb: Data Evaluation Record for the Study "Dislodgeable Residue Study of SCH 783460 from Spot-On Treated Beagle Dogs (MRID 478345-02)." W. Britton. D369009.

MRID 478345-02 - Dislodgeable Residue Study of SCH 783460 from Spot-On Treated Beagle Dogs: The purpose of the study was to measure the transferability of the test substance, a spot-on formulation of indoxacarb, over time from the haircoat of treated dogs to a gloved hand. The test substance, SCH 783460, was administered to 10 beagle

dogs by topical application to the back using plastic syringes. Indoxacarb residues were measured on treated dogs after stroking the dogs three times per simulation, for 10 simulations (30 strokes total) with a mannequin hand fitted with two cotton gloves over top of a nitrile glove. Residues were extracted from the nitrile and cotton gloves. Samples were collected from each dog at the following intervals: prior to treatment, at 4, and 8 hours after treatment and at 1, 2, 4, 7, 14, 21, and 28 days after treatment. The cotton and nitrile glove samples were analyzed for indoxacarb (SCH 783460) and the active metabolite JT333. No detectable residues of the metabolite, JT333, were determined in the inner glove or nitrile glove samples, therefore only outer glove results are presented.

Residue levels were corrected using the fortification samples prepared in the laboratory and run with each sample set. Residues were only corrected when the average recovery was less than 90%. Additionally, the Agency used the recovery values from the fortification level closest to the field residue. The registrant did not correct the residues based on the fortification results. When residues were reported as less than the LOQ, the registrant reported results as 0.00 µg and the Agency used a finite value of ½ LOQ. The Agency calculated residues in µg/glove, µg/cm^2 of dog surface area, and percent of applied dose transferred.

For indoxacarb, average residues from all three gloves combined increased from 4,037 µg/glove (1.78% of applied dose and 0.65 µg/cm^2) at 4 hours after application to a maximum of 5,690 µg/glove (2.55% of applied dose and 0.926 µg/cm^2) at 1 day after application. Residues then declined to 177 µg/glove (0.078% of applied dose and 0.028 µg/cm^2) by Day 28 after application.

General assumptions and factors used in the risk calculations include:

- Based upon HED's review of the indoxacarb dog residue transfer study (478345-02), the maximum daily transfer was 2.6% (1 day after treatment). This measure is used to assess exposure from the proposed dog spot on product in lieu of the Agency's default value for transfer, 20%.

- Daily dose is based upon the amount of active ingredient handled on the day of treatment (i.e., a single pet treatment) which results in the most conservative and, therefore, health protective estimate. The Agency always considers the maximum application rates allowed by product labeling. Estimated risks are typically based on an even loading of residues across the entire surface of the animal, where Surface Area (cm^2) = ((12.3*((BW (lb)*454)^0.65)) from HED's 1993 Wildlife Exposure Factors Handbook.

- For the purposes of this assessment, a representative (average) dog size was assumed to be 30 lbs. Using the above formula, the surface area of a 30 lb dog is 5986 cm^2. The appropriate spot-on application size (23 – 44 pounds) and corresponding application rate (285 mg ai/ treatment) were used for the estimation of exposure to a treated dog. Application rates representative of a small (10

pounds) and large (90 pounds) dog were also assessed. Surface areas were calculated for the 10 and 90 lb dogs and the corresponding application rates were determined based on dog size.

- Post-application activities must be assessed on the same day that the pesticide is applied because it is assumed that individuals could handle/touch their pets immediately after application.

- It is assumed that one pet is contacted per day.

- 3 year old children are expected to weigh 15 kilograms (representing an average weight from 1 to 6), and adults are expected to weigh 70 kg.

- The dermal absorption factor is 100 % as determined by HED. Since dermal studies were used for estimating dermal risks, no adjustment for dermal absorption is required.

- HED default for the surface area of an adult hug is 5625 cm^2, a child 3 to < 6 years old hug is 1875 cm^2 (US EPA, 1999 SAP).

- Saliva extraction efficiency is 50 percent (i.e., every time the hand goes in the mouth approximately half of the residues on the hand are removed).

- The approach used to address the hand-to-mouth exposure pathway has been modified since 1999 Draft Policy 13, "Post-application Exposure Assessment for Children from Treated Pets." In the draft policy, contact with treated pets is based on 40 events per day (20 mouthing events/day for 2 hours). For each event, the palmar surface of the hands (i.e., 20cm^2/event) is placed in the mouth of the child contributing to non-dietary ingestion exposure. In the revised approach, the frequency term has been modified to an equilibrium approach analogous to the dermal exposure component (i.e., the frequency = 1 event/day). The approach was revised since the data from which the transferable residue concentrations are determined rely on a continuous contact technique that would lead to concentrations on the hands significantly higher than would result from a single contact.

- The Agency combines or aggregates risks resulting from exposures to individual chemicals when it is likely they can occur simultaneously based on the use pattern and the behavior associated with the exposed population, except when risks are already of concern for the separate scenarios or routes of exposure.

The algorithms used for residential post-application dermal and incidental oral (hand-to-mouth) pet exposure scenarios are presented below.

Adult and child 3 to < 6 years old exposure from dermal activity (hug) to treated companion animal (spot-on):

The following demonstrates the method used to calculate dermal exposures that are attributable to an adult and child 3 to < 6 years old touching a treated dog. A summary of adult and child 3 to < 6 years old dermal exposure is presented in Tables 5 and 6, respectively.

Where:

$$\text{PDR (mg/kg/day)} = \frac{[((AR * F_{AR}) / (SA_{pet})) * (SA_{hug}) * (DA)]}{BW\ (kg)}$$

PDR	=	potential dose rate (mg/kg/day)
AR	=	application rate or amount applied to animal (115, 285, 912 mg ai/ treatment)
F_{AR}	=	fraction of the application rate available as transferable residue (0.026)
SA_{pet}	=	surface area of a treated dog (2931, 5986, 12225 cm^2/ animal)
SA_{hug}	=	surface area of a hug (5625 cm^2 (adult), 1875 cm^2 (child 3 to < 6 years old))
DA	=	dermal absorption factor (100 %)
BW	=	body weight (70 kg (adult), 15 kg (child 3 to < 6 years old))

And:

MOE = NOAEL (mg/kg/day) / PDR (mg/kg/day)

MOE	=	margin of exposure
NOAEL	=	no observed adverse effect level (38 mg/kg/day)
PDR	=	potential dose rate (mg/kg/day)

Child 3 to < 6 years old exposure from hand-to-mouth activity to treated companion animal (spot-on):

The following demonstrates the method used to calculate oral (hand-to-mouth) exposures that are attributable to a child touching a treated dog and exhibiting mouthing behavior. A summary of child 3 to < 6 years old oral exposure is presented in Table 7.

Where:

$$\text{PDR (mg/kg/day)} = \frac{[((AR * F_{AR}) / SA_{pet})) * (SAL) * SA_{hands} * Freq)]}{BW\ (kg)}$$

PDR	=	potential dose rate (mg/kg/day)

AR	=	application rate or amount applied to animal (115, 285, 912 mg ai/ treatment)
F_{AR}	=	fraction of the application rate available as transferable residue (0.026)
SA_{pet}	=	surface area of a treated dog (2931, 5986, 12225 cm^2/ animal)
SA_{hands}	=	surface area of a child's hands (20 cm^2)
SAL	=	saliva extraction factor (50%)
Freq	=	frequency of hand-to-mouth events (1 event/day)
BW	=	child 3 to < 6 years old body weight (15 kg)

And:

MOE = NOAEL (mg/kg/day) / PDR (mg/kg/day)

MOE	=	margin of exposure
NOAEL	=	no observed adverse effect level (1.5 mg/kg/day)
PDR	=	potential dose rate (mg/kg/day)

Table 5. Short- and Intermediate-Term Residential Adult and Child 3 to < 6 Years Old Dermal Post-application Risk Estimates

Exp. Scenario	Dog Size	Dog Weight (lb)	Surface Area Dog (cm^2)	Application Rate (mg ai/ treatment)	Surface Area Hug (cm^2)	PDR (mg/kg/day)	MOE
Adult							
Dermal	Small	10	2931	115	5625	0.08	460
	Medium	30	5986	285		0.10	380
	Large	90	12225	912		0.16	240
Child 3 to < 6 years old							
Dermal	Small	10	2931	115	1875	0.13	300
	Medium	30	5986	285		0.15	250
	Large	90	12225	912		0.24	160

Table 6. Short- and Intermediate-Term Residential Child 3 to < 6 Years Old Oral (Hand-to-Mouth) Post-application Risk Estimates

Exp. Scenario	Application Rate (mg ai/ treatment)	Dog Weight (lb)	Surface Area Dog (cm^2)	Salivary Extraction Factor	Surface Area Hands (cm^2)	Freq.	PDR (mg/kg/day)	MOE
Oral	115	10	2931	0.5	20	1	0.00068	2200
	285	30	5986				0.00083	1800
	912	90	12225				0.0013	1200

Table 8. Combined Short- and Intermediate-Term Residential Child 3 to < 6 Years Old Dermal and Oral (Hand-to-Mouth) Post-application Risk Estimate

Oral MOE	Dermal MOE	Combined MOE[1]
1200	160	140

1. Combined MOE = 1/ ((1/ Oral MOE) + (1/ Dermal MOE))

Summary of Residential Post-application Risk Concerns

Adult and child 3 to < 6 years old dermal post-application exposure to dogs (all application sizes) treated with the proposed indoxacarb spot-on product result in an estimated MOE > 100 and, therefore, are of not concern to HED. Child 3 to < 6 years old oral (hand-to-mouth) exposure to treated dogs resulted in an estimated MOE > 100 and, therefore, is not of concern to HED. Combined child 3 to < 6 years old dermal and oral exposure is not of concern to the Agency.