

Hemolytic effects were present only through the 6-month evaluation and only in females. The regenerative nature of indoxacarb-induced hemolytic anemia was demonstrated by the absence of significant changes in indicators of circulating erythrocyte mass at later evaluations. In mice, the chronic NOAEL of 2.6 mg/kg/day for males was based on deceased body weight and weight gain effects and food efficiency at 13.8 mg/kg/day and above. The NOAEL for females was 4.0 mg/kg/day based on body weight nutritional effects, neurotoxicity, and clinical signs at 20 mg/kg/day. In dogs, the chronic NOAEL was about 2.3 and 2.4 mg/kg/day in males and females, respectively based on hemolytic effects similar to those seen in the subchronic dog study.

6. *Animal metabolism—i. Livestock animal metabolism.* Animal metabolism has been studied in the rat, hen, and cow and is well understood. In contrast to crops, indoxacarb is extensively metabolized in animals.

ii. *Poultry.* In poultry, hens were fed at 10 ppm/day for 5 days, 87–88% of the total administered dose was excreted; parent comprised 51–54% of the total dose in excreta. Concentration of residues in eggs were low, 0.3–0.4 of the total dose, as was the concentration of residues in muscle, 0.2% of the total dose. Parent and metabolite IN-JT333 were not detected in egg whites; only insecticidally inactive metabolites were identified. Parent and IN-JT333 were found in egg yolks; however, their concentrations were very low—0.01–0.02 ppm. Concentrations of parent and IN-JT333 in muscle were at or below the limit of quantitation, (LOQ) (0.01 ppm).

iii. *Cattle. For the cow study,* the cattle were fed at 10 ppm/day for 5 days; approximately 20% of the total administered dose was excreted in urine and 53–60% was excreted in feces in 5 days. Four-tenths to 1.2% of the total dose in urine was parent indicating extensive metabolism; parent represented 46–68% of the fecal activity. Thus, most residues were not absorbed; those residues that were absorbed were extensively metabolized. Less than 1% of the total administered dose was in milk, most of which was parent compound. The insecticidally active metabolite IN-JT333 was not found in milk. Residues in muscle represented less than 0.01% of the total administered dose most of which was parent. IN-JT333 was not detected in muscle. No other metabolites were seen above 10% of the dose, thus only parent and IN-JT333 were monitored in the cattle feeding study.

iv. *Cattle feeding study.* A cattle feeding study was conducted with

indoxacarb at doses of 7.5 ppm, 22.5 and 75 ppm. The mean KN128/KN127 concentrations were proportional to the dosing level in whole milk, skim milk, cream, muscle, fat, liver and kidney. Based on final residue values for the respective commodities contributing to the cattle diet, the anticipated dietary burden in dairy cattle is 51.7 ppm and the anticipated dietary burden in beef cattle is 49.1 ppm. The proposed grape use will not increase the animal dietary burden. Based on standard curves constructed from data in the cattle feeding study, KN128/KN127 concentrations at the 51.7 ppm feeding level are 0.123 ppm for whole milk, 0.033 ppm for skim milk and 1.46 ppm for cream. The KN128/KN127 concentrations at the 49.1 ppm feeding level are 0.046 ppm for muscle, 1.37 ppm for fat, 0.012 ppm for liver and 0.026 ppm for kidney. Tolerances have been established at 1.5 ppm in fat (cattle, goat, horse, sheep and hog), 0.05 ppm in meat, 0.03 ppm in meat by-products, 0.15 ppm in milk and 4.0 ppm in milk fat.

7. *Metabolite toxicology.* In rats, indoxacarb was readily absorbed at low dose (5 mg/kg), but saturated at the high dose (150 mg/kg). Indoxacarb was metabolized extensively, based on very low excretion of parent compound in bile and extensive excretion of metabolized dose in the urine and feces. Some parent compound remained unabsorbed and was excreted in the feces. No parent compound was excreted in the urine. The retention and elimination of the metabolite IN-JT333 from fat appeared to be the overall rate determining process for elimination of radioactive residues from the body. Metabolites in urine were cleaved products (containing only one radiolabel), while the major metabolites in the feces retained both radiolabels. Major metabolic reactions included hydroxylation of the indanone ring, hydrolysis of the carboxylmethyl group from the amino nitrogen and the opening of the oxadiazine ring, which gave rise to cleaved products. Metabolites were identified by mass spectral analysis, NMR, ultraviolet (UV), and/or by comparison to standards chemically synthesized or produced by microsomal enzymes.

8. *Endocrine disruption. Lifespan, and multigenerational bioassays in mammals, and acute and subchronic studies* on aquatic organisms and wildlife did not reveal endocrine effects. Any endocrine related effects would have been detected in this definitive array of required tests. The probability of any such effect due to agricultural uses of indoxacarb is negligible.

### C. Aggregate Exposure

Tolerances for indoxacarb are proposed to support agricultural use on grapes. There are residential uses of indoxacarb pending (fire ant bait), however, the risk from that use has been found to be negligible.

1. *Dietary exposure.* The chronic reference dose (RfD) of 0.02 mg/kg bwt/day is based on a NOAEL of 2.0 mg/kg bwt/day from the subchronic rat feeding study, the subchronic rat neurotoxicity study, and the chronic/carcinogenicity study, using an uncertainty factor of 100. The acute RfD for the general population is 0.12 mg/kg/day, based on the NOAEL of 12.5 mg/kg in the acute neurotoxicity study and an uncertainty factor of 100. The acute RfD for females 13–50 years of age is 0.02 mg/kg/day, based on the NOAEL of 2 mg/kg/day observed in the developmental rat toxicity study and using an uncertainty factor of 100.

i. *Food. Chronic dietary exposure assessment.* Chronic dietary exposure resulting from the currently approved use of indoxacarb on apples, Crop group 5 (brassica vegetables), cotton, pears, peppers, sweet corn, tomatoes, eggplant, alfalfa, head and leaf lettuce, peanuts, potatoes, soybeans, cranberries (current Section 18 use) and the proposed use on grapes are well within acceptable limits for all sectors of the population. The Chronic Module of the Dietary Exposure Evaluation Model (DEEM™, Exponent, Inc., formerly Novigen Sciences, Inc., Version 7.76) was used to conduct the assessment with the reference dose (RfD) of 0.02 mg/kg/day. The analysis used overall mean field trial values, processing factors and projected peak percent crop treated values. Secondary residues in milk, meat and poultry products were also included in the analysis. The chronic dietary exposure to indoxacarb is 0.000089 mg/kg/day, and utilizes 0.4% of the RfD for the overall U.S. population. The exposure of the most highly exposed subgroup in the population, children age 1–6 years, is 0.000238 mg/kg/day, and utilizes 1.2% of the RfD. The table below lists the results of this analysis, which indicate large margins of safety for each population subgroup and very low probability of effects resulting from chronic exposure to indoxacarb.

Subgroup	Maximum Dietary Exposure (mg/kg/day)	% RfD
U.S. Population	0.000089	0.4