

residues from the proposed uses of dinotefuran on cotton and potatoes would be 1.9 ppm, for dairy and beef cattle, the proposed tolerances in milk, meat, and meat byproducts, would be sufficient to provide for potential transmittal of residues from livestock diets containing residues of dinotefuran and its metabolites.

The maximum theoretical poultry dietary burden from feeding cotton commodities containing residues of dinotefuran and its metabolites at the proposed tolerance levels was calculated to be 0.09 ppm. Since the TRR in meat and eggs from hens fed 10 ppm of radiolabeled dinotefuran in the poultry metabolism study was less than 0.05 ppm it can be concluded that there is no reasonable expectation of transmittal of finite residues of dinotefuran and its metabolites to meat and eggs, for poultry fed cotton commodities treated with dinotefuran. Therefore no tolerances are proposed for combined residues of dinotefuran and its metabolites in poultry or eggs.

B. Toxicological Profile

1. *Acute toxicity.* Dinotefuran has low acute oral, dermal, and inhalation toxicity. The oral lethal dose (LD)₅₀ in rats is 2,450 mg/kg, the dermal LD₅₀ is >2,000 mg/kg and the inhalation 4-hour lethal concentration (LC)₅₀ is >4.09 milligrams/Liter (mg/L) air. Dinotefuran is not a skin sensitizer in guinea pigs, but is slightly irritating to the skin and eyes of rabbits. End-use formulations of dinotefuran have similar low acute toxicity profiles.

2. *Genotoxicity.* Dinotefuran and its metabolites do not induce gene mutations in bacterial and mammalian cells, chromosome aberrations in mammalian cells or deoxyribonucleic acid (DNA) damage in bacterial cells in *in vitro* test systems. Similarly, it does not exhibit a clastogenic effect *in vivo* in the mouse micronucleus test. Therefore, there is no evidence to suggest a genotoxic hazard at any of the three main levels of genetic organization.

3. *Reproductive and developmental toxicity.* In rat and rabbit developmental toxicity studies with dinotefuran, there was no evidence of teratogenicity or other embryotoxic effects at the highest dose levels, although maternal toxicity was evident. There were no treatment-related effects on litter parameters at any dose level in either species. In rats, 1,000 mg/kg produced decreased food consumption, body weight gain, and increased water intake. In rabbits, 300 mg/kg produced hypoactivity, prone position, panting, flushing of the nose and ears, tremors, reduced weight gain, food consumption, and water intake.

Necropsy revealed pale brown discoloration of liver and gray/white plaques in the stomach at 125 and 300 mg/kg. The no adverse effect level (NOAEL) values in maternal rats and rabbits were 300 and 52 mg/kg/day, respectively. The NOAEL values in rats and rabbits for embryonic development and teratogenicity were the highest dose levels administered, 1,000 and 300 mg/kg/day, respectively. In a 2-generation study, parental animals of both sexes and both generations showed reduced body weight gain and food consumption at the highest dose level evaluated (10,000 ppm), but there was no effect of treatment at any dose level in either generation on reproductive performance indicators. There were no treatment-related effects at any dose level on the histopathological appearance of the reproductive organs of either sex. Similarly, there were no effects at any dose level in either generation on quantitative ovarian histopathology or on sperm counts, motility and morphology. Reduced spleen weight in probit dose extrapolation model (P) generation animals and reduced thyroid weight in F1 generation parental females were apparent at 10,000 ppm. F1 pup behavioral and sexual development was unaffected by treatment at all dose levels but pup weight gain during lactation was reduced at 10,000 ppm in both generations. Furthermore, the spleen weight of F1 generation progeny was reduced at 10,000 ppm. Based on reduced weight gain and food consumption in parental animals at 10,000 ppm and reduced pre-weaning weight gain in the offspring, the NOAEL value for parental animals and offspring is 241 mg/kg.

4. *Subchronic toxicity.* Dinotefuran was evaluated in a 13-week oral (diet) toxicity studies in rats, mice, and dogs. No specific target organs were identified in any species. In the rat study, a NOAEL of 500 ppm (34/38 mg/kg/day for males and females) was established, based on minimal growth retardation in females and adrenal cortical vacuolation in males. A NOAEL was established at 5,000 ppm (336/384 mg/kg/day for males/females) based on marked growth retardation at 25,000 ppm (adrenal cortical vacuolation not adverse). In the mouse study, a NOAEL of 25,000 ppm (4,442/5,414 mg/kg/day for males/females) was established based on growth retardation at 50,000 ppm. In the dog study, a NOAEL of 8,000 ppm (307/323 mg/kg/day in males/females) was established based on growth retardation. Dinotefuran was also evaluated for dermal and inhalation toxicity for 4

weeks in rats. Daily inhalation exposure of rats for 6 hours/day for 4 weeks did not elicit toxicologically significant effects at any exposure concentration up to and including the highest technically achievable concentration (2.08 mg/L) with a low mass median aerodynamic diameter) (MMAD \leq ±GSM of 2.03 μ m±3.60. Dinotefuran was well tolerated and there were no treatment-related effects on clinical condition, hematology, and clinical chemistry profiles, organ weights, macroscopic, and microscopic pathology. Dermal application for 4 weeks at dose levels up to 1,000 mg/kg/day did not elicit any local or systemic effects on any of the parameters examined. Therefore, no target organs were identified in the rat either by dermal or inhalation exposure.

5. *Neurotoxicity.* Dinotefuran did not produce any functional or histomorphological evidence of neurotoxicity in acute (gavage) and 13-week (dietary) neurotoxicity studies in rats. The NOAEL for neurotoxicity in the acute study was 1,500 mg/kg, the highest dose level administered. The NOAEL for neurotoxicity in the 13-week dietary study was 50,000 ppm (3,413/3,806 mg/kg/day for males and females). The NOAEL for all effects in this study was 5,000 ppm (327/400 mg/kg/day for males and females) based on reduced body weight gain and food consumption.

6. *Chronic toxicity.* Chronic toxicity studies with dinotefuran have been conducted in rats, mice, and dogs. In common with the subchronic studies in these species, no specific target organs could be identified. In the 52-week dog study, a NOAEL of 559/512 mg/kg/day for males/females was established based on decreased weight gain in both sexes and decreased food consumption in females. In the 78-week mouse study, a NOAEL of 345/441 mg/kg/day for males/females was established, based on decreased weight gain and a decrease in circulating platelet counts. In the 104-week rat study, a NOAEL of 991/127 mg/kg/day for males/females was established. This was based on a decrease in weight gain in females.

7. *Carcinogenicity.* The carcinogenic potential of dinotefuran has been evaluated in rats and mice. Survival incidences in the oncogenicity studies were unaffected by treatment at all dose levels. There were no treatment-related effects on the nature and incidence of neoplastic and adverse non-neoplastic histomorphological findings in either species at any dose level. Therefore, the NOAEL values for all effects, 991/127 mg/kg/day (male/female rats) and 345/441 mg/kg/day (male/female mice) are based on reduced weight gain, and also