

on reduced numbers of platelets in mice.

8. *Animal metabolism.* In the rat, dinotefuran is rapidly and almost completely absorbed from the gastrointestinal tract into the general circulation, and is widely distributed throughout the tissues and fluids of the body. Elimination is rapid, predominantly by urinary excretion and almost complete within 7 days of administration. There is no evidence for tissue accumulation. Dinotefuran is rapidly transferred to maternal milk and widely distributed into fetal tissues but rapidly eliminated from them. More than 90% of orally and intravenously administered dinotefuran is eliminated as unchanged parent molecule, which is also the major radioactive component in plasma, milk, bile, and most tissues. The major route of metabolism is an initial enzymatic hydroxylation of the tetrahydrofuran ring to form isomers of 6-hydroxy-5-(2-hydroxyethyl)-1-methyl-1,3-diazinane-2-ylidene-*N*-nitroamine, followed by further oxidation, reduction and acetylation of 6-hydroxy-5-(2-hydroxyethyl)-1-methyl-1,3-diazinane-2-ylidene-*N*-nitroamine, to produce possible isomers of 1-methyl-2-nitro-3-(2-oxotetrahydro-3-furylmethyl)guanidine, 1-[4-hydroxy-2-(hydroxymethyl)butyl]-3-methyl-2-nitroguanidine, 6-hydroxy-5-(2-hydroxyethyl)-1-methyl-1,3-diazinane-2-ylidene-*N*-nitroamine acetyl conjugate and 3-hydroxymethyl-4-(3-methyl-2-nitroguanidine) butyric acid. Several minor pathways of metabolism of dinotefuran were identified in animals. The absorption, distribution, metabolism and elimination of dinotefuran is unaffected by sex and treatment regimen. In hens and goats, the metabolite profile was similar as in plant metabolism.

9. *Metabolite toxicology.* The metabolism profile for dinotefuran supports the use of an analytical enforcement method that accounts for parent dinotefuran, and 1-methyl-3-(tetrahydro-3-furylmethyl)guanidine and 1-methyl-3-(tetrahydro-3-furylmethyl)-urea. Other metabolites are considered of equal or lesser toxicity than parent compound.

10. *Endocrine disruption.* Dinotefuran does not belong to a class of chemicals known or suspected of having adverse effects on the endocrine system. There is no evidence that dinotefuran has any effect on endocrine function in developmental or reproduction studies. Furthermore, histological investigation of endocrine organs in chronic dog, rat, and mouse studies did not indicate that the endocrine system is targeted by dinotefuran.

C. Aggregate Exposure

1. *Dietary exposure.* Chronic dietary exposure assessments were conducted using a Tier I approach. This Tier I assessment incorporated tolerance level residues and 100% crop-treated in the EXP estimated dietary intake trends evaluation system (EXPedite™ system, Version 4.1). EXPedite™ utilized the food consumption data derived from the 1994–1996 U.S. Department of Agriculture (USDA) Continuing Surveys of Food Intake by Individuals (CSFII) with the 1998 supplemental children's survey. The resulting exposures were compared to a RfD of 1.27 mg/kg/day, which was based on the female NOAEL of 127 mg/kg/day from the 104-week rat study and a 100-fold uncertainty factor. Chronic dietary exposure estimates for the overall U.S. population and 25 population subgroups are well below the chronic RfD. Results of these analyses are summarized below.

TABLE 1.—CHRONIC DIETARY RISK (DEEM™) ANALYSIS OF DINOTEFURAN

Population Subgroup	Mg/Kg Bwt/Day	%RfD
U.S. population	0.004109	0.32%
All infants (<1-year old)	0.002815	0.22%
Non-nursing infants	0.003438	0.27%
Children (1 to 6)	0.007247	0.57%
Children (7 to 12)	0.004348	0.34%
Females (13 to 50)	0.003350	0.26%
Males 13+ years	0.003173	0.25%

There are no acute toxicity concerns with dinotefuran as there is no toxicological endpoint attributable to a single exposure in the dinotefuran toxicology data base, including the rat and rabbit developmental studies. Therefore, only chronic dietary exposures have been assessed.

2. *Non-dietary exposure.* Mitsui also requests registrations for the use of dinotefuran on cats, turf, ornamentals, indoor foggers, and ready to use sprays. Mitsui has considered potential non-dietary and aggregate (non-dietary + dietary) exposures to adults, adult females, and toddlers (1 to 3 years of age) for these uses.

Applicator and post-application exposures can result from dermal and inhalation routes for both adults and

toddlers. Additionally, toddlers can be exposed through the post-application incidental ingestion route via hand-to-mouth behavior. Based on the label instructions and typical use patterns of these product types, only short-term and intermediate-term exposure scenarios should be considered for dinotefuran products. However, since there are no toxicological endpoints attributable to a single or possible multiple exposures in a very short duration, as in a short-term scenario, only the intermediate-term exposure scenario has been evaluated for this document.

Dermal exposures for applicator and post-application activities were not assessed because the very high dermal NOAEL (>1,000 mg/kg/day) for dinotefuran indicates that dermal exposures are not of concern. Short-term oral (e.g., incidental ingestion) exposures for toddlers, as mentioned above, were not assessed because there are no toxicological endpoints attributable to a single exposure or multiple exposures during a very short-term time frame in the dinotefuran toxicology data base. Since the oral endpoint is used to calculate inhalation risks, short-term inhalation exposures for toddlers and adults were also not evaluated since there is no toxicological endpoint attributable to a short-term endpoint. Intermediate-term inhalation exposures for applicator and post-application activities also were not assessed because the very high inhalation NOAEL (>7,000 mg/kg/day) for dinotefuran indicates that inhalation exposures are not of concern. Therefore, only intermediate-term oral (incidental ingestion) exposures for toddlers were assessed. These exposures were assessed for each individual dinotefuran product, as well as for the aggregation of all products. In the aggregate assessment, it was assumed that the toddlers would be exposed to residues resulting from the agricultural uses (chronic dietary), all within 1-day.

These non-dietary assessments were conducted using equations and default parameters from EPA's Residential Standard Operation Procedures (SOPs) (EPA, 1997 and 2001) and maximum application rates. Although these exposures are based on the intermediate-term time frame, the residue on the day of application was used in the SOP equations in order to maintain an extra level of conservatism. This assumption implies that the toddlers are exposed to residue levels, which are equivalent to levels resulting on the day of application, every day over an intermediate-term time frame. The resulting oral and aggregate exposures were compared to the NOAEL