

the Pacific coastal area of Ecuador. Imidacloprid residues in banana whole fruit were quantitated by GC using a mass selective detector. The limit of quantitation (LOQ) was 0.01 ppm. The highest average field trial (HAFT) was 0.01 ppm in bananas.

#### B. Toxicological Profile

1. *Acute toxicity.* The acute oral LD<sub>50</sub> values for imidacloprid technical ranged from 424 milligrams/kilograms (mg/kg) in the male rat and <450 mg/kg in the female rat. The acute dermal LD<sub>50</sub> was <5,000 mg/kg in the rat. The 4-hour rat inhalation LC<sub>50</sub> was <5.33 mg/L. Imidacloprid was not irritating to rabbit skin or eyes. Imidacloprid did not cause skin sensitization in guinea pigs. In an acute neurotoxicity study the lowest observed adverse effect level (LOAEL) = 42 mg/kg body weight day (bwt/day).

2. *Genotoxicity.* Mutagenicity studies have demonstrated that imidacloprid is non-mutagenic both *in vivo* and *in vitro*.

3. *Reproductive and developmental toxicity.* In a developmental toxicity study with Sprague-Dawley rats, groups of pregnant animals (25/group) received oral administration of imidacloprid (94.2%) at 0, 10, 30, or 100 mg/kg bwt/day during gestation days 6 through 16. Maternal toxicity was manifested as decreased body weight gain at all dose levels and reduced food consumption at 100 milligrams/kilograms of body weight/day (mg/kg bwt/day). No treatment-related effects were seen in any of the reproductive parameters (i.e., Cesarean section evaluation). At 100 mg/kg bwt/day, developmental toxicity manifested as wavy ribs (fetus = 7/149 in treated vs. 2/158 in controls and litters, 4/25 vs. 1/25). For maternal toxicity, the LOAEL was 10 mg/kg bwt/day lowest dose tested (LDT) based on decreased body weight gain; a NOAEL was not established. For developmental toxicity, the NOAEL was 30 mg/kg bwt/day and the LOAEL was 100 mg/kg bwt/day based on increased wavy ribs master record identification (MRID No. 42256338). In a developmental toxicity study with Chinchilla rabbits, groups of 16 pregnant does were given oral doses of imidacloprid (94.2%) at 0, 8, 24, or 72 mg/kg bwt/day during gestation days 6 through 18. For maternal toxicity, the NOAEL was 24 mg/kg bwt/day and the LOAEL was 72 mg/kg bwt/day based on mortality, decreased body weight gain, increased resorptions, and increased abortions. For developmental toxicity, the NOAEL was 24 mg/kg bwt/day and the LOAEL was 72 mg/kg bwt/day based on decreased fetal body weight, increased resorptions, and increased skeletal abnormalities (MRID No. 42256339). In a 2-generation

reproductive toxicity study, imidacloprid (95.3%) was administered to Wistar/Han rats at dietary levels of 0, 100, 250, or 700 ppm (0, 7.3, 18.3, or 52.0 mg/kg bwt/day for males and 0, 8.0, 20.5, or 57.4 mg/kg bwt/day for females) (MRID No. 42256340, Doc. No. 010537). For parental/systemic/reproductive toxicity, the NOAEL was 250 ppm (18.3 mg/kg bwt/day) and the LOAEL was 750 ppm (52 mg/kg bwt/day), based on decreases in body weight in both sexes in both generations. Based on these factors, EPA recommended that the Data Evaluation Record should be revised to indicate the parental/systemic/reproductive NOAEL and LOAEL to be 250 and 700 ppm, respectively, based upon the body weight decrements observed in both sexes in both generations.

4. *Subchronic toxicity.* In a dermal toxicity study, groups of five male and five female New Zealand white rabbits received repeated dermal applications of imidacloprid (95%) at 1,000 mg/kg bwt/day (LD), 6 hours/day, 5 days/week for 3 weeks. No dermal or systemic toxicity was seen. For systemic and dermal toxicity, the NOAEL was <1,000 mg/kg bwt/day, a LOAEL was not established (MRID No. 42256329). In an oral toxicity study, groups of Fischer 344 rats (12/sex/dose) were fed diets containing imidacloprid (98.8%) at 0, 150, 1,000, or 3,000 ppm (0, 9.3, 63.3, or 196 mg/kg bwt/day in males and 0, 10.5, 69.3 or 213 mg/kg bwt/day in females, respectively) for 90 days. No treatment-related effects were seen at 150 ppm. Treatment-related effects included decreases in body weight gain during the first 4 weeks of the study at 1,000 ppm (22% in males and 18% in females) and 3,000 ppm (50% in males and 25% in females) with an associated decrease in forelimb grip strength especially in males. The NOAEL was 150 ppm (9.3 and 10.5 mg/kg bwt/day in males and females, respectively) and the LOAEL was 1,000 ppm (63.3 and 69.3 mg/kg bwt/day in males and females, respectively) (MRID No. 43286401). In a rat inhalation study (28-day study in which rats were exposed 6 hours/day, 5 days/week for 4 weeks), the NOAEL for imidacloprid was 5.5 mg/m<sup>3</sup> (MRID No. 422730-01).

5. *Chronic toxicity.* In a chronic toxicity study, groups of beagle dogs (4/sex/dose) were fed diets containing imidacloprid (94.9%) at 0, 200 or 1,250/2,500 ppm (0, 6.1, 15 or 41/72 mg/kg bwt/day, respectively) for 52 weeks. The 1,250 ppm dose was increased to 2,500 ppm from week 17 onwards. The threshold NOAEL was 1,250 ppm (41 mg/kg bwt/day). The LOAEL was 2,500 ppm (72 mg/kg bwt/day) based on

increased cytochrome-P-450 levels in both sexes and was considered to be a threshold dose. Due to the lack of toxicity at 1,250 ppm, a LOAEL was not established in this study following the dose increase to the 2,500 ppm level, toxicity was observed, thus making 1,250 ppm the threshold NOAEL and 2,500 ppm the threshold LOAEL (MRID No. 42273002).

6. *Animal metabolism.* The metabolism imidacloprid in rats was reported in seven studies. These data show that imidacloprid was rapidly absorbed and eliminated in the excreta (90% of the dose within 24 hours), demonstrating no biologically significant differences between sexes, dose levels, or route of administration. Elimination was mainly renal (70–80% of the dose) and fecal (17–25%). The major part of the fecal activity originated in the bile. Total body accumulation after 48 hours consisted of 0.5% of the radioactivity with the liver, kidney, lung, skin and plasma being the major sites of accumulation. Therefore, bioaccumulation of imidacloprid is low in rats. Maximum plasma concentration was reached between 1.1 and 2.5 hours. Two major routes of biotransformation were proposed for imidacloprid. The first route included an oxidative cleavage of the parent compound rendering 6-chloronicotinic acid and its glycine conjugate. Dechlorination of this metabolite formed the 6-hydroxynicotinic acid and its mercapturic acid derivative. The second route included the hydroxylation followed by elimination of water of the parent compound rendering imidacloprid. A comparison between [methylene-<sup>14</sup>C]-imidacloprid and [imidazolidine-4,5-<sup>14</sup>C]-imidacloprid showed that while the rate of excretion was similar, the renal portion was higher with the imidazolidine-labeled compound. In addition, accumulation in tissues was generally higher with the imidazolidine-labeled compound. A comparison between imidacloprid and one of its metabolites, WAK 3839, showed that the total elimination was the same for both compounds. The proposed metabolic pathways for these two compounds were different. WAK 3839 was formed following pretreatment (repeated dosing) of imidacloprid.

7. *Endocrine disruption.* The toxicology data base for imidacloprid is current and complete. Studies in this data base include evaluation of the potential effects on reproduction and development, and an evaluation of the pathology of the endocrine organs following short-term or long-term exposure. These studies revealed no