

with residues at or above the levels set in these proposed tolerances. Abbott Laboratories has submitted a practical analytical methodology for detecting and measuring levels of aviglycine HCl in or on raw agricultural commodities (RACs). The proposed analytical method for determining residues is by high-performance liquid chromatography (HPLC). The HPLC/fluorescence detector analytical method used in the apple residue studies has been validated by an independent laboratory and provided to the Food and Drug Administration (FDA). This method was modified slightly for analysis of residue on peaches, plums, and cherries. This modified method has been validated by an independent laboratory. The limit of quantitation (LOQ) was 0.080 ppm for all matrices analyzed by either method. It was determined that residues on treated commodities were stable for a period of 22 months in frozen storage.

#### C. Mammalian Toxicological Profile

1. *Acute toxicity.* Aviglycine HCl has low acute oral, dermal, and inhalation toxicity. The oral lethal dose (LD)<sub>50</sub> in rats is >5,000 milligrams/kilogram (mg/kg), the dermal LD<sub>50</sub> is >2,000 mg/kg and the inhalation 4-hour lethal concentration (LC)<sub>50</sub> is >5.00 milligrams/Liter (mg/L) air. Aviglycine HCl is not a skin sensitizer in guinea pigs, and is not irritating to the skin and eyes of rabbits. End-use formulations of aviglycine HCl have similar low acute toxicity profiles.

2. *Genotoxicity.* Aviglycine HCl does 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 rat 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 the rabbit developmental toxicity study with aviglycine HCl, there was no evidence of teratogenicity or other embryotoxic effects at the highest dose levels tested, although maternal toxicity was evident. The rabbit maternal no observed adverse effect level (NOAEL) was established at 0.4 mg a.i./kg body weight/day (mg a.i./kg bwt/day) based on reduced body weight gains and food consumption, and decreased defecation. The developmental NOAEL was established at 0.4 mg a.i./kg bwt/day based on fetal body weights. In the rat test the maternal NOAEL was established at 1.77 mg a.i./kg bwt/day based on

inhibition of body weight gain and reduced food consumption. The developmental NOAEL was found to be 1.77 mg a.i./kg bwt/day based on decreased mean fetal body weights and reduced ossification. The developmental and maternal lowest observed adverse effect levels (LOAELs) were established at 8.06 mg a.i./kg bwt/day. Aviglycine HCl was evaluated in a rat 2-generation reproduction study submitted by Abbott Laboratories. Based on reductions in body weight, changes in organ weights, and an increased incidence of microscopic findings, the parental NOAEL was established at 0.8 mg a.i./kg bwt/day. The NOAEL for reproductive toxicity was established at 4.0 mg a.i./kg bwt/day and the neonatal toxicity NOAEL was established at 2.5 mg a.i./kg bwt/day.

4. *Subchronic toxicity.* Subchronic 90-day feeding studies were conducted with rats, mice, and dogs. In a 90-day feeding study in rats, the NOAEL was 0.4 mg a.i./kg bwt/day for males and females based on increased incidence of periportal hepatocellular vacuolation in the liver. In the 90-day feeding study in mice, the NOAEL was established at 10 mg a.i./kg bwt/day for males and females - based on decreased body weight and histopathological changes in the liver (both sexes), in the testis (males) and the adrenal (females) at 25 mg a.i./kg bwt/day. For dogs, the NOAEL was established at 0.6 mg a.i./kg bwt/day - based on inappetence, low body weight gain and centrilobular histopathological changes in the liver at 1.2 mg a.i./kg bwt/day. Note that the liver vacuolation is considered an adaptive change. Increased vacuolation of the liver was not observed in the 52-week chronic rat study or the 104-week rat oncogenicity study. A 21-day repeat dose dermal toxicity study in rats was carried out at 0, 100, 500, and 1,000 mg a.i./kg bwt/day. The NOAEL is 1,000 mg a.i./kg bwt/day; a LOAEL was not determined.

5. *Chronic toxicity.* Chronic studies with aviglycine HCl were conducted on rats to determine oncogenic potential and/or chronic toxicity of the compound. The NOAEL for the 1-year chronic study was 0.7 mg a.i./kg bwt/day for males and females based on decreases in body weights, food consumption, testicular tubular and epithelial vacuolation, and pancreatic acinar cell atrophy. The rat carcinogenicity study with aviglycine HCl confirmed the substance has no carcinogenic potential. There was no evidence of cell necrosis that could be a preliminary stage before tumor genesis, and time of death was similar to controls. During the 2-year

carcinogenicity study, the administration of aviglycine HCl at 7 mg a.i./kg bwt/day was associated with body weight and food consumption reductions, increases in the incidence of adrenal focal medullary cell hyperplasia, testicular tubular atrophy, and other associated findings in the testis and epididymis, ocular cataracts, and pancreatic lobular/acinar cell atrophy. The NOAEL was established at 0.7 mg a.i./kg bwt/day.

#### D. Aggregate Exposure

1. *Dietary exposure—i. Food.* Expected dietary exposures from residues of aviglycine HCl would occur through apples, pears, peaches, nectarines, plums, and processed pome and stone-fruits. Acute and chronic dietary exposure assessments were conducted using a Tier I approach. This Tier I assessment incorporated; tolerance level residues for all commodities; assumption of 100% crop-treated for all crops; default processing factors and consumption data from the 1994 through 1998 U.S. Department of Agriculture (USDA) Continuing Surveys of Food Intakes by Individuals (CSFII) (USDA, 1994, 1995, 1996, and 1998). Estimates of chronic and acute dietary exposure were calculated using Dietary Exposure Evaluation Module Food Commodity Intake Database (DEEM-FCID™) software (Novigen, 2001). The resulting exposures were compared to a chronic reference dose (RfD) of 0.007 mg a.i./kg bwt/day and an acute NOAEL of 1.77 mg a.i./kg bwt/day. The RfD is based on the NOAEL of 0.7 mg a.i./kg bwt/day from the rat chronic toxicity study (52-week) and the rat carcinogenicity feeding study (104-week) with a 100-fold uncertainty factor (UF) to account for intraspecies and interspecies variations. The acute NOAEL is based on the rat oral developmental toxicity study.

Chronic dietary exposure estimates for the overall U.S. population and 24 population subgroups, including infants and children, are well below the chronic RfD. Estimated daily exposures from tolerance level residues and a 100% crop treated assumption for all crops were 15.9% of the RfD or less for all populations examined. Acute dietary exposure was estimated for the overall U.S. population and the population subgroups:

- a. All infants.
- b. Nursing infants.
- c. Non-nursing infants.
- d. Children 1 to 2 years of age.
- e. Adult 20 to 49 years of age.
- f. Females 13 to 49 years of age.
- g. Adults 50 years and older.