

NOAEL of 20,000 ppm HCT (approximately 1,695 mg/kg b.w./day for males, 1,785 mg/kg b.w./day for females, as based on food consumption data).

ii. A 21-day rabbit dermal toxicity study at doses of 0, 100, 200, or 400 mg/kg b.w./day resulted with the NOAEL of 400 mg/kg b.w./day HDT.

5. *Chronic toxicity*—i. A 1-year chronic toxicity study in dogs at doses of 0, 1,000, 5,000, or 10,000 ppm yielded a NOAEL of 10,000 ppm HCT (equivalent to 250 mg/kg b.w./day).

ii. A 2-year chronic toxicity/carcinogenicity study in rats at doses of 0, 1,000, 5,000, or 10,000 ppm provided NOAELs for both systemic toxicity and oncogenicity of 10,000 ppm HCT (approximately 500 mg/kg b.w./day for males, 640 mg/kg b.w./day for females, as based on food consumption data).

iii. An 18-month oncogenicity study in mice at doses of 0, 1,000, 5,000, or 10,000 ppm provided NOAELs for both systemic toxicity and oncogenicity of 10,000 ppm HCT (equivalent to 1,500 mg/kg b.w./day).

6. *Animal metabolism*. Results from a rat metabolism study indicated that imazapyr was rapidly absorbed and excreted by 7 days post-dosing, with the majority of the administered <sup>14</sup>C-label (90%) eliminated in the urine within 48 hours. Metabolite characterization studies showed that essentially all the test material was excreted unchanged. Two minor metabolites were detected in the urine or feces of treated rats; however, their contribution combined was less than or equal to 0.5% of the administered dose. An additional 12 unidentified metabolites were isolated, but they contributed less than 3% of the total dose.

7. *Metabolite toxicology*. There were no metabolites identified in plant or animal commodities which require regulation.

8. *Endocrine disruption*. There is sufficient data from the 2-generation rat reproduction study as well as from the subchronic (90-day) rat feeding study and chronic feeding studies in the dog (1-year), rat (24-month), and mouse (18-month), to determine whether imazapyr has potential estrogenic properties or causes other endocrine effects. The collective data from these studies, indicate that imazapyr is not associated with any treatment-related estrogenic or endocrine effects.

The 2-generation rat reproduction study, conducted at dietary concentrations up to 10,000 ppm, showed no treatment-related effects on reproductive performance (including estrous cycle data, mating indices, pregnancy rates, fertility indices,

gestational length, and gestation indices) or on pup growth and development from parturition to adulthood for both litter intervals. Histopathological examinations of the testes, epididymides, prostate gland, and seminal vesicles, were conducted for high-dose and control P<sub>1</sub> and F<sub>1</sub> adult males. Histopathological examinations of the mammary gland, ovaries, uterus (corpus and cervix), and vagina, were conducted for high-dose and control P<sub>1</sub> and F<sub>1</sub> adult females. In addition, for F<sub>2b</sub> pups, histopathological examinations of the adrenal glands, pancreatic islets, pituitary gland, thyroid gland, parathyroid glands, testes, epididymides, prostate gland, seminal vesicles, mammary gland, ovaries, uterus (corpus and cervix), and vagina, were conducted. For all of these tissue examinations, no treatment-related microscopic findings were observed in either males or females. Further, no treatment-related macroscopic findings were observed for either parental or pup generations.

Organ weight data and histopathological examinations from the subchronic (90-day) rat feeding study and chronic feeding studies in the dog (1-year), rat (24-month), and mouse (18-month), may also be utilized to determine whether imazapyr has potential estrogenic properties or causes other endocrine effects. Absolute and relative weights of the adrenal glands (not measured in the dog study), pituitary gland, thyroid/parathyroid gland, ovaries, and testes (with/without epididymides) were recorded for animals at the interim (if applicable) and terminal sacrifice periods in these studies. In addition, detailed macroscopic and microscopic examinations of the following organs were performed: Pituitary gland, thyroid gland, parathyroid glands, pancreatic islets, adrenal glands, testes, epididymides, prostate gland, seminal vesicles (not performed in the dog study), mammary gland, ovaries, uterus (corpus and cervix), and vagina. No information was found from the organ weight data or macroscopic and microscopic examinations, from the subchronic (90-day) rat feeding study and chronic feeding studies in the dog (1-year), rat (24-month), and mouse (18-month), that suggests that imazapyr is associated with any treatment-related estrogenic effects or effects on the endocrine system.

#### C. Aggregate Exposure

1. *Dietary exposure*—i. *Food*—a. *Acute dietary exposure*. An acute dietary risk assessment is not required because no acute toxicological

endpoints were identified by the EPA for imazapyr.

b. *Chronic dietary exposure*. Novigen Sciences, Inc. conducted a Tier 1 assessment of potential chronic dietary exposure from the proposed uses of imazapyr for weed control in pasture/range grasses and for aquatic weed control. These uses may result in dietary residues in shellfish, freshwater finfish, milk, and tissues of cattle, sheep, goats, and horses. This assessment also included the current tolerances on field corn commodities. For this Tier 1 analysis, tolerance values were used for fish at 1.0 ppm; shellfish at 0.1 ppm; kidney of cattle, sheep, goats, and horses at 0.5 ppm; other meat byproducts of cattle, sheep, goats, and horses at 0.05 ppm; meat of cattle, sheep, goats, and horses 0.05 ppm; fat of cattle, sheep, goats, and horses at 0.05 ppm; and milk at 0.01 ppm. Tolerance level residues were assumed, including those for field corn grain (0.05 ppm). Chronic dietary exposure analyses for the overall U.S. population and 25 population subgroups, including infants and children, were compared to the chronic Reference Dose (RfD) of 2.5 mg/kg b.w./day. Results of the chronic dietary analyses for all population subgroups examined were less than 0.1% of the chronic RfD. Exposure estimates for children 1 to 6 years of age, the most highly exposed population group, were only 0.000575 mg/kg b.w./day or less than 0.1% of the RfD. Therefore, the results of the chronic dietary assessment demonstrate a reasonable expectation of no harm from the proposed and existing uses of imazapyr.

ii. *Drinking water*. According to label restrictions, ARSENAL herbicide will not be applied directly to water within  $\frac{1}{2}$  mile upstream of an active potable water intake in flowing water (i.e., river, stream, etc.) or within  $\frac{1}{2}$  mile of an active potable water intake in a standing body of water such as lake, pond or reservoir. However, for purposes of demonstrating the large margin of exposure to imazapyr residues in drinking water, no label restrictions will be presumed. Rather, a level of 0.200 ppm in the water will be used, as based upon data from Missouri and Florida sites at 1-hour after treatment (maximum levels of imazapyr were approximately 0.197 ppm and 0.092 ppm, respectively). If 0.200 ppm is chosen as the maximum potential residues in the aquatic dissipation studies, then the standard (chronic) exposure analyses would be:

Adult male (200 µg/L × 10<sup>-3</sup> mg/µg × 2 L/day) / 70 kg = 0.0057 mg/kg/day  
Adult female (200 µg/L × 10<sup>-3</sup> mg/µg × 2 L/day) / 60 kg = 0.0067 mg/kg/day