

The results from the 2-generation reproduction toxicity study in rats with imazethapyr technical support a NOAEL for reproductive toxicity of 10,000 ppm (equivalent to 800 mg/kg bwt/day). The NOAEL for non-reproductive parameters (i.e. decreased weanling body weights) is 5,000 ppm.

4. *Subchronic toxicity.* A short-term (21-day) dermal toxicity study in rabbits was conducted with imazethapyr technical. No dermal irritation or abnormal clinical signs were observed at dose levels up to and including 1,000 mg/kg bwt/day (highest dose tested), supporting a NOAEL for dermal irritation and systemic toxicity of 1,000 mg/kg bwt/day.

In a subchronic (13-week) dietary toxicity study in rats with imazethapyr technical, no signs of systemic toxicity were noted, supporting a NOAEL of 10,000 ppm the highest concentration tested (equivalent to 820 mg/kg bwt/day).

In a subchronic (13-week) dietary toxicity study in dogs with imazethapyr technical, no signs of systemic toxicity were noted, supporting a NOAEL of 10,000 ppm (equivalent to 250 mg/kg bwt/day), the highest concentration tested.

5. *Chronic toxicity.* A 1-year dietary toxicity study was conducted with imazethapyr technical in Beagle dogs at dietary concentrations of 0, 1,000, 5,000, and 10,000 ppm. In this study, the NOAEL for systemic toxicity was 1,000 ppm (equivalent to 25 mg/kg bwt/day), based on slight anemia, i.e., decreased red cell parameters observed at 5,000 and 10,000 ppm concentrations. No treatment-related histopathological lesions were observed at any dietary concentration, including the highest concentration tested (10,000 ppm).

In a 2-year chronic dietary oncogenicity and toxicity study in rats conducted with imazethapyr technical, the NOAEL for oncogenicity and chronic systemic toxicity was 10,000 ppm (equivalent to 500 mg/kg bwt/day), the highest concentration tested. An 18-month chronic dietary oncogenicity and toxicity study in mice with imazethapyr technical supports a NOAEL for oncogenicity of 10,000 ppm, the highest concentration tested (equivalent to 1,500 mg/kg bwt/day), and a NOAEL for chronic systemic toxicity of 5,000 ppm (equivalent to 750 mg/kg bwt/day), based on decreased body weight gain in both sexes).

EPA has classified imazethapyr as negative for carcinogenicity (evidence of non-carcinogenicity for humans) based on the absence of treatment-related tumors in acceptable carcinogenicity studies in both rats and mice.

6. *Animal metabolism.* The rat, goat, and hen metabolism studies indicate that the qualitative nature of the residues of imazethapyr in animals is adequately understood.

In three rat metabolism studies conducted with radiolabeled imazethapyr technical, the major route of elimination of the herbicide was through rapid excretion in urine and to a much lesser extent in feces. In the first study, almost 100% of the administered material was recovered in excreta within 96 hours (89–95% in urine, 6–11% in feces). The major residue in urine and feces was parent compound. Approximately 2% of the dose was metabolized and excreted as the α -hydroxyethyl derivative of imazethapyr. In the second study, the test material was rapidly and completely eliminated unchanged in the urine within 72 hours of dosing. After 24 hours, 92.1% of radioactivity was excreted in the urine with 4.67% in the feces. There was no significant bioaccumulation of radioactivity in the tissues from this rat metabolism study (< 0.01 ppm after 24 hours). In the third study, four groups treated with radiolabeled imazethapyr readily excreted > 95% of the test material in the urine and feces within 48 hours. A high percentage (97–99%) of the test material was excreted in the urine as unchanged parent, the remainder as the α -hydroxyethyl derivative of imazethapyr. For all three studies, the major route of elimination of the herbicide in rats was through rapid excretion of unchanged parent compound in urine. It is clear that imazethapyr and its related residues do not accumulate in tissues and organs.

In the goat metabolism study, parent ^{14}C -imazethapyr was dosed to lactating goats at 0.25 ppm and 1.25 ppm. Results showed ^{14}C -residues of < 0.01 ppm in milk and < 0.05 ppm in leg muscle, loin muscle, blood, fat, liver and kidney. Laying hens dosed at 0.5 ppm and 2.5 ppm with ^{14}C -imazethapyr showed ^{14}C -residues of < 0.05 ppm in eggs and all tissues (blood, muscle, skin/fat, liver and kidney).

Additional animal metabolism studies have been conducted with CL 288511 (main metabolite in treated crops fed to livestock) in both laying hens and lactating goats. These studies have been repeated to support subsequent use extensions on crops used as livestock feed items which would theoretically result in a higher dosing of imazethapyr derived residues to livestock (i.e., corn, alfalfa). In these studies, lactating goats dosed at 42 ppm of ^{14}C -CL 288511 showed ^{14}C -residues of < 0.01 ppm in milk, leg muscle, loin muscle and omental fat. ^{14}C -Residues in blood were

mostly < 0.01 ppm but reached 0.01 ppm on two of the treatment days. ^{14}C -Residue levels in the liver and kidney were 0.02 and 0.09 ppm, respectively. Laying hens dosed at 10.2 ppm of ^{14}C -imazethapyr showed ^{14}C -residues of < 0.01 ppm in eggs and all tissues (blood, muscle, skin/fat, liver and kidney). ^{14}C -imazethapyr or ^{14}C -CL 288511 ingested by either laying hens or lactating goats was excreted within 48 hours of dosing. These studies indicate that parent imazethapyr and CL 288511-related residues do not accumulate in milk or edible tissues of the ruminant.

7. *Metabolite toxicology.* Metabolism studies in soybean, peanut, corn, alfalfa, and canola indicate that the only significant metabolites are the α -hydroxyethyl derivative of imazethapyr, CL 288511 and its glucose conjugate CL 182704. The α -hydroxyethyl metabolite has also been identified in minor quantities in the previously submitted rat metabolism studies and in goat and hen metabolism studies. No additional toxicologically significant metabolites were detected in any of the plant or animal metabolism studies.

8. *Endocrine disruption.* Collective organ weight data and histopathological findings from the 2-generation rat reproductive study, as well as from the subchronic and chronic toxicity studies in three different animal species demonstrate no apparent estrogenic effects or treatment-related effects of imazethapyr on the endocrine system.

C. Aggregate Exposure

1. *Dietary exposure.* The potential dietary exposure to imazethapyr has been calculated from the proposed tolerance for use on rice and previously established tolerances for peanuts, legume vegetables, soybeans, alfalfa, endive, lettuce, and corn. This very conservative chronic dietary exposure estimate used the proposed tolerance of 0.5 ppm for rice, and tolerance values of 0.1 ppm for peanuts, 0.1 ppm for legume vegetables, 0.1 ppm for soybeans, 3.0 ppm for alfalfa, 0.1 ppm for endive (escarole), 0.1 ppm for lettuce, and 0.1 ppm for corn. In addition, these estimates assume that 100% of these crops contain imazethapyr residues. In support of this import tolerance petition, a proposed tolerance of 0.1 ppm for canola would not be expected to contribute significantly to this dietary risk assessment.

i. *Food.* Potential exposure to residues of imazethapyr in food will be restricted to intake of rice, peanuts, legume vegetables, soybeans, alfalfa (sprouts), endive, lettuce, and corn. Using the assumptions discussed above, the