Summary of Toxicology Data

Imazapyr

Chemical Code # 2256, Document Processing Number (DPN) 52122
SB 950 # NA
9/25/15

Data Gap Status

Chronic toxicity, rat: No data gap, no adverse effect
Chronic toxicity, dog: No data gap*, no adverse effect
Oncogenicity, rat: No data gap, no adverse effect
Oncogenicity, mouse: No data gap, no adverse effect
Reproduction, rat: No data gap, no adverse effect
Developmental toxicity, rat: No data gap, no adverse effect
Developmental toxicity, rabbit: No data gap, no adverse effect
Gene mutation: No data gap, no adverse effect
Chromosome effects: No data gap, no adverse effect
DNA damage: No data gap, no adverse effect
Neurotoxicity: No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers for the above study types through 261724 (Document No. 52122-0033) were examined. This includes all relevant studies indexed by DPR as of 9/25/15.

In the 1-liners below:
- indicates an acceptable study.
- Bold face indicates a possible adverse effect.
- ## indicates a study on file but not yet reviewed.

File name: T150925
Revised by T. Moore, 9/25/15

* Although the dog chronic toxicity study was deemed to be unacceptable for inadequate dose level selection, the Medical Toxicology Branch considered the NOEL value of >10,000 ppm to be valid. Therefore, no further chronic feeding study in dogs were required at that time.
NOTE: The following symbols may be used in the Table of Contents which follows:
* = data adequately address FIFRA requirement
† = study(ies) flagged as “possible adverse effect”
N/A = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

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METABOLISM AND PHARMACOKINETICS
52122-016 149081 851 “CL 243,997: Rat Metabolism Study” by N.M. Mallipudi & D. Wu, XenoBiotic Laboratories, Inc., Plainsboro, NJ (project #RPT0074; 6/8/94). 5 rats/sex were dosed w/\(^{14}\)C-CL 243,997 (radiolabel batch #AC4831-8A, 96.8% radiochemically pure & 93.4% chemically pure; non-radiolabel batch #AC 5561-133, 99.5% pure) in each of the following groups: Group A: low oral single dose, 9.05 & 9.94 mg/kg in males & females, respectively; Group B: high oral single dose, 955 & 893 mg/kg; Group C: animals dosed orally on 14 consecutive days w/ \(\sim\) 10 mg/kg unlabeled CL 243,997 before a low single dose of \(^{14}\)C-CL 243,997 (9.21 & 9.31 mg/kg); Group D: 9.47 & 10.40 mg/kg intravenous dose. Group E: 2/sex were dosed orally w/corn oil. Urine & feces were collected over 7-day intervals. Excreta & tissues were examined for radioactivity & the metabolites analyzed. Urine was the major route of excretion, with >50% of the dose excreted by 24 hr and >70% by 168 hr (1 week). The intravenously-dosed Group D animals excreted a noticeably higher fraction via the urine than the orally-dosed groups (Groups A-C). A significant fraction of the dose was also found in the feces, which contained >15% of the dose at 24 hr (except for Group D, which contained 3-5.4%) and >20% of the dose at 168 hr (Group D: >5%). The calculated percent of absorption (mean percent dose in urine of oral low dose group divided by mean percent dose in urine of the intravenous low dose group) in the oral dose groups was 85.73% & 90.75% for Group A males & females, and 79.28% & 78.38% for Group C males & females. The only tissues containing measurable radiolabel after 7 days were liver (0.447 µg equivalents in females) & kidneys (0.358 & 0.518 µg equivalents in males & females) of Group B and the ovaries of Group C (0.031 µg equivalents in females). Solvent partition behavior indicated the polar nature of the liver/kidney residues. ~94-100% of urinary radioactivity & 86-98% of fecal radioactivity was parent CL 243,997. 8 minor metabolites appeared in urine w/none exceeding 0.1% of the dose. CL 252,974 (a hydrolysis product of CL 243,997) & CL 60,032 (an acetamide) were the major fecal metabolites, but also were found in selected urinary samples. Overall, 78.3%-96.0% of the dose was excreted unchanged, non-detectable-0.2% as CL 252,974, non-detectable-0.5% as CL 60,032, and 1.3-2.3% as the combined unknown compounds. Acceptable. (Rubin, 5/8/97)

52122-015 149080 851 “Herbicide AC 243,997: The Absorption, Excretion, Tissue Residues, and Metabolism of Carboxyl Carbon-14 Labeled AC 243,997 in the Rat” by N.M. Mallipudi, Agricultural Products Research Division, American Cyanamid Company, Princeton, NJ (report #PD-M Vol. 20-13; 6/6/83). 12 male rats were gavaged with 1.1 mg (~4.4 mg/kg; 33 µCi) of \(^{14}\)C-AC 243,997. 3 rats/sacrifice time were sacrificed at 1, 2, 5 & 8 days. One control was sacrificed on day 5, 2 on day 8. Urine & feces were collected daily. Blood, liver, kidney, muscle & fat were taken for analysis of radioactivity at the time of sacrifice. By day 1, 55.3% & 31.9% of the administered dose was excreted in urine & feces, respectively. By day 2 these values were 57.7% & 35.6% and by day 8 they were 58.8% & 36.3% (which, when combined with 2.9% in the cage rinse summed to an overall recovery of 98.0%). Label half-life was less than 1 day. Only residual label was detected in tissues and did not accumulate (0.03 ppm in liver & 0.02
ppm in kidney on day 1, <0.01 in all tissues by day 8). The urinary & organosoluble fecal label was shown by chemical analysis to be the parent compound. Supplemental. (Rubin, 5/9/97)

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat
52122-006 149050 811 “Oral LD₅₀ Study in Albino Rats with AC 243,997” by J. Fischer, Toxicology Dept., American Cyanamid Co., Princeton, NJ (report #T-0222; 6/14/90). 5 fasted rats/sex were dosed by oral gavage w/2500 mg/kg-bw AC 243,997 (ref. #AC 4866-62; 99.5% Imazapyr) as a 20% w/v suspension in corn oil (~5 ml/kg-bw). (Note: This is a corrected dose level based on information supplied in volume #52122-024.) Daily observations were conducted to detect mortality or morbidity. Body weights were determined on days 0, 7 & 14. Necropsies were performed on all survivors at sacrifice. There were neither deaths nor overt toxic signs. All animals gained weight during both weeks post dose. There were no treatment-related gross lesions observed at necropsy. Reported LD₅₀ (M/F) > 2500 mg/kg-bw. Toxicity Category not designated. Unacceptable (not upgradeable; insufficient dose for a limit test). (Rubin, 3/17/97)

: 52122-024 154226 811 “AC 243,997 Technical: Acute Oral Toxicity Study in Albino Rats” by J.E. Fischer, Agricultural Products Research Division, American Cyanamid Co., Princeton, NJ (report #A83-24; 7/19/83). 5 fasted rats/sex were dosed by oral gavage w/5000 mg/kg-bw of AC 243,997 (ID #AC 4361-97 (83-62); 93% Imazapyr) as a 20% w/v suspension in Mazola corn oil (25 ml/kg-bw). Observations for mortality & toxicity were conducted several times on the day of dosing and 1x/day for the following 2 wks. Body weights were determined on days 0, 7 & 14. Necropsies were performed on all decedents & survivors. There were neither deaths nor toxic signs. Body weights appeared unaffected by treatment. Necropsies did not reveal treatment-related abnormalities. LD₅₀ (M/F) > 5000 mg/kg. Toxicity Category IV. Acceptable. (Rubin, 5/6/97)

Acute dermal toxicity
52122-006 149053 812 “Dermal LD₅₀ Study in Albino Rats with AC 243,997” by J. Fischer, Toxicology Dept., American Cyanamid Co., Princeton, NJ (report #T-0226; 6/14/90). 2000 mg/kg-bw AC 243,997 (ref. #AC 4866-62; 99.5% Imazapyr) was spread on plastic wrap, moistened w/tap water, and applied to a clipped trunk area under the plastic wrap + a cloth bandage on each of 5 rabbits/sex. The exposure period was 24 hr followed by removal of the wraps & wiping clean the test site. Mortality & morbidity were checked several times on the dosing day and at intervals for the 14-day post dose period. Body weights were determined on days 0, 7 & 14. Necropsies were performed on all survivors following sacrifice. There were neither deaths nor toxic signs. Body weights appeared unaffected by treatment. Necropsies did not reveal treatment-related abnormalities. LD₅₀ (M/F) > 2000 mg/kg-bw. Toxicity Category III. Acceptable. (Rubin, 3/19/97)

Acute inhalation toxicity, rat
52122-006 149054 814 “Acute Inhalation Toxicity of AC 243,997 in Sprague-Dawley Rats” by B. Houghtaling & K.A. Voss, Food and Drug Research Laboratories, Inc., Waverly, NY (report #FDRL 7624; 9/1/83). 10 rats/sex were exposed to aerosolized AC 243,997 (no lot #: 93% Imazapyr) at a gravimetric and analytic concentration of 1.3 mg/L (nominal concentration: 5.1 mg/L), MMAD (GSD) = 3.3 µm (2.5), for 4 hr in a 309-L stainless steel/glass whole-body chamber. Mortality & morbidity were checked during exposure, 0.5, 1 & 24 hr post exposure and twice daily for the following 2 weeks. Body weights were determined prior to and on the day of exposure (days -1 & 1) and on days 8 & 15. Necropsies were conducted upon sacrifice at 2 weeks. There were no deaths. Nasal discharge was noted in all animals on day 1 only. All
males gained weight during both weeks post exposure. While three females maintained their weight and 1 lost 2 g during the 1st post exposure week, all gained during the 2nd week. Absolute & relative heart, kidney, liver, lung, ovary & testes weights did not appear affected by treatment, though the lack of control animals makes this conclusion difficult to verify. Terminal necropsies revealed a small tracheal clot in 1 male not considered to be treatment-related. LC\textsubscript{50} (M/F) > 1.3 mg/L. Toxicity Category III. Acceptable. (Rubin, 3/19/97)

Primary eye irritation, rabbit
52122-006 149055 814 "Eye Irritation Study in Albino Rabbits with AC 243,997" by J. Fischer, Toxicology Dept., American Cyanamid Co., Princeton, NJ (report #T-0224; 6/14/90). 0.1 g of AC 243,997 (ref. #AC 4866-62; 99.5% Imazapyr) was instilled into the conjunctival sac of the left eye of each of 6 male rabbits. A tap water rinse & fluorescein/uv examination were conducted at 24 hr. Draize eye exams were conducted pretreatment (-4 hr), at 1, 24, 48 & 72 hr, and at 4, 7, 10, 14, 17 & 21 days. Corneal irritation: grade 1 in 6/6 animals @ 24 & 48 hr post dose, grade 2 in 1/6 & grade 1 in 4/6 @ 72 hr, grade 3 in 1/6 & grade 1 in 4/6 @ 4 days, grade 2 in 1/6 & grade 1 in 2/6 @ 7 days, grade 1 in 3/6 @ 10 days, grade 2 in 1/6 & grade 1 in 1/6 @ 14 & 17 days, and grade 1 in 2/6 @ 21 days. Iris irritation: none observed. Conjunctival irritation (max. scores: 2/redness, 3/chemosis, 1/discharge): grade 3 in 6/6 @ 1 & 24 hr, grade 3 in 4/6 & grade 2 in 2/6 @ 48 hr, grade 3 in 1/6, grade 2 in 3/6 & grade 1 in 2/6 @ 72 hr, grade 2 in 3/6 & grade 1 in 3/6 @ 4 days, grade 2 in 1/6 & grade 1 in 4/6 @ 7 days, grade 1 in 4/6 @ 10 days, clearing by 14 days. Slight or moderate corneal vascularization was observed in 1/6 @ 4 & 7 days, 3/6 @ 10 days, 2/6 @ 14 & 17 days, and 1/6 @ 21 days. Toxicity Category I. Acceptable. (Rubin, 3/19/97)

Primary dermal irritation
52122-006 149056 815 "Skin Irritation Study in Albino Rabbits with AC 243,997" by J. Fischer, Toxicology Dept., American Cyanamid Co., Princeton, NJ (report #T-0229; 6/14/90). 0.5 g AC 243,997 (ref. #AC 4866-62; 99.5% Imazapyr) was applied to a 1 in\textsuperscript{2} gauze pad, moistened w/tap water, and applied to clipped intact skin on one side of the trunk midline of 6 male rabbits (the other side was used as a control). The patches were held in place with adhesive tape and impervious plastic sheeting. Exposure was for 4 hr. Draize skin exams were conducted at 1, 24, 48 & 72 hr post patch removal. Grade 1 erythema was observed in 1/6 animals at the 1-hr point, clearing by 24 hr. Edema was not noted at any time post dose. Toxicity Category IV. Acceptable. (Rubin, 3/19/97)

Dermal sensitization
52122-0006; 149057; "Evaluation of the Sensitization Potential of AC 243,997 in Guinea Pigs"; Worker Health and Safety Memorandum of 7/30/97 (C. Rech) noted that the test material did not elicit a dermal sensitization reaction under the study conditions.

SUBCHRONIC STUDIES

Rat subchronic dietary toxicity study
52122-007 149059 821 "AC 243,997: A 13-Week Dietary Toxicity Study in the Albino Rat" by J.E. Fischer, Toxicology Dept., American Cyanamid Co., Princeton, NJ (report #T0486; 9/9/92). 10 rats/sex/dose were exposed via the diet to AC 243,997 (lot #AC 4866-62; 99.3% Imazapyr) at 0, 15,000 or 20,000 ppm for 13 weeks. Observations for mortality & toxic signs were performed daily. Ophthalmology was performed prior to and after the exposure period. Clinical exams, body weights & food consumption were determined weekly. Hematology, blood chemistry, urinalysis, necropsy, organ weight determinations & histopathology of selected tissues were performed at termination. There were neither deaths nor signs of overt toxicity
during the 13-week dosing period. Food consumption & body weights in treated animals were at or slightly above control values. Final mean body weight gains were 2.5-6.5% above control values. However, test article-relatedness in these observations is not clear. Mean daily test article consumption for both sexes was 1336 mg/kg/day at 15,000 ppm and 1740 mg/kg/day at 20,000 ppm. Abnormalities were not evident in hematology, blood chemistry or urinalysis. Necropsies, organ weights & histopathology were unremarkable. There were no adverse effects. NOAEL/NOEL (M/F) > 20,000 ppm (∼1740 mg/kg-bw/day; no effects at HDT). Acceptable. (Rubin, 3/21/97)

**Rat repeated dosing dermal toxicity study**
52122-006 149058 822 “Twenty-one Day Dermal Toxicity Study with AC 243,997 in Rabbits” by D.M. Larson, Toxicology & Pathology Services for Safety, Mount Vernon, IN (study #186B-301-230-83; 8/8/83). AC 243,997 (lot #AC 4361-97; 93% Imazapyr) was applied 5 days/wk, 6 hr/day, for 21 days to clipped dorsal skin of 10 rabbits/sex/dose at 0, 100, 200 & 400 mg/kg-bw/day. The test site was covered with a gauze patch moistened w/5 ml 0.9% saline. The test site was abraded weekly in 50% of the rabbits at each dose. Observations for toxic signs & mortality were performed daily. Body weights & food consumption were determined every 3 days. Blood samples for hematology & blood chemistry were taken from the vena cava of all animals after the dosing period (pretest clinical chemistry data were derived from 5/sex using ear blood). Rabbits were fasted overnight prior to necropsy. Histopathology was also performed on a range of tissues from the control & HD groups. 2 males (1 each at 200 & 400 mg/kg) died of pneumonia (day 16 & 13), not considered due to treatment. There were no treatment-related clinical signs. Body weight and food consumption were unaffected. A statistically significant increase in leukocyte counts in 400 mg/kg males compared to controls was considered to be incidental. While some statistically significant blood chemistry data were obtained, all were deemed incidental. Gross necropsies and organ weight determinations did not reveal treatment-related abnormalities. Histopathology revealed an increase at the HD of focal inflammatory infiltrate at the treatment site in both sexes (M, 0/10 in controls vs. 3/10 at the HD; F, 2/10 vs. 6/10), but test article relatedness is discounted due to a lack of change in severity and a high incidence of the condition in untreated skin both from control and HD rabbits. Reported NOAEL/NOEL (M/F) > 400 mg/kg-bw/day (no effects at HDT). Unacceptable (but possibly upgradeable w/submission of justification of dose level selection and analysis of dosing material). (Rubin, 3/21/97)

52122-006, -025 149058, 156568 822 “Twenty-one Day Dermal Toxicity Study with AC 243,997 in Rabbits” by D.M. Larson, Toxicology & Pathology Services for Safety, Mount Vernon, IN (study #186B-301-230-83; 8/8/83). AC 243,997 (lot #AC 4361-97; 93% Imazapyr) was applied 5 days/wk, 6 hr/day, for 21 days to clipped dorsal skin of 10 rabbits/sex/dose at 0, 100, 200 & 400 mg/kg-bw/day. The test site was covered with a gauze patch moistened w/5 ml 0.9% saline. The test site was abraded weekly in 50% of the rabbits at each dose. Observations for toxic signs & mortality were performed daily. Body weights & food consumption were determined every 3 days. Blood samples for hematology & blood chemistry were taken from the vena cava of all animals after the dosing period (pretest clinical chemistry data were derived from 5/sex using ear blood). Rabbits were fasted overnight prior to necropsy. Histopathology was also performed on a range of tissues from the control & HD groups. 2 males (1 each at 200 & 400 mg/kg) died of pneumonia (day 16 & 13), not considered due to treatment. There were no treatment-related clinical signs. Body weight and food consumption were unaffected. A statistically significant increase in leukocyte counts in 400 mg/kg males compared to controls was considered to be incidental. While some statistically significant blood chemistry data were obtained, all were deemed incidental. Gross necropsies and organ weight determinations did not reveal treatment-related abnormalities. Histopathology revealed an increase at the HD of
focal inflammatory infiltrate at the treatment site in both sexes (M, 0/10 in controls vs. 3/10 at the HD; F, 2/10 vs. 6/10), but test article relatedness is discounted due to a lack of change in severity and a high incidence of the condition in untreated skin both from control and HD rabbits. NOAEL/NOEL (M/F) > 400 mg/kg-bw/day (no effects at HDT). Unacceptable (but possibly upgradeable w/submission of justification of dose level selection). (Rubin, 3/21/97; status unchanged after review of dose justification submitted by Registrant, 10/7/97)

CHRONIC STUDIES

Chronic, rat
52122-010, -011 149062,149067 835 “A Chronic Dietary Toxicity and Oncogenicity Study with AC 243,997 in Rats” by I. Daly, Bio/dynamics, Inc., East Millstone, NJ (report #84-2862; 4/6/88). AC 243,997 (lot #AC 4866-062; 99.5% Imazapyr) was administered in the diet to 65 rats/sex/dose at 0, 1000, 5000 & 10,000 ppm for up to 24 months. 10/sex/dose were sacrificed @ 12 months which, along with 10/sex/dose sacrificed at 24 months, were analyzed for organ weights. Physical observations were made 2x/day, with a more detailed clinical exam conducted weekly. Body weights & food consumption were determined weekly through 14 weeks, biweekly from 16-40 weeks and monthly thereafter. Blood for hematology & clinical chemistry was withdrawn from 10 fasted rats/sex/dose at 3, 6, 12, 18 & 24 months. Urinalyses were conducted at approximately the same periods. Gross necropsy & histopathology on an extensive range of tissues were conducted on all animals. The estimated median survival time may have decreased slightly among males in a dose responsive fashion (at ascending doses, males: 677, 689, 660 & 655 days; females: 726, 734+, 708 & 740 days). Survivorship at termination may also have been somewhat lowered in HD males. Slight, but often statistically significant, increases in food consumption occurred in both sexes during the 1st year, though dose responsiveness was not always evident. No other parameter showed evidence of a treatment effect. There was no clear evidence of oncogenicity, though slight increases in tumor incidence at the high dose were noted in the thyroid, adrenal medulla & brain. A treatment effect in these cases was discounted based on historical control data & other considerations. NOEL (M/F) = NOAEL (M/F) > 10,000 ppm (M, 503.0 mg/kg/day; F, 638.6 mg/kg/day; no adverse effects). Acceptable. (Rubin, 4/10/97)

Chronic, dog
52122-008 149060 831 “One Year Dietary Toxicity Study in Purebred Beagle Dogs with AC 243,997” by T. Shellenberger, Tegeris Laboratories, Inc., Laurel, MD (report #86002; 5/29/87). 6 beagles/sex/dose were exposed via the diet to AC 243,997 (lot #AC 4866-62; 99.5% Imazapyr) to 0, 1000, 5000 or 10,000 ppm for 1 year. Twice daily exams were conducted for mortality & toxic signs. Body weights were determined weekly & food consumption daily. Hematology, clinical chemistry & urinalysis were conducted on all dogs pretest, at 6 weeks and at 3, 6 & 12 months. Ophthalmoscopy was conducted pretest and at 6 & 12 months. Gross necropsy, organ weight analysis & histopathology were conducted at 12 months. There were neither deaths nor treatment-related clinical signs. Body weights of HD males tended to be higher & HD females lower than the corresponding controls. Thus a treatment effect on body weight is considered unlikely. Similarly, food consumption among treated males was generally higher and treated females often lower than controls. This observation was not accorded toxicologic significance. There were no effects on organ weights or hematologic, clinical chemistry, urinalysis or ophthalmologic parameters. Gross necropsies & histopathology did not reveal clearly treatment-related abnormalities. There were no adverse effects. NOAEL/NOEL > 10,000 ppm (no effect at HDT). Unacceptable (but possibly upgradeable with submission of dose justification). (Rubin, 3/27/97)
One Year Dietary Toxicity Study in Purebred Beagle Dogs with AC 243,997 by T. Shellenberger, Tegeris Laboratories, Inc., Laurel, MD (report #86002; 5/29/87). 6 beagles/sex/dose were exposed via the diet to AC 243,997 (lot #AC 4866-62; 99.5% Imazapyr) to 0, 1000, 5000 or 10,000 ppm for 1 year. Twice daily exams were conducted for mortality & toxic signs. Body weights were determined weekly & food consumption daily. Hematology, clinical chemistry & urinalysis were conducted on all dogs pretest, at 6 weeks and at 3, 6 & 12 months. Ophthalmoscopy was conducted pretest and at 6 & 12 months. Gross necropsy, organ weight analysis & histopathology were conducted at 12 months. There were neither deaths nor treatment-related clinical signs. Body weights of HD males tended to be higher & HD females lower than the corresponding controls. Thus a treatment effect on body weight is considered unlikely. Similarly, food consumption among treated males was generally higher and treated females often lower than controls. This observation was not accorded toxicologic significance. There were no effects on organ weights or hematologic, clinical chemistry, urinalysis or ophthalmologic parameters. Gross necropsies & histopathology did not reveal clearly treatment-related abnormalities. There were no adverse effects. NOAEL/NOEL > 10,000 ppm (no effect at HDT). Unacceptable (but possibly upgradeable w/submission of justification of dose level selection). (Rubin, 3/26/97; statusunchanged after review of dose justification submitted by Registrant, 10/7/97)

Oncogenicity, rat
See Chronic, rat above.

Oncogenicity, mouse
52122-009 149061 832 “A Chronic Dietary Toxicity and Oncogenicity Study with AC 243,997 in Mice” by C. Auletta, Bio/dynamics, Inc., East Millstone, NJ (report #86-3074; 11/3/88). 65 mice/sex/dose were exposed via the diet to AC 243,997 (lot #AC 4866-062; purity, 99.5%) at 0, 1000, 5000, or 10,000 ppm for 18 months with an interim sacrifice of 10/sex/dose at 12 months. Twice daily exams were conducted for mortality & toxic signs with a more detailed weekly exam also conducted. Body weights and food consumption were determined weekly through 14 wks, biweekly from 16-26 wks and monthly thereafter. Blood from fasted animals was obtained at 12 & 18 months for hematology. Necropsy was performed on all interim & terminal sacrifices and premature decedents. Organ weights were determined and histopathology conducted on an extensive range of tissues. Certain necropsy & histopathologic parameters appeared to rise in dosed animals, though causation by treatment was not clearly established. Examples of these are emphysema in females (incidence at ascending doses: 0/65, 0/65, 1/65, 4/65), discolored pituitary in females (0/65, 1/65, 0/65, 5/65), kidney cysts in males (3/65, 2/65, 3/65, 8/65), cloudy swelling in male liver (1/65, 4/65, 7/65, 8/65), and brain congestion in females (3/65, 2/64, 3/65, 7/65). A tendency toward neoplasm formation in dosed animals may be present (females show higher rates in liver, stomach, ovaries, uterus & muscle, males show higher rates in liver), but the diversity of tissues and low incidence rates make this difficult to verify as treatment related. NOEL (M/F) = 5000 ppm (M: >674-1194 mg/kg/day; F: >776-1501 mg/kg/day; necropsy & histopath. observations). NOAEL (M/F) > 10,000 ppm (M: > 1301-2409 mg/kg/day; F: > 1639-3149 mg/kg/day). Acceptable. (Rubin, 4/3/97)

GENOTOXICITY

Gene mutation
dependent *Escherichia coli* strain WP2 *uvrA* were exposed in triplicate +S9 microsomes in 2 separate experiments to CL 243,997 (batch #AC 4361-97; 93% Imazapyr) at 0 (solvent control: acetone), 50, 158, 500, 1581 & 5000 µg/plate for 48±6 hr @ 37°C. A “disc test” was also run at 1000 µg/plate using each tester strain to confirm the results of the plate incorporation assays. Despite the success of the positive controls in both the plate incorporation assay and the disc test, no concentration of CL 243,997 induced a reversion to histidine (*S. typhimurium*) or tryptophan (*E. coli*) independence regardless of the absence or presence of microsomal activating system. CL 243,997 is not considered to be mutagenic in the system under the conditions tested. **Acceptable.** (Rubin, 5/12/97)

52122-015 149079 842 “Mutagenicity Testing of AC 243,997 in the *In Vitro* CHO/HGPRT Mutation Assay” by E. Johnson & J. Allen, Agricultural Products Research Division, American Cyanamid Company, Princeton, NJ (report #GTOX Vol. 4, No. 1; 2/17/84). 24 hr after seeding 5x10⁵ cells/25 cm² flask the cultures were washed and treated w/AC 243,997 (medium + serum for tests -S9, medium w/o serum for tests +S9) for 5 hr @ 37°C. Following exposure the cultures were washed and incubated overnight w/fresh medium before replating of 10⁶ cells at 2-day intervals over a 9-day period for phenotypic expression. 2x10⁵ cells were then plated on each of 5 100-mm dishes (10⁶ cells total) in the presence of 10 µM 6-thioguanine for mutant colony determination. Mutant frequency was defined as the # of mutant clones per 10⁶ survivors. Colony forming ability was assessed at the time of phenotypic expression (cytotoxicity determination) and at the time of mutant selection. 2 complete experiments were run, with each dose run in triplicate. Doses were as follows: Expt. #1, +S9: 0 (DMSO control), 125 (-S9 only), 250, 500, 1000, 2500 & 5000 (+S9 only) µg/ml; Expt. #2, -S9: 0, 1000, 2500, 3750 & 5000 µg/ml (7500 & 10,000 µg/ml were also run but proved too toxic for mutagenicity analysis); Expt. #2, +S9: 0, 250, 2500, 6000 & 9000 µg/ml (12,000 µg/ml was also run, but proved too toxic; also, a precipitate was noted at 6000, 9000 & 12,000 µg/ml). Negative controls were the solvent and 7 µg/ml dimethylbenzanthracene (-S9). Positive controls were 200 µg/ml ethane methyl sulfonate (-S9) and 7 µg/ml dimethylbenzanthracene (+S9). Despite the ability of the positive controls to markedly increase the mutation frequency, cultures exposed to test article showed frequencies not convincingly different from control values. AC 243,997 is not considered mutagenic under the conditions tested. **Acceptable.** (Rubin, 5/19/97)

**Chromosome damage**

52122-014 149074 843 “*In Vitro* Chromosomal aberrations in Chinese Hamster Ovary Cells with AC 243,997” by M. Farrow & T. Cortina, Hazleton Laboratories America, Inc., Vienna, VA (report #362-169; 2/2/84). 24 hr after plating 4.5x10⁵ CHO cells/25 cm² culture dish, they were exposed in triplicate to 0, 50, 170, 500, 1700 or 5000 µg/ml AC 243,997 (lab. #462; 93% Imazapyr). The dose range was based on a preliminary cytotoxicity test. For those cultures exposed to S9 enzymes, test article exposure was for 2 hr @ 37±0.5°C, after which the cells were washed and incubation @ 37°C continued. For all cells (+S9), at ~1, 6 or 10 hr after addition of test material 0.2 µg/ml colcemid was added for 2 hr to induce metaphase arrest (making the test article exposure -S9 equal to 3, 8 or 12 hr). Metaphases were collected at each dose from 2 of the 3 flasks by mitotic shake-off (the 3rd flask was trypsinized) and the cells processed for karyotype analysis. 50 metaphases/replicate (100 metaphases total) were analyzed for chromosomal aberrations & modal number. Positive controls were 1 µg/ml Mitomycin C (-S9) and 140 µg/ml cyclophosphamide (+S9). The test article did not produce any significant increases in percent aberrant cells or mean aberrations/cell, - or + S9. A weakly positive result may have occurred at the high dose, +S9, 12-hr harvest time, but did not achieve statistical significance. Cyclophosphamide (+S9) induced significant increases in percent aberrations & mean aberrations/cell at 8 & 12 hr. Mitomycin C produced a significant increase in percent aberrations at 12 hr (-S9). Among the positive controls and the possible weak positive
cited above at the high dose +S9, chromatid breaks appear to be the most common aberration. Slight, but statistically significant increases in modal number were seen at 50, 170, 500 & 5000 µg/ml AC 243,997 -S9, but, considering the inherent variation of CHO karyotype, these were not considered to be biologically significant. A decrease in mitotic index -S9 was apparent among dosed cultures at the 12-hr point. AC 243,997 is not considered to be clastogenic in this system under the conditions tested. **Acceptable.** (Rubin, 5/14/97)

**DNA damage or miscellaneous effects**

52122-014 149075 844 “Unscheduled DNA Synthesis Rat Hepatocyte Assay; Compound AC 243,997” by M. Farrow & R.C. Sernau, Hazleton Laboratories America, Inc., Vienna, VA (report #362-170; 1/30/84). 0.5x10^6 rat primary hepatocytes were plated on 35 mm^2 dishes (in 1 ml medium) containing a coverslip & allowed to attach for 90 min before replacement of the medium with medium containing 10 µCi/ml ³H-thymidine and 0 (DMSO control), 50, 100, 500, 1000 or 5000 µg/ml AC 243,997 (laboratory #462; 93% Imazapyr) for 24 hr. The high dose was selected based on the solubility of the test article. Dishes containing test article or DMSO controls were run in triplicate while those containing medium or positive controls (0.05, 0.1 & 0.5 µg/ml 2-acetylaminofluorene) were run as single cultures. Extra single dishes for cytotoxicity determination by trypan blue exclusion were also prepared. Following exposure, the coverslips were processed for autoradiography, allowing 4 days at 4°C for exposure to photographic emulsion. The net nuclear grain count was obtained for each cell by subtracting the mean cytoplasmic grain count from the nuclear grain count. Despite the success of the positive controls, no dose of AC 243,997 caused an increase in net nuclear grain count. Relative survival, based on trypan blue dye exclusion, was also unaffected by the test article. AC 243,997 did not induce unscheduled DNA synthesis in this system under the conditions tested. **Acceptable.** (Rubin, 5/15/97)

**REPRODUCTIVE TOXICITY, RAT**

52122-014 149072 834 “A 2-Generation (2-Litter) Reproduction Study of AC 243,997 Administered in the Diet to the Rat” by K. Robinson, Bio-Research Laboratories, Ltd., Sennerville, Quebec, Canada (report #82408; 5/6/87). 25 male & 25 female F0 rats/dose were exposed via the diet to w/AC 243,997 at 0, 1000, 5000 or 10000 ppm for 64 days before mating, throughout the 2 mating periods, and until sacrifice at ~3 wks after the 2nd mating period. At 21 days post partum the F1b litters were weaned and 25/sex/dose selected to form the F1b adult generation. These animals were treated at the same doses as their parents for 78 days before mating to produce the F2a & F2b generations. Treatment was maintained throughout the gestation & lactation periods in females and in males until ~4 wks after the end of the 2nd mating period. F2 pups were killed following weaning. F0 & F1b adult generations: There were no treatment-related deaths, clinical signs or pathologic findings. Body weights & food intakes were unaffected. Conception rate was significantly decreased (p<.05) at the HD during the 1st F0 mating period, but statistical significance was not corroborated at other matings (though HD values were lower than controls and other doses for both of the F1b matings). In addition, litter parameters were similar to controls. Therefore, while test article involvement in conception rate suppression is possible, the data do not clearly support it. Other parameters of parental & maternal performance (fertility indices, mating day, gestation index, gestation length, # live & dead pups at birth, sex ratio) were unaffected. F1a, F1b, F2a & F2b pup generations: viability, survival & lactation indices were unaffected by exposure. There were no treatment-related clinical or pathologic signs. Pup weights appeared unaffected by exposure. Reproductive NOAEL/NOEL > 10000 ppm (F0 males > 738.0 mg/kg/day; F0 females > 933.3 mg/kg/day; F1b males > 849.9 mg/kg/day; F1b females > 1026.4 mg/kg/day). **Acceptable.** (Rubin, 5/5/97)
DEVELOPMENTAL TOXICITY

Rat
156576 833 “Teratology Study in Albino Rats with AC 243,997” by P. Enloe & C. Salamon, Toxigenics, Inc., Decatur, IL (report #450-1222; 9/9/83). 25 bred females/dose were exposed by oral gavage to 0 (vehicle control: 10 ml/kg 0.1% Tween 80), 100, 300 or 1000 mg/kg/day ground AC 243,997 (lot #AC 4361-97; 93% Imazapyr) between gestation days (GD) 6-15 inclusive. Observations for toxic signs and mortality were made at least 2x/day. Maternal body weights were recorded on GD 0, 6, 9, 12, 15 & 20. Food consumption was monitored visually, but not measured. Dams were sacrificed on GD 20 and the gravid uterus examined for # of implantation sites, resorption sites (early or late), corpora lutea & fetuses. Thoracic & abdominal organs of each dam were examined for gross morphological changes. Fetuses were examined for external developmental anomalies, then weighed, measured and tagged to indicate position in the uterine horn. ~⅔ of each litter was processed for skeletal examinations and the remaining for visceral examinations. All dams survived to scheduled sacrifice. Pregnancy occurred in 22, 24, 23 & 22 dams at ascending doses. Salivation was the only clearly test article-related clinical sign, occurring between GD 8-14 in 6 HD females. While the mean weight change both between GD 6-20 and GD 0-20 appeared lower at the MD & HD (for GD 6-20 these values were, at ascending doses: 122, 119, 116 & 113 g; for GD 0-20 these values were 150, 148, 143 & 140 g), these differences can be accounted for by differences in mean gravid uterus weight (82.4, 82.9, 78.5 & 73.6). Thus the actual net weight change (total weight change minus gravid uterine weight) was not affected by dose (67, 65, 64 & 67 g). While none of these differences attained statistical significance, they are largely accounted for by an increase in early resorptions/litter (0.4, 0.7, 0.4 & 0.9 at ascending doses) and a decline in viable fetuses (14.3, 14.3, 13.9 & 12.9). Test article involvement was unlikely because 1 litter skewed the data in each case. Fetal crown-rump length & weight appeared unaffected by dose. There were no clear findings of test article-related fetal external, skeletal or visceral abnormalities. Gross pathology of the dams revealed focal lung discoloration in 1 MD and 2 HD dams with treatment relation unclear. Maternal & fetal NOAEL/NOEL > 1000 mg/kg/day. **Acceptable.** (Rubin, 10/6/97; upgraded from Rubin, 4/17/97, with submission of a dose suspension analysis)

52122-012 149068 833 “Teratology Pilot Study in Albino Rats with AC 243,997” by P. Enloe & C. Salamon, Toxigenics, Inc., Decatur, IL (report #450-1221; 8/2/83). 5 pregnant females/dose were exposed by oral gavage to 0 (vehicle control: 10 ml/kg 0.1% Tween 80), 250, 500, 1000 or 2000 mg/kg/day ground AC 243,997 (lot #4361-97; 93% Imazapyr) between gestation days (GD) 6-15 inclusive. Observations for toxic signs and mortality were made at least 2x/day. Maternal body weights were recorded on GD 6. Food consumption was monitored visually, but not measured. Dams were sacrificed on GD 20 and the gravid uterus examined for # of implantation sites, resorption sites (early or late), corpora lutea & fetuses. Gross necropsies were performed on the dams. All dams survived to scheduled sacrifice. Salivation was the only clearly test article-related clinical sign, occurring between GD 9-15. Gross necropsy did not reveal test article-related abnormalities. Numbers of corpora lutea, implantation sites, resorption sites & viable fetuses appeared to be unaffected by any concentration of test article. Maternal and developmental NOEL/NOAEL > 2000 mg/kg. **Supplemental.** ( Rubin, 4/14/97)

Rabbit
52122-013, -025 149071, 156568, 156576 833 “Teratology Study in Albino Rabbits with AC 243,997” by P. Enloe & C. Salamon, Toxigenics, Inc., Decatur, IL (report #450-1224; 9/21/83). 18 bred females/dose were exposed by gavage on gestation days (GD) 6-18 inclusive to 0 (vehicle control: 4 ml 0.1% Tween 80/kg), 25, 100 or 400 mg/kg/day AC 243,997 (lot #AC 4361-97; 93% Imazapyr). Observations for mortality & toxic signs were made at least twice
daily, with a “hands-on” exam performed each week. Maternal body weights were determined on GD 0, 6, 12, 15, 18, 24 & 28. Food consumption was monitored visually. Following sacrifice on GD 28, the gravid uterus was weighed & the # of implantation & resorption (early or late) sites, corpora lutea & fetuses determined. Maternal thoracic & abdominal organs were examined for gross abnormalities. Each fetus was weighed and the crown-rump length & uterine position determined, after which it was examined for internal development, sexed & eviscerated. Heads were removed & examined from &lt;¼ of the fetuses/litter. Skeletal exams were performed on all fetuses. Breeding trials resulted in 17, 18, 16 & 17 pregnancies at ascending doses (all maternal data except mortalities, clinical signs & necropsies were derived from the pregnant animals only). Mortalities included 2 control females (both gravid, both on GD 12) and 2 HD females (one non-gravid female found dead on day 7, one gravid female found dead on GD 10). Neither the antemortem observations nor maternal weight changes indicated clear treatment effects. Necropsy on the decedents revealed diffuse or multifocal lung discoloration. Necropsy on survivors revealed a relatively high incidence of lung discoloration, but w/o an obvious treatment relation. Reproductive/developmental parameters were generally unaffected by exposure. Fetal external abnormalities increased at the HD ((fetal (litter) incidence at ascending doses: 0/100 (0/13), 1/152 (1/17), 0/147 (0/16), 4/144 (3/16), though the data were not sufficiently convincing to ascribe this to the test article. Maternal NOAEL/NOEL &gt; 400 mg/kg/day. Developmental NOAEL &gt; 400 mg/kg/day. Fetal NOEL &gt; 400 mg/kg/day. Acceptable (Rubin, 10/6/97; upgraded from unacceptable, Rubin, 4/25/97, with submission of a dose suspension analysis)

52122-013 149070 833 "Teratology Pilot Study in Albino Rabbits with AC 243,997" by P. Enloe & C. Salamon, Toxigenics, Inc., Decatur, IL (report #450-1223; 8/2/83). 5 bred females/dose were exposed by gavage on gestation days (GD) 6-18 inclusive to 0 (vehicle control: 4 ml 0.1% Tween 80/kg), 250, 500, 1000 or 2000 mg/kg/day AC 243,997 (lot #AC 4361-97; 93% Imazapyr). Observations for mortality and toxic signs were made at least twice daily. Maternal body weights were determined on GD 0, 6, 12, 18, 24 & 28. Food consumption was monitored visually. Following sacrifice on GD 28, gravid uteri were examined for # of implantation & resorption sites (early or late), corpora lutea and fetuses. Dams were examined for gross morphologic change. Breeding trials resulted in 4, 5, 3, 5 & 5 pregnancies at ascending doses (all maternal data except mortalities, clinical signs & necropsies were derived from the pregnant animals only). Mortalities at ascending doses were 0/5, 2/5 (found dead on GD 10 & 14), 0/5, 4/5 (found dead on GD 12, 15, 17 & 18) & 5/5 (found dead on GD 8, 9 & 10). Test article may have effected weakness, lethargy, staggered gait, & slowed respiration, but these were not consistently observed even in animals fated to die from exposure. Necropsies of the decedents revealed gastric ulcers or erosive gastric lesions, a possible adverse effect, in every decedent (except one LD animal showing consolidative nonsuppurative pneumonia). Exudates, foreign material or discoloration were noted in the lungs or tracheas of 2, 0, 1 & 2 decedents at ascending doses (excluding controls, which had no decedents). However, lung discoloration was also commonly noted among the terminal sacrifices, including the controls. Maternal body weights do not appear to have been severely affected, though the high death rate precludes precise analysis. There was no test article effect on numbers of corpora lutea, implantation sites, resorption sites, or viable fetuses (however, no does survived to term at the HD). NOAEL/NOEL (maternal) &lt; 250 mg/kg/day (gastric ulcers or erosive gastric lesions). NOAEL/NOEL (developmental) &gt; 2000 mg/kg/day. Supplemental. (Rubin, 4/21/97)
NEUROTOXICITY

Acute neurotoxicity, rat
52122-0031; 261722; “Acute Oral Neurotoxicity Study in Wistar Rats, Administration via Gavage”; (R. Buesen, S. Groters, M. Becker, B. van Ravenzaay; Experimental Toxicology and Ecology, BASF SE, 67056 Ludwigshafen, Germany; Project No. 61C0141/04I018; 3/7/11); Ten Wistar rats/sex/group were dosed orally by gavage with 0 (vehicle: aqueous 1% carboxymethyl cellulose), 200, 600 or 2000 mg/kg of BAS 693 H (Imazapyr Technical) (Batch No. 9129H01HA; purity: 99.4% BAS 550 F). No unscheduled deaths occurred during the study. In the functional observational battery, no treatment-related effects were noted. No treatment-related lesions were observed in the neuropathology evaluation. No adverse effect indicated. Acute Neurotoxicity NOEL: (M/F) 2000 mg/kg (based upon the lack of a treatment-related effect noted for the animals in the 2000 mg/kg treatment group); Study acceptable. (Moore, 8/3/15)

90-day neurotoxicity, rat
** 52122-0032; 261723; “Repeated Dose 90-Day Oral Neurotoxicity Study in Wistar Rats, Administration via the Diet”; (R. Buesen, S. Groters, M. Becker, W. Mellert; Experimental Toxicology and Ecology, BASF SE, 67056 Ludwigshafen, Germany; Project No. 63C0141/04S019; 4/29/11); Ten Wistar rats rats/sex/group received 0, 100, 300, or 1000 mg/kg/day (nominal) of BAS 693 H (Imazapyr Technical) (Batch No. 9129H01HA; purity: 99.4%) in the diet for 13 weeks (((M) 0, 89, 272, 924 mg/kg/day, (F) 0, 92, 283, 933 mg/kg/day). There was no treatment-related effect upon the mean body weights. No apparent treatment-related effects were evident in the FOB or motor activity assessments. No lesions were noted in the histopathological examination of the nervous tissue. No adverse effect was noted. Rat Subchronic Neurotoxicity NOEL: (M) 924 mg/kg/day, (F) 933 mg/kg/day) (based on the lack of neurotoxic effects on both sexes in the highest treatment group) Study acceptable, (Moore, 8/4/15)

Developmental neurotoxicity, rat
No study has been submitted nor is required at this time.

Delayed neurotoxicity, hen
No study has been submitted nor is required at this time.

IMMUNOTOXICITY
** 52122-0033; 261724; “BAS 693 H (Imazapyr) – Immunotoxicity Study in Female C57BL/6 J Rj Mice, Administration via the Diet for 4 Weeks (Including Amendment No. 1)”; (R. Buesen, V. Strauss, H.A. Marxfeld, E. Fabian, W. Mellert; Experimental Toxicology and Ecology, BASF SE, 67056 Ludwigshafen, Germany; Study ID No. 43C0141/04S020; 4/29/11, amendment, 5/18/11); Eight C57BL/6 J Rj female mice/group received 0, 500, 1000, or 5000 ppm of BAS 693 H (Imazapyr Technical) (Batch No. 9129H01HA; purity: 99.4%) in the diet for 4 weeks (0, 155, 525, 1668 mg/kg/day). On study day 23, the study animals were injected ip with 0.5 ml of 4x10^6 sheep red blood cells (SRBC)/ml. On study day 29, prior to necropsy, blood was collected from each animal during exsanguination at the time of necropsy and humoral function was evaluated by analyzing the SRBC-specific IgM levels in the serum by means of an enzyme-linked immunosorbent assay (ELISA). No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weights. There was no treatment-related effect upon the mean absolute or relative thymus or spleen weights. The treatment did not suppress the primary humoral response to SRBC. No adverse effect indicated. The positive control was functional. Mouse 28-Day Immunotoxicity NOEL: (F) 5000 ppm, (1668 mg/kg/day)
(based upon the lack of treatment-related effects at the highest treatment level on the immunologically-related organs); **Study acceptable.** (Moore, 8/5/15)

**ENDOCRINE DISRUPTOR STUDIES**
No study has been submitted nor is required at this time.

**SUPPLEMENTAL STUDIES**
No study has been submitted nor is required at this time.