CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

IMAZAMETHABENZ-METHYL

Chemical Code # 2240, Tolerance # 50502

4/6/99

I. DATA GAP STATUS

Combined, rat:	No data gap; No adverse effects
Chronic toxicity, dog:	No data gap; No adverse effects
Oncogenicity, mouse:	No data gap; No adverse effects
Reproduction, rat:	No data gap; No adverse effects
Teratology, rat:	No data gap; No adverse effects
Teratology, rabbit:	No data gap; No adverse effects
Gene mutation:	No data gap; No adverse effects
Chromosome effects:	No data gap; No adverse effects
DNA damage:	No data gap; No adverse effects
Neurotoxicity:	Not required at this time.

Toxicology one-liners are attached.

All record numbers through 166465 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T169364
Peter Leung, 4/6/99

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

50502-025, -026 157899, 157913 "Chronic Dietary Toxicity and Oncogenicity Study in Rats Fed with AC 222,293" (Weltman, R., Hazleton Laboratories America, Inc., Madison, Wisconsin. Study # 6123-100, 5/17/85). AC 222,293 Technical (Imazamethabenz-Methyl, lot# AC 4281-72, purity of 94.2%) was administered in the feed to 65 Crl:CD®(SD)BR rats/sex/dose at levels of 0, 250, 1000 or 4000 ppm for 24 months. There was no apparent compound-related effect on mortality. High-dose males showed slight differences in mean body weight; females at 4000 ppm showed consistently and significantly lower body weights compared to control throughout the test period. Clinical chemistry values showing significant changes included increased glutamic oxaloacetic transaminase (SGOT) and glutamic pyruvic transaminase (SGPT) at 12, 18 and 24 months. At 6 months, males and females at 4000 ppm and males at 1000 ppm had mean SGOT and SGPT levels that were slightly (but not significantly) different from control. At 12 and 18 months, compound-related increases in SGOT and SGPT levels were seen in males at 1000 and 4000 ppm and females at 4000 ppm. At 18 months, Alkaline phosphatase (ALK PHOS) and gamma glutamyl transferase (GGT) levels were increased in 4000 ppm males. At 24 months, SGOT, SGPT, ALK PHOS and GGT levels were elevated in 1000 and 4000 ppm males. Proliferation of the thymic epithelium, not seen at the 12-month interim sacrifice, was reported with increased frequency in females at 4000 ppm. Increased incidence of hepatocellular degeneration in males and increased hepatocellular vacuolation in females, was noted **(NOEL)(M)=250 ppm** (based on increased incidence of hepatocellular degeneration and increased levels of SGOT and SGPT in the 1000 and 4000 ppm dose groups). **(F)=1000 ppm** (based on hepatocellular vacuolation and increased SGOT and SGPT in the 4000 ppm dose group). **Unacceptable**, due to lack of ophthalmology data. Kellner, 12/16/97.

The combined chronic/oncogenicity study in rats was found to be unacceptable due to a lack of ophthalmology data. However, this deficiency was filled by using ophthalmology data from the chronic dog study (DPR# 50502-022:157881).

CHRONIC TOXICITY, DOG

** 50502-022 157881 "One-Year Dietary Toxicity Study in Purebred Beagle Dogs with AC 222,293" (Seely, J. 831-Pharmacopathics Research Laboratories, Inc., Laurel, Maryland. Report # 981-82-110, 12/14/83). AC 222,293 Technical (Imazamethabenz-Methyl, lot# AC 4281-72, purity of 94.2%) was administered in the feed to 8 beagle dogs/sex/dose at levels of 0, 250, 1000 or 4000 ppm for 52 weeks. There were no unscheduled deaths during the study. Mean body weights of high-dose males were consistently lower than controls throughout the study (although difference not statistically significant). In males, hematologic changes that achieved statistical significance included decreased hemoglobin in the high-dose group and decreased lymphocyte counts in the mid- and high-dose groups at week 13. At week 26, differential counts showed the following changes: PMNs were elevated in the mid- and high-dose groups and lymphocytes were decreased in the high-dose group. By week 52, mid- and high-dose males had slightly decreased MCHC (%). Female liver weights were significantly increased in the 1000 and 4000 ppm dose groups. There were no dose-related gross or microscopic pathologic changes or ophthalmologic findings reported. **(NOEL)(M) =1000 ppm**; **(F)=250 ppm** (based on slight reductions in high-dose male body weights and increased female liver weight at and 1000 and 4000 ppm). **No adverse effects**. **Acceptable**. Kellner, 12/10/97.

ONCOGENICITY, MOUSE

50502-025, -027 to -029, -038; 157899, 157921, 157929, 157934, 161938; "Chronic Dietary Toxicity and Oncogenicity Study with AC 222,293 In Mice" (Stanzione, T. and Shellenberger, T., 832-Tegeris Laboratories Inc., Laurel, Maryland. Study # 981-83-122, 4/24/85). AC 222,293 Technical (Imazamethabenz-Methyl, lot# AC 4281-72, purity of 94.2%) was administered in the feed to 65 CD-1 mice/sex/dose at levels of 0, 130, 525 or 2100 ppm for 18 months. There was no apparent compound-related effect on mortality. Mean body weights were significantly lower than controls for high-dose males at weeks 4, 5 and 8 and for mid-dose males at weeks 4 and 8. High-dose females showed significantly lower body weights at the start of the experiment (day 0) and at weeks 1-5 and 8. Mean thyroid/parathyroid weights of the high-dose males were less than control at the 12-month sacrifice and greater than control by month 18. Mid-dose females had significantly elevated mean thyroid/parathyroid weights at 12-months; mid- and high-dose females had significantly higher thyroid/parathyroid weights at 18 months. At the 18-months, mean adrenal weights of the high-dose males and mid-dose females were significantly increased compared to controls. Microscopic lesions in the thyroid/parathyroid or adrenal glands showed no dose-related increases in either sex. Mean liver weights in the mid- and high-dose females were increased at 12 months, but not at the terminal sacrifice. There were no compound-related microscopic lesions in female livers at 12 months or study termination. Slight increased incidence of hepatic hemangiosarcomas (malignant tumors of endothelial origin) in high-dose males (3/46 vs. 0/53, p = 0.0967, Fisher-Exact Test) was not significantly different from control; not considered to be treatment-related. **Non-oncogenic NOEL(M/F)= 130 ppm (based on decreased body weight and increased absolute and relative thyroid/ parathyroid weights). **No adverse effects. Acceptable**. (Kellner, 1/6/98; revised, Leung, 7/15/98).

REPRODUCTION, RAT

** 024, 041; 157896, 166465; "A Three-Generation Reproduction Study With AC 222.293 in the Rat; A Three-Generation Reproduction Study with AC 222,293 in the Rat (Addendum-Pathology Report)" (Luke, N. (original report), R.E. Schroeder and R.E. Cimprich; Bio/dynamics, Inc., East Millstone, New Jersey, Project No. 82-2680, 4/30/85, 1/19/99 (addendum)). AC 222,293 technical (Imazamethabenz-Methyl, Lot# AC 4281-72, purity 94.2%) was administered in the diet at levels of 0, 250, 1000 or 4000 ppm to 12 male and 24 female Sprague-Dawley CD® rats/dose (2 matings per generation for 3 generations; each male mated to 2 females), with 12 males and 24 females/dose selected for the F1 mating. F0 animals were treated for 190 days prior to mating, and then during mating, gestation and lactation. At weaning, the F1 pups were given the same dosage as their parents for 203 days. Treatment continued for both sexes throughout the mating, gestation and lactation periods, until selection of F2 rats for third mating (treated 202 days before mating). Mean intake (mg/kg/day): low dose (M/F)- F0 (23.2/25.9), F1 (20.0/22.4) and F2 (22.0/25.2); mid-dose (M/F)-F0 (91.9/103.3), F1 (82.8/93.2), F2 (87.2/101.0); high-dose (M/F)-F0 (374.4/405.6), F1 (328.8/358.2), F2 (352.6/391.8); There were no deaths attributed to test-compound intake. Mean body weight data during the growth period for F0, F1 and F2 generations indicated no treatment effect on male body weight at any dose level. During the gestation/lactation periods, high-dose maternal body weight was slightly lower than control at all intervals tested. **Maternal NOEL=1000 ppm** (based on reduced weight gain during gestation/lactation). Food consumption showed no dose-related effects. All of the mating parameters (mating performance, pregnancy and fertility indices) were similar to control in all dosage groups and litter size showed no compound-related effects. At day 4, mean pup weight for the high-dose F1b litter was slightly lower than control (about 8.0% less); this difference was not statistically significant. At day 21 in the F3b litter, mean pup weight was slightly lower than control in both the mid- and high-dose groups, although this difference was statistically significant at the mid-dose only. **Reproductive NOEL= 4000 ppm** (no adverse effects). Study previously unacceptable (microscopic examinations were not reported on reproductive organs

from F0, F1 or F2 adults); information submitted on the microscopic examinations of the reproductive organs from the F2 adults which indicated no treatment-related effects); **Study acceptable**. (Kellner, 2/18/98, upgraded, Moore, 3/31/99)

TERATOLOGY, RAT

** 50502-023 157883 "Teratology Study with AC 222,293 in Rats" (MacKenzie, K. 833-Hazleton Raltech, Inc., Madison, WI, Study # 6123-102, 6/20/83). CL 222,293 technical (Imazamethabenz- Methyl, Lot# AC 4281-72, purity 94.2%, dissolved in corn oil) was administered via oral gavage to 25 pregnant CD® (SD)BR rats/dose at levels of 0, 250, 500 or 1000 mg/kg/day on days 6 through 15 of gestation. All surviving dams underwent cesarean sectioning on day 20 of gestation and the uteri were examined for the number and distribution of implantation sites, total resorptions and live and dead fetuses; the ovaries were examined for the number of corpora lutea. No effects on mortality, bodyweight, or macroscopic findings were reported. Clinical signs were limited to slightly increased incidence of salivation and pawing of the cage bottom in the mid- and high-dose group and moderately increased incidence of reddish-brown discharge around the mouth and nasal areas and dry-stained urogenital areas in the high-dose dams. **Maternal NOEL =500 mg/kg/day** (based on staining). There were no dose-related findings reported after cesarean section, fetal external or visceral surveys. Fetal skeletal evaluations revealed variations in the form of delayed ossification, but no dose-related major malformations. [No adverse effects]. **Developmental NOEL>1000 mg/kg**. **Acceptable**. Kellner, 2/4/98.

50502-023 157882 "Pilot Teratology Study with AC 222,293 in Rats" (MacKenzie, K., Hazleton Raltech, Inc., Madison, Wisconsin, Study # 6123-101, 1/18/83). CL 222,293 technical (Imazamethabenz-Methyl, Lot# AC 4281-72, purity 94.2%, dissolved in corn oil) was administered by oral gavage to 5 mated female Sprague-Dawley rats/dose at levels of 0, 125, 250, 500, 1000 mg/kg/day via oral gavage on days 6 through 15 of gestation. One dam from the 500 mg/kg dosage group was sacrificed on Day 13 of gestation because it showed signs of abortion. Despite this, necropsy revealed that it had 16 normally developing implants. Compound-related clinical signs were limited to salivation (all treatment levels, with dose-related increases) and there were no significant body weight or food consumption changes noted. Fetal data indicated no significant differences in the number of corpora lutea, implantation efficiency, litter size or in the number or percent of live or resorbed fetuses. Suggested dosage levels for the subsequent definitive study would include a 1000 mg/kg dose group. **Supplemental**. Kellner, 2/2/98.

TERATOLOGY, RABBIT

** 50502-023 157895 "A Teratology Study with AC 222,293 in Rabbits" (Adam, G., 833-WIL Research Laboratories, Inc., Ashland, OH, Project # WIL-35002, 9/26/83). CL 222,293 technical (Imazamethabenz-Methyl, Lot# AC 4281-72, purity 94.2%, dissolved in 0.5% aqueous methylcellulose) was administered via oral gavage to 18 artificially inseminated pregnant New Zealand White Rabbits/dose at levels of 0, 250, 500 or 750 mg/kg/day on days 6 through 18 of gestation. All surviving dams underwent cesarean sectioning on day 29 of gestation and the uteri were examined for the number and distribution of implantation sites, total resorptions and live and dead fetuses; the ovaries were examined for the number of corpora lutea. No effects on mortality, clinical signs or macroscopic findings were reported. Mid- and high-dose does showed slightly reduced mean body weight gain during days 6 through 12 and during the last three days (15-18) of treatment**. Maternal NOEL =250 mg/kg/day** (based on reduced weight gain at 500 and 750 mg/kg/day). There were no dose-related findings reported after cesarean section, fetal external or visceral surveys. Fetal skeletal evaluations revealed no dose-related variations or major malformations. [No adverse effects]. **Developmental NOEL=750 mg/kg**. **Acceptable.** Kellner, 2/6/98.

50502-023 157894 “A Range-Finding Teratology Study with AC 222,293 in Rabbits” (Adam, G., 833-WIL Research Laboratories, Inc., Ashland, OH, Project # WIL-35001, 3/23/83). CL 222,293 technical (Imazamethabenz-Methyl, Lot# AC 4281-72, purity 94.2%, dissolved in 0.5% aqueous methylcellulose) was administered once daily by oral gavage to 5 artificially inseminated New Zealand White rabbits/group from gestation days 6 through 18 at dose levels of 0, 50, 150, 300, 650 and 1000 mg/kg/day. On gestation day 29, all surviving animals were sacrificed. The high-dose does showed many toxic effects, with four of five dying between gestation day 8 and 26. Three of the deaths were considered treatment-related, with the fourth attributed to pasteurellois-induced septicemia. Marked maternal body weight losses in this group were accompanied by congested epithelial membrane in the stomach and passive congestion/biliary stasis with accentuation of lobular markings in the liver. Reduced defecation and urination were also observed in these females a few days prior to death. In the 650 mg/kg group, slight mean body weight losses were reported from gestation days 6 to12. Mean body weights and body weight gains were generally similar in the 50, 150 and 300 mg/kg/day groups throughout the gestation period when compared to control. After necropsy, no differences were reported in the mean number of viable fetuses, early resorptions, postimplantation loss, or corpora lutea at 650 mg/kg/day and lower dose groups (excessive mortality prevented these evaluations at the 1000 mg/kg level). Surveys of the remaining does revealed one instance of hydrothorax, hydrocele, small gallbladder and accessory spleen tissue at 650 mg/mg. Based on these data, the 1000 mg/kg/day dose level was considered excessive for the definitive developmental study in rabbits. Instead, the MTD was considered to be in the range of 750 mg/kg/day. **Supplemental.** Kellner, 2/5/98.

GENE MUTATION

50502-030 157935 “Bacterial/Microsome Reverse Mutation (Ames) Test on CL 222,293” (Allen, J. S. 842-American Cyanamid Co., Princeton, NJ. Project #0494, 8/11/82). CL 222,293 Technical (Imazamethabenz-Methyl, lot# and purity not specified) was tested for mutagenic potential in the Salmonella/Mammalian-Microsome Mutagenicity Assay at levels of 50, 158, 500, 1581 and 5000 ug/plate (triplicate plating) using *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and *E. coli* stain WP-2 uvrA$^-$ with and without metabolic activation (Aroclor 1254-induced rat liver S-9 fraction) in two trials (disc and plate incorporation tests were used). All colony counts in the plate incorporation tests and revertant patterns in the disc test indicated that the test article was negative for mutagenicity. **Unacceptable**. Possibly upgradeable with submission of data concerning test chemical (e.g., lot number, stability and purity) and the state of the background lawn (i.e., some assessment of chemical toxicity). Kellner, 1/13/98.

** 50502-030 157940, 157942, 157945 “Mutagenicity Testing of AC 222,293 in the *in vitro* CHO/HGPRT Mutation Assay” (Allen, J. and Johnson, E., 842-American Cyanamid Co., Princeton, New Jersey , Study # CHO4601, 6/9/83). AC 222,293 Technical (lot# AC 4281-72, purity of 94.2%) was tested for mutagenic potential in Chinese hamster ovary cells using the CHO/HGPRT mutation assay with and without metabolic activation (Aroclor 1254-induced rat liver S-9 fraction) at dose levels of 10, 50, 125, 250, 500, 750, 1000, 2500, 5000 µg/ml (with S-9) and 1, 10, 100, 250, 500, 1000, 5000 µg/ml (without S-9); 5 hr incubation at 37EC. None of the treated cultures consistently exhibited mutant frequencies of more than 40 mutants per 10^6 clonable cells, indicating that the test article was negative for mutagenicity. **Acceptable**. Kellner, 1/23/98.

CHROMOSOME EFFECTS

50502-030 157936 157938 “Dominant Lethal Study in Rats” (MacKenzie, K. 843-Hazleton Raltech, Inc., Madison, WI, Project #A93-3832, 7/11/83). CL 222,293 technical (Imazamethabenz-Methyl, Lot# AC 4281-71, purity 94.2%) was tested in the dominant lethal mutation assay by treating 10 male CD®(SD)BR rats/dose with 0, 100, 300 or 1000 mg a.i./kg by oral gavage for 5 days. Each male was mated to 2 nontreated virgin females/week for 8 weeks and the mated females were sacrificed about 14 days after mating to evaluate dominant

lethality. Corpora lutea (Cl) and numbers/distribution of implants were reported. All treated males showed moderate to severe salivation during the dosing period. Although there was a decrease in the mating index and implantation efficiency in all groups on the first mating, these changes did not show a dose-response relationship. In the following seven weeks, there were no significant differences between control and treated groups in mating index, number and percent of viable or nonviable implants, number of corpora lutea or implantation efficiency. Positive control data in 157938. **Unacceptable** (dose selection not justified). Kellner, 1/21/98.

** 50502-030 157947 "Chromosome Aberrations in Chinese Hamster Ovary Cells with AC 222,293" (Thilagar, A. 843-Microbiological Associates, Inc., Rockville, Maryland, Study # 981-82-149, 1/19/83). AC 222,293 Technical (lot# AC 4281-72, purity of 94.2%) was tested for clastogenic potential in Chinese hamster ovary cells at concentrations of 250, 500, 1000, 2000 and 4000 ug/ml with and without metabolic activation (Aroclor 1254 induced rat liver microsomal enzyme). In the absence of S-9 activation, cells were exposed for 12-14 hours; in the presence of S-9 activation cells were exposed for 2 hours. Fifty metaphase spreads/duplicate flask or 100 metaphases/dose were scored. Results from the assay both with and without S-9 activation were negative for chromosome aberrations. **Acceptable**. Kellner, 1/27/98.

DNA DAMAGE

** 50502-030 157951 "Unscheduled DNA Synthesis in Primary Cultures of Rat Hepatocytes" (Thilagar, A. , 844; Microbiological Associates, Inc., Rockville, MD., Study #981-82-148, 1/19/83). AC 222,293 Technical (Imazamethabenz-Methyl, lot# AC 4281-72, purity of 94.2%) was tested for potential DNA damage in primary rat liver cell cultures (from adult male Sprague-Dawley rats) using concentrations of 0, 31.25, 62.5, 125, 250, or 500 µg/ml with 3 plates/dose being exposed to the test article for 18 hours. Nuclear grains were counted in 25 cells in each of three cultures/dose. The mean net nuclear grains per nucleus for the 31.25, 62.5, 125, 250, and 500 µg/kg groups were 0.29, 0.66, 0.40, 0.43, 0.60, respectively. These values were comparable to the mean control values of 0.46 (WME) and 0.30 (1% DMSO). **No Adverse Effects**. **Acceptable.** Kellner, 1/28/98.

NEUROTOXICITY

Not required at this time.

SUBCHRONIC

(Oral)

019; 157878; "CL 222,293: A 13-Week Rat Feeding Study" (Fischer, J.E., American Cyanamid Company, Agricultural Research Division, Princeton, NJ, Report No. AX83-7, 7/14/83). 821. CL 222,293 (Lot No. AC 4093-8, purity=91.9%) was admixed to the feed at concentrations of 0, 1000, 5000, or 10,000 ppm and fed to 30 Charles River CD$^{(R)}$, Sprague-Dawley derived, [Crl:CD(SD)BR] rats per sex per dose level continuously for a period of 13 weeks (10 animals per sex per dose level were sacrificed at days 44-45 for clinical chemistry). No animals died. No treatment-related systemic clinical signs were observed. Statistically significant increases in mean SGOT levels in males and in mean SGPT levels in females at 10,000 ppm were observed. A statistically significant increase in mean relative liver weights in males at 10,000 ppm was observed at termination. Also, a statistically significant increase in mean relative weights of the testes in treated males was observed but was not considered to be toxicologically significant in the absence of abnormal histological changes. Microscopic examination revealed diffuse hepatic cell hypertrophy in males at 5000 and 10,000 ppm. **No adverse effects.** NOEL (M)=82.4 mg/kg/day (1000 ppm) (based on diffuse hypertrophy of hepatic cells), NOEL (F)=442.5 mg/kg/day (5000 ppm) (based on a statistically significant

increase in mean SGPT levels). **Unacceptable and not upgradeable** because no ophthalmological examinations were performed on the test animals. (Corlett, 1/2/98)

(Dermal)

020; 157879; "Subacute Dermal Study with AC 222,293 Lot No. 4281-72 in Rabbits" (Madison, W.A., Hazleton Laboratories America, Inc., Madison, WI, Study No. 6123-119, 7/19/84). 822. AC 222,293 (Lot No. 4281-72, purity=94.2%), moistened with deionized water, was applied to the clipped skin of 6 New Zealand White rabbits per sex per dose at concentrations of 0, 50, 100, or 200 mg/kg/day for 6 hours per day, 5 days per week for 3 weeks. No animals died. No treatment-related systemic clinical signs were observed. At the test sites, treatment-related erythema and edema were observed at all dose levels and treatment-related desquamation and fissuring were observed at the 50 mg/kg/day dose level. A statistically significant increase in mean glucose levels in females at 200 mg/kg/day was observed but was not considered to be toxicologically significant because it was within baseline values. Macroscopic examination revealed thickened skin with red and/or raised areas at the test site at all dose levels. Microscopic examination revealed treated skin with superficial crusting, microabscess(es), epidermal hyperplasia, and chronic dermatitis at 50 mg/kg/day. **No adverse effects.** NOEL (systemic, M/F)=200 mg/kg/day (no systemic effects at HDT), NOEL (dermal, M/F)< 50 mg/kg/day (based on red areas, raised areas, and thickened skin at the test site)**. Acceptable.** (Corlett, 12/17/97)

012; 157818; "Twenty-One Day Dermal Toxicity Study with AC222,293 300LC in Rabbits" (Deskin, R. et al., Battelle, Columbus Laboratories, Columbus, OH, Project No. N0740-4700, 6/6/85). 822. AC 222,293 300LC (Lot No. AC4778-53, 30.5% a.i.), dissolved in distilled water, was applied to the clipped skin of 6 New Zealand White rabbits per sex per dose at concentrations of 0, 50, 250, or 1000 mg/kg/day for 6 hours per day, 5 days per week for 3 weeks. No animals died. No treatment-related systemic clinical signs were observed. Slight to marked atonia, slight to moderate fissuring, and slight to marked desquamation of the treated skin were observed in animals at 500 and 1000 mg/kg/day. A statistically significant decrease in mean direct bilirubin levels in males at 500 and 1000 mg/kg/day was observed. A statistically significant increase in mean relative brain weights in females at 1000 mg/kg/day was observed but was not considered to be toxicologically significant in the absence of abnormal histological changes. Macroscopic examination revealed treated skin exhibiting a white crusty material in 1 animal at 250 mg/kg/day and in 21/24 animals at 500 and 1000 mg/kg. Microscopic examination revealed treated skin exhibiting hyperkeratosis, acanthosis, and/or chronic inflammation in all animals. **No adverse effects.** Systemic NOEL (M/F)=1000 mg/kg/day (no effects at HDT), Dermal NOEL (M/F)< 250 mg/kg/day (based on hyperkeratosis, acanthosis, and inflammation of the treated skin). **Supplemental study** (test article, a liquid, was dissolved in distilled water). (Corlett, 12/12/97)

METABOLISM STUDIES

50502-030 157957 "Herbicide CL 222,293: Disposition and Metabolic Fate of the Carbon-14 Labeled Isomers CL 239,589 and CL 252,767 in the Rat" (Chiu, T. 851-, American Cyanamid Co., Princeton, NJ Project # 0494, 10/13/83) Para- and meta-substituted isomers of CL 222,293 (Imazamethabenz-Methyl), (CL 239,589 and CL 252,767 labeled at the carboxyl carbon, with specific activities of 19.3 and 18.9 µCi/mg, respectively, both having a radiopurity of 99+% in corn oil) were given separately to 11 male Sprague-Dawley rats (^{14}C-CL 239,589) or 13 rats (^{14}C-CL 252,767) by oral gavage at 25 mg/kg. About 78 and 77%, respectively was excreted in the urine within 24 hours. Fecal elimination was 19 and 13% during this period, respectively. Total ^{14}C-CL 239,589 residues (ppm equivalents) in liver, kidney, muscle, fat and blood at 24 h were 0.44, 0.06, 0.05, 0.06 and 0.04 ppm, respectively (all <0.05 ppm at 96 h).

These values for ^{14}C-CL 252,767 were 0.33, 0.27. 0.12, 0.13 and 0.39 ppm, respectively with all <0.05 ppm at 48 h. Major metabolites from ^{14}C-CL 239,589 in tissue extracts were mainly the acid CL 252,768 and its p-hydroxymethyl analog, CL 119,543, which accounted for 89.7 and 5.8% of the extractable activity, respectively, in liver; 16.9 and 58.5% in muscle; and 16.3 and 77.2% in fat; after ^{14}C-CL 252,767 treatment, metabolites in extracts of liver, kidney, muscle and fat were CL 222,575 (65.2, 42.0, 45.9 and 81%, respectively) and CL 119,610 (4.2, 13.6, 45.2 and 17.6%, respectively). Major urinary metabolites (with % distribution) for ^{14}C-CL 239,589 were CL 252,768 (79.2), CL119,543 (12.1) and CL 119,544 (2.6); for ^{14}C-CL 252,767, these were CL 222,575 (82.7), CL 119,610 (4.4) and CL 119,611 (3.2). Suggested degradation pathways of ^{14}C-CL 239,589 and ^{14}C-CL 252,767 were hydrolytic cleavage of the methyl ester linkage and hydroxylation of the methyl group in the benzene ring, leading to formation of the parent acid as the major metabolite, with hydroxymethyl analog of the acid, and hydroxymethyl analogs of the parent ester as the minor metabolites. **Unacceptable** (only one dose level used, set of organs assayed for radiolabel incomplete, no females dosed and no multiple-dose group included). **Not upgradeable**. Kellner, 1/29/98.

040; 164047; "Metabolism Study with AC 222,293 in Albino Rats; Imazamethabenz (AC 222,293): Metabolic Fate of the Carbon-14 Labeled Regioisomers CL 239,589 and CL 252,767 in Albino Rats"; (M. Spindler and T.M. Lee *et. al.*; Hazleton Laboratories America, Inc., Madison, WI and American Cyanamid Company, Agricultural Research Division, Princeton, NJ; Report No. PD-M Volume 26-1; 12/23/87 and 6/21/89); Male and female rats were dosed by intravenous injection (Group A) or orally by gavage (Groups B, C and D) with either AC 222,293-p-C^{14} (spec. act.: 25.650 µCi/mg (Groups A1, B1, C1) or 2.75 µCi/mg (Group D1), radiochemical purity: 98%) or AC 222,293-m-C^{14} (spec. act.: 28.545 µCi/mg (Groups A2, B2, C2) or 2.577 µCi/mg (Group D2), radiochemical purity:99%). Five animals/sex/group were treated (except for the B1 females in which only 4 animals were dosed due to limited quantity of test material). Groups A1 and A2 were injected with 1.0 mg/kg of the respective radiolabeled material. Groups B1 and B2 were dosed with 10 mg/kg, Groups C1 and C2 were pretreated with 14 daily doses of unlabeled test material, AC 222,293-m-p-C^{12} (purity: 96.4%), followed by 10 mg/kg of labeled material and Groups D1 and D2 were dosed with 400 mg/kg of the respective radiolabeled isomer. Urine and feces samples were collected up to 7 days from all of the test animals. Approximately 80% of the administered dose was recovered in the urine. The excretion profiles were quite similar regardless of the route of dosing. The fraction of the administered dose excreted within 24 hours of dosing ranged from 90 to 95%, indicating the dose was rapidly absorbed in the gastrointestinal tract. Repeated dosing or treatment with low or high dosing levels did not alter the excretion profiles. There was no apparent sex-related difference in the uptake, metabolism or excretion of the test material. There was no apparent difference in the uptake, metabolism and excretion of either isomer. The predominant metabolite was the p- or m-toluic acid moieties which constituted from 50 to 60% of the administered dose. Other sites of metabolism included the a-hydroxylation of p-or m-toluic acid and the p- or m-toluic acid, methyl ester moieties and the further oxidation of these methyl groups to the carboxyl groups. Residue levels of radiolabel were quite low 7 days after dosing with 0.04 to 0.34% of the administered dose recovered in the carcass. **Study acceptable.** (Moore, 3/30/99)