CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH

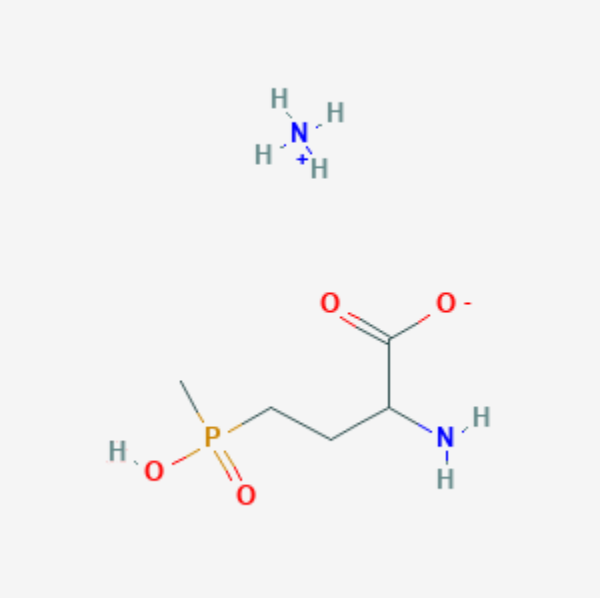
SUMMARY OF TOXICOLOGY DATA

GLUFOSINATE- AMMONIUM (Racemate), L-GLUFOSINATE - AMMONIUM

Chemical Code # 3946, 6544 **Document Processing Number (DPN)**: 52007, 53586
SB 950 # NA
12/21/94
Revised: 6/26/95, 11/23/20

IUPAC Name: (RS)-2-amino-4-[hydroxy(methyl)phosphinoyl]butyric acid, (S)-2-amino-4-[hydroxy(methyl)phosphinoyl]butyric acid[1]
CAS No.: 77182-82-2 (DL-glufosinate), 73777-50-1 (L-glufosinate)
Chemical: MW 198.16 g[1]
Vapor Pressure (log P): 2.33 x 10^{-7} mm Hg[2]
Melting Point: 215.0° C[1]
Boiling Point: decomposes before boiling[2]
Density: 1,4 g/ml[1]
Oil/Water Partition Coefficient: (log P): -4.01[2]
Water solubility:1370 g/l [1]
Use: Herbicide

[redacted] 12/7/2020



[1] Volume No. 53586-0012, rec. no. 324452
[2] https://sitem.herts.ac.uk/aeru/ppdb/en/Reports/372.htm
Source of chemical structure: https://pubchem.ncbi.nlm.nih.gov/compound/Glufosinate-ammonium#section=Chemical-and-Physical-Properties

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SUMMARY:

The L-glufosinate isomer has been identified as the active component of the molecule in which the mechanisms of action are inhibition of glutamine synthetase and activation of the N-methyl-D-aspartate receptor in the brain. A majority of the toxicity studies on file with the department are on the DL racemate. The L-isomer and the racemate are qualitatively similar in their toxicity profile as the racemate is comprised of a 50:50 ratio of the two isomers. The purity of the DL glufosinate used in the guideline studies ranged from 92.1 to 97.2%. Thereby the L-glufosinate isomer comprised 46 to 48.5% of the test material in these studies. In a comparison of the relative toxicity of the racemate to the L-isomer, the rat and mouse oral LD50 values for the racemate are 2000 and 1600 mg/kg for the male and female rats and 431 and 416 for the male and female mice, respectively for the purified isomer. For L-glufosinate the values were 709 and 669 mg/kg for the male and female rats and 137 and 122 mg/kg for the male and female mice, respectively.

Glufosinate-ammonium is rapidly eliminated essentially unchanged from the body following oral or iv administration. No sex differences in the excretion route or rate were reported. Over 92% of the administered radioactivity is eliminated within 48 hours. Glufosinate-ammonium is eliminated in the feces (81-89%) and urine (7-14%) after oral dosing and the reverse is true after iv dosing. Approximately 12% of (d/l)-glufosinate was absorbed at a treatment of 2 mg/kg. No evidence of bioaccumulation is evident following multiple dosing. Highest concentrations of radioactive residues were found in liver and kidney. .

The acute toxicity hazard profile for both chemical entities are Categories III or IV. Neurotoxicity is the significant endpoint of concern. In a rat 4-week inhalation toxicity study, signs of neurotoxicity were evident at 0.02 mg/l. A treatment of 300 mg/kg/day resulted in signs which included convulsions with jumping and rolling spasms in the rat 4-week dermal toxicity study. In the dog chronic toxicity study, a treatment level of 8.5 mg/kg/day induced signs of stiff gait and tremors. Retinal atrophy was noted in the eyes of the rats at a treatment level of 5000 ppm in the rat combined chronic toxicity and oncogenicity study along with an increased incidence of histocytic sarcoma. Effects on fetal survival were also identified in the rat reproductive and rabbit developmental toxicity studies at a treatment level as low as 2.5 mg/kg/day.

Toxicology one-liners are attached.

All record numbers for the above study types through 324546 (Document No. 53586-0030) were examined. This includes all relevant studies indexed by DPR as of 11/23/20.

In the 1-liners below:
** indicates an acceptable study.

File name: T201123
Revised by [redacted], 11/23/20

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

D/L Glufosinate-Ammonium

METABOLISM AND PHARMACOKINETICS

Metabolism, Rat

011; 126679; "HOE 39866 Ammonium-DL-homoalanin-4-yl(methyl)phosphinate - Summary on Pharmacokinetics and Metabolism in Animals" (M. Schwable-Fehl, Hoechst AG, Frankfurt, Germany, Report # A34283, 11/10/86); maximum blood concentrations were reached as early as 1 to 4 hours after oral or dermal exposure in rats and dogs; analysis of urine and fecal extracts showed that 80 to 90% of the excreted radioactivity consisted of the unchanged parent compound; HOE 61517, a metabolite was also detected in urine and feces, but it did not exceed 5 to 8 % of the administered radioactivity; radioactivity was not bound or adsorbed to red blood cells; liver and kidney show the highest level of radioactivity; repeated dosing did not lead to any accumulation of the test material; **supplemental**; ([redacted], 12/1/94).

011; 126680; "HOE 39866-^{14}C Study on Kinetics and Residue Analyses in Rats" (Kellner and Eckert; Radiochemical Lab., Hoechst AG, Franfurt, Germany, Report # A28927, 8/17/83); HOE 39866-[2-^{14}C] (Batch # 8110 I, 97% radiochemical purity, 353 mCi/mmol) administered orally or intravenously at 2 mg/kg to 5 Wistar rats/dose; blood levels after oral dosing were low and detected in males and females for up to 3 and 8 hours, respectively; however, the blood levels after iv dosing could be followed for up to 2 days; test material eliminated mainly (81-89%) in the feces and urine (7-14%) after oral dosing; however, after iv administration, elimination was predominantly renal (85-93%) with fecal elimination ranging from 8-18%; liver and kidney showed the highest concentrations of radioactivity; no radioactivity was detected in expired air; absorption after oral administration is low (8% in males and 13% in females); **supplemental**; ([redacted], 12/2/94).

011; 126681; "HOE 39866-^{14}C, Metabolism in Male and Female Rats After a Single Oral Administration of 2 mg/kg body Weight Each" (O. Wink, et. al., Hoechst AG, Frankfurt, Germany, Report # A33895, 7/24/86); HOE 39866 OH ZB98 0001 (98.6% purity), HOE 39866-[3,4-^{14}C] (49.41 mCi/g, radiochemical purity not provided) administered orally to 10 rats/sex at 2 mg/kg; 2 rats/sex served as control; no sex differences in the excretion route or rate was observed; 84.4% of the administered radioactivity was eliminated via feces and 7.3% via urine during the first 24 hours; highest concentrations of radioactivity were detected in liver and kidney; analyses by high pressure liquid chromatography demonstrated that 100% of the radioactivity in the urine and more than 86% of the radioactivity in the feces was represented by unchanged parent compound HOE 39866; **supplemental;** ([redacted], 12/5/94).

011; 126682; "HOE 39866-^{14}C, Metabolism in Male and Female Rats After Repeated Oral Administration of 2 mg/kg Body Weight Each on 15 Consecutive Days" (O. Wink, et. al., Hoechst AG, Frankfurt, Germany, Report # A33893, 7/30/86); 10 rat/sex were pretreated for 14 daily oral doses of nonlabeled HOE 39866 at 2 mg/kg prior to be treated with a single oral dose of HOE 39866-[3,4-^{14}C] (43.58 mCi/g, radiochemical purity not provided); 2 rats/sex served as controls; no sex differences in the excretion route or rate were reported; HOE 39866 was rapidly excreted with 77.0% and 4.4% of the administered radioactivity detected in feces and urine, respectively, during the first 24 hours; 80% of the radioactivity in feces and urine consisted of unchanged HOE 39866; two main metabolites (HOE 61517 and HOE 86486) were found in

urine and feces and comprised 8% and 4% of the administered dose, respectively; highest concentrations of radioactivity were detected in liver and kidney; no evidence of bioaccumulation was evident after multiple dosing regimen; **supplemental**; [redacted], 12/6/94).

011; 126683; "HOE 39866-^{14}C: Studies of Kinetics and Residue Determinations in Male and Female Rats After Repeated Oral Doses of 2 mg/kg Body Weight X Day on 15 Consecutive Days" (H.-M. Kellner & H.G. Eckert, Hoechst AG, Frankfurt, Germany, Report # A33975, 11/8/85); 5 rat/sex were pretreated for 14 daily oral doses of nonlabeled HOE 39866 (HOE 39866 OH ZB98 0001, 98.6% purity) at 2 mg/kg prior to be treated with a single oral dose of HOE 39866-[3,4-^{14}C] (21.87 mCi/g, 97% radiochemical purity); after oral dosing, excretion took place mainly via feces (90%) and urine (9%); 92% of the administered radioactivity was eliminated from the body after 24 hours; elimination in the feces and urine is biphasic with half-lives of 5 - 6 hours and 1.3 - 2 days; 7 days after the final dose, radioactive residues detected in kidney, liver, testes, and spleen (females); no evidence for bioaccumulation; **supplemental**; ([redacted], 12/6/94).

012; 126684; "HOE 39866-^{14}C, Metabolism Study on Female Rats after a Single Oral Dose of the Active Ingredient" (E. Dorn, et. al., Hoechst AG, Frankfurt, Germany, Report # A25656, 8/1/83); HOE 39866-[3,4-^{14}C] (HOE 39866 OH ZE98 0002, Batch 11076a, 98% radiochemical purity, 4.91 mCi/g) in water was administered by oral gavage to 20 female SPF Wistar rats at 10 mg/kg; within 48 hours, 82% and 10.6% of the administered radioactive dose was eliminated via feces and urine, respectively; after oral administration, 90% of the administered dose is excreted unchanged and 10% was metabolized prior to excretion; HOE 61517 or 3-methylphosphinico-propionic acid was a major metabolite detected in urine and feces; **supplemental**; ([redacted], 12/6/94).

012; 126685; "HOE 39866-^{14}C Metabolism and Residue Determination in Female Rats After Repeated Oral Administrations of 10 and 100 mg/kg Body Weight/Day, Respectively" (M. Schwalbe-Fehl, et. al., Hoechst AG, Frankfurt, Germany, Report # A33268, 5/13/86); 15 female SPF Wistar rats/dose were pretreated with 10 daily oral doses of HOE 39866 (HOE 39866 OH ZB98 0001, 19.6% purity) at 10 or 100 mg/kg prior to being treated with a single oral dose of HOE 39866-[3,4-^{14}C] (43.6 mCi/g, 99% radiochemical purity); maximum blood concentrations were reached within 1 hour after administration and were almost linear with dose level; administered radioactivity was rapidly excreted mainly via feces (73 - 103% of the administered dose) and less than 5% was eliminated via urine; repeated dosing did not influence the route and rate of excretion; 94% of the excreted radioactivity consisted of unchanged parent compound HOE 39866; two metabolites, HOE 61517 and HOE 86486, consisting of 5% and 1% of the excreted radioactivity were detected in feces and urine; no bioaccumulation of radioactivity in the liver, kidneys, spleen and brain were noted after multiple dosing; **supplemental**; [redacted], 12/7/94)

012; 126686; "HOE 39866-^{14}C Metabolism in Male and Female Rats After A Single Administration of 30 mg/kg Body Weight Each" (O. Wink, et. al., Hoechst AG, Frankfurt, Germany, Report # A33894, 5/8/86); HOE 39866 [3,4-^{14}C] mixed with unlabeled HOE 39866 (HOE 39866 OH ZB99 0002, 99.5% purity) in distilled water (21.86 mCi/g) was administered orally at 30 mg/kg to 20 SPF Wistar rats/sex; no relevant sex differences in metabolism or excretion were observed; the administered radioactivity is mainly eliminated via feces; more than 70% of the dose was excreted during the first 48 hours; approximately 15% of the administered dose was excreted in the urine; by HPLC more than 95% of the radioactivity in feces and urine consisted of unchanged HOE 39866; one metabolite, HOE 61517 was identified in urine and feces extract; **supplemental**; ([redacted], 12/7/94)

012; 126687; "HOE 39866-^{14}C: Studies of Kinetics and Residue Determinations in Rats Following Oral Administration of 30 mg/kg Body Weight" (H.M.- Kellner and H.G. Eckert, Hoechst AG, Frankfurt, Germany, Report # A33239, 11/13/85); HOE 39866 [3,4-^{14}C] mixed with unlabeled HOE 39866 (HOE 39866 OH ZB99 0002, 99.5% purity, final specific activity 2.0 and 2.12 mCi/g after dilution 1:10 with unlabelled HOE 39866) in distilled water was administered orally at 30 mg/kg to 5 SPF Wistar rats/sex; no sex difference in the route or rate of excretion after oral administration; elimination is rapid; 84 to 88% the administered dose is excreted in feces and 7 to 12% via urine; by 24 hours, 93% and 92% of the total radioactivity was eliminated from the body; 1/2 a and t1/2b for fecal and urine excretion were estimated to be 5 to 7 hours and 1.5 days, respectively; **supplemental**; ([redacted], 12/8/94).

012; 126688; "HOE 39866-^{14}C Metabolism and Residue Determinations in Rats After Single Oral Administration of 800 mg/kg Body Weight" (M. Schwalbe-Fehl, et. al., Hoechst AG, Frankfurt, Germany, Report # A32953, 12/17/85); HOE 38966 [3,4-^{14}C] mixed with unlabeled HOE 39866 (HOE 39866 OH ZB99 0002, 99.5% purity) in potato starch (final specific activity 1.58 mCi/g) was administered by gavage to 9 SPF Wistar rats/sex at 800 mg/kg; 3 rats/sex were sacrificed at 6 and 24 hours after dosing and another 3 rats/sex sacrificed at 24 hours for the determination of radioactivity in blood; unchanged HOE 39866 was excreted mainly in feces and urine; 24 hours after dosing, 21 - 24% and 3% of the administered radioactivity was detected in feces and urine, respectively; two metabolites, HOE 61517 and HOE 86486, were found in urine and extracts of liver and kidneys; these metabolites are exclusively excreted via urine; no sex-related differences in metabolism or excretion were observed; **supplemental**; ([redacted] 12/8/94).

012; 126689; "Pharmacokinetic Study with ^{14}C-HOE 39866 on Various Organs of Male and Female Beagle Dogs and Excretion Pattern of Radioactivity After Single Oral Administration of the Test Article" (H. Ellgehausen, RCC, Umweltchemie AG, Itingen, Switzerland, Report # A34282, 4/28/86); aqueous solution of HOE 39866 [3,4-^{14}C] and unlabeled HOE 39866 (HOE 39866 OH ZC95 0001, 95.3% purity) (2.443 mCi/g, >98% radiochemical purity) was administered orally by gelatin capsule to Beagle dogs at 0 (untreated, 3M/3F) or 8 (2M/2F) mg/kg; almost complete excretion of the administered radioactivity was observed at 24 hours and no sex difference in excretion rate; 9.5% and 82.4% of the radioactivity was excreted in urine and feces; maximum blood levels were achieved in 2 to 4 hours after dosing with terminal half lives of 9.2 and 14.1 hours for males and females,respectively; liver and kidney contain the highest concentrations of radioactivity at 6 and 24 hours after dosing; analysis of urinary radioactivity and of the extractable radioactivity in feces, kidney and liver and plasma showed that predominantly the unchanged parent compound was present; in addition to HOE 39866, a metabolite, HOE 61517, was detected in urine; **supplemental;** ([redacted], 12/9/94).

013; 126690; "28-Day Oral Toxicity (Capsule) Study in the Dog with HOE 39866 Technical (Code HOE 39866 OH ZC95 0001) and ^{14}C-HOE 39866" (K. Sachsse et. al., Research & Consulting Company AG, Itingen, Switzerland, Report # A34048, 9/16/86); unlabeled HOE 38966 OH ZC95 0001 (95.3% purity) was administered orally by capsule to 6 Beagle dogs/dose for 18 days followed by ^{14}C-HOE 39866 (98% purity, 148.8 mCi/mole) for 10 days at 0, 1, or 8 mg/kg; No animals died during the study; high dose animals showed marginal signs of increased motor activity indicative of increased CNS stimulation, but no changes in excitatory and inhibitory amino acid transmitters were reported; no treatment-related effects in ophthalmology, hematology, urinalysis, clinical chemistry and necropsy were noted; examinations of tissues of the brain (midbrain and cerebellum) and liver from high dose animals indicated a slight to moderate inhibition of glutamine synthetase (47.3 - 72.1 %, $p < 0.05$); after

2 to 5 days of daily administration of ^{14}C-HOE 39866, steady state conditions between absorption and elimination was achieved; significant amounts of radioactivity were found in the midbrain (0.181 - 0.573 µg/g), brain stem (0.206 - 0.455 µg/g) and cerebellum (0.139 - 0.263 µg/g); liver and kidney contain the highest amounts of radioactive residues; elimination of radioactivity is rapid (elimination half life = 24 hours); 96.5 to 98.4% of the dose totally administered to animals at both levels were excreted; **supplemental**; ([redacted], 11/30/94).

Glufosinate-ammonium is rapidly eliminated essentially unchanged from the body following oral or iv administration. No sex differences in the excretion route or rate were reported. Over 92% of the administered radioactivity is eliminated within 48 hours. Glufosinate-ammonium is eliminated in the feces (81-89%) and urine (7-14%) after oral dosing and the reverse is true after iv dosing. No evidence of bioaccumulation is evident following multiple dosing. Highest concentrations of radioactive residues were found in liver and kidney. .

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat

001; 126612; "Acute Oral Toxicity of Hoe 39866-active ingredient (Code: Hoe 39866 O H AS201) to the Male Rat" (Author: Mayer et al, Hoechst-Roussel Agri-Vet Co., Pharma Forschung Toxikologie, Frankfurt, Germany, Report No. 587/80, 11/13/80); 811; HOE 39866 O H AS201 (purity=92.1%) dosed by gavage as a 25% w/v solution in deionized water; 10 males/dose; single doses of 630, 1000, 1600, 2500, 3150 mg/kg; mortalities- 0/10, 1/10, 2/10, 7/10, 9/10, respectively; observations- 630 mg/kg group: no clinical signs; other dose groups: hyperreflexia, Dalrymple's sign, exophthalmus, squatting, straddled legs, retracted abdomen or flank, hyporeflexia, bristled hair, poor grooming, ataxia, bloodcrusted eyes, and decreased, irregular respiratory rate; necropsy- mortalities: dark (brown) discolored liver and dark, discolored adrenals; survivors: no abnormal macroscopic findings; NOEL (M)=630 mg/kg; LD_{50} (M)=2000 (1600-2490) mg/kg; Category not determined; **Unacceptable and not upgradeable** (only male test animals used). ([redacted], 8/10/94)

001; 126613; "Acute Oral Toxicity of Hoe 39866-active ingredient (Code: Hoe 39866 O H AS201) to the Fe**m**ale Rat" (Author: Mayer et al, Hoechst-Roussel Agri-Vet Co., Pharma Forschung Toxikologie, Frankfurt, Germany, Report No. 588/80, 11/13/80); 811; HOE 39866 O H AS201 (purity=92.1%) dosed as a 25% w/v solution in deionized water; 10 females/dose; single doses of 630, 1000, 1600, 1800, 2000 mg/kg; mortalities- 0/10, 0/10, 4/10, 9/10, 9/10, respectively; observations- 630 and 1000 mg/kg groups: no clinical signs; other dose groups: passiveness, disequilibrium, ataxia, hyperreflexia, high-legged posture, abdominal and lateral position, squatting, straddled legs, trembling, convulsions, clonic convulsions, rolling spasms, bristled hair, poor general condition, bloodcrusted eyes and snouts, and decreased, irregular respiratory rate; necropsy- mortalities: dark brown, discolored liver, dark, discolored adrenals, and, in some instances, blood congested lungs; survivors: no abnormal macroscopic findings; NOEL (F)=1000 mg/kg; LD_{50}(F)=1620 (1190-1740) mg/kg; Category not determined; **Unacceptable and not upgradeable** (only female test animals used). ([redacted], 8/10/94)

001; 126614; "Acute Oral Toxicity of Hoe 39866-active ingredient (Code: Hoe 39866 O H AS201) to the Male Mouse" (Author: Mayer et al, Hoechst-Roussel Agri-Vet Co., Pharma Forschung Toxikologie, Frankfurt, Germany, Report No. 547/80, 10/30/80); 811; HOE 39866 O H AS201 (purity=92.1%) dosed by gavage as a 5% w/v solution in deionized water; 10 males/dose; single doses of 315, 500, 800 mg/kg; mortalities- 2/10, 6/10, 10/10, respectively; observations- ataxia, bizarre movements, squatting, abdominal position, clonic convulsions, convulsive jumping and rolling spasms, "Straub" phenomenon, bristled hair, poor general

condition, and irregular, jerky respiration; necropsy- mortalities that died prior to day 2: translucent and in some instances marked livers and blood congested lungs; mortalities that occurred after day 2 and the survivors: no abnormal macroscopic findings; LD_{50} (M)=431 (337-533) mg/kg; Category not determined; **Unacceptable and not upgradeable** (only male test animals used). ([redacted], 8/11/94)

001; 126615; "Acute Oral Toxicity of Hoe 39866-active ingredient (Code: Hoe 39866 O H AS201) to the Fe**m**ale Mouse" (Author: Mayer et al, Hoechst-Roussel Agri-Vet Co., Pharma Forschung Toxikologie, Frankfurt, Germany, Report No. 546/80, 11/3/80); 811; HOE 39866 O H AS201 (purity=92.1%) dosed as a 5% w/v solution in deionized water; 10 females/dose; single doses of 315, 500, 800 mg/kg; mortalities- 1/10, 8/10, 10/10, respectively; observations- ataxia, bizarre movements, squatting, lateral position, clonic convulsions, saltatory and rolling spasms, "Straub" phenomenon, increased salivation, bristled hair, poor general condition, and irregular, jerky respiration; necropsy- mortalities that died in the first days after treatment: translucent livers with hepatic marking at the edge in some instances and pulmonary plethora; mortalities that occurred after the first days and the survivors: no abnormal macroscopic findings; LD_{50} (F)=416 (345-498) mg/kg; Category not determined; **Unacceptable and not upgradeable** (only female test animals used). ([redacted], 8/11/94)

001; 126616; "Acute Oral Toxicity of Hoe 39866-active ingredient (Code: Hoe 39866 O H AS201) to the Male and Female Beagle Dog" (Author: Mayer et al, Hoechst-Roussel Agri-Vet Co., Pharma Forschung Toxikologie, Frankfurt, Germany, Report No. 543/80, 10/16/80); HOE 39866 O H AS201 (purity=92.1%) dosed by gavage as a 10% w/v solution in deionized water; 1 animal/sex/dose; single doses of 200 and 400 mg/kg; mortalities - males: 0/1, 1/1, respectively; females: 0/1, 1/1, respectively; observations- squatting, benumbedness, trembling, diarrhea, disequilibrium, abdominal position, retracted flank, hyporeflexia, increased lacrimation, salivation, rhinorrhea, paresis or paralysis of the hindlegs, occasional quick turning of the body on the hindlegs, extension spasms, marked dyspnea accompanied by loud cries, bluish tongues, reddened ocular and oral mucosa, ataxia, emesis, noisy jerky respiration, tonoclonic convulsions, orthotonus, opisthotonous, and miosis; necropsy- mortalities: extreme filling of the gall bladder, outer gastric wall with dark red spotted areas, accumulation of reddish-black-brown liquid in the gastric lumen, ulcerous gastroenteritis and swollen liver; **Supplemental study** (Beagle dog used as test animal). ([redacted], 8/11/94)

Acute dermal toxicity

001; 126617; "Acute Percutaneous Toxicity of Hoe 39866-active ingredient (Code: Hoe 39866 O H AT203) to the Male Rat" (Author: Mayer et al, Hoechst-Roussel Agri-Vet Co., Pharma Forschung Toxikologie, Frankfurt, Germany, Report No. 495/82, 9/2/82); 812; HOE 39866 O H AT203 (97.2% a.i.) applied to the shaved skin as a 40% or 80% w/v solution in deionized water; 24 hr exposure, occluded; 6 males/dose; doses of 2000 and 4000 mg/kg; no mortalities; observations- 2000 mg/kg group: no clinical signs; 4000 mg/kg group: hyperactivity, Dalrymple's sign, convulsions, retracted abdomen, retracted flanks, increased salivation, and aggressiveness; necropsy- dark discoloration of the kidneys in both groups; LD_{50} (M)>4000 mg/kg; Category not determined; **Unacceptable and not upgradeable** (only male test animals used). ([redacted], 8/12/94)

001; 126619; "Acute Percutaneous Toxicity of Hoe 39866-active ingredient (Code: Hoe 39866 O H AT203) to the Female Rat" (Author: Mayer et al, Hoechst-Roussel Agri-Vet Co., Pharma Forschung Toxikologie, Frankfurt, Germany, Report No. 496/82, 9/2/82); 812; HOE 39866 O H AT203 (97.2% a.i.) applied to the shaved skin as a 40% or 80% w/v solution in deionized water; 24 hr exposure, occluded; 6 females/dose; doses of 2000 and 4000 mg/kg;

mortalities- 1/6, 2/6, respectively; observations- hyperactivity, Dalrymple's sign or blepharophimosis, passiveness, benumbedness, disequilibrium, squatting, high-legged posture, abdominal position, trembling, convulsions, retracted abdomen, retracted flanks, convulsive jumping, "Straub"-phenomenon, bristled hair, increased salivation, blood-colored urine, aggressiveness, masticatory movements, emaciation, and poor general condition; necropsy- mortalities: all viscera markedly atrophied and dark in color; survivors: no abnormal findings; LD_{50} (F)>4000 mg/kg; Category not determined; **Unacceptable and not upgradeable** (only female test animals used). ([redacted], 8/12/94)

Acute inhalation toxicity, rat

001; 126620; "Aerosol Inhalation of Hoe 39866-active ingredient techn. (Code: Hoe 39866 O H AT203) to the Male and Female SPF-Wistar-Rat 4 h-LC 50" (Author: Hollander et al, Hoechst-Roussel Agri-Vet Co., Pharma Forschung Toxikologie, Frankfurt, Germany, Report No. 564/82, 9/20/82); 813; HOE 39866 O H AT203 (purity=97.2%) administered as an aerosol to 6 animals/sex/dose; doses of 0.192 mg a.i./l (as a 40% dilution in water) and 0.621 mg a.i./l (as a 80% dilution in water); 96.0% of the particles in the 0.192 mg/l group less than 6.00 µm and 90.4% of the particles in the 0.621 mg/l group less than 6.00 µm; 4 hr exposure (nose-only); mortalities- males: 1/6, 2/6, respectively; females: 0/6, 1/6, respectively; observations- hyperactivity, passivity, disequilibrium, analgesia, narrowed eye opening, blood-crusted nares, and forced and spastic breathing with all signs clearing in the survivors by day 9; necropsy- survivors: no abnormal macroscopic findings; LC_{50} not determined; Category not determined; **Unacceptable and not upgradeable** (only 2 dose groups used). ([redacted] 8/22/94)

001; 126621; "Hoe 39866-active ingredient technical (Code: Hoe 39866 OH ZC95 0001) Testing for Acute Dust Inhalation Toxicity in Male and Female SPF Wistar Rats 4 Hours-LC 50" (Author: Hollander et al, Hoechst-Roussel Agri-Vet Co., Pharma Forschung Toxikologie, Frankfurt, Germany, Report No. 84.0889, 3/26/85); 813; Hoe 39866 OH ZC95 0001 (purity=95.3%) administered as a dust to 5 animals/sex/dose; doses (reported analytical concentrations) of 0.12, 0.19, 0.38, and 2.00 mg/l with particle size distribution analysis of the above dose groups' test atmospheres showing 95.0%, 95.8%, 96.5%, and 98.7%, respectively, of the particles less than or equal to 10.3 µm; 4 hr exposure (nose-only); mortalities- males: 0/5, 1/5, 1/5, 3/5, respectively; females: 0/5, 0/5, 1/5, 2/5, respectively; observations- hyperactivity, passivity, squatting position, tremors, clonic convulsions, piloerection, increased salivation, and narrowed eye openings; necropsy- survivors: no macroscopic abnormalities; Reported LC50 (M)=1.26 mg/l; Reported LC50 (F)=2.60 mg/l; Category not determined; **Unacceptable but possibly upgradeable** with the submission of the calculations used to determine the analytical concentrations. ([redacted], 8/22/94)

Primary eye irritation, rabbit

001, 020; 126622, 137284; "Hoe 39866-active ingredient techn. (Code: Hoe 39866 OH AT203) Irritance to the Rabbit Skin and Eye Mucosa" (Author: Mayer et al, Hoechst-Roussel Agri-Vet Co., Pharma Forschung Toxikologie, Frankfurt, Germany, Report No. 476/82, 9/1/82); 814; Hoe 39866 OH AT203 (purity = 97.2%) applied to the conjunctival sac of 9 New Zealand rabbits (6 nonwashed, 3 washed); 100 mg/treated eye (each dose premixed with 1 drop of 0.9% NaCl solution); observations (nonwashed treated eyes)- no corneal opacity; iritis: grade 1 in 3/6 1 hr after exposure, clearing in all by 7 hrs; conjunctival irritation: grade 1 in 4/6 24 hrs after exposure, clearing in all by 72 hrs; since each dose of the test article was premixed with 1 drop of 0.9% NaCl solution, this study was regarded as **supplemental** ([redacted], 8/23/94; updated, [redacted], 6/22/95).

021, 142664; "A Primary Eye Irritation Study in Rabbits with Glufosinate-Ammonium Technical (HOE 039866)", (T.N. Merriman; Springborn Laboratories, Inc., Spencerville, OH; Study No. 3361.35; 11/2/95); Glufosinate-Ammonium Technical (purity: 95.2%); 6 rabbits; Dose: 0.1 ml (69 mg equivalent)/eye; Results: no corneal opacity, iritis-grade 1 (5/6) at 1 hour, clear by 24 hours, Conjunctiva (redness)-grade 1 (6/6) at 24 hours, clear by 10 days in all animals, (chemosis)-grade 1 (2/6) at 24 hours, clear by 72 hours in all animals, (discharge)-all effects clear by 24 hours; Toxicity Category IV; **Study acceptable.** ([redacted], 1/5/96)

Primary dermal irritation

001; 126622; "Hoe 39866-active ingredient techn. (Code: Hoe 39866 O H AT203) Irritance to the Rabbit Skin and Eye Mucosa" (Author: Mayer et al, Hoechst-Roussel Agri-Vet Co., Pharma Forschung Toxikologie, Frankfurt, Germany, Report No. 476/82, 9/1/82); 815; Hoe 39866 O H AT203 (purity=97.2%) applied to the shaven skin of 6 New Zealand rabbits; 500 mg (premixed with 0.1 ml of 0.9% NaCl solution)/animal; 24 hr exposure, occluded; observations- no edema; erythema: grade 1 in 1/6 24 hrs after the initiation of exposure, clearing in all 72 hrs after the initiation of exposure; Category IV; **Acceptable**. ([redacted], 8/23/94)

Dermal sensitization

52007-0001; 126623; Worker Health and Safety memorandum of 8/8/95. The technical grade glufosinate was deemed not to be a dermal sensitizer.

SUBCHRONIC STUDIES

Rat 2-Week Dietary Toxicity Study

00l; 126628; "Two-Week Subacute Toxicity of Hoe 39866 (technical) (Code: Hoe 39866 O H AS2Ol) in Rats" (Author: Otaka et al, Nomura Research Institute, Life Sciences Department, Kamakura-City, Kanagawa, Japan, Experiment No. NRI 81-7850, August 1981); Hoe 39866, Lot number: Hoe 39866 OH AS 2Ol, purity = 92.1%, administered, in the diet, to F344/DuCrj rats for 14 days; 10/sex/dose; doses of O, 8, 16, 32, 64, 320, 3200 ppm; no mortalities; observations- no clinical signs; suppression in body weight gain (p< 0.0l) in both sexes of the 3200 ppm group throughout administration; reduction in the relative weights of both heart (p< 0.05) and ovaries (p<0.05) females of the 3200 ppm group; necropsy- no treatment-related alterations; NOEL (M/F) =320 ppm (based on body weight suppression); **Supplemental** (animals dosed for 14 days only). ([redacted], 9/1/94)

Rat Subchronic Dietary Toxicity Study

002; 126629; "13-Week subchronic toxicity of HOE 39866 (Technical) in Rats" (Ohtaka, T. and Takahashi, T., Life Science Dept., Nomura Research Institute, Kanagawa, Japan, Document # A24715, 9/82); 821; HOE 39866 OH AS201 (Lot # Lfd. Nr. 9773, Op. Nr. 1-3/80, 92.1% purity) administered in diet to 30 rats/sex/dose at 0, 8, 64, 500 and 4000 ppm for 13 weeks followed by a 4-week recovery period for 10 rats/sex from each group; one male from the 4000 ppm group died on day 71 with a miliary-size tumor in the thoracic cavity; urinalysis revealed the pH of both sexes fed 4000 ppm fell at the termination of administration and that the reduced pH continued after the recovery period; kidneys of males treated at doses $\geq$ 500 ppm and females treated at 4000 ppm exhibited dose-related increase in absolute and relative weight; the kidney weight increases of males at 500 and 4000 ppm remained after the 4-week recovery period; no treatment-related changes in histopathology were reported; NOEL (M) = 64 ppm (4.1 mg/kg/day), (F) = 500 ppm (39 mg/kg/day) (based on changes in kidney weight); **no adverse effects**; **acceptable**; ([redacted], 9/8/94).

Rat 28-Day Inhalation Toxicity Study

52007-0119; 230772; "Glufosinate Toxicity Study by Inhalation Administration to CD Rats for 4 Weeks"; (Huntingdon Life Science Ltd; project #: BAG 0408/063551; 02/09/07); CD-rats (5/sex/group) were treated with 0, 0.056, or 0.105 mg GA/L Glufosinate-Ammonium (gravimetric values; equivalent to 0, 0.109, and 0.205 mg/L of technical glufosinate-ammonium) nose-only inhalation exposure for 6 hours per day, 5 days per week for 4 weeks; composition: a. i., 51.2% w/w Glufosinate-Ammonium TK; batch #: 2005-001955; nominal concentration: 0.525 and 0.977 mg/L, respectively; no treatment-related deaths occurred during the study at any treatment level. Clinical signs: ungroomed appearance in 5/5 M at the high exposure level and 2/5 F at the low-exposure level; bite marks in the dorsal body surface in 5/5 M; vocalization, shallow, slight breathing, slight piloerection, moderate, partially closed eyelids, moderate hunched posture, and slightly pale skin color in 1/5 F; abnormal or brown coloration on some males at the high exposure concentration and some females at the low and high exposure concentrations; all reported values reported were statistically significant ones. Body weights were not different after test-article exposure than in controls in males or females. Exposure of males to the high, test-article concentration induced increases in the following parameters: hematocrit, hemoglobin, MCH, MCHC, LUC, and chloride. The following parameters were decreased in males following exposure to the high-exposure concentration: eosinophil, AST, and phosphorus. A decrease in the average eosinophil titer was observed following exposure to the low-exposure level in males as well. In females, exposed to the high, test-article concentration exhibited increases in the following parameters: hematocrit, hemoglobin, MCH, MCV, and LUC. Mean decreases were observed in the following parameters in females exposed to the high, test-article concentration: ALP, bilirubin, and urea. The mean bilirubin level was decreased following exposure to the low-exposure concentration in females. A Urinalysis examination was not performed. NOAEL was stated to be 0.056 mg/L (LUC at high exposure). Supplemental. ([redacted], 07/13/07)

Rat 4-Week Repeated Dosing Dermal Toxicity Study

004; 126631; "HOE 39866 - Active Ingredient Technical - Testing for Subchronic Dermal Toxicity in Wistar Rats (21 Applications over 30 Days)" (Ebert, E. and Kramer, M., Hoechst AG, Frankfurt, Germany, Report # A31477, 5/10/85); 822; HOE 39866 OH ZD95 0001 (95.3% purity, 0 (saline), 100, 300, or 1000 mg/kg/day) applied dermally to 6 rats/sex/dose for 6 hrs/day, 5 days/week over a 30-day period; intact skin sites under occlusive conditions; 2 additional groups of 5 rats/sex at 0 and 1000 mg/kg were used in the recovery groups; no mortalities or signs of dermal irritation were reported; one high dose male was killed in a moribund state and the cause of its condition was unknown; one male treated at 300 mg/kg exhibited aggressive behavior, squatting position, piloerection and convulsive jumping and rolling spasms at the end of the treatment period; similar clinical signs were reported in 4 males and 2 females treated at 1000 mg/kg; dose-related increase in serum uric acid noted in males from the 300 and 1000 mg/kg groups which was within the range of normal variation for the strain of rats used in this study and was not regarded as toxicologically significant; **no adverse effect;** NOEL (M) = 100 mg/kg,(F) = 300 mg/kg (based on clinical signs); **acceptable**; ([redacted], 9/14/94).

Dog Subchronic Dietary Toxicity Study

003; 126630; "Subchronic (90-Day) Oral Toxicity Study in Dogs with HOE 39866" (Lina, B.A.R., et. al., Civo Institutes TNO, Zeist, Netherlands, Project # B80-1720, 11/82); HOE 39866 OH AS 201 (Lot # Lfd. Nr. 9773, Op. Nr. 1-3/80, 92.1% a.i.) administered to 4 dogs/sex/dose at dietary concentrations of 0, 4, 8, 16, 64, or 256 ppm for 13 weeks; **no adverse effects indicated**; no mortalities occurred throughout the study; no compound-related changes in body weight, food consumption, clinical chemistry, organ weights, gross necropsy or histopathology

were reported; NOEL (M/F) ≥ 256 ppm (7.81 mg/kg/day; no effects at the HDT); inadequate dose level selection; **unacceptable**; ([redacted], 9/13/94).

CHRONIC STUDIES

Chronic, rat

006, 020; 126647, 137284; "Combined Chronic Toxicity/Oncogenicity Study in the Rat Dietary Administration and 28-Day Range Finding Study in Rats" (P. Suter, et. al., Research & Consulting Company AG, Intingen, Switzerland, Report #'s A33811 and A29425, 9/19/86 and 2/10/84, respectively); HOE 39866 OH ZC95 0001 (95.3% purity) administered orally to 80 rats/sex/dose in the diet at 0, 40, 140 or 500 ppm for 2 years; 30 rats/sex and 50 rats/sex were assigned to the chronic toxicity and oncogenicity testing, respectively; increased mortality were observed in females from the mid and high dose groups in the oncogenicity portion of the study (27/50 and 29/50 vs. 15/50, respectively, p <0.05); no treatment-related clinical signs or changes in body weight and food consumption were noted; slight inhibition of liver glutamine synthetase activity (75 - 84% of control, p <0.05) reported in mid and high dose animals; after 130 weeks, increased incidence of benign adrenal medullary tumors were reported in mid and high dose males (6 and 10% vs. 2%, respectively) but were within historical control values (13.9% and 6% on average for males and females after 130 weeks, respectively); **no adverse effects indicated;** NOEL (M/F) > 500 ppm (no treatment-related effects were observed); no signs of toxicity reported at HDT; inadequate dose level selection; **unacceptable and not upgradeable**; ([redacted], 10/26/94; updated, 6/23/95).

****52007-032 161191** Schmid, H., B. Keller, H. Luetkemeier, H. Westen, and K. Biedermann, "Glufosinate-ammonium, substance technical (Code: Hoe 039866 00 ZD96 0001): Oncogenicity study in rats", RCC Research and Consulting Co., Ltd., Itingen, Switzerland, 3/19/98, RCC Project # 344766. Groups of 60/sex HanIbm:Wist (SPF quality) rats were dosed in diet for 2 yr with 0, 1000, 5000, or 10000 ppm glufosinate-ammonium in an acceptable oncogenicity study. Aside from initial decrements in food consumption and body weight among the two higher dose groups, there were no in-life manifestations of toxicity. The NOEL for toxicologically-significant non-neoplastic findings is 1000 ppm (57 mg/kg/day), based on retinal atrophy in 5000 ppm females (both sexes were markedly affected at 10000 ppm). Kidney weights were elevated in males and females at all dose levels, but in the absence of increased histopathology at any dose level, this was not considered to be a toxicologically significant change. Incidences of histiocytic sarcoma, a comparatively uncommon tumor type, appear to have been elevated by treatment at 5000 to 10000 ppm in males and at 10000 ppm in females (incidences out of 60/sex/group were 0, 0, 2, and 3 in controls through progressively higher dose levels in males: corresponding incidences in females were 1,0,1, and 3). This, along with retinal histopathology, constitute "possible adverse effects". Historical incidence data on hemolymphoreticular system tumors, particularly of histiocytic tumors, would be welcome for additional perspective on the latter tumor observations. Acceptable. [redacted], 6/22/98.

Chronic, dog

** 007; 126650; "HOE 39866 substance Technical Grade - 12-Month Oral Toxicity (Feeding) Study in Beagle Dogs and Stability and Homogeneity Study in Dog Feed" (R. Bathe, et. al., Research & Consulting Company AG, Intingen, Switzerland, Report # A29827, 11/27/84); HOE 39866 OH ZC95 0001 (95.3% purity) administered orally in diet at 0, 2, 5, or 8.5 mg/kg/day to 8 Beagle dogs/sex/dose; interim sacrifice consisted of 4 dogs/sex at the lowest three dose levels and 3 dog/sex at the high dose level; One high dose male and female died on day 14 and 10, respectively, after rapidly consuming the entire 300 g daily feed ration one to two days prior to death; clinical signs noted in these two dogs included trismus, salivation and hyperactivity

followed by somnolence and hypoactivity, as well as stereotypic stiff gait, tremor, ataxia, opisthotonus and lateral recombency; no treatment-related changes in body weight, food consumption, clinical chemistry, urinalysis, ophthalmology and hematology were reported; **possible adverse effect:** histopathology exam indicated that the deaths of the two high dose dogs were caused by heart and circulatory failure due to marked myocardial necrosis in one dog, and to slight myocardial necrosis and severe necrotizing aspiration pneumonia in the other dog; no treatment-related morphological findings were noted in any of the dogs which survived until scheduled termination; NOEL (M/F) = 5 mg/kg/day (based on unscheduled deaths due to heart/circulatory failure); **acceptable** ([redacted] 11/2/94).

Oncogenicity, rat

See Chronic Rat above.

Oncogenicity, mouse

** 008; 126654; "Two-Year Oncogenicity Study with HOE 39866 Technical in Mice - Dietary Administration and Addendum to Final Report and 13-Week Oral Toxicity (Feeding Study)" (P. Suter, et. al., Research & Consulting Company AG, Intingen, Switzerland, Report #'s A33219, A33991, and A30381, 4/29/86, 9/19/86, and 7/3/84, respectively); HOE 39866 OH ZC95 0001 (95.3% purity) administered orally to 60 mice/sex/dose in the diet at 0, 20, 80, 160 (males only) or 320 (females only) ppm for 2 years; High dose males exhibited significantly higher mortality rate (38/50 vs. 26/50, $p < 0.05$) as compared to control; no treatment-related clinical symptoms or signs of toxicity were noted; sporadic reduction in mean body weight without any changes in mean food consumption was reported in high dose animals (M: 84.3 - 91.7% of control, $p < 0.05$, weeks 3 - 33; F: 90.9 - 96.8% of control, $p < 0.05$, weeks 7 - 31); reduced absolute and relative liver weight in females from all 3 treated groups after 104 weeks was not considered to be treatment-related because of the wide variations in individual organ weights and the absence of any abnormal changes in liver histopathology; NOEL (M/F) = 80 ppm (unscheduled deaths in males and reduced mean body weights in females); no adverse effects; acceptable; ([redacted] 10/31/94).

GENOTOXICITY

Gene mutation

011; 126670; "Test for Mutagenicity in Bacteria Strains in the Absence and Presence of a Liver Preparation" (D. Gericke, Hoechst AG, Frankfurt, Germany, Report # A18971, 8/28/78); HOE 39866 OH RH 012 (liquid concentrate, 40%) ; tested with Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 with or without activation by Aroclor 1254 induced rat liver S9 fraction; four plates; 1 trial; concentration range 0 to 0.5 µl/plate; 48 hour incubation; positive controls functional; **no adverse effects indicated;** no increase in reversion rate reported; exact composition of formulated test material not provided and technical grade material not used; **unacceptable and not upgradeable**; [redacted], 12/12/94).

** 011; 126671; "In Vitro Microbial Assay for Mutagenicity Testing of HOE 39866 OH AS 201" (Y. Ohtaki, et. al., Nomura Research Institute, Kanagawa, Japan, Report # A24713, April, 1981); HOE 39866 OH AS 201 (Lfd. Nr. 9773, Op. Nr. 1-3/80, 92.1% purity); tested with Bacillus subtilis M45 rec and H17 wildtype strains without activation (duplicate plates/dose, 1 trial, 24 hr incubation, dose range: 0 - 10 mg/well), Escherichia coli WP2 $Hcr^{-}Try^{-}$ with and without activation (duplicate plates/dose, 1 trial, 72 hr incubation, dose range: 0 - 1 mg/plate), and Salmonella typhimurium strains TA98, TA100, TA1538, TA1537, and TA1535 with and without activation (duplicate plates/dose, 1 trial, 48 hour incubation, dose range: 0 - 1 mg/plate); positive

controls functional; **no adverse effects**; HOE 39866 is not mutagenic under present experimental conditions; **acceptable** ([redacted], 12/13/94)

011; 126672; "Study of the Mutagenic Activity in In Vitro of the Compound HOE 39866 Substance Technical (Code HOE 39866 OH ZC95 0001) with Schizosaccharomyces Pombe" (E. Hirsch and M.F. Milone, Istituto Di Ricerche Biomediche "Antoine Marxer" S.P.A., Italy, Report # A29303, 6/19/84); HOE 39866 OH ZC95 0001 (97.3% purity); tested with Schizosaccharomyces Pombe with and without activation by Aroclor 1254-induced rat liver S9 fraction; 14 plates/determination; 1 trial; 4 hour incubation; concentration range of 0, 125, 250, 500, and 1000 µg/ml; **no adverse effects indicated**; positive controls functional; test article up to the concentration of 1 mg/ml did not induce significant increase in gene mutation of Schizosacchararomyces pombe in vitro either in the presence or absence of S9 activation; individual values not included with study report and results of preliminary toxicity test to justify concentrations not reported; **not acceptable but possibly upgradeable**; [redacted], 12/14/94).

** 011; 126673; "Mutagenicity Evaluation of HOE 39866 Substance Technical in the Mouse Lymphoma Forward Mutation Assay" (M.A. Cifone and B.C. Myhr; Litton Bionetics, Inc., Kensington, MD, Report # A30380, 1/85); HOE 39866 OH ZC95 0001 (95.3% purity); tested with L5178Y TK+/- cells (3.7.2C) with and without activation by aroclor 1254-induced rat liver S9 fraction; 2 replicates/dose; 2 trials; but first trial with activation had erratic background mutant frequencies and the results were not presented or used; 4 hour incubation; concentration range of 0 (water) to 5000 µg/ml; **no adverse effects**; no increase in mutation frequency; **acceptable**; [redacted] 12/15/94)

Chromosome damage

011; 126674; "HOE39866 Substance Technical Chromosome Aberration in Cultured Human Lymphocytes" (E. Hirsch and M.F. Milone, Istituto Di Ricerche Biomediche "Antoine Marxer" S.P.A., Italy, Report # A30977, 2/26/85); HOE 39866 OH ZC95 0001 (95.3% purity); tested with cultured human lymphocytes in the presence and absence of metabolic activation by aroclor 1254-induced rat liver S9 fraction; 3 hour exposure followed by 23 hour incubation after which 0.2 ml colchicine was added; concentration range of 0 (deionized water), 1, 10, 100, and 1000 µg/ml; 2 glass slides/dose; single trial; **no adverse effects indicated**; positive controls functional; test article up to the concentration of 1000 µg/ml did not induce statistically significant increase in chromosomal aberration in the presence or absence of metabolic activation; no individual data; single culture/concentration; **unacceptable and not upgradeable**; [redacted] 12/16/94).

011; 126675; "Micronucleus Test in Male and Female NMRI Mice After Oral Administration" (R. Jung, et. al., Hoechst Ag, Frankfurt, Germany, Report # A31610, 7/12/85); HOE 39866 OH ZC95 0001 (95.3% purity); two consecutive daily oral doses to 5 NMRI mice/sex/dose at 0 (deionized water), 8, 40, or 200 mg/kg; cyclophosphamide (100 mg/kg, positive control); bone marrow samples taken at 6 hrs after the second dose; **no adverse effects indicated**; positive controls functional; HOE 39866 did not induce any significant increases in micronuclei frequency; The ratio of polychromatic to normocytes remained unaffected by HOE 39866 OH ZC95 0001; inadequate number bone marrow sampling times; **unacceptable and not upgradeable**; [redacted], 12/19/94).

** 011; 126676; "HOE 39866 - Substance Technical (Code: HOE 39866 OH ZC95 0001) Micronucleus Test in Male and Female NMRI Mice After Oral Administration" (Jung and Weigand, Hoechst AG, Frankfurt, Germany, Report # A34419, 10/9/86); HOE 39866 OH ZC96 0002 (96.9% purity); single oral dose to 15 NMRI mice /sex/dose at 0 (deionized water), 10,

200, or 350 mg/kg; cyclophosphamide (50 mg/kg, positive control); bone marrow samples taken at 24, 48, and 72 hours after dosing 5/sex/dose; **no adverse effect**; 2 high dose females which died exhibited panting, uncoordinated gait and abdominal position; these mice were replaced; other signs of toxicity reported in other high dose mice included increased spontaneous activity, aggressivity, tactile hyperaesthesia, motor excitation, narrowed palpebral fissures, and clonic convulsions; administration of HOE 39866 OH ZC96 0002 did not lead to an increase of micronucleated polychromatic erythrocytes; **acceptable**; ([redacted], 12/19/94).

DNA damage or miscellaneous effects

** 011; 126677; "Study of the Mutagenic Activity of the Compound HOE 39866 Substance Technical with Saccharomyces Cerevisiae Gene Conversion - DNA Repair Test" (I.E. Hirsch and M.F. Milone, Instituto Di Ricerche Biomediche "Antoine Marxer" S.P.A., Italy, Report # A29302, 6/19/84); HOE 39866 OH ZC95 0001 (95.3% purity); mitotic gene conversion in Saccharomyces cerevisiae strain D4 tested in the presence or absence of activation by Aroclor 1254-induced rat liver S9 fraction; 0 (deionized water), 1000, 2500, 500, or 10000 ug/ml; 4 hour incubation followed by further incubation for 4 days for convertants; 4 plates/dose; 1 trial; **no adverse effects indicated**; positive controls functional; test article did not induce significant increases in gene conversion in the Saccharomyces cerevisiae strain in vitro in the presence or absence of metabolic activation; **acceptable**; ([redacted], 12/20/94).

011; 126678; "Evaluation of HOE 39866 Substance Technical in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay" (M.A. Cifone et. al, Litton Bionetics, Inc., Kensington, MD, Report # A29999, 11/84; HOE 39866 OH ZC95 0001 (95.3% purity); tested with primary rat hepatocytes; concentrations 0 (deionized water), 26.2, 52.4, 105.0, 262.0, 524.0, 1050.0, 2620.0, and 5240.0 ug/ml; primary rat hepatocytes labeled in vitro with 3H=Tdr and chased with unlabeled thymidine; 18 to 19 hour exposure to test article; UDS by autoradiography; triplicate coverslip cultures/dose; 50 cells scored on each coverslip or 150 cells; **no adverse effects indicated**; positive controls functional; test material did not induce significant changes in nuclear labeling of primary rat hepatocytes; individual data not included; **unacceptable but possibly upgradeable** with submission of individual data; ([redacted], 12/20/94).

REPRODUCTIVE TOXICITY, RAT

** 010; 126666; "HOE 39866 Technical (Code: HOE 39866 OH ZC95 0001) Multiple Generation Study in Rats and Preliminary Study to the Multiple Generation Study in Rats" (H. Becker et. al., Research & Consulting Company AG, Intingen, Switzerland, Report #'s A35589 and A33217, 5/20/86); HOE 39866 OH ZC95 0001 (95.3% purity) administered in the diet to 4 groups (26 - 30 rats/sex/group) at concentrations of 0, 40, 120, or 360 ppm for 2 generations; one mid dose male and one low dose female in the $F_{\leftarrow}$ generation died; no treatment-related clinical signs or changes in body weight and food consumption were recorded; **possible adverse effect:** significant reduction in litter size were noted in litters from both generations treated at 360 ppm; this effect was caused by pre- and postimplantation losses in the parental female as indicated by the preliminary study; no histopathological changes were detected in testes and ovaries as well as in the other associated reproductive organs; parental NOEL = 360 ppm (no effects at HDT); reproductive NOEL = 120 ppm (reduced litter sizes); **acceptable**; ([redacted] 11/4/94).

DEVELOPMENTAL TOXICITY

Rat

** 009, 020; 126660, 126661, 137284; "HOE 39866 - Pure Active Ingredient: Testing for Embryotoxicity in Wistar Rats Following Oral Administration" (Baeder, et. al., Pharma Forschung

Toxikologie, Frankfurt, Germany, Report #s 85.0771 (9/22/82), 85.0748 (10/20/80); HOE 39866 OH AT 201 (97.2 - 97.7% purity) in distilled water, was administered by gavage once daily to 20 pregnant rats/dose at 0, 0.50, 2.24, or 10.0 mg/kg for the 1st study and 0, 10.0 , 50.0, or 250.0 mg/kg for the 2nd study on days 7 - 16 of gestation; motorial unrest was reported in pregnant rats treated at doses ≥ 10 mg/kg; one high dose pregnant rat died between days 16 and 17 of gestation; possible adverse effects: 4 dams from the 50 mg/kg group and 8 dams from the 250 mg/kg group were killed interconcurrently due to vaginal hemorrhage; the vaginal hemorrhages were connected with the abortions because vacant implantation sites as well as dead fetuses were detected in the uterus; morphological exam of the fetuses indicated dose-related increase in the frequency of pelvic and ureteral distension at the three highest dose groups (10 mg/kg: 18.4%, 50 mg/kg: 25.2%, 250.0 mg/kg: 31.4% vs. 0 mg/kg: 10.0%); nominal maternal NOEL = 2.24 mg/kg/day (motorial unrest), nominal developmental NOEL = 2.24 mg/kg/day (pelvic and ureteral distension); initially reviewed as unacceptable but possibly upgradeable with submission of dosing solution analysis; ([redacted] 11/9/94); study rereviewed with dosing preparation records; acceptable; (updated, [redacted], 6/23/95)

009; 126662; "HOE 39866 - Active Ingredient Technical: Testing for Embryotoxicity and Effects on Postnatal Development in Wistar Rats Following Oral Administration" (Pensler, M., et. al., Hoechst AG, Frankfurt, Germany, Report # A33812, 6/18/86); HOE 39866 OH ZD97 0001 (Serial # 13143, 96.9% purity) in distilled water was administered by gavage once daily to 20 pregnant rats/dose at 0, 0.50, 2.24, or 10.0 mg/kg on days 7 - 16 of gestation; except for one dam each in the 0.50 and 2.24 mg/kg groups, all of the animals survived the study until scheduled termination; these two dams were killed on day 25 of gestation since they had not delivered; the dam treated at 0.50 mg/kg exhibited empty implantation sites in the uterus and the dam at 2.24 mg/kg showed only two implantation sites and one normally developed dead fetus; no increase in the incidence of pelvic or ureteral distension was detected in offsprings at the dosages tested; viability and physical development of the offspring of the dams treated with HOE 39866 were not impaired during the first three weeks after birth; nominal maternal NOEL = nominal developmental NOEL = 10 mg/kg/day (no effect at HDT); **supplemental**; ([redacted] 11/16/94).

Rabbit

009, 020; 126663, 137284; "HOE 39866 - Active Ingredient Technical: Testing for Embryotoxicity in Himalayan Rabbits Following Oral Administration and Supplement to Report" (C. Baeder, et. al., Hoechst AG, Frankfurt, Germany, Report #s A29082 (4/9/84) and A32874 (2/5/86); HOE 39866 OH ZC95 0001 (Serial # 12027, 95.3% purity) in distilled water was administered by gavage once daily to 15 pregnant Himalayan rabbits/dose at 0, 2.0, 6.3 or 20 mg/kg/day from days 7 to 19 of gestation; one dam from the 6.3 mg/kg group died on day 29 of gestation while giving premature birth; at 20 mg/kg, one dam was killed intercurrently and 2 dams aborted their fetuses; **no adverse effects indicated**; live fetuses delivered in all treated groups were normally developed and their bodyweights and body lengths did not differ from those of the control group; dilated renal pelves were noted in one fetus from a dam treated at 20 mg/kg; nominal maternal NOEL = nominal developmental NOEL = 6.3 mg/kg/day (increased in the number of premature births and abortions); skeletal and visceral examinations were not performed in each fetus; **unacceptable and not upgradeable**; [redacted], 11/23/94; updated, 6/23/95)

NEUROTOXICITY

Acute neurotoxicity, rat

The required study has not been submitted.

90-day neurotoxicity, rat

The required study has not been submitted.

Developmental neurotoxicity, rat

The required study has not been submitted.

Delayed Neuropathy, Chicken

00l; 126627; "Neurotoxicity Study with White Leghorn-Hens HOE 39866 OH RHO12-(Liquid Concentrate 4O)" (Author: Leist et al, Pharma Research Toxicology and Pathology. Hoechst AG, Frankfurt, Germany, Report No. A21969, 11/29/79); 817; HOE 39866 liquid concentrate 4O, 40% a.i. administered by gavage in 2 single doses at 21 day intervals in all treatment groups (except for one dose only in the case of the positive control) to White Leghorn hens; 6 animals/treatment group with treatment groups of 1. 10000 mg/kg of test article without antidote, 2. 10000 mg/kg of test article with antidote (10 mg/kg atropine and 4 mg/kg Toxogonin), 3. 500 mg/kg TOCP (positive control), 4. 8.7 ml/kg sesame oil (negative control); no mortalities; observations- treated groups without antidote: slight diarrhea after the first dose; treated group with antidote: increased discharge of feces; slight weight loss was observed in both of the treated groups during the first 3 weeks; necropsy-no gross abnormalities in any of the dose groups; histopathological examination- no treatment-related alterations; N0EL< 10,000 mg/kg; **Unacceptable and not upgradeable** because the test animals were not subjected to periods of forced motor activity during the observation period; ([redacted] 8/31/94)

IMMUNOTOXICITY

The required study has not been submitted.

ENDOCRINE DISRUPTOR STUDIES

Study not required at this time.

L-GLUFOSINATE AMMONIUM

METABOLISM AND PHARMACOKINETICS

No studies submitted.

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat

022; 142841; "Testing for the Acute Oral Toxicity in the Male and Female Wistar Rat", (K.H. Diehl and K.H. Leist; Pharma Research Toxicology and Pathology, Hoechst Aktiengesellschaft, Frankfurt, Germany; Study No. 88.0180; 3/11/88); L-enantiomer of glufosinate-ammonium technical (Hoe 058192) (purity: 88.2%); 5 animals/sex/group (unless otherwise indicated); Doses: 500, 630, 800, 1000, 1600, 1800 (F only), 2000 (F only), 2500 (M only), 3150 (M only) mg/kg; Mortality: 500 (M:0/5, F:1/5), 630 (M/F:2/5), 800 (M:3/5, F:4/5), 1000 (M:5/5, F:4/5), 1600 (M/F:5/5), 1800 (F:5/5), 2000 (F:5/5), 2500 (M:5/5), 3150 (M:5/5); Clinical Observations: high legged gait, prone or lateral position, uncoordinated gait, ataxia, agitation, bizarre movements, aggressiveness, hypersensitivity to touch, trembling, clonic spasms, saltatory and rolling spasms, negative placing reflex, piloerection, narrowed palpebral fissures, miosis, salivation, crusted blood around nose and mouth, diarrhea, irregular breathing; Necropsy: (decedents) congestion of the lungs, mottled liver, dark red mass in intestines, spleen and kidneys light in color; **NOEL< 500 mg/kg**; LD50 (95% confidence limits): (M) 709 (546 to 916) mg/kg, (F) 669 (378 to 905) mg/kg; Toxicity Category III; **Study acceptable.** ([redacted] 1/5/96)

53586-0005; 324440; “L-Glufosinate Ammonium TGAI: Acute Oral Toxicity-Up-and-Down Procedure in Rats”; (C. Lowe; Product Safety Labs, Dayton, NJ; Study No. 51214; 12/30/19); Female Sprague-Dawley rats were dosed orally by gavage with 158 (1 animal), 500 (3 animals) or 2000 (4 animals) mg/kg of L-Glufosinate Ammonium TGAI (lot no. AG-0000990-6-27; purity 76.62%) in the Up-and-Down procedure. The four animals in the 2000 mg/kg group died. All of the decedents died within two days of dosing. At a treatment level of 2000 mg/kg clinical signs included irregular respiration, hunched posture, hypoactivity, and piloerection. In the necropsy examination of the decedents, distention of the stomach and intestines were noted. For those that survived the observation period, no treatment-related lesions were evident. 500 mg/kg <LD50(F)<2000 mg/kg; Toxicity Category III; Study acceptable. ([redacted], 6/24/20)

Acute oral toxicity, mouse

023; 142842; "Testing for the Acute Oral Toxicity in the Male and Female NMRI Mouse", (K.H. Diehl and K.H. Leist; Pharma Research Toxicology and Pathology, Hoechst Aktiengesellschaft, Frankfurt, Germany; Study No. 88.0181; 3/30/88); L-enantiomer of glufosinate-ammonium technical (Hoe 058192) (purity: 88.2%); 5 animals/sex/group; Doses: 125, 200, 315, 500, 800 mg/kg; Mortality: 125 (M:2/5; F:3/5), 200 (M/F:4/5), 315 (M/F:5/5), 500 (M/F:5/5), 800 (M/F:5/5); Clinical Observations: reduced activity, hypersensitive to touch, clonic spasms, high legged gait, prone or in lateral position, straub tail, trembling, negative placing reflex, reduced corneal reflex, narcosis, piloerection, reduced corneal reflex, narrowed palpebral fissures, salivation, state of agitation, irregular breathing; Necropsy: (decedents) lung congestion, light-colored liver, kidneys and spleen, small intestine filled with dark red mass; **NOEL < 125 mg/kg**; reported LD50 (95% confidence limits): (M) 137 (27.7 to 208) mg/kg, (F) 122 (17.4 to 186) mg/kg; Toxicity Category not assigned; **Study unacceptable**, not upgradeable (dose-response for females not adequately characterized). ([redacted], 1/8/96)

Acute dermal toxicity

53586-0005; 324441; “L-Glufosinate Ammonium TGAI: Acute Dermal Toxicity in Rats L-Glufosinate Ammonium TGAI: Acute Dermal Toxicity in Rats”; (C. Lowe; Product Safety Labs, Dayton, NJ; Study No. 51791; 11/27/19); The skin of 5 Sprague-Dawley rats/sex was exposed to 2000 mg/kg of L-Glufosinate Ammonium TGAI (lot no. AG-0000990-6-27; purity 76.62%) for 24 hours under an occlusive wrap. No deaths resulted from the treatment. Red nasal discharge and dermal erythema (one animal through day 3) were noted as clinical signs. No treatment-related lesions were evident in the necropsy examination. LD50 (M/F) > 2000 mg/kg; Toxicity Category III; Study acceptable. ([redacted], 6/24/20)

Acute inhalation toxicity, rat

025; 142844; "Testing for Acute Dust Inhalation Toxicity in the Male and Female SPF Wistar Rat, 4-Hour LC50", (TH. Hoffman and R. Jung; Pharma Research Toxicology and Pathology, Hoechst Aktiengesellschaft, Frankfurt, Germany; Study No. 88.0187, 6/6/88); L-enantiomer of glufosinate-ammonium technical (Hoe 058192) (purity: 88.2%); 5 animals/sex/group (unless otherwise noted); Reported Exposure Concentrations (analytical): 0.051, 0.116, 0.175 (F only), 0.202 (M only), 0.293, 0.659 (F only) mg/l, range of MMAD values: 3.1 to 4.6 µm, nose-only 4 hour exposure; Mortality: 0.051 (M:1/5; F:0/5), 0.116 (M:2/5; F:1/5), 0.175 (F:1/5), 0.202 (M:2/5), 0.293 (M:5/5; F:1/5), 0.659 (F:5/5); Clinical Observations: irregular breathing, red discharge around mouth and nose, hunched posture, uncoordinated or stilted gait, ataxia, narrowed palpebral fissures, delayed righting-, paw pinch-, and corneal reflexes, miosis, tonic-clonic spasms, saltatory convulsions, increased fright reaction; Necropsy: (decedents) dark discolored lungs; reported LC50 (95% confidence limits) (M) 0.138 (0.066 to 0.270) mg/l, (F) 0.314 (0.174 to 0.762) mg/l; Toxicity Category not assigned; **Study unacceptable,** possibly upgradeable with

the submission of analytical data and calculations used to determine the exposure concentration). ([redacted], 1/8/96)

53586-0005; 324442; "L-Glufosinate Ammonium TGAI: Acute Inhalation Toxicity in Rats"; (C. Lowe; Product Safety Labs, Dayton, NJ; Study No. 51215; 11/18/19); Five Sprague-Dawley rats/sex were exposed nose-only to 0.60 mg/l (gravimetric) of L-Glufosinate Ammonium TGAI (lot no. AG-0000990-6-27; purity 76.62%) for 4 hours. The mean MMAD (GSD) value was 2.56 (2.36) µm. One female died within one day of exposure. Clinical signs included hypoactivity and hypersensitivity. In the necropsy examination of the female which died, the lungs exhibited moderately red discoloration. No treatment-related lesions were evident for the other study animals. LC50 (M/F) > 0.60 mg/l; Toxicity Category III; Study acceptable. ([redacted], 6/24/20)

Primary eye irritation, rabbit

53586-0005; 534443; "L-Glufosinate Ammonium TGAI: Primary Eye Irritation in Rabbits"; (C. Lowe; Product Safety Labs, Dayton, NJ; Study No. 51216; 11/6/19); The eyes of three New Zealand albino rabbits were treated by ocular instillation with 0.1 ml (49 mg)/eye of L-Glufosinate Ammonium TGAI (lot no. AG-0000990-6-27; purity 76.62%). No corneal opacity nor iritis was evident during the 72-hour observation period. Conjunctival redness, grade 1 (3/3) was evident at 24 hours, clearing by 48 hours. Chemosis, grade 1 (1/3) was noted at 24 hours, clearing by 48 hours. No discharge was evident at 24 hours. Toxicity Category IV; Study acceptable. ([redacted], 6/24/20)

Primary dermal irritation

53586-0005; 324444; "L-Glufosinate Ammonium TGAI: Primary Skin Irritation in Rabbits"; (C. Lowe; Product Safety Labs, Dayton, NJ; Study No. 51217; 9/25/19); The skin of 3 New Zealand albino rabbits was treated with 0.5 gm/site, one site/animal, of L-Glufosinate Ammonium TGAI (lot no. AG-0000990-6-27; purity 76.62%) for 4 hours under a semi-occlusive wrap. The test material was moistened with distilled water. Erythema, grade 1 (3/3) was noted at 1 hour post-exposure, diminishing to grade 2 (2/3) at 24 hours, clearing by 48 hours. No edema was evident throughout the 72-hour observation period. Toxicity Category IV; Study acceptable. ([redacted], 6/24/20)

Dermal sensitization

53586-0005; 324445; "L-Glufosinate Ammonium TGAI: Local Lymph Node Assay in Mice"; (C. Lowe; Product Safety Labs, Dayton, NJ; Study No. 51218; 9/27/19); Both ears of five CBA/J mice/group were treated topically with 25 µl/ear/day of either 1% Pluronic L92 or a 10% preparation of the L-Glufosinate Ammonium TGAI (lot no. AG-0000990-6-27; purity 76.62%) in 1% Pluronic L92 for 3 consecutive days. On day 6, each animal received a dose of 20 µCi of tritiated thymidine in the tail vein. Five hours post-dose, the animals were euthanized and the auricular lymph nodes excised. Nodal cell preparations were analyzed by scintillation counting. A positive control group of 5 animals was treated in the same manner with a 25% preparation of α-hexylcinnamaldehyde in propylene glycol. The stimulation index for the treated group was 2.02. The test material did not demonstrate a positive sensitization potential in the LLNA. The positive control was functional. Study acceptable. ([redacted], 6/24/20)

Acute Intraperitoneal Injection Study, Rat

024; 142843; "Testing for Acute Peritoneal Toxicity in the Male and Female Wistar Rat; (K.H. Diehl and K.H. Leist; Pharma Research Toxicology and Pathology, Hoechst Aktiengesellschaft, Frankfurt, Germany; Study No. 88.0185; 8/9/88); L-enantiomer of glufosinate-ammonium, technical (Hoe 058192) (purity: 88.2%); 5 animals/sex/group (unless otherwise indicated); Doses: 10, 25, 50 (F only), 100, 315 (F only), 500 (M only), 800 (M only); Mortality: 10 (M/F:0/5),

25 (M:1/5; F:4/5), 50 (F:5/5), 100 (M/F:4/5), 315 (F:4/5), 500 (M:4/5), 800 (M:4/5); Clinical Observations: high-legged gait, straddling of legs, prone or lateral position, uncoordinated gait, crawling, agitation, reduced activity, bizarre movements, clonic spasms, negative placing reflex, negative paw-pinch reflex, piloerection, narrowed or closed palpebral fissures, exophthalmos, miosis, salivation, blood encrusted nose and eyes, irregular breathing, reduced surface body temperature, ataxia; Necropsy: (decedents) congestion of lungs, mottling of liver, spleen light in color, thoracic cavity filled with fluid; LD50 (95% confidence limits): (M) 94.9 (22.4 to 381), (F) 20.5 (3.27 to 62.6) mg/kg; **Study supplemental**. ([redacted], 1/8/96)

SUBCHRONIC STUDIES

Rat 5-Day Inhalation Toxicity Study

53586-0010; 324450; "L-Glufosinate Ammonium Salt: 5-Day Repeat Dose Inhalation Range-Finder Toxicity in Rats"; (M. Bauter; Product Safety Labs, Dayton, NJ; Study No. 49879; 12/10/19); Five Sprague-Dawley rats/sex/group were exposed nose-only to reported concentrations of 0, 0.004, 0.04 or 0.07 mg/l of L-Glufosinate Ammonium Salt (lot no. AG-0000990-6-26; purity: 82.45%). The respective MMAD (GSD) values were 2.24 (2.91), 3.64 (2.61), 1.64 (2.24) and 1.72 (2.12) µm. However, the test material was diluted in distilled water. When it was aerosolized, no data were presented which determined what quantity of the test material was actually recovered from the chamber atmosphere. There was no way to identify what the actual exposure to the test material was. No animals died. Ocular discharge was reported for a few of the test material-exposed animals. Mean body weights and food consumption were not affected by the treatment. There were no treatment-related lesions noted in the necropsy examination. A no-effect level cannot be established due to a lack of adequate documentation of how the exposure concentrations were determined. Study supplemental. ([redacted], 7/3/20)

Rat 28-Day Inhalation Toxicity Study

53586-0011; 324451; "L-Glufosinate Ammonium Salt: A 28-Day Repeat Inhalation Toxicity Study in Rats"; (J. Blum; Product Safety Labs, Dayton, NJ, K.R Vygantas DVM, Robbinsville, NJ, Histo-Scientific Research Laboratories (HSRL), Mount Jackson, VA, Eurofins Advinus, Bengaluru 560 058, India; Study No. 49880; 12/18/19); Ten Sprague-Dawley rats/sex/group were exposed nose-only to 0, 0.08, 0.14 or 0.30 mg/l (analytical) of L-Glufosinate Ammonium Salt (lot no. AG-0000990-6-26; purity: 82.45%) for 6 hours/day, 5 days/week for 4 weeks. The range of MMAD (GSD) values were as follows: 0.08: 1.43 to 4.58 (2.29 to 2.70) µm, 0.14: 1.34 to 2.87 (1.73 to 3.07) µm, 0.30:1.54 to 2.66 (1.87 to 3.02) µm. No deaths resulted from the exposures. The mean body weights and food consumption were not affected by the treatment. In the hematological evaluation, the mean white blood cell, lymphocyte and monocyte counts were increased for the 0.30 mg/l females ($p<0.05$). The mean reticulocyte count for these females was less than that of the control group ($p<0.05$). There was no treatment-related effect noted in the clinical chemical evaluation, ophthalmological examination, and the urinalysis. The mean relative lung weight of the 0.30 mg/l females was greater than that of the control group females ($p<0.05$). In the histopathological examination, hepatic necrosis was noted in the livers of 2 males in the 0.30 mg/l group. Hepatic necrosis was a significant toxicological effect. Rat 28-day Inhalation Toxicity NOEL: (M/F) 0.14 mg/l (based upon the apparent treatment-related effect on the liver of the 0.30 mg/l males and the increased white blood count and increased relative lung weight of the 0.30 mg/l females); Study acceptable. ([redacted], 7/8/20)

CHRONIC STUDIES

Chronic, rat
Study not submitted.

Chronic, dog
Study not submitted.

Oncogenicity, rat
Study not submitted.

Oncogenicity, mouse
Study not submitted.

GENOTOXICITY

Gene mutation
** 53586-0006; 324446; "L-Glufosinate Ammonium TGAI: Bacterial Reverse Mutation Test (Ames Test)"; (M. Rao; Product Safety Labs, Dayton, NJ; Study No. 50761; 11/13/19); *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2uvrA were treated with L-Glufosinate Ammonium TGAI (lot no. AG-0000990-6-27; purity 76.62%) at concentrations ranging from 2.06 to 6250 µg/plate using plate incorporation for 65 hours at 37° C under conditions of activation and non-activation in the 1st trial. In the 2nd trial, the strains were exposed to the same concentrations with a preincubation of 30 minutes and an incubation for 65 hours at 37° C under conditions of activation and non-activation. Triplicate samples were incubated for each treatment level. A phenobarbital/5,6-benzoflavone-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. The positive controls were functional. Study acceptable. ([redacted], 6/29/20)

Chromosome damage
Study not submitted.

DNA damage or miscellaneous effects
53586-0007; 324447; "L-Glufosinate Ammonium TGAI: Mammalian Erythrocytes Micronucleus Test (Peripheral Blood, Flow Cytometry-Mouse)"; (J. Blum; Product Safety Labs, Dayton, NJ and Litron Laboratories, Rochester, NY; Study No. 50762; 11/21/19); Five CD1 mice/sex/group/time point were treated orally by gavage with 0 (vehicle: distilled waterl) 25, 50 or 100 mg/kg of L-Glufosinate Ammonium TGAI (lot no. AG-0000990-6-27; purity 76.62%) twice, 24-hours apart. Blood samples were drawn at 44 to 48 hours post final-dose. As a positive control, another group of 5 mice/sex was treated by oral gavage with 40 mg/kg of cyclophosphamide once, on the 2nd day. The percentage of micronucleated reticulocytes in 4000 reticulocytes, the ratio of reticulocytes to mature erythrocytes and the percentage of micronucleated erythyrocytes were determined by flow cytometry. There was no treatment-related increase in the percentage of micronucleated reticulocytes. Positive control was functional. Study acceptable. ([redacted] 6/29/20)

REPRODUCTIVE TOXICITY, RAT
No study submitted.

DEVELOPMENTAL TOXICITY

Rat

53586-0009; 324449; “An Oral (Dietary) Dose Range-Finding Developmental Neurotoxicity Study of L-Glufosinate in Rats”; (D.G. Stump; Charles River Laboratories Ashland, LLC, Ashland, OH, and Charles River Laboratories, Mattawan, MI; Project ID No. 01162002; 11/22/19); Ten time-mated Sprague-Dawley female rats/group received 0, 100, 600 or 3000 ppm of L-Glufosinate Ammonium technical (batch no. AG-0000990-6-13; purity: 80.5% (glufosinate ammonium racemic), 57.57% (L-glufosinate ammonium) from gestation day 6 through lactation day 21 (nominal a.i. consumption, gestation: 0, 5, 31, 149 mg/kg/day, lactation: 0, 12, 70, 303 mg/kg/day). One female in the 3000 ppm group died on lactation day 15. One dam in the 600 ppm group died on gestation day 23 with 17 stillborn fetuses. The mean maternal body weight of the 3000 ppm dams was less than that of the control group over most of the treatment period particularly during the lactation period. The mean food consumption of this group was also less than that of the control group during the lactation period ($p<0.01$). There was no treatment-related effect upon the gestation index or pup viability. The mean pup weight of the 3000 ppm group was less than that of the control group over the course of the lactation period ($p<0.01$). The motor activity of the male pups was increased in a treatment-related manner at both post-natal days 17 and 21 although statistical significance was not demonstrated. Maternal NOEL: 600 ppm (70 mg/kg/day) (based upon the lower mean body weight of the 3000 ppm dams); Developmental NOEL: (M/F) 600 ppm (70 mg/kg/day) (based upon the lower mean body weight of the 3000 ppm pups during the lactation period). Supplemental study ([redacted] 7/2/20)

Rabbit

** 025; 142846; "Embryotoxocity Study (including Teratogenicity) with Hoe 058192 Substance Technical (Code: Hoe 058192 OH ZC88 0002) in the Rabbit", (Becker, H., *et.al.*; RCC, Research and Consulting Company Ltd, Itingen, Switzerland; Project No. 207257; 5/21/92); L-enantiomer of Glufosinate-Ammonium Technical (Hoe 058192) (purity: 88.0%); 16 Chinchilla *post-coitum*; Maternal: one apparent treatment-related mortality (5.00 mg/kg); Clinical Observations: severe spasms, muscle twitching, ataxia (animal which died), two females aborted (5.00 mg/kg), reduced food consumption (2.50, 5.00 mg/kg); Necropsy: no treatment-related lesions; Developmental: increased incidence of late post-implantation loss (2.50, 5.00 mg/kg), no treatment-related effects upon other developmental parameters; Possible adverse effect: increased incidence of late post-implantation loss; Maternal NOEL: 1.25 mg/kg/day (based upon reduced food consumption in the 2.50 mg/kg/day treatment group), NOAEL: 2.50 mg/kg/day (based upon maternal mortality and abortions in 5.00 mg/kg/day treatment group); Developmental NOEL=NOAEL: 1.25 mg/kg/day (based upon increased incidence of late post-implantation loss in the 2.50 mg/kg/day treatment group); Study acceptable. ([redacted], 1/12/96)

NEUROTOXICITY

Acute neurotoxicity, rat

Study not submitted.

90-day neurotoxicity, rat

Study not submitted.

Developmental neurotoxicity, rat

Study not submitted.

IMMUNOTOXICITY

Study not submitted.

ENDOCRINE DISRUPTOR STUDIES

Study not required at this time.

SUPPLEMENTAL STUDIES

53586-0008; 324448; "Neuronal Health Assessment Using Human Induced Pluripotent Stem Cell-derived Glutamatergic Neurons Toxicity of Racemic Glufosinate vs. L-Glufosinate"; (J. Evans; PhenoVista Biosciences, San Diego, CA; Study ID No. QU-180193; 11/30/18); A comparison of the relative neurotoxicity of L-glufosinate and racemic glufosinate was performed, using the Induced Pluripotent Stem (iPS) Cell-derived Neuronal Assay. The iPS cells were derived from human peripheral blood which were differentiated to be a human cortical glutamatergic cell line with demonstrable functional networks. The neuronal cells, after being cultured for 3 or 7 days, were exposed to at least 0, 0.01, 1, 50 or 1000 µM concentrations (other treatment concentrations were not identified in the text although they are indicated in the graphs) of L-glufosinate or racemic D/L glufosinate (50:50) for 24 or 96 hours in 384 well plates. Identical treatments were also performed in which the glutamatergic cells were co-cultured with a specialized cell line of astrocytes for 3 or 7 days prior to exposure to the test materials. At the end of the exposure period the cells were fixed and co-stained with Hoescht (nuclear dye), DRAQ7 (dye for dead cells) and Tuj1 (neuronal antibody marker). With the use of imaging technology, a viable neuron count/well and neurite area/viable cell were determined. IC50s were calculated. Control compounds, kainate, N-methyl-D-aspartic acid and glutamate at concentrations 4, 111 and 1000 µM (other treatment levels are indicated in the graphs) were also incubated and processed in the same manner. The toxic effects manifested by reduced cell viability and neurite area/viable cell were quite similar for L-glufosinate and racemic D/L glufosinate (50:50) based upon the calculated IC50 values. It is the contention of the registrant that the L-isomer is no more neurotoxic than is the racemic mixture. Summary Report. ([redacted] 7/3/20)

DATA GAP STATUS

Chronic toxicity, rat:	No data gap, retinal atrophy noted
Chronic toxicity, dog:	No data gap, neurotoxic clinical signs and myocardial necrosis in the heart noted
Oncogenicity, rat:	No data gap, incidence of histocytic sarcoma
Oncogenicity, mouse:	No data gap, no significantly toxic effect
Reproduction, rat:	No data gap, significant effect on fetal survival
Developmental toxicity, rat:	No data gap, no significantly toxic effect
Developmental toxicity, rabbit:	No data gap, significant effect on fetal survival
Gene mutation:	No data gap, no significantly toxic effect
Chromosome effects:	No data gap, no significantly toxic effect
DNA damage:	No data gap, no significantly toxic effect
Neurotoxicity:	Data gap, studies have not been submitted