4-18-85

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

004403

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Experimental Use Permit (8340-EUP-RN) and Temporary Tolerance Petition (4G3156) for HOE 39866. Accession Nos. 072961-6, 072979.
CASWELL #580I

TO: Richard Mountfort (23)
Registration Division (TS-767)

FROM: D. Stephen Saunders Jr., Ph.D.
Toxicologist, Section V
TOX/HED (TS-769)
D. Stephen Saunders Jr 4/16/85

THRU: Laurence D. Chitlik, DABT
Head, Section V
TOX/HED (TS-769)
4/17/85
and
Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)
4/18/85

Chemical: HOE 39866; Monoammonium [2-amino-4-(hydroxymethylphosphinyl)butanoate]

Action Requested

Review studies submitted in support of an Experimental Use Permit (8340-EUP-RN) and temporary tolerance (4G3156) for the new chemical HOE 39866. A temporary tolerance of 0.02 ppm of the parent compound and its metabolite 3-methylphosphinicopropionic acid on soybean seeds was requested, in conjunction with a request for an experimental use permit to assess the efficacy of the chemical in the control of grasses and broadleaf weeds for non-crop, homeowner, nonbearing tree and vine crops, and soybean crop uses.

Recommendations

1. Experimental Use Permit: (a) Non-crop- The test chemical possesses a moderate hazard for acute toxicity (Category II) based on primary eye irritation and acute dermal toxicity of the water-soluble formulation. Because of an unresolved teratology issue, the risk to female applicators of child-bearing age cannot be evaluated at present.

1.(b) Homeowner- The stated purpose of an EUP is to assess the efficacy of a test chemical under controlled, experimental conditions. There is no information to be gained from a domestic use that could not be obtained from a test plot under well-controlled conditions, with less opportunity for accidental exposure to humans or domestic animals.

Recommendations (con't)

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1.(c) Non-bearing tree and vine crops- Residue Chemistry Branch has determined that a tolerance of 0.02 ppm for the crops that result from this use is appropriate. The fate of these crops, other than a statement that they would not be harvested during the 1985 growing season, was not disclosed. Therefore, a crop-destruct restriction for this proposed use is appropriate. As noted in the RCB memorandum of 1/2/85, a restriction against feeding or grazing of treated cover crops is appropriate. As noted in 1(a), the risk to female applicators of child-bearing age cannot be evaluated at present.

1.(d) Soybean crops- A temporary tolerance for this crop was requested at the limit of detection, 0.02 ppm. This proposed tolerance would result in a Theoretical Maximum Residue Contribution of 0.007 ug/kg/day, averaged for the entire population, which is 3.4% of the Acceptable Daily Intake based on a NOEL of 8 ppm from the 90-day rat feeding study (see attached printout). The highest dietary exposure would occur in non-nursing infants, who would receive a dose of 0.033 ug/kg/day, equivalent to 16.3% of the ADI.

Because of the unresolved issue of the teratogenic potential of the test compound, a margin-of-safety (MOS) for this use was calculated using the "worst case" of a positive teratogen with a NOEL for this effect of 2.24 mg/kg/ day. It should be recognized, however, that a final assessment of the teratogenic potential of the test compound will not be completed until additional data are submitted (see reviews, pages 48 to 56). It is quite possible that after submission of the requested data, Toxicology Branch will conclude that no teratogenic potential exists.

The daily dose of HOE 39866 due to consumption of soybeans by females, as determined under the Tolerance Assessment System, was calculated to be 0.07 ug/kg/day. This value provides a MOS of:

$$MOS = \frac{NOEL}{Exposure} = \frac{2.24 \text{ mg/kg/day}}{0.07 \text{ ug/kg/day}} = 3.2 \times 10^4$$

Alternatively, if one assumes that a pregnant woman consumed 6 ounces/day of soybeans, the MOS would be:

6 oz. = 170.1 g x 0.02 ug/g = 3.4 ug HOE, divide by 60 kg average body weight

$$= \frac{3.4 \text{ ug}}{60 \text{ kg}} = 0.06 \text{ ug/kg, therefore the MOS} = \frac{2.24 \text{ mg/kg/day}}{0.06 \text{ ug/kg/day}} = 3.7 \times 10^4$$

Therefore, even assuming a "worst case" positive teratogenic response, the risk to pregnant women due to dietary exposure to HOE 39866 on soybeans is negligible. The risk to female applicators of child-bearing age cannot be fully evaluated at present. As noted in the RCB memorandum of 1/2/85, a restriction against feeding or grazing of treated soybean forage is appropriate.

Because of the structural similarity of the test article to the amino acid glutamate, numerous questions remain regarding the potential of the test article to cause subtle chronic effects due to interference with endogenous biochemical processes (see "Discussion"). Therefore, additional data are necessary before

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Recommendations (con't)

tolerances above the limit of detection can be supported. Specifically, the effect of the test article on other biochemical processes which involve glutamic acid should be experimentally assessed (see "Discussion").

1.(e) Inerts have been cleared (IC #148, review of David L. Ritter 7/6/84).

DER Summary

Study Type (#)	Core-Classification
Acute oral- male rat (587/80)	Minimum
Acute oral- female rat (588/80)	Minimum
Acute oral- male mice (547/80)	Minimum
Acute oral- female mice (546/80)	Minimum
Acute dermal- male rat (495/82)	Minimum
Acute dermal- female rat (496/82)	Minimum
Acute inhalation- rat (564/82)	Supplementary
Primary eye irritation- rabbit (476/82)	Guideline
Primary skin irritation- rabbit (476/82)	Guideline
Skin sensitization- rabbit (83.0701)	Guideline
Mutagenicity- reverse mut. (56/78)	Unacceptable
Mutagenicity- reverse mut. (NRI 81-7359)	Acceptable
Mutagenicity- Primary DNA (NRI 81-7359)	Acceptable
Mutagenicity- mouse micronucleus (83.0165)	Inconclusive
2-week feeding- rat (NRI 81-7850)	Supplementary
13-week feeding- rat (NRI 81-7860)	Guideline
90-day feeding- dog (V 82.318/201720)	Guideline
Teratology- rat (545/80)	Supplementary
Teratology- rat (570/82)	Supplementary
Metabolism- rat (321/82)	Supplementary
Metabolism- rat (01-L42-0400-83)	Supplementary
Antidote- rat (83.0625)	Acceptable
Acute oral (WSL)- male rat (755/81)	Minimum
Acute oral (WSL)- female rat (756/81)	Minimum
Acute dermal (WSL)- female rat (760/81)	Supplementary
Acute inhalation (WSL)- rat (5/82)	Guideline
Primary eye irritation (WSL)- rabbit (166/82)	Minimum
Primary skin irritation (WSL)- rabbit (166/82)	Minimum

1. The oral LD_{50} in male rats (study #587/80) is 2.0 g/kg with a 95% c.i. of 1.6-2.49 g/kg. These values correspond to Toxicity Category III (0.5 to 5.0 g/kg). The study was classified as Core-Minimum data when combined with the data for males (study #588/80).

2. The oral LD_{50} in female rats (study #588/80) is 1.62 g/kg with a 95% c.i. of 1.19-1.74 g/kg. These values correspond to Toxicity Category III (0.5 to 5.0 g/kg). The study was classified as Core-Minimum data when combined with the data for males (study #587/80).

DER Summary (con't)

3. The oral LD_{50} in male mice (study #547/80) is 431 mg/kg with a 95% c.i. of 337-533 mg/kg. These values correspond to Toxicity Category II (50 to 500 mg/kg). The study was classified as Core-Minimum data when combined with data for females (study #546/80).

4. The oral LD_{50} in female mice (study #546/80) is 416 mg/kg with a 95% c.i. of 345-498 mg/kg. These values correspond to Toxicity Category II (50 to 500 mg/kg). The study was classified as Core-Minimum data when combined with data for males (study #547/80).

5. The oral LD_{50} in male and female dogs (study #543/80) is between 200 and 400 mg/kg, the only doses tested. The study was classified as Core-Supplementary data since an insufficient number of animals was studied for calculation of the LD_{50}.

6. The dermal LD_{50} in male rats (study #495/82) is >4.0 g/kg. This value corresponds to Toxicity Category III (0.5 to 5.0 g/kg). Although an exact dermal LD_{50} was not calculated, Agency guidelines allow limit testing at 2.0 g/kg. The study was classified as Core-Minimum data when combined with the data for females (study #496/82).

7. The dermal LD_{50} in female rats (study #496/82) is >4.0 g/kg. This value corresponds to Toxicity Category III (0.5 to 5.0 g/kg). Agency guidelines allow limit testing at 2.0 g/kg provided that no mortalities are observed. Although an insufficient number of doses was tested to determine an LD_{50} in female rats, when combined with the data for males (study #495/80), this study was classified as Core-Minimum data

8. The LC_{50} in rats (study #564/82) was not calculated because an insufficient number of doses was studied. The Registrant submitted a letter stating that higher doses could not be attained for "physical reasons". Toxicology Branch does not consider the submitted "explanation" adequate, particularly since an LC_{50} was calculated with the water-soluble formulation. Since the test compound is a "white powder", the Registrant may wish to consider testing the undiluted powder. The highest concentration studied in the present study, 0.62 mg/L, caused death in 2/6 male and 1/6 female rats after 4 hours, which suggests that the LC_{50} is near this value, which corresponds to Toxicity Category II (0.2 to 2.0 mg/L). The study was classified as Core-Supplementary data.

9. The primary eye and skin irritation study (#476/82) revealed slight irritation to the eyes and skin that was reversible by 72 hours. The eye effects correspond to Toxicity Category III, and the skin effects correspond to Toxicity Category IV. Both studies were classified as Core-Guideline data.

10. The skin sensitization study (#83.0701) demonstrated that the test compound is not a sensitizer. The data were classified as Core-Guideline.

11. The mutagenicity requirements for gene mutation and primary DNA damage were satisfied, whereas that for chromosomal abberations was not. Two gene mutation studies were submitted. Study #56/78 was classified as Unacceptable

(con't)

DER Summary (con't)

11. (con't) because no rationale for the selection of doses was presented, and the 40% liquid concentrate rather than the technical grade of active ingredient was the test material in this study. Study #NRI 81-7359 assessed DNA damage and gene mutation effects in a single report. The study was negative for both effects, and was classified as Acceptable. The mouse micronucleus test (study #83.0165) was classified as Inconclusive because no evidence that the test chemical reached the bone marrow in sufficient concentration to produce a toxic effect was presented.

12. The two-week feeding study in rats (#NRI 81-7850) was intended as a range-finding study for the 90 day rat feeding study. After 2 weeks of treatment, an LEL of 16 ppm and a NOEL of 8 ppm was established based on serum chemistry effects. The study was classified as Core-Supplementary data.

13. The 13-week feeding study in rats (#NRI 81-7860) established an LEL of 64 ppm and a NOEL of 8 ppm based on increased absolute and relative kidney weights in males. The study was classified as Core-Guideline data.

14. The 90-day feeding study in dogs (#V 82.318/201720) established an LEL of 64 ppm and a NOEL of 16 ppm based on decreased weight gain and decreased absolute and relative thyroid weights in females. The study was classified as Core-Guideline data.

15. Two rat teratology studies were submitted. In the first study (#545/80), an apparent dose-related increase in the fetal and litter incidences of dilated renal pelvis with hydroureter was noted at all dose levels. Frank maternal toxicity as evidenced by vaginal bleeding with severe weight gain deficits was observed in dams at the mid and high doses of 50 and 250 mg/kg, however the data were inadequate for determination of the extent of maternal toxicity in this study. Apparently, none of the above effects were noted in the range-finding study, which tested doses up to and including 250 mg/kg. No explanation for the disparity in results between the range-finding study and the primary study was offered by the investigators.

The second study (#570/82) failed to demonstrate any of these effects at the highest dose of 10 mg/kg.

Therefore, NOELs and LELs cannot be determined at this time. The study report was inadequate. Numerous deficiencies in the submitted study report were noted, and a re-write of the final report is requested with several additions (please see "Conclusions" of study reviews, pages 52 - 60a).

When the requested data and report re-write have been submitted, a final evaluation of these studies will be completed.

16. Two rat metabolism studies were submitted. Neither of the studies conforms to the 1982 Pesticide Assessment Guidelines for metabolism studies, and if considered together only partially satisfy the data requirement for a rat metabolism study. The first study (#321/83) identified the metabolic pathway of HOE 39866 in females only after a single dose of 10 mg/kg by gavage. The second study (#01-L42-0400-83) compared the kinetics of excretion after a

(con't)

DER Summary (con't)

16. (con't) single i.v. dose of 2 mg/kg with a single oral dose of 2 mg/kg. Studies that must still be submitted are: (1) the effect of a minimally toxic dose on excretion, metabolic profile, and tissue distribution in both males and females; and (2) a study in which the effect of repeated doses of a low dose (in this case 2 mg/kg) on excretion, metabolic profile, and tissue distribution is assessed. Both studies are tentatively classified as Core-Supplementary data. If additional studies are submitted to fulfill the missing requirements, these studies can be upgraded.

17. An antidote study (#83.0625) was submitted in which male and female rats were given a lethal dose of the test article, and the therapeutic efficacy of phenobarbital was compared to that of atropine and pralidoxime. Phenobarbital proved to be an effective antidote, whereas atropine and pralidoxime had no effect on lethality. The study was classified as Acceptable (no core guidelines have been established for this type of study).

18. The oral LD_{50} of the water-soluble formulation (WSL) in male rats (study #755/81) was determined to be 2.98 g/kg, with a 95% c.i. of 2.46 - 3.63 g/kg. This value corresponds to Toxicity Category III. The study was classified as Core-Minimum data when considered with the data for females (study #756/81).

19. The oral LD_{50} of the water-soluble formulation (WSL) in female rats (study #756/81) was determined to be 1.45 g/kg, with a 95% c.i. of 1.11-2.00 g/kg. This value corresponds to Toxicity Category III. The study was classified as Core-Minimum data when considered with the data for males (study #755/81).

20. The acute dermal LD_{50} of the WSL in females (study #760/81) was determined to be 0.804 g/kg, with a 95% c.i. of 0.225-1.31 g/kg. This value corresponds to Toxicity Category II. The formulation is apparently more toxic by the dermal route than the TGAI, since the unformulated product had a dermal $LD_{50} > 2$ g/kg in female rats. Since only female rats were assessed in this study, it is classified as Core-Supplementary data.

21. The acute inhalation 4-hour LC_{50} of the WSL (study #5/82) was calculated to be 4170 mg/m^3 (4.17 mg/L) of the formulation. This value corresponds to Toxicity Category III, and the study was classified as Core-Guideline data.

22. The primary eye and skin irritation study (#166/82) demonstrated that the WSL was more of an irritant than the TGAI. The PIS for skin irritation was 2.7, which corresponds to Toxicity Category III. This study was classified as Core-Minimum data. The primary eye irritation study demonstrated reversible irritation to the cornea, iris, and conjunctiva. These effects correspond to Toxicity Category II, and the study was classified as Core-Minimum data.

PADI Calculation

The Provisional Acceptable Daily Intake (PADI) was based on a NOEL of 8 ppm obtained in the 90-dav rat feeding study, which is equivalent to 0.40 mg/kg (1 ppm = 0.05 mg/kg). Using a 2000-fold safety factor, the PADI of 0.20 ug/kg/day (0.C002 mg/kg/day) is obtained, which correlates to an MPI of 0.012 mg/day in a 60 kg adult. The proposed tolerance of 0.02 ppm on soybeans results in a TMRC of 0.007 ug/kg/day (1.5 kg diet), which would occupy 3.4% of the PADI for the entire population of the U.S. (calculated under the Tolerance Assessment System). The highest potential exposure would occur in non-nursing infants fed formula, who would receive a dose of 0.033 ug/kg/day, which would occupy about 16.3% of the PADI (see attached printout).

Under the "old" tolerance system, average consumption of soybean products would result in a TMRC that occupies 2.3% of the PADI (see attached printout).

RDV USED IN ANALYSIS =0.0002

SUMMARY BY POPULATION SUBGROUP

	TOTAL TMRC ADJUSTED FOR BODY WT (MG/KG BODY WEIGHT/DAY) PRIOR TMRC	NEW TMRC	NEW TMRC AS PCT OF RDV	EFFECT OF NEW ACTION DIFF. (NEW MINUS PRIOR)	DIFF. AS PCT OF RDV	DIFF. AS PCT OF PRIOR
U.S. POP.--48 STATES	0.000000	0.000007	3.399	0.000007	3.399	.
U.S. POP.--SPRING	0.000000	0.000007	3.279	0.000007	3.279	.
U.S. POP.--SUMMER	0.000000	0.000007	3.391	0.000007	3.391	.
U.S. POP.--FALL	0.000000	0.000007	3.508	0.000007	3.508	.
U.S. POP.--WINTER	0.000000	0.000007	3.419	0.000007	3.419	.
NORTHEAST REGION	0.000000	0.000006	3.075	0.000006	3.075	.
NORTH CENTRAL REGION	0.000000	0.000007	3.419	0.000007	3.419	.
SOUTHERN REGION	0.000000	0.000007	3.427	0.000007	3.427	.
WESTERN REGION	0.000000	0.000008	3.760	0.000008	3.760	.
HISPANICS	0.000000	0.000007	3.553	0.000007	3.553	.
NON-HISPANIC WHITES	0.000000	0.000007	3.427	0.000007	3.427	.
NON-HISPANIC BLACKS	0.000000	0.000006	3.164	0.000006	3.164	.
OTHER NON HISPANICS	0.000000	0.000007	3.258	0.000007	3.258	.
NURSING INFANTS (<1)	0.000000	0.000008	3.891	0.000008	3.891	.
NON-NURSING INFANTS	0.000000	0.000033	16.308	0.000033	16.308	.
FEMALES(13+,PREG.)	0.000000	0.000005	2.266	0.000005	2.266	.
FEMALES(13+,NURS.)	0.000000	0.000006	2.979	0.000006	2.979	.
CHILDREN(1-6 YRS)	0.000000	0.000013	6.362	0.000013	6.362	.
CHILDREN(7-12 YRS)	0.000000	0.000010	4.892	0.000010	4.892	.
MALES(13-19 YRS)	0.000000	0.000007	3.528	0.000007	3.528	.
FEMALES(13-19 YRS)	0.000000	0.000006	2.943	0.000006	2.943	.
MALES(20+ YRS)	0.000000	0.000005	2.699	0.000005	2.699	.
FEMALES(20+ YRS)	0.000000	0.000005	2.406	0.000005	2.406	.
ALASKA	0.000000	0.000000	0.000	.	.	.
HAWAII	0.000000	0.000000	0.000	.	.	.
PUERTO RICO	0.000000	0.000000	0.000	.	.	.
LOW INCOME-48 STATES	0.000000	0.000000	0.000	.	.	.

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Background

The EUP proposes to examine the efficacy of the test article in 4 uses: (1) non-crop, (2) homeowner, (3) non-bearing vines and trees and (4) soybean crop use. A total of 185 test sites will be studied, utilizing a maximum of 2,115 lbs a.i. over a maximum area of 1,043 acres. The geographical locations of test sites were not disclosed. The EUP is requested for 1985 only. Summaries of the proposed studies follow:

(1) Non-crop: Three aerial treatment studies will be conducted at an application rate of 2.0 lb a.i./acre, on an area of 2 acres. Thirty-seven ground treatment studies will be conducted at application rates of 1.5-2.0 lbs a.i./acre. The areas to be treated are from 0.5 to 2.0 acres. A repeat application after 4-6 weeks is proposed if necessary. The maximum total amount of active ingredient to be used is 271 lbs, on a maximum total of 80 acres. The types of areas to be treated include highway rights-of-way, airports, storage yards, fencelines, etc. The geographical locations of test sites were not disclosed.

(2) Homeowner: A total of 25 test sites will be studied, which will vary in size from 0.1 to 0.5 acres. The rate of application is proposed at 1.5 to 2.0 lbs. a.i./acre. A repeat application after 4-6 weeks is proposed if necessary. The maximum amount of active ingredient to be used is 44 lbs, over a maximum area of 12.5 acres. Only ground treatments will be used. The geographical locations of test sites were not disclosed.

(3) Non-bearing Tree and Vine Crops: The test will be conducted on non-bearing orchards, groves and vineyards, and the crops of stone fruits, citrus fruits, pome fruits and grapes will not be harvested during the 1985 growing season. A total of 50 test sites ranging in size from 2 to 5 acres will be studied. Only ground treatments will be used at a rate of 1.0 to 2.0 lbs a.i./acre, for a maximum total of 750 lbs a.i. over a maximum area of 100 to 250 acres. A repeat application after 4-6 weeks is proposed if necessary. The geographical locations of test sites were not disclosed.

(4) Soybeans: Both aerial and ground treatment programs are proposed, and growing methods will include no-till, minimum-till, and double crop. For aerial treatments, a total of 10 test sites will be studied at an application rate of 0.5 to 1.5 lbs a.i./acre over 5-10 acres per test site. A total of 60 test sites will be studied for ground treatments at the same application rate and acreage as for aerial treatments. The maximum total amount of test compound to applied in this use is 1,050 lbs a.i. over a maximum total area of 700 acres. A crop tolerance of 0.02 ppm (limit of detection) of HOE 39866 and its principal metabolite 3-methylphosphinicopropionic acid is requested on the soybean crops.

Discussion

The chemical HOE 39866 is a close structural analogue of the amino acid glutamate (see figure 1). The ability of this chemical to interfere with at least one biochemical pathway, the synthesis of the amino acid glutamine, was demonstrated by the submitted toxicology data. Because of this structural similarity, and the fact that glutamate plays a pivotal role in a large number of biochemical and neurochemical reactions, the test chemical possesses an unusual (relative to other pesticides) potential for inducing subtle, chronic effects in humans. Specifically, the following areas are of potential toxicological concern:

1) The potential for human health hazard due to inhibition of the synthesis of glutamine and/or other amino acids. There are 20 principal amino acids that form the "building blocks" of proteins, which are the fundamental unit of life. Under normal conditions, humans possess the capacity to synthesize glutamine and a number of other amino acids endogenously. These amino acids are called "non-essential", meaning that under normal conditions they do not have to be eaten as part of the diet. However, if synthetic pathways are blocked, these amino acids obviously must be replaced as part of the diet, and therefore become "essential". However, in terms of basic biology, all 20 amino acids are "essential" in that all are necessary to support life.

In addition to glutamine, the amino acid proline is directly synthesized from glutamate, and the amino acids serine, glycine, asparagine, aspartate, and alanine directly or indirectly utilize glutamate as a donor of an amino group in transaminase reactions during synthesis. The only reaction that was experimentally assessed was the glutamine synthetase pathway (which was inhibited); the effect of the test article on the synthesis of other amino acids is unknown at present (see review of 13-week rat feeding study, #NRI 81-7860).

2) The effect of the test chemical on other biochemical reactions that use glutamic acid as a substrate. These reactions are too numerous to list, however some important examples of such reactions include glutathione synthesis, and intermediary (i.e. energy) metabolism.

(a) Glutathione- This compound is a very important endogenous antioxidant and substrate for drug conjugation reactions. It binds non-enzymatically to free radicals and other highly reactive species, thereby protecting critical cellular macromolecules from attack. It also binds enzymatically to many drugs and chemicals to facilitate their excretion from the body. Glutathione is synthesized in the body from the amino acids glutamic acid, cysteine, and glycine. This synthesis must be intracellular, as dietary or other extracellular glutathione cannot be absorbed into cells. It seems likely that the test compound could inhibit this reaction also, raising the question of possible potentiation of the toxicity of other chemicals due to delays in excretion or depletion of the important protective antioxidant glutathione.

(con't)

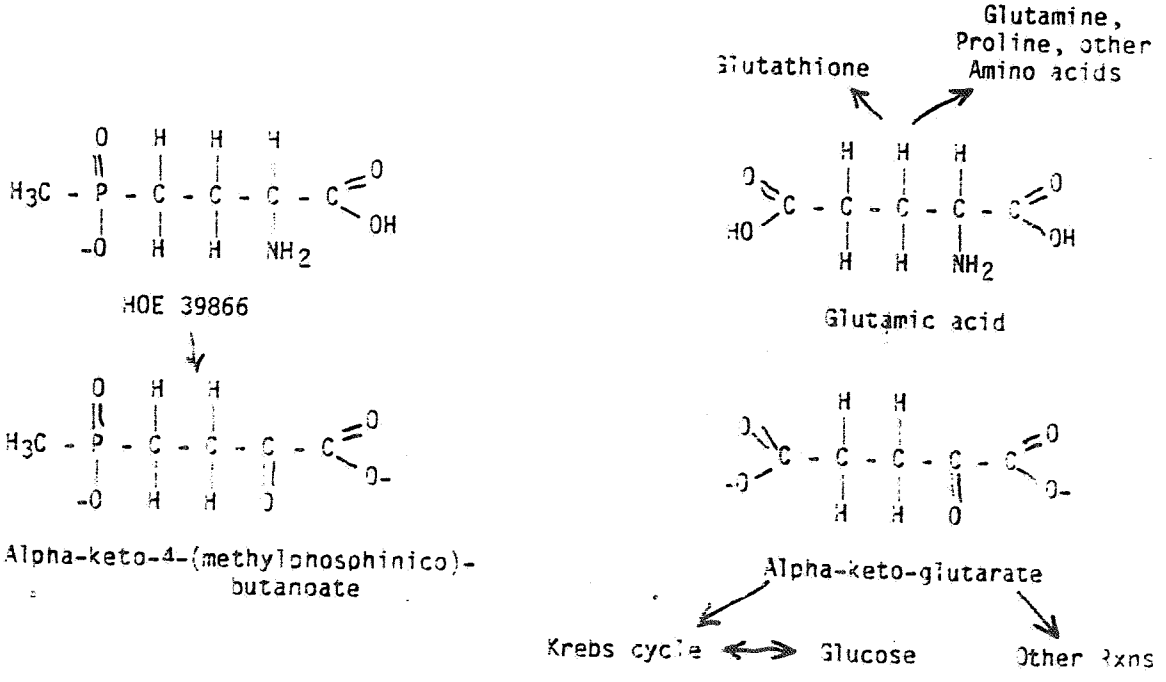
Discussion (con't)

(b) Energy metabolism- A number of amino acids serve as substrates in the synthesis of glucose (so-called "glucogenic" amino acids), or as substrates in the generation of energy via the Krebs cycle and the electron transport chain. The point of entry into these reactions for many amino acids is by degradation to glutamate and then to alpha-keto-glutarate. A metabolite of HOE 39866 identified in the rat metabolism study is the alpha-keto acid of HOE 39866, which bears a close structural similarity to alpha-keto-glutarate (fig. 1). The effect of this metabolite on the activity of enzymes in the Krebs cycle and the gluconeogenesis pathway is unknown.

3) The effect on neural pathways in the brain which utilize glutamate. Glutamate is an "excitatory" neurotransmitter in the brain. The test compound apparently crosses the blood-brain barrier and affects the central nervous system as evidenced by the fact that the acute toxicity studies demonstrated that an effect on the CNS is a likely mechanism of lethality (i.e. the animals died of convulsions). Glutamic acid analogues are known to affect behavior and to cause subtle lesions in the brain which are not detected by conventional toxicology methods.

Because of the questions identified above, Toxicology Branch cannot support, at this time, any food uses for this chemical that will result in residues above the limit of detection, 0.02 ppm. In the opinion of this reviewer, the potential effects outlined above should be experimentally assessed before substantial food residues are allowed.

Fig 1. Structures of HOE 39866, Glutamate, and Metabolites



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Data Evaluation Review

Study Title: Acute Oral Toxicity of HOE 39866 to the Male Rat.

Accession No.: 072962

Study No.: 587/80

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 11-13-80/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH AS201; 92.1% a.i.

Doses Tested: 0.63, 1.00, 1.60, 2.50, and 3.15 g/kg by oral gavage.

Test Animal: Male Wistar (Hoe WISKf[SPF71]) rats, Hoechst breeding. 10 rats/dose.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following points were noted:

1) The body weights of animals in test groups were not homogeneous. Test animals in the 2.00 and 3.15 g/kg groups weighed significantly more than other test animals. The methods stated that the study was conducted between the dates of 9-23-80 and 11-5-80, which seems excessively long for an acute oral study. When coupled with the large difference in the average body weights of test groups, it appears to this reviewer that the study was not conducted such that all dose groups were treated simultaneously.

2) Only males were studied, however when combined with the data for females (study #588/80), the two studies are acceptable for the acute oral toxicity requirement.

Results

A. Mortality- All animals that died after the single dose of the test article expired within 6 days of treatment (table 1).

One day after treatment the following clinical signs were noted in animals treated with doses of 1 g/kg and higher: protruding eyes, bristled hair, and "poor general condition". Animals in the higher dose groups additionally showed ataxia, blood-crusted eyes, hyperreflexia, and decreased irregular respiration.

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[redacted]

Table 1. 14-Day Mortality[a]

Dose (g/kg)	Number of deaths/ number of animals
0.63	0/10
1.00	1/10
1.60	2/10
2.50	7/10
3.15	9/10

[a]data excerpted from submitted study.

The LD_{50} was calculated by the investigators as 2.00 g/kg (95% confidence limits = 1.60-2.49 g/kg).

B. Body Weights- A dose-related decrease in mean body weight gain over the 14 day observation period was noted. The investigators stated that animals that died "in some instances showed marked reductions in body weight".

C. Necropsy Data- Gross observations of animals that died included "dark brown discoloured livers and dark discoloured adrenals". No "abnormal macroscopic findings" were noted in animals that survived to termination.

Conclusion

The oral gavage LD_{50} in male Wistar rats was calculated as 2.00 g/kg, with a 95% c.i. of 1.60-2.49 g/kg. These values correspond to toxicity category III (0.50 to 5.00 g/kg).

Any study in which a dose-response relationship is established should use animals of the same population, age, and body weight. This was apparently not the case in the present study. However, in consideration of the low degree of acute toxicity of the test compound, this deficiency does not alter the interpretation of this study.

Classification: Core-Minimum When combined with data in females from study #588/80; body weights of test groups not evenly distributed.

Abteilung Pharma Forschung Toxikologie
Verfasser Dr. Mayer, Dr. Weigand

Datum 13.11.1980
Bericht-Nr. 587/80
Seite 2 (8)

Hoe 39866, acute oral male rat

TEST PROCEDURE

Hoe 39866 O H AS201 (certificate of analysis No. 01537) was supplied as a white powder. For the acute treatment a 25 % solution was prepared in deionized water (25 g/ ad 100 ml) and administered once by gavage at various dose levels to male Wistar-rats (strain:Hoe WISKf(SPF71); Hoechst breeding), 142 - 256 g in weight ($\bar{x}$ = 175.7 g, s.d. = ± 39.77 g, n = 50). Each dosage was tested with 10 rats. The animals were deprived of feed for 16 hours before and 2 hours after dosing. During the 14-day follow - up period after the treatment the animals received ALTROMIN 1324, the maintenance diet produced by Altromin GmbH, Lage/Lippe) and tap water ad libitum. The animals were grouped and housed in plastic cages on wood shavings.

The symptoms of intoxication, the mortality rate and the time of death were registered after the treatment. During the follow-up period the animals were weighed weekly. Lethally intoxicated animals were dissected and the macroscopic autopsy findings were recorded. After termination of the follow-up period the surviving experimental animals were killed by CO_2-gas, dissected and also gross-examined.

The LD 50 was determined by probit analysis (LINDER/ WEBER method); the confidence limits were calculated according to FIELLER (programmed in the Practical Mathematics Department of Hoechst Aktiengesellschaft).

The experiment was carried out between 23.09. and 05. 11.1980.

004403

Study Title: Acute Oral Toxicity of HOE 39866 to the Female Rat.

Accession No.: 072962

Study No.: 588/80

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 11-13-80/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH AS201; 92.1% a.i.

Doses Tested: 0.63, 1.00, 1.60, 1.80, and 2.00 g/kg of 25% (w/v) solution by oral gavage.

Test Animal: Female Wistar (Hoe WISKf[SPF71]) rats, Hoechst breeding. 10 rats/dose.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) Only females were examined in this study, however when combined with the data for males (study #587/80), the two studies are acceptable.

Results

A. Mortality and Clinical Signs- The majority of deaths resulting from treatment with the test compound occurred within 7 days after dosing. Mortality rates are tabulated in table 1.

Signs observed in animals treated with 1.60 g/kg or more included ataxia, hyperreflexia, trembling, convulsions, irregular respiration, and "poor general condition".

Table 1. 14 Day Mortality[a]

Dose (g/kg)	Number of deaths/ number of animals
0.63	0/10
1.00	0/10
1.60	4/10
1.80	9/10
2.00	9/10[b]

[a]data excerpted from submitted study.

[b]this group contained an animal that died day 15.

The acute oral LD_{50} was calculated by the investigators as 1.62 g/kg, with a 95% confidence interval of 1.19-1.74 g/kg.

B. Body Weights- A dose-related decrease in body weight gain was noted in treated animals. The two animals surviving to 14 days in the high dose group (2.0 g/kg) lost body weight over the observation period.

C. Necropsy Data- Gross observations of animals that died included "dark brown discoloured livers, dark discoloured adrenals and in some cases blood-congested lungs". Necropsy of animals surviving to termination revealed "no abnormalities".

Conclusion

The oral LD_{50} of female rats = 1.62 g/kg (95% c.i. = 1.19-1.74 g/kg). This value corresponds to toxicity category III (0.5 to 5.0 g/kg).

Classification: Core-Minimum When combined with data from study #587/80.

Hoechst

FR 004403
A 21789

Abteilung: Pharma Forschung Toxikologie
Verfasser: Dr. Mayer, Dr. Weigand

Datum: 13.11.1980
Betreff: 560/80
Seite: 2 (8)

Hoe 39866, acute oral female rat

TEST PROCEDURE

Hoe 39866 C H AS201 (certificate of analysis No. C1337) was supplied as a white powder. For the acute treatment a 25 % solution was prepared in deionized water (25 g/ ad 100 ml) and administered once by gavage at various dose levels to female Wistar-rats (strain:Hoe WISKf(SPF71); Hoechst breeding); 180 - 206 g in weight ($\bar{x}$ = 194.5 g, s.d. = ± 7.75 g, n = 50). Each dosage was tested with 10 rats. The animals were deprived of food for 16 hours before and 2 hours after the treatment. During the 14-day follow-up period the animals received ALTROMIN 1324, the maintenance diet produced by Altromin GmbH, Lage/Lippe and tap water ad libitum. The animals were grouped and housed in plastic cages on wood shavings.

The symptoms of intoxication, the mortality rate and the time of death were registered after the treatment. During the follow-up period the animals were weighed weekly. Lethally intoxicated animals were dissected and the macroscopic autopsy findings were recorded. After termination of the follow - up period the surviving experimental animals were killed by CO_2-gas, dissected and also gross-examined.

The LD 50 was determined by probit analysis (LITCHFIELD / WILCOXON method); the confidence limits were calculated according to FIELLER (programmed in the Practical Mathematics Department of Hoechst Aktiengesellschaft).

The experiment was conducted between 23.09. and 05.11.1980.

Study Title: Acute Oral Toxicity of HOE 39866 to the Male Mouse.

Accession No.: 072962

Study No.: 547/80

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 10-30-80/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH AS201; 92.1% a.i.

Doses Tested: 315, 500, and 800 mg/kg of 5% (w/v) solution by oral gavage.

Test Animal: Male NMRI (strain Hoe:NMRKf[SPF71]) mice, Hoechst breeding stock. 10 mice/dose.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) Only males were examined in this study, however when combined with the data for females (study #546/80), the two studies are acceptable.

Results

A. Mortality and Clinical Signs- All animal deaths were noted within 7 days of treatment (table 1).

Observed clinical signs included ataxia, clonic convulsions, and irregular respiration. Animals that survived treatment showed "improvement of general condition" from day 2 after treatment.

Table 1. 14 Day Mortality[a]

Dose (mg/kg)	Number of deaths/ number of animals
315	2/10
500	6/10
800	10/10

[a]data excerpted from submitted study.

The oral LD_{50} was calculated by the investigators as 431 mg/kg, with a 95% confidence interval of 337-533 mg/kg.

B. Body Weights- No significant effect on weight gain in surviving mice was apparent.

C. Necropsy Data- Animals that died by day 2 were observed grossly to have "translucent and in some instances marked livers and blood-congested lungs". Animals that died later or that survived to termination "produced no abnormal macroscopic findings".

Conclusion

The oral LD_{50} of male mice = 431 mg/kg (95% c.i. = 337-533 mg/kg). These values correspond to toxicity category II (50 to 500 mg/kg).

Classification: Core-Minimum When combined with data for females (study #546/80).

Abteilung: Pharma Forschung Toxikologie
Verfasser: Dr. Mayer, Dr. Weigand

Datum: 30.10.1980
Bericht-Nr.: 547/80
Seite: 2 (-)

Hoe 39866, acute oral male mouse

TEST PROCEDURE

Hoe 39866 C H AS201 was supplied as a white powder. For the acute treatment a 5 % solution was prepared in deionized water (5 g/ad 100 ml) and administered once by gavage at various dose levels to male NMRI-mice (strain: Hoe:NMRI(SPF71) from our own breeding stock), 22 - 26 g in weight ($\bar{x}$ = 24.1 g, s.d. = ± 1.11 g, n = 30). Each dosage was tested with 10 mice. During the 14-day follow-up period after the treatment the animals received ALTROMIN 1324, the maintenance diet produced by Altromin GmbH, Lage/Lippe and tap water ad libitum. The animals were grouped and housed in plastic cages on granulated light wood bedding.

The symptoms of intoxication, the mortality rate and the time of death were registered after the treatment. During the follow-up period the animals were weighed weekly. Lethally intoxicated animals were dissected and the macroscopic autopsy findings were recorded. After termination of the follow-up period the surviving animals were killed by CO_2-gas, dissected and also gross-examined.

The LD 50 was determined by probit analysis (LINDER/WEBER method); the confidence limits were calculated according to FIELLER (programmed in the Practical Mathematics Department of Hoechst Aktiengesellschaft).

The experiment was conducted between 23.09. and 14.10. 1980.

004403

Study Title: Acute Oral Toxicity of HOE 39866 to the Female Mouse.

Accession No.: 072962

Study No.: 546/80

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 11-3-80/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH AS201; 92.1% a.i.

Doses Tested: 315, 500, and 800 mg/kg of 5% (w/v) solution by oral gavage.

Test Animal: Female NMRI (strain Hoe:NMRKf[SPF71]) mice, Hoechst breeding stock. 10 mice/dose.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) Only females were examined in this study, however when combined with the data for males (study #546/80), the two studies are acceptable.

Results

A. Mortality and Clinical Signs- All animal deaths were noted within 8 days of treatment (table 1).

Observed clinical signs included ataxia, clonic convulsions, and irregular respiration.

Table 1. 14 Day Mortality[a]

Dose (mg/kg)	Number of deaths/ number of animals
315	1/10
500	8/10
800	10/10

[a]data excerpted from submitted study.

The oral LD_{50} was calculated by the investigators as 416 mg/kg, with a 95% confidence interval of 343-498 mg/kg.

B. Body Weights- No effect of the test article on weight gain in surviving mice was apparent. Animals that died were reported to have a "marked decrease in body weight until their exitus".

C. Necropsy Data- Animals that died "during the first days after the treatment revealed translucent marked livers with hepatic marking at the edge in some instances and pulmonary plethora". Animals that died later or that survived to termination "produced no abnormal macroscopic findings".

Conclusion

The oral LD_{50} of female mice = 416 mg/kg (95% c.i. = 345-498 mg/kg). These values correspond to toxicity category II (50 to 500 mg/kg).

Classification: Core-Minimum When combined with the data for males (study #547/80).

Hoechst

004403

Abteilung: Pharma Forschung Toxikologie
Verfasser: Dr. Layer, Dr. Weigand

Datum: 3.11.1980
Bericht-Nr.: 3+6/80
Seite: - (7)

Hoe 39666, acute oral female mouse

TEST PROCEDURE

The active ingredient Hoe 39666 C H AS2C1 was supplied as a brown powder. For the acute treatment a 5 % solution in deionized water (5 g/ad 100 ml) was prepared and administered once by gavage at various dose levels to female NMRI-mice (strain:Hoe:NMRI(SPF71) from our own breeding stock), 17 - 23 g in body weight ($\bar{x}$ = 20.4 g, s.d. = $\hat{=}$ 1.33 g, n = 50). Each dosage was tested with 10 mice. During the 14-day follow-up period after the treatment, the animals received ALTROMIN 1324, the maintenance diet produced by Altromin GmbH, Lage/Lippe and tap water ad libitum. The animals were grouped and housed in plastic cages on granulated light wood bedding.

After the treatment the symptoms of intoxication, the mortality rate and the time of death were registered. During the follow-up period the animals were weighed weekly. Lethally intoxicated animals were dissected and the macroscopic autopsy findings were recorded. After termination of the follow-up period the surviving experimental animals were killed by CO_2 - gas, dissected and also gross - examined.

The LD 50 was determined by probit analysis (LINDER & WEBER method); the confidence limits were calculated according to FIELLER (programmed in the Practical Mathematics Department of Hoechst Aktiengesellschaft).

The experiment was conducted between 23.09. and 14.10.1980.

004403

Study Title: Acute Oral Toxicity of HOE 39866 to the Male and Female Dog.

Accession No.: 072962

Study No.: 543/80

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 10-16-80/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH AS201; 92.1% a.i.

Doses Tested: 200 and 400 mg/kg of 10% (w/v) solution by oral gavage.

Test Animal: Male and female pure-bred beagle dogs, Hoechst breeding stock. 1/sex/dose.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) Only 1 dog of each sex was tested at each of two doses, therefore an insufficient number of animals was used for calculation of the LD_{50}.

Results

Neither of the dogs given 200 mg/kg died, however both animals that received 400 mg/kg died between days 2 and 3 of the 14 day observation period.

Clinical signs observed in the dogs treated with 200 mg/kg included "squatting, benumbness, trembling, diarrhea, and disequilibrium", commencing about 22 hours after treatment. During subsequent hours, increased lacrimation and reddened ocular mucosae, salivation, rhinorrhea, paresis or paralysis of the hindlegs, and bluish discoloration of the tongue were noted. All symptoms had disappeared by 8 days after treatment. The body weights of these animals were essentially unchanged over the 14 day observation period.

Signs observed in the dogs given 400 mg/kg included those described for animals given the low dose, and the following: ataxia, emesis, and labored respiration. Both animals lost about 2 kg from their initial body weight before expiration.

Necropsy of the animals that died (400 mg/kg) resulted in gross observations of "extreme filling of the gall bladder, outer gastric wall with dark red spotted areas and accumulation of reddish-black-brown liquid in gastric lumen. Ulcerous gastroenteritis and swollen liver were observed in the female only."

Conclusion

The oral LD_{50} in male and female is >200 mg/kg and <400 mg/kg.

Classification: Core-Supplementary Insufficient number of animals and doses for calculation of LD_{50}.

Hoechst

004403
A21750

Abteilung: Pharma Forschung Toxikologie
Verfasser: Dr. Mayer, Prof. Kramer

Datum: 16.10.1980
Seite: 2 (5)

Hoe 39666, acute oral beagle

TEST PROCEDURE

Hoe 39866 - active ingredient was supplied as a colourless powder. For the acute treatment a 10 % suspension was prepared in deionized water (10 g/ad 100 ml) and administered once by gavage at various dose levels to pure-bred beagle dogs (Hoechst breeding), 9.10 - 13.75 kg in weight (mean weight 11.71 kg). Each dosage was tested with one male and one female animal. The animals were deprived of feed for 15 hours before and 5 - 6 hours after the treatment with Hoe 39866 - active ingredient. During the first three days after dosing the animals received a feed mixture composed of Latz feed-mash (Purina GmbH, Duskirchen) and PAL (Effem, Verden/Aller) in a ratio of 4 : 1. During the subsequent follow-up period the mixed diet ERKA H 8500 (Robert Koch oHG, Hamm/Westf.) was given. Food and water were provided ad libitum. The dogs were housed singly in boxes during the experiment.

During the first 8 hours after the treatment the dogs were closely observed in order to to register possible toxic symptoms, if any. During the subsequent 14-day follow-up period the behaviour and the general state of health of the dogs were inspected several times daily. The body weight was recorded three times a week.

The experiment was conducted between 29.09. and 13.10.1980.

RESULTS

The following mortality rate was established in the various dosage groups after termination of the 14-day follow-up period:

Study Title: Acute Percutaneous Toxicity of HOE 39866 to the Male Rat.

Accession No.: 072962

Study No.: 495/82

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 9-2-82/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH AT203; 97.2% a.i.

Doses Tested: 2.0 and 4.0 g/kg, applied dermally as 40 or 80% solutions, respectively.

Test Animal: Male Wistar (strain Hoe:WISKf[SPF71]) rats, Hoechst breeding stock; 6 rats/dose.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) Only males were studied, however when combined with the data for females in study #496/82, the two studies satisfy the requirement for acute dermal toxicity studies.

Results

No mortalities were noted at either dose level, 2.0 or 4.0 g/kg.

No clinical signs were noted in rats treated with 2.0 g/kg. Rats treated with 4.0 g/kg exhibited the following signs within 48 hours of treatment: "hyperactivity, convulsions, retracted abdomen, retracted flanks, Dalrymple's sign, increased salivation, and aggresivity".

No effect of treatment on body weight gain during the 14 day observation period was evident.

Necropsy of treated animals revealed "dark discolouration of the kidney" in both treatment groups.

Conclusion

The dermal LD_{50} in male rats is >4.0 g/kg. This value corresponds to toxicity category III.

Classification: Core-Minimum When combined with the data for females in study #496/82.

Abteilung Pharma Forschung Toxikologie
Verfasser Dr.Mayer, Dr. Weigand

Hoe 5 866 a.i.techn., acute dermal male rat

TEST PROCEDURE

The substance Hoe 59866 O H AT203 was supplied in the form of a white powder. For the acute treatment a 40 or 80 % solution was prepared in deionized water (40 or 80 g/ad 100 ml) and applied once at dose lelels of 2 000 and 4 000 mg/kg body weight to the shaven dorsal skin of groups of 6 male Wistar-rats (strain:Hoe WISKf (SPF); Hoechst breed), 198 - 207 g in weight ($\bar{x}$ = 202.4 g, s.d. = $\pm$ 2.94 g, n = 12). The animals were housed singly in plastic cages on granulated light wood bedding. They received ALTROMIN 1324, the maintenance diet produced by Altromin GmbH, Lage/Lippe and tap water ad libitum.

After the treatment, the mechanically shaven and intact dorsal skin (area of exposure appr. 30 cm^2) was covered with a strip of aluminum foil (6 x 8 cm) and secured in position around the animal's trunk by an elastic plaster bandage (Elastoplast(R), 8 cm in width). After a 24-hour exposure the dressing was removed and the treated site was washed with tepid water.

The symptoms of intoxication were registered after the dermal application. During the 14-day follow-up period the animals were weighed weekly. After termination of the follow-up period the surviving experimental animals were killed with CO_2-gas, dissected and examined macroscopically.

The test No. 329/82 was conducted between 26.07. and 09.08.82.

Study Title: Acute Percutaneous Toxicity of HOE 39866 to the Female Rat.

Accession No.: 072962

Study No.: 496/82

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 9-2-82/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH AT203; 97.2% a.i.

Doses Tested: 2.0 and 4.0 g/kg, applied dermally as 40 or 80% solutions, respectively.

Test Animal: Female Wistar (strain Hoe:WISKf[SPF71]) rats, Hoechst breeding stock.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) Only females were studied, however when combined with the data for males in study #495/82, the two studies satisfy the requirement for dermal toxicity studies.

2) Only two dose levels studied, insufficient to calculate a dermal LD_{50}. In consideration of the low order of dermal toxicity of this compound, and the fact that no mortality was observed in males at the high dose of 4 g/kg, a repeat study will not be required.

Results

One of 6 rats treated with 2 g/kg, and 2/6 rats treated with 4 g/kg died between 7 and 10 days after application of the test material. Clinical signs that were observed included: "hyperactivity, passiveness, benumbness, disequilibrium, squatting, high-legged posture, abdominal position, trembling, convulsions, retracted abdomen, retracted flanks, convulsive jumping, 'Straub' phenomenon, bristled hair, Dalrymple's sign or blepharophimosis, increased salivation, blood-coloured urine, aggressivity, masticatory movements, emaciation, and poor general condition."

The body weights of animals that died were greatly decreased. Of the animals that survived to day 14, one animal from each treatment group lost weight during the first week. All animals that survived showed a gain over initial body weights, and no dose-related effect on average body weight was apparent in these animals.

Necropsy of animals that died revealed gross signs of "all viscera markedly atrophied and dark in color". Necropsy of animals that survived to termination revealed "no abnormal findings".

Conclusion

The dermal LD_{50} in female rats $\geq$ 4.0 g/kg. This value corresponds to toxicity category III.

Classification: Core-Minimum When considered with the data for males in study #495/82.

Abteilung Pharma Forschung Toxikologie
Verfasser Dr. Mayer, Dr. Weigand

004403

Datum 2.9.1982
Berichts-Nr 496/82
Seite 2 (4)

Hoe 39866 a.i. techn., acute dermal female rat

TEST PROCEDURE

The substance Hoe 39866 O H AT203 was provided in the form of a white powder. For the acute treatment a 40 or 80 % solution was prepared in deionized water (40 or 80 g/ad 100 ml) and applied once at dose levels of 2 000 and 4 000 mg/kg body weight to the shaven dorsal skin of groups of 6 female Wistar-rats (strain:Hoe WISKf(SPF71); Hoechst breed), 175 - 187 g in weight ($\bar{x}$ = 180.4 g, s.d. = ± 4.05 g, n = 12). The animals were housed singly in plastic cages on granulated light wood bedding. They received ALTROMIN 1324, the maintenance diet produced by Altromin GmbH, Lage/ Lippe and tap water ad libitum.

After the treatment, the mechanically shaven and intact dorsal skin (area of exposure appr. 30 cm^2) was covered with a strip of aluminium foil (6 x 8 cm) and secured in position around the animal's trunk by an elastic plaster bandage (Elastoplast(R), 8 cm in width). After a 24-hour exposure the dressing was removed and the treated site was washed with tepid water.

The symptoms of intoxication, the mortality rate and the time of death were registered after the dermal application. During the 14-day follow-up period the animals were weighed weekly. Lethally intoxicated animals were dissected and the macroscopic autopsy findings were recorded. After termination of the follow-up period the surviving experimental animals were killed with CO_2-gas, dissected and also gross-examined.

The test No. 330/82 was conducted between 26.07. and 09.08.82.

Study Title: Aerosol Inhalation of HOE 39866 to the Male and Female SPF-Wistar Rat.

Accession No.: 072962

Study No.: 564/82

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 9-20-82/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH AT203; 97.2% a.i.

Doses Tested: 192 and 621 mg/m^3 (0.192 and 0.621 mg/L) for 4 hours by inhalation exposure to a 40% or 80% solution, respectively.

Test Animal: Male and female SPF-Wistar rats, Hoechst breeding stock. 6 rats/sex/dose.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) An insufficient number of doses was used for calculation of the 4-hour LC_{50}. The high dose in the present study (621 mg/m^3) is equal to 0.62 mg/L. The investigators stated that they were apparently unable to achieve a higher concentration due to the physical properties of the test article solution, however no explanation was provided beyond that statement. A more complete description of the reasons for the inability to generate a test atmosphere above 0.62 mg/L is required.

Results

A. Mortality and Clinical Signs- One of 6 males of the low dose (0.19 mg/L) group died by the fifth day after treatment. No females from this dose group died. Two of 6 males from the 0.62 mg/L group died, both between days 5 and 6. One of the 6 female rats exposed to 0.62 mg/L died between days 8 and 9.

Rats were reported to have "dose-dependent hyperactivity, passiveness, disequilibrium, blepharophimosis and jerky respiration". These findings were not quantified in the study report as to the number of animals affected.

B. Body Weights- No significant differences in the effect of the two concentrations of test article (0.19 or 0.62 mg/L) on body weights were noted. All animals lost weight the first day after treatment, however by day 14 all animals had exceeded their initial body weights.

Conclusion

An insufficient number of doses was tested for calculation of the 4-hour LC_{50}. The registrant submitted an addendum to the study report that stated that the investigators were unable to achieve a concentration in air greater than 0.62 mg/L. Since no explanation for the "technical" difficulties was provided, the study is not acceptable. The registrant may alternatively wish to test the undiluted technical material since it is a powder. Two of 6 males and 1/6 females died after exposure at this dose, which suggests that the LC_{50} is near 0.62 mg/L. This value corresponds to toxicity category II.

Classification: Core-Supplementary Insufficient number of doses for calculation of LC_{50}.

RIN 5218-93 Toxicological Review for Glufosinate (128850)

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Pages 34 through 36 are not included.

The material not included contains the following type of information:

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____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

__✓__ FIFRA registration data.

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____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Study Title: Irritance to the Rabbit Skin and Eye Mucosa.

Accession No.: 072962

Study No.: 476/82

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 9-1-82/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH AT203; 97.2% a.i.

Doses Tested: Skin irritation- 500 mg dermally applied for 24 hours; Eye irritation- 100 mg applied to conjunctival sac for 24 hours.

Test Animal: New Zealand rabbits, sex not specified, Hoechst breeding stock.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

None.

Results

A. Skin Irritation- Reactions to the test compound were assessed at 24, 48 and 72 after application to the skin. Grading was based on a range of 1 (very slight) to 4 (severe). Four of 6 rabbits with abraded skin showed "very slight" erythema 24 hours after treatment, and 1/6 rabbits with intact skin had the same reaction. Edema was not noted in any rabbits. At 48 hours 1/6 rabbits with abraded skin had "very slight" erythema. All other animals were normal at 48 hours, and by 72 hours all animals had fully recovered. The Primary Irritation Score (PIS), based on average effects at 24 and 72 hours, was 0.2. This value corresponds to Toxicity Category IV.

B. Eye Irritation- Reactions to the test compound were assessed at 1, 7, 24, 48 and 72 hours after treatment. Grading was based on combined effects on the cornea, iris, and conjunctivae (appendix 2 of study). The left eye of 9 rabbits was treated with 100 mg of the test compound; the eye was rinsed 1 minute later for 3/9 rabbits and for the remaining 6 the eye was rinsed 24 hours later. The highest score of 10 (out of 110 possible) was observed 1 hour after application in either rinsed or unrinsed eyes. No corneal lesions were noted in any animals, and 3/6 unrinsed eyes and 1/3 rinsed eyes showed inflammation of the iris, whereas 6/6 unrinsed and 3/3 rinsed eyes had inflammation of the conjunctivae. All eyes were unaffected by 72 hours after treatment. These values correspond to Toxicity Category III.

Conclusion

A. The primary skin irritation study demonstrated only "slight" erythema in 4/6 rabbits with abraded skin and 1/6 rabbits with intact skin at 24 hours after treatment. All animals appeared normal at 72 hours after treatment. The PIS = 0.2, which corresponds to Toxicity Category IV.

Classification: Core-Guideline

B. The primary eye irritation study demonstrated irritation to the iris and conjunctivae. This response was not affected by rinsing. No corneal lesions were noted, and all eyes appeared normal by 72 hours after treatment. These values correspond to Toxicity Category III.

Classification: Core-Guideline

RIN 5218-93 Toxicological Review for Glufosinate (128850)

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Study Title: Testing for Sensitizing Properties in Pirbright-White Guinea Pigs According to the Method of BUEHLER. 004403

Accession No.: 072962

Study No.: 83.0701

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 12-27-83/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH ZC95 0001; 95.3% a.i.

Doses Tested: Sensitizing- 0.5 ml of 50% solution in normal saline = 250 mg; 9 exposures for 6 hours/day over a 19 day period.
Challenge- same dose, 14 days after the last sensitizing dose.

Test Animal: Female Pirbright-White guinea pigs (Hoe: DHPK[SPFLac]), obtained from Hoechst AG, Kastengrund, SPF breeding colony.
10 in control group, 20 in sensitization/challenge group.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

None.

Results

No irritation of the application site was noted during the sensitization phase, nor were any clinical signs reported. Body weight gain was equal in treated and control animals.

Upon challenge (14 days after the last sensitization dose), no sensitization reaction was noted in any of the 20 treated animals.

Conclusion

Under the conditions of this study, the test compound failed to elicit a skin sensitization reaction.

Classification: Core-Guideline

RIN 5218-93 Toxicological Review for Glufosinate (128850)

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Study Title: Test for Mutagenicity in Bacteria Strains in the Absence and Presence of a Liver Preparation.

Accession No.: 072962

Study No.: 56/78

Sponsor/Contracting Lab.: Hoechst/Same, Krebsforschungslabor, Frankfurt.

Report Date/Submitted: 8-28-78/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH RH 012; "flussiges konzentrat 40" (liquid concentrate 40%).

Doses Tested: 0.0008 to 0.5 ul/plate, or 0.32 to 200 ug/plate.

Test System: Salmonella typhimurium, strains TA98, TA100, TA1535, and TA1537.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) No data demonstrating cytotoxicity were submitted. The rationale for the selection of doses was not documented.

2) Reported "doses" were as uL/plate. Doses should be reported as ug (or umole) of active ingredient per plate, not as the volume of test material on each plate.

3) The liquid concentrate formulation was apparently the test material used in this study. Agency guidelines require that mutagenicity testing be conducted with the Technical grade of test material. Further, the purity of the test material should be provided in English.

Results

No increase in mutation frequency was noted in any of the tester strains at any dose, with or without metabolic activation. These data are presented in Table 1. The positive controls demonstrated that the test strains of bacteria were susceptible to mutation.

Discussion

No measure of cytotoxicity was provided, although the highest dose tested (0.5 ug/plate) caused an unexplained decrease in mutation frequency in all strains as compared to the respective control. The statistical significance of this finding was not assessed by the investigators. These data suggest that this dose may have been cytotoxic, however no assessment of viability was provided. Agency guidelines for gene mutation testing require that compounds be tested to the limits of cytotoxicity or solubility.

004403

Table 1. Mutagenic Effects in Salmonella[a]

Dose (uL/plate)	S-9	TA98	TA100	TA1535	TA1537
0	-	33.8 ± 6.7	156.5 ± 19.2	22.8 ± 2.2	6.0 ± 1.8
0.0008	-	29.3 ± 3.8	148.8 ± 9.7	26.0 ± 1.6	5.5 ± 1.7
0.004	-	28.3 ± 2.9	147.8 ± 8.3	28.0 ± 2.0	5.8 ± 3.0
0.02	-	29.8 ± 5.4	151.8 ± 13.9	42.8 ± 5.7	7.0 ± 2.2
0.1	-	29.5 ± 3.3	134.0 ± 9.9	28.0 ± 4.7	5.8 ± 1.5
0.5	-	10.5 ± 2.1	78.8 ± 12.0	6.5 ± 2.5	3.3 ± 1.0
Procarbazin (5 ug/plate)	-	4365[b]	3585[b]	-	-
Streptozotocin (10 ug/plate)	-	-	-	3920[b]	-
9-Aminoacridine (100 ug/plate)	-	-	-	-	2775[b]
0	+	50.8 ± 8.9	130.0 ± 8.5	13.8 ± 2.9	10.8 ± 3.6
0.0008	+	45.0 ± 1.8	134.8 ±17.0	10.8 ± 3.3	11.0 ± 2.4
0.004	+	42.0 ±11.3	129.5 ± 6.4	16.0 ± 1.6	12.0 ± 3.7
0.02	+	45.0 ± 5.0	128.8 ± 9.3	11.3 ± 2.9	8.8 ± 2.9
0.1	+	37.8 ± 6.3	119.8 ± 6.3	7.5 ± 1.7	8.8 ± 2.9
0.5	+	14.5 ± 3.7	39.3 ±13.1	1.0 ± 1.2	4.8 ± 1.0
2-Aminoanthracene (5 ug/plate)	-	24.5[b]	142.5[b]	19.0[b]	9.0[b]
2-Aminoanthracene (5 ug/plate)	+	3175[b]	3700[b]	274[b]	82[b]

[a]data excerpted from submitted study. Values are mean ± std. dev. revertants/plate, calculated by reviewer from submitted individual data. All values are the average of 4 plates, except where noted.

[b]average of two values only.

Conclusion

Under the conditions of the test, the test compound failed to induce reverse mutations in 4 strains of S. typhimurium, with or without metabolic activation.

Classification: Unacceptable No rationale for selection of doses; no evidence of cytotoxicity; actual doses of the test material not reported (only volumes of test material applied); technical grade of test material not used in study.

I concur with the conclusions presented in this review.

4-5-85

Irving Mauer, Ph.D
Geneticist
TOX/HED (TS-769C)

RIN 5218-93 Toxicological Review for Glufosinate (128850)

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Study Type: Mutagenicity- DNA damage/repair in bacteria, and gene mutation in bacteria.

Study Title: In Vitro Microbial Assay for Mutagenicity Testing.

Accession No.: 072962

Study No.: NRI 81-7359

Sponsor/Contracting Lab.: Hoechst/Nomura Research Institute, Kanagawa, Japan

Report Date/Submitted: 4-81/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH AS 201; 92.1% a.i.

Doses Tested: 0, 50, 100, 500, 1000, 5000, and 10,000 ug/plate (Rec Assay) or 0, 5, 10, 50, 100, 500 and 1000 ug/plate (Reverse mutation).

Test System: Rec Assay- Bacillus subtilis H17 (rec+) and H45 (rec-), obtained from Natl. Research Inst. Genetics (NRIG).
Reverse Mutation- E. coli B/r WP2 Hcr$^-$Try$^-$, obtained from NRIG. S. typhimurium TA1535, TA1537, TA1538, and TA100 were obtained from SRI International, TA98 obtained from Doshisha University.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

None.

Results

A. Rec Assay- This test assesses the ability of a chemical to cause DNA damage by comparing the amount of growth in a stain of B. subtilis that lacks the capacity for DNA repair (H45) with growth in an isogenic sister-strain which has the capacity for DNA repair (H17). Under the conditions of the test, no difference in the inhibition of growth between these two strains was noted at any of the doses tested. Since the test measures the inhibition of growth in response to the test article, the requirement that chemicals be tested to the limits of cytotoxicity is satisfied. The positive control, 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2), caused a differential growth inhibition, whereas the negative controls (NaOH, HCl, and Kanamycin) produced no significant difference in growth inhibition. The test system was therefore sensitive to agents that damage DNA.

B. Reverse Mutation- No increases in mutation frequencies, with or without metabolic activation, were noted in any of the test strains at any of the doses tested (Table 1). Virtually total inhibition of growth was noted in all strains at the highest dose, 1000 ug/plate. Therefore, the requirement that chemicals be tested to the limits of cytotoxicity is satisfied. The positive controls, 2-aminoanthracene (2-AA), AF-2, 1-ethyl-2-nitro-3-nitroso-guanidine (ENNG), 9-amino-

acridine (9AC), and 2-nitrofluorene (2-NF), induced the appropriate responses. Therefore, the test systems were sensitive to agents that induce gene-mutations.

Table 1. Mutagenicity of HOE 39866 in Bacteria[a]

Dose (ug/plate)	S-9	E. coli	TA1535	TA100	TA1537	TA1538	TA98
0	-	31	8	103	10	12	24
5	-	32	9	106	8	16	29
10	-	29	8	99	10	17	26
50	-	31	7	83	9	9	16
100	-	26	5	58	8	8	16
500	-	1	2	8	5	1	3
1000	-	0	0	0	3	0	0
0	+	33	13	105	17	37	47
5	+	35	10	91	17	49	40
10	+	27	13	137	15	40	44
50	+	30	8	92	16	25	40
100	+	25	7	78	12	25	29
500	+	4	1	20	12	9	6
1000	+	1	0	0	5	0	0
DMSO	-	23	10	88	10	17	21
	+	27	11	119	14	40	44
AF-2	-	59		251			352
2-AA	-	26	8	108	9	16	22
	+	1086	112	302	121	173	136
ENNG	-		78				
9-AC	-				871		
2-NF	-					382	

[a]data excerpted from submitted study. Values are the mean number of colonies, (average of two plates), rounded to the nearest integer.

Conclusion

A. Rec Assay- Under the conditions of the test, the test article failed to cause damage to DNA that could be detected by this repair assay.

Classification: Acceptable

B. Gene Mutation- Under the conditions of the test, the test article failed to cause reverse mutations in bacteria with or without metabolic activation.

Classification: Acceptable

I concur with the conclusions presented in this review.

4-5-88

Irving Mauer, Ph.D
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RIN 5218-93 Toxicological Review for Glufosinate (128850)

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004403

Study Type: Mutagenicity- Cytogenetic assay in mice.

Study Title: Micronucleus Test With Male and Female NMRI Mice Following Oral Administration.

Accession No.: 072962

Study No.: 83.0165

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxicologie

Report Date/Submitted: 10-21-83/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH ZC95 0001; 95.3% a.i.

Doses Tested: 0, 8, 40, and 200 mg/kg (gavage) in distilled water, 2 doses 24 hours apart.

Test Animal: Male and female NMRI (Hoe: NMRKf[SPF71]) mice, obtained from Hoechst SPF breeding colony; 5/sex/dose.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) Although the doses used in this study were about 1/2 of the LD50 in mice, no evidence was presented to indicate that the test compound reached the target tissue (bone marrow) in sufficient concentration to produce an effect.

2) The route of administration of the positive control, endoxan, was not stated.

Results

The investigators stated that the "behavior of the animals remained unaffected" by treatment. No data for clinical signs or body weight were submitted.

Examination of bone marrow from treated rats revealed no difference in the number of polychromatic red blood cells (PRBCs) or normocytes (NRBCs) with micronuclei (table 1). The ratio of PRBCs to normocytes (P/N ratio) was also unaltered by treatment. Treatment with the positive control (cyclophosphamide, 100 mg/kg) caused an increase in the number of micronuclei/2000 PRBCs, and a decrease in the P/N ratio. The number of micronuclei/1000 NRBCs was not affected by cyclophosphamide.

004403

Table 1. Mouse Micronucleus Test[a]

Dose (mg/kg)	Sex	Micronuclei/ 2000 PRBCs	Micronuclei/ 1000 NRBCs	P/N Ratio
0	M	9.2 ± 1.5	2.4 ± 0.9	0.81 ± 0.06
	F	5.2 ± 1.9	1.4 ± 0.9	0.98 ± 0.09
8	M	7.6 ± 3.5	2.2 ± 0.4	0.79 ± 0.08
	F	4.8 ± 1.6	1.8 ± 1.3	0.83 ± 0.06
40	M	9.0 ± 2.2	1.8 ± 1.3	0.90 ± 0.19
	F	3.4 ± 1.5	1.6 ± 1.1	1.00 ± 0.19
200	M	4.8 ± 2.2	1.0 ± 0.7	0.83 ± 0.21
	F	4.8 ± 2.3	1.2 ± 0.8	0.99 ± 0.07
CP	M	139.0 ±41.7	2.4 ± 1.1	0.57 ± 0.06
	F	137.6 ±32.1	2.4 ± 0.5	0.60 ± 0.08

[a]data excerpted from submitted study. Values are mean ± std. dev., calculated by reviewer from submitted individual animal data.

CP = cyclophosphamide (Endoxan), 100 mg/kg; route of adminostration not described.

P/N = ratio of polychromatic erythrocytes to normochromatic erythrocytes.

Conclusion

Under the conditions of the test, the test article failed to have an effect on the number of micronuclei found in polychromatic or normochromatic erythrocytes. No effect on the ratio of the two types of erythrocytes was noted, therefore no evidence of a toxic effect on bone marrow cells was observed. The positive control, cyclophosphamide, caused an increase in the incidence of micronuclei, and a decrease in the ratio of polychromatic to normochromatic RBCs. The test system was therefore sensitive to agents which disrupt chromosome and/or mitotic spindle formation.

Classification: Inconclusive No evidence was presented to document that the test article reached the bone marrow in sufficient concentration to produce any effect.

I concur with the conclusions presented in this review.

4-15-85

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Study Title: Two-Week Subacute Toxicity in Rats.

Accession No.: 072963

Study No.: NRI 81-7850

Sponsor/Contracting Lab.: Hoechst/Nomura Research Institute, Kanagawa, Japan

Report Date/Submitted: 8-81/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH AS 201; 92.1% a.i.

Doses Tested: 0, 8, 16, 32, 64, 320, 3200 ppm in feed.

Test Animal: Male and female F344/DuCrj rats, obtained from Nihon Charles River Co., Ltd.; 10/sex/dose.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) No histological examination of tissues.

2) Range-finding study for 90-day feeding study.

Results

A. Clinical Signs and Mortality- The methods specified that animals were examined daily. The only data for clinical signs that were submitted were in a chart which indicated that no signs were noted in any animals at any dose.

No animals died during treatment.

B. Body Weight- Statistically significant decreases in body weight were noted in male and female high dose (3200 ppm) rats as early as day 3 of treatment, although by day 14 (termination) only males were significantly decreased (Table 1). Body weight gain over the 14-day treatment period was significantly decreased in males fed 64 ppm or more, and in females fed 3200 ppm.

004403

Table 1. Effect of Treatment on Body Weight Gain[a]

Dose (ppm)	MALES Day 0	Day 6	Day 14	Total BW Gain	FEMALES Day 0	Day 6	Day 14	Total BW Gain
0	108±4	134±5	175±8	67±5	92±3	105±3	123±4	32±3
8	108±4	134±6	174±12	66±10	91±3	105±4	124±5	32±3
16	108±4	131±5	169±9	62±7	91±3	105±4	125±5	34±4
32	108±4	133±8	171±14	64±11	91±3	104±3	122±4	31±3
64	108±3	132±5	169±7	61±7*	91±3	104±3	122±4	31±3
320	108±4	131±4	170±8	62±5*	91±3	104±3	122±4	31±3
3200	108±4	122±5**	161±8**	53±7**	91±3	98±3**	120±5	28±4*

[a]data and statistics excerpted from submitted study.

*p < 0.05, **p < 0.01 by Student's t-test.

C. Food Consumption and Compound Intake- Food consumption (determined once per week) was decreased in males fed 64 ppm during week 2 only, and was decreased in weeks 1 and 2 in males fed 320 and 3200 ppm (table 2). Consumption in females was decreased only in high dose animals during weeks 1 and 2.

Water intake was measured on the same schedule as food consumption. This parameter was significantly decreased only in high dose males during week 1, and was unaffected in other animals at other times.

The dose of the test article that was received by treated animals was greater during the second week compared to the first, and was higher in males than in females (table 2).

004403

Table 2. Food Consumption and Compound Intake[a]

Dose (ppm)	Week 1 Males	Week 1 Females	Week 2 Males	Week 2 Females
0	13.0 ± 0.6[b]	11.4 ± 0.6	15.4 ± 0.6	12.6 ± 0.8
8	12.8 ± 1.0 (0.10 ± 0.01)[c]	11.1 ± 0.6 (0.09 ± 0.01)	15.0 ± 1.2 (0.12 ± 0.01)	12.0 ± 0.8 (0.10 ± 0.01)
16	12.4 ± 0.7 (0.20 ± 0.01)	11.1 ± 0.6 (0.18 ± 0.01)	14.2 ± 1.0** (0.23 ± 0.02)	12.5 ± 0.5 (0.20 ± 0.01)
32	12.7 ± 0.8 (0.41 ± 0.03)	11.2 ± 0.4 (0.36 ± 0.01)	14.6 ± 1.4 (0.47 ± 0.05)	12.3 ± 0.6 (0.40 ± 0.02)
64	12.3 ± 0.9 (0.79 ± 0.06)	10.9 ± 0.5 (0.70 ± 0.03)	14.7 ± 0.8* (0.94 ± 0.05)	12.5 ± 0.9 (0.80 ± 0.06)
320	12.1 ± 0.7** (3.88 ± 0.22)	11.1 ± 1.2 (3.55 ± 0.39)	14.5 ± 1.1[+] (4.64 ± 0.34)	12.7 ± 1.4 (4.05 ± 0.45)
3200	9.5 ± 0.5** (30.3 ± 1.7)	8.6 ± 0.6** (27.6 ± 1.8)	13.8 ± 1.0[++] (44.3 ± 3.3)	11.5 ± 0.7** (36.9 ± 2.1)

[a]data and statistics excerpted from submitted study.

[b]food consumption in grams/rat/day, mean ± std. dev. calculated by investigators.

[c]compound intake in mg/kg/day, mean ± std. dev. calculated by investigators.

*$p < 0.05$, **$p < 0.01$ by Student's T-test.

[+]$p < 0.05$, [++]$p < 0.01$ by Aspin-Welch's T-test.

D. Clinical Pathology (1) Hematology- (a) Males- Statistically significant differences were occassionally noted in several of the measured parameters, however apparent dose-dependent trends were noted only for white blood cell (WBC) count and platelet count (table 3). Although hematocrit was decreased in high dose (3200 ppm) males, no effects on red blood cell (RBC) count, hemoglobin concentration or content, or mean cell volume were apparent. The clinical significance of slight (approximately 15%) decreases in WBCs or platelets is not clear, however these data may indicate an effect of the test compound on the synthesis of these cells in the bone marrow. No significant effects on the differential cell count were apparent.

(b) Females- As was noted for males, apparent dose-related decreases in WBC and platelet counts were noted in treated females. Unlike males, these changes were accompanied by an increase in RBC count and hematocrit. Total hemoglobin concentration, mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCC) were significantly decreased. The clinical signficance of these changes is not obvious, however the data suggest an effect

of the test article on the bone marrow resulting in a decreased synthesis of leukocytes and thrombocytes. The effects on erythrocytes noted in females may be an adaptive response to the test article since the data are consistent with a release of immature erythrocytes. No significant effects on the differential leukocyte count were apparent.

D. (2). Clinical Chemistry- (a) Males- No dose-related trends were apparent for SGOT, SGPT, LDH, ALP, glucose, BUN, total protein or albumin/globulin concentrations, bilirubin, uric acid, inorganic phosphorus, calcium, or potassium. Apparent dose-related increases in serum creatinine, sodium and choride were noted. These changes are consistent with an effect on kidney function.

(b) Females- The only parameter which was affected in an apparent dose-related manner was serum creatinine. Unlike the effects noted in males, these changes were not accompanied by effects on serum sodium or chloride, although a statistically significant decrease in serum calcium was noted in high dose females. An approximately 40% ($p < 0.05$) decrease in LDH was also noted in high dose females, however the clinical significance of a decrease in this parameter is unknown.

D. (3) Urinalysis- No signficant effects on this parameter were noted in male or female rats at any dose.

E. Necropsy Data: (1) Gross Observations- No toxicologically significant observations were noted at necropsy.

(2) Organ Weights and Ratios- Statistically significant decreases in the absolute organ weights of high dose males were noted for brain, thymus, heart, lung, liver, and spleen. The only tissues for which this change appeared to be dose-related were liver and spleen. Liver/body weight and spleen/body weight ratios were also significantly decreased ($p < 0.05$) only in high dose males. Since no effects on liver enzymes were noted, these changes in organ weights may be related to the decrease in body weight gain noted in treated males.

In females, statistically significant decreases in the absolute weights of heart, lung, liver, spleen, and ovaries were noted in high dose animals. The only tissues in which this decrease appeared to be dose-related were liver and ovary. Heart/body weight and ovary/body weight ratios were also significantly decreased in high dose females.

Table 3. Effects on Hematological Parameters- Males[a]

Dose (ppm)	RBC (10^4/ul)	WBC (10^2/ul)	Hematocrit (%)	Hemoglobin (g/dl)	Platelets (10^3/ul)	MCH	MCV	MCC
0	675±27	71±5	42.7±1.6	15.3±0.3	677±20	23±1	63±0	36±1
8	680±34	65±4*	42.8±2.0	15.3±0.3	662±17	23±1	63±1	36±2
16	683±34	66±5	42.7±2.2	15.3±0.3	628±38++	22±1	62±1**	36±2
32	684±17	63±5**	43.0±0.6	15.2±0.3	614±31**	22±0	63±1	35±1
64	701±27*	64±4**	44.7±3.8	15.3±0.2	649±33*	22±1*	64±3	34±2
320	692±29	61±4**	43.5±1.6	15.1±0.2	650±22*	22±1	63±1	35±1
3200	653±23	60±4**	40.9±1.5*	15.0±0.3	613±38++	23±1	63±1**	37±2
				FEMALES				
0	637±38	72±6	39.2±2.8	16.6±0.2	579±36	26±2	62±2	43±3
8	621±33	69±5	38.7±2.2	16.5±0.2	580±23	27±1	62±1	43±2
16	641±49	64±4**	40.0±2.9	16.5±0.3	600±36	26±2	62±0	41±2
32	674±25*	63±3++	41.8±1.6+	16.6±0.2	551±25	25±1*	62±0	40±1+
64	666±41	58±8*	41.3±2.2	16.5±0.2	559±37	25±1	62±1	40±2
320	680±37*	60±11++	42.2±2.1*	16.3±0.8	573±43	24±2*	62±0	39±3*
3200	678±36*	59±7**	42.0±2.1*	16.1±0.3++	537±42*	24±1**	62±1	38±2**

[a]data and statistics excerpted from submitted study. Values are mean ± std. dev.

*p<0.05, **p<0.01 by Student's T-test; +p<0.05, ++p<0.01 by Aspin-Welch's T-test.

Conclusion

The test article caused a decrease in body weight gain in males fed 64 ppm or more, and in females fed 3200 ppm. These decreases were likely related to decreased food consumption, which was significantly decreased in a pattern similar to the observed decreases in weight gain.

Apparent dose-related decreases in leukocyte and platelet counts were noted in male and female rats. Increases in erythrocyte count and related changes in corpuscular hemoglobin concentration were noted in females only.

Dose-related increases in serum creatinine and electrolyte (Na and Cl) concentrations were noted in treated males. A similar dose-related increase in creatinine was also noted in females, however the only effect on electrolytes was a slight decrease in serum calcium levels. These effects on serum chemistries suggest an effect of the test article on kidney function.

NOEL = 8 ppm
LEL = 16 ppm Decreased leukocyte and platelet counts, increased serum creatinine, increased serum Na and Cl (males only).

Classification: Core-Supplementary No histological examination of tissues. This study was designed as a range-finding study for the 90-day subchronic study.

RIN 5218-93 Toxicological Review for Glufosinate (128850)

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Study Title: Thirteen-Week Subchronic Toxicity in Rats.

Accession No.: 072963

Study No.: NRI 81-7860

Sponsor/Contracting Lab.: Hoechst/Nomura Research Institute, Kanagawa, Japan

Report Date/Submitted: 9-82/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH AS201; 92.1% a.i.

Doses Tested: 0, 8, 64, 500, 4000 ppm in feed.

Test Animal: Male and female F344/DuCrj rats, obtained from Charles River Japan Inc.; 30/sex/dose.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1. For each group, 20 rats/sex/dose were sacrificed after 13 weeks (Group I), and an additional 10 rats/sex/dose were allowed a 4-week recovery period before sacrifice (Group II).

2. An additional 10 rats/sex/dose were treated for 13 weeks for measurement of liver glutamine synthetase activity. At termination (week 13) 5 rats/sex/dose were assayed for this enzyme activity. The remaining 5 rats/sex/dose were allowed a 4-week recovery period before assay of activity.

Results

A. Clinical Signs and Mortality- No treatment-related clinical signs were noted. One high dose (4000 ppm) male died on day 71; necropsy revealed "miliary" tumors of the thoracic cavity. No other animals died during the study.

B. Body Weights- Statistically significant decreases in body weight gain were noted in high dose male and female rats during the first 3 weeks of the study, however by termination (day 91) these animals had an average body weight that was greater than the respective controls (Table 1).

The weight gain of animals during the recovery period (days 91-119) was similar in control and treatment groups (Table 1).

Table 1. Effect of Treatment on Body Weight Gain[a]

Dose (ppm)	Day 0	Day 21	Day 56	Day 91	Weight Gain Days 0-91	Weight Gain Days 91-119
			MALES			
0	95 ± 3	180 ± 13	249 ± 26	290 ± 26	195 ± 27	24 ± 7
8	95 ± 3	181 ± 16	259 ± 24	302 ± 26	207 ± 26	24 ± 5
64	95 ± 3	177 ± 10	254 ± 16	300 ± 19	204 ± 19	22 ± 8
500	95 ± 3	178 ± 13	260 ± 20	304 ± 18+	209 ± 18+	24 ± 5
4000	95 ± 3	168 ± 11**	257 ± 18	301 ± 16	205 ± 16	19 ± 5
			FEMALES			
0	83 ± 3	128 ± 5	157 ± 8	171 ± 9	87 ± 8	9 ± 3
8	83 ± 3	128 ± 6	156 ± 9	170 ± 10	87 ± 10	5 ± 4*
64	83 ± 3	129 ± 4	158 ± 7	172 ± 9	89 ± 9	9 ± 2
500	83 ± 3	127 ± 6	157 ± 9	172 ± 9	89 ± 9	8 ± 4
4000	83 ± 3	126 ± 5*	160 ± 8	177 ± 9**	94 ± 9**	8 ± 3

[a]data and statistics excerpted from submitted study. Values are mean ± std. dev. in grams.

*$p < 0.05$, **$p < 0.01$ by Student's T-test

+$p < 0.05$ by Aspin-Welch's T-test.

C. Food Consumption and Compound Intake- The test compound had an effect on food consumption that was similar to the effect on weight gain. During the first weeks of the study, high dose males and females ate less than control, however by the final weeks of the study these animals ate significantly more than control (table 2). Males differed from females, however, in that all treated males ate significantly more than control from week 9 to termination, whereas only high dose females showed this response. This pattern continued during the first part of the recovery period (i.e. weeks 14 and 15), however by the final week of recovery (week 17) no difference in food consumption was apparent in any of the test groups. Therefore, the increased food consumption appears to be treatment-related, and is not a simple rebound due to food rejection during the early part of the study.

Food efficiency (calculated by the investigators) was related to the effects of the test compound on food consumption. In the first weeks efficiency was decreased in the high dose rats relative to control, however in later weeks efficiency was greater than control as animals ate more food and gained more weight than control. At termination (week 13), efficiency was significantly lower in high dose males compared to control, but was similar to control in females. During the recovery period, efficiency was similar in all groups.

Water consumption was affected in a manner similar to food intake. High dose males drank less water than control in the first weeks of the study, but in the latter portion of the study, these animals drank significantly more water than control. High dose females also drank significantly less water initially, but in the latter part of the study no difference from control was apparent.

All treated rats received a higher dose (mg/kg) of the test material in the initial part of the study relative to the later parts. As is commonly observed, females received a higher dose in mg/kg than males that received the same dietary dose in ppm.

Table 2. Food Consumption and Compound Intake[a]

Dose (ppm)	Week 1		Week 13		Week 17	
	Male	Female	Male	Female	Male	Female
0	12.1±0.7[b]	10.7±0.9	14.2±1.4	11.0±1.6	14.6±1.2	12.2±1.5
8	12.3±0.8 (0.80±0.04)[c]	11.0±0.7 (0.87±0.05)	15.0±1.5* (0.40±0.02)	10.9±1.3 (0.51±0.05)	15.2±1.0	12.0±1.5
64	11.9±0.7 (6.23±0.24)	10.8±0.8 (6.90±0.53)	15.4±1.5** (3.28±0.19)	10.5±1.1 (3.92±0.42)	15.7±1.6	11.5±1.2
500	11.6±0.6** (47.4±1.84)	10.4±0.6 (53.0±3.08)	15.6±1.6** (25.7±1.97)	10.9±1.1 (31.8±3.14)	15.6±2.4	11.4±0.9
4000	9.0±0.9** (328±25)	8.0±1.0** (352±40)	16.0±1.3** (213±10)	12.0±1.7* (271±38)	15.7±1.1	12.4±1.5

[a]data and statistics excerpted from submitted study.

[b]food consumption, grams/rat/day, mean ± std. dev.

[c]compound intake, mg/kg/day, mean ± std. dev.

*$p < 0.05$, **$p < 0.01$ by Student's T-test.

D. Clinical Pathology: (1) Hematology- These parameters were measured in 10 rats/sex/dose after 47 days of treatment and at termination (table 3). No toxicologically significant effects were noted in males after 47 days of treatment. In females at 47 days, a decrease in leukocyte (WBC) count was noted in high dose animals that appeared to be dose-related. An increase in erythrocyte (RBC) count was also noted in 8, 64, and 500 ppm females, however high dose (4000 ppm) females had RBC counts similar to control. Corresponding changes in hemoglobin (Hb) content and hematocrit (Ht) were also noted in these females.

At termination, decreases in WBC count that were apparently inversely dose-related were noted in treated males. A statistically significant increase in RBC count was also noted in 500 ppm but not other treated males. In females at termination, no dose-related effects on WBC count were apparent. However, a decrease in RBC count was noted that appeared to be treatment-related but was not statistically significant. Corresponding decreases in Hb and Ht were also noted in these animals.

Table 3. Effects on Hematological Parameters[a] - Day 47

Dose (ppm)	MALES RBC (10^4 /ul)	WBC (10^2 /ul)	Hematocrit (%)	Hemoglobin (g/dl)	FEMALES RBC (10^4 /ul)	WBC (10^2 /ul)	Hematocrit (%)	Hemoglobin (g/dl)
0	785±67	62±6	43.5±3.2	16.1±0.6	819±30	57±10	46.1±1.5	15.9±0.4
8	797±36	63±6	44.1±2.2	16.1±0.3	875±20**	59± 6	48.9±1.2**	16.5±0.2**
64	800±32	65±6	44.3±2.4	16.2±0.3	864±40*	55± 5	48.0±2.4*	16.3±0.3**
500	794±38	64±7	44.0±1.9	16.2±0.2	843±33	54± 7	47.1±1.8	16.1±0.4
4000	741±50	61±6	41.3±2.5	16.0±0.2	819±41	48± 5+	46.1±2.2	16.0±0.4
				WEEK 13 (TERMINATION)				
0	851±29	72±4	46.5±2.3	16.6±0.6	852±53	66±11	49.1±3.1	17.0±0.2
8	878±44	64±4**	47.5±2.1	16.9±0.1	836±44	58± 6	48.0±2.4	16.7±0.2**
64	863±32	65±5**	46.8±1.4	16.9±0.2	815±37	57± 7*	47.0±2.0	16.4±0.3**
500	907±31**	66±6*	48.8±1.1+	17.0±0.2	823±41	62± 5	46.8±2.0	16.9±0.3
4000	863±19	69±4	46.8±0.8	16.8±0.3	818±49	64± 7	46.6±2.5	16.7±0.2**

[a]data and statistics excerpted from submitted study. Values are mean ± std. dev.

*p<0.05, **p<0.01 by Student's T-test; +p<0.05, ++p<0.01 by Aspin-Welch's T-test.

D. Clinical Pathology: (2) Serum Chemistry- These parameters were measured at 47 days and at termination in 10 rats/sex/dose that were not measured for hematology. At 47 days, 64 and 500 ppm males had increases in lactate dehydrogenase activity (LDH) that were statistically significant. However, this effect was not strictly dose-related since 4000 ppm males were not different from control. Statistically-significant decreases in blood glucose and calcium were also noted at this time in all male treatment groups, although the decrease in blood glucose was not significant in low dose (8 ppm) rats.

High dose females at 47 days had treatment-related decreases in LDH activity. Blood glucose and uric acid were also decreased in all dose groups, however the decrease was judged statistically significant only in the 8, 500, and 4000 ppm groups. Neither effect was strictly dose-dependent since in both cases the largest decrease was noted in the low dose (8 ppm) group.

At termination, the only apparent treatment-related changes noted in males were decreases in uric acid content, and total and direct bilirubin. The toxicological significance of decreases in these parameters is unclear. Typically, an effect on liver function is indicated by an increase in total serum bilirubin and/or an alteration in the ratio of direct to indirect bilirubin. The clinical correlates of decreases in serum levels of bilirubin have not been described. Similarly, disease states which affect serum uric acid content typically cause an increase rather than a decrease in this parameter. Therefore these effects are not considered to be toxicologically significant.

The only change noted in females at termination that could possibly be treatment-related was an increase in serum creatinine content in the 64 and 500 ppm treatment groups. Although this was also noted at 47 days, no effect on electrolytes or blood urea nitrogen was noted in these animals at

Table 4. Effects on Serum Chemistry[a]

Dose (ppm)	LDH (IU/L)	Glucose (mg/dL)	Creat. (mg/dL)	Urate (mg/dL)	Calcium (mg/dL)	LDH (IU/L)	Glucose (mg/dL)	Creat. (mg/dL)	Urate (mg/dL)	Calcium (mg/dL)
	MALES				DAY 47			FEMALES		
0	676±211	140±8	0.57±0.09	1.3±0.4	10.4±0.3	518±121	133±5	0.48±0.03	1.2±0.3	10.3±0.6
8	707±119	134±6	0.55±0.06	0.7±0.2^{++}	10.1±0.2*	530±123	124±8**	0.48±0.03	0.6±0.1^{++}	10.3±0.7
64	888±153*	130±7**	0.56±0.05	1.0±0.2	10.0±0.4*	459± 55	129±5	0.53±0.05*	0.8±0.5	10.5±0.4
500	874±194*	127±6**	0.55±0.06	0.9±0.1^{+}	9.9±0.2^{++}	438± 99	129±4*	0.51±0.03	0.6±0.1^{++}	10.2±0.5
4000	714±132	134±10	0.56±0.08	0.9±0.2^{+}	9.6±0.3**	365± 49^{++}	127±6*	0.54±0.03**	0.7±0.2**	10.7±0.3
					WEEK 13					
0	497±215	181±14	0.63±0.05	1.3±0.4	10.5±0.3	283±165	180±21	0.59±0.07	1.1±0.5	10.2±0.3
8	542±243	185± 8	0.65±0.07	0.9±0.3*	10.4±0.2	176±108	191±13	0.65±0.08	1.0±0.4	10.1±0.3
64	418±141	186±12	0.66±0.04	0.8±0.3**	10.5±0.2	205± 78	178±23	0.68±0.05**	1.0±0.3	10.1±0.2
500	454±209	180±20	0.67±0.04	0.8±0.3**	10.5±0.2	162± 52	173±14	0.69±0.09*	1.0±0.4	10.3±0.2
4000	342±112	173± 8	0.65±0.02	0.7±0.3**	10.4±0.2	252±136	174±17	0.63±0.05	1.0±0.4	10.2±0.3

[a]data and statistics excerpted from submitted study. Values are mean ± std. dev.

*$p < 0.05$, **$p < 0.01$ by Student's T-test; $^{+}p < 0.05$, $^{++}p < 0.01$ by Aspin-Welch's T-test.

either time point, nor was the increase in serum creatinine at termination dose-dependent since the effect was greatest in the intermediate dose groups, and the low and high dose groups were not different from control. Other effects noted at 47 days, such as the apparent decrease in blood glucose, were not apparent at termination in males or females.

D. (3) Urinalysis- An apparent treatment-related decrease in the pH of urine in high dose males and females was noted, and the specific gravity of urine in high dose females was also significantly increased compared to control. After the 4-week recovery period, the decrease in pH was still apparent, however the specific gravity of urine in high dose females was not different from control.

D. (4) Glutamine Synthetase Activity (appendix)- 10 rats/sex were fed the test diets for 13 weeks. At the end of the treatment period, 5 rats/sex/dose were sacrificed and the liver removed for determination of glutamine synthetase (GS) activity. The remaining 5 rats/sex/dose were allowed a 4-week recovery period before assay of liver GS activity.

A dose-related decrease in GS activity was noted in male and female rats assayed at 13 weeks (table 5). Activity in high dose males and females was about 30% of the control value. No significant differences were noted between control and treated animals allowed a 4-week recovery period, and no effect on serum ammonia concentration was noted in any of the treated animals. Therefore, the effect of the test article on GS activity was consistent with a reversible type inhibition. Because of the structural similarity of the test article to glutamic acid, the endogenous substrate for glutamine synthetase, the investigators speculated that the inhibition was competitive. However, the submitted data do not demonstrate competition for the enzyme by the test article.

Further, the use of only 5 animals/sex/dose is insufficient for an accurate quantitation of an effect on this enzyme activity. For example, low dose (8 ppm) males had liver GS activity that was decreased by 17% relative to control, and although apparent dose-related decreases were noted in the 64 and 500 ppm groups, the effect was judged statistically significant only in the high dose (4000 ppm) group (60% decrease, $p < 0.05$). Therefore, although these data demonstrate a mechanism of activity of the test article, they are inadequate for determination of a NOEL for this effect.

Table 5. Effect on Liver Glutamine Synthetase Activity[a]

Dose (ppm)	Week 13		Week 17	
	Male	Female	Male	Female
0	1.36±0.34	1.53±0.11	1.40±0.36	1.30±0.10
8	1.13±0.13	1.54±0.06	1.33±0.08	1.34±0.07
64	0.99±0.22	1.28±0.19	1.22±0.08	1.41±0.10
500	0.97±0.06	0.94±0.06*	1.39±0.07	1.36±0.09
4000	0.54±0.06*	0.63±0.05*	1.26±0.09	1.50±0.10

[a]data and statistics excerpted from submitted study. Values are umol product/mg protein/20 min., mean ± std. dev.

*$p < 0.05$ by Student's T-test.

E. Necropsy Data: (1) Gross Observations- No significant macroscopic findings were noted at necropsy in animals sacrificed at week 13 or at week 17.

(2) Organ Weights and Ratios- Apparently dose-related increases in the absolute weights of thymus (significant at 500 and 4000 ppm), kidneys (significant at all dose levels), and adrenals (significant at all dose levels) were noted in treated males (table 6).

Increases in thymus (significant at 500 ppm only), and kidney weights (significant at high dose only) were also noted in treated females, however adrenal weights were not significantly different from control. The absolute weights of brain appeared to be decreased in a dose-related manner in treated females (significant at 8, 500, and 4000 ppm dose levels) but not males.

Kidney/body weight ratios were increased in treated males and females in a dose-related manner, with statistical significance for this effect at 64 ppm and above in males and at 4000 ppm in females. Thymus/body weight ratios were also increased in males fed 4000 ppm (table 6). Decreased brain/body weight ratios in females (statistically significant at 500 and 4000 ppm), and testis/body weight ratios in males (statistically significant at 64 ppm and above), were noted that were apparently treatment-related. The decrease in absolute and relative brain weights is of toxicological concern because these animals actually gained more body weight than control, and the brain typically does not fluctuate in weight as much as other organs. Since a similar decrease in brain weight was not apparent in rats allowed a 4-week recovery period, the findings noted at the 13-week sacrifice may have been spurious and not related to treatment. However, because of the apparent dose-dependency of the effect at 13 weeks, and the well-known biological activity of glutamate and structural analogues in the brain, this reviewer believes that the conservative approach is to consider the brain findings as treatment-related until longer-term studies are submitted by the registrant which demonstrate otherwise.

The only statistically significant effect noted in males allowed a 4-week recovery period was an increase in absolute and relative kidney weights in 500 and 4000 ppm rats. An increase in absolute thymus weight was noted in high dose females, however thymus/body weight ratios were not significantly different from control. Absolute kidney weights were decreased in 64 and 500 ppm females, and increased in 4000 ppm females, however kidney/body weight ratios were not affected in a toxicologically meaningful manner.

(3) Histology- Microscopic examination of treated tissues revealed no treatment-related changes. Congestion and focal necrosis of the liver were noted in the single high dose male that died on day 71. This animal also had a mesothelioma of the chest and thickening of the pericardium. No other significant findings were noted in treated rats sacrificed at termination (week 13) or in animals allowed to recover for 4-weeks (sacrificed at week 17).

Table 6. Organ Weights and Ratios[a]

	MALE					FEMALE				
DOSE (ppm)	0	8	64	500	4000	0	8	64	500	4000
Brain	1860±54	1892±68	1875±33	1907±46**	1865±62	1775±44	1743±34*	1751±32	1746±37*	1733±36**
/BW	654±54	634±52	633±40	629±35	633±34	1051±50	1035±44	1030±59	1007±48**	995±54**
Thymus	169±19	177±22	182±22	186±15**	188±20**	144±13	148±10	150±13	155±10**	151±14
	59±7	59±5	61±7	61±6	64±6*	86±9	88±7	88±7	89±7	86±8
Kidney	1773±172	1900±165*	1900±142*	1996±144**	2106±184**	1173±99	1160±82	1177±71	1217±63	1297±81**
	620±27	634±29	639±30*	656±26**	712±36**	693±45	687±36	691±21	701±34	743±30+
Adrenals	35±5	38±4*	39±4**	40±5**	40±5**	44±5	43±4	44±5	46±4	46±6
	12±2	13±1	13±1	13±2	13±1*	26±2	25±2	26±3	27±2	26±3
Gonads	2752±109	2800±160	2727±115	2796±78	2739±123	56±6	55±7	56±7	57±6	57±8
	967±71	936±54	920±63*	922±47+	928±41+	33±3	33±3	33±4	33±3	33±5

Organ Weights After 4-Week Recovery[a]

Brain	1943±85	1917±41	1913±45	1942±43	1908±53	1767±23	1764±40	1779±23	1765±36	1788±35
/BW	612±42	585±36	593±26	596±32	585±26	976±50	993±67	976±46	1003±43	942±43
Thymus	149±18	151±11	144±15	145±16	146±18	126±11	127±10	130±11	123±18	138±14*
	47±4	46±4	45±4	44±4	45±6	69±7	72±6	71±6	69±8	73±7
Kidney	1907±130	1964±134	1952±101	2060±74**	2091±136**	1230±48	1206±86	1179±41*	1182±47*	1305±47**
	599±18	598±18	604±29	631±33*	640±24**	679±26	677±31	647±37*	671±32	687±19
Adrenals	38±5	40±4	38±3	38±3	40±3	48±4	48±4	45±3	46±4	50±3
	12±1	12±1	12±1	12±1	12±1	26±2	27±1	25±2	26±3	26±2
Gonads	2832±133	2908±142	2806±121	2848±118	2830±161	56±5	56±4	56±7	53±3	62±7*
	891±60	887±44	866±52	872±31	866±28	31±3	31±2	31±3	30±3	33±3

[a]data and statistics excerpted from submitted study. Values are mean ± std. dev. in mgs. or mg% (ratios).

*p < 0.05, **p < 0.01 by Student's T-test; +p < 0.05, ++p < 0.01 by Aspin-Welch's T-test.

Conclusion

Increased food consumption was noted in males fed diets containing 8 ppm (LDT) and above, and in females fed the high dose (4000 ppm) diet. This effect was reversible as animals allowed a 4 week recovery period had food consumption that was similar to control. A statistically significant increase in body weight gain was only noted in 500 ppm males and 4000 ppm females.

Alterations in RBC and WBC counts were also noted in males and females. Erythrocyte counts in 8 and 64 ppm females were increased at 47 days. The RBC count was not significantly different from control at termination, although hemoglobin concentration was significantly decreased in 8, 64 and 4000 ppm females at 13 weeks. In contrast, no effects on erythrocytes were noted in males at day 47, however a decrease in the WBC count was noted at 13 weeks in 8, 64 and 500 ppm males that appeared to be treatment-related.

A number of changes in serum chemistries were noted at 47 days. Dose-related decreases in serum glucose, uric acid and bilirubin were noted in male and female rats. As noted previously, the clinical significance of decreases in urate or bilirubin is unclear. A decrease in blood glucose could be due to oversecretion of insulin, inhibition of gluconeogenesis, or increased utilization of glucose as an energy source. An increase in serum creatinine in females and a decrease in serum calcium in males were also noted at 47 days. Either of these effects could indicate an effect on kidney function, although blood calcium levels are normally under close hormonal regulation. The only effects noted at termination were an increase in serum creatinine in females fed diets of 64 and 500 ppm, and a decrease in serum urate in all treated males. Blood glucose levels were not statistically different from control at termination in either males or females. Other serum chemistry parameters were not significantly altered at this time.

At necropsy, the only significant findings noted were a dose-related decrease in absolute and relative kidney weights in both male (64 ppm and above) and female (4000 ppm) rats, and an apparent dose-related decrease in absolute and relative brain weights in 500 and 4000 ppm females. The only significant change noted in rats allowed a 4-week recovery period was an increase in absolute and relative kidney weights in 500 and 4000 ppm males. Although the decrease in brain weights was not observed in animals provided a recovery period, the effect on brain weights noted at 13 weeks is considered treatment-related until evidence to the contrary is presented.

In summary, the test article appears to have an effect on the kidney as evidenced by increased organ weights in males, and on the brain as evidenced by decreased absolute and relative weights in females. Other alterations in hematology and serum chemistry measurements may be related to the apparent ability of the test compound to inhibit enzyme reactions involving glutamate as a substrate.

NOEL = 8 ppm
LEL = 64 ppm Increased absolute and kidney/body weight ratios in males.

Classification: Core-Guideline

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RIN 5218-93 Toxicological Review for Glufosinate (128850)

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Study Title: Subchronic (90-Day) Oral Toxicity Study in Dogs.

Accession No.: 072964

Study No.: V 82.318/201720

Sponsor/Contracting Lab.: Hoechst/Inst. CIVO-Tox. and Nutrition TNO, Netherlands

Report Date/Submitted: 11-82/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH AS201; 92.1% a.i.

Doses Tested: 0, 4, 8, 16, 64, 256 ppm in feed.

Test Animal: Male and female Beagle dogs, obtained from Central Inst. for the Breeding of Lab. Animals TNO, Zeist, Netherlands; 4/sex/dose.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

None.

Results

A. Stability and Homogeneity of the Test Diet- Test diets were prepared approximately every 2 weeks. Diets were analyzed approximately once/month for content of the test article. The diets were within 10% of the targeted levels, with the exception of the first batch of the low dose (4 ppm) diet, which had an average content of 6 ± 1.8 ppm based on 6 samples of this diet. No test compound was detected in the control diets.

The concentration of the test article in prepared diets was found to decrease by about 10% over 2 weeks when stored at room temperature.

B. Clinical Signs and Mortality- No significant clinical signs were noted that could be considered to be treatment-related. No mortalities were reported.

C. Body Weights- Statistically significant decreases in mean body weights were noted at termination only in female dogs fed diets containing 8, 64 and 256 ppm. The average body weights of males fed diets containing 16 ppm or more of the test article were about 5% less than control, however the differences were not statistically significant (table 1).

Table 1. Effect of Treatment on Body Weights[a]

Dose (ppm)	MALES Day 0	MALES Day 49	MALES Day 91	FEMALES Day 0	FEMALES Day 49	FEMALES Day 91
0	12.5±1.4	13.5±1.5	14.3±1.7	11.3±1.2	12.7±1.1	13.1±1.1
4	12.4±1.1	13.3±1.2	14.1±1.2	11.7±1.2	12.9±1.2	13.1±1.2
8	12.7±1.2	13.7±1.0	14.2±0.9	11.0±0.6	12.2±0.9	11.7±0.8**
16	12.2±0.7	13.2±0.8	13.6±0.9	11.5±1.3	12.2±1.0	12.5±1.3
64	12.3±0.7	13.3±0.7	13.8±0.6	11.3±1.1	12.4±1.2	12.2±1.2*
256	12.0±0.7	12.9±1.0	13.6±0.8	11.1±0.9	11.7±1.0	11.8±1.0**

[a]data and statistics excerpted from submitted study. Values are mean ± std. dev. in kg.

*$p < 0.05$, **$p < 0.01$ by Dunnett's T-test

D. Food Consumption and Test Compound Intake- Food consumption appeared to decrease in a dose-related manner in the first week in both males and females (table 2). In subsequent weeks, food consumption in males recovered so that by the end of the study no substantial difference in mean food intake was apparent between treated and control males. High dose females appeared to consume less food throughout the study as average consumption in this group was about 15% less than control if averaged over the entire treatment period. Because all dogs in each group were caged together, only average intake for each cage could be determined, and a statistical analysis of food consumption was not possible.

No significant effects on water intake were noted.

Test compound intake remained constant over the treatment period and no significant differences between male and female dogs were apparent.

Table 2. Food Consumption[a]

Dose (ppm)	MALES Day 7	MALES Day 49	MALES Day 91	MALES Average	FEMALES Day 7	FEMALES Day 49	FEMALES Day 91	FEMALES Average
0	3.46[b]	2.58	2.89	3.00	3.34	2.80	2.25	2.86
4	3.51	2.73	3.18	3.12	3.05	3.25	2.53	2.84
8	3.23	2.90	3.12	3.18	3.25	2.58	2.08	2.60
16	3.58	2.88	3.30	3.29	3.16	2.35	2.60	2.61
64	3.18	2.73	3.17	3.00	2.75	2.50	2.35	2.63
256	2.70	2.55	3.08	2.89	1.93	2.42	1.90	2.46

[a]data and statistics excerpted from submitted study.

[b]mean food consumption, kg/dog/week.

E. Clinical Pathology: (1) Hematology- No treatment-related changes in erythrocyte count, total or corpuscular hemoglobin content, hematocrit, platelet count, clotting time, or total or differential white cell count were apparent. Although some differences between control and an individual treatment group were statistically significant, no dose-related effects were noted nor were any differences consistent at all time points.

(2) Serum Chemistry- Plasma concentrations of protein, albumin, globulin, total and direct bilirubin, cholesterol, glucose, urea, GPT, GOT, ALP, LDH, calcium, potassium, sodium, chloride, creatinine and inorganic phosphate were measured in each dog on days 0, 44-45, and 85-86. Although occassional statistically significant changes were noted, none of the changes were dose-related or consistent over time and are therefore not considered treatment-related.

Decreases in direct bilirubin were noted in high dose males at termination, however this difference from control was apparent at day 0 before initiation of treatment. Similar decreases were noted in serum protein, albumin and globulin in high dose females, however these differences from control existed at initiation.

(3) Urinalysis- No significant effects were noted that could be considered treatment-related.

F. Organ Function Tests (1) Phenolsulfonephthalein (PSP) and Bromsulfophthalein (BSP) Clearance- PSP clearance, an indirect measure of renal tubular secretion, and BSP retention, a measure of liver function, were determined in dogs from the control, 64, and 256 ppm groups on day 80 (PSP) and 87 (BSP). Although apparent treatment-related decreases in plasma PSP concentration were noted in males and females, the manner in which this test was conducted makes interpretation of the results uncertain. Typically, a known amount of PSP is injected i.v. and urine samples are analyzed for PSP content at 15, 30, 60 and 120 minutes post-injection (Ref. "Clinical Diagnosis by Laboratory Methods", I. Davidson and J. B. Henry, eds.). In the present study, a dose of PSP was injected and the plasma concentration of PSP was measured at 60 minutes post-injection. Therefore, plasma clearance rather than renal secretion of PSP was measured. Further, the toxicological significance of the decrease in plasma concentration relative to control that was noted in treated animals is unclear. A decrease in secretion, which could suggest impaired renal function, would be expected to cause an increase in the plasma concentration of PSP.

No significant effect of treatment on BSP clearance was apparent.

(2) Electrocardiography (ECG)- The electrical activity of the heart was recorded in dogs from the control and 256 ppm groups during week 13. Although the amplitudes of the various waves tended to be quite variable between dogs, the PR, QRS, and ST intervals were consistent and no treatment-related effects were apparent.

F. Necropsy Data (1) Organ Weights- Apparent dose-related decreases in thyroid (males and females) and brain (females only) weights were noted, however the changes were not judged to be statistically significant by the Dunnett's T-test. Absolute thyroid weights were decreased by about 25% in 16 ppm males and by about 20% in 64 and 256 ppm males. Thyroid/body weight ratios were not different from control in these animals (0.08 control vs 0.07 treated). Absolute

thyroid weights in 64 and 256 ppm females were decreased by about 30% compared to control, and thyroid/body weight ratios were decreased by about 25% in these animals.

Absolute brain weights were decreased by about 15% in high dose females relative to control, and brain/body weight ratios were decreased by about 8% relative to control in these animals.

(2) Gross Observations- No treatment-related macroscopic changes were noted at necropsy. Lesions commonly noted without apparent relation to treatment included ascarisis of the small intestine, slight hemorrhage in the caecum, and "pneumonic" lesions in the lung.

(3) Histopathology- No treatment-related microscopic changes were noted upon microscopic examination of treated tissues. Lesions commonly noted without apparent relation to treatment included "slight" calcareous deposits in the renal papillary collecting ducts, and aggregates of inflammatory cells in the liver, gall bladder, peribronchial region of the lung, the stomach, and salivary glands.

Table 3. Organ Weights and Ratios[a]

Dose (ppm)	MALE Thyroid	%C[b]	Brain	%C	FEMALE Thyroid	%C	Brain	%C
0	1.14±0.01[c] (0.08±0.01)[d]	- -	81.59±1.66 (6.3±0.8)	- -	0.98±0.16 (0.08±0.01)	- -	83.37±3.15 (6.9±0.5)	- -
4	1.01±0.07 (0.08±0.01)	88.7 100.0	85.81±0.80 (6.5±0.5)	105.2 103.2	0.92±0.04 (0.07±0.01)	93.9 87.5	80.67±1.11 (6.5±0.5)	96.8 94.2
8	0.95±0.10 (0.07±0.01)	83.3 87.5	86.24±3.16 (6.4±0.4)	105.7 101.6	0.82±0.15 (0.07±0.01)	83.7 87.5	83.01±1.85 (7.3±0.5)	99.6 106.3
16	0.86±0.07 (0.07±0.01)	75.4 87.5	84.27±2.06 (6.6±0.6)	103.3 104.8	0.93±0.15 (0.08±0.01)	94.9 100.0	80.62±4.51 (6.9±0.6)	96.7 100.0
64	0.93±0.09 (0.07±0.01)	81.6 87.5	80.55±3.34 (6.2±0.5)	98.7 98.4	0.69±0.09 (0.06±0.01)	70.4 75.0	78.35±3.02 (7.0±0.5)	94.0 101.4
256	0.93±0.15 (0.07±0.01)	81.6 87.5	78.92±2.97 (6.2±0.3)	96.7 98.4	0.70±0.10 (0.06±0.01)	71.4 75.0	71.04±3.40 (6.4±0.7)	85.2 92.8

[a]data excerpted from submitted study.

[b]%C = percent of control value.

[c]absolute organ weight in grams, mean ± SEM.

[d]organ/body weight ratio in g/kg, mean ± SEM.

Conclusion

The only significant effects of the test article were a decrease in body weight gain in high dose females, non-significant decreases in body weight gain in high dose males, and decreases in absolute and relative thyroid weights in females. A decrease in absolute but not relative brain weights was also noted in high dose females. The decreases in body weight gain may have been partially related to decreased food consumption in the high dose groups. No changes in thyroid histology were noted that could be related to the effects on organ weight, however this lack of correlation does not preclude an effect of the test article on thyroid function.

NOEL = 16 ppm
LEL = 64 ppm Decreased body weight gain, decreased absolute and relative thyroid weights in females.

Classification: Core-Guideline

RIN 5218-93 Toxicological Review for Glufosinate (128850)

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Pages 92 through 101 are not included.

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00440?

Study Title: Embryotoxic Effect in Wistar Rats After Oral Administration.

Accession No.: 072965

Study No.: 545/80

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 10-20-80/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH AT201; 97.2% a.i.

Doses Tested: 0, 10, 50, and 250 mg/kg by gavage, days 7-16 of gestation.

Test Animal: Female Wistar rats strain Hoe:WISKf(SPF71), obtained from Hoescht breeding stock; 20/dose.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) No statistical assessment of fetal malformations or variations.

2) Inadequate reporting of fetal variation data.

3) Incomplete reporting of dam necropsy data.

Results

A. Clinical Signs and Mortality- No summary or individual animal tabulations of clinical signs were reported. The investigators stated in the report narrative that hyperactivity was observed in 2, 7, and 5 dams from the low, mid and high dose groups, respectively. Bristled fur and drowsiness were also noted in "1-3 dams from the 50 mg/kg group and in 5-9 dams from the 250 mg/kg group". Dams from the high dose group only were also observed with purulent lacrimation (1) and blood around the mouth (3). The frequency and duration of these signs were not quantitated, although it was stated that "the symptoms listed above emerged throughout the individual test periods, in some cases shortly after the first administration, in others not until after the last, and were observed singly or in various combinations".

In addition to the above mentioned signs, 4 dams from the mid dose and 8 dams from the high dose groups were noted to have vaginal bleeding between days 10 and 20 of gestation, and were sacrificed. One other dam from the high dose group, who was observed with blood around the mouth, died between days 16 and 17.

Summary and individual animal data for the duration and severity of clinical signs must be submitted before a final assessment of this study can be made.

B. Body Weights and Food Consumption- The mean body weight of high dose dams surviving to termination (day 21) was about 10% less than control on days 7, 14 and 17 as indicated by the summary tabulation (Appendix 1 of submission). Only limited individual animal data for body weight measurements were submitted. Individual animal tabulations of observations at cesarean sectioning included individual weight gain over days 0-21, however the reproduction of the report was poor and many numbers were illegible.

As best as could be determined, animals that were sacrificed in extremis either lost body weight over the treatment period or gained substantially less than other animals in that group that survived to termination.

The slight decrease in average body weight of surviving high dose dams was possibly related to decreased mean food consumption in these animals during the period of treatment (days 7-16). Although a summary tabulation of mean food consumption was submitted (Appendix 1 of study report), no individual animal data for food consumption were submitted, therefore the food consumption of animals sacrificed in a moribund condition or that died is unknown.

Individual animal data for body weights and food consumption must be submitted before a final assessment of this study can be made.

C. Necropsy Data: (1) Reproductive Parameters- The major effect of treatment on reproductive parameters appeared to be a dose-related increase in the incidence of "fetal wastage" (post-implantation loss) in mid and high dose dams. This effect appeared to be associated with pronounced maternal toxicity in these particular dams as evidenced by a failure to gain body weight, and "vaginal bleeding", during gestation. Of the 4 mid dose (50 mg/kg) dams that were sacrificed due to bleeding, 3 dams were sacrificed before day 14 and had only implantation sites or resorptions; one other dam from this group was sacrificed on day 20 and had 12 stunted, live fetuses and a single resorption site. Of the 8 high dose (250 mg/kg) dams that were observed with vaginal bleeding, 7 were sacrificed before day 16, and had only implantation sites or resorptions. One dam was sacrificed on day 20, and had 12 stunted fetuses, of which 4 were alive and 8 were dead at necropsy. The dam that died between days 16 and 17 with bleeding from the mouth had 7 implantation sites.

The effects noted above were not presented as a summary tabulation, and were determined by the reviewer from the individual animal cesarean section data. The investigators stated that "these findings suggest a link between the vaginal haemorrhages and abortions". However, this theory does not explain the finding of resorptions sites only in dams with vaginal bleeding, nor was it stated whether products of conception were noted in the litter pans of animals with implantation sites only.

For animals that survived to day 21, the only significant findings were an increase in the mean number of dead fetuses/litter in the high dose group and a slight (10%) decrease in mean placental weights. The statistically significant increase in the mean number of dead fetuses was attributable to one dam (#73) that had 12 dead, stunted fetuses at necropsy. This dam lost 5 grams of body weight over days 0-21, therefore the dead fetuses appeared to associated with maternal toxicity. No other dead fetuses were noted in animals surviving to termination.

004403

(2) Necropsy Data: Dams- The major finding in dams at necropsy was distension of one or both renal pelvises. This finding was noted in 2/20 control, 2/20 low dose, 4/16 mid dose and 1/11 high dose dams surviving to day 21 termination. This finding was also noted in 0/4 and 1/8 mid and high dose dams, respectively, sacrificed due to bleeding. Enlarged adrenals were noted in 1/4 mid dose and 5/8 high dose dams that were sacrificed moribund, however was not reported for any dams surviving to termination. No effect on organ weights was apparent in dams surviving to day 21, although only a summary table was submitted.

Table 1. Reproductive Data[a]

	DOSE (mg/kg)			
	0	10	50	250
Number of dams:				
-Pregnant	20	20	20	20
-deaths	0	0	0	1
-sacrificed	0	0	4	8
Dams on Day 21:				
-alive	20	20	16	11
-with fetal death only	0	0	0	1
-with live fetuses	20	20	16	10
-mean weight gain day 0-21 (g)	123	121	120	112
Mean Number/Dam:				
-corpora lutea	12.6	13.0	13.3	13.4
-implantations	11.9	11.9	12.6	12.8
-resorptions	0.60	0.55	0.81	0.91
Mean Fetal Data:				
-no. dead/litter	0	0	0	1.09*
-no. live/litter	11.3	11.3	11.8	10.8
-% male	54	53	47	53
-body weight (g)	3.29±0.36	3.41±0.41	3.20±0.28	3.19±0.28
-crown-rump (cm)	3.57±0.17	3.66±0.18	3.53±0.16	3.49±0.18
-placental weight (g)	0.53±0.07	0.51±0.06	0.47±0.05*	0.48±0.09

[a]data excerpted from submitted study. *$p < 0.05$

D. Malformation Data: The reported malformation data are inadequate because litter incidences of findings were not included in summary tables, and statistical assessments of findings were not conducted. These deficiencies should be corrected in a report re-write.

(1) External Malformations- An apparent increase in the incidence of "stunted" fetuses was noted in mid and high dose dams, however the operating definition of "stunted" fetuses used by the investigators was not provided. This effect was noted in a single mid dose dam, sacrificed on day 20 due to "vaginal bleeding", that had 12 stunted, live fetuses; and in 2 high dose dams. One of the high dose dams survived to day 21 sacrifice and had 12 stunted, dead fetuses; the other dam was sacrificed on day 19 due to "vaginal bleeding", and had 4 live and 8 dead, stunted fetuses. All of these dams either lost body weight or had large weight gain deficits compared to control, and therefore "stunted" fetuses appeared to be associated with pronounced maternal toxicity.

D. Malformation Data: (2) Soft Tissue- A dose-related increase in the incidence of distended renal pelvis and dilated ureter (together) was noted (table 2). Both fetal and litter incidences of this anomaly were increased in a dose-related manner. The incidence of dilated renal pelvis alone was increased in the low and mid dose groups, but not in the high dose group. If the incidences of dilated renal pelvis alone are combined with the incidence of this finding with hydroureter, then a dose-related increase in incidence is apparent.

(3) Skeletal- No significant effects on skeletal development were noted in the summary tabulations. The individual animal data should be retabulated, however, so that it can be determined which effects occurred in the same fetuses. Further, fetal and litter incidences should be included in summary tables.

Table 2. Incidences of Distended Renal Pelvis and Ureter[a]

	DOSE (mg/kg)			
	0	10	50	250
No. fetuses examined	109	108	91	57
No. litters examined	19	19	16	10
Fetuses With:				
Dilated renal pelvis, one or both sides	10/6[b] (9.2/31.6)[c]	17/10 (15.7/52.6)	19/10 (20.9/62.5)	8/5 (14.0/50.0)
Hydroureter only	0	0	0	1/1 (1.8/10.0)
Dilated renal pelvis and hydroureter	1/1 (0.9/5.3)	3/3 (2.8/15.8)	4/3 (4.4/18.8)	9/5 (15.8/50.0)
Dilated renal pelvis and/or hydroureter	11/6 (10.1/31.6)	20/11 (18.5/57.9)	23/10 (25.3/62.5)	18/7 (31.6/70.0)

[a]data excerpted from submitted study.

[b]No. affected fetuses/litters (litter incidence calculated by reviewer).

[c]percent affected fetuses/litters (calculated by reviewer).

E. Fetal Variations- An apparent increase in the fetal incidence of "poor ossification of one or more headbones" was noted in fetuses from high dose dams, however the litter incidences of this finding were not different from control. The affected headbones were not identified in the submitted report; a complete description of the affected bones is required. Also, not all reported variations were tabulated in the summary tables, e.g. incomplete ossification of metacarpal 5. The individual fetal variation data should be retabulated so that it can be determined what effects are noted in the same fetuses, and all reported effects should be included in summary tables as fetal and litter incidences.

004407

Conclusion

An apparent dose-related increase in the incidence of dilated renal pelvis with distended ureter was noted in fetuses from dams treated with 10, 50 or 250 mg/kg over days 7-16 of gestation. An increase in litters with stunted fetuses was also noted in the 50 and 250 mg/kg groups, and was associated with maternal toxicity as evidenced by severe weight gain deficits in the dams. The definition of "stunted" fetuses used by the investigators was not provided.

Although the mid and high doses in this study were apparently toxic to dams as evidenced by "vaginal bleeding", the submitted data are inadequate for an assessment of extent of maternal toxicity in treated dams. Individual animal data for body weights, food consumption, and clinical signs (frequency, duration, and severity) must be submitted.

Further, although the range-finding data were not submitted, it was stated in the report narrative that "doses up to and including 125 mg/kg....had no discernible effect on dams or fetuses". Apparently none of the dams in the range-finding study, including those treated with 250 mg/kg, were observed with "vaginal bleeding".

Therefore, a NOEL and LEL for maternal toxicity cannot be determined at this time. The study report is inadequate. A re-write of the final report is requested with the following additions:

(a) All individual fetal variations are tabulated such that it can be determined which effects occurred in the same fetuses.

(b) All fetal variations reported as individual animal data should be included in summary tables.

(c) All data (malformations and variations) should be tabulated by fetal and litter incidences for each dose group.

(d) A statistical assessment of all fetal findings should be conducted, based on both fetal and litter incidences. Where findings are related, e.g. dilated renal pelvis and hydroureter, statistical assessments should be performed on the incidences of each finding alone and on the incidences of combined findings.

(e) All necropsy data, submitted both as summary tabulations of all findings, and as individual animal data.

(f) All range-finding data.

(g) Operating definition of "stunted" fetuses.

Also, the following additional data are requested to complete the assessment of this study:

(1) Historical data for the incidence of dilated renal pelvis and hydroureter in fetuses and hydronephrosis in dams, and for stunted fetuses, from the

(con't)

Conclusion (con't)

laboratory that performed the study, for a period of two years prior to, and, if possible, two years after the present study. The data should be tabulated by study, and fetal and litter incidences should be provided.

(2) Individual animal data for clinical signs that includes the frequency, severity, and duration of observed signs.

(3) Individual animal data for weight gain in dams. At the minimum, body weight gain over days 0-7, 7-14, 14-17, and 17-21 is required.

(4) Individual animal data for food consumption in dams.

(5) A complete description of the "headbones" which were affected by ossification delay.

When the requested data and report re-write have been submitted, a final evaluation of this study will be completed.

Classification: Core-Supplementary Deficiencies as noted above.

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Pages 108 through 111 are not included.

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004403

Study Title: Embryotoxic Effect in Wistar Rats After Oral Administration.

Accession No.: 072965

Study No.: 570/82

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 9-22-82/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH AT201; 97.2% a.i.

Doses Tested: 0, 0.50, 2.24, and 10 mg/kg by gavage, days 7-16 of gestation.

Test Animal: Female Wistar rats strain Hoe:WISKf(SPF71), obtained from Hoescht breeding stock; 20 gravid females/dose.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) This study is a repeat of a previous teratology study (#545/80) in which higher doses were used. Although the two studies have been reviewed separately, data from both studies will be used to establish NOELs for teratogenic, fetotoxic, embryotoxic, and maternal effects.

2) No statistical assessment of fetal malformations or variations.

3) Inadequate reporting of fetal variation data.

4) Incomplete reporting of dam necropsy data.

Results

A. Clinical Signs and Mortality- No summary or individual animal tabulations of clinical signs were reported. The investigators stated in the report narrative that "no disturbance in behaviour and general state of health were [sic] seen". Apparently the signs noted in the previous study, specifically hyperactivity and vaginal bleeding, were not observed.

No dams died during the course of the study.

B. Body Weights and Food Consumption- No individual animal data for body weight measurements were submitted, however individual animal tabulations of observations at cesarean sectioning included individual weight gain over days 0-21. Mean body weights on days 0, 7, 14, and 21 were submitted ("enclosure 1" of study report). No effect of treatment on mean body weight was apparent at any time point, and the increase in body weight during gestation (days 0-21) was similar in control and treated dams.

Individual animal data for food consumption were not submitted. A summary tabulation of mean food consumption of days 1-7, 7-14, and 17-21 ("enclosure 1" of study report) indicated that no effect of treatment on food consumption was apparent.

C. Necropsy Data: (1) Reproductive Parameters- Decreases in the mean number of live fetuses/litter and corresponding increases in the mean number of resorptions were noted in mid and high dose fetuses (2.24 and 10 mg/kg, respectively; table 1 of review). These effects were not judged to be statistically significant by the investigators. No effects on fetal body weights, crown-rump lengths, sex ratio, number of dead fetuses, number of implantations or placental weights were noted (table 1).

(2) Necropsy Data: Dams- The major findings in the previous study at higher doses were "dilated renal pelvis" and enlarged adrenals in dams sacrificed due to bleeding. In the present study, the incidences of unilateral or bilateral "dilated renal pelvis" were: 2/20 control, 1/20 low dose, 2/20 mid dose, and 1/20 high dose dams.

Apparent treatment-related increases of about 10% were noted in the absolute organ weights of kidney and spleen in high dose dams.

Table 1. Reproductive Data[a]

	DOSE (mg/kg)			
	0	0.50	2.24	10.0
Number of dams:				
-pregnant/inseminated	20/21	20/21	20/24	20/21
-deaths	0	0	0	0
-sacrificed	0	0	0	0
Dams on Day 21:				
-alive	20	20	20	20
-with live fetuses	20	20	20	20
-weight gain days 0-21 (g ± s.d.)	123±19	135±14	130±12	125±10
Mean Number/Dam:				
-corpora lutea	13.1	12.8	14.3	13.8
-implantations	12.3	12.6	12.6	12.2
-resorptions	0.25	0.35	0.70	0.80
Mean Fetal Data:				
-no. dead/litter	0	0.05	0	0
-no. live/litter	12.0	12.3	11.9	11.4
-% male	51	52	53	51
-body weight (g)	3.27±0.21	3.35±0.19	3.32±0.17	3.42±0.27
-crown-rump (cm)	3.64±0.12	3.61±0.07	3.58±0.10	3.65±0.12
-placental weight (g)	0.49±0.05	0.48±0.05	0.49±0.03	0.51±0.06

[a]data excerpted from submitted study. Fetal weight and length data do not include values of dead fetus from 0.50 mg/kg group.

[b]calculated by reviewer.

D. Malformation Data (1) External Malformations- No effect of treatment on the incidence of externally-visible malformations was apparent. No stunted fetuses were reported.

(2) Soft Tissue- No effect of treatment on the incidences of renal pelvis and/or dilated ureter, the major findings of the previous study, was noted (table 2 of this review). No fetuses were observed to have both findings, as was noted in the previous study. Only one low dose fetus was observed to have hydroureter. Cleft palate was observed in one high dose fetus, but no others.

(3) Skeletal- No significant effects on skeletal development were noted. Common findings noted in all groups without apparent dose relationship included "weak ossification of one or several cranial bones" and "anlage of a short and/or normal length 14th rib at the 1st lumbar vertebra, one or both sides".

Table 2. Incidences of Fetal Malformations[a]

	DOSE (mg/kg)			
	0	0.5	2.24	10.0
No. fetuses examined	118	118	112	110
No. litters examined	20	20	20	20
Fetuses With:				
Dilated renal pelvis, one or both sides	2/2[b] (1.7/10.0)[c]	1/1 (0.8/5.0)	1/1 (0.9/5.0)	0
Hydroureter only	0	1/1 (0.8/5.0)	0	0
Dilated renal pelvis and hydroureter	0	0	0	0
Dilated renal pelvis and/or hydroureter	2/2 (1.7/10.0)	2/2 (1.7/10.0)	1/1 (0.9/5.0)	0

[a]data excerpted from submitted study.

[b]no. affected fetuses/litters (litter incidences calculated by reviewer).

[c]percent affected fetuses/litters (calculated by reviewer).

Conclusion

004403

This study is a repeat of a previous study (#545/80) in which doses of 0, 10, 50 and 250 mg/kg caused clear signs of toxicity in dams at the mid and high dose levels. In that study, a dose-related increase in the incidence of dilated renal pelvis and hydroureter was noted in fetuses from all treatment groups. An increased incidence of stunted fetuses was also noted in mid and high dose dams, and appeared to be associated with maternal toxicity in the form of severe weight gain deficits and/or "vaginal bleeding". Because the investigators believed that all of the observed effects were due to maternal toxicity, the present study was conducted with lower doses of 0, 0.50, 2.24 and 10.0 mg/kg/day.

In the present study, no effect of treatment on fetal malformations or variations was apparent. An increase in the number of resorptions and the number of dams with resorptions was noted, however the increase was not statistically significant, nor was this finding observed at 10 mg/kg in the previous study. Other parameters such as fetal body weight and length, placental weight, sex ratio, and fetal death were unaffected by treatment.

No signs of maternal toxicity were noted at any of the tested doses. In the previous study, an increase in the incidences of hyperactivity and vaginal bleeding was reported, mainly in the 50 and 250 mg/kg groups, although 2/20 dams from the 10 mg/kg group in the first study were also observed to be hyperactive. Because individual animal data for clinical signs and body weight measurements were not submitted, the data are inadequate for an assessment of maternal toxicity in either study.

A NOEL and LEL for maternal toxicity cannot be determined at this time. The study report is inadequate. A re-write of the final report is requested with the following additions:

(a) All individual fetal variations are tabulated such that it can be determined which effects occurred in the same fetuses.

(b) All fetal variations reported as individual animal data should be included in summary tables.

(c) All data (malformations and variations) should be tabulated by fetal and litter incidences for each dose group.

(d) A statistical assessment of all fetal findings should be conducted, based on both fetal and litter incidences. Where findings are related, e.g. dilated renal pelvis and hydroureter, statistical assessments should be performed on the incidences of each finding alone and on the incidences of combined findings.

(e) All necropsy data, submitted both as summary tabulations of all findings, and as individual animal data.

(f) All range-finding data.

004403

Conclusion (con't)

Also, the following additional data are requested to complete the assessment of this study:

(1) Historical data for the incidence of dilated renal pelvis and hydroureter in fetuses and hydronephrosis in dams, and for stunted fetuses, from the laboratory that performed the study, for a period of two years prior to, and, if possible, two years after the present study. The data should be tabulated by study, and fetal and litter incidences should be provided.

(2) Individual animal data for clinical signs that includes the frequency, severity, and duration of observed signs.

(3) Individual animal data for weight gain in dams. At the minimum, body weight gain over days 0-7, 7-14, 14-17, and 17-21 is required.

(4) Individual animal data for food consumption in dams.

(5) A complete description of the "headbones" which were affected by ossification delay.

When the requested data and report re-write have been submitted, a final evaluation of this study will be completed.

Classification: Core-Supplementary Deficiencies as noted above.

RIN 5218-93 Toxicological Review for Glufosinate (128850)

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004403

Study Title: Metabolism Study on Female Rats After A Single Oral Dose of the Active Ingredient.

Accession No.: 072965

Study No.: 321/83

Sponsor/Contracting Lab.: Hoechst/Same, Analytical Laboratory

Report Date/Submitted: 8-1-83/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH ZE98; 98% a.i.

Doses Tested: 10 mg/kg by gavage

Test Animal: Female SPF Wistar rats, obtained from Winkelmann, Borchen

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following points were noted:

The 1982 Pesticide Assessment Guidelines recommend that at least 4 treatment groups be examined in a metabolism study:

Group A- single i.v. low (NOEL) dose.

Group B- single oral low dose.

Group C- minimum of 14 consecutive daily oral low doses of unlabeled test compound, followed by a single oral low dose of radiolabeled test compound 24 hours later.

Group D- single oral high dose sufficient to produce some pharmacological or toxic signs.

Urine and feces from all groups should be analyzed for metabolites and rate of excretion. Tissues from groups B, C, and D should be analyzed for retention of label at sacrifice (after 7 days or excretion of 90% of administered dose).

The submitted study could be used as "group D", however only female rats were studied, and tissue residues were not determined. A repeat study is required. Male and female rats should be studied, and the dose given should be a minimally toxic dose. Acute oral toxicity studies submitted along with this study appear to support a minimally toxic dose higher than 10 mg/kg. Also, urinary and fecal excretion should be measured at the same time points as in the second metabolism study (#01-L42-0400-83) submitted in this data package, i.e. 4, 8, and 24 hours, and at 2, 3, 4, 5, 6, and 7 days for urine, and daily for feces. In this manner the effect of dose on excretion can be assessed.

The registrant is referred to the 1982 Pesticide Assessment Guidelines for information as to the design, conduct and reporting of the rat metabolism study.

Results

00440?

A. Excretion- Elimination of the test article was rapid, as most of the radiolabel (92.6%) was eliminated within 48 hours of administration (table 1). The preferred route of elimination after oral dosing was via the feces, as 83.2% of the administered dose was excreted by this route after 5 days. Urinary excretion accounted for 11.9% of the administered dose.

Table 1. Percent of Dose Excreted in Female Rats[a]

Days	Urine	Feces	Total
0-2	10.6	82.0	92.6
3-5	1.3	1.2	2.5
Total	11.9	83.2	95.1

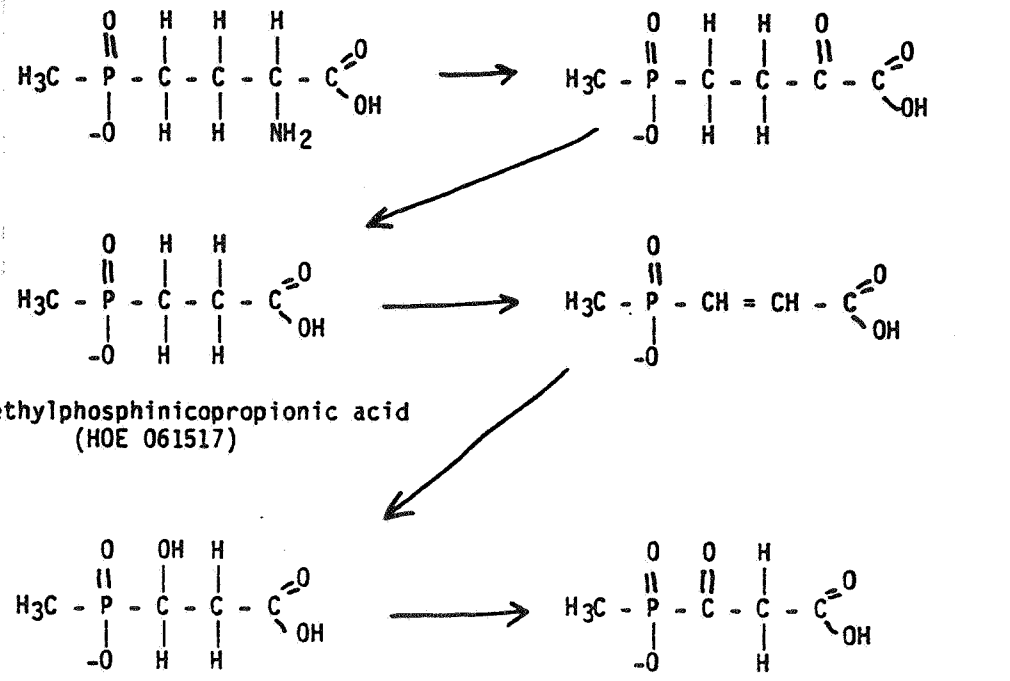
[a]data excerpted from submitted study.

B. Metabolites- The metabolites excreted between days 0-2 were identified by conventional analytical techniques. Of the 10.6% of the administered dose that was excreted in the urine over days 0-2, 8.5% was the unmetabolized parent compound. Of the remainder, about 1% was 3-methylphosphinicopropionic acid (code HOE 061517) and about 0.5% was 3-methylphosphinico-3-oxo-propionic acid.

Fecal radioactivity excreted between days 0-2 consisted of 74% parent compound and 2.6% was HOE 061517. The remainder of fecal radioactivity was not characterized.

Based on the identified metabolite structures, a metabolic pathway was proposed which parallels the amino acid degradation pathway. The first step is oxidative deamination, followed by oxidative decarboxylation of the N-terminus carboxyl group. The product of these two steps is 3-methylphosphinicopropionic acid (HOE 061517). In the next steps, the propionic acid side chain is dehydrogenated to form a double bond between carbons 2 and 3, then hydrated and oxidized to form the 3-oxo group. The proposed pathway is depicted in figure 1.

Figure 1. Proposed metabolic pathway for HOE 039866



3-methylphosphinicopropionic acid
(HOE 061517)

3-methylphosphonico-3-oxo-propionic acid

Conclusion

The majority (about 85%) of the administered dose of the test article was excreted in the feces, and about 12% was excreted in the urine. Of the excreted radioactivity (urine and feces), the majority was the unmetabolized parent compound. Metabolites identified in urine were 3-methylphosphinicopropionic acid and the 3-oxo form, which accounted for about 10% and 5%, respectively, of the radioactivity excreted in the urine (1.0% and 0.5% of the administered dose). Metabolites accounted for about 11% of the radioactivity excreted in feces, of which 3.5% was 3-methylphosphinicopropionic acid and 7.5% was an unidentified metabolite.

Classification: Core-Supplementary Only females studied, no tissue residues, dose not a minimally toxic acute dose. See discussion under "Methods".

RIN 5218-93 Toxicological Review for Glufosinate (128850)

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Study Title: Study on Kinetics and Residue Analysis in Rats.

Accession No.: 072965

Study No.: 01-L42-0400-83

Sponsor/Contracting Lab.: Hoechst/Same, Radiochemical Laboratory

Report Date/Submitted: 8-17-83/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OT ZE98; 98% a.i.

Doses Tested: 2 mg/kg by gavage; 2 mg/kg by i.v. injection.

Test Animal: Male and female SPF Wistar rats, obtained from Ivanovas, Kissleg, Allgau.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following points were noted:

The 1982 Pesticide Assessment Guidelines recommend that at least 4 treatment groups be examined in a metabolism study:

Group A- single i.v. low (NOEL) dose.

Group B- single oral low dose.

Group C- minimum of 14 consecutive daily oral low doses of unlabeled test compound, followed by a single oral low dose of radiolabeled test compound 24 hours later.

Group D- single oral high dose sufficient to produce some pharmacological or toxic signs.

Urine and feces from all groups should be analyzed for metabolites and rate of excretion. Tissues from groups B, C, and D should be analyzed for retention of label at sacrifice (after 7 days, or excretion of 90% of administered dose).

In the present study, 2 mg/kg was given orally and i.v. These groups would correspond to groups "A and B" described above. The kinetics of excretion and plasma decay were calculated for these groups, and tissue residues were determined in rats 7 days after the oral dose. No identification of metabolites was provided. It is useful to identify the structure of metabolites after the low (group B) and high (group D) dose exposures to determine if any unusual metabolites are formed under conditions of high dose exposure. Since metabolite structures were identified in the previous study (#321/83), a repeat of these low dose studies to identify metabolites will not be required provided that an acceptable repeat of the high dose study is submitted in which the metabolic profiles for males and females are characterized.

Methods (con't)

The effects of repeated exposure to the test article on excretion, metabolite profile, and tissue distribution were not assessed (group D). This study will be required before the metabolism data requirement will be satisfied.

The registrant is referred to the 1982 Pesticide Assessment Guidelines for information regarding the design, conduct, and reporting of the rat metabolism study.

Results

A. Plasma Decay Curve- Similar curves for plasma decay were obtained in male and female rats after an intravenous infusion of the test article. The study authors stated that decay occurred in 3 phases, with t(1/2)s of 0.33, 3.7, and 97.2 hours in males, and 0.35, 2.7, and 125.8 in females. The first half-life value of about 0.3 hours likely represents distribution from the vascular compartment to tissues rather than metabolism or excretion. The longer half-lives likely represent processes of metabolism and excretion, and the biphasic decay curve is similar to the biphasic curve for urinary elimination.

Plasma levels after the oral dose were insufficient for accurate calculation of plasma decay kinetics.

B. Excretion- Elimination of the test article after the oral dose was primarily via the feces, as 89% and 81% of the administered dose was eliminated by this route after 7 days for males and females, respectively (table 1). The majority of the excretion occurred after 1 day, although males excreted more label during the first day than did females.

The pattern of elimination after i.v. infusion was reversed, i.e. the majority of administered label was excreted via the urine rather than feces (table 1). As was noted for oral administration, most excretion occurred during the first day, and males excreted a greater percentage of the administered dose during the first day than did females.

These data suggest that the majority of the test article given orally was not absorbed from the G.I. tract. Absorption was estimated to be 7.8% and 13.0% of an administered dose in males and females, respectively, based on relative urinary excretion after oral and i.v. administration.

No radioactivity was detected in expired air (limit of detection = 0.1% of administered dose).

The kinetic curves for renal excretion were similar to those obtained for plasma decay, i.e. were biphasic (table 2). The shapes of the elimination curves were similar for oral and i.v. administration, and for females the half-life of renal elimination was the same for either route of administration. For males, the phase II (short) half-life of elimination after i.v. infusion was about 50% longer than after oral administration, and may have toxicological significance (see section C. "Tissue Distribution").

Table 1. Percent of Administered Dose Excreted[a]

Dose/ Route	Days	Male Urine	Male Feces	Male Cage Wash	Male Total	Female Urine	Female Feces	Female Cage Wash	Female Total
2 mg/kg i.v.	0-1	73.60	11.08	1.49	86.17	86.13	4.31	0.79	91.23
	0-7	82.50	17.70	2.13	102.33	91.80	8.09	1.22	101.11
2 mg/kg oral	0-1	5.60	86.60	0.27	92.47	7.84	58.20	0.98	67.02
	0-7	6.46	89.10	0.44	96.00	11.94	81.40	1.66	95.00

[a]data excerpted from submitted study.

Table 2. Half-lives of Renal Elimination[a]

Dose/Route	Phase	Male	Female
2 mg/kg i.v.	II	7.9 ± 1.5	8.0 ± 1.2
	III	64.3 ± 42.7	52.3 ± 23.0
2 mg/kg oral	II	5.3 ± 0.3	7.4 ± 2.1
	III	58.4 ± 24.0	52.1 ± 19.0

[a]data excerpted from submitted study; values are in hours, mean ± std. dev.

C. Tissue Distribution- The only tissues which had detectable residues of radioactivity 7 days after oral administration were kidneys, liver, and testes (table 3). An amount of radioactivity at the limit of detection (0.01 ppm) was detected in the bones of 3/5 female rats, but was undetectable in males. No residues were detected in any other tissues. Males retained about 30x as much radioactivity in the kidney (expressed as % of administered dose) as females, in spite of the fact that males excreted less of an administered dose via the urine. The fact that the half-life for renal excretion (phase II) increased in males when the plasma concentration of the test article was increased (i.e. after the i.v. infusion) may be related to accumulation in the kidneys of these animals.

Table 3. Tissue Residues 7-Days After a Single Oral Dose[a]

Tissue	Male	Female
Kidneys	0.173[b] (0.086)[c]	0.014 (0.003)
Gonads	0.068 (0.050)	<0.01 -
Liver	0.024 (0.060)	0.045 (0.095)

[a]data excerpted from submitted study.

[b]ug HOE 39866/g tissue.

[c]percent of administered dose.

Conclusion

The test article was shown to be poorly absorbed from the gastrointestinal tract, as only 8% and 13% of the administered dose was absorbed in males and females, respectively. The kidneys were the primary route of excretion for the chemical that was absorbed into the blood. Most excretion occurred within the first 24-48 hours, and about 95% was eliminated from the body by 7 days after a single oral or intravenous dose. Elimination was biphasic, with short and long half-lives of 5-8 hours and 52-64 hours, respectively.

The only tissues which accumulated detectable amounts of radioactivity were kidney, liver and testes. Males accumulated 30-fold more radioactivity in the kidneys than did females, whereas females did not accumulate any chemical in their gonads. The amount accumulated in the liver was similar in males and females.

In the present study, the kinetics of excretion and plasma decay were calculated after oral and i.v. administration, and tissue residues were determined in rats 7 days after the oral dose. No identification of metabolites was provided. It is useful to identify the structure of metabolites after low and high dose exposures to determine if any unusual metabolites are formed under conditions of high dose exposure. Since metabolite structures were identified in the previous study (#321/83), a repeat of these low dose studies to identify metabolites will not be required provided that an acceptable repeat of the high dose study is submitted in which the metabolic profiles for males and females are characterized.

Classification: Core-Supplementary No assessment of the effect of repeated doses on excretion, metabolic profile, or tissue distribution. May be upgraded if an acceptable high dose study is submitted.

RIN 5218-93 Toxicological Review for Glufosinate (128850)

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Study Title: Experimental Assessment of the Therapeutic Action of Atropine Sulfate + 2-PAM Iodide and Phenobarbital Sodium in Case of an Acute Intoxication With HOE 039866 in Wistar Rats.

Accession No.: 072965

Study No.: 83.0625

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 11-18-83/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH ZC95; 95.3% a.i.

Doses Tested: 3200 mg/kg (males) and 2200 mg/kg (females), by gavage.

Test Animal: Male and female Wistar (HOE:WISKf[SPF71]) rats, obtained from Hoechst breeding colony, Kastengrund. 10/sex/group.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) This study compares the effect of atropine and pralidoxime (2-PAM) with the effect of phenobarbital on the acute toxicity of the test article. Rats were given a lethal dose of HOE 39866 and then treated with the putative antidotes. Atropine and 2-PAM were chosen because of the similarity of the symptoms of intoxication (i.e. convulsions, spasms, lacrimation, salivation) with the test article to the classical signs of cholinesterase inhibition. The rationale for using phenobarbital was not explicitly stated, however this drug has been routinely used clinically to control convulsions for which a specific antagonist does not exist. Test groups were organized as follows:

Group	HOE 39866 (mg/kg p.o.)	Therapeutic Agent	Treatment Time (Hours Post-HOE)
		MALES	
1	3200	None	
2	3200	Phenobarbital, 20 mg/kg i.p.	3, 4, 7, 8, 24
3	3200	Atropine Sulfate 10 mg/kg i.p.	24
		2-PAM 75 mg/kg i.p.	8, 24
		FEMALES	
1	2200	None	
2	2200	Phenobarbital, 20 mg/kg i.p.	3, 4, 7, 24
3	2200	Atropine Sulfate 10 mg/kg i.p.	24
		2-PAM 75 mg/kg i.p.	7, 24

Results

A. Mortality and Clinical Signs- All 10 male and 9/10 female rats that were not given any therapeutic treatment (groups 1) died by 7 days after treatment with the test article (table 1). The majority of the deaths occurred within 24 hours for males and within 48 hours for females. Clinical signs observed in these animals included tremors, spasms, hyperreflexia, and convulsions.

Atropine and pralidoxime (groups 3) proved to be ineffective as antidotes to acute intoxication with HOE 39866 (table 1). Nine of 10 males and 8/10 females died in spite of the attempted therapy, and the clinical signs that were observed before death were similar to those observed in group 1 animals (no therapy).

Phenobarbital (groups 2) was an effective antidote to acute intoxication with the test article (table 1). Only one male rat and 0/10 females died after treatment with the test article. The single death occurred at night between days 1 and 2, when due to "technical difficulties [it was] impossible for therapeutic measures to be taken". Clinical signs observed in these animals included hypoactivity, drowsiness, and hyperreflexia.

Table 1. Effect of Antidotes on HOE 39866 Lethality[a]

Group	Therapeutic Agent	Mortality	
		Males[b]	Females[c]
1	None	10/10	9/10
2	Phenobarbital, 20 mg/kg i.p.	1/10	0/10
3	Atropine 10 mg/kg i.p. 2-PAM 75 mg/kg i.p.	9/10	8/10

[a]data excerpted from submitted study.

[b]dose of HOE 39866 for males = 3200 mg/kg by gavage.

[c]dose of HOE 39866 for females = 2200 mg/kg by gavage.

B. Necropsy Data- Animals that died after treatment with the test article were observed to have areas of light coloration on the liver, kidneys, and spleen, and darkly colored areas on the intestines, lungs, and adrenals. Animals that survived to the termination of the study did not have any macroscopically visible alterations.

Conclusion

Phenobarbital, given at a dose of 20 mg/kg i.p. at several intervals during the first 24 hours after intoxication with HOE 39866, proved to be an effective antidote. Atropine and pralidoxime were ineffective, in spite of the similarity of some clinical signs observed after intoxication with the test article to those commonly associated with cholinesterase inhibition.

Classification: Acceptable

RIN 5218-93 Toxicological Review for Glufosinate (128850)

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Study Title: Acute Oral Toxicity of HOE 39866 Water-Soluble Formulation to the Male Rat.

Accession No.: 072966

Study No.: 755/81

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 12-29-81/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH VD072; 19.9% a.i.

Doses Tested: 1.25, 2.00, 3.15, and 5.00 g/kg by oral gavage.

Test Animal: Male Wistar (Hoe WISKf[SPF71]) rats, Hoechst breeding; 10/dose.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) Only males were tested. When combined with data for females (study #756/81), the requirement for acute toxicity testing of the formulation is satisfied.

Results

A. Mortality- All animals that died after the single dose of the test article expired within 6 days of treatment (table 1). All animals given the highest dose (5.0 g/kg) died between days 1 and 2.

One day after treatment the following clinical signs were noted in lethally intoxicated animals: bristled hair, aggressive behavior, trembling, and convulsions.

Table 1. 14-Day Mortality[a]

Dose (g/kg)	Number of deaths/ number of animals
1.25	0/10
2.00	1/10
3.15	5/10
5.00	10/10

[a]data excerpted from submitted study.

The LD_{50} was calculated by the investigators as 2.98 g/kg (95% confidence limits = 2.46-3.63 g/kg).

B. Body Weights- A decrease in mean body weight gain over the 14 day observation period was noted in animals given doses of 3.15 g/kg. No effect on weight gain was noted in animals given lower doses.

C. Necropsy Data- Gross observations of animals that died included discoloration of adrenals, lungs, and pancreas, extreme filling of the urinary bladder and yellowish liquid in the small intestine. No "abnormal macroscopic findings" were noted in animals that survived to termination.

Conclusion

The oral gavage LD_{50} in male Wistar rats of the water-soluble formulation of HOE 39866 was calculated as 2.98 g/kg, with a 95% c.i. of 2.46-3.63 g/kg. These values correspond to toxicity category III (0.50 to 5.00 g/kg).

Classification: Core-Minimum Although only males were tested, when combined with data for females (study #756/81), the requirement for acute oral toxicity of the formulation is satisfied.

Abteilung Pharma Forschung Toxikologie
Verfasser Dr. Hollander, Dr. Weigand

TEST PROCEDURE

Hoe 39866 C H VDC72 was provided in the form of a turquoise-green liquid. For the acute treatment a 25 % dilution was prepared in deionized water (25 g/ad 100 ml) and administered once by gavage at various dose levels to male Wistar-rats (strain:Hoe WISKf(SPF71) from our own breeding stock), 195 - 233 g in weight ($\bar{x}$ = 207.4 g, s.d. $\hat{\sigma}$ = 8.69 g, n = 40). Each dosage was tested with 10 rats. The animals were deprived of feed for 16 hours before and 2 hours after the treatment. During the 14-day follow-up period after dosing the animals received the maintenance diet ALTROMIN 1324 (producer: Altromin GmbH, Lage/Lippe) and tap water ad libitum. The animals were grouped and housed in plastic cages on granulated light wood bedding.

The symptoms of intoxication, the mortality rate and the time of death were registered after the treatment. During the follow-up period the animals were weighed weekly. Lethally intoxicated animals were dissected and the macroscopic autopsy findings were recorded. After termination of the follow-up period, the surviving experimental animals were killed with CO_2-gas, dissected and also gross-examined.

The LD 50 was determined by probit analysis (LINDER/WEBER method); the confidence limits were calculated according to FIELLER (programmed in the Practical Mathematics Department of Hoechst Aktiengesellschaft).

The experiment No. 682/81 was conducted between 30.11. and 23.12.1981.

004403

Study Title: Acute Oral Toxicity of HOE 39866 Water-Soluble Formulation to the Female Rat.

Accession No.: 072966

Study No.: 756/81

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 12-29-81/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH VD072; 19.9% a.i.

Doses Tested: 0.63, 1.00, 1.60, and 2.50 g/kg by oral gavage.

Test Animal: Female Wistar (Hoe WISKf[SPF71]) rats, Hoechst breeding; 10/dose.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) Only females were tested, however when combined with the data for males, (study #755/81), the requirement for acute oral toxicity testing of the formulation is satisfied.

Results

A. Mortality- Most of the animals that died after the single dose of the test article expired within 6 days of treatment (table 1).

Clinical signs noted following treatment included: hyperactivity, bristled hair, aggressive behavior, trembling, convulsions, and respiratory difficulty.

Table 1. 14-Day Mortality[a]

Dose (g/kg)	Number of deaths/ number of animals
0.63	1/10
1.00	2/10
1.60	5/10
2.50	9/10

[a]data excerpted from submitted study.

The LD_{50} was calculated by the investigators as 1.45 g/kg (95% confidence limits = 1.11-2.00 g/kg).

B. Body Weights- Doses up to 1.60 g/kg had no effect on mean body weight gain over the 14 day observation period. The two animals from the 2.5 g/kg group that survived to day 7 lost body weight from their initial values; one animal died, and the other apparently recovered and gained about 20 grams over its initial weight.

C. Necropsy Data- Gross observations of animals that died included discoloration of adrenals, lungs, liver, and pancreas, extreme filling of the urinary bladder and yellowish liquid in the small intestine. Necropsy of animals that survived to termination revealed "renal marking" and "diffuse reddening of the pancreas".

Conclusion

The oral gavage LD_{50} of the water-soluble formulation of HOE 39866 in female Wistar rats was calculated as 1.45 g/kg, with a 95% c.i. of 1.11 - 2.00 g/kg. These values correspond to toxicity category III (0.50 to 5.00 g/kg).

Classification: Core-Minimum Only females were tested, however when combined with data for males (study #/55/81), the requirement for acute oral toxicity testing of the formulation is satisfied.

TEST PROCEDURE

Hoe 39866 O H VD072 was provided in the form of a turquoise-green liquid. For the acute treatment a 25 % dilution was prepared in deionized water (25 g/ad 100 ml) and administered once by gavage at various dose levels to female Wistar-rats (strain:Hoe WISKf(SPF71) from our own breeding stock), 218 - 239 g in body weight ($\bar{x}$ = 230.8 g, s.d. = 4.8 g, n = 40). Each dosage was tested with 10 rats. The animals were deprived of feed for 16 hours before and 2 hours after the treatment. During the 14-day follow-up period after dosing the animals received the maintenance diet ALTROMIN 1324 (producer: Altromin GmbH, Lage/Lippe) and tap water ad libitum. The animals were grouped and housed in plastic cages on granulated light wood bedding.

The symptoms of intoxication, the mortality rate and the time of death were registered after the treatment. During the follow-up period the animals were weighed weekly. Lethally intoxicated animals were dissected and the macroscopic autopsy findings were recorded. After termination of the follow-up period, the surviving experimental animals were killed with CO_2-gas, dissected and also gross-examined.

The LD 50 was determined by probit analysis (LINDER/WEBER method); the confidence limits were calculated according to FIELLER (programmed in the Practical Mathematics Department of Hoechst Aktiengesellschaft).

The experiment No. 683/81 was conducted between 30.11. and 23.12.1981.

004403

Study Title: Acute Percutaneous Toxicity of HOE 39866 Water-Soluble Formulation to the Female Rat.

Accession No.: 072966

Study No.: 760/81

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 1-7-82/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH VD072; 19.9% a.i.

Doses Tested: 0.50, 0.80, 1.20, 2.00, 3.15 and 5.00 g/kg, applied dermally in an undiluted form.

Test Animal: Female Wistar (strain Hoe:WISKf[SPF71]) rats, Hoechst breeding stock; 6/dose.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) Only females were studied, no data on males were submitted.

Results

Mortality did not occur as an exact dose-effect relationship since 5/6 rats from the 0.80 g/kg group died, but only 3/6 rats from the 2.00 g/kg group died. All animals from the 3.15 and 5.00 g/kg groups died. The majority of deaths occurred before day 7. Clinical signs that were observed included: passiveness, trembling, convulsions, convulsive jumping, bristled hair, blepharophimosis, increased salivation, respiratory difficulty, and poor general condition.

Rats from the 2.00 g/kg group that survived to day 14 gained less body weight than animals from lower dose groups animals that survived to day 14. All animals that survived showed a gain over initial body weights.

Necropsy of animals that died revealed discoloration of the liver, adrenals, lungs, and intestines, extreme filling of the urinary bladder and dark liquid in the gastrointestinal tract.

Conclusion

The dermal LD_{50} of the water soluble formulation of HOE 39866 in female rats was calculated to be 0.804 g/kg with a 95% c.i. of 0.225-1.31 g/kg. These values correspond to Toxicity Category II.

Classification: Core-Supplementary Only females were studied.

TEST PROCEDURE

Hoe 39866 O H VD072 was provided in the form of a turquoise-green liquid. For the acute dermal treatment the substance was applied once at various dose levels to the shaven dorsal skin of 6 female Wistar-rats each (strain:Hoe WISKf (SPF71); from the company's breeding stock), 160 - 200 g in body weight ($\bar{x}$ = 175.9 g, s.d. = 12.09 g, n = 36). The animals were housed singly in plastic cages on granulated light wood bedding. They received ALTROMIN 1324, the maintenance diet produced by Altromin GmbH, Lage/Lippe and tap water ad libitum.

After the treatment, the mechanically shaven and intact dorsal skin (area of exposure appr. 30 cm^2) was covered with a strip of aluminium foil (6 x 8 cm) and secured in position around the trunk of the animals by an elastic plaster bandage (Elastoplast(R), 8 cm in width). The dressing was removed after a 24-hour exposure and the treated site was washed with tepid water.

The symptoms of intoxication, the mortality rate and the time of death were registered after the dermal application. During the 14-day follow-up period, the animals were weighed weekly. Lethally intoxicated animals were dissected and the macroscopic autopsy findings were recorded. After termination of the follow-up period, the surviving experimental animals were killed with CO_2-gas, dissected and also gross-examined.

The LD 50 was determined by probit analysis (LINDER/WEBER method); the confidence limits were calculated according to FIELLER (programmed in the Practical Mathematics Department of Hoechst Aktiengesellschaft).

Study Title: Aerosol Inhalation of HOE 39866 Water-Soluble Formulation to the Male and Female SPF-Wistar Rat.

Accession No.: 072966

Study No.: 5/82

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 1-14-82/9-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH VD072; 19.9% a.i.

Doses Tested: 0.35, 0.40, 0.90, and 1.18 mg/L (of the active ingredient) for 4 hours by inhalation exposure to the undiluted formulation.

Test Animal: Male and female SPF-Wistar rats, Hoechst breeding stock.

Methods

The submitted methods were reviewed and the following point(s) were noted:

1) An obvious error in the reporting of doses was noted. The report narrative stated that the 4-hour LC_{50} was 4170 mg/m^3 (4.17 mg/L) of HOE 39866 OH VD072. The data tables listed the doses as 0.35 to 1.18 mg/m^3, an error that obviously affects the interpretation of this study. In a telephone conversation with the registrant (2-8-85 with V. Dorr and E. Kamines), the error was acknowledged, and a revised study report was submitted.

Results

Clinical signs noted after exposure to the formulated product included irregular, noisy respiration, sneezing, and CNS signs including hyperactivity, trembling, and "convulsive jumping and rolling". These signs were reported to increase in a dose-related manner, although were not quantified as to the number of animals affected.

Based on the 14-day mortality, the LC_{50} was calculated to be 4.17 mg/L of the water-soluble formulation (table 1).

Table 1. 14-Day Mortality After Inhalation Exposure[a]

Dose (mg/L)	Male	Female
1.76[b] (0.35)[c]	0/6	0/6
2.01 (0.40)	0/6	1/6
4.52 (0.90)	2/6	3/6
5.93 (1.18)	5/6	6/6

[a]data excerpted from submitted study.

[b]dose in mg/L of the formulation.

[c]dose in mg/L of the active ingredient.

Conclusion

The LC_{50} of the water-soluble formulation (200 g/L) was calculated by the investigators to be 4.17 mg/L (95% c.i. = 3.35-5.20 mg/L) after a 4-hour exposure. This value corresponds to Toxicity Category III.

Classification: Core-Minimum LC_{50} not calculated separately for males and females.

RIN 5218-93 Toxicological Review for Glufosinate (128850)

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Pages 154 through 156 are not included.

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____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

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004403

Study Title: Irritance to the Rabbit Skin and Eye Mucosa [of HOE 39866 Water-Soluble Formulation (200 g/L)].

Accession No.: 072966

Study No.: 166/82

Sponsor/Contracting Lab.: Hoechst/Same, Pharma Forschung Toxikologie

Report Date/Submitted: 4-21-82/0-25-84

Test Material: Monoammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate; Code HOE 39866 OH VD072; 19.9% a.i.

Doses Tested: Skin irritation- 0.5 ml of the undiluted formulation, dermally applied for 4 hours;

Eye irritation- 0.1 ml of the undiluted formulation, applied to the conjunctival sac for 24 hours.

Test Animal: New Zealand rabbits, sex not specified, Hoechst breeding stock.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) The sex of the test animals was not specified.

Results

A. Skin Irritation- Reactions to the test compound were assessed at 4.5, 24, 48 and 72 hours, and 7 days after application to the skin. Grading was based on a range of 1 (very slight) to 4 (severe) for erythema, eschar, and edema formation. The effect of the formulation on abraded skin was not assessed.

All 6 rabbits showed erythema that ranged from slight to moderate 30 minutes after removal of the test article (4.5 hours after application). Edema that ranged from very slight (1) to slight (2) was also noted in 5/6 rabbits at this time. By 72 hours all 6 rabbits still had erythema that ranged from slight to moderate. Only 1/6 rabbits had "very slight" edema at this time. All effects were apparently reversible since only 1 rabbit had "very slight" erythema at 7 days, and all other animals were normal at this time. The Primary Irritation Score (PIS), calculated from average effects at 24 and 72 hours, was 2.7, which corresponds to Toxicity Category III.

B. Eye Irritation- Reactions to the test compound were assessed at 1, 7, 24, 48 and 72 hours, and 7 days after treatment. Grading was based on combined effects on the cornea, iris, and conjunctivae (appendix 2 of study). The left eye of 9 rabbits was treated with 0.1 ml of the test compound; the eye was rinsed 1 minute later for 3/9 rabbits and for the remaining 6 rabbits the eye

was rinsed 24 hours later. The highest score of 33 (out of 110 possible) was observed 7 hours after application in unrinsed eyes. Rinsing apparently had little effect as the score for these rabbits was 30 at 7 hours. Corneal opacity, involving from 50-100% of the corneal surface, was noted in 9/9 rabbits (rinsed and unrinsed) at 7 hours, along with inflammation of the iris (4/6 unrinsed, 2/3 rinsed) and the conjunctivae (9/9 rinsed and unrinsed). All eyes were normal by 7 days after treatment. These effects correspond to Toxicity Category II.

Conclusion

A. The primary skin irritation study demonstrated erythema and edema at 4.5 hours that persisted for 48 hours. By 72 hours only erythema was present. These effects were reversible since all animals appeared normal 7 days after treatment. The PIS was 2.7, which corresponds to Toxicity Category III.

Classification: Core-Minimum Sex of test animals not specified.

B. The primary eye irritation study demonstrated irritation to the cornea, iris, and conjunctivae. This response was not affected by rinsing. All eyes appeared normal by 7 days after treatment. These effects correspond to Toxicity Category II.

Classification: Core-Minimum Sex of test animals not specified.

RIN 5218-93 Toxicological Review for Glufosinate (128850)

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