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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

MAR 19 1990

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Ignite® (Hoe 039866): Evaluations of the supplemental toxicology data

Caswell No. 580I
EPA ID No. 8340-EI
8F3607

HED Project No. 9-1809 OR 9-1968
MRID No. 411447-01 to
411447-05

TO: J. Miller / R. Ikada, PM Team 23
Fungicide-Herbicide Branch
Registration Division (H7505C)

FROM: Whang Phang, Ph.D. 3/8/90
Pharmacologist
HFAS-Tox. Branch II / HED (H7509C)

THROUGH: K. Clark Swentzel, Section 3/12/90
and
Marcia van Gemert, Ph.D. 3/13/90
Branch Chief
HFAS-Tox. Branch II / HED (H7509C)

Introduction

In response to the Toxicology Branch reviews transmitted in December 7, 1988 on toxicology data of Ignite®, the registrant currently submitted the supplemental data on the following studies to address the deficiencies identified in the transmitted reviews:

1). Chronic feeding/oncogenicity study in rats
2). Mouse oncogenicity study
3). Rabbit teratology study
4). Micronucleus assay (mice)

In addition, the registrant also submitted a summary of metabolic fate of Hoe 039866. This summary is intended for "possible future reference by the Agency", and a response is not necessary.

Discussion and Conclusion

This reviewer had evaluated the supplemental data in conjuction with the previously submitted reports and the Tox. Branch's Data Evaluation Report of each study. The following are conclusions for the individual studies:

1. Suter, P. et al. Hoe 039866 Technical (Code: Hoe 039866 OH ZC95 0001) Combined chronic toxicity/oncogenicity study in the rat - dietary administration. RCC, Research & Consulting Co., AG; Report No. A33811 (Original study); Report No. A29425 (Supplemental report) Sept. 19, 1986.

The deficiencies found in the previous report have been satisfactorily addressed. Based upon the dose-related effects on the mortality rates in females at 140 and 500 ppm and the increases in the absolute and relative kidney weights of the 140 and 500 ppm males, the NOEL for systemic toxicity for Hoe 039866 was 40 ppm. This study has been classified as minimum, and it satisfies the data requirements for a combined chronic feeding / oncogenicity study in rodents (Guideline Nos. 83-1 and 83-2).

2. Suter, P. et al. (1986) Two year oncogenicity study with Hoe 039866 technical in mice-dietary administration. RCC, Research & Consulting Co., AG; Project No. 018527 (original study); Report No. A30381 (supplemental report).

The deficiencies found in the previous report of this study have been appropriately addressed in the supplemental report. The increase in liver weights in all treated females and the increases in the incidence of chronic nephropathy and of thyroid cystic follicles in all dosed males were not treatment-related. No increase in tumor incidence was found in any dosed group. Based upon the treatment-related effects on the mortality in the high dose (160 ppm) males, the increase in glucose level in the high dose males and females, and the consistent changes in the glutathione levels in the high dose males, the NOEL for systemic toxicity was established at 80 ppm (10.82 mg/kg/day for males and 16.19 mg/kg/day for females). This study is classified as minimum, and it satisfies the data requirements for a mouse oncogenicity study (Guideline No. 83-2).

3. Baeder, C., Kramer, M., et al. (1984) Hoe 039866-- Active ingredient technical; testing for embryotoxicity in Himalayan rabbits following oral administration. Hoechst AG, FRG; Study No. G2K0402. Project No. 84.0177. 4/9/84

The deficiencies identified in the previous DER have been properly addressed in the supplemental data. Based upon the data presented in the original and in the supplemental reports, dams which received 20 mg/kg showed increases in the incidence of premature delivery and of abortion or early resorption, decreases in body weight and food consumption, and an increase in the kidney weights. The LEL for maternal toxicity was 20 mg/kg; NOEL, 6.3 mg/kg. No developmental toxicity was seen; Therefore, the NOEL for developmental

toxicity was 20 mg/kg. This study is upgraded from supplementary to minimum, and it satisfies the data requirements for a rabbit teratology study (Guideline No. 83-3).

4. Jung, R and Weigand. Hoe 039866- Substance Technical (Code: Hoe 039866 OH ZC96 0002) Micronucleus Test in Male and female NMRI Mice After Oral Administration. Hoechst AG; Study No. 86.0702 and Lab. Report No. A34419. Oct. 9, 1986.

Thirteen Groups of mice (5/sex/dose) received a single administration of Hoe 039866 at dose levels of 100, 200, and 350 mg/kg by gavage. A positive control group received 50 m/kg of cyclophosphamide (Endoxan®). After dosing, the animals were sacrificed at 24, 48, and 72 hrs, and the erythrocytes from the bone marrows were sampled at these times. The results indicated that the test agent had no effect on micronucleus formation. This observation was consistent with that of a previous in vivo micronucleus assay (Document No's. 004403,004928, & 006936).

This study is classified as acceptable, and it satisfies the data requirements for a structural chromosomal aberration test (Guideline No. 84-2).

It should be noted that the toxicology data requirements for the registration of Ignite® for food use have been satisfied as indicated below:

Technical product	Required	Satisfied
Acute oral LD_{50}	Yes	Yes
Acute dermal LD_{50}	Yes	Yes
Acute inhalation LC_{50}	Yes	Yes
Primary eye irritation	Yes	Yes
Primary dermal irritation	Yes	Yes
dermal sensitization	Yes	Yes
90-day feeding- rodent	Yes	Yes
90-day feeding- non-rodent	Yes	Yes
21-day dermal	Yes	Yes
Chronic feeding- rodent	Yes	Yes
- non-rodent	Yes	Yes
Oncogenicity - rat	Yes	Yes
- mouse	Yes	Yes
Teratology - rat	Yes	Yes
rabbit	Yes	Yes
Reproduction	Yes	Yes
Gene mutation	Yes	Yes
Structural chromosome aberration	Yes	Yes
Other genotoxic effects	Yes	Yes
Metabolism	Yes	Yes

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Reviewer: Whang Phang, Ph.D. 3/8/90
HFAS/Tox. Branch II/HED (H5709C)
Secondary Reviewers: K. Clark Swentzel, Section Head
HFAS/Tox. Branch II/HED (H5709C)

DATA EVALUATION REPORT

Chemical: Ignite; Hoe 039866; Ammonium-(3-amino-3-carboxy-propyl) methyl phosphinate

Study type: Supplemental Data to a teratology study in Himalayan rabbits (MRID No. 403456-11)

Caswell No.	580I	**HED Proj. #:**	9-1809
EPA ID No.:	8340-EI	**Record No.:**	203,178
	8F3607		243,256
MRID No.:	411447-03		

Testing Laboratory: Pharma Research Toxicology and Pathology, Hoechst AG, Germany

Sponsor: Hoechst Celanese Corp., Somerville, NJ

Citation: Baeder, C., Kramer, M., et al. (1984) Hoe 039866--Active ingredient technical; testing for embryotoxicity in Himalayan rabbits following oral administration. Hoechst AG, FRG; Study No. G2K0402. Project No. 84.0177. 4/9/84

Discussion & Conclusion:

The rabbit embryotoxicity study was previously evaluated (EPA MRID No. 403456-11) (Tox. Doc. No. 006936). Groups of pregnant Himalayan rabbits (15/dose) were treated by gavage with Hoe 039866 at doses of 0, 2.0, 6.3, and 20 mg/kg from gestation days 7 to 19. There were increases in the incidence of premature delivery, of abortion, or of resorption. There was a decrease in body weight and food consumption in 20 mg/kg dams. A drop in food consumption was also seen in 6.3 mg/kg dams. In the 20 mg/kg group, there was an increase in the number of dead fetus/litter and increased kidney weights in the dams. Increased incidences of incomplete or absent ossification of skeletal bones in fetuses were observed in the 6.3 and 20 mg/kg groups.

The report had several deficiencies which did not allow proper evaluation of the developmental effects of the test agent. The deficiencies were (1) discrepancies in the food consumption and in the body weight data between the summary tables and the individual animal data, (2) incomplete food consumption data for individual 20 mg/kg dams, and (3) vague diagnoses of the skeletal examination of the fetuses. The currently submitted supplemental data address all these deficiencies, and the analyses of the supplemental data are as follows:

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1). Discrepancies in the food consumption and in the body weight data between the summary tables and the individual animal data were caused by two different data analysing programs. One for analyzing the individual animal data and other for intergroup comparisons which excluded all dams which had a premature delivery, an abortion or were killed in moribund condition from the summary table. For the individual animal data, these animals were retained in the analyses.

2). The current EPA Guidelines do not specifically require the food consumption data for a rabbit teratology. In addition, the registrant also noted that it would be difficult to obtain valuable food consumption
data from rabbits because of the food spillage due to their "digging behavior".

3). The registrant submitted additional data on the skeletal examinations of fetuses to correct the deficiency in the vague diagnoses of the fetal skeletal examinations. The supplemental data contained more details, and the results of the skeletal examinations were divided into findings in the live fetuses, in the dead fetuses delivered at caesarian section, and in the aborted or prematurely delivered fetuses from the dams which were sacrificed in moribund state. These data were excerpted from the supplemental report and presented in this DER as Tables 1, 2, and 3.

The re-organized data presented a better understanding of any developmental effects of the test material. The results indicated that the increase in the incidence of skeletal retardations in 6.3 and 20 mg/kg groups presented in the previous report (Attachment 1) was found predominately in one litter of prematurely delivered or aborted fetuses of a dam sacrificed in moribund condition (Table 3). It would be difficult to accurately determine whether this finding was due to the chemical or the prematurity of the fetuses.

The deficiencies identified in the previous DER have been properly addressed in the supplemental data. Based upon the data presented in the original report and in this supplemental report, dams which received 20 mg/kg showed increases in the incidence of premature delivery and of abortion or early resorption, decreases in body weight and food consumption, and an increase in the kidney weights. The LEL for maternal toxicity was 20 mg/kg; NOEL, 6.3 mg/kg. No developmental toxicity was seen; Therefore, the NOEL for developmental toxicity was 20 mg/kg. This study is upgraded from supplementary to minimum, and it satisfies the data requirements for a rabbit teratology study (Guideline No. 83-3).

RIN 5218-93 Toxicological Review for Glufosinate (128850)

Page_____ is not included in this copy.

Pages 6 through 9 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

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007817

Reviewer: Whang Phang, Ph.D. 3/1/90
HFAS/Tox. Branch II/HED (H5709C)
Secondary Reviewers: K. Clark Swentzel, Section Head 3/2/90
HFAS/Tox. Branch II/HED (H5709C)

DATA EVALUATION REPORT

Chemical: Ignite; Hoe 039866; Ammonium-(3-amino-3-carboxy-propyl) methyl phosphinate

Study type: Supplemental Data of Combined Chronic Toxicity/Oncogenicity study (rat) (EPA MRID No. 403456-07)

Caswell No.	580I	**HED Proj. #:**	9-1809
EPA ID No.:	8340-EI	**Record No.:**	203,178
	8F3607		248,256
MRID No.:	411447-01		

Testing Laboratory: Hoechst AG, Germany

Sponsor: Hoechst Celanese Corp., Somerville, NJ

Citation: Suter, P. et al. Hoe 039866 Technical (Code: Hoe 039866 OH ZC95 0001) Combined chronic toxicity/oncogenicity study in the rat - dietary administration. RCC, Research & Consulting Co., AG; Report No. A33811 (Original study); Report No. A29425 (Supplemental report) Sept. 19, 1986.

Discussion & Conclusion

The combined chronic toxicity/oncogenicity rat study on Hoe 039866 (MRID No. 403456-07) was previously reviewed (Document No. 006936) and was classified as a minimum study. The data showed that there were increases in absolute and relative (kidney/body weight) weights and in glutamine synthetase (GS) activity in treated females of all dose levels (Table 1A & 1B). Based upon these results a NOEL could not be established. However, the compound did not cause any oncogenic effects under the conditions of the study.

Currently, the registrant submitted supplemental data to explain the increases in kidney weights and in the glutamine synthetase activity of the kidney in treated females at all dose levels. With respect to the increase in the GS activity, the information indicated that, in the kidney, GS is involved in the excretion of ammonia, and the process applied a rather complex regulatory system which maintained a steady-state among ammonia, glutamate, and glutamine. The increase in the GS activity in the kidney could be a response to the presence of Hoe 039866, which is a structural analog of glutamate. Therefore, this change would be considered as an adaptive response.

The increase in the kidney weights of females in all dose

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groups appeared to be closely related to the increase in the GS level. The recently submitted data indicated that while the increase in kidney weights in the dosed females was statistically significantly different from the controls at 130 weeks, this increase was within the range of values of the historical controls (Table 1A). In addition, this change was not seen in female rats which were sacrificed at 52 and 104 weeks, and there were no associated histopathological changes in the kidneys of these animals. In considering these factors, the increases in kidney weight and in the kidney GS activity in female rats would not be considered as toxicological responses to the administration of the test material.

Therefore, based upon the dose-related effects on the mortality rates in females at 140 and 500 ppm and the increases in the absolute and relative kidney weights of the 140 and 500 ppm males, the NOEL for systemic toxicity for Hoe 039866 was 40 ppm. This study has been classified as <u>minimum</u>, and it satisfies the data requirements for a combined chronic feeding / oncogenicity study in rodents (Guideline Nos. 83-1 and 83-2).

TABLE 1+

A. CLINICAL BIOCHEMISTRY SUMMARY

FEMALES

GLUTAMINE SYNTHETASE ACTIVITY

	LIVER ***	KIDNEY ***	BRAIN ***
AFTER 26 WEEKS			
GROUP 1	---	---	---
GROUP 2	---	---	---
GROUP 3	---	---	---
GROUP 4	---	---	---
AFTER 52 WEEKS			
GROUP 1	2.85	0.79	2.35
GROUP 2	2.67	1.19 *	2.37
GROUP 3	2.38 *	1.27 *	2.19
GROUP 4	2.29 *	1.52 *	2.14
AFTER 78 WEEKS			
GROUP 1	---	---	---
GROUP 2	---	---	---
GROUP 3	---	---	---
GROUP 4	---	---	---
AFTER 104 WEEKS			
GROUP 1	2.92	1.19	2.53
GROUP 2	3.29	1.61 *	2.32 *
GROUP 3	3.56 *	2.01 *	2.44
GROUP 4	3.27	2.28 *	2.24 *

MALES

GLUTAMINE SYNTHETASE ACTIVITY

	LIVER ***	KIDNEY ***	BRAIN ***
AFTER 26 WEEKS			
GROUP 1	---	---	---
GROUP 2	---	---	---
GROUP 3	---	---	---
GROUP 4	---	---	---
AFTER 52 WEEKS			
GROUP 1	2.28	1.23	2.48
GROUP 2	2.07	1.41	2.49
GROUP 3	1.80 *	1.51 *	2.52
GROUP 4	1.71 *	1.72 *	2.34
AFTER 78 WEEKS			
GROUP 1	---	---	---
GROUP 2	---	---	---
GROUP 3	---	---	---
GROUP 4	---	---	---
AFTER 104 WEEKS			
GROUP 1	2.33	1.47	---
GROUP 2	2.39	2.03	---
GROUP 3	2.21	2.15 *	2.34
GROUP 4	2.35	2.25 *	2.19

B.

Comparison of Hoe 039866 Treated Rat Kidney Weights++ with Historical Controls

Males

Study Week	Hoe 039866 (ppm) 0	40	140	500	Historical Control Mean	Range
52	2.23±0.24	2.47±0.25	2.70±0.25*	2.71±0.25*	2.38±0.22	1.83-2.80
104	2.99±0.72	3.09±0.72	3.03±0.40	3.19±0.38	3.03±0.58	2.12-5.00
130	3.00±0.37	3.08±0.58	3.64±1.00*	3.58±0.91*	3.28±0.87	2.13-6.98

Females

52	1.45±0.10	1.51±0.22	1.50±0.16	1.54±0.14	1.51±0.17	1.11-1.91
104	1.80±0.21	1.84±0.18	1.92±0.23	1.95±0.31	1.88±0.22	1.41-2.61
130	1.86±0.25	2.01±0.26*	1.96±0.22	2.09±0.22*	2.11±0.26	1.68-2.79

* $P \leq 0.05$

+: DATA EXCERPTED FROM THE REPORT (EPA MRID. ~~ACCESSION~~ No. 403456-07)

++: TABLE EXCERPTED FROM THE SUBMISSION DATA (EPA MRID No. [illegible])

Reviewer: Whang Phang, Ph.D.
HFAS/Tox. Branch II/HED (H7509C)
Secondary Reviewers: John Chen, DVM
K. Clark Swentzel, Section Head
HFAS/Tox. Branch II/HED (H7509C)

DATA EVALUATION REPORT

Chemical: Ignite; Hoe 039866; Ammonium-(3-amino-3-carboxy-propyl) methyl phosphinat

Study type: Micronucleus assay (mice)

Caswell No.	580I	**HED Proj. #:**	9-1809
EPA ID No.:	8340-EI	**Record No.:**	203,178
	8F3607		248,256
MRID No.:	411447-04		

Testing Laboratory: Hoechst AG, Germany

Sponsor: Hoechst Celanese Corp., Somerville, NJ

Citation: Jung, R and Weigand. Hoe 039866- Substance Technical (Code: Hoe 039866 OH ZC96 0002) Micronucleus Test in Male and female NMRI Mice After Oral Administration. Hoechst AG; Study No. 86.0702 and Lab. Report No. A34419. Oct. 9, 1986.

Conclusion: Thirteen Groups of mice (5/sex/dose) received a single administration of Hoe 039866 at dose levels of 100, 200, and 350 mg/kg by gavage. A positive control group received 50 mg/kg of cyclophosphamide (Endoxan^{R}). After dosing, the animals were sacrificed at 24, 48, and 72 hrs, and the erythrocytes from the bone marrows were sampled at these times. The results indicated the test agent had no effect on micronucleus formation. This observation was consistent with that of a previous in vivo micronucleus assay (Document No's. 004403, 004928, & 006936).

This study is classified as acceptable.

Material and Methods:

Test article: Hoe 039866 (Technical grade) with Code: Hoe 039866 OH ZC96 0002; purity, 96.9%; white powder; batch No.: Op. 27/85

Positive control: cyclophosphamide - Endoxan^{R} (Charge 044439)

Solvent: distilled water for both the test compound and Endoxan^{R}

Test animals: Seven to 8 weeks old NMRI mouse (Hoe: NMRKf (SPF71)) were obtained from Hoechst AG, Kastengrund, SPF breeding colony. At the initiation of the study

these mice weighed 23-34 gm for males and 21-29 gm for females. These animals were housed in environmentally controlled rooms.

Study design: Mice were divided into 3 dose groups, each of which consisted of 5 males and 5 females. The animals received (by gavage) a single administration of the test article at dose levels of 0, 100, 200, and 350 mg/kg. The positive controls received Endoxan® at 50 mg/kg (Table 1). At 24, 48, and 72 hrs after dosing 5 males and 5 females from each dose group were sacrificed as indicated in Table 1. Both femora were removed from each test animal, and the bone marrow was freed of muscle. The proximal ends of the femora wee opened to flush out the bone marrow into a centrifuge tube containing fetal bovine serum. The suspension was centrifuged for 5 minutes at 1200 rpm. The supernatant was discarded. A drop of the mixed sediment was smeared on a slide which was air-dried, fixed and stained with Giemsa solution.

From each animal, 1000 polychromatic erythrocytes were counted. The number of cells with micronuclei were determined. For a negative control, 1000 mature erythrocytes were also counted and examined for micronuclei. The ratio of polychromatic to normachromatic erythrocytes was calculated. Statistical method of Wilcoxon (paired, one-sided increase) was applied in comparison for dose groups with the concurrent control group.

Results

Toxicity: No death occurred in 100 and 200 mg/kg, but 2/30 females in 350 mg/kg died. They were replaced with two other females which were treated with 350 mg/kg. Some animals of the 350 mg/kg group showed signs of increased spontaneous activity, aggressivity, tactile hyperaesthesia, motor excitation, uncoordinated gait, narrowed palpebral fissures, and clonic convulsion. The two females, which died, had uncoordinated gait, abdominal position, and panting.

Macroscopic examination did not show any toxic effects except the presence of foamy, yellow liquid in the intestinal tract of 4/30 females in the 350 mg/kg group.

Micronucleus examination: The incidence of micronucleated polychromatic erythrocytes is summarized in Table II. The incidence of erythrocytes with micronuclei in all of the test article treated animals was comparable to that of the vehicle controls at 24, 48, and 72 hrs after dosing. The positive control, cyclophosphamide caused a statistically significant increase (0.05) in the incidence of erythrocytes with micronuclei in both males and female mice. Relative to the concurrent controls, a small decrease in the number of polychromatic erythrocytes was seen in 200 and 350 mg/kg females at 72 hrs after treatment.

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Compliance: Signed and dated statements of data confidentiality, GLPs, and QAU were included.

Discussion

The results indicated that, under the conditions of the assay, Hoe 039866 did not cause an increase in the incidence of polychromatic erythrocytes with micronucleus in mice. These results are consistent with those of a previous study (Document No's. 004403 & 004928). The previous study was classified as unacceptable because the protocol was not scientifically sound. " The sampling of bone marrow only six hours after the last dose does not allow adequate time for micronuclei to form from the last administration, and the sampling time does not allow for possible effects on cell cycle time to be taken into account" (Memorandum, Dearfield to Phang, May 5, 1988; Document No. 006936).

The dose levels in this study were selected based upon a preliminary toxicity study in which 200, 250, 300, 350, and 400 mg/kg were tested in groups of mice (3/sex/dose). At 350 mg/kg or lower, no death occurred in both males or females, but signs of toxicity which included increased spontaneous activity aggressive behavior, were seen in 200, 250 and 300 mg/kg animals. At 350 mg/kg, the animals showed signs of widened palpebral fissures and increased grooming. At 400 mg/kg, all treated females died, and animals showed motor excitation, panting, ataxic gait, and clonic convulsions. Based upon these preliminary observations and toxicity results of the assay, the highest dose, 350 mg/kg, selected for this in vivo micronucleus assay appeared to be a sufficient top dose.

The spontaneous rates of micronuclei in the polychromatic erythrocytes of vehicle controls (distilled water) were found from 0.02% (females) to 0.03% (males) in this study. These results are within the normal range for performing the mouse micronucleus test as described by Heddle et al. (Mutation Res. 123: 61-118). Therefore, the test material, Hoe 039866, had negative responses in this mouse micronucleus test at all the intervals (24, 48, & 72 hrs) evaluated.

This study is classified as acceptable.

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RIN# 5218-93 Tox Review GLWfosinate

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Reviewer: Whang Phang, Ph.D. 3/7/90
HFAS/Tox. Branch II/HED (H5709C)
Secondary Reviewers: K. Clark Swentzel, Section Head
HFAS/Tox. Branch II/HED (H5709C)

DATA EVALUATION REPORT

Chemical: Ignite; Hoe 039866; Ammonium-(3-amino-3-carboxy-propyl) methyl phosphinate

Study type: Supplemental Data for mouse oncogenicity study (EPA MRID No. 403456-09)

Caswell No.	580I	**HED Proj. #:**	9-1809
EPA ID No.:	8340-EI	**Record No.:**	203,178
	8F3607		248,256
MRID No.:	411447-02		

Testing Laboratory: Hoechst AG, Germany

Sponsor: Hoechst Celanese Corp., Somerville, NJ

Citation: Suter, P. et al. (1986) Two year oncogenicity study with Hoe 039866 technical in mice-dietary administration. RCC, Research & Consulting Co., AG; Project No. 018527 (original study); Report No. A30381 (supplemental report).

Discussion & Conclusion

The mouse oncogenicity study was previously evaluated (EPA MRID No. 40356-09) (Tox. Document No. 006936). The results showed that there were statistically significant decreases in liver weight of all treated female mice and increases in the incidence of cystic follicles of the thyroid and chronic nephropathy in all treated males relative to those of the controls (Tables 5 and 6 of Tox. Document No. 006936)(Attachments 1 and 2). Although these findings did not showed a clear dose-related effect, the report did not present any explanation for these observations. Based upon these findings, an NOEL could not be established. This reviewer suggested that additional information be provided to explain any possible cause of these findings.

Currently, the registrant submitted supplemental data to address these findings. These data were evaluated in conjunction with the original report. Each finding is discussed below:

1). The decrease in liver weight in all treated female mice: A statistically significant decrease in absolute and relative liver weights seen in female NMRI mice of all dose groups could be attributed to the heavier liver weights of the concurrent control females which survived to the final sacrifice. It should be noted that the survival rates dropped sharply after 18 months, but at 18 months they were accept-

able. The survival rates for female mice at 18 months and at final sacrifice were as follows:

	Control	20 ppm	80 ppm	320 ppm
18 months	43/50	43/50	41/50	38/50
24 months (final sacrifice)	8/50	11/50	15/50	6/50

At final sacrifice, only one control female showed microscopically normal liver. Three out of 8 surviving animals had enlarged livers and heavy liver weights which contributed to the unusually heavy mean liver weights in the control group. The increased liver weights in the controls led to a comparative drop in liver weights of the treated females in all dose groups. As a final analysis, the liver weights of females were compared to those of the males; it was found that values of treated females were comparable to those of both the control and the treated males. Therefore, the decrease in liver weights in the treated females would not be considered as a compound-related effect.

2). Chronic nephropathy: The incidence of chronic nephropathy in male rats of all dose groups was increased relative to that of the controls (control, 3/50; 20 ppm, 12/50; 80 ppm, 13/50; 160 ppm, 15/50). The supplemental data indicated that this chronic nephropathy was "characterized by a relatively severe diffuse tubular atrophy and tubular dilation with or without casts. Often the lesion associated with eosinophilic homogeneous glomerular and/or interstitial deposits ---. In many cases these deposits were considered to be 'amyloid'. Frequently, lesions diagnosed as 'chronic nephropathy' coincided with 'amyloidosis' in spleen and/or liver". In the interim sacrificed animals which received the test article for one year, the incidence of "amyloidosis" was not seen, and the incidence of nephropathy was not reported. Based upon these observations, the pathologist considered the "chronic nephropathy" seen in the treated animals to be a "sequela to the systemic 'amyloidosis'". Considering these explanations, the renal lesion was not be a compound-related effect. The fact that the incidence of chronic nephropathy in all females was greater than that seen in the treated males lends additional support to the above conclusion (Attachment 2).

3). Cystic follicles of the thyroid gland: An increase in the incidence of the cystic follicles of the thyroid was found in all Hoe 039866 treated males relative to the concurrent controls (control, 4/50; 20 ppm, 6/50; 80 ppm, 18/50; 160 ppm, 17/50). The supplemental data package provided a

summarized table of the historical control data on the incidence of cystic follicle of thyroid in NMRI mice of the performing laboratory. The table was excerpted from the supplemental report and presented as Table 1. The historical control data demonstrated that the incidence of the thyroid cystic follicles in older NMRI male mice was common, and it ranged from 4.1% to 54.6% among the animals which were sacrificed at 104 weeks. The incidence of the thyroid cystic follicle seen in this study (Attachment 2) was within the range of the historical control, and it was not treatment-related.

Based upon the above discussions, the increase in liver weights in all treated females and the increases in the incidence of chronic nephropathy and of thyroid cystic follicles in all dosed males were not treatment-related. No increase in tumor incidence was found in any treatment group. Based upon the treatment-related effects on the mortality in high dose (160 ppm) males, the increase in glucose level in high dose males and females, and the consistent changes in the glutathione levels in the high dose males, the NOEL for systemic toxicity was established at 80 ppm (10.82 mg/kg/day for males and 16.19 mg/kg/day for females). This study is classified as <u>minimum</u>, and it satisfies the data requirements for a mouse oncogenicity study (Guideline No. 83-2).

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PIN# 5218-93 Glufosinate

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Pages 21 through 23 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.

____ Information about a pending registration action.

____ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ 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.
