1-28-93

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

009985

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

Subject: Response to RfD/Peer Review report of Glufosinate-ammonium (Ignite) re: Historical control data (rat)
MRIDs 00142445, 00142446, 40345610
CAS No. 77182-82-2
EPA Chem No. 128850
Caswell No. 580I
Reg Group: New Chem.

From: James N. Rowe, Ph.D. James N. Rowe 1/27/93
Toxicology Branch II
Health Effects Division (H7509C)

To: Ms. Joanne Miller, PM 23
Fungicide-Herbicide Branch
Registration Division (H7505C)

Thru: Marcia van Gemert, Ph.D., Chief M van Gemert 1/28/93
Toxicology Branch II
Health Effects Division (H7509C)

ACTION: Review resubmission of rat historical control data from the registrant, Hoechst Celanese, regarding soft tissue finding of distended renal pelvis with hydroureter (distended ureter).

BACKGROUND:

The RfD committee (Developmental/Reproduction Toxicity Peer Review group) recommended that the kidney effects observed in the Baeder developmental toxicity study (No. G2R0303, 1982) be reevaluated in light of historical control data. The registrant has faxed this information to Tox BrII for their review. Based on reanalysis of the historical control data (ad hoc committee of the Developmental/Reproduction Toxicity Peer Review group), a NOEL for developmental toxicity in the rat study has been achieved and this is no longer considered a toxicology data gap. In consultation with George Ghali of the RfD committee, an updated Data Evaluation Record has been completed by the Review Section III and will be forwarded to the RfD committee (see attached updated DER and one-liner).

No remaining data gaps remain for developmental toxicity. This study satisfies the requirements for a rodent developmental toxicity study (§83-3) and is Core Minimum.

cc G. Ghali (H7509C)
W. Phang (H7509C)

Primary Review by: James N. Rowe, Ph.D. James N. Rowe 11/27/95
Review Section III, Toxicology Branch II/HED
Secondary Review by: See attached memoranda

DATA EVALUATION RECORD

Study Type: Teratology - Developmental Toxicity
Species: Rat
Guideline: 83-3

EPA Identification No.s: EPA MRID Nos.
00142445, 00142446, 40345610
CAS No. 77182-82-2
EPA Chem No. 128850
Caswell No. 580I
Reg Group: New Chem.

Test Material: Ignite

Synonyms: Glufosinate-ammonium

Sponsor: American Hoechst Corporation

Study Number(s): G2R0303, P2R0486, G2R0342

Testing Facility: Hoechst Aktiengesellschaft
Frankfurt, W. Germany

Title of Report: Study for Embryotoxic Effects on Rats after Dermal Administration

Author(s): 1)G2R0303, G2R0342- Baeder, Weigand and Kramer, 2) P2R0486- Pensler, M. et al.

Report Issued: 1)G2R0303, G2R0342- 7/19/85 and 7/26/86, 2) P2R0486- 6/18/86

Conclusions:

Attachment 1 includes the findings from the three studies, i.e., from the high dose study and the low dose study (pre- and post-natal phases), on the issue of dilated renal pelvis and/or hydroureter. Comparison of these findings with the historical control data indicates that the combined finding ranges from 0 to 21.1% for litters and 0 to 3.5% for fetal incidences. In three studies the respective litter and fetal incidences ranged from 15-21.1% and 2.5-3.5%. Thus it appears that in the high dose study (Baeder, 1982) that the 10 mg/kg dose findings are within the historical control range and that the subsequent low dose studies support the lack of a true effect at this dose level. This assessment was supported by the review of an Ad Hoc Peer Review Committee for Developmental Toxicity (Attachment 2).

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The developmental NOEL = 50 mg/kg/day based on a significantly increased severity of arrested renal and ureter development. The maternal toxicity NOEL = 10.0 mg/kg/day based on hyperactivity and other more severe forms of maternal toxicity (i.e, vaginal bleeding forcing sacrifice of 4 and 8 dams) at 50, 250 mg/kg/day observed in the original high dose study. Although hyperactivity was observed in the original study in 2 animals at 10 mg/kg/day (G2R0303), it was not confirmed in the two subsequent studies with doses up to 10 mg/kg/day (G2R0342, P2R0486).

Core Classification: Minimum.

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Attachment 1

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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JAN 5 1993

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MEMORANDUM

Subject: Response to RfD/Peer Review report of Glufosinate-ammonium (Ignite) re: Historical control data
CAS No. 77182-82-2
EPA Chem No. 128850
Caswell No. 580I
Reg Group: New Chem.

From: James N. Rowe, Ph.D. James N. Rowe 12/1/92
Toxicology Branch II
Health Effects Division (H7509C)

To: George Ghali, Ph.D.
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

Thru: Marcia van Gemert, Ph.D., Chief Marcia van Gemert 12/8/92
Toxicology Branch II
Health Effects Division (H7509C)

ACTION: Review resubmission of rat historical control data from the registrant, Hoechst Celanese, regarding soft tissue finding of distended renal pelvis with hydroureter (distended ureter).

DISCUSSION:

The RfD committee recommended that the kidney effects observed in the Baeder study (No. G2R0303, 1982) be reevaluated in light of historical control data. The registrant has faxed information indicating that this historical control data was previously submitted (see Attachments 1, 2) and should be adequate to address the findings of dilated renal pelvis with hydroureter noted in the original high dose study (0, 10, 50, 250 mg/kg). Also note that the first low dose study (Baeder et al., 1982; G2R0342) was not included in the Peer review except by referral in the DER for the post-natal study by Pensler et al. (1986). This should be rectified.

Attachment 3 includes the findings from the three studies, i.e., from the high dose study and the low dose study (pre- and post-natal phases). Comparison of these findings with the historical control data (pgs. 154, 155 of fax) indicates that the combined finding ranges from 0 to 21.1% for litters and 0 to 3.5% for fetal incidences. In three studies the respective litter and

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fetal incidences ranged from 15-21.1% and 2.5-3.5%. Thus it appears that in the high dose study (Baeder, 1982) that the 10 mg/kg dose findings are within the historical control range and that the subsequent low dose studies support the lack of a true effect at this dose level. The clarification of this issue should allow the RfD committee to finalize the developmental NOEL for these studies. Resolution of this is important to the registrant since this is the last remaining toxicological issue remaining for product registration for use on lawns and ornamentals.

cc Joanne Miller (H7505C)
W. Phang (H7509C)

Attachment 1

Hoechst Celanese

009935

Hoechst Celanese Corporation
Route 202-206
PO Box 2500
Somerville, NJ 08876-1258
908 231 2000
Telex 833 449
Fax 908 231 3225

November 24, 1992

VIA FAX: (703) 305-5147

Mr. James N. Rowe
Toxicology Branch, Health Effects Division
Office of Pesticide Programs - H7509C
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460-0001

Dear Mr. Rowe:

Subject: Glufosinate-Ammonium
CAS No. 77182-82-2
EPA Chem. No. 128850
RfD/Peer Review Report Dated
May 13, 1992
Applicant Response to Rat
Teratology Issues

As I discussed with you today, Joanne Miller (Product Manager 23) has relayed your concern over the glufosinate-ammonium rat teratology issue raised in the subject RfD/Peer Review Report dated May 13, 1992. We agreed that I would fax our response to you for your prior examination before discussing the issue again in a conference call with our toxicologist. A copy of our response to the rat teratology issue prepared by Dr. Linda Dulak is attached to this letter.

The RfD Committee has stated that the kidney effects observed in one of the original rat teratology studies should be reevaluated in light of historical control data. It appears that the RfD Committee has overlooked a submission of a third rat teratology study (containing historical control data) from Hoechst Celanese Corporation made on September 26, 1984 and again on September 26, 1985 in reformatted form. This study was not referenced in the RfD Committee report but it was reviewed and accepted by the Agency's reviewer (D. Stephen Saunders) on February 7, 1986. Dr. Saunders compared the instances of kidney effects to the historical control data and accepted the findings at that time.

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Hoechst

The full details of the rat teratology submissions and the Agency's prior reviews and acceptance of these data are contained in the enclosure. Because it appears that the Committee has erred in not evaluating all the previously submitted, reviewed and accepted data that should be in the Agency's files, we are asking for your immediate assistance and attention to this matter so that we may proceed without further undo delay towards the first registration of our pending glufosinate-ammonium product registrations. In this regard, Dr. Dulak and I will plan to call you in the morning of Monday, November 30, 1992 to discuss this matter and resolve the outstanding issue pertaining to the glufosinate-ammonium rat teratology studies. We thank you in advance for you attention to this matter.

Very truly yours,

Victor A. Dorr
Regulatory Affairs
Phone: (908) 231-2028
Fax: (908) 231-4462

cc: Ms. Joanne Miller - w/att. (Via Fax)

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Hoechst Celanese Corp. Response to EPA Peer Review of Glufosinate Ammonium Teratology Studies in Rats

Peer Review Report Dated May 13, 1992

This response is restricted to the issues which were raised on the teratology studies in rats which were reviewed by the EPA Peer Review Committee. The studies which were referenced by EPA in their report are listed below:

Study Reference Number 6. Baeder, C., Weigand, and Kramer, M. (1982). Testing for embryotoxicity in Wistar rats following oral administration. Unpublished report by Pharma Forschung Toxikologie, Hoechst AG, Study No. G2R0303, dated October 20, 1980, MRID No. 00142446, 00151500, Guideline requirement 83-3.

Study Reference Number 7. Pensler, M., et al. (1986). Testing for embryotoxicity in Wistar rats following oral administration. Unpublished report prepared by Hoechst AG, Study No. A33812, dated June 18, 1986. MRID No. 00142446, 00151500, Guideline No. 83-3.

It should be noted that these two studies do not represent the total database of rat teratology studies on the technical active ingredient of glufosinate ammonium. also referred to as Ignite and HOE 39866. One additional study was submitted (EPA Accession No. 072965) and is fully referenced below. In addition, two studies were reformatted and resubmitted (EPA Accession No. 073916) with additional individual animal data and historical control data. These data were not referenced in the Peer Review Committee report and thus were apparently not considered by the committee.

EPA Concern: The Committee recommended that the kidney effects observed in the Baeder study should be reevaluated in light of historical control data. This is particularly important since similar kidney effects were observed also in other studies indicating that these effects might be treatment-related effects.

Petitioner's Response: The kidney effects observed in the Baeder study have been addressed in data previously submitted to EPA but not referenced by the Peer Review Committee. In the study referenced by the Peer Review Committee (Study Reference Number 6), frank maternal toxicity as evidenced by vaginal bleeding with severe weight gain deficits was observed in the intermediate (50 mg/kg body weight/day) and high dose (250 mg/kg body weight/day) dams. It was concluded by the authors that embryo/fetal findings in these two dose groups were a result of maternal toxicity induced embryo- or fetal toxicity.

An additional embryotoxicity study in rats was submitted to EPA in the same submission as the Baeder study referred to above.

Baeder, Weigand, and Kramer, Test Report on the Embryotoxic Effect of HOE 39866 - Pure Active Ingredient - on Wistar Rats After Oral Administration. Unpublished report prepared by Hoechst AG, Study No. G2R0342, A25626, dated September 22, 1982. EPA Accession No. 072965, Submitted to EPA September 26, 1984.

This study has not been referenced as being considered by the Peer Review Committee in their evaluation of the database on reproductive toxicology. This study is critical to the evaluation of developmental toxicity since it was conducted to determine the significance of the distended renal pelvises and distended ureters at the dose of 10 mg/kg body weight/day. This study was conducted in rats at doses of 0.5, 2.24, and 10 mg/kg body weight/day to evaluate the significance of the distended renal pelvises and distended ureters observed in the first embryotoxicity study on this compound (Study Reference Number 6). The incidence of distended renal pelvises and distended ureters in this study are tabulated in Table 1.

Table 1

Summary of Kidney and Ureter Findings in Embryotoxicity Study in Rats on HOE 39866[a]				
Finding	0 mg/kg	0.5 mg/kg	2.24 mg/kg	10 mg/kg
Renal Pelvises Distended, Uni- or Bilateral	2/118[b] (1.7%)	1/118 (0.9%)	1/112 (0.9%)	0/110 (0%)
Ureter Distended, Bilateral	0/118 (0%)	1/118 (0.9%)	0/112 (0%)	0/110 (0%)

[a]Data summarized based on total number of fetuses affected/total number of fetuses examined in group.
[b]These two affected fetuses were found in two different litters.

In all four groups, a total of 20 pregnant animals were treated and 20 live litters were evaluated for fetal effects. It should be noted that among control dams (as well as treated dams) in this study the incidence of dilated renal pelvises was approximately 10%. This incidence in the dams is in the range of the incidence seen in fetuses in the initial Baeder study.

In addition, both Baeder studies were reformatted and resubmitted to EPA on September 26, 1985 (EPA Accession No. 073916). In the reformatted study, the issue of the historical control data on distended renal pelvises and distended ureters was addressed. Historical control data from March 1978 to November 1981 were included with the report.

These two reformatted Baeder studies were reviewed by D. Stephen Saunders Jr. in a review dated February 7, 1986. Dr. Saunders stated in his review:

> "The original review of this study identified the major findings in dams at necropsy as dilation of one or both renal pelvises, which was present at a rate of about 10-20% in all treatment groups. The incidence of this finding did not appear to be related to treatment with the test compound. Historical control data, included with the present submission, indicate that this finding exists at an average background rate of about 10%, and ranged as high as 25%, in this strain of rat. Therefore, the incidences of this finding in the present study are considered normal for this strain of rat."

Dr. Saunders goes on to discuss the incidence of dilated renal pelvis with hydroureter as follows:

> "As was noted in the original review, a dose-related increase in the incidence of dilated renal pelvis with hydroureter was noted in all treatment groups. Although statistically significant ($p<0.05$) only in the high dose group, the increases in the low and mid dose groups clearly appear to be related to treatment with the test compound. Historical control data for this finding indicate that the average fetal incidence of distended renal pelvis with hydroureter was $1.13 \pm 1.15\%$, with a range of 0-3.5%, and the historical litter incidence of this finding was $6.53 \pm 6.37\%$, with a range of 0-21.1%. Although the findings in the low and mid dose groups of the present study lie at the upper end of the historical control range, they must be considered as treatment-related in the present study in consideration of the relatively low concurrent control incidence, the apparent dose-dependency of the effect in all treatment groups, and the significantly higher incidence in the high dose groups."

It was to evaluate the significance of the dilated renal pelvises at 10 mg/kg body weight/day that the second Baeder study was conducted. Dr. Saunders concluded in his review of this second study as follows:

> "As was noted in the original review of this study, no effect of treatment on the incidence of soft tissue malformations/variations was apparent. Specifically, dilated renal pelvis with hydroureter, which was noted in all treatment groups of the high dose study, was not noted in any control or treated fetuses in the present low dose study. Dilated renal pelvis or hydroureter were noted (separately) in several fetuses and litters of the present low dose study, however the incidences did not appear to be treatment-related and were within the range of historical control values."

The classification of the study was described as follows:

> "Based on the joint consideration of high dose study #G2R0303 with low dose study #G2R0342:
>
> Maternal NOEL = 2.24 mg/kg/day
> Maternal LEL = 10 mg/kg/day Hyperactivity
>
> Developmental NOEL = 2.24 mg/kg/day
> Developmental LEL = 10 mg/kg/day Increased incidence of dilated renal pelvis wh hydroureter.
>
> Classification: Core-Minimum When considered with the results of study # G2R0303, Report # 85.0771"

In conclusion, it appears that the Committee did not consider all of the data which has been submitted to EPA by Hoechst Celanese Corp in this matter. The committee did not review the reformatted studies or their DER's. The questions of the significance of the findings of dilated renal pelvises appear to have been addressed as completely as is possible in these prior submissions and EPA DER's indicate concurrence with this conclusion.

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Attachment 2

Hoechst Celanese

Hoechst Celanese Corporation
Route 202-206
PO Box 2500
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908 231 2000
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November 30, 1992

VIA FAX: (703) 308-1825 (FHB FAX MACHINE)

Mr. James N. Rowe
Toxicology Branch, Health Effects Division
Office of Pesticide Programs - H7509C
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460-0001

Dear Mr. Rowe:

Subject: Glufosinate-Ammonium ← PMN-93
CAS No. 77182-82-2
EPA Chem. No. 128850
Submission of Historical Control Teratology Data

Per your telephone request of this afternoon, I have attached the historical control data of findings at soft tissue examination (Wilson Methods) in rat fetuses from teratology studies conducted at Hoechst AG in the period from 1978 to 1983. These pages (from Hoechst AG report numbers A 31635 and 31636) were originally submitted to the Agency on September 26, 1985 and were assigned Accession Number 073916.

I understand that you will be examining these data upon receipt for discussion at tomorrow's meeting of the Developmental Peer Review subcommittee. Please call me back if you need any further information or assistance.

1 of 4

We are very appreciative of your responsiveness in the last few days in working with this issue and we hope that we can resolve it quickly.

Very truly yours,

Victor A. Dorr

Victor A. Dorr
Regulatory Affairs
Phone: (908) 231-2028
Fax: (908) 231-4462

cc: Ms. Joanne Miller - w/att. (Via Fax)

File: f:\group\regaff\vad1130.921

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RIN 5218-93 Toxicological Review for Glufosinate (128850)

Page_____ is not included in this copy.

Pages 16 through 23 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.

____ 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.

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. *$p < 0.05$

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).

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Attachment 3 - Baeder et al. (1982)/Low Dose/Pre-Natal 009985

005365 Page 19a 004923

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.

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).

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The body weights of the offspring at birth were comparable between those of control and treated groups (Table 3).

3). Lactation period examinations: Survival rate and body weights of the offspring were comparable between offspring from the treated dams and those from the controls (Table 3). Significant increases in the incidence of external anomalies were not observed in any group of the test animals (Table 3).

4). Autopsy of dams and offsprings: The data showed that incidence of renal pelvic dilatation in either dams or offspring of the treated groups was comparable to that of the control animals (Table 4). No compound-related skeletal anomalies were reported.

TABLE 4†

Incidence of Hydronephrosis or Renal Pelvic Dilatation in Dams or Offspring, Respectively

	Control	0.50 mg/kg	2.24 mg/kg	10.00 mg/kg
Dams	1/20	3/20	2/20	2/20
Offspring	5/242	4/227	2/224	4/227

† Data excerpted from the submitted report (EPA Accession No. 403456-10).

5). Organ weights: There were no differences in organ weights between dams or offspring of the treatment groups and those of the controls (Tables 5 & 6).

DISCUSSION:

The results indicated that there were no significant differences in clinical observations, food consumption, body weights, implantations, resorptions, and autopsy findings between treated and control dams.

In offspring, survival rates and body weight (at birth or sacrifice) were comparable between those from treated groups and those from controls. No increases in the incidence of soft tissue and skeletal anomalies were found in the offspring of the treated animals relative to those of the controls. In contrast to the present study, a teratology study using higher doses (10, 50, & 250 mg/kg) of HOE 039866 and the same strain of rats

Attachment 2

009985

009985

Roger Gardner 1/6/93
Stephen C. Dapson 1/8/93
Larry Brenan 1/12/93

January 8, 1993

George,

As you requested, We have reviewed the rat teratology data on the incidence of hydroureter and dilated renal pelvis in two rat developmental toxicity studies with Ignite. Since the litter is the experimental unit, I looked at that data rather than the fetal incidence results.

The following table represents a statistical analysis I conducted using Fisher's Exact and Cochran-Armitage trend tests. These tests are appropriate because there are no significant effects on the numbers of corpora lutea, implantation sites or live fetuses per litter in the study. The p values for pairwise comparisons of each treated group with the control are listed under the three treated group columns, and the p value from the trend test is listed under the control group's column in the table that follows:

Observation				
Dose (mg/kg/day)	0	10	50	250
Number of litters examined	19	19	16	10
No. litters with "dilated renal pelvis and/or hydroureter"	6	11	10	5
p value.	0.16	0.1	0.07	0.06
No. litters with "dilated renal pelvis and hydroureter"	1	3	3	5
p value	<.01	-	0.24	0.11
Historical control studies	16			
Range (%)	0 to 21			

The first important point about the data on renal effects is that the control incidences for combined data exceeds the high end of the historical range (6/19 = 31.5% > 21%). Secondly, the pairwise comparisons all show no significant differences between the control and treated groups, and there is no significant trend in the incidence of combined renal effects.

For data on the incidence of dilated renal pelvis and hydroureter (in the same fetus), only the highest dosed group has an incidence greater than historical range (5/10 = 50% > 21%). Since hydroureter and dilated renal pelvis are manifestations of the same type of devevelopmental toxicity, combining the effects is appropriate, but a dose-related trend in the incidence of litters containing one or more fetuses with both hydroureter and dilated renal pelvis suggests a dose-related increase in severity of effects. Therefore, establishing a NOEL based on the incidence

data for hydroureter and dilated renal pelvis could be done. On that basis, the data from the earlier of the two studies suggests that the NOEL = 50 mg/kg/day as indicated by a significantly increased severity of arrested renal and ureter development.

Results from the later rat study (doses of 0.5 to 10 mg/kg/day) confirm that the NOEL is greater than 10 mg/kg/day. In addition, it should be noted that at 250 mg/kg, there was severe maternal toxicity, but the incidence of the renal developmental toxicity is not significantly increased at levels below maternally toxic doses.

Subject: RfD/Peer Review of Glufosinate-ammonium (Ignite) (ToxChem 580I). Review requested 1/11/93.

January 11, 1993.

From: David G Anderson, PhD D G Anderson 1/11/93
Section 3, Toxicology Branch-1
HED (H7509C)

To: George Ghali, PhD
Science Analysis and Coordination Branch
HED (H7509C)

cc Karen Hamernik

I do not remember reviewing this pesticide before, but I will comment on the data in the folder. After reviewing the data, there appears to be dose related effects possibly at all dose levels in only the one study at 10, 50 and 250 mg/kg/day. The dose relationship could be detected only when hydroureter and/or dilated renal pelvis were combined in that special fashion, otherwise the dose relationship was within historical control range.

Of relevance is that none of the historical studies had 0% incidence of distended renal pelvis, distended renal pelvis and hydroureter, or hydroureter, i.e., 1 to 4 litters (5% to 20%) were affected in each of the studies (≈20 animals) presented. This is a high background incidence compared with most American based studies. In addition, both studies conducted at 0.5, 2.24 and 10 mg/kg/day confirmed that there was no problem at 10 mg/kg/day.

The lack of maternal toxicity in neither study, conducted at 0.5, 2.24, and 10 mg/kg/day, should present an obstacle to the acceptability of the studies (the two studies were 1) the dams were killed at day 20 of gestation and 2) the dams were killed at post-natal days 21-23). Both studies were conducted because of the dilated renal pelvis noted in a previous study at [illegible] and 250 mg/kg/day; thus, the argument is not valid that unless maternal toxicity is determined, one cannot be certain that [illegible] relevant endpoints were examined with sufficient care.

In the memo from Roger Gardener and Stephen [illegible] 1/8/93, on this subject, they suggest that [illegible] the NOEL. This appears to be a logical and [illegible] treat the data. I agree with the NOEL [illegible] glufosinate-ammonium determined in this [illegible]

Memo on the Rfd Peer review pesticide [illegible]
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