JAN 24 1992

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

009066

JAN 24 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: 2-chloro-N-(ethoxymethyl)-N-(2-ethyl-6-methylphenyl)acetamide (Acetochlor): Review of additional Toxicology Data Submitted by the Registrant.

Caswell No: 003B
HED Project No: 2-0470
MRID Nos: 420549-01 through 420549-03; 420771-01
: two attachments #1 and one attachment #3

FROM: Timothy F. McMahon, Ph.D., Toxicologist 1/15/92
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

TO: Joanne Miller / PM Team 23
Registration Division (H7505C)

THRU: Yiannakis M. Ioannou, Ph.D., Section Head 1/16/92
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia Van Gemert, Ph.D., Branch Chief 1/21/92
Toxicology Branch II
Health Effects Division (H7509C)

Registrant: ICI Agricultural Products

Action Requested: Review of additional Toxicology data submitted by ICI in support of an Experimental Use Permit and Temporary Tolerance (G2) Petition for Acetochlor on corn. Review of worker exposure study and request for increased acreage under G2 petition.

I. Toxicology Data Review

The registrant (ICI Agricultural Products) submitted a response to concerns raised by the Agency in the review of Toxicology data submitted in support of an Experimental Use Permit and Temporary Tolerance Petition for Acetochlor on corn. The specific issues raised by the Agency and the response of ICI to each of these concerns is summarized in the following paragraphs.

Studies in support of an EUP for Acetochlor

1) Acute Oral Toxicity in the Rat MRID # 415651-04

The Agency noted that the purity of the technical material used in this study, SC-5676, was not provided by the registrant. ICI responded to this concern by providing the relevant Certificate of Analysis for SC-5676, which stated a purity of 91.0%.

The Agency considers this response adequate, and this study is upgraded to core minimum data.

2) Acute Dermal Toxicity in the Rat MRID # 415651-05

The Agency noted that in this study, the purity of the technical material, as well as a detailed explanation of test article administration to the skin site, was not provided. ICI responded to this by submitting a copy of the relevant Certificate of Analysis for SC-5676, which stated the purity to be 91.0%. In addition, a detailed explanation of application of SC-5676 technical to the skin of rats was provided.

The Agency considers the response to these concerns adequate. This study is upgraded to core minimum data.

3) Dermal Sensitization in Guinea Pigs MRID # 415651-14

The Agency noted that in this study with the 760 g/l EC formulation of Acetochlor (71.6% a.i.), a lack of dermal sensitization was observed. However, application of the technical grade of Acetochlor in MRID # 415651-08 resulted in extreme sensitization, and a 30% dilution of the technical grade in corn oil resulted in a strong sensitization response in this same study. Thus, it was not readily apparent why the 760 g/l EC formulation of acetochlor did not cause sensitization.

ICI responded by stating that the Magnusson and Kligman test maximizes the possibility of observing a response to the test chemical, due to the injection of test substance in the presence of Freund's Complete Adjuvant, as well as topical application of test material. The Buehler test, in contrast, involves only topical

application of test material, and is more relevant to the exposure conditions likely to be encountered in the field. The registrant noted that the study with the 760 g/l EC formulation was done according to a valid protocol with an appropriate positive control.
The Agency considers the response to these concerns adequate. The study is upgraded to core minimum data.

4) Developmental Toxicity in the Rat MRID # 415920-05

In this study, the Agency noted that maternal toxicity was observed at the highest dose tested in this study (600 mg/kg), but that additional data were required before an adequate assessment of maternal and developmental toxicty could be made. Specifically, data were requested in the following areas:

a) Food and water consumption data for gestation days 2 through 6, 6 through 15, 15 to the end of the study, and 6 through the end of the study.

b) Cesarean section data for total corpora lutea, total implantations, total live fetuses, total resorptions, total dead fetuses, and dead fetuses/dam.

c) Skeletal observation data separated into the individual bones affected in both fetal and litter incidence.

d) Historical control data addressing all measured parameters in both fetal and litter incidence for a period of 2 years prior and 2 years subsequent to this study (if possible) for comparison to concurrent control data.

e) The preliminary study in pregnant rats performed at HRC (study # ISN 198/89180)upon which the doses for the present study were selected.

The response of the registrant (ICI) to each of these issues, as well as the Agency's assessment of these responses, is detailed in an attached memorandum from Dr. Stephen Dapson, Toxicology Branch II, Health Effects Division. This study is upgraded to core minimum data.

5) Developmental Toxicity in Rabbits MRID # 415920-06

The Agency noted several data deficiencies in this study. Data in the following areas were requested from the registrant:

a) Food consumption data for gestation days 1 through 6, 6 through 18, 18 to the end of the study, and 6 through the end of the study.

b) Cesarean section data for total corpora lutea, total implantations, total live fetuses, total resorptions, total dead fetuses, and dead fetuses/dam.

c) Separate mean data for external examinations.

d) For the skeletal observation data, the meaning of fetuses observed with 12 or 13 ribs and variant sternebrae. These data should also be divided into full ribs, partial ribs, separate sternebrae, etc., and should be provided in both fetal and litter incidence.

The response of the registrant (ICI) to each of these issues, as well as the Agency's assessment of these responses, is detailed in an attached memorandum from Dr. Stephen Dapson, Toxicology Branch II, Health Effects Division. This study is upgraded to core minimum data.

Studies Not Required for an EUP

1) Metabolism in Rats

MRID #'s 415651-25 through 415651-27; 415920-07 through 415920-08.

In these studies on the metabolism and pharmacokinetics of 14-C Acetochlor, the Agency requested a justification for the omission of intravenous dosing data. In addition, the percentage recovery of radiolable from tissues and feces during processing was requested. Information on the species bound to red blood cells was also requested, as this may be toxicologically relevant. Purity of unlabelled acetochlor in studies 1 through 3 was requested.

ICI responded to these concerns by stating that the water solubility of acetochlor (223 mg/l at 25 ^{o}C) was insufficient to conduct an intravenous study.

With regard to percentage recovery of radiolabel, it was stated that oxidation efficiencies at Huntingdon Research Centre of less than 95% are not acceptable.

The purity of the sub-batch of acetochlor used in the studies 1 through 3 was provided and stated to be 90.5%.

The blood binding phenomenon observed in these studies was stated by ICI to be rat specific, and that no adverse effects from blood binding of acetochlor were observed in the 2 year rat feeding study.

The Agency considers the response to these concerns adequate. These studies are upgraded to core minimum data.

2) Carcinogenicity in Mice MRID # 415651-19

In this study, information on the site and type of pulmonary tumors observed in treated mice was requested. In addition, it was found after review of the mouse carcinogenicity study as well as a six week range finding study that the Maximum Tolerated Dose had been achieved for male mice, but not for female mice.

ICI responded to these concerns by stating that the study pathologist was consulted to render an opinion regarding the site and type of pulmonary tumors. The pulmonary tumors were re-examined and confirmed as adenomas or carcinomas of the lung parenchyma and were all of the alveologenic type.

ICI also presented additonal historical control data in support of the carcinogenicity of SC-5676. According to these data, the reported incidence of pulmonary adenoma in male mice ranged from 4-17.3%, while in female mice pulmonary adenoma incidence ranged from 0.0-9.6%. The reported incidence of pulmonary carcinoma in male mice ranged from 3.8-13.5% and from 0.0-9.6% in female mice. In comparison to the historical control data provided, the incidence of pulmonary adenoma in male mice observed in the 78-week study was 24% at the 1000 ppm dose level, and was 14% in female mice at the 1000 ppm dose level. These incidences are outside the provided historical control range. The incidence of pulmonary carcinoma at the 1000 ppm dose level was 8% for both sexes, within historical control range. Thus, a biologically significant increase in pulmonary adenoma was observed in both male and female mice at the 1000 ppm dose level of Acetochlor.

From review of the mouse carcinogenicity study, it was determined that the Maximum Tolerated Dose was not achieved in female mice. However, the presence of lung tumors in statistically significant increased incidence reduces the need for testing of Acetochlor at higher doses in this study.

The Agency considers the response by ICI to the concerns raised in the mouse carcinogenicity study adequate. Based upon the information provided by ICI, this study is upgraded to core minimum data.

3) Mutagenicity-Mouse Micronucleus Assay (Structural Chromosome Aberrations)

MRID # 415651-23

In this study, the Agency raised concerns regarding the stability and storage of the test material. In addition, no information on the coding of slides prior to scoring was provided.

ICI responded to these concerns by providing certificates of analysis for the test material. These certificates show the stability of test material over a period of six years, during which the mouse micronucleus test was conducted. In addition, it was stated

that test material preparations were formulated immediately prior to dosing of animals and were used within 60 mintues of preparation.

With regard to slide coding, ICI stated that slides were coded prior to analysis as found in Appendix A, page 26 of the study.

The Agency considers the responses to these concerns adequate. This study is upgraded to acceptable.

II. Toxicology Profile for Acetochlor

A. Data Requirements for Food Use Registration (40 CFR 158.340):

Data Requirement	Submitted	Satisfied
SC-5676 Technical		
81-1 Acute Oral Toxicity	Y	Y
81-2 Acute Dermal Toxicity	Y	Y
81-3 Acute Inhalation Toxicity	Y	Y
81-4 Primary Eye Irritation	Y	Y
81-5 Primary Dermal Irritation	Y	Y
81-6 Dermal Sensitization	Y	Y
Acetochlor 760g/l EC formulation		
81-1 Acute Oral Toxicity	Y	Y
81-2 Acute Dermal Toxicity	Y	Y
81-3 Acute Inhalation Toxicity	Y	Y
81-4 Primary Eye Irritation	Y	Y
81-5 Primary Dermal Irritation	Y	Y
81-6 Dermal Sensitization	Y	Y
82-1 90 Day Feeding Study-Rodent	Y	N[1]
82-1 90 Day Feeding Study-Nonrodent	Y	N[2]
82-2 Twenty-One Day Dermal-Rodent	Y	Y
82-3 90 Day Dermal	N	n/a
82-4 Subchronic Inhalation	N	n/a
82-5 Subchronic Neurotoxicity	N	n/a
83-1 Chronic Toxicity-Rodent	Y	Y[3]
83-1 Chronic Toxicity-Nonrodent	Y	Y
83-2 Carcinogenicity-Rat	Y	Y[3]
83-2 Carcinogenicity-Mouse	Y	Y
83-3 Developmental Toxicity Rat	Y	Y
83-3 Developmental Toxicity Rabbit	Y	Y
83-4 Reproductive Toxicity Rat	Y	Y
83-5 Carcinogenicity/Chronic Toxicity-Rat	Y	Y
84-1 Mutagenicity-Gene Mutation	Y	Y
84-1 Mutagenicity-Structural Chromosome Aberrations	Y	Y
84-1 Mutagenicity-Other Genotoxic Effects	Y	Y
85-1 Metabolism	Y	Y
85-2 Domestic Animal Safety	N	n/a
85-3 Dermal Absorption	Y	Y

[1]Data requirement fulfilled by an acceptable chronic toxicity/carcinogenicity study in rats.

[2]Data requirement fulfilled by an acceptable chronic toxicity study in dogs.

[3]Data requirement fulfilled by an acceptable chronic toxicity/carcinogenicity study in rats.

II. Toxicology Issues

Acetochlor has been classified as a **Group B2-Probable Human Carcinogen** with a Q^* of 1.7×10^{-2} mg/kg/day by the HED Carcinogenicity Peer Review Committee. This classification was based upon the appearance of nasal epithelial adenoma, thyroid follicular cell adenoma, benign chondroma of the femur, and basal cell tumor of the stomach in both male and female CD rats, and the appearance of pulmonary adenomas in both male and female CD-1 mice. Tumor data were analyzed solely from data submitted to the Agency by ICI.

Based upon evidence of neurotoxicity observed from administration of Acetochlor to dogs (MRID # 415651-18), acute and subchronic neurotoxicity testing of Acetochlor in rats is requested by the HED Carcinogenicity Peer Review Committee.

A dominant lethal assay in rats submitted by ICI is currently under Agency review. This study will not affect the issuance of an EUP for Acetochlor, as the data requirement for Structural Chromosomal Aberrations has already been fulfilled by the registrant.

III. Review of Worker Exposure Study

The worker exposure study is being referred to the Occupational and Residential Exposure Branch (OREB) for review.

IV. Review of Revised G2 Temporary Tolerance

The registrant (ICI Agricultural Products) submitted information which indicated that the acres needed under the G2 petition would be doubled to approximately 3800 acres in 1992 and 3300 acres in 1993. The Agency has no objection to this request.

V. Recommendation

Toxicology Branch II has determined that, based on the additional information supplied regarding the Toxicology of Acetochlor, the existing database for Acetochlor supports the request for an Experimental Use Permit for use of Acetochlor on corn.

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MEMORANDUM

SUBJECT: Review of additional data and/or clarifications submitted by the registrant for Acetochlor: Teratogenicity Study in the Rat, Huntingdon Research Centre Ltd., Report No. ISN 204/89369, Study No. RR 0431, August 14, 1989, and for Acetochlor: Teratogenicity Study in the Rabbit, Huntingdon Research Centre Ltd, Report No. ISN 205/89432, August 9, 1989. EPA MRID No. 415920-05 and 415920-06, Toxicology Chemical Code 03B-ICI.

TO: Timothy F. McMahon, Ph.D.
Toxicologist, Review Section I
Toxicology Branch II/HED (H7509C)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 12/7/92
Senior Pharmacologist, Review Section I
Toxicology Branch II/HED (H7509C)

THRU: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y.M. Ioannou 1/8/92
Section Head, Review Section I

Action Requested : Review additional data and/or clarifications submitted by the registrant for Acetochlor: Teratogenicity Study in the Rat, Huntingdon Research Centre Ltd., Report No. ISN 204/89369, Study No. RR 0431, August 14, 1989, EPA MRID No.415920-05, and for Acetochlor: Teratogenicity Study in the Rabbit, Huntingdon Research Centre Ltd, Report No. ISN 205/89432, August 9, 1989, EPA MRID No.415920-06.

Recommendations : The following are revised conclusions on the study based on additional information provided by the registrants for Acetochlor: Teratogenicity Study in the Rat, Huntingdon Research Centre Ltd., Report No. ISN 204/89369, Study No. RR 0431, August 14, 1989, EPA MRID No.415920-05:

The maternal toxicity NOEL is 150 mg/kg/day with a LOEL of 600 mg/kg/day based on animals sacrificed moribund, clinical observations, decreased body weight gain during the dosing period, the entire gestation period and corrected body weight gain for gestation day 6 through 20. Developmental toxicity NOEL is 150 mg/kg/day with a LOEL of 600 mg/gm/day based on an increase in resorptions per dam, postimplantation loss, and a decrease in mean fetal weight.

Maternal Toxicity NOEL = 150 mg/kg/day
Maternal Toxicity LOEL = 600 mg/kg/day
Developmental Toxicity NOEL = 150 mg/kg/day
Developmental Toxicity LOEL = 600 mg/kg/day

Core Classification: The study is upgraded to Core-Minimum Data. With the addition of the requested data, this study satisfies the guideline requirement, §83-3, for a teratology study in rats.

The following are revised conclusions on the study based on additional information provided by the registrants for Acetochlor: Teratogenicity Study in the Rabbit, Huntingdon Research Centre Ltd, Report No. ISN 205/89432, August 9, 1989, EPA MRID No.415920-06.

Based on the data provided, no significant effects on either the maternal animal or the fetus were noted at the dose levels tested; however, since the range-finding study was submitted and it indicated that the LOEL should be between 200 and 400 mg/kg/day based on body weight decrements (usually a poor indicator of maternal toxicity in the rabbit), the Agency position is that the rabbit teratology study requirements have been met.

Maternal Toxicity NOEL => 300 mg/kg/day
Maternal Toxicity LOEL > 300 mg/kg/day
Developmental Toxicity NOEL => 300 mg/kg/day
Developmental Toxicity LOEL > 300 mg/kg/day

Core Classification: The study is upgraded to Core-Minimum Data. This study combined with the range finding study satisfy the guideline requirement, §83-3(b), for a teratolcgy study in rabbits.

I. Review of additional data and/or clarifications submitted by the registrant for Acetochlor: Teratogenicity Study in the Rat, Huntingdon Research Centre Ltd., Report No. ISN 204/89369, Study No. RR 0431, August 14, 1989, EPA MRID No.415920-05.

BACKGROUND:

The following are the Discussion/Conclusions from the DER:

Maternal Toxicity:

Maternal toxicity was observed at the high dose group in the form of clinical signs, and reduced body weight gain and food consumption; however, additional data are required before an adequate assessment of maternal toxicity can be made.

Developmental Toxicity:

Additional data are required before an adequate assessment of developmental toxicity can be made.

Study Deficiencies:

The major deficiency is that time-pregnant animals were used, the stress induced by such a situation can be unacceptable; however, in this case it appears not to have affected the outcome of the study. The "preliminary study in pregnant rats performed at these laboratories (HRC Report No. ISN 198/89180; ICI Study No. RR 0429)" upon which the dosages were based was not provided. The registrant is asked to provide food and water consumption data in the format of values for gestation days 2 through 6, 6 through 15, 15 to end of study, and 6 through end of study also to provide the cesarean section data for total corpora lutea, total implantations, total live fetuses, total resorptions, total dead fetuses, and dead fetuses/dam. Also the registrant is asked to separate the skeletal observation data into the individual bones affected in both fetal and litter incidence. Further, the registrant should provide historical control data addressing all measured parameters in both fetal and litter incidence (for fetal observations) for a period of 2 years before and 2 years subsequent to this study (if possible) to be adequate for comparison with concurrent control.

Core Classification: Core-Supplementary Data.

Additional data are required before Maternal NOEL and LOEL and Developmental Toxicity NOEL and LOEL can be determined. The study may be upgraded if the requested information is submitted and accepted by the Agency. This study does not satisfy the guideline requirement, §83-3, for a teratology study in rats.

DISCUSSION OF COMPANY RESPONSES

a. EPA COMMENT:

The major deficiency is that time-pregnant animals were used, the stress induced by such a situation can be unacceptable; however, in this case it appears not to have affected the outcome of the study.

COMPANY RESPONSE:

It is a routine practice for most laboratories in Europe and North America obtain time-mated rats from the breeders for teratology studies. Huntingdon Research Centre (HRC) have considerable experience in using time mated rats (29 full teratology studies since 1987) and have not experienced any problems arising from the transport of the animals, eg. no adverse effect on pregnancy rate.

EPA RESPONSE:

The Agency stated in the above response: the stress induced by such a situation can be unacceptable; however, **in this case it appears not to have affected the outcome of the study.** No further discussion is warranted.

b. EPA COMMENT:

The "preliminary study in pregnant rats performed at these laboratories (HRC Report No. ISN 198/89180; ICI Study No. RR 0429)" upon which the dosages were based was not provided.

COMPANY RESPONSE:

The preliminary study (Reference 1) is now submitted and confirms that 600mg acetochlor/kg/day is the maximum tolerated dose (MTD) for a teratology study in the rat with an unacceptable level of maternal mortality at the next dose tested (800mg acetochlor/kg/day). It is not ICI's policy to routinely submit data from preliminary studies when, as in this case, there is unequivocal evidence of maternal toxicity.

EPA RESPONSE:

It is the Agency policy to require submission of any data pertaining to a Guideline requirement; in this case a range-finding study.

The following are the results and conclusions from the submitted range-finding study (Acetochlor: A Preliminary Study of the Effect on Pregnancy of the Rat, Huntingdon, Report No. ISN 198/89180, 8/9/89):

The investigators administered by oral gavage 0, 200, 400, 600, and 800 mg/kg/day (actual doses were 0, 196, 394, 590, and 787 mg/kg/day) of acetochlor to pregnant rats from day 6 through 15 of gestation. Mortality was noted in the high dose where 6 out of 10 animals died. Clinical signs of toxicity were noted in all treated groups in a dose related manner with only "post-dosing" salivation noted in the 2 lower dose groups. Maternal body weight decrements were noted at 400 mg/kg/day and above ("slight" at 400 mg/kg/day). Decreased food consumption was noted in the 2 higher dose groups. In the high dose group, the investigators noted a reduction in litter and mean fetal body weight with slight effects noted in the 2 mid dose groups. No fetal or litter effects were noted in the low dose group. The investigators stated that the 600 mg/kg/day dose group was the "MTD" and selected 0, 40, 150, and 600 mg/kg/day as the dose levels for the primary study. Based on the data submitted, the study appears to be adequate as a range-finding study for the primary teratology study in rats; no specific effects of concern were noted on the fetus.

c. EPA COMMENT:

The registrant is asked to provide food and water consumption data in the format of values for gestation days 2 through 6, 6 through 15, 15 to end of study, and 6 through end of study...

COMPANY RESPONSE:

The data have been presented by period as requested (Reference 2, Tables 1 and 2) and ICI appreciate this may aid interpretation on some occasions, but both ICI and HRC believe daily data as presented to be the most precise.

EPA RESPONSE:

The following table presents the requested data; the requested data on gestation days 6 through the end of the study were not provided:

TABLE 1

Water consumption - animals with live young - group mean values

Group:	1	2	3	4
Compound:	Control		Acetochlor	
Dose (mg/kg/day):	-	40	150	600

Group	Number of animals	Water consumption (g/rat/day) on Days post coitum		
		2 - 5	6 - 15	16 - 19
1	23 (9)	40.6	44.9	58.0
2	22 (8)	37.4	40.6	50.7
3	23 (10)	39.5	47.2	55.3
4	21 (9)	38.3	62.3	55.5

Treatment period Days 6 to 15 inclusive
Numbers in brackets indicate number of animals on Day 2 only

TABLE 2

Food consumption - animals with live young - group mean values

Group:	1	2	3	4
Compound:	Control		Acetochlor	
Dose (mg/kg/day):	-	40	150	600

Group	Number of animals	Food consumption (g/rat/day) on Days post coitum		
		2 - 5	6 - 15	16 - 19
1	23 (9)	25.3	24.6	32.8
2	22 (8)	24.8	23.8	33.1
3	23 (10)	24.7	23.7	33.2
4	21 (9)	24.6	22.5	31.0

Treatment period Days 6 to 15 inclusive
Numbers in brackets indicate number of animals on Day 2 only

No effects on food consumption were noted in the provided data, although the original table showed a slight decrease in the high dose at the beginning of dosing. This was apparently a transient effect that did not persist throughout the dosing period and thus probably not true maternal toxicity. Provided water consumption data indicated a slight increase in water consumption in the high dose; however, the biological relevance of this observation is unclear.

d. EPA COMMENT:

Also...to provide the cesarean section data for total corpora lutea, total implantations, total live fetuses, total resorptions, total dead fetuses, and dead fetuses/dam.

COMPANY RESPONSE:

The total number of live foetuses is given in Table 12 of the original report. All the totals have been tabulated as requested (Reference 2, Table 3). To aid ICI on future occasions, guidance is sought from the EPA on how totals will be used, since the litter is the unit of treatment and the presented group mean values are the critical areas for evaluation.

EPA RESPONSE:

The following table presents the cesarean section data with the recently submitted information (bold):

Table IV: Cesarean Section Observations

Dose:	Control	LDT	MDT	HDT	HCD+
#Animals Assigned	25	25	25	25	
#Animals Mated/Inseminated	25	25	25	25	
#Animal pregnant	24	23	23	23	
Pregnancy Rate (%)	96	92	92	92	
Maternal Wastage					
#Died	1	1	0	2	
#Died/pregnant	0	0	0	0	
#Non pregnant	1	2	2	2	
#Aborted	0	0	0	0	
#Premature Delivery	0	0	0	0	
#Litters for examination	23	22	23	21	23.4
Total Corpora Lutea	**308**	**299**	**298**	**291**	
Corpora Lutea/dam	13.4	13.6	13.0	13.9	13.3
Total Implantations	**281**	**269**	**273**	**263**	
Implantations/Dam	12.2	12.2	11.9	12.5	12.0
Total Live Fetuses	**273**	**257**	**262**	**243**	
Live Fetuses/Dam	11.9	11.7	11.4	11.6	11.4
Total Resorptions	**8**	**12**	**11**	**20**	
Early	**5**	**12**	**11**	**16**	
Late(+dead)	**3**	**0**	**0**	**4**	
Total Resorptions/dam	0.3	0.5	0.5	1.0**	0.6
Early/dam	0.2	0.5	0.5	0.8**	0.5
Late/dam	0.1	0	0	0.2	0.1
Total Dead Fetuses	not available				
Dead Fetuses/Dam	not available				
Mean Fetal Weight (gm)	3.37	3.32	3.36	3.13**	3.29
Preimplantation Loss(%)	9.2	8.5	8.6	8.8	9.2
calculated from totals	**8.7**	**10.0**	**8.4**	**9.6**	
Postimplantation Loss(%)	3.5	4.4	4.3	7.6**	4.8
calculated from totals	**2.9**	**4.5**	**4.0**	**7.6**	
Sex Ratio (% Male)	55.0	48.3	48.5	45.5	

** = $p < 0.05$

+ = Historical Control Data (means)

a = Data extracted from Study No. RR0431.

Again the conclusion that can be drawn that it is apparent from the provided data that there was an increase in the high dose of resorptions per dam, postimplantation loss, and a decrease in mean fetal weight. These data also exceed provided historical control data.

e. **EPA COMMENT:**

No data were provided for external examinations, this must be addressed by the registrant.

COMPANY RESPONSE:

External abnormality data are included in Tables 12, 13 and 14 of the original report and the tables have been annotated to clarify the presentations (Reference 2, Tables 4, 5 and 6). In order to assist ICI in the future, guidance is requested from the EPA on how this presentation helps in their evaluations.

EPA RESPONSE:

The following tables present the visceral observation data with the external observations annotated. Fetal observation data must be separated into external, visceral and skeletal observations as these are the usual observations made at different steps in the experimental design of a developmental (teratology) study and the Agency evaluates each group of observations separately and then looks for correlations between observations. No treatment related effects were noted in the external observations.

f. **EPA COMMENT:**

Also the registrant is asked to separate the skeletal observation data into the individual bones affected in both fetal and litter incidence.

COMPANY RESPONSE:

In many cases, the skeletal data are presented by area and not for individual bones. Except where the incidence of anomalies or variants approaches 100% in all groups (which did not occur in this study), this method of data analysis is more likely to detect statistical differences than one examining individual bones and, therefore, generally should be regarded as a more sensitive method. For these reasons, it is respectively submitted that additional presentations of the data are unnecessary.

This method of presentation is one which HRC have used for many years and which has always been found to be acceptable to Regulatory Authorities.

ACETOCHLOR

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Page_____ is not included in this copy.

Pages 18 through 20 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.

X 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.

EPA RESPONSE:

The registrant must provide data in the future as described (for example to divide these data into full ribs, partial ribs, separate sternebrae, etc., and to provide these data in both fetal and litter incidence. The Agency assesses the skeletal observation data both as individual bone observations and as a group of related bones.

g. EPA COMMENT:

Further, the registrant should provide historical control data addressing all measured parameters in both fetal and litter incidence (for fetal observations) for a period of 2 years before and 2 years subsequent to this study (if possible) to be adequate for comparison with concurrent control.

COMPANY RESPONSE:

Historical controls are clearly useful to put into perspective values which differ significantly from those of the concurrent control but which the study director considers are not effects of the compound. Reduced ossification of sacrocaudal arches falls into this category and the table of historical controls presented in the report (Appendix 16) has now been extended to include data to the end of 1990 (Reference 2, Appendix 2).

Other historical control data can be provided where the reviewer considers this to be of specific value. Providing data on all parameters is clearly a mammoth task, which is unwarranted.

An extension to the general historical control data (Appendix 16 in original report) is presented in the report supplement (Reference 2, Appendix 1).

EPA RESPONSE:

Historical control data provided for maternal parameters were added to the cesarean section data presented above. Appendix 1, attached, does not provide useful data as combining effects such as this can either dilute real effects or give multiple individual effects more weight than they deserve. Appendix 2, attached (mean added to skeletal observation data

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Pages 22 through 24 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

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____ Description of the product manufacturing process.

____ Description of quality control procedures.

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____ Sales or other commercial/financial information.

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table above), was provided to present historical control data for "reduced ossification of sacrocaudal vertebral arches". The comparison between historical control data and concurrent control data as well as the treated group data from this study shows that the low and high dose exceed the mean historical control data; however, since there is no real dose response as the mid dose is lower than the low and high dose groups, the biological relevance of this observation is unclear. If the investigators had provided the individual "bone" data, this argument could be resolved, since there may be individual bones that are affected that increase the total numbers affected. Further, the investigators must remember that it is the maternal "unit" that is treated; therefore the litter is the statistical unit.

ORIGINAL EPA CONCLUSIONS:

Core Classification: Core-Supplementary Data.
Additional data are required before Maternal NOEL and LOEL and Developmental Toxicity NOEL and LOEL can be determined. The study may be upgraded if the requested information is submitted and accepted by the Agency. This study does not satisfy the guideline requirement, §83-3, for a teratology study in rats.

COMPANY CONCLUSIONS

On the basis of these additional data, ICI requests that the study be upgraded and believes the original conclusions drawn were valid ie both maternal and foetal toxicity were seen at 600mg/kg and that the no effect level for maternal and foetal toxicity is 150mg/kg.

EPA CONCLUSIONS:

The following are the revised conclusions on the study based on additional information provided by the registrants.

The maternal toxicity NOEL is 150 mg/kg/day with a LOF of 600 mg/kg/day based on animals sacrificed moribund, clinical observations, decreased body weight gain during the dosing period, the entire gestation period and corrected body weight gain for gestation day 6 through 20. Developmental toxicity NOEL is 150 mg/kg/day with a LOEL of 600 mg/gm/day based on an increase in resorptions per dam, postimplantation loss, and a decrease in mean fetal weight.

Maternal Toxicity NOEL = 150 mg/kg/day
Maternal Toxicity LOEL = 600 mg/kg/day
Developmental Toxicity NOEL = 150 mg/kg/day
Developmental Toxicity LOEL = 600 mg/kg/day

Core Classification: The study is upgraded to Core-Minimum Data.

With the addition of the requested data, this study satisfies the guideline requirement, §83-3, for a teratology study in rats.

II. Review of additional data and/or clarifications submitted by the registrant for Acetochlor: Teratogenicity Study in the Rabbit, Huntingdon Research Centre Ltd, Report No. ISN 205/89432, August 9, 1989, EPA MRID No. 415920-06.

BACKGROUND:

The following are the Discussion/Conclusions from the DER

Maternal Toxicity:

Additional data are required before an adequate assessment of maternal toxicity can be made.

Developmental Toxicity:

Additional data are required before an adequate assessment of developmental toxicity can be made.

Study Deficiencies:

The registrant is asked to supply food consumption data as follows: data in the format of values for gestation days 1 through 6, 6 through 18, 18 to end of study, and 6 through end of study. Also the registrant is asked to provide the total corpora lutea, total implantations, total live fetuses, total resorptions, total dead fetuses and dead fetuses/dam from cesarean section data. Further, the registrant must address the reason for not providing separate mean data for external examinations and in reference to the skeletal observation data, the registrant is asked to explain Table 13 in terms of what is meant by fetuses with 12 ribs or 13 ribs and variant sternebrae. Also, the registrant is asked to divide these data into full ribs, partial ribs, separate sternebrae, etc., and to provide these data in both fetal and litter incidence. These data must be provided before maternal and developmental toxicity can be assessed. The "preliminary study in pregnant rabbit performed at these laboratories (ISN/199-R)" upon which the dosages were based must be provided by the registrant.

Core Classification: Core-Supplementary Data.

Additional data are required before Maternal NOEL and LOEL and Developmental Toxicity NOEL and LOEL can be determined. The study may be upgraded if the requested information is submitted and accepted by the Agency; however, it must be noted that if no maternal or developmental toxicity LOEL's are established, a new study may be required. This study does not satisfy the guideline requirement, §83-3(b), for a teratology study in rabbits.

DISCUSSION OF COMPANY RESPONSES

a. EPA COMMENT:

Additional data are required before an adequate assessment of maternal toxicity can be made.

COMPANY RESPONSE:

Both ICI and Huntingdon Research Centre (HRC) consider that adequate maternal toxicity was achieved in this study, based on two compound-related mortalities at the top dose, together with the increased weight loss early in the dosing period (days 6-8). The choice of dose levels is reinforced by the preliminary study (Reference 3) where there was a dose-related increase in mortality rate at the top two doses (400 or 600mg acetochlor/kg/day). This report is now submitted. ICI consider that the dose level selection is consistent with the 1984 FIFRA Guidelines which recommend that maternal mortality at the top dose should not exceed 10%. Had a dose higher than 300mg acetochlor/kg/day been used, there was a high probability that mortalities in excess of 10% would have occurred since 400mg acetochlor/kg/day is considered to exceed the MTD.

EPA RESPONSE:

There is no indication that the one high dose animal that was sacrificed following aborting (the other was due to gavage error) and the mid dose animal that was found dead after aborting, was due to treatment; further, no clinical signs were noted. Abortions are common in rabbits (historical control data were not provided for this observation).

The following are the results and conclusions from the submitted range-finding study (Acetochlor: A Preliminary Study of the Effect on Pregnancy of the Rabbit, Huntingdon Research Centre Ltd., Report No. ISN 199, 8/9/89):

The investigators administered by oral gavage 0, 100, 200, 400, and 600 mg/kg/day (actual doses were 0, 98, 197, 393, and 590 mg/kg/day) of acetochlor to pregnant rabbits (naturally mated) from day 6 through 18 of gestation. Mortality was noted in the high dose where one animal died and the remaining 5 were sacrificed moribund following marked weight loss and inappetence. Two animals in the 400 mg/kg/day dose group were sacrificed due to marked weight loss, inappetence and abnormal posture. Further

maternal toxicity was noted as clinical signs including reduced fecal output and cold ears post dose in the 400 mg/kg/day dose group with similar effects in the 200 mg/kg/day dose group (except for abnormal posture. The 100 mg/kg/day dose group presented with signs of inappetence and a transient body weight loss. Reduced food consumption was noted in the 400 mg/kg/day dose group with slight effects noted in the 100 and 200 mg/kg/day dose groups. developmental toxicity was noted in the form of a "suggestion" of an increase in post implantation loss (27.7% in the 400 mg/kg/day dose group vs 18.1% in the control along with a smaller litter size, also a decrease in litter and mean fetal body weight. The investigators believed that the "MTD" was considered to be in the region of 300 mg/kg/day; therefore, they decided to use dose levels of 0, 30, 100, and 300 mg/kg. Based on the data submitted, the study appears to be adequate as a range-finding study for the primary teratology study in rats; no specific effects of concern were noted on the fetus; however, the investigators appear to have been a little too conservative on the dose level choice, as the MTD appears to be closer to 400 mg/kg/day.

b. EPA COMMENT:

The registrant is asked to supply food consumption data as follows: data in the format of values for gestation days 1 through 6, 6 through 18, 18 to end of study, and 6 through end of study.

COMPANY RESPONSE:

The data have been presented by period as requested (Reference 4, Table 1) and ICI appreciate this may aid interpretation on some occasions, but both ICI and HRC believe the data as presented is the most precise.

EPA RESPONSE:

The following table presents the requested data and previously submitted data combined, the requested data of gestation days 6 through the end of the study was not provided:

Table II: Food Consumption Data (gm/rabbit/day)[a]

animals with live young - group mean values

Group:	1	2	3	4
Compound:	Control		Acetochlor	
Dose (mg/kg/day):	-	30	100	300

Group	Number of animals	Food consumption (g/rabbit/day) during Days:								
		1 - 5	6 - 7	8 - 9	10 - 13	14 - 18	19 - 22	23 - 28	6 - 18	19 -
1	14	153	125	129	117	103	153	149	115	151
2	14	153	126	126	114	109	144	136	116	139
3	14	151	120	126	110	103	143	145	111	144
4	10	156	86*	102	110	106	171	163	103	160

Statistical analysis: Analysis of variance followed by intergroup comparison with the control (Williams' test) significant at * P<0.05

The above data indicate a slight decrease in food consumption in the high dose animals during the dosing period with an apparent rebound following dosing. This may be an indication of maternal toxicity at this dose.

b. **EPA COMMENT:**

Also the registrant is asked to provide the total corpora lutea, total implantations, total live fetuses, total resorptions, total dead fetuses and dead fetuses/dam from cesarean section data.

COMPANY RESPONSE:

The total number of live foetuses was given in Tables 9-12 of the original report. All the totals have been tabulated as requested (Reference 4, Table 2). To aid ICI on future occasions, guidance is sought from the EPA on how totals will be used, since the litter is the unit of treatment and the presented group mean values are the critical ones for evaluation. The number of dead foetuses per dam is not presented because there were no dead foetuses.

EPA RESPONSE:

The following table presents the cesarean section data with the recently submitted information (bold):

Table III: Cesarean Section Observations *

Dose:	Control	LDT	MDT	HDT
#Animals Assigned	16	16	16	16
#Animals Mated/Inseminated	16	16	16	16
#Animals with litters	14	14	14	14
Pregnancy Rate (%)				
Maternal Wastage				
#Died	0	0	1	3
#Died/pregnant				
#Non pregnant	1	2	1	2
#Aborted	1	0	0	1
#Premature Delivery	0	0	0	0
Total Corpora Lutea	148	152	163	113
Corpora Lutea/dam	10.6	10.9	11.6	11.3
Total Implantations	145	136	147	101
Implantations/Dam	10.4	9.7	10.5	10.1
Total Live Fetuses	123	110	128	79
Live Fetuses/Dam	8.8	7.9	9.1	7.9
Total resorptions	22	26	19	22
Early	9	17	5	14
Late (+dead)	13	9	14	8
Total Resorptions/dam	1.6	1.9	1.4	2.2
Early/dam	0.6	1.2	0.4	1.4
Late/dam	0.9	0.6	1.0	0.8
Total Dead Fetuses	not available			
Dead Fetuses/Dam	not available			
Mean Fetal Weight (gm)	43.0	42.9	42.3	43.4
Preimplantation Loss(%)	2.3	11.1	8.6	10.4
calculated from totals	2.0	10.5	9.8	10.6
Postimplantation Loss(%)	15.5	20.5	11.8	20.3
calculated from totals	15.3	19.1	12.9	21.8
Sex Ratio (% Male)	49.6	51.5	47.0	44.9

* = Data extracted from Study No. RB0432

From the above provided data, increased post implantation loss was noted in the high dose; however, since the mean litter size was unchanged, the biological relevance of this observation is unclear and most likely was not an effect of treatment.

d. EPA COMMENT:

Further, the registrant must address the reason for not providing separate mean data for external examinations.

COMPANY RESPONSE:

External abnormality data are included in Tables 10, 11 and 12 of the original report and the tables have now been annotated to clarify the presentations (Reference 4, Tables 3, 4 and 5). To aid ICI on future occasions, guidance is sought from the EPA on how this presentation aids interpretation.

EPA RESPONSE:

The following tables present the visceral with the external observations annotated; no treatment related external observations were noted in the provided data):

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____ Description of quality control procedures.

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e. EPA COMMENT:

...and in reference to the skeletal observation data, the registrant is asked to explain Table 13 in terms of what is meant by fetuses with 12 ribs or 13 ribs and variant sternebrae. Also, the registrant is asked to divide these data into full ribs, partial ribs, separate sternebrae, etc., and to provide these data in both fetal and litter incidence.

COMPANY RESPONSE:

Explanation of foetuses with 12 or 13 ribs: this refers to a count of the total number of ribs in the foetus. The New Zealand White rabbit can have 12 or 13 ribs as the normal value, which varies with time and supplier. In this particular experiment 13 is more common. The observation of 12 and 13 ribs are classified as variants.

Explanation of foetuses with normal or variant sternebrae: typical variants are considered by HRC to include reduced ossification and unossified, asymetric or bipartite sternebrae. Normal sternebrae are self-explanatory.

There were no compound-related effects on skeletal parameters in the study. As the above changes (vis. 12 or 13 ribs and variant sternebrae) are variants, which by their nature, are very minor, ie. normal variations, it is considered unnecessary to re-present these skeletal data.

EPA RESPONSE:

The Agency accepts the explanation provided by the registrant in terms of fetuses with 12 or 13 ribs and fetuses with normal or variant sternebrae. However, since there appears to be no dose related effects in the visceral observation data from the original report, no further action is required, but the registrant must provide data in the future as described (for example to divide these data into full ribs, partial ribs, separate sternebrae, etc., and to provide these data in both fetal and litter incidence).

f. EPA COMMENT:

The administration of luteinizing hormone is not considered as standard technique, however, it should not affect the outcome of the experiment.

COMPANY RESPONSE:

ICI are not aware of any laboratory in the UK which does not use chorionic gonadotrophin in rabbits after natural mating or to 'prime' females prior to artificial insemination and we know of US laboratories which also use similar techniques, eg. WIL Research Laboratories Inc. use chorionic gonadotrophin following artificial insemination to stimulate ovulation. Chorionic gonadotrophin has been used in rabbit teratolcgy studies for at least 25 years (and both controls and test animals are treated in an identical way).

EPA RESPONSE:

The comment was not meant to site a deficiency; however, the Agency stands by the comment since the use of luteinizing hormone is recognized for artificial insemination and not generally used in this country for naturally mated animals. In this instance, it apparently did not affect the outcome of this study.

EPA COMMENT:

Historical control data were not provided to allow comparison with concurrent controls.

COMPANY RESPONSE:

ICI believes historical control data are clearly useful to put into perspective values which differ significantly from those of the concurrent control but which the report author considers are not effects of compound, and ICI endeavours to do this. Routine presentations of historic control data for all parameters is a mammoth task, which is unwarranted.

EPA RESPONSE:

The Agency considers the presentation of historical control data as necessary for full evaluation of a study; to determine if concurrent controls are in a "normal range".

g. GENERAl COMPANY COMMENT:

It should be noted that a maternally toxic dose will not necessarily cause developmental toxicity and, therefore, it may not be possible to establish a LOEL for developmental toxicity. In this instance the chemical would then not be considered to be a developmental toxicant in that species, but provided a sufficiently high dose level was tested to establish maternal toxicity than the study should be valid.

EPA RESPONSE:

If neither a maternal toxicity NOEL or a developmental toxicity NOEL is established for a study, then it is unacceptable (except at the limit dose); if a study has a maternal toxicity NOEL with a developmental toxicity NOEL below the lowest dose tested, it must be repeated; if a study has a developmental toxicity NOEL but no maternal toxicity NOEL (or the maternal toxicity NOEL is below the lowest dose tested) if may be acceptable.

ORIGINAL EPA CONCLUSIONS:

Core Classification: Core-Supplementary Data.
Additional data are required before Maternal NOEL and LOEL and Developmental Toxicity NOEL and LOEL can be determined. The study may be upgraded if the requested information is submitted and accepted by the Agency; however, it must be noted that if no maternal or developmental toxicity LOEL's are established, a new study may be required. This study does not satisfy the guideline requirement, §83-3(b), for a teratology study in rabbits.

COMPANY CONCLUSIONS

On the basis of these additional data ICI requests that the study be upgraded and believes the original conclusions drawn were valid ie that adequate maternal toxicity, seen as mortalities, reductions in bodyweight and food consumption, was observed at 300mg/kg without developmental toxicity.

EPA CONCLUSIONS:

The following are the revised conclusions on the study based on additional information provided by the registrants.

Based on the data provided, no significant effects on either the maternal animal or the fetus were noted at the dose levels tested; however, since the range-finding study was submitted and it indicated that the LOEL should be between 200 and 400 mg/kg/day based on body weight decrements (usually a poor indicator of maternal toxicity in the rabbit), the Agency position is that the rabbit teratology study requirements have been met.

Maternal Toxicity NOEL => 300 mg/kg/day
Maternal Toxicity LOEL > 300 mg/kg/day
Developmental Toxicity NOEL => 300 mg/kg/day
Developmental Toxicity LOEL > 300 mg/kg/day

Core Classification: The study is upgraded to Core-Minimum Data.

This study combined with the range finding study satisfy the guideline requirement, §83-3(b), for a teratology study in rabbits.