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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of additional data on acute inhalation study in rats with acetochlor (formulated as Harness herbicide). EPA Identifying No.: 282478, HED Project No. 1-1295, EPA Pesticide Chemical Code 121601-9, Caswell No. 003B-MON.

TO: Robert Taylor/Vickie Walters (PM 25)
Herbicide-Fungicide Branch
Registration Division (H7505C)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 6/14/91
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Toxicology Branch II/Health Effects Division (H7509C)

THRU: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y M Ioannou 6/18/91
Section Head, Review Section I
and
Marcia van Gemert, Ph.D. Marcia van Gemert 6/20/91
Chief, Toxicology Branch II
Health Effects Division (H7509C)

Registrant: Monsanto Agricultural Company
800 N. Lindbergh Boulevard
St. Louis, Missouri 63167

Action Requested: Review additional data on acute inhalation study in rats with acetochlor.

Recommendations: Based on the additional information provided by the registrant the Acute Inhalation Toxicity Study of Harness in the Rat (MRID No. 409988-05) can be upgraded to **Core-Minimum Data** and fulfills the guideline requirement (§81-3) for an acute inhalation toxicity study in rats with the end use product.

NOTE: This chemical is classified as a Group B2 carcinogen (see page 6).

DISCUSSION

I. Background Information:

Monsanto submitted a request for renewal of temporary tolerances for acetochlor and renewing EUP Number 524-EUP-56 (for acetochlor as MON 8437 [Harness] Herbicide); with this action a number of acute toxicity studies using either technical acetochlor or the formulation Harness-PC were submitted and reviewed. The acute inhalation toxicity study (§81-3) with the formulation was classified as **Core-Supplementary Data**; the following are the conclusions from the review:

> This study as presented is not acceptable, because the investigator failed to keep a consistent chamber test material concentration, failed to generate respirable particles (since MMAD was > 1 µm, at least 25% of the particles must be 1 micron or less), and did not indicate why smaller respirable particle could not be generated in the chamber. Variation of test animal ages is considered too great. The mean body weight difference between group I and group III males at the start of the study exceeded 20%.

The registrant submitted a response to the review and this is discussed below.

II. Review of Additional Data to Support Toxicology Database

Additional data submitted for "An Acute Inhalation Toxicity Study of Harness in the Rat" (Bio/dynamics, Study No's. BD-88-174 and 88--8072, 10/31/88, MRID No. 409988-05).

EPA POSITION

1. Not enough respirable particles of test material were generated into the test atmosphere (at least 25% particle size must be of 1 um or less) and The investigator did not attempt to generate or indicate why smaller particles could not be generated

COMPANY RESPONSE

Firstly, the final report was issued on October 31, 1988 which precedes by 3 months the issuance of and our first receipt of the EPA SEP's for Inhalation Toxicity Testing. Thus, at the time of performing this test, we had no knowledge of the need to attempt the achievement of a certain submicron aerosol fraction. Secondly, had we been aware of this need and done additional trials, most likely we would have demonstrated that the generating system actually used was optimal for particle size. Over the past 2 years since receiving the SEP's, we have mostly demonstrated that other generators or conditions are less useful than the system employed during this study. I have attached two examples for review in Appendix A which demonstrate this point. I have also attached in Appendix B the NACA comments on FIFRA Subdivision F Guidelines of January 17, 1991 which have a salient review of this issue. As these comments conclude, "the current guidance for 25% of the particulates with MMAD of 1 um or less is considered to be inappropriate" and "impossible to achieve in many instances despite sincere effort."

EPA COMMENT

The Agency agrees that this study was conducted prior to the issuance of the SEP for inhalation studies (also the guidelines are presently under revision), and that it was apparent that the generating system used was "optimal for particle size" and further, there is an Acceptable inhalation study with the technical grade of Acetochlor, and it would be inappropriate at this time to request a repeat study with "ground up" material.

EPA POSITION

2. Failure to maintain a consistent chamber concentration

COMPANY RESPONSE

The reviewer only commented on the chamber sampling during the third hour of Group I when 3 gravimetric samples during an 8 minute time span showed 3.9, 2.8 and 4.8 mg/l. Considering that the 99% equilibrium time for the chamber was 23 minutes, the variability noted was probably not due to chamber instability but more likely due to a transient sampling problem, especially for the second of the 3 samples. Overall, the chambers were considered reasonably stable as illustrated by the relatively low standard deviation for each of the groups (refer to the following table):

Gravimetric Total Formulation (mg/l)

Group	Mean	Standard Deviation
I	5.3	0.74
II	3.2	0.34
III	0.94	0.35

EPA COMMENT

The Agency agrees with the company response.

EPA POSITION

3. Variation in the ages of the test animals was too great

COMPANY RESPONSE

This was a valid point reflecting that Group III animals were 7 weeks old at initiation while Group I and II animals were 8 to 11 weeks old at initiation. While not intentionally done, this occasionally happens because of the logistical problems of running an acute inhalation program. Unlike many other study designs, where all of the animals can be placed on test on the same day or within a few days, an inhalation LC_{50} study requires exposures on separate days, and with longer intervals between exposures, to allow time to evaluate the mortality from each exposure and usually to perform trials for subsequent exposure levels. This study, for example, was performed with approximately 1 week between exposures necessitating 3 different colonies of animals being used. Unfortunately, this resulted in the discrepancy regarding weight and age.

However, despite the disparity with Group III, these animals reacted to the exposure in a generally dose-related fashion as regards to clinical observations, body weights, and mortality. Thus, in my professional opinion, this deviation from guidelines did not adversely impact the validity of the study for assessing the acute hazard of Harness.

EPA COMMENT

The Agency accepts the company response.

CONCLUSIONS

Based on the additional information provided by the registrant the Acute Inhalation Toxicity Study of Harness in the Rat (MRID No. 409988-05) can be upgraded to **Core-Minimum Data** and fulfills the guideline requirement (§81-3) for an acute inhalation toxicity study in rats with the end use product.

III. Toxicology Profile for Acetochlor (CFR 180.XXX)

Technical: Acetochlor
Use Pattern: food, terrestrial nonfood
Action Type: additional information for database

This compound is a registered active ingredient. The following data are required for technical acetochlor.

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes
§82-1(a) 90 day feeding study - rat	Yes	Yes
§82-1(b) 90 day feeding study - nonrodent	Yes	Yes[1]
§82-2 21 day dermal - rabbit	Yes	Yes
§83-1(a) 2-year feeding - rodent	Yes	Yes
§83-1(b) 1-year feeding - nonrodent	Yes	Yes[2]
§83-2(a) Carcinogenicity - rat	Yes	Yes
§83-2(b) Carcinogenicity - mouse	Yes	Yes
§83-3(a) Teratology - rat	Yes	Yes
§83-3(b) Teratology - rabbit	Yes	Yes
§83-4 Multigeneration reproduction-rat	Yes	Yes
§84-2(a) Mutagenicity - Gene Mutation	Yes	Yes
§84-2(b) Muta - Struct. Chromosome Aberr.	Yes	Yes
§84-4 Muta - Other Genotoxic Effects	Yes	Yes
§85-1 General metabolism - rat	Yes	Yes
§85-2 Dermal Penetration	Yes	No

[1] = This requirement is satisfied by a 120-day feeding study in dogs.
[2] = This requirement is satisfied by a 2-year feeding study in dogs

Formulation: Harness-PC

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes[1]
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes

[1] = see review included with this memo and discussion above.

IV. Data Gaps

The following is the study reviewed in this document to resolve a data gap in the formulation, Harness-PC database:

§81-3 Acute inhalation toxicity with the formulation, Harness PC.

The only existing data gap in the technical grade acetochlor database is a dermal penetration study (§85-2).

There are no data gaps in the formulation Harness-PC database.

V. Actions Being Taken to Obtain Additional Information or Clarification

None at this time.

VI. Reference Dose

The RfD (PLD) is 0.1 mg/kg/day based on the chronic feeding study in the rat with a NOEL of 10.0 mg/kg/day and an uncertainty factor (UF) of 100. This RfD will be revisited when the data from the other "acetochlor" is reviewed.

VII. Pending Regulatory Actions

None at this time.

VIII. Additional Toxicological Information

This chemical has been classified as a Group B2 Carcinogen (Probable Human Carcinogen) by the HED Peer Review Committee (PRC), CRAVE and the Science Advisory Panel (SAP). This is based on the evidence that administration of acetochlor causes increased incidence of benign and malignant tumors at multiple sites in Sprague-Dawley rats (papillary adenomas of the nose/turbinates in both sexes at doses below the MTD; hepatocellular carcinomas in both sexes and thyroid follicular cell adenomas in males at levels exceeding the MTD). Also, increased incidence of benign and malignant tumors at multiple sites in Swiss albino CD-1 mice (hepatocellular carcinoma in both sexes; lung carcinomas in females; uterine histiocytic sarcoma and benign ovarian tumors in females; kidney adenomas in females). There is positive mutagenicity data and structural analogues to Acetochlor that have positive carcinogenicity data.

The unit risk, Q_1^* of acetochlor is $10^{-2}(mg/kg/day)^{-1}$ in human equivalents. This estimate of the Q_1^* is based upon papillary adenomas (of the nose/turbinates) in both male and female Sprague-Dawley rats fed 0, 40, 200, or 1000 ppm in the diet.