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

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MAY 13 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM:

SUBJECT: RfD/Peer Review Report of Glufosinate-ammonium (Ignite)
CAS No. 77182-82-2
EPA Chem. No. 128850
Caswell File No. 580 I
Reg. Group: New Chem.

FROM: George Z. Ghali, PhD G. Ghali 2.21.92
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Joanne Miller, PM 23
Fungicide-Herbicide Branch
Registration Division (H7505C)

The Health Effects Division RfD/Peer Review Committee met on November 8, 1991 to evaluate data submitted in support of glufosinate-ammonium (Ignite) registration with particular emphasis on long term toxicity in rodent and non-rodent species, carcinogenicity in two species, and developmental and reproductive toxicity.

The Committee concluded that the high dose tested in both the rat and mouse carcinogenicity studies were inadequate for a reliable assessment of the carcinogenic potential of this chemical and recommended the repeat of the carcinogenicity studies in rats and mice. Subchronic studies (90 day range finding studies) in rats and mice did not show any toxicity up to the highest dose tested. There was also a concern that the incidence of combined benign and malignant "adrenal medullary tumors" were marginally increased at the high dose level in the rat study though the high dose level was not considered high enough for carcinogenicity testing. The Committee downgraded the carcinogenicity phase of the study to Core-supplementary. The Chronic toxicity phase remains as Core-minimum. The Committee recommended that neurotoxicity issues in the chronic studies should be addressed.

As per the Committee recommendation, mutagenicity data on this chemical were checked after the meeting. An overview report by K. Dearfield (HED Doc. No. 006936 dated May 5, 1988) indicated that the chemical was negative in the Salmonella assay, B.

subtillis rec assay, mouse micronucleus and S. pombe forward mutation assay.

The Committee did not deliberate on the long-term study in the dog. However, the study was originally classified by the respective branch as Core-minimum data.

The Committee considered the reproductive toxicity study in the rat and the developmental toxicity study in the rabbit to be acceptable. Two developmental toxicity studies in the rat were available for evaluation by the Committee. The information in the two studies, when combined, might be sufficient to address the developmental toxicity potential of this chemical in rats. However, the Committee recommended that the classification of the developmental toxicity study in the rat be reserved until the requested historical background information ~~are~~ is received and the kidney effects observed in these studies (as well as in other studies) are evaluated in light of these information.

The Committee recommended that the RfD should be based on a NOEL of 40 ppm (2.1 mg/kg/day and 2.5 mg/kg/day for males and females respectively) for increased absolute and relative kidney weights in males in a chronic toxicity study in rats, using an uncertainty factor of 100 to account for the intra- and inter-species differences. The Committee recommended that the developmental toxicity study in rats (MRID No. 403456-10) with a NOEL of 2.24 mg/kg/day for maternal and developmental toxicity should be used as a co-critical study.

A. Individual in Attendance

1. Peer Review Committee Members and Associates (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

Reto Engler

Karl Baetcke

Marcia Van Gemert

Henry Spencer

Gary Burin

James Rowe

Stephen Dapson

Esther Rinde

George Ghali

Rick Whiting

2. Peer Review Members in Absentia (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the committee)

None

3. Scientific Reviewer (Committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

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B. Material Reviewed

The material available for review consisted of an RfD summary document and data evaluation records (DER's) of the following Studies:

1. Suter, P., Sachsse, K. et. al. (1986). Combined chronic toxicity / oncogenicity study in the rat - dietary administration. Unpublished report prepared by Research Consultant Co., AG, Switzerland. Project No. A33811, dated September 19, 1986, submitted to the Agency by Hoechst Celanese Corp. MRID No. 403456-07, HED Doc No. 006936 and 007817. Guideline requirement 83-1a and -2a.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The Committee considered the increase in kidney weight and the accompanied increase in the glutamine synthetase to be adaptive effects. The NOEL was considered to be the lowest dose tested. The consideration of the kidney effects as adaptive effects may explain also why the subchronic study in rats demonstrated a lower NOEL than the chronic study for the same effects. The Committee requested that the issue of neurotoxicity observed in this study to be adequately addressed.

The Committee concluded that the high dose tested in the rat carcinogenicity study was inadequate for a reliable assessment of the carcinogenic potential of this chemical and recommended the repeat of the study. Based on signs of toxicity observed in a subchronic study (90 day range finding) in rats, it was evident that animals could have tolerated higher doses. There was also a concern that the incidence of combined benign and malignant "adrenal medullary tumors" were marginally increased at the high dose level in the rat study though the high dose level was considered inadequate for carcinogenicity testing. The chronic toxicity phase of the study was considered to be Core-minimum data, and thus satisfies data requirement 83-1a. The carcinogenicity phase of the study was downgraded to Core-supplementary, and thus it does not satisfy the intended Guideline requirement 83-2a of Subpart F of the Pesticide Assessment Guideline.

2. Suter, P., Sachsse, K. et al. (1986). Two-year oncogenicity study with HOE 039866 technical in mice - dietary administration. Unpublished report prepared by Research and Consulting Co. AG, Switzerland. Project No. 018527, dated April 29, 1986, submitted to the Agency by Hoechst Celanese Corp. MRID No. 40345609, 41144702, HED Doc. No. 006936,

007817. Guideline requirement 83-2b.

Core-Classification: Core- minimum data.

Committee's Conclusions and Recommendations:

The Committee down-graded the study from Core-minimum to Core-supplementary data and recommended the repeat of the study. The highest dose tested was considered inadequate for a reliable assessment of the carcinogenic potential of this chemical in mice. Based on signs of toxicity observed in a subchronic study (90 day range finding) in mice, it was evident that animals could have tolerated higher doses. Furthermore, the data suggested possible concern of carcinogenic response in this species although the high dose tested was considered inadequate for carcinogenic testing. The study does not satisfy the intended Guideline requirement 83-2b of Subpart F of the Pesticide Assessment Guideline.

After the meeting, it was noted that the last paragraph of the conclusion stated that "however, with no NOEL, it [the study] is not useful for regulatory purposes". This statement may be inappropriate since the main objective of the mouse carcinogenicity study is the assessment of carcinogenic potential of the chemical.

3. Bathe, R., Frei, Th. et al. (1984). Twelve-month oral toxicity (feeding) study in Beagle dogs and stability and homogeneity study in dog feed. Unpublished report prepared by Research and Consulting Co., AG, Intingen, Switzerland and submitted to the Agency by Hoechst Celanese Corporation. Project No. 019203, report dated November 27, 1984. MRID No. 403456-08, HED Doc. No. 006936. Guideline requirement 83-1b.

Core-Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The Committee did not deliberate on the long-term study in the dog. However, the study was originally classified by the respective branch as Core-minimum data. However the Committee requested that the issue of neurotoxicity observed in the chronic toxicity studies to be adequately addressed. It is assumed that the Committee has no objection to the study's classification as Core-minimum data, and thus, based on this assumption the study satisfies data requirement 83-1b of subpart F of the Pesticide Assessment Guideline.

4. Becker, H. Muller, E. et al. (1986). Multiple generation study in rats and a preliminary study to the multiple generation study in rats. Unpublished report prepared by Research and Consulting Co., AG, intingen, Switzerland,

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submitted to the Agency by Hoechst Celanese Corp. Project No. A35589 and A33217, MRID No. 403456-12, HED Doc. No. 006936. Guideline requirement 83-4.

Core-Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer's conclusions. The study and the data evaluation records are acceptable. The study satisfies data requirement 83-4 of Subpart F of the pesticide assessment Guideline .

5. Baeder, C., Kramer, M., et al. (1984). Testing for embryotoxicity in Himalayan rabbits following oral administration. Unpublished report prepared by Hoechest AG, 1984, study No. G2k0402, project No. 84.0177, report dated April 9, 1984. MRID No. 403456, HED Doc. No. 007817. Guideline requirement 83-3, one species.

Core-Classification: Core minimum data.

Committee/s Conclusions and Recommendations:

The Committee agreed with the reviewer conclusions. The study satisfies data requirement 83-3 of Subpart F of the Pesticide Assessment Guideline.

6. Baeder, C., Weigand, and kramer, M. (1982). Testing for embryotoxicity in Wistar rats following oral administration. Unpublished report prepared by Pharma Forschung Toxikologie, Hoechst Corporation, study No. G2R0303, report dated October 20, 1980. MRID No. 00142446, 00151500, HED Doc. No. 004923. Guideline requirement 83-3, one species.

7. Pensler, M. et al. (1986). Testing for embryotoxicity and effects on post-natal development in Wistar rats following oral administration. Unpublished report prepared by Hoechst, AG., study No. P2R0486, report No. A33812 dated June 18, 1986. MRID No. 403456-10. HED Doc. No. 006936.

Core-Classification: When considered together, the above two studies may be considered as Core-minimum data.

Committee's Conclusions and Recommendations:

When the results of these two studies were evaluated together, the overall maternal and developmental toxicity NOEL was considered to be 2.24 mg/kg/day and not 10 mg/kg/day as stated in the data evaluation record of the Pensler study (No. P2R0486, 1986). The Committee recommended that the kidney effects observed in the Baeder study (No. G2R0303, 1982)

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 effect might be treatment-related effects. The classification of these developmental toxicity studies will be reserved until the receipt and evaluation of historical background on kidney effects in this strain of rats.

CC: Penny Fenner-Crisp
Richard Schmitt
Esther Saito
Kerry Dearfield