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

JUN 26 1987

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Peer Review of Alachlor - Reconsideration of Classification

From: Judith W. Hauswirth, Ph.D. Judith W. Hauswirth 5/18/87
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The Toxicology Branch Peer Review Committee met on April 15, 1987 to reconsider the classification of Alachlor as a B_2 oncogen in light of the conclusions of the Science Advisory Panel (SAP) (November 19, 1976) and the registrant's rebuttal to the Agency's Position Document 2/3.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with peer review unless otherwise stated).

Theodore M. Farber	Theodore M. Farber
Reto Engler	Reto Engler
Louis Kasza	Louis Kasza
Judith W. Hauswirth	Judith W. Hauswirth
William Marcus	W. Marcus
Gary Burin	Gary Burin
Robert Beliles	Robert Beliles
Donald Barnes	Donald E. Barnes

2. Peer Review Members in Absentia: (Committee members who were not able to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

John A. Quest

Esther Rinde

Anne Barton

William Burnam

Diane Beal

B. Material Reviewed:

The following material was made available to the Committee for review:

1. Toxicology Branch Peer Review Report on Alachlor (meeting of 3/25/86 and report dated 5/20/86, copy appended);

2. Report of Panel Recommendations (SAP report dated 11/25/87);

3. Partial transcript of SAP meeting (11/19/86); and

4. Comments in Reply to EPA's Federal Register Notice of October 8, 1986. The Alachlor Special Review Technical Support Document dated September 1986 (submission by the registrant).

C. Background Information:

On March 25, 1987 the Toxicology Branch Peer Review Committee met to discuss and evaluate the weight-of-the-evidence on alachlor, with particular reference to its classification by the Agency as a B_2 oncogen in the Special Review Position Document 1 (December 1984). After considering the criteria in the EPA Guidelines for classifying a carcinogen, the Committee concurred with the original classification concluding that:

> Alachlor met all but one of the criteria specified for the B-2 classification, any of which alone can be sufficient for such a classification. That is, alachlor produced an increased incidence in malignant, or combined malignant and benign, nasal turbinate tumors (and other tumor types) in Long-Evans rats in three different experiments at more than one dose level via dietary administration. Alachlor also produced a statistically significant increase in lung tumors in female CD-1 mice at 2 dose levels. In another experiment with Long-Evans rats, nasal turbinate tumors occurred after only 5-6 months of exposure. The tumor incidence was as high as 50% and tumor site was unusual; i.e., not an increase of a normal high background tumor type. Additionally, a metabolite of alachlor was mutagenic in the Ames Test at 6 dose levels.

The SAP upheld the B_2 classification but felt that the mouse study was not positive for oncogenicity. They concluded that alachlor was a B_2 oncogen since it produced "an unusual type of neoplasm [nasal turbinate tumors] in the

rat, coupled with the finding that two metabolites of alachlor are mutagenic." They further stated that "the data available clearly meet the criteria for a B_2 classification."

D. Reevaluation of Classification:

The Committee was asked to address the following points which summarize the registrant's conclusion that alachlor should be reclassified as category C oncogen:

1. Lack of oncogenicity in multiple species (since the mouse study was considered negative by the SAP);

2. Questionable malignant tumor response in multiple experiments (nasal turbinate tumors were mostly benign);

3. Lack of unusual degree, site, type or early onset (at doses below the MTD, there was not an unusually high incidence of nasal turbinate tumors; nasal turbinates were not routinely examined at the time of the alachlor study); and

4. Alachlor is not a genotoxic oncogen and there are species differences in its metabolism.

Point #1:

Both the SAP and the registrant felt that the mouse study was negative for oncogenicity since the incidence of lung tumors in female mice was within the historical control range for this strain of mouse as reported by Sher (Toxicology Letters 11: 103-110, 1982). The average incidence of lung tumors, as cited in this paper in CD-1 female mice is 17% with a range of 0-41%. The incidence of lung tumors at the high dose in the alachlor study was 22%. The SAP also stated that this conclusion was supported "by the lack of evidence of progression from benign to malignant tumors, and the lack of an increase in tumor multiplicity in treated mice".

The Committee disagreed with both the SAP and the registrant on this point. They felt that historical control data derived from the literature was at best tertiary information for consideration and that concurrent control data should be primarily relied upon followed by contemporaneous data from the conducting laboratory. They concluded that the mouse study was positive for oncogenicity since:

1. The incidence of lung tumors was significantly ($p < 0.05$) increased at the high dose in female mice;

2. The incidence of lung tumors in female mice that died in extremis was significantly ($p < 0.01$) induced indicating early onset; and

3. Historical control data from the performing laboratory (Bio/dynamics) on studies that were conducted for at least 5-6 months longer than the alachlor study indicated that the incidence of lung tumors at the high dose (22%) was just within the historical range (0-23%). The spontaneous incidence of lung tumors is known to increase significantly with age. Therefore, it would not be

unexpected that the tumor incidence in the alachlor study would be ~~within~~ outside the historical control range of studies conducted for 18 months at Bio/dynamics.

Point #2:

The registrant claims that the nasal turbinate tumors, induced by alachlor, were mostly benign, especially at dosages which they considered to be at or below the maximum tolerated dose (42 mg/kg/day) (MTD).

The Committee agreed that at 15 and 42 mg/kg/day of alachlor, the nasal turbinate tumors were mostly benign since only two carcinomas (1 male and 1 female) were found, both at 42 mg/kg/day. However, at 126 mg/kg/day malignant nasal turbinate tumors were induced indicating that this tumor type progresses to malignancy.

Point #3:

The registrant argues that the nasal turbinate tumors were not induced to an unusual degree at dosages at or below the MTD, nor are they rare tumors especially since this tumor type was not routinely looked for at the time of the alachlor study and would not be considered uncommon today.

The Committee noted that the registrant submitted no data to support their contention that nasal turbinate tumors are no longer considered rare tumors or that they occur spontaneously in Long-Evans rats.

The Committee also reconsidered their determination of the MTD in the two alachlor studies in rats. In the high dose study (0, 14, 42 and 126 mg/kg/day), they originally concluded (see atached Peer Review Report of 5/20/86) that each of these doses exceeded the MTD. However, upon reconsideration they felt that in this study, based upon increased mortatlity, 42 mg/kg/day approximated the MTD in females and 14 mg/kg/day in males. In the low dose study (0, 0.5, 2.5 and 15 mg/kg/day), they originally concluded that the MTD was exceeded at 15 mg/kg/day. Upon reexamination of the mortality data upon which this decision was made, the Committee felt that they had erred and there was no evidence from the results of the study that 15 mg/kg/day even approached an MTD. They concluded that 42 mg/kg/day best approximated an MTD for alachlor.

Point #4:

The registrant claims that alachlor is not a genotoxic oncogen since alachlor was not mutagenic in several short-term assays. The Committee agrees that the weight-of-the-evidence indicates that alachlor, itself, is not a mutagen. However, two metabolites of alachlor, both identified in rat, were mutagenic in the Ames assay. These two metabolites are N-2-ethyl-6-(1-hydroxyethyl)-phenyl-2-(methylsulfonyl) acetamide and N-[2-ethyl-6-(1-hydroxyethyl)-pheny]-N-(methoxymethyl) acetamide.

The registrant also claims that the monkey is a better model than the rat for determining the onogenic potential of alachlor in man. The Committee noted that the registrant has identified one of the mutagenic metabolites of alachlor in monkey urine, as well as rat, and that without any evidence on the oncogenicity of alachlor in the monkey, they must rely upon rodent data to

make a determination.

E. Conclusions on the Reevaluation:

The Committee felt upon reconsideration of the available data and review of the registrant's arguments and the SAP's decision, that alachlor should be classified as a B_2 oncogen (probable human carcinogen), corroborating their initial decision. They further felt that the conclusions reached in their initial review still stood, that is that administration of alachlor was associated with an increased incidence of benign and maligant tumors in male and female rats in multiple experiments to an unusual degree and at an unusual site (nasal turbinates) and of benign lung tumors in female CD-1 mice. These conclusion meet all three criteria of a Category B_2 classification, any one of which is sufficient for classification in this category.