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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

CASWELL #11

Subject: Addenda to Two Chronic Feeding Studies in Rats and Mice with Alachlor

To: Robert Taylor, PM #25
Registration Division (TS-767)

and Michael McDavit, PM #61
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Action Requested:

Review an Addendum to a Special Chronic Feeding Study with Alachlor in Long-Evans Rats (Monsanto R. D. #533, MSL #3492, 2/12/85, Accession #256735) and an Addendum to Eighteen Month Chronic Feeding Study of Alachlor in Mice (Monsanto R. D. #365, MSL #1649, 2/12/86 Accession #256735).

Recommendation:

1. The addendum to the 18 month mouse study contains an evaluation done by Bio/dynamics on the nasal turbinates of mice in the control and high dose groups. Originally, examination of this tissue was done on only 10 mice/sex/group. Tissues from all remaining animals have now been examined. No nasal tumors/lesions were found. Alachlor did not induce nasal turbinate tumors in mice in this study.

2. The addendum to the special chronic feeding study in Long-Evans rats contains a reevaluation of the brain tumors (neuroepitheliomas) found in this study. Three brain tumors were reported, two in female rats and one in males.

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Reevaluation indicated, according to the report, that these tumors were extensions of nasal adenocarcinomas and not brain tumors. However, several discrepancies between the original report of this study and the addendum need to be resolved prior to accepting the conclusion reached in the addendum, that alachlor does not induce neuroepithelionas of the brain. (See the review portion of this report).

The registrant's explanation for why brain weights were not recorded in this study and for why all animals with compression of the brain did not have pituitary tumors is acceptable to this reviewer.

REVIEW

1. An Eighteen Month Chronic Feeding Study of Alachlor in Mice. Addendum to Pathology Report.

Conducted By: Bio/dynamics

Study No.: BD 84-014 (Addendum)
BD 77-423 (Original Report)

Project No.: 77-2064

Purpose of Evaluation:

When the tissues of mice (CD-1) from this study were initially evaluated histologically only 10 mice/sex/group were examined for treatment related effects of the nasal cavity. Since nasal turbinate tumors were induced by alachlor in two separate chronic feeding studies in male and female Long-Evans rats, it was decided to examine the remaining nasal tissues from mice in the control and high dose groups. The examination was done by the same pathologist that evaluated the study initially.

Results:

The number of animals examined were 35 males and 35 females in the control group and 36 males and 35 females in the high dose group (260 mg alachlor/kg/day). The total number of mice examined for nasal turbinate lesions in the study were 45 males and females in the control group and 46 and 45 females in the high dose group. All tissues examined were "within normal histological limits".

Conclusion: Alachlor did not induce nasal turbinate lesions or tumors in CD-1 mice.

2. An Addendum to a Special Chronic Feeding Study with Alachlor in Long-Evans Rats.

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Conducted By: Monsanto and C.I.I.T.

Purpose of Reevaluation:

In our Special Review Position Document 1 (PD-1) the Agency requested historical control data for the incidence of neuroepitheliomas in Long-Evans rats in order to assess the biologicl significance of these tumors. Neuroepitheliomas were seen only in alachlor treated rats in the study, Special Chronic Feeding Study of Alachlor in Long-Evans (Monsanto, R.D. #533, MSL #253306 and 253307). The level of alachlor administered to rats in this study was equivalent to 126 mg/kg/day.

Instead of submitting historical control data Monsanto has done a reevaluation of these tumors.

Results:

According to the addendum, brain tissue from animal numbers 1F051, 1F079, 1M030 and 1M068 were examined. Number 1M068 had an astrocytoma. The other mice were originally diagnosed as having neuroepitheliomas. In the original report the following information was found:

Animal #	Brain	Nasal Turbinate
1F051	-	-
1F050	neuroepithelioma	adenocarcinoma
1F079	neuroepithelioma	adenocarcinoma
1M030	astrocytoma	adenoma/papillary adenoma
1M068	neuroepithelioma	adenoma/papillary adenoma

C.I.I.T.'s neuropathologists confirmed that animal 1M068 had an astrocytoma. They diagnosed the lesions in the brain of 1F051, 1F079 and 1M030, not as neuroepithelioms, but as extensions of nasal adenocarcinomas. This reviewer has problems with this conclusion since:

- animal 1F051 did not have a neuroepithelioma of the brain nor an adenocarcinoma in the nasal turbinates according to the original report; however, animal 1F050 had both of these tumors. The registrant needs to resolve this discrepency

- animal 1M030 did have a neuroepithelioma but did not have a adenocarcinoma of the nasal cavity. It did have an adenoma/papillary adenoma of the nasal cavity. If, indeed, this animal did not have a malignant nasal cavity tumor, the brain tumor found in this animal cannot be an extension of a nasal adenocarcinoma. This

discrepency also needs to be resolved.

Also included in this addendum was an explanation of why brain weights were not taken in this study as noted by the original reviewer of this study. The report explains this as follows:

> This was a planned procedure as it was considered more important to obtain and identify all nasal tumors including those which penetrated the boney cribiform plate posteriorly and entered the cranial cavity. Thus, the anterior tip of each brain was severed and left intact next to the cribiform plates. Weights of such trimmed brains would have been meaningless.

This explanation is acceptable to this reviewer.

The original reviewer of this study also questioned the finding that of 24 animals with compression of the brain only 8 had pituitary tumors. The report states that enlargement of the pituitary in the absence of a tumor is fairly common and explains the compression. This explanation is acceptable to this reviewer.

Conclusions:

1. The addendum to the 18 month mouse study contains an evaluation done by Bio/dynamics on the nasal turbinates of mice in the control and high dose group. Originally, examination was done on only 10 mice/sex/group. Tissues from all remaining animals have not been examined. No nasal tumors were found. Alachlor did not induce nasal turbinate tumors in mice.

2. The addendum to the special chronic feeding study in Long-Evans rats contains a reevaluation of the brain tumors (neuroepitheliomas) seen in this study. The only level of alachlor administrered in the feed was equivalent to 126 mg/kg/day. Three brain tumors were reported, two in female rats and one in males. Reevaluation, according to the report, indicated that these tumors were extensions of nasal adenocarcinomas and not brain tumors. However, several discrepencies between the original report of this study and the addendum need to be resolved prior to accepting the conclusion reached in the addendum, that alachlor does not induce neuroepitheliomas of the brain. These include:

- In the addendum, brain tissue from animal #1F051 was examined as having a neuroepithelioma. In the original report, 1F050 was listed as having a neuroepithelioma not 1F051. Which is correct or did both animals have this tumor?

- The conclusion reached in the addendum would not hold for animal #1M030 since according to the original report it did not have an adenocarcinoma of the nasal turbinates but an adenoma/papillary adenoma. Did this animal have a neuroepithelioma or was the nasal tumor misdiagnosed in the original report?

The registrant's explanation for why brain weights were not recorded in this study and why all animals with compression of the brain did not have pituitary tumors is accepatable to this reviewer.