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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

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OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Pyrethrin Data Call-In Submission of Preliminary Results from Long-Term Feeding Studies in Mice and Rats.

Tox. Chem. No.: 715
HED Project No.: 0-0353
EPA ID No.: 58223
Record No.: 256521

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Recommendations and Conclusions

1. At this time there is insufficient information available to determine whether or not the apparently increased incidence of three types of tumors in rats and mice treated with pyrethrum extract represents an unreasonable adverse effect. Reasons for this conclusion are:

   a. The examination of lung tissue may not have been extensive enough in the mouse study (one section per animal), and multiple sections are to be examined to improve the likelihood of diagnosing alveolar bronchiolar adenomas in the control and high dose group mice. Multiple sections should be taken from mice in the low and mid dose groups also.

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b. The increased incidence of thyroid tumors in rats given the high dose level may be the result of an hormonal imbalance that is reversible. Protocols for further short-term studies should be submitted to the Agency for comment. In addition, related tissues such as the pituitary and liver from all test groups should be examined microscopically to provide any available evidence of a thyroid/pituitary hormone imbalance.

c. The biological significance of keratoacanthomas in male rats is subject to question because those lesions are self-limiting and are often spontaneously resolved.

d. Other factors to be considered in an interpretation of the reported tumor incidences include the incidence of non-neoplastic changes in the affected tissues as well as related tissues, the incidence of gross lesions associated with the findings, the size and location of the lesions, and the time course of the events leading up to the occurrence of the tumors.

e. The adequacy of the doses selected for the studies (i.e., whether or not a Maximum Tolerated Dose was reached or exceeded at the highest levels tested) should also be determined.

2. Detailed historical control data should be submitted for alveolar bronchiolar tumors in mice, thyroid follicular cell tumors in rats, and skin tumors in rats when the final reports are sent to the Agency.

3. Additional sections should be taken for lungs from all groups in the mouse study since the re-evaluation of that tissue may change the overall response observed.

4. Protocols for the proposed short-term thyroid function studies should be submitted to the Agency for comment before the studies are initiated.

Background and Discussion

In a letter dated November 27, 1989, the Registrant (Chemical Specialties Manufacturers Association/Pyrethrin Joint Venture) submitted preliminary data from chronic toxicity/oncogenicity studies in rats and mice treated with pyrethrum extract. These data were submitted in accordance with Section 6 (a) (2) of FIFRA because animals in the high dose groups from both studies had increased incidences of benign tumors at three sites.

A. The Mouse Study

The Registrant noted that the in-life phase of the mouse study was completed on March 31, 1989, and a draft final report on this study was scheduled for completion on December 21, 1989. The final report is to be submitted to the Agency in April, 1990.

In the study, groups of 60 male and 60 female Charles River CD-1 strain mice (including two control groups) were given diets containing 0, 100, 2500, or 5000 ppm pyrethrum extract for 18 months. The Registrant noted that there was an increased incidence of alveolar bronchiolar adenomas in female mice given the 5000 ppm diet. The letter discussed these tumors as follows:

> While the incidence of alveolar bronchiolar adenomas in female mice at the high-dose level is higher than the incidence in either concurrent control group, most of these tumors are very small and are only observed microscopically. Therefore, a much larger number of control mice may have lung tumors than that represented by examination of one section of lung from each mouse, which was the way lung tissue was processed in this study. The background incidence of lung tumors in female mice at the contract laboratory for studies processed in this manner is as high as 20%. However, the control tumor incidence for female mice is as high as 40% for studies in which multiple sections of lung are processed for each animal.

The historical control data cited by the Registrant was described briefly in an abstract attached to the letter. The incidence of alveolar bronchiolar tumors was reported in an attachment to the letter and is summarized in Table 1 below.

The Registrant indicated that additional sections of lungs from female mice in the two control groups and the high dose group would be examined to determine the "true incidence" of the alveolar bronchiolar adenomas in those groups.

Table 1

Summary of the incidence of alveolar bronchiolar adenomas in female mice treated with pyrethrum extract in their diets for 18 months.

Dose group	Incidence* (%) Died on study	Terminal sacrifice	Total
Control 1	2/15 (13)	6/45 (13)	8/60 (13)
Control 2	1/19 (3)	3/41 (7)	4/'60 (7)
100 ppm	1/11 (9)	10/49 (20)	11/60 (18)
2500 ppm	1/16 (6)	4/44 (9)	5/60 (8)
5000 ppm	2/18 (11)	17/42 (40)	19/60 (32)

* Incidence = number with tumor/number examined.

B. The Rat Study

The Registrant indicated that the in-life phase of this study was completed on June 7, 1989, and a draft final report on the study was scheduled for completion on March 1, 1990. The final report is scheduled for submission to the Agency in June, 1990.

In this study, groups of 60 male and 60 female Charles River CD strain rats (including two control groups) were given diets containing 0, 100, 1000, or 3000 ppm pyrethrum extract for 24 months. The Registrant noted that there were increased incidences of follicular cell adenomas in thyroid glands of male and female rats given the 3000 ppm diet. The letter discussed these tumors as follows:

> ...(follicular cell adenoma) has been associated with the administration of numerous compounds which interfere with the feedback mechanism associated with the production and maintenance of thyroid hormone. According to a document prepared by the Environmental Protection Agency entitled "Hazard Evaluation Division, Standard Evaluation Procedures, Neoplasia Induced by Inhibition of Thyroid

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> Gland Function (Guidance of Analysis and Evaluation)" a threshold mechanism is indicated.
>
> The biological significance of...(keratoacanthomas in the skin of male rats) in terms of a neoplastic change is questionable due to the self limiting nature of the lesions, i.e., it is defined as a rapidly growing papular lesion with a crater filled keratin plug which reaches maximum size and then resolves spontaneously.

The incidences of thyroid follicular cell tumors and keratoacanthomas were reported in an attachment to the letter and are summarized in Tables 2 and 3 below.

The November letter indicated that additional short-term studies would be conducted to determine the relationship between the dose of pyrethrum extract and thyroid hormone levels in the blood of treated rats. In addition to these studies, the thyroid tissues from low and mid dose group rats would be examined microscopically since the original protocol did not call for the thyroid to be examined in those groups.

C. Conclusions

The Registrant concluded, "...further work and analysis must be completed before any decision on this issue can be made." Other factors which the Registrant feels should be considered in an interpretation of the tumor incidences include:

1. non-neoplastic changes in the affected tissues as well as related tissues,

2. gross lesions associated with the findings,

3. the size and location of the lesions, and

4. the time course of the events leading up to the occurrence of the tumors.

The Registrant also indicated that re-examination of the slides by a second pathologist would be considered.

Finally, the Registrant concluded, "Because of the nature of these findings and the need to perform additional work..., it is not possible to determine if these findings represent...unreasonable adverse effects...of pyrethrum extracts..."

Table 2

Summary of the Incidence of thyroid follicular cell adenomas in male and female rats treated with pyrethrum extract in their diets for 24 months.

Dose group	Incidence* (%) Died on study	Terminal sacrifice	Total
	Males		
Control 1	1/27 (4)	1/33 (3)	2/60 (3)
Control 2	0/33 (0)	1/27 (4)	1/60 (2)
100 ppm	1/4 (25)	0/3 (0)	1/7 (15)
1000 ppm	0/3 (0)	0/2 (0)	0/5 (0)
3000 ppm	6/27 (22)	5/33 (15)	11/60 (18)
	Females		
Control 1	0/33 (0)	0/27 (0)	0/60 (0)
Control 2	1/45 (2)	0/15 (0)	1/60 (2)
100 ppm	0/1 (0)	0/1 (0)	0/2 (0)
1000 ppm	0/1 (0)	0/1 (0)	0/2 (0)
3000 ppm	2/28 (7)	5/32 (15)	7/60 (12)

* Incidence = number with tumor/number examined.

Table 3

Summary of the incidence of keratoacanthomas in male rats treated with pyrethrum extract in their diets for 24 months.

Dose group	Incidence* (%) Died on study	Terminal sacrifice	Total
Control 1	3/27 (11)	1/33 (3)	4/60 (7)
Control 2	3/33 (9)	2/27 (7)	5/60 (8)
100 ppm	6/20 (30)	1/4 (25)	7/24 (29)
1000 ppm	4/6 (67)	2/8 (25)	6/14 (43)
3000 ppm	8/27 (29)	6/33 (18)	14/60 (33)

* Incidence = number with tumor/number examined.

END