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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Parathion, Rereading of Thyroid Slides for Thyroid
Follicular Adenomas in the Chronic Rat Study

TO: Edward Allen, PM-12
Registration Division (TS-767)

FROM: Robert P. Zendzian PhD
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[Signature] 4/54/86

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5/8/86

Compound; Parathion

Tox Chem #637

Registration #524-27

Registrant; Monsanto

Accession #262086

Tox Project #1637

Action Requested

Review the following submission.

Histopathological Evaluation of Thyroid and Parathyroid
Glands from Male Sprague-Dawley Rats Fed Ethyl Parathion, C.
Capen DVM, Biodynamics, Project No. BD-78-5; 77-2055, Feb
21, 1986.

Conclusions

Based on the information presented it is concluded that
the incidence of follicular cell adenomas in the high dose
group does not represent an oncogenic response in this study.

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However, an NCI study of ethyl parathion has shown an excess of adrenal tumors (adenomas and carcinomas) in the high-dose animals of both sexes. Because of this study the Toxicology Branch Peer Review Committee will formally evaluate the evidence in regard to the oncogenicity of ethyl parathion.

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Background

In 1984 the Registrant Submitted the report of a 2-year rat feeding study with ethyl parathion. The study was reviewed with the conclusions and recommendations noted below in reference to possible oncogenic effects in the thyroid gland.

Daly, I.W. & G.K. Hogen, Two-Year Chronic Feeding Study of Ethyl Parathion in Rats, Biodynamics Incorporated, Project # 87-005, Study #77-20-55, Jan 23, 1984, Accession #s 252702

Follicular adenomas of the thyroid gland were reported in 9% of the high dose males compared with 2% of the control males. Historical control data was requested on follicular adenomas.

The Registrant replied as follows;

"3. Thyroid Follicular Tumors

A slightly increased incidence of thyroid follicular adenomas was noted in high-dose males from the ethyl parathion study. The incidence observed in the high-dose was slightly above the range observed historically in control animals at the testing laboratory (see attached tables). However, no carcinomas were observed in these animals and the combined incidence of follicular adenomas and carcinomas falls very close to the upper range seen historically. In addition, no increase in follicular adenomas was observed in a previous chronic rat study conducted by the NCI. Therefore, Monsanto believes that the slight increase noted in the ethyl parathion study may be spurious and not related to treatment."

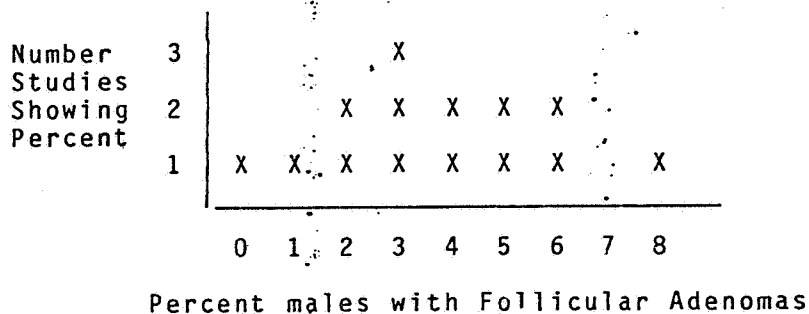
The Registrant provided a table of historical control data on the strain of rats used [Charles River Albino (CD®)] from the contract laboratory which performed the reference study (Bio/dynamics Inc).

Data was provided on 14 studies having a total of 1163 male rats "sacrificed post 12 months" and examined, which showed a total of 45 "polymorphofollicular/follicular adenoma/papillary adenoma/adenoma". The incidence ranged from zero to eight percent with a mean of 3.9 percent.

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Distribution of incidence by study is shown in Figure 1 below.

Figure 1. Frequency distribution of follicular adenoma of the thyroid gland in male rats used as controls in two year feeding studies. Percent incidence per study is rounded off.



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Incidence of follicular adenomas in the male rats treated with ethyl parathion was.

Dose (ppm)	0	0.5	5.0	50
# of rats examined	59	58	58	58
Follicular adenomas #	1	1	2	5
%	2	2	3	9

This subject was discussed with Dr Louis Kasza, Branch Pathologist, who examined all data presented above as well as the summary table of histopathological findings in the thyroid from the rat study of ethyl parathion. Dr Kasza concluded that the observed incidence of follicular adenomas was 'real' representing an increase over controls both concurrent and historical. However the distribution of histopathological observations in the thyroid was somewhat unusual. In particular no increase in incidence of hyperplasia was reported in the high dose group. Such an increase usually precedes the appearance of neoplastic changes. Considering this unusual pathology, Dr Kasza recommended that the slides be examined by an expert in endocrine pathology.

New data submitted

The results of the reevaluation of thyroid tissue are presented in table 1 from the pathologist's report. It should be noted that Dr. Capan identified only four follicular cell adenomas in the high group as opposed to five identified in the first histopathological evaluation.

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Dr. Kasza has examined this new information and concludes that the Follicular Cell Adenomas of the thyroid seen in this study do not represent an oncogenic response. His conclusion is based on the following;

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- 1) The effect was seen in only one species.
- 2) The effect was seen in only one sex.
- 3) The tumors are nonmalignant
- 4) There was no associated hyperplasia.
- 5) The incidence was within historical controls.
- 6) The increased incidence was seen only in the high dose.

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Parathion

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