7/31/89

007840

FILE COPY

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

JUL 31 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Second Peer Review of Parathion

FROM: Esther Rinde, Ph.D. E. Rinde 3/31/89
Science Analysis and
Coordination Branch
Health Effects Division (H-7509c)

TO: Dennis Miller
Product Manager #12
Registration Division (H-7505c)

The Health Effects Division Peer Review Committee met on March 7,1989 to discuss and evaluate the weight-of-the-evidence on Parathion with particular reference to its oncogenic potential.

A. Individuals in Attendance:

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

William L. Burnam	
Reto Engler	
Marcia Van Gemert	
Diane Beal	
Lynnard Slaughter	
William Sette	
George Ghali	
Esther Rinde	

007840

Peer Review Documents
(Memo dates)

A. 2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Robert Zendzian — 4/1/89

Bernice Fisher — Bernice Fisher

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

Judith Hauswirth — Judith W. Hauswirth

Richard Hill —

Robert Beliles — Robert Beliles

Kerry Dearfield — Kerry Dearfield

Richard Levy — Richard A. Levy

Marion Copley — Marion P. Copley

John Quest — John A. Quest

B. Background

Parathion was originally classified by the Toxicology Branch Peer Review Committee as a Group C (potential human carcinogen), without a quantitative risk assessment (Parathion Peer Review Memo, 8/1/86). The Registrant subsequently submitted an additional chronic/oncogenicity study in the Wistar rat and four new mutagenicity studies [memo (11/2/88) and DER from Dr. Zendzian are attached to the file copy of this report].

C. Evaluation of Oncogenicity Evidence for Parathion

Summary of Oncogenicity Evidence

I. Previous studies: The following studies were discussed in the first Peer Review Memo (8/1/86) and are briefly summarized below.

1. NCI B6C3F1 Mouse Study - An MTD was reached in male, but not in female mice; only 2 doses were used. There was no evidence for oncogenicity in this study; however, the study was flawed in that the concurrent control groups consisted of only 10 mice/sex, some tissues were not microscopically examined, and some males were only dosed for 62 weeks; concerns were raised during audits of the test facility (Gulf South Res. Inst.).

2. NCI Osborne-Mendel Rat Study - An MTD was reached in both sexes. A statistically significant increase in adrenal cortical tumors (adenomas plus carcinomas) was found in low and high dose males and in the high dose females (as compared to pooled controls). A statistically significant trend was also found in male rats for thyroid follicular cell adenomas and pancreatic cell carcinomas (as compared to pooled controls). This study was also flawed: concurrent control groups consisted of only 10 rats/sex, some tissues were not microscopically examined and rats were only dosed for 80 weeks of an 112 week study; concerns were raised in audits of test facility (Gulf South Res. Inst.).

3. Bio/Dynamics Sprague-Dawley Rat Study - An MTD was reached in both sexes. This study was considered to be adequate by the Peer Review Committee. In male rats there were increased incidences of thyroid follicular cell adenomas, which were within the historical control range (after the second reading of the slides).

C. Oncogenicity Evidence (contd.)

II. New Data: The following additional study was reviewed at this time.

Bayer AG Wistar Rat Study

Parathion was administered in the diet to 50 male and 50 female Wistar rats at doses of 0,2,8 or 32 ppm for 26 months.

Signs indicative of cholinergic toxicity (treatment-related plasma, erythrocyte and brain cholinesterase depression) were observed in both sexes at 32 ppm (HDT). There were also decreased body-weight gains (>10%) in both sexes at 32 ppm throughout the study and a treatment-related increase in mortality in females at 32 ppm throughout the study. In addition, significant toxic effects on the eyes of female rats at 32 ppm were reported at terminal observation. Effects on the eyes of males at 32 ppm were possible but not clear-cut. The Committee concluded that the doses used in this study were adequate for assessing the oncogenic potential of Parathion.

Results: Although not significant by pairwise comparison, there was a statistically significant trend in the increase of benign pancreatic tumors (seen only at the end of the study) in male rats only. This was the only treatment-related neoplastic lesion reported. The incidences for pancreatic tumors are given in Table 1 (pg. 4a).

The increases, although marginal and within the upper range of the historical control range for male rats in the laboratory, were nevertheless considered to be biologically significant (for each tumor type only one out of 30 groups of controls showed an incidence comparable to that in treated males, and pancreatic tumors were also seen in the NCI rat study).

The Peer Review Committee evaluated the additional evidence, which demonstrated a statistically significant positive trend in the increase of benign pancreatic tumors (seen only at end of study) in male Wistar rats only. The Committee concluded that these data, although biologically significant, were not suitable for quantitative risk assessment. The Committee also noted that the Wistar rat study was the only adequately conducted one showing an oncogenic response.

PARATHION

TABLE 1*

Incidence of nonneoplastic and neoplastic lesions in the pancreas at termination

	Males				Females			
Dose (ppm)	0	2	8	32	0	2	8	32
number animals	50	50	49	50	50	50	50	50
basophilic foci	0(0)	0(0)	3(6)	2(4)	0(0)	0(0)	2(4)	1(2)
acinar hyperplasia	0(0)	0(0)	1(2)	3(6)	0(0)	0(0)	0(0)	2(4)
islet cell hyperplasia	2(4)	0(0)	0(0)	1(2)	1(2)	0(0)	2(4)	0(0)
exocrine adenoma	0(0)	0(0)	1(2)	3(6)	0(0)	0(0)	0(0)	0(0)
exocrine carcinoma	0(0)	0(0)	0(0)	1(2)	0(0)	0(0)	0(0)	0(0)
islet cell adenoma	0(0)	0(0)	1(2)	3(6)	1(2)	0(0)	0(0)	0(0)

numbers in () are percent

The tumors of the exocrine tissue are discussed in detail in the conclusions of the pathology report which includes a statistical analysis. The author concludes "The number of male rats with exocrine pancreatic neoplasms exhibited a statistically significant positive trend with respect to dose ($Z = 2.86$, one-tailed $P = 0.0022$)."[1] The equally rare endocrine (islet cell) adenomas were not discussed by the author.[2]

Historical control data, for pancreatic tumors, were included in the study report. One study showed an incidence of islet cell tumors equal to that seen in this study (6%). One study (number 22) showed an incidence of exocrine adenomas equal to that in this study (6%).

---

*This page is taken from the reviewer's DER.
[1]Cochran Armitage analysis gave essentially the same result (p=.002)
[2]Cochran Armitage analysis yielded a p value of 0.007.

D. Mutagenicity Evidence

I. Previous studies: Only one acceptable assay was available for consideration at the time of the first Peer Review: an unscheduled DNA synthesis assay in human WI-38 cells. This assay was positive for induction of repair at Parathion dose levels of 10^{-5}M and 10^{-6}M. A dominant lethal assay in mice, the Ames salmonella assay, a reverse mutation assay in E. coli and B. subtilis were all negative; however, all these assays were considered as inadequately performed.

II. Additional Mutagenicity Studies: The following studies were reviewed at this time.

1. MRID 406447-05 Acceptable

Parathion was not active in the reverse mutation assay with S. typhimurium (Strains TA98, TA100, TA1535, TA1537 and TA1538) with or without metabolic activation, at doses up to 10,000 ug per plate.

2. MRID 406447-06 Acceptable

Parathion was equivocally active in the CHO/HGPRT forward gene mutation assay with or without metabolic activation at doses of 0.03 to 0.3 ul/ml. Results were not dose-related.

3. MRID 406447-07 Acceptable

Parathion did not induce micronucleated polychromatic erythrocytes in male or female CD-1 mice at IP doses of 3, 13 or 26 mg/kg.

4. MRID 406447-08 Acceptable

Parathion did not produce evidence of unscheduled DNA synthesis at doses of 0.0001, 0.0003, 0.0006, 0.001 and 0.003 ul/ml in the rat primary hepatocyte.

The Committee concluded that the overall evidence appears to present only minimal concern for mutagenicity; the CHO/HGPRT assay should be repeated, however, because of the equivocal results.

E. Conclusions

The HED Peer Review Committee reviewed the additional oncogenicity and mutagenicity data and concluded that Parathion should remain classified as a Group C, Potential Human Carcinogen, without quantitative risk assessment.

> In the first Peer Review, "The Committee felt that the weight-of-the-evidence did not warrant a quantitative estimation of the oncogenic potential of Parathion because of the deficiencies of the NCI study and the negative results for oncogenicity obtained in another strain of the same species" (Memo, 8/1/86).

The new evidence in the Wistar rat was limited to an increased incidence in benign tumors (which were seen only at the end of the study) with a significant positive dose-related trend in just one sex; there were no significant increases by pair-wise comparison. This study was the only one (that was adequately performed) demonstrating an oncogenic response.

This Committee felt that the weight of evidence did not warrant a quantitative estimation of risk, based on the above (benign tumors limited to one sex, trend only) and based on the two other rat studies (one of which was inadequate, the other negative for oncogenicity). The new mutagenicity data, along with the overall mutagenicity evidence, was not supportive of quantitation and the CHO/HGPRT assay should be repeated because of the equivocal results. The Committee also reaffirmed that the B6C3F1 mouse study was not adequate for judging the oncogenic potential of Parathion in the mouse and that, therefore, it should be repeated.