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

SEP 11 1991

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Carcinogenicity Peer Review of Parathion (3rd)

FROM: Esther Rinde, Ph.D. E. Rinde 7/26/91
Science Analysis and
Coordination Branch
Health Effects Division (H7509c)

TO: Jan Auerbach, Chief
Special Review Branch
Special Review and Reregistration Division (H7508c)

The Health Effects Division Carcinogenicity Peer Review Committee met on June 12, 1991 to discuss and evaluate new data on Parathion with particular reference to its bearing on the classification of Parathion's carcinogenic potential. The Committee concluded that the new data do not affect the existing classification and Parathion remains classified as a **Group C (possible human carcinogen) without quantification,** which is to say: without the use of a low dose extrapolation model (Q1*) for quantitative risk assessment; instead a Reference Dose (RfD) approach will be used.

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

Karl Baetcke

Robert Beliles

Lucas Brennecke

Marion Copley

A. 1. Peer Review Committee (contd.)

Kerry Dearfield

Hugh Pettigrew

Esther Rinde

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

Robert Zendzian 2/5/91

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.)

Penelope A. Fenner-Crisp

Julie Du

George Ghali

Richard Hill

Jean Parker

William Sette

Yin-Tak Woo

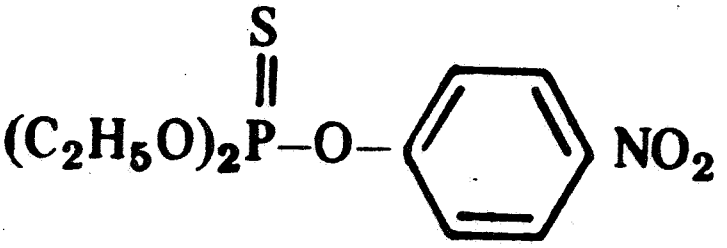
John Quest

B. Material Reviewed:

The material available for review consisted of a DER and summary memo prepared by Dr. Zendzian; tables and statistical analysis were provided by the Registrant (HED statistician, Ms. Fisher determined that additional analysis was not warranted); Peer Review documents for the 1st and 2nd meetings, dated Sept. 8, 1986 and July 31, 1989, respectively. The material reviewed is attached to the file copy of this report.

C. Background Information:

Parathion, a Special Review chemical, was classified as a Group C (possible human carcinogen) without quantitative risk assessment by the Peer Review Committee (PRC) at its meetings on July 1, 1986 and on March 7, 1989. A new mouse study, submitted by the Registrant, has been reviewed and the PRC was asked to consider whether the new data have any bearing on the classification of Parathion.



* * STRUCTURE OF PARATHION * *

O,O-diethyl (O-4-nitrophenyl) phosphorothioate

PRESENTATION OF NEW DATA

Reference: Carcinogenicity study of ethyl parathion administered by dosed feed to B6C3F1 mice, J.G. Page & J.E. Heath, Southern Research Institute, Project ID A21-CRM-1, 1/21/91, MRID 418173-01.

a. Experimental Design

Parathion was administered in the diet to groups of 50 male and 50 female B6C3F1 mice at 0 (control), 60, 100 or 140 ppm for 18 months.

A mis-dosing incident, however, involving the 60 ppm dose "was reported to the Agency when detected and a joint decision was made to continue the study" [R. Zendzian].

> Dr. Zendzian quotes the Registrant's report as follows: "Due to a technical error in diet preparation, mice in the 60 ppm dose group were fed a diet containing approximately 500 ppm ethyl parathion between Days 300 and 307 of this study. The mice in this dose group were switched to control diet (i.e., untreated) diet (sic) following detection of the misdosing incident for 17 days (Days 300 to 323) to allow these mice to regain lost weight and recover from the acute toxicity induced by exposure to an excessive dose of test article. The incident is highlighted here because it had an impact on study parameters (e.g., mortalities, body weights, food consumption) and study interpretation." (Six males and two females died within 14 days of the misdosing.)

b. Discussion of Tumor Data

The only increases in tumor occurrence that were statistically significant were observed at 60 ppm; these were lung alveolar/bronchiolar adenomas in males and systemic malignant lymphoma in females (Tables 1 and 2 - taken from the Registrant's submission). The incidence of adenomas in male mice at 60 ppm exceeded the upper range reported for historical controls at the testing facility; the incidence of malignant lymphoma in females was within the range of historical controls (Tables 3 and 4).

c. Consideration of Adequacy of Dosing for Assessment of Carcinogenic Potential:

Both male and female mice were considered to have been adequately, but not excessively dosed (at 140 ppm), based on dose-related decreases (less than 5%) in body-weight gain and significant brain, plasma and RBC cholinesterase inhibition (without a compound-induced increase in mortality).

The low dosed animals ("60" ppm) were, of course, overdosed during the mis-dosing incident.

Table 1

CARCINOGENICITY STUDY OF ETHYL PARATHION ADMINISTERED BY DOSED FEED TO B6C3F1 MICE
Study: A21-CRM-1
Analysis of Histopathology Findings - Males
Tumor Pathology

	Untreated	60 PPM	100 PPM	140 PPM
Lung - Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	5/50 (10.0%)	13/50 (26.0%)	6/50 (12.0%)	4/50 (8.0%)
Terminal Rates (b)	5/49 (10.2%)	12/39 (30.8%)	6/47 (12.8%)	4/50 (8.0%)
Life Table Test (c)		p = 0.009*	p = 0.471	p = 0.513
Incidental Tumor Test (d)		p = 0.014*	p = 0.457	p = 0.500
Cochran-Armitage Trend Test (e)	p = 0.206			
Fisher Exact Test (e)		p = 0.033*	p = 0.500	p = 0.500
Lung - Alveolar/Bronchiolar Carcinoma				
Overall Rates (a)	0/50	1/50 (2.0%)	0/50	0/50
Terminal Rates (b)	0/49	1/39 (2.6%)	0/47	0/50
Life Table Test (c)		p = 0.454	p = 1.000	p = 1.000
Incidental Tumor Test (d)		p = 0.450	p = 1.000	p = 1.000
Cochran-Armitage Trend Test (e)	p = 0.500			
Fisher Exact Test (e)		p = 0.500	p = 1.000	p = 1.000
Lung - Alveolar/Bronchiolar Adenoma and Carcinoma Combined				
Overall Rates (a)	5/50 (10.0%)	14/50 (28.0%)	6/50 (12.0%)	4/50 (8.0%)
Terminal Rates (b)	5/49 (10.2%)	13/39 (33.3%)	6/47 (12.8%)	4/50 (8.0%)
Life Table Test (c)		p = 0.005*	p = 0.471	p = 0.513
Incidental Tumor Test (d)		p = 0.007*	p = 0.457	p = 0.500
Cochran-Armitage Trend Test (e)	p = 0.185			
Fisher Exact Test (e)		p = 0.020*	p = 0.500	p = 0.500

Table 2

CARCINOGENICITY STUDY OF ETHYL PARATHION ADMINISTERED BY DOSED FEED TO B6C3F1 MICE
Study: A21-CRM-1
Analysis of Histopathology Findings - Females
Tumor Pathology

	Untreated	60 PPM	100 PPM	140 PPM
Harderian Gland - Adenoma				
Overall Rates (a)	1/50 (2.0%)	1/50 (2.0%)	0/50	0/50
Terminal Rates (b)	1/44 (2.3%)	1/42 (2.4%)	0/48	0/44
Life Table Test (c)		p = 0.751	p = 0.517	p = 0.500
Incidental Tumor Test (d)		p = 0.756	p = 0.517	p = 0.500
Cochran-Armitage Trend Test (e)	p = 0.170			
Fisher Exact Test (e)		p = 0.753	p = 0.500	p = 0.500
Systemic - Lymphoma Malignant				
Overall Rates (a)	0/50	5/50 (10.0%)	3/50 (6.0%)	2/50 (4.0%)
Terminal Rates (b)	0/44	3/42 (7.1%)	2/48 (4.2%)	1/44 (2.3%)
Life Table Test (c)		p = 0.033*	p = 0.140	p = 0.242
Incidental Tumor Test (d)		p = 0.033*	p = 0.060	p = 0.240
Cochran-Armitage Trend Test (e)	p = 0.332			
Fisher Exact Test (e)		p = 0.028*	p = 0.121	p = 0.247
Systemic - Histiocytic Sarcoma				
Overall Rates (a)	0/50	1/50 (2.0%)	0/50	2/50 (4.0%)
Terminal Rates (b)	0/44	0/42	0/48	0/44
Life Table Test (c)		p = 0.504	p = 1.000	p = 0.249
Incidental Tumor Test (d)		p = 0.500	p = 1.000	p = 0.223
Cochran-Armitage Trend Test (e)	p = 0.149			
Fisher Exact Test (e)		p = 0.500	p = 1.000	p = 0.247

Table 3

TOXICOLOGY DATA MANAGEMENT SYSTEM
TUMOR INCIDENCE FOR SELECTED CONTROL ANIMAL GROUPS

VERSION: 09/17/90 PAGE: 441

CONTRACT/LAB: SRI
SPECIES: MICE
STRAIN: MICE-B6C3F1
LENGTH OF STUDY: CHRONIC

ROUTE: ORAL
VEHICLE: FEED

DATE OF
INPUT FILE: 15-SEP-1990

INCIDENCE DATA FOR VEHICLE CONTROL GROUPS

	MALE			FEMALE		
*LIVER: HEPATOCELLULAR CARCINOMA, HEPATOCELLULAR ADENOMA, HEPATOBLASTOMA OR NEOPLASTIC NODULE	10/50 (20%)	13/49 (27%)	12/50 (24%)	2/50 (4%)	8/50 (16%)	3/50 (6%)
TOTAL % INCIDENCE	35/149 (23%)	S.D. = 3.51		13/150 (9%)	S.D. = 6.43	
*LIVER: HEPATOCHOLANGIOCARCINOMA	0/50 (0%)	0/49 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
TOTAL % INCIDENCE	0/149 (0%)	S.D. = 0.00		0/150 (0%)	S.D. = 0.00	
*LIVER: ITO CELL TUMOR BENIGN	0/50 (0%)	0/49 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
TOTAL % INCIDENCE	0/149 (0%)	S.D. = 0.00		0/150 (0%)	S.D. = 0.00	
*LIVER: LEUKEMIA ERYTHROCYTIC	0/50 (0%)	0/49 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
TOTAL % INCIDENCE	0/149 (0%)	S.D. = 0.00		0/150 (0%)	S.D. = 0.00	
*LIVER: SARCOMA	0/50 (0%)	0/49 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
TOTAL % INCIDENCE	0/149 (0%)	S.D. = 0.00		0/150 (0%)	S.D. = 0.00	
*LUNG: ALVEOLAR/BRONCHIOLAR ADENOMA	5/50 (10%)	6/50 (12%)	5/50 (10%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
TOTAL % INCIDENCE	16/150 (11%)	S.D. = 1.15		6/150 (4%)	S.D. = 2.00	
*LUNG: ALVEOLAR/BRONCHIOLAR ADENOMA OR ADENOMA	5/50 (10%)	6/50 (12%)	5/50 (10%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
TOTAL % INCIDENCE	16/150 (11%)	S.D. = 1.15		6/150 (4%)	S.D. = 2.00	
*LUNG: ALVEOLAR/BRONCHIOLAR CARCINOMA	1/50 (2%)	3/50 (6%)	6/50 (12%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
TOTAL % INCIDENCE	10/150 (7%)	S.D. = 5.03		4/150 (3%)	S.D. = 1.15	
*LUNG: ALVEOLAR/BRONCHIOLAR CARCINOMA OR ALVEOLAR/BRONCHIOLAR ADENOMA	6/50 (12%)	9/50 (18%)	11/50 (22%)	3/50 (6%)	4/50 (8%)	3/50 (6%)
TOTAL % INCIDENCE	26/150 (17%)	S.D. = 5.03		10/150 (7%)	S.D. = 1.15	
*LUNG: CARCINOMA	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
TOTAL % INCIDENCE	0/150 (0%)	S.D. = 0.00		0/150 (0%)	S.D. = 0.00	
*LUNG: CARCINOMA, ALVEOLAR/BRONCHIOLAR CARCINOMA OR ADENOSQUAMOUS CARCINOMA	1/50 (2%)	3/50 (6%)	6/50 (12%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
TOTAL % INCIDENCE	10/150 (7%)	S.D. = 5.03		4/150 (3%)	S.D. = 1.15	

*: DENOMINATOR IS NUMBER OF ANIMALS WITH TISSUES EXAMINED MICROSCOPICALLY
#: DENOMINATOR IS NUMBER OF ANIMALS NECROPSIED

Table 4

VERSION: 09/17/90

TOXICOLOGY DATA MANAGEMENT SYSTEM
TUMOR INCIDENCE FOR SELECTED CONTROL ANIMAL GROUPS

CONTRACT/LAB: SRI
SPECIES: MICE
STRAIN: MICE-B6C3F1
LENGTH OF STUDY: CHRONIC

ROUTE: ORAL
VEHICLE: FEED

DATE OF
INPUT FILE: 15-SEP-1990

INCIDENCE DATA FOR VEHICLE CONTROL GROUPS

	MALE			FEMALE		
ALL ORGANS BENIGN TUMORS	12/50 (24%)	18/50 (36%)	18/50 (36%)	15/50 (30%)	13/50 (26%)	11/50 (22%)
TOTAL % INCIDENCE	48/150 (32%)	S.D. = 6.93		39/150 (26%)	S.D. = 4.00	
ALL ORGANS MALIGNANT TUMORS	28/50 (56%)	30/50 (60%)	26/50 (52%)	21/50 (42%)	21/50 (42%)	18/50 (36%)
TOTAL % INCIDENCE	84/150 (56%)	S.D. = 4.00		60/150 (40%)	S.D. = 3.46	
ALL ORGANS MALIGNANT AND BENIGN TUMORS	31/50 (62%)	39/50 (78%)	35/50 (70%)	30/50 (60%)	29/50 (58%)	24/50 (48%)
TOTAL % INCIDENCE	105/150 (70%)	S.D. = 8.00		83/150 (55%)	S.D. = 6.43	
ALL ORGANS: HEMANGIOMA	0/50 (0%)	1/50 (2%)	0/50 (0%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
TOTAL % INCIDENCE	1/150 (1%)	S.D. = 1.15		2/150 (1%)	S.D. = 1.15	
ALL ORGANS: HEMANGIOSARCOMA	3/50 (6%)	1/50 (2%)	3/50 (6%)	2/50 (4%)	2/50 (4%)	0/50 (0%)
TOTAL % INCIDENCE	7/150 (5%)	S.D. = 2.31		4/150 (3%)	S.D. = 2.31	
ALL ORGANS: HEMANGIOSARCOMA OR HEMANGIOMA	3/50 (6%)	2/50 (4%)	3/50 (6%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
TOTAL % INCIDENCE	8/150 (5%)	S.D. = 1.15		5/150 (3%)	S.D. = 3.06	
ALL ORGANS: HISTIOCYTIC SARCOMA	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
TOTAL % INCIDENCE	0/150 (0%)	S.D. = 0.00		0/150 (0%)	S.D. = 0.00	
ALL ORGANS: LEUKEMIA: LYMPHOCYTIC, MONOCYTIC, MONONUCLEAR, OR UNDIFFERENTIATED	1/50 (2%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
TOTAL % INCIDENCE	1/150 (1%)	S.D. = 1.15		0/150 (0%)	S.D. = 0.00	
ALL ORGANS: MALIGNANT LYMPHOMA AND HISTIOCYTIC SARCOMA	5/50 (10%)	5/50 (10%)	5/50 (10%)	12/50 (24%)	16/50 (32%)	13/50 (26%)
TOTAL % INCIDENCE	15/150 (10%)	S.D. = 0.00		41/150 (27%)	S.D. = 4.16	
ALL ORGANS: MALIGNANT LYMPHOMA: HISTIOCYTIC, LYMPHOCYTIC, MIXED, NOS, OR UNDIFFERENTIATED CELL TYPE	5/50 (10%)	5/50 (10%)	5/50 (10%)	12/50 (24%)	16/50 (32%)	13/50 (26%)
TOTAL % INCIDENCE	15/150 (10%)	S.D. = 0.00		41/150 (27%)	S.D. = 4.16	
ALL ORGANS: MESOTHELIOMA BENIGN, MALIGNANT, NOS	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
TOTAL % INCIDENCE	0/150 (0%)	S.D. = 0.00		0/150 (0%)	S.D. = 0.00	

*: DENOMINATOR IS NUMBER OF ANIMALS WITH TISSUES EXAMINED MICROSCOPICALLY
#: DENOMINATOR IS NUMBER OF ANIMALS NECROPSIED

Conclusion

The PRC concluded that, despite the mis-dosing, the new mouse study was acceptable since the incident was reported to the Agency at the point of discovery by the Registrant, and the Agency agreed that the study could be continued.

The Committee discussed the finding of tumors at the low dose (60 ppm) in light of the mis-dosing incident and concluded that they could not be discounted, despite the difficulty in interpreting the dose actually administered to this group of animals. The PRC unanimously concluded that this new information does not affect the existing classification of Parathion as **Group C (possible human carcinogen), without quantification,** which is to say: without the use of a low dose extrapolation model (Q1*) for quantitative risk assessment; instead a reference dose (RfD) approach will be used.

Previously submitted data, and their contribution to the weight of evidence for Parathion, were fully discussed in the memos documenting Peer Review Meetings 1 and 2 (dated Sept. 8, 1986 and July 31, 1989, respectively).