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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

007096

MAR 23 1989

OFFICE OF  
PESTICIDES AND  
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Parathion, Chronic/oncogeneicity study in Rats

TO: Dennis Edwards PM-12  
Registration Division (TS-767)

FROM: *[Signature]* 3/15/89  
Robert P. Zenzian Ph.D.  
Senior Pharmacologist  
RSSR, SACB  
HED (H 7509C)

THROUGH: Albin Kocialski Ph.D. *AKC 3/22/89*  
Head RSSR Section  
  
Reto Engler Ph.D.  
Chief  
SCAB, HED

Compound; Parathion

Tox Chem #637

Registration #01782-3

Registrant; Chem Nova

MRID # 406447-04

Tox Project #8-0809

Action Requested

Review the following study;

Parathion, study for chronic toxicity and cancerogenicity in Wistar rats (administration in diet for twenty-six months). R. Eiben; Histopathology report, Pappritz; Report on ERG examination, Rubin; Report on EM examination, Liebich; Bayer AG, Toxicology Division, Study No. T 1016770, Report No. 16305, Dec 16, 1987, MRID 406447-04 (2 vols)

Conclusions

Doses of 0, 2, 8 & 32 ppm produced mean doses of 0, 0.1, 0.42 & 1.75 mg/kg males and 0.014, 0.53 & 2.47 mg/kg females. Compound-related effects at 32 ppm consisted of cholinergic signs, increased female mortality, and decreased weight gain. Decreased cholinesterase activity, (plasma and RBC LELs 8 ppm NOELs 2 ppm and brain LEL 32 ppm NOEL 8 ppm) was observed. Terminal observations on the eyes indicated decreased ERG

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(LEL 8 ppm, NOEL 2 ppm), gross retinal abnormalities, histopathology indicative of blindness and possible increase in cataracts (LEL 32 ppm, NOEL 8 ppm) in the females. Effects on the eyes of the males at 32 ppm were possible but not clearcut. A statistically significant trend of increased pancreatic tumors, exocrine and endocrine, was observed in the males.

#### Core Classification, Guideline

#### Discussion

The study as reported satisfies the requirements for a chronic and an oncogenic study in the rat. In general one observes the expected dose-related depression of cholinesterase activity with clear cut LELs and NOELs. However, one also sees in this study toxic effect(s) on vision from a functional (ERG), gross observational and histological view point. Depression of ERG, gross retinal abnormalities and histological abnormalities of retina and optic nerve indicate that most, if not all, of the high dose animals are blind as a result of treatment. A possible oncogenic response in the pancreas was also observed.

The special observations on the eye were added to the end of this study following an Agency DCI requiring that Registrants of parathion perform a specific set of tests on the toxic effect of the compound on the visual system. Although add-ons, the tests clearly showed toxic effects in the female and possible in the males. The sex difference is most probably due to the higher actual dose ingested by the female (2.47 mg/kg/day versus 1.75). Parathion has a very steep dose-response curve.

A determination of blindness in rats on a multidose study is not easily made. The rat, a creature of darkness, can function very well in a small, single animal cage. The normal handling and observations of rats on such studies will not detect blindness. Thus, it is probable that others animals, perhaps at all doses, would have been detected as blind with specific functional/observational testing.

A testing problem identified in this study was the lack of correlation between the results of the various optic tests. The animal selected for special histopath were grossly normal by direct ophthalmoscopic examination but histological abnormalities of the retina were severe. Animals with severe histological abnormalities showed ERGs which could not be distinguished from histologically normal controls. The study clearly shows that histopathology is the most sensitive indicator of optic abnormality and that specific preservation procedures are necessary for histological evaluation of the eye.

The possible oncogenic response has been Peer Reviewed. Delays on scheduling the review have resulted in a delay in responding to the review request from RD. A peer review of parathion oncogenicity was held on July 1, 1986. The committee classified parathion as a Class C oncogen with no Q\* required (Hauswirth 1986). On March 8, 1989 a Peer Review was held to consider the new information presented in this study. The committee considered the information and the newly submitted mutagenicity studies (negative). It was concluded that parathion should remain classified as a Class C oncogen with no Q\*. The report of the meeting will be forwarded to you when it is available.

Attachments

DER Parathion chronic/onco study, reviewed by Zendzian with one-liner

Memo Hauswirth to Allen, Peer Review of Parathion, Aug 1, 1986

Memo Zendzian to Quest, Parathion request for Peer Review re Possible Oncogenic Effect, Nov 2, 1988

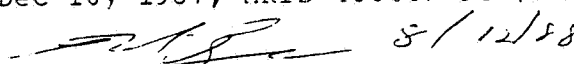
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Data Evaluation Report

Compound Parathion (ethyl parathion)

Citation

Parathion, study for chronic toxicity and cancerogenicity in Wister rats (administration in diet for twenty-six months). R. Eiben; Histopathology report, Pappritz; Report on ERG examination, Rubin; Report on EM examination, Liebich; Bayer AG, Toxicology Division, Study No. T 1016770, Report No. 16305, Dec 16, 1987, MRID 406447-04 (2 vols)

 8/12/88  
Reviewed by Robert F. Zendzian PhD  
Senior Pharmacologist

Core Classification Guideline

Conclusions

Doses of 0, 2, 8 & 32 ppm produced mean doses of 0, 0.1, 0.42 & 1.75 mg/kg males and 0, 0.14, 0.53 & 2.47 mg/kg females. Compound-related effects at 32 ppm consisted of cholinergic signs, increased female mortality, and decreased weight gain. Decreased cholinesterase activity, (plasma and RBC LELs, 8 ppm NOELs 2 ppm and brain LEL 32 ppm NOEL 8 ppm) was observed. Terminal observations on the eyes indicated decreased ERG (LEL 8 ppm, NOEL 2 ppm), gross retinal abnormalities, histopathology indicative of blindness and possible increase in cataracts (LEL 32 ppm, NOEL 8 ppm) in the females. Effects on the eyes of the males at 32 ppm were possible but not clearcut. A statistically significant trend of increased pancreatic tumors, exocrine and endocrine, was observed in the males.

Materials

Parathion,  
batch # 230300004-008  
Bayer AG PF - P/ve  
96.7% pure  
yellowish fluid

SPF-bred Wister rats, five-six weeks old  
Bor: WISW (SPF Cpb) strain  
breeder Winkelmann, Borchon

Experimental Design

Animals were assigned randomly to the following test groups. Test compound was administered in the diet.

-2-

Dose (ppm)	<u>Interim Sacrifice (12 months)</u>				<u>Terminal (24 months)</u>	
	necropsy and histopath		necropsy and brain CHE		necropsy and histopath	
	M	F	M	F	M	F
0	10	10	5	5	50	50
2	10	10	5	5	50	50
8	10	10	5	5	50	50
32	10	10	5	5	50	50

Animals were observed twice daily and examined individually weekly for signs of toxicity. Animals were weighed before the start of the test, weekly to week 13 inclusive and biweekly to week 104. Food consumption was determined weekly.

Blood was collected at the end of months 3, 6, 12, 18 and 24 from 10 animals per sex per dose (20 at 24 months) and the following hematological and clinical chemistry determinations made.

#### Hematology

Differential count	Thrombocyte count
Erythrocyte morphology	Mean hemoglobin
Erythrocyte count	Mean hemoglobin concentration
Hemoglobin concentration	Mean red cell volume
Hematocrit	Coagulation time
Leucocyte count	

#### Clinical chemistry

Alkaline phosphatase	Total Protein
Aspartate aminotransferase	Urea
Creatinine kinase	Inorganic phosphate
Glucose	Calcium
Bilirubin	Potassium
Cholesterol	Sodium
Creatinine	Chloride

Plasma and red cell cholinesterase activity was determined at 3, 6, 12 and 18 months. Brain cholinesterase activity was determined in 5 rats per sex at 12 and 24 months.

Urine was collected at the end of months 6, 12, 18 and 24 from 10 animals per sex per dose (20 at 24 months).

Blood	Total bilirubin
Protein	Urobilirubin
Ketone bodies	Sediment
pH	Specific gravity
Glucose	Volume

Ophthalmological examinations were conducted, by an unidentified staff member, at the start of the study (10 males and 10 females from the control and 32 ppm groups) and on all surviving rats at the end of the study.

At the end of the study, Ophthalmological examinations were conducted on all surviving animals by Dr. Lionel Rubin who also obtained electroretinograms (ERG) from ten males and ten females, having visually normal eyes, in each dose group. A report of this examination was available separately (July 23, 1986) and is also a part of this report.

Electron microscopy was performed, By Dr. H.G. Liebich, on an eye from each of 5 males and 5 females per dose at the end of the study. Animals were selected, randomly from the animals which had ERG examinations. A report of this examination was available separately (Dec 22, 1986) and included as part of this report.

All animals that died on study, were sacrificed at 12 months and were sacrificed at termination were necropsied. The following tissue and organs were collected for histopathological examination. Asterixed organs were weighed.

aorta	mammary glands
eye	spleen*
eyelids	musculature (thigh)
caecum	epididymis
colon	adrenals*
duodenum	nervous ischiadicus
femur	nervous opticus
brain*	kidneys*
urinary bladder	oesophagus
Harder's gland	ovaries
Skin	oviduct
heart*	pancreas
testicles*	prostate
pituitary	rectum
ileum	spinal cord ( 3 x)
jejunum	seminal vesicle
larynx	thyroid/parathyroids
bone marrow	salivary glands
(femur and sternum)	sternum
liver*	thymus
lung*	trachea
lymph nodes	lachrymal glands
(mesenteric and cervical)	uterus
head	vagina
stomach	tongue

### Results

Signs indicative of cholinergic toxicity were observed in both sexes at 32 ppm. Signs were generally more severe in the females consisting of generally poor condition, uncoordinated gait and tremors.

A compound-related increase in mortality was observed in the females at 32 ppm throughout the study (Fig 1 & 2 from the report). At termination mortality was 22, 28, 18 and 36% for 0, 2, 8, and 32 ppm respectively.

A decreased body-weight gain was observed in both males and females at 32 ppm throughout the study. (Figure 3 & 4 from the report).

Mean daily food and compound consumption in the animals carried for two years was as follows (data from table 3a of the report).

Dose (ppm)	Food consumption (grams/kg)		Parathion dose (mg/kg)	
	M	F	M	F
0	53.0	68.9	0.00	0.00
2	52.1	68.1	0.10	0.14
8	52.2	65.8	0.42	0.53
32	54.8	77.2	1.75	2.47

No treatment-related effects were observed in the hematological parameters.

Aspartate aminotransferase (ASAT, GOT) activity was depressed in a dose-related manner in the females at 6, 12 and 18 months but not at termination.

Dose ppm	test time (months)			
	6	12	18	24
0	44.1	59.2	68.0	55.7
2	36.1*	45.1	55.9*	40.9
8	36.3**	40.9*	50.9**	45.2
32	37.6*	37.4*	44.6**	50.2

\* p < 0.05  
\*\* p < 0.01

No treatment-related effects were observed in the urine.

**Parathion**

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Treatment-related depression of activity was observed in plasma, erythrocyte and brain cholinesterase. Data are summarized in table 16 from the report. Plasma cholinesterase appeared to be most sensitive. LELs and NOELs for plasma and erythrocyte effects were 8 and 2 ppm respectively. Depression of brain cholinesterase activity was observed at 8 and 32 ppm but is only considered significant at 32 ppm (LEL 32 ppm and NOEL 8 ppm).

Results of the terminal ophthalmological examination are summarized in the table from the report (pages 606 and 607). The total number of eyes showing lens 'turbid' per total number of eyes examined are presented below. Indications of a compound-related effect are seen in the females. No other possible effect(s) was (were) observed.

Dose ppm	Males		Females	
	# ob/#t	%	# ob/#t	%
control	14/88	16	5/80	6
2	13/92	14	4/80	5
8	13/90	14	8/82	10
32	8/92	9	16/62	25

Results of the ophthalmological examinations and electroretinograms performed by Rubin and the electronmicroscopy of the eye performed by Liebich were presented separately in earlier reports and reviews of those reports are attached.

Treatment-related abnormalities were not observed at necropsy. Organ weights, both absolute and relative, were not effected by treatment other than relative to the decrease in total body weight noted at 32 ppm.

In general histopathology did not show any pattern of nonneoplastic lesions which could be attributed to treatment. However, because of the neoplastic observations in the pancreas, nonneoplastic lesions in that organ are summarized below.

Except in the pancreas, neoplastic lesions were distributed in a random pattern which did not appear treatment-related. Adenomas were observed in the exocrine and endocrine (islet cells) tissue of the male pancreas. As seen below, the distribution of these relatively rare tumors appears to be dose related.

**Parathion**

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Incidence of nonneoplastic and neoplastic lesions in the pancreas at termination (data from table 24 and 27 of the report).

Dose (ppm) number animals	Males				Females			
	0 50	2 50	8 49	32 50	0 50	2 50	8 50	32 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 (pages 656, 657 & 659 from the report). 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  $P = 0.0022$ )." The equally rare endocrine (islet cell) adenomas were not discussed. However, considering that their numbers and dose distribution was identical with that of the endocrine tumors, one can conclude that they also showed a statistically significant trend.

Historical control data, for pancreatic tumors, were included in the report (pages 103 and 104). One study (number 27) 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%).

**Parathion**

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Discussion

The study as reported satisfies the requirements for a chronic and an oncogenic study in the rat. In general one observes the expected dose-related depression of cholinesterase activity with clear cut LELs and NOELs. However, one also sees in this study toxic effect(s) on vision from a functional (ERG), gross observational and histological view point. Depression of ERG, gross retinal abnormalities and histological abnormalities of retina and optic nerve indicate that most, if not all, of the high dose animals are blind as a result of treatment. A possible oncogenic response in the pancreas was also observed.

The special observations on the eye were added to the end of this study following an Agency DCI requiring that Registrants of parathion perform a specific set of tests on the toxic effect of the compound on the visual system. Although add-ons, the tests clearly showed toxic effects in the female and possible in the males. The sex difference is most probably due to the higher actual dose ingested by the female (2.47 mg/kg/day versus 1.75). Parathion has a very steep dose-response curve.

A determination of blindness in rats on a multidose study is not easily made. The rat, a creature of darkness, can function very well in a small, single animal cage. The normal handling and observations of rats on such studies will not detect blindness. Thus, it is probable that others animals, perhaps at all doses, would have been detected as blind with specific functional/observational testing.

A testing problem identified in this study was the lack of correlation between the results of the various optic tests. The animal selected for special histopath were grossly normal by direct ophthalmoscopic examination but histological abnormalities of the retina were severe. Animals with severe histological abnormalities showed ERGs which could not be distinguished from histologically normal controls. The study clearly shows that histopathology is the most sensitive indicator of optic abnormality and that specific preservation procedures are necessary for histological evaluation of the eye.

The possible oncogenic response will be presented for Peer Review.

## Data Evaluation Report

Compound ParathionCitationElectroretinographic evaluation, G.A. Edwards, Monsanto,  
R.D. No. 693, July 23, 1986, Accession # 263986Reviewed by *RPZ 5/86*  
Robert P. Zendzian PhD  
PharmacologistCore classification AcceptableConclusion

Statistically significant depression of the amplitude of the b-wave of the ERG of female rats dosed for two years at 8 and 32 ppm was observed. The b-wave of females dosed at 2 ppm and males dosed at 2, 8 and 32 ppm also appeared to be depressed but the large individual variation in b-wave amplitude made evaluation impossible. Focal posterior subcapsular cataract and choridal pallor also appeared to be increased in a dose-related manner but the conditions of the study make it impossible to be certain of these effects.

Background

A chronic feeding study of ethyl parathion in rats was conducted by Bayer (T1016770). Rats were dosed at 0, 2, 8 or 32 ppm parathion in the diet for 24 months. The detailed materials, methods and results of this study are not available. Shortly before termination of this study, electroretinographic (ERG) evaluations and direct ophthalmoscopic examinations were performed on animals from the study. The evaluations were performed by Lionel F. Rubin V.M.D. whose report is included in the document being evaluated.

Materials

Rats that had been dosed with ethylparathion for 24-months at doses of 0, 2, 8 or 32 ppm in the diet.

Methods

Examinations were performed on the following rats:

Dose ppm	# Males	# Females
0	12	10
2	9	11
8	11	10
32	10	10

Rats were anesthetized with pentobarbital sodium and the pupils dilated with tropicamide. "Recording needle electrodes were placed subcutaneously lateral to the lateral canthus anterior to the ear and subconjunctivally into the inferior conjunctival fornix. The subconjunctival electrode was placed after instillation of tetracaine solution. A needle electrode for grounding was placed subcutaneously at the occiput. The recording was made without reference to maintaining the same polarity. Some recordings appear to be cornea-negative, while others were cornea-positive, this occurring because of the random placement of the recording electrode at either conjunctiva or skin. Prior to recording the electroretinogram (ERG), the rats were dark adapted for at least 8 hours.

The ERG was recorded in a room illuminated only by dim red light. The ERG was elicited using a single stroboscopic blue-white flash provided by a Grass PS22 photostimulator set at intensity 1 approximately 30 cm from the eye. Recordings were taken from the right eye in all animals. A recording was taken from the left eye as well in rat 197F, a 2 ppm level female, because of the presence of a very low amplitude response from the right eye."

"The ERG was evaluated by qualitative inspection and by measurement of the b-wave parameters. The implicit time of the b-wave was measured from stimulus onset; the b-wave amplitude was measured from the baseline. Because of the presence of a large stimulus artifact distorting the a-wave, the usual measurement of b-wave amplitude from maximum deflection of the a-wave to b-wave peak could not be done. The a-wave appeared to be present in all recordings."

Results

The following table is from page 2 of Dr. Rubin's report.

Animal #	<u>b-wave latency</u> msec	<u>b-wave amplitude</u> uV
Control		
males		
3M	100	60
9M	100	110
12M	100	140
20M	60	100
21M	60	160
23M	90	50
24M	60	60
29M	80	150
37M#2	70	140
40M	80	30
41M	100	120
mean n=12	81	mean n=12 98

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Animal #	<u>b-wave latency</u> msec	<u>b-wave amplitude</u> uV
<u>Control</u>		
<u>females</u>		
51F	70	120
55F	100	100
56F	90	40
59F	100	140
61F	90	30
75F	90	180
76F	80	150
79F	80	160
93F	80	160
100F	60	10
mean n=10	84	mean n=10 101
<u>2 ppm</u>		
<u>males</u>		
102M	70	40
109M	90	70
112M	90	80
114M	80	150
119M	90	50
130M#2	90	50
138M	70	160
142M	80	100
148M	60	20
148M#2	70	10
(ERG from rat 115 missing)		
mean n=9	80	mean n=9 79
<u>females</u>		
152F	90	60
161F	60	20
162F	80	50
168F	80	100
173F	80	120
178F	90	60
183F	90	100
188F	80	160
191F#2	80	70
194F	80	50
197F	80	5
197F(left eye)	70	20*
mean n=11	81	mean n=11 72
*not included in calculations		



Animal #    b-wave latency    b-wave amplitude  
                                  msec                                   uV

8 ppm

males

205M	70	25
208M	70	100
212M	60	30
222M	60	140
223M	70	80
225M	80	55
231M	90	160
236M#2	40	20
237M	80	45
243M	80	80
248M	60	25

mean n=11    70    mean n=11    71

8 ppm

females

259F	80	10
266F	70	160
277F	60	20
280F	90	30
281F	80	60
288F	60	30
293F	80	90
294F	80	90
294F#2	80	70
295F	80	50
297F	80	10
297F#2	80	15

mean n=10    74    mean n=10    48

32 ppm

males

302M	70	170
307M	70	40
311M	90	70
334M	90	130
336M	70	50
337M	90	60
342M	80	80
343M	80	50
349M	80	85

mean n=10    80    mean n=10    77

Animal #	<u>b-wave latency</u> msec	<u>b-wave amplitude</u> uV	
<u>32 ppm</u>			
<u>females</u>			
395F	80	60	
360F	70	70	
362F	70	10	
365F	70	20	
366F	90	70	
371F	80	40	
374F#2	70	10	
375F	70	55	
379F	70	50	
400F	70	70	
mean n=10	74	mean n=10	45

The major abnormalities seen in the ophthalmoscopic examinations were focal posterior subcapsular cataract and choroidal pallor. The incidence of these observations, as total number of eyes showing the effect per total number of eyes observed, is given below.

Focal Posterior Subcapsular Cataract

Dose ppm	Males		Females	
	#ob/#t	%	#ob/#t	%
control	5/24	21	0/20	0
2	3/20	15	3/22	14
8	5/22	26	3/20	15
32	9/20	45	4/20	20

Choroidal pallor

Dose ppm	Males		Females	
	#ob/#t	%	#ob/#t	%
control	2/24	8	8/20	40
2	4/20	20	9/22	41
8	6/22	27	6/20	20
32	10/20	50	12/20	60

Under his detailed presentation of observations of choroidal pallor Dr. Rubin made special notations on the 32ppm females as follows;

"32 ppm female: 360B\*\*\*\* 371B\* 374B 375B\*\* 379B\*\*\*\*  
400B\*\*

B both eyes  
\*retinal vessels narrow  
\*\*severe pallor  
\*\*\* slight pallor  
\*\*\*\* vessels in choroid narrowed"

Conclusions

Dr. Rubin concluded as follows;

"The presence of choroidal pallor (in 2 above) may indicate a closure of the small vessels in the choroid and may infer that these vessels are no longer functional because of an underlying retinal disorder. The presence of relatively normal retinal blood vessels should indicate that the inner retinal layers are still functional, thus implying that the outer layers of the retina are affected. It is also possible that the pallor is secondary to a thickening of the choroidal vascular walls. Were there an outer retinal degeneration, the ERG should be extinguished. There seems to be no correlation between choroidal pallor and low ERG amplitudes in this study, and there does not appear to be a statistically significant dose related relationship to the presence of choroidal pallor.

In summary, there appears to be no ophthalmoscopically visible effect associated with the administration of the test compound in the animals examined. Whether there is an electroretinographic effect is equivocal."

Dr. G.A. Edwards, of Monsanto, provided his own summary of Dr. Rubin's report and concluded as follows;

"Dr. Rubin concluded that there were no visible treatment-related ophthalmological effects in rats as a result of chronic administration of diets containing up to 32 ppm ethyl parathion and that the electroretinographic effects were equivocal. However, it is my opinion that there was a clear, dose-related decrease in b-wave amplitude in mid (8 ppm) and high-dose (32 ppm) females. Whether or not these decreased amplitudes represent an adverse functional defect is unclear. Further evaluation of the possible chronic ocular effects of ethyl parathion must await the results of the light and electron microscopic pathological examinations."

Dr. Edwards provided a statistical evaluation of the b-wave effects in his table 1 which is presented below.

Table 1

Electroretinographic B-Wave Amplitudes of Rats Fed Diets Containing Ethyl Parathion for Two Years.

Dietary Concentration (ppm)	B-Wave Amplitude <sup>a</sup> (uV)	
		control <sup>b</sup>
	<u>Males</u>	
0	98 ± 46	100
2	79 ± 49	80
8	69 ± 48	79
32	77 ± 43	79
	<u>Females</u>	
0	101 ± 59	100
2	72 ± 45	71
8	48 ± 45*	43
32	46 ± 24*	46

(a) Mean ± SD. Where more than 1 ERG was conducted on a given animal, the average of the values reported was used for that animal.

(b) Values calculated by this reviewer

\*  $p < 0.05$  using Dunnett's test

### Discussion

There are several problems associated with the evaluation and interpretation of this study. First, we have no information on the feeding study in which the rats were included other than the statement of dose and duration. The report of the study will not be available for at least a year. At this time we have no information on what toxic effects were observed in this study. In 1984 we received a report of a two-year rat feeding study. The doses used in that study were 0, 1, 5, and 50 ppm. A spectrum of toxic effects were reported at 50 ppm which included retinal degeneration, observed directly and by histopathology, and cholinesterase inhibition. At the next lower dose, 5 ppm, only cholinesterase inhibition in a single sex was reported. Thus, we have no direct comparison by dose to make an estimation of the toxicity of the maximum dose tested in this study, 32 ppm.

The most impressive item in this study is the wide range of individual variation recorded in the ERGs. Considering b-wave amplitude in uV, the means and SD are  $98 \pm 46$  and  $101 \pm 59$  for the control males and females respectively. Also the polarity of the recording was either positive or negative because of the "random placement of the recording electrode". We cannot say whether the variation reported is intrinsic or

is due to the conditions under which each recording was taken or a combination of both. No doubt the individual variation, whatever its source, will act to obscure any compound-related effects.

Despite these problems I agree with Dr. Edwards that there is a compound-related depression of the amplitude of the b-wave in the females at 8 and 32 ppm. In the previously submitted study the females were the most sensitive sex in that they showed effects on the eyes and the males did not. Considering the mean b-wave amplitude as percent of control there could be a compound-related depression in the females at 2 ppm and in the males at all doses. However, the individual variation in each group makes it impossible to verify this possibility.

The ophthalmoscopic observations are of necessity somewhat subjective and hard to quantitate but there does appear to be a compound-related increase in the percent of eyes examined showing focal posterior subcapsular cataract and choroidal pallor. Organophosphate cholinesterase inhibitors, applied topically for glaucoma, have been shown to produce cataract in human patients. Thus the observation of cataract in this study is not a new observation for this class of compounds and could be compound-related. Dr. Rubin considered that the choroidal pallor may be due to decreased circulation in the choroidal layer of the retina. A small degree of cholinesterase inhibition in the end arteriols to this area could result in increased tonal constriction of the vessels and a decreased circulation to the area. This would agree with his observation of 'retinal vessels narrow' in one female at 32 ppm and 'vessels in choroid narrowed' in two females at 32 ppm.

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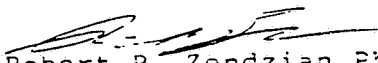
Data Evaluation Report

006009

Compound Parathion

Citation

Report of results of findings of electron microscopy of retina, nervus opticus, mm. recti oculi med. and lat. and m. ciliaris., H.G. Liebich, B. Vollmerhaus & F. Sinowatz, Institut für Tieranatomie der Universität München, Bayer Project T 1016770 Parathion (Chronic toxicology long-term study in rats) Dec 22, 1986; MRID 401887-01; In translation from the German.

Reviewed by  = 1/187  
Robert P. Zendzian PhD  
Pharmacologist

Core classification Acceptable

Conclusion

Electron microscopy of tissue from the eyes of treated rats showed compound-related toxicity in the retina and the optic nerve of males and females at 32 ppm (HDT) [NOEL 8 ppm]. Extensive age-related abnormalities in the control rats were impossible to distinguish from those in the 2 and 8 ppm groups.

Materials

Information on the compound tested and rat strain utilized are to be contained in the Bayer final report of study [Bayer Project T 1016770 Parathion (Chronic toxicology long-term study in the rat)].

Experimental Design

Rats for this study were selected from the survivors of a 26 month feeding study in which they were fed 0 (control, 2, 8 or 32 ppm parathion in the diet.

Five male and five female rats were selected from each treatment group. "The animals used for the examination by electro microscopy were randomly selected from the clinically healthy and ophthalmologically normal rats intended for the ERG examination."

Animals were perfused in situ in order to fix the eyes and associated tissue before dissection. "For preparation the right eye together with the Harder's gland, the ocular muscles, fatty tissue and parts of the nervus opticus were removed--" The following tissues were prepared for light and EM examination.

A = m. ciliaris  
B = sector of pars optica retinae  
C = sector of pars optica retinae  
D = sector of pars optica retinae  
E = nervus opticus  
F = m. rectus oculi med.  
G = m. rectus oculi lat.

### Results

Compound-related toxic effects were observed in the retina and the optic nerves of the high dose males and females. Copies of the Microscopic Finding Tables; Semithin Sections - Retinaatrophy and Electron microscopic Finding Tables: Retina and Pigmentepithelium from the report are attached. These summary tables present the toxic effects on the retina of dosing with parathion. Copies of the Electronmicroscopic Finding Tables: Nervous opticus from the report are attached. These summary tables present the toxic effects on the optic nerve of dosing with parathion.

In relation to toxic effects the report states;

1. "The female rats in the test group administered a high dose of parathion (five animals - 32 ppm), on the strength of all the light and electron microscopic individual data, consistently exhibited the most marked retina alterations within the entire test series. Complete impairment of the functional efficiency of the retina may be assumed. The nervus opticus is also affected by these structural deformations to almost the same severe extent. Here too electron microscopy detected structural alterations in the axon and stratification of the myelin sheaths of substantial to severe degree. Massive impairment of conduction of the nervous stimuli may be assumed in four animals of five by morphological criteria. The external ocular muscles appear unchanged in their cytoplasmic structure from an electron microscopic viewpoint."

2. "Male rats after administration of parathion at the highest dose (five rats - 32 ppm) exhibited consistent marked to severe retina atropy by light histology. Electron microscopy in addition detected more extensive degeneration in the area of the first and second neurons and the pigment epithelia. It may be seen as certain that retinal sensual perception was considerably impaired.

The alterations in the nervous opticus were slightly less extent. Moderate to severe myelin degeneration involves functional alteration within these nervous pathways.

The mm. recti oculi showed an unchanged ultra-structure by

electron microscopy. The myofibrils of the m. ciliaris were mostly moderately to slightly reduced by electron microscopy, only in one case was degeneration marked. If the test group is considered overall, moderate impairment of lens motility appears to be present."

"The structural changes in the eye detected by electron microscopy in the cases of the low and medium dose groups (2 ppm and 8 ppm) may not be attributed to the treatment; the reason is that the rats in these groups had reached an age, by the end of the chronic long-term study, which made it difficult to assess to what extent the described retina, muscle and nerve changes might be regarded as a result of the animals advanced ages, or as a result of treatment with parathion. The latter interpretation is supported by the sometimes considerable retina degeneration occurring in the control groups of both sexes."



**Parathion**

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Pages 31 through 54 are not included in this copy.

The material not included contains the following type of information:

- \_\_\_\_\_ Identity of product inert ingredients.
- \_\_\_\_\_ Identity of product inert impurities.
- \_\_\_\_\_ Description of the product manufacturing process.
- \_\_\_\_\_ Description of product quality control procedures.
- \_\_\_\_\_ Identity of the source of product ingredients.
- \_\_\_\_\_ Sales or other commercial/financial information.
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- \_\_\_\_\_ Information about a pending registration action
- X FIFRA registration data.
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- \_\_\_\_\_ The document is not responsive to the request.

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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: Peer Review of Parathion

From: Judith W. Hauswirth, Ph.D. *Judith W. Hauswirth 8/1/86*  
Mission Support Staff  
Toxicology Branch/HED (TS-769C)

To: Ed Allen  
Product Manager #12  
Registration Division (TS-767C)

The Toxicology Branch Peer Review Committee met on July 1, 1986 to discuss and evaluate the data base on Parathion (ethyl parathion). Particular attention was focused on the oncogenic potential of the chemical toward Osborne-Mendel rats.

A. Individuals in Attendance:

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

Theodore Farber

*Theodore M. Farber*

William Burnam

*Wm J. Burnam*

Anne Barton

*Anne Barton*

Reto Engler

*Reto Engler*

Louis Kasza

*Louis Kasza*

Bertram Litt

*Bertram Litt*

Esther Rinde

*Esther Rinde*

Judith Hauswirth

*Judith W. Hauswirth*

Robert Beliles

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

Robert Zendzian

*Robert Zendzian*

George Ghali

*G. Ghali*

3. Peer Review Committee Members in Absentia: (Committee members who were not able to attend the discussion; signature indicate concurrence with the overall conclusions of the Committee).

Stephen Johnson

*Stephen Johnson*

John A. Quest

*John A. Quest*

Richard Hill

*Richard Hill*

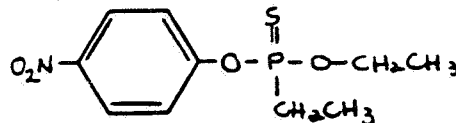
B. Material Reviewed:

The material available for review consisted of the toxicology chapter of the registration standard for parathion and DER's of the NCI and Bio/dynamics chronic rat studies and of the NCI mouse oncogenicity study and a memorandum of 4/24/86 by Robert Zerdzian on the rereading of thyroid slides for the Bio/dynamics chronic rat study.

C. Overview of Toxicology Issues:

Parathion is an organophosphorus pesticide which is used on a wide variety of fruit and nut trees, berries, vegetables, field crops and ornamental plants. Several toxicological issues, in addition to oncogenicity, are linked to parathion. These include its extreme acute toxicity typical of cholinergic poisoning and retinal atrophy and sciatic nerve degeneration observed in rats after chronic exposure.

Structure:



Parathion  
(O,O-diethyl O-4-nitrophenyl phosphorathioate)

D. Evaluation of the Evidence:

1. NCI Mouse Oncogenicity Study of Parathion

a. Discussion of the Study

B6C3F<sub>1</sub> mice were exposed to Parathion (99.5% purity) in the diet at levels of 80 and 160 ppm. Male mice were exposed for 71 and 62 weeks to the low and high dose diets, respectively; female mice were exposed for 80 weeks. Mice were then placed on control diets until termination (90 weeks). Fifty mice of each sex were assigned to each dose level; however, only 10 matched controls/sex were included since the NCI used "pooled" controls for statistical comparison purposes.

Abdominal distention, tremors and alopecia were observed in all treated groups, males and females. Males also exhibited rough hair coat, diarrhea and hyperexcitability. Body weight gain was decreased in a dose-related manner in male but not female mice and returned to normal after mice were taken off the test diet. Mortality could have been affected in the high dose male mice but because of the limited number of matched controls, this was difficult to determine.

b. Study Evaluation and MTD Consideration:

As evidenced by the dose-related decreased body weight gain, the MTD was reached in male mice; however, available evidence indicates that it was probably not reached in female mice.

This study is flawed in that 1) only two doses were used; 2) the concurrent control contained only 10 mice per sex; 3) some tissues were not examined microscopically; 4) some male mice were dosed only for 62 weeks instead of the usual 80 weeks; and 5) concerns have been raised in audits of the test facility (Gulf South Research Institute).

2. NCI Rat Oncogenicity Study of Parathion

a. Discussion of Study

Osborne-Mendel rats were exposed to Parathion (99.5 % purity) in the diet at time-weighted average dose levels of 32 and 63 ppm for male rats and 23 and 45 ppm for female rats. Fifty rats/sex were used for the dosed groups but only 10 rats/sex were used in the matched control group.

Due to excessive toxicity seen in male rats at the original dosage levels of 40 and 80 ppm these dosages were changed to 30 and 60 ppm after week 13 of the study. The original dosages (20 and 40 ppm) for females were also increased at this time to 30 and 60 ppm; however, this level was too high and the dosages were returned to 20 and 40 ppm at week 46.

A depression of body weight gain remained at approximately 10% for male rats while they were on test diets despite lowering the dose levels at week 13 of the study. Raising the dosage levels for female rats resulted in a depression of body weight gain of 10-15%. Weight gain returned to control levels once both male and female rats were removed from the test diets.

There was no difference in survival between the control and dosed groups. Treatment related clinical signs observed in both male and female rats were tremors, hyperexcitability and hyperactivity.

The incidence of pertinent neoplastic lesions seen in this study is summarized in the following table.

Neoplastic Lesions Seen in Rats Fed Parathion

	Pooled Controls	Matched Controls	Low Dose	High Dose
<u>Males</u>				
<u>Origin of Neoplasia</u>				
<u>Adrenal</u>				
Cortical adenoma	2/80(2.50) <sup>1</sup>	0/9(0)	5/49(10.20)	9/46(19.56)
Cortical carcinoma	1/80(1.25)	0/9(0)	2/49(4.08)	2/46(4.35)
Cortical adenoma + carcinoma	3/80(3.75)	0/9(0)	7/49(14.28)	11/46(23.91)
Pheochromocytoma	-	0/9(0)	2/49(4.08)	2/46(4.35)
<u>Thyroid</u>				
Follicular-cell adenoma	5/76(6.57)	3/10(30.0)	2/46(4.35)	8/43(18.60)
C-cell carcinoma	0/76(0)	0/10(0)	1/46(2.17)	1/43(2.33)
<u>Pancreatic Islets</u>				
Islet-cell carcinoma	0/79(0)	0/9(0)	1/49(2.04)	3/46(6.52)
<u>Pituitary</u>				
Adenoma	21/72(29.17)	4/9(44.44)	10/42(23.81)	13/43(30.23)
<u>Adrenal</u>				
Cortical adenoma	4/78(5.13)	1/10(10.00)	4/47(8.51)	11/42(26.19)
Cortical carcinoma	0/78(0)	0/10(0)	2/47(4.25)	2/42(4.76)
Cortical adenoma + carcinoma	4/78(5.13)	1/10(10.00)	6/47(12.76)	13/42(30.95)
Pheochromocytoma	-	1/10(10.00)	2/47(4.25)	2/42(4.76)
<u>Thyroid</u>				
Follicular-cell adenoma	3/80(3.75)	1/10(10.00)	4/45(8.89)	1/43(2.32)
C-cell carcinoma	7/80(8.75)	2/10(20.00)	2/45(4.44)	3/43(6.98)
<u>Mammary Gland</u>				
Fibroadenoma	9/85(10.59)	2/10(20.00)	16/50(32.00)	8/50(16.00)

<sup>1</sup> The number in parenthesis is the percent incidence.

Statistical significance was reached for the following tumor types:

For Males:

1. A significant linear trend ( $p < 0.001$ ) for adrenal cortical adenomas and adrenal cortical adenomas plus carcinomas when comparing dosed groups with pooled controls;
2. A significant difference ( $p < 0.05$ ) for adrenal cortical adenomas and pancreatic islet-cell carcinomas in the high dose groups, adrenal cortical adenomas plus carcinomas for the low dose group and thyroid follicular-cell adenomas in the high and mid dose group compared to the pooled controls;
3. A significant linear trend ( $p < 0.05$ ) for combined adrenal cortical adenomas and carcinomas and thyroid follicular-cell adenomas when comparing dose groups with matched controls;
4. A significant difference ( $p < 0.001$ ) between the high dose group and pooled controls for combined adrenal cortical adenomas and carcinomas; and
5. A significant linear trend ( $p < 0.05$ ) for thyroid follicular-cell adenomas and pancreatic cell carcinomas when comparing dosed groups with pooled controls.

For Females:

1. A significant linear trend ( $p < 0.05$ ) for adrenal cortical adenomas and combined adrenal adenomas and carcinomas when comparing dosed groups with pooled and matched controls;
2. A significant difference ( $p < 0.001$ ) for adrenal cortical adenomas and combined adrenal cortical adenomas and carcinomas between the high dose group and pooled controls; and
3. A significant difference ( $p < 0.05$ ) for mammary gland fibroadenomas between the low dose group and the pooled controls.

The NTP report concludes, "In the male and female Osborne-Mendel rats receiving parathion in their diet, there was a higher incidence of cortical tumors of the adrenal in pooled or historical controls, suggesting that parathion is carcinogenic to this strain of rat".

Historical control data on this strain of rat, derived from the NCI's Carcinogenesis Testing Program was available to the Committee (Goodman *et al.* Toxicology and Applied Pharmacology 55, 433-447, 1980).

Neoplasms in Control Osborne-Mendel Rats

Site	Tumor Type	Number of Rats (%)	
		Of 975 Males	Of 970 Females
Adrenal gland	cortical adenoma	17 (1.7)	33 (3.4)
	cortical carcinoma	8 (0.8)	3 (0.3)
Thyroid gland	follicular-cell adenoma	42 (4.3)	18 (1.9)
	follicular-cell carcinoma	27 (2.8)	15 (1.5)
Pancreatic islet	islet-cell adenoma	1 (0.1)	0
Mammary gland	fibroadenoma	13 (1.3)	213 (22.0)

10 Study Evaluation and MTD Consideration:

The MTD was reached in this study in both male and female rats as evidenced by a 10% or greater depression in body weight gain and by physical signs of cholinergic-related toxicity.

This study, like the mouse study, was flawed due to 1) only two dose groups were used; 2) only 10 rats/sex were used in the control group; 3) the test material was fed to rats for only 80 weeks of the 112 week study and 4) lab audit of the study indicated non-adherence to GLP's by the conducting laboratory (Gulf South Research Institute).

3. Oncogenicity Study of Parathion in Sprague-Dawley CD Rats Conducted by Bio/dynamics:

a. Study Discussion

Sixty male and sixty female Sprague-Dawley rats were maintained containing 0, 0.5, 5.0 and 50.0 ppm Parathion (95.11% purity) for 110 and 120 weeks, respectively.

In the males excessive mortality occurred in the 5 ppm group between months seven and 23 but total mortality was comparable in all groups at termination. Weight gain was depressed in both sexes in the 50 ppm dose group. The mean body weights were approximately 16 and 18 percent lower than controls in high dose males and females, respectively at termination. Food consumption was significantly increased in the high dose animals.

Tremors were noted in the high dose male and female rats, frequently at the beginning of the study and sporadically thereafter. Starting at week 21, several high-dose females exhibited an abnormal gait in the hind limbs.

In addition the following toxicity was seen 1) depression in all RBC parameters (hemoglobin and hematocrit) measured in the high dose group, males and females; 2) depression of brain cholinesterase activity in males and females of the high dose group and plasma cholinesterase activity in both males and females of the mid and high dose groups in the high dose group; 3) an increase in retinal atrophy in the high dose female rats; 4) increased loss and/or degeneration of myelinated nerve fibers in the sciatic nerve and its branches for which a clear-cut NOEL could not be determined; and 5) significantly increased brain to body weight ratio in male and female rats.

The incidence of pertinent neoplastic and non-neoplastic lesions found in this study can be found in the following table.

Incidence of Pertinent Neoplastic and Non-neoplastic Lesion  
in Sprague-Dawley Rats fed Parathion in the Diet

Organ/Lesion	Dose Level (ppm)			
	0	0.5	5.0	50.0
<u>Males</u>				
<u>Adrenal</u>				
Cortical adenoma	25/60(41.67) <sup>1</sup>	30/59(50.85)	23/58(39.65)	27/59(45.76)
Cortical carcinoma	3/60(5.00)	3/59(5.08)	3/58(5.17)	0/59(0)
<u>Thyroid</u>				
Follicular adenoma	1/59(1.69)	1/58(1.72)	2/58(3.45)	5/58(8.62)
Follicular papillary carcinomas	0/59(0)	0/58(0)	0/58(0)	0/58(0)
Hypertrophy/hyperplasia	1/59(1.69)	3/58(5.17)	3/58(5.17)	0/59(0)
<u>Brain</u>				
Glioma	0/55(0)	3/55(5.45)	1/55(1.82)	0/55(0)
<u>Females</u>				
<u>Adrenal</u>				
Cortical adenoma	41/60(68.33)	35/59(59.32)	36/59(61.01)	24/58(41.38)
Cortical carcinomas	7/60(11.67)	4/59(6.78)	4/59(6.78)	3/58(5.17)
<u>Thyroid</u>				
Follicular adenoma	1/59(1.69)	0/57(0)	0/57(0)	0/56(0)
Follicular papillary carcinomas	0/59(0)	0/57(0)	2/57(3.51)	0/56(0)
Hypertrophy/hyperplasia	0/59(0)	0/57(0)	0/57(0)	0/58(0)
<u>Brain</u>				
Glioma	0/55(0)	1/54(1.85)	1/53(1.89)	2/55(3.64)

<sup>1</sup> The number in parentheses represents the percentage incidence.

There was an increased incidence of thyroid follicular adenomas in the high dose male rats (1.69% in the control versus 8.62% in the high dose



group). The low and mid dose group male rats had a slightly higher incidence of thyroid hypertrophy/hyperplasia when compared to the control group. In addition gliomas (brain), which are relatively rare tumors, were seen at a low incidence in the low and mid dose male rats and all dosage groups of female rats.

The thyroid slides from this study were reread by another pathologist. The results are found in the following table.

Thyroid Tumors/Lesions in  
the Parathion Study in Male Rats

Tumor/Lesion	Dose (ppm)			
	0	0.5	5.0	50.0
Follicular cell adenoma	0/60 (0) <sup>1</sup>	1/60(1.60)	1/59(1.70)	4/59(6.80)
Follicular cell carcinomas	0/60(0)	0/60(0)	0/59(0)	0/59(0)
Cystic follicular hyperplasia	1/60(1.60)	2/60(3.33)	2/59(3.40)	1/59(1.70)
Diffuse or focal follicular hyperplasia	6/60(10.00)	2/60(3.33)	4/59(6.80)	2/59(3.40)

<sup>1</sup> The number in parentheses indicates the percentage incidence.

The Registrant provided a table of historical control data on the strain of rats used from Bio/dynamics. Data was provided on 14 studies having a total of 1163 male rats "sacrificed post 12 month" and examined, which showed a total of 45 polymorphofollicular/follicular adenoma/papillary adenoma/adenoma". The incidence ranged from 0-8.0% with a mean of 3.9%.

b. Study Evaluation and MTD Consideration

This was an adequately performed oncogenicity study. As evidenced by a 16% and 18% body weight depression in male and female rats, respectively, signs of cholinergic toxicity, depressed hematocrit and hemoglobin values, increased incidence of retinal atrophy in female rats, increased brain to body weight ratio and increase loss and/or degeneration of myelinated nerve fibers in the sciatic nerve, the MTD was slightly exceeded at the high dose in this study.

E. Additional Toxicity Data:

1. Reproductive and Developmental Toxicity:

Parathion was not teratogenic to rats up to 1.5 mg/kg nor to rabbits

up to 16.0 mg/kg. Fetotoxicity was seen in the rabbit at 4.0 and 16.0 mg/kg as shown by an increased number of resorption sites, accompanied by a decrease in the number of live fetuses and percent implantation. Parathion was not fetotoxic to the rat at 1.5 mg/kg. A reliable study for the assessment of the reproductive effects of Parathion was not available for review.

2. Mutagenicity:

Only one acceptable assay was available for consideration, an unscheduled DNA synthesis assay in human WI-38 cells. This assay was positive for induction of repair at dose levels of  $10^{-5}M$  and  $10^{-6}M$  Parathion. A dominant lethal assay in mice, the Ames Salmonella assay, a reverse mutation assay in E. coli, mitotic recombination in yeast and a DNA repair test in E. coli and B. subtilis were all negative but the assays as performed were considered inadequate.

3. Metabolism:

Parathion is rapidly metabolized in the liver to its oxygen analog, paraoxon. Paraoxon is known to be about ten times more acutely toxic than Parathion, itself, and a few orders of magnitude more potent as a cholinesterase inhibitor.

p-Nitrophenol could be produced from the hydrolytic cleavage of the ester bond and subsequently p-aminophenol from the reduction of the nitro group.

4. Structure Activity Information:

Limited structure activity information was made available. It was postulated that p-nitrophenol could be a metabolite of Parathion. Chemicals of this type have been frequently mentioned in the open literature associated with mutagenic and/or oncogenic activity.

F. Weight of Evidence Consideration:

The Committee considered the following facts regarding the toxicology data on Parathion to be important in a weight-of-the-evidence determination of oncogenic potential.

1. Parathion was not oncogenic in a study (NCI) using B6C3F<sub>1</sub> mice; however, this study was also flawed for the reasons listed elsewhere in this report (Section E.1.).

2. In a study conducted for the NCI, Parathion induced a statistically significant increase in adrenal cortical tumors (adenomas plus carcinomas) in the low and high dose male, Osborne-Mendel rats and in the high dose females when compared to the pooled controls. A statistically significant trend was also found in male rats for thyroid follicular cell adenomas and pancreatic cell carcinomas when comparing dosed groups with pooled controls. This study was flawed for the reasons listed elsewhere in this report (Section E.2.).

3. Historical control data on Osborne-Mendel rats obtained from the NCI Carcinogenesis Testing Program indicated that the percent incidence of adrenal

cortical tumors in this study was well above (6-8x) the average incidence of the historical controls for both male and female rats, the percentage incidence of thyroid adenomas in males of this study was approximately 4 times that of the historical controls, and the percentage incidence of pancreatic islet-cell carcinomas in males of this study was approximately 60 fold greater than the historical controls.

4. The MTD was reached in the NCI rat study as evidenced by a 10% or greater depression in body weight gain and by physical signs of cholinergic-related toxicity.

5. In a well-conducted study (Bio/dynamics) in Sprague-Dawley rats, Parathion induced an increased incidence of thyroid follicular cell adenomas in male rats. A rereading of the thyroid slides from this study resulted in one less thyroid adenoma diagnosed (5/58, first reading; 4/59 second reading).

6. Historical control data provided by Bio/dynamics indicated that the incidence of thyroid follicular cell adenomas was just outside the historical range (8.62% vs 0-8.0%) for the original diagnosis and within the historical control range (6.8% vs 0-8.0%) after the second reading of the thyroid slides.

7. The MTD was probably slightly exceeded in Sprague-Dawley rats at the high dose in this study as evidenced by a 16% and 18% body weight depression in males and females, respectively, signs of cholinergic toxicity, depressed hematocrit and hemoglobin values, increased incidence of retinal atrophy in female rats, increased brain to body weight ratio and increased loss and/or degeneration of myelinated nerve fibers in the sciatic nerve. However, since this was a combined chronic/oncogenicity study, the high dose was appropriate for chronic toxicity.

8. Parathion was not teratogenic to rats or rabbits and did not affect reproduction in rats. A chronic dog study was not available for evaluation.

9. Parathion was positive for DNA repair in human WI-38 cells. This assay was conducted in an adequate manner and was considered acceptable. Parathion was negative in several other assays for mutagenicity (including the Ames Salmonella assay and dominant lethal assay in mice), but these were all considered to be unacceptable.

10. Parathion could be metabolized to p-nitrophenol which belongs to a class of chemicals that are associated with mutagenic and/or oncogenic activity.

#### G. Classification Oncogenic Potential:

The Committee concluded based upon the available evidence that Parathion meets the criteria of a category C oncogen. The NCI study on parathion did not specifically or exactly meet the verbiage used in any of the four criteria of category C; however, it meets a combination of criteria (a) definitive malignant tumor response in a single well-conducted experiment and criteria (b) marginal tumor response in studies having an inadequate design or reporting. Parathion produced a definitive tumor response at one site and a marginal response at two sites in an inadequately designed study. The weight-of-evidence did not meet any of the criteria listed as "sufficient evidence" of carcinogenicity which would categorize it as a B-2 oncogen.

Results from the NCI study, indicated an increased incidence of adrenal cortical tumors in male and female Osborne-Mendel rats and to a lesser degree an increase in thyroid follicular cell adenomas and pancreatic islet-cell carcinomas in male Osborne-Mendel rats. The second rat study conducted with Parathion using Sprague-Dawley rats was considered by the Committee to be negative for oncogenicity. The initial review of the study indicated an increased incidence of follicular cell adenomas of the thyroid gland in the high dose males. A re-reading of the slides showed one less high dose tumor and no accompanying hyperplasia. Historical control data showed the high dose effect to be within the historical control range. The mouse study conducted on Parathion was negative but was not considered by the Committee to be adequate for judging the oncogenic potential of Parathion in the mouse. The Committee recommended that another oncogenicity study in the mouse be required.

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. Although the Committee decided that a repeat study in the Osborne-Mendel rat should not be required at this time, they thought that the results of such a study would be a better indicator of the oncogenicity of Parathion in the rat. Emphasis would be placed on the results of this study along with a repeat mouse study for the determination of the oncogenic potential of Parathion.

Moreover, the Committee noted that additional and adequate short-term (mutagenicity) tests are required on Parathion. The results of these tests will be valuable in further evaluations on Parathion.

The Committee considered whether the results of the Osborne-Mendel rat study indicated that Parathion possessed hormonal activity, since adrenal cortical tumors were induced by Parathion in this study and to a lesser extent pancreatic islet-cell and thyroid follicular-cell tumors. Since Parathion does not belong to a class of compounds known to have hormonal activity, a secondary mechanism for this effect was postulated. However, the Committee concurred that Parathion was exerting some yet unknown effect on the endocrine system.

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

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Nov 2, 1988

SUBJECT: Parathion, Request for Peer Review re Possible  
Oncogenic Effect

TO: John Quest Ph.D.  
Head, Science Support Section  
SAC Branch, HED

FROM: Robert E. Zenzarian Ph.D. 11/3/88  
Senior Pharmacologist  
Registration Standards & Special Review Section  
SAC Branch, HED

THROUGH: Albin Kocialski Ph.D.  
Head, Registration Standards & Special Review  
Section

A Peer review is requested to evaluate the oncogenic potential of parathion as observed in a recently received Rat Chronic/Oncogenicity study.

On July 1, 1986 a Peer Review was held on Parathion (Ethyl Parathion). This review classified parathion as a Class C oncogen without requiring quantitation. A copy of that review is attached.

The Registrant has submitted an additional chronic/ oncogenicity study in the rat which shows a statistically significant trend of increased pancreatic tumors, exocrine and endocrine, in the males (MRID 406447-04). The study has been classified Core Guideline for a chronic/oncogenic study. A copy of the DER is attached. The DER presents the data on the possible oncogenic response and historical control data on pages 10 through 14. This data has been given to Dr. Levy for statistical evaluation.

Additionally, since the July 1986 Peer Review, we have received reports of four mutagenicity studies. Review of the studies concluded that;

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

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2. Parathion was equivocally active in the CHO/HGPRT, forward gene mutation assay with or without metabolic activation when tested at doses from 0.03 to 0.3 ul/ml. Results were not dose-related and require a repeat study for verification.

3. 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. 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.

A copy of the cover memo and DERs of these studies is attached.

#### Attachments

Memo, Peer Review of Parathion from Hauswirth to Allen Sept 1988

DER, Zendzian 8/12/88 re Parathion, study for chronic toxicity and carcinogenicity in Wistar rats (administration in diet for twenty-six months). R. Eiben; Histopathology report, Pappritz; Report on ERG examination, Rubin; Report on EM examination, Liebich; Bayer AG, Toxicology Division, Study No. T 1016770, Report No. 16305, Dec 16, 1987, MRID 406447-04 (2 vols)

Memo, Parathion, Mutagenicity Studies, from Zendzian to Edwards, 7/26/88

cc  
Engler