6-14-91 637 CASWELL FILE

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

008429

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDOM

SUBJECT: Parathion, Oncogneicity study in the mouse

TO: Joanne Edwards, RM 74
Reregistration Branch
Special Review and Registration Division (H708W)

FROM: Robert P. Zendzian Ph.D. 6/14/91
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THROUGH: Albin Kocialski Ph.D.
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Compound; Parathion Tox Chem #637 MRID #418173-01

Registration #057501 Registrant; Chem Nova Tox Project #1-0928

Action Requested

Review the following study;

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

Conclusions

The study is core Guideline

Doses tested 0, 60, 100 & 140 ppm. MTD; decreased weight gain males 100 and 140 ppm females 140 ppm, cholinesterase inhibition 140 ppm both sexes. No dose-related increase in tumors. 60 ppm groups overdosed (500 ppm) 7 days w/significant signs of cholinesterase inhibition toxicity, extra deaths (6 males, 2 females), significant increase alveolar/bronchiolar adenoma males and malignant lymphoma females.

Recommendation

Because of its previous classification as a C oncogin, the data were presented to the HED peer review committee on June 12, 1991. The committee evaluated the data and came to a conclusion which will be available when their report is finalized.

Data Evaluation Report

008129

Compound Parathion

Citation
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

5/22/91

Reviewed by Robert P. Zendzian Ph.D.
Senior Pharmacologist

5/27/91

Core Classification Guideline

Conclusions

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Materials

Ethyl parathion, Lot/Batch #DK-7620/70818-01
from Cheminova
purity 96.7%

B6C3F1 mice from Charles River, Portage, Michigan

Experimental Design

Animals were assigned to the following treatment groups and dosed for 18 months with test compound in the diet.

Treatment Group	Diet concentration (pm)	(percent)	Number of Animals Males	Females
Vehicle Core	0	0.0	50	50
Vehicle Satellite	0	0.0	35	35
Low Dose	60	0.006	50	50
Mid Dose	100	0.010	50	50
High Dose core	140	0.014	50	50
High Dose Satellite	140	0.014	35	35
Sentinals	0	0.0	15	15

Dose preparation and analysis

Treated diets were prepared weekly and used within 14 days. Stability and homogeneity analysis were performed prior to the start of the study. Dosed feed was analysed for concentration at approximately eight week intervals during the study.

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Observations

Animals were observed twice daily. "Each core group animal was removed from its cage twice each week and given a close inspection for signs of physical change."

"(I)ndividual weekly food consumption was measured during the first 13 weeks of this study and then once every 4 weeks for the remainder of the study."

"Core and satellite animals were weighed individually on Day 1, once each week for the first 13 weeks and then once every 4 weeks for the remainder of the study. The male core and satellite groups were weighed weekly Day 308 to Day 371 and female core and satellite groups were weighed weekly Day 304 to Day 374."

Blood was taken from 10 core group mice/sex from each treatment group at 12 and 18 months for hematology.

RBC count	MCH
hemoglobin	MCHC
hematocrite	Platelet count
MCV	Leukocyte count

Differental and RBC morphology was performed on control and high dose animals.

Blood was taken from control and high dose satellite groups, 15 males and females Day 10, 20 males and females 12 and 18 months for plasma and RBC cholinesterase analysis. The 18 month animals were sacrificed and the brain taken for cholinesterase analysis.

On Day 10, 15 mice/sex in the control and high dose satellite groups were sacrificed. All surviving mice in core and satellite groups were sacrificed at 18 months. All mice found dead, sacrificed in extremis and at termination were necropsied. The following tissues were collected;

Adrenal glands
Brain (three sections, including medulla/pons, cerebellar cortex, and cerebral cortes
Esophagus
Eyes
Femur, w/marrow cavity and epiphysis
Gall Bladder
Gross lesions and tissue masses
Heart and aorta
Kidneys
Pituitary
Preputial or clitoral glands (paired)
Prostate
Salivary gland
Sciatic gland
Skeletal muscle (thigh)
Skin
Small intestine (duodenum, jejunum, ileum)

Large intestine (cecum, colon rectum)
Liver
Lungs and mainstem bronchi
Lymphn nodes, mandibular and mesenteric
Mammary gland (to include surface skin)
Ovaries
Pancreas
Parathyroid glands
Pharynx (if grossly abnormal)
Spinal cord at three levels (cervical, midthoracic, lumbar)
Spleen
Stomach
Testes/epididymis/seminal vesicle
Thymus
Thyroid gland
Trachea
Urinary bladder
Uterus

From ten randomly selected animals in each treatment group liver, kidneys, brain and testes were weighed.

All control and high tissues were examined microscopically. Gross lesions, target tissues and lung, liver and kidneys were examined in the low and mid dose animals.

Statistical analysis was performed on numerical data.

Results

Misdosing incident

"Due to a technical error in diet preparation, mice in the 60 ppm dose group were fed a diet containing aproximately 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 following detection of the misdosing incident for 17 days (Days 307 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.

In general diet analysis showed actual concentration to be within ±5% of nominal.

Correcting for animals that died during the misdosing incident, there was no compound-related mortality.

Dose-related signs indicative of cholinesterase inhibition were observed during the first month of the study and in the misdosed animals.

Masses detected by palpation were not dose-related.

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Mean body weights are presented in Figures 3-6 from the report. Dose-related decreased weight gain was observed in the males at 100 and 140 pm throughout the study. The 60 ppm group was indistingusable from controls except during the misdosing incident when weights fell precipitously. A less obvious depression was observed in the females at 100 and 140 ppm with only the high dose effect being maintained throughout the study. The 60 ppm group was similar to the males.

Food consumption was significantly depressed in the 140 ppm males and less obviously in the females.

In the males at 12 months WBC counts were significantly elevated in all treated groups ($p<0.05$) but there was no difference between groups. No effects were observed in RBCs, platlets or between control and 140 ppm differental counts. At 18 months WBC counts were elevated in the treated groups but no other parameters differed from controls.

In general plasma and RBC cholinesterase values were depressed significantly from control in the 140 ppm groups. No determinations were performed for the 60 and 100 ppm groups. Brain cholinesterase values were significantly depressed at 140 ppm. The 60 and 100 ppm values were not determined.

Gross necropsy showed no evidence of a compound-related effect(s).

Table 12 from the report summarizes the tumor incidence data. No apparent compound-related effects were reported. However, statistically significant increases were observed in two tumors at 60 ppm, alveolar/bronchiolar adenoma in the males and systemic malignant lymphoma in the females.

Discussion

The dose-related decreased weight gain and cholinesterase inhibition at the high dose without a compound induced increase in mortality show that an MTD was reached in this study.

The combination of an overdosing incident with the 60 ppm group, where the mice received approximately 500 ppm for one week, and the significant increases in tumor incidence at this dose has created somewhat of a delemma. Clear signs of cholinesterase inibition toxicity, severe weight loss and associated deaths (6 males and 2 females) showed that this dose exceeded an MTD.

Pages 1169 and 1177 from the report present the historical control data for these two tumor types. Incidence of alveolar/ bronchiolar adenoma in males was 11% (range 10-12%) in the

only three 18 month studies available (the laboratory noted that they usually perform 24 month studies with this mouse strain). Incidence in this study was 10, 26, 12 and 8% for control, 60, 100 and 140 ppm respectively. Tumor incidence at 60 ppm was over twice the upper value of the control data.

Incidence of malignant lymphoma is combined with histiocytic sarcoma in the historical control data. Incidence in females was 27% (range 24-32%). Incidence in females in this study was as follows;

	Percent Incidence			
	0ppm	60ppm	100ppm	140ppm
Malignant Lymphoma	0	10	6	4
Histiocytic Sarcoma	0	2	0	4
Combined	0	12	6	8

All values in this study, particularly controls, were less than the historical range.

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Parathion toxicology review

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Pages 7 through 28 are not included in this copy.

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