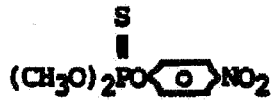
DATA EVALUATION REPORT 11/5/1985 005588

A. Compound:

Methyl Parathion; (O,O-dimethyl O-p-nitrophenyl phosphorothioate)



B. Study Report Citation:

Title: A Two Generation Reproduction Study of Methyl Parathion in Rats

Testing Facility: Bio/dynamics, Inc.
East Millstone, NJ

Project Number: 80-2456 (BD-80-139)

Date: August 18, 1982

Submitted to EPA by: Monsanto Co.
St. Louis, MO 63166

Authors: I. Daly and G. Hogan

C. Reviewed By: Alan C. Katz, M.S., D.A.B.T.
Toxicologist
Toxicology Branch
Hazard Evaluation Division (TS-769C)
(Signature)
11/5/85
(Date)

D. Secondary Review By: Robert P. Zendzian, Ph.D.
Acting Head, Review Section IV
(Signature)
11/5/85
(Date)

E. Classification: CORE Minimum

F. Conclusions:

Methyl parathion exposure at dietary levels up to and including 25 ppm did not appear to cause any abnormalities in parental activities from mating through pregnancy, parturition or lactation. Mean F_0 and F_1 maternal body weights in the high dose group were significantly reduced during lactation. No treatment-related effects on reproductive indices were observed. No abnormalities were found in the development of offspring in treated groups. No treatment-related gross or microscopic morphologic changes were apparent.

G. Materials:

Test compound: Methyl parathion, lot no. AK 0911
Purity: 93.65% a.i.

Vehicle: Acetone

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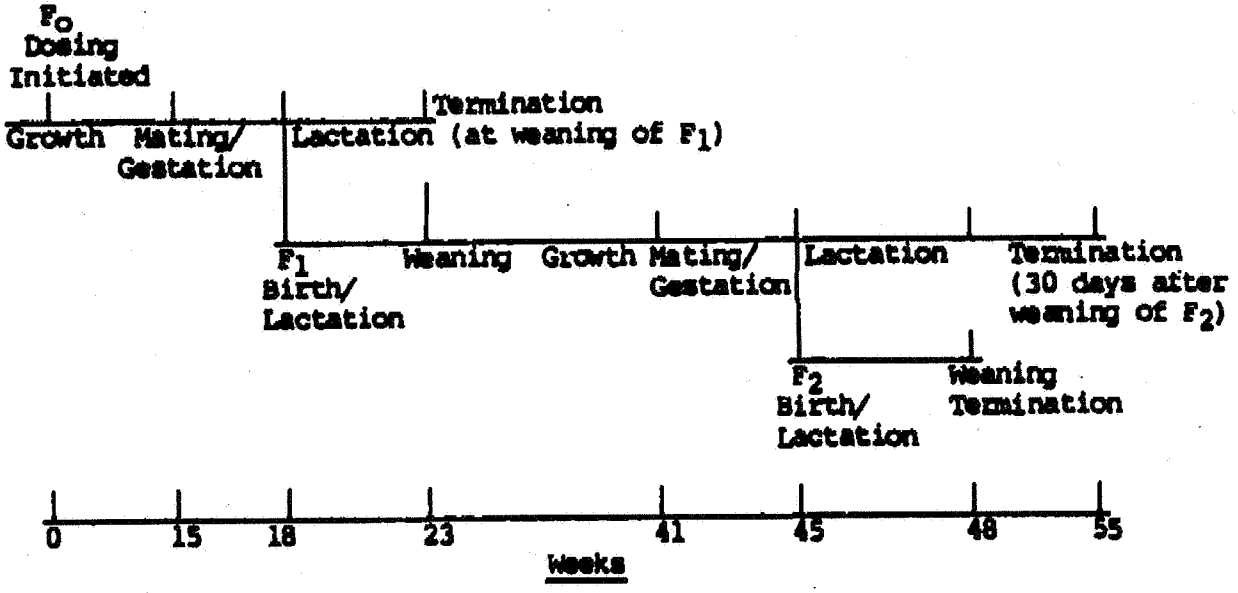
G. Materials (cont'd):

Animals: CD® Rats; 60 males and 120 females (F_0 generation)
Supplier: Charles River Breeding Laboratories, Wilmington, MA 01887
Age: At receipt- 4 weeks
At start of dosing- 6 weeks

Basal feed: Purina Laboratory Chow #5001

H. Methods:

The following diagram, excerpted from the study report, outlines the time frame of major events in the 2-generation testing program:



Rats were fed diet containing methyl parathion at concentrations of 0, 0.5, 5.0 and 25.0 ppm. The test substance was dissolved in acetone prior to incorporation into the diet. Control diet was blended with an amount of acetone which was equivalent to that used in the test diets. "Fresh" food was given twice weekly. According to the study report (p.4, "Test Substance Administration"), "Treated diets were stored frozen until presented." Apparently, the control diet was not similarly stored. Treatment began 14 weeks prior to mating of the F_0 generation, and continued through the mating, gestation and lactation periods.

Sixty males and 120 females were selected from the F_1 weanling groups, and the corresponding treatments were continued for approximately 18 weeks prior to mating, and throughout the subsequent mating, gestation, and lactation, until termination of the study approximately 5 weeks after weaning of the last F_2 litter. The F_2 animals were sacrificed at weaning.

All adult and weanling animals were necropsied. Tissues were collected from all F_1 parents, and 15 randomly selected animals/sex/dose group/generation from the F_1 and F_2 weanlings. Histopathologic evaluation included tissues from 80 F_1 parents (10/sex/group) and 40 weanlings (5/sex/group) each from the F_1 and F_2 generations.

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H. Methods (cont'd):

Tissues examined microscopically included:

Adrenal (1)	Nerve (sciatic)
Brain (2 levels)	Ovaries
Eye (right; incl. optic nerve and Harderian gland)	Pituitary
Heart	Prostate/seminal vesicles
Intestine (colon; duodenum)	Salivary glands
Kidneys (2)	Spleen
Liver (sections from at least 2 lobes)	Stomach
Lungs (2) with mainstem bronchi	Testes with epididymides (2)
Lymph nodes (mesenteric)	Thymus
Mammary gland (inguinal)	Thyroid with parathyroid
	Uterus (corpus and cervix uteri)
	Gross lesions

Body weights, food consumption, and litter data were statistically analyzed by Bartlett's test to determine whether the groups had equal variance, as well as by ANOVA and Dunnett's test (parametric), or Kruskal-Wallis and Dunn's Rank Sum test (non-parametric). The data were analyzed for significant differences (2-sided risk) at the levels of 1% and 5%, except for Bartlett's test which was conducted only at the 1% level.

I. Results and Discussion

The data provided in this study appeared to be sufficient to demonstrate adequate homogeneity, concentration and stability of methyl parathion in the diet at all dose levels.

Selection of 25 ppm as the highest dietary concentration of methyl parathion in this study is considered appropriate. In a previous 90-day subchronic feeding study, effects in rats given methyl parathion at a concentration of 25 ppm included depressed RBC, brain and plasma cholinesterase, lowered hematocrit and elevated serum alkaline phosphatase and urine specific gravity. In the present study, maternal body weights were reduced in the 25 ppm group.

Observations of clinical signs of toxicity should be reported for each individual animal. Such observations are not included in the study report.

Mean body weights and food consumption of methyl parathion treated F_0 males and females did not differ significantly from control values during the 14-week period prior to mating. Among F_1 animals, body weights of high dose females were significantly lower than those of controls during the first 2 months of the postweaning/premating period, but were comparable for the remainder of this phase of the study. Food consumption of high dose F_1 males and females was sporadically increased throughout the premating period.

I. Results and Discussion (cont'd)

No significant body weight differences were found between treated and control F_0 or F_1 females during pregnancy (as determined on gestational days 0, 6, 15 and 20); however, mean maternal body weights in the high dose group of both generations were significantly reduced during lactation. No statistically significant differences were found with respect to F_1 or F_2 pup weights prior to weaning. No significant treatment-related changes were found with respect to F_0 or F_1 gestation length, or the F_1 pup viability, pup survival or litter survival indices (as determined on days 0, 4 and 21 of the lactation period). Pup viability, pup survival and litter survival data, adapted from the study report, are summarized in the following table:

Group (ppm)	Viability at Birth Live/Total Born No.	%	Postnatal Offspring Survival Day 0-4 No.	%	Day 4-21 No.	%	Litter Survival[a] No.	%
			F_1 GENERATION					
I (0)	190/195	97.4	187/190	98.4	187/187	100.0	17/17[b]	100.0
II (0.5)	290/305	95.1	281/290	96.9	279/281	99.3	27/27	100.0
III (5.0)	269/271	99.3	267/269	99.3	267/267	100.0	22/22[c]	100.0
IV (25.0)	292/298	98.0	290/292	99.3	287/290	99.0	25/25	100.0
			F_2 GENERATION					
I (0)	263/273	96.3	258/263	98.1	255/258	98.8	22/22	100.0
II (0.5)	284/289	98.3	280/284	98.6	277/280	98.9	23/24[d]	95.8
III (5.0)	223/231	96.5	219/223	98.2	217/219	99.1	18/18	100.0
IV (25.0)	213/217	98.2	199/213*	93.4	198/199	99.5	18/19[e]	94.7

[a] Number of litters with live pups at weaning/number of litters with live pups at birth
[b] One litter was comprised of 2 dead pups (Day 0).
[c] One litter was comprised of 1 dead pup (Day 0).
[d] One litter (1 male; 1 female), born live, died prior to day 21.
[e] One litter (1 male; 1 female), born live, died prior to day 4.
* Significantly different from control value, $p < 0.05$.

Results and Discussion (cont'd):

During the first 4 days of the lactation period, F_2 pup survival in the high dose group was slightly, but significantly reduced. The deaths of 6 pups in one litter was cited as the reason for this reduction. Although the authors of the study report considered these deaths to be unrelated to methyl parathion administration because "[pup] survival in the remaining high-dose litters was generally comparable to control for the remainder of the lactation period," no gross or histopathologic evidence relating to the possible cause of death was presented.

F_0 and F_1 mating, pregnancy and fertility rates were not affected by treatment with methyl parathion, as shown in the following table:

Group (ppm)	Mating[a] (%) Females F_0	Females F_1	Males F_0	Males F_1	Pregnancy (%) Females F_0	Females F_1	Fertility[b] (%) Males F_0	Males F_1
I (0)	83	93	87	100	72	79	92	87
II (0.5)	97	90	100	93	93	89	100	93
III (5.0)	80	87	80	87	96	69	100	85
IV (25.0)	93	83	100	93	89	79	100	86

[a] Females: % showing plug and/or sperm and/or pregnancy
Males: % for which mating was confirmed in at least one of two females

[b] % of males mated with at least one female for which parturition was evident

No gross or microscopic morphologic changes were considered to be related to treatment. It is noted, however, that adrenal cortical adenomas were found in 2 of 10 adult F_1 high dose males and 1 of 10 adult F_1 mid-dose females; none were observed in the 10 male or 10 female adult F_1 controls.

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