A. **Compounds**

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

\[
\text{S} \quad \text{(CH}_3\text{O)}_2\text{PO(OH)}\text{O} \quad \text{NO}_2
\]

B. **Study Report Citation**

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

**Testing Facility:** Bio/ynamics, Inc.
East Millstone, NY

**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]

D. **Secondary Review By:**

Robert P. Zendo, Ph.D.
Acting Head, Review Section IV [Signature]

E. **Classification:** CORE Minimum

F. **Conclusion:**

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 F0 and F1 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
G. Materials (cont’d):

Animals: CD® Rats; 60 males and 120 females (F₀ generation)
Supplier: Charles River Breeding Laboratories, Wilmington, MA 01887
Ages: 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:

```
F₀
Dosing
Initiated

Growth Mating/
Gestation

Lactation (at weaning of F₁)

F₁
Weaning Growth Mating/
Gestation
Birth/
Lactation

Lactation
Termination
(30 days after
weaning of F₂)

F₂
Weaning
Birth/
Lactation

Termination

0  15  18  23  41  45  48  55
Weeks
```

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 F₀ generation, and continued through the mating, gestation and lactation periods.

Sixty males and 120 females were selected from the F₁ weaning 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 F₂ litter. The F₂ animals were sacrificed at weaning.

All adult and weanling animals were necropsied. Tissues were collected from all F₁ parents, and 15 randomly selected animals/sex/dose group/generation from the F₁ and F₂ weanlings. Histopathologic evaluation included tissues from 80 F₁ parents (10/sex/group) and 40 weanlings (5/sex/group) each from the F₁ and F₂ generations.
H. Methods (cont'd):

Tissues examined microscopically included:

- Adrenal (1)
- Brain (2 levels)
- Eye (right; incl. optic nerve and Harderian gland)
- Heart
- Intestine (colon; duodenum)
- Kidneys (2)
- Liver (sections from at least 2 lobes)
- Lungs (2) with mainstem bronchi
- Lymph nodes (mesenteric)
- Mammary gland (inguinal)
- Nerve (sciatic)
- Ovary
- Pituitary
- Prostate/seminal vesicles
- Salivary glands
- Spleen
- Stomach
- Testes with epididymides (2)
- Thymus
- 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 10 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 F0 males and females did not differ significantly from control values during the 14-week period prior to mating. Among F1 animals, body weights of high dose females were significantly lower than those of controls during the first 2 months of the postweaning/premeating period, but were comparable for the remainder of this phase of the study. Food consumption of high dose F1 males and females was sporadically increased throughout the pre-mating period.
I. Results and Discussion (cont'd)

No significant body weight differences were found between treated and control F₀ or F₁ 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 F₁ or F₂ pup weights prior to weaning. No significant treatment-related changes were found with respect to F₀ or F₁ gestation length, or the F₁ 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:

<table>
<thead>
<tr>
<th>Group (ppm)</th>
<th>Viability at Birth</th>
<th>Postnatal Offspring Survival</th>
<th>Litter Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Live/Total Born No.</td>
<td>Day 0-4 No.</td>
<td>Day 4-21 No.</td>
</tr>
<tr>
<td>F₁ GENERATION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (0)</td>
<td>190/195</td>
<td>97.4</td>
<td>187/190</td>
</tr>
<tr>
<td>II (0.5)</td>
<td>290/305</td>
<td>95.1</td>
<td>281/290</td>
</tr>
<tr>
<td>III (5.0)</td>
<td>269/271</td>
<td>99.3</td>
<td>267/269</td>
</tr>
<tr>
<td>IV (25.0)</td>
<td>292/298</td>
<td>98.0</td>
<td>290/292</td>
</tr>
<tr>
<td>F₂ GENERATION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (0)</td>
<td>263/273</td>
<td>96.3</td>
<td>258/263</td>
</tr>
<tr>
<td>II (0.5)</td>
<td>284/289</td>
<td>98.3</td>
<td>280/284</td>
</tr>
<tr>
<td>III (5.0)</td>
<td>223/231</td>
<td>96.5</td>
<td>219/223</td>
</tr>
<tr>
<td>IV (25.0)</td>
<td>213/217</td>
<td>98.2</td>
<td>199/213⁺</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Group (ppm)</th>
<th>Matinga (%)</th>
<th>Pregnancy (%)</th>
<th>Fertilityb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td>Fn. Fi.</td>
<td>Fn. Fi.</td>
<td>Fn. Fi.</td>
</tr>
<tr>
<td>I (0)</td>
<td>83 93</td>
<td>87 100</td>
<td>72 79</td>
</tr>
<tr>
<td>II (0.5)</td>
<td>97 90</td>
<td>100 93</td>
<td>93 89</td>
</tr>
<tr>
<td>III (5.0)</td>
<td>80 87</td>
<td>80 87</td>
<td>96 69</td>
</tr>
<tr>
<td>IV (25.0)</td>
<td>93 83</td>
<td>100 93</td>
<td>89 79</td>
</tr>
</tbody>
</table>

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.