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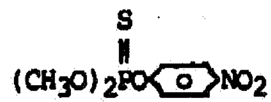
DATA EVALUATION REPORT

12/10/1985

A. Compound:

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



B. Study Report Citation:

Title: "Parathion-methyl: Evaluation for Embryotoxic and Teratogenic Effects on Rats Following Oral Administration"

Testing Facility: Bayer AG, Institut Fur Toxikologie, Wuppertal-Elberfeld

Report Number: 6825

Date: 6/3/77

Submitted to EPA by: A/S Cheminova, Lemvig, Denmark

Author: Dr. L. Machemer

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

(Signature)
12/10/85
(Date)

D. Secondary Review By: Robert P. Zendzian, Ph.D.
Acting Head, Review Section IV

(Signature)
12/10/85
(Date)

E. Classification:

Supplementary data. This classification may be upgraded following submission of additional data (see "Discussion/Recommendations").

F. Conclusions:

Results of this study suggest that methyl parathion is embryotoxic or fetotoxic at 1.0 mg/kg, but not at 0.3 mg/kg. Maternal toxicity was not established. Additional data are required.

G. Materials:

Test compound:	Methyl parathion; BAYER 11405; Parathion M 100 technical; Prod. No. 2830
Purity:	94.4%
Animals:	Wistar SPF
Supplier:	F. Winkelmann, Borchen
Age:	Females: 2 1/2 - 3 1/2 months (192-239 g) Males: 3 - 5 months (300-400 g)
Diet:	Altromin R feed

H. Methods:

Pregnant females (20-24 per group) were administered methyl parathion in 1.0% aqueous Cremophor EL emulsion by gavage (10 ml/kg body weight) on Days 6 through 15 of gestation. The doses were 0, 0.1, 0.3 and 1.0 mg/kg. The control animals received the Cremophor EL emulsion.

The selection of doses for this study was based on the results of a rangefinding experiment in non-pregnant rats, using doses of 1, 3 and 7.5 mg/kg/day. Five rats per group were treated. All of the rats given 7.5 mg/kg/day died within 3 days. Two animals in the 3 mg/kg group died within 5 days, and dosing was discontinued for this group. No adverse clinical signs or reduced weight gain were reported in any of the rats given 1 mg/kg/day during the 10-day experimental period.

Except during mating, the animals were individually housed in Type II Makrolon cages. Room temperature was within a range of 20-23°C and relative humidity was approximately 60 %. Lighting in the room was on a 12-hour on/off cycle. Food and water were provided ad libitum. Quarantine/acclimation conditions and duration were not specified.

Untreated virgin rats were mated overnight, with 1 male and 2 females per cage. Mating was confirmed by observation of sperm in vaginal smears the morning after mating. The methods of identification and randomization of animals was not specified.

The study was terminated on Day 20. Fetuses were removed by caesarian section and subjected to examination for external anomalies; measurement of litter weight and calculation of average fetus weight per litter; determination of sex; and examination for visceral and skeletal malformations. About 30% of the animals were examined for visceral malformations by the author's modification[1] of the Wilson technique[2]. The nature of this modification was not specified in the report. The remaining fetuses were eviscerated and the abdominal and thoracic organs were examined; they were then cleared with potassium hydroxide solution and the skeletal system was evaluated after staining with Alizarin Red S. The report does not mention the method used to designate which of these examination techniques would be applied to each fetus. Reference was made to "standardized" methods of examination[3,4] which were not described in the report itself, and copies of the reference articles were not provided with the report.

H. Methods (cont'd):

Data for weight gain, fetal and placental weights, and numbers of implantations, fetuses and resorptions were analyzed using the U test of Wilcoxon, Mann and Whitney. The Chi-square test with the Yates correction was used to analyze numbers of fetuses with bone alterations, as well as stunted fetuses and fetuses with other anomalies.

I. Results:

None of the treated or control rats died during the study. No treatment-related clinical signs were reported.

The following table, excerpted from the study report, summarizes the body weight gains of the pregnant females during the treatment period as well as over the course of the entire gestation period.

Dose in mg./kg.	Average weight gain in grams during treatment period	entire gestation period
0	21.3	74.2
0.1	18.8	72.3
0.3	22.2	74.9
1.0	12.2*	63.1

*significantly different from control at $p < 0.01$

According to the investigator for the study, the above data indicate that "treatment with the 1 mg./kg./day dose had a toxic effect on the dams." Data for individual weight gains were included in a separate table in the study report. However, no absolute body weight data were presented for the dams. Using the limited data presented in the study report, we have derived the following table, which demonstrates a wide range of values:

Dose (mg/kg)	Range of weight gain (loss) during treatment period	entire gestation period
0	6 - 27	47 - 91
0.1	(-43)- 31	(-24)- 99
0.3	15 - 28	53 - 95
1.0	(-23)- 28	13 - 97

There were a total of 20 pregnant rats in each of the 4 groups. There was no apparent case in which an entire litter may have been lost.

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I. Results (cont'd):

Implantation, resorption and litter data may be summarized as follows:

Dose (mg/kg)	Mean No. of Implantations	Mean No. of Fetuses Male	Female	Total	Dead and Resorbed Embryos
0	10.4	3.9	5.1	9.0	1.4
0.1	11.3	3.9	6.1	10.0	1.2
0.3	10.2	4.4	4.1	8.5	1.7
1.0	9.3	3.7	3.9	7.5	1.7

The slightly lower number of implantations in the high dose group is not attributable to methyl parathion administration, since treatment did not begin until day 6. Although the number of fetuses in the high dose group was slightly reduced, it does not appear to represent a significant difference when viewed in the context of the non-treatment-related reduction in the number of implantations. The following calculations, although not included in the study report, are presented here to augment this evaluation:

Dose (mg/kg)	% Viable fetuses†	% Dams with 1 or more dead/resorbed embryos
0	87	75
0.1	88	45
0.3	83	60
1.0	81	55

†Number of fetuses divided by number of implantations.

No treatment-related fetal malformations were apparent. However, reduced mean fetal weights and an increased incidence of stunted fetuses (weighing less than 3 grams) were reported to be related to treatment at the high dose level. The incidence of stunted fetuses was also increased in the low dose group; however, the likelihood of a relationship to treatment was discounted on the basis that "the difference between the 0.1 mg./kg. group and the control resulted mainly from light fetuses of 2 dams." Fetal and placental weight data may be summarized as follows:

Dose (mg/kg)	Mean wt. (g) Fetus	Placenta	Mean number of stunted fetuses/litter	No. of litters with 1 or more stunted fetuses
0	3.40	0.62	0.50	5
0.1	3.27	0.57	1.65**	7
0.3	3.39	0.64	0.95	7
1.0	3.25*	0.62	1.35**	11

* significantly different from control at $p<0.05$
** significantly different from control at $p<0.01$

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J. Discussion/Recommendations:

The data presented in the study report were not sufficient to conclude that maternal toxicity was demonstrated. While reporting the group mean body weight gain data in grams during the treatment period offers useful information, it does not provide a complete picture. Individual and group mean absolute body weight data must be presented for review.

Since dead fetuses were apparently counted with resorbed embryos, the combined data do not provide a sensitive means of analysis; these data should be separated in a manner which would allow evaluation of possible treatment-related differences with respect to the approximate time of death in utero.

In order to complete its evaluation, the Agency requires, in addition to the data cited above: a copy of the protocol and a description of any deviations from the protocol; a copy of each of the References (in English) #1, 3 and 4; individual clinical observations and necropsy findings for the dams; a description of conditions of storage of the test material and dosing mixtures; and analytical results with respect to homogeneity, concentration and stability of the test material in the dosing mixtures.

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K. References:

1. Machemer, L. and Stenger, E. Zur Beurteilung der Foeten im teratologischen Experiment. Modifikation dr "Wilson-Technik". Arzneim. Forsch. (Drug Res.) 21, 144-145, 1971.

2. Wilson, J. In: Teratology, Principles and Techniques. Eds.: J.Wilson and J. Warkany, The University of Chicago Press, Chicago and London, 1965, 262-277.

3. Lorke, D. Zur Methodik der Untersuchungen embryotoxischer und teratogener Wirkungen an der Ratte. Arch. exp. Path. u. Pharmak. 246, 147-151, 1963.

4. Lorke, D. Embryotoxische Wirkungen an der Ratte. Arch. exp. Path. u. Pharmak. 250, 360-382, 1965.