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Malathion: Developmental Toxicity Study in Rabbits. Food and Drug Research Laboratories. 1985. MRID 00152569, 40812001. HED Doc No. 007376.

DATA EVALUATION RECORD

Study Type: Developmental Toxicity Study, Rabbits
OPP Guideline 83-3

P.C. Code: 057701 Tox. Chemical No.: 535

Test Material (purity): Malathion; (92.4% a.i.)

Synonyms O,O-dimethyl dithiophosphate of diethyl mercaptosuccinate; O,O-dimethyl phosphorodithioate of diethyl mercaptosuccinate; diethyl mercaptosuccinate, S-ester with O,O-dimethyl phosphorodithioate; Cythion; AC6,601.

Citation: Joseph C. Siglin, Kenneth A. Voss and Peter J. Becci, 1985. A Teratology Study with AC6,601 in Rabbits. Food and Drug Research Laboratories, Inc., Waverly, NY. Study No. 8171. February 28, 1985. Unpublished. MRID 152569

Sponsor American Cyanamid Company, Princeton, NJ.

Executive Summary:

In a developmental toxicity study in rabbits, malathion (92.4% purity) was administered by daily oral gavage to groups of 20 pregnant New Zealand White does on days 6 through 18 of gestation at dose levels of 0 (corn oil control), 25, 50 or 100 mg/kg/day. In a previously conducted range finding study, increased mortalities were observed at dose levels of 200 and 400 mg/kg/day. Females were impregnated by 1:1 matings with males followed by intravenous administration of 200 IU of human chorionic gonadotropin. Does were observed daily for mortality, clinical signs of toxicity and other signs of pregnancy status. Body weights were determined frequently throughout the study. On day 29 of gestation, the does were euthanized and subjectd to complete gross necropsy. All fetuses were weighed, sexed and examined for external abnormalities, visceral soft tissue abnormalities and skeletal abnormalities by standard procedures.

Several mortalities occurred during the study, but none were attributed to treatment with malathion. Decreased activity, anorexia, soft stools, diarrhea and nasal discharge were observed in both control and treated animals. Anorexia and soft stools, however, may have occurred at a slightly higher incidence in the 100 mg/kg/day animals. Significantly decreased mean body weight gains were observed in the 50 and 100 mg/kg/day animals during days 6-18 of gestation (period of treatment with malathion). During this period, mean body weight gains were 0.19, 0.06, -0.03 and -0.03 kg for the control, 25, 50 and 100 mg/kg/day groups

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respectively. For the entire period of gestation (days 0-29), no statistically significant differences in mean body weight gains were observed between control and treated animals, although a trend toward reduced corrected body weight gains (body weight minus gravid uterine weight) with increasing dose level was observed. No treatment-related effects on reproductive parameters were observed except for an increase in the mean number of resorption sites per doe at 50 and 100 mg/kg/day. Mean resorption sites per doe were 0.9, 0.7, 2.3 and 2.0 for the control, 25, 50 and 100 mg/kg/day groups respectively. These increases were considered to be developmental toxicity effects. Mean fetal weights were not affected by treatment with malathion. Fetal external examinations, visceral soft tissue examinations and skeletal examinations revealed no treatment-related effects. **The maternal NOEL is 25 mg/kg/day and the maternal LOEL is 50 mg/kg/day based on reduced mean body weight gains during days 6-18 of gestation (period of treatment with malathion). The developmental toxicity NOEL is 25 mg/kg/day and the developmental toxicity LOEL is 50 mg/kg/day based on an increased incidence of mean resorption sites per doe.**

This study is **ACCEPTABLE-GUIDELINE** and **SATISFIES** guideline 83-3 for a developmental toxicity study in rabbits.

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This study is **ACCEPTABLE** and **SATISFIES** guideline 83-3 for a developmental toxicity study in rabbits.

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Reviewed by: Brian Dementi, Ph.D. Brian Dementi 7/10/87
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Section I, Toxicology Branch (TS-769C)

DATA EVALUATION REPORT 007376

Study Type: Teratology

Tox. Chem. No.: 535

Accession No.: 260123

MRID No.: 152569

Test Material: Malathion

Synonym: AC6,601

Study Number: 8171

Sponsor: American Cyanamid Company
Princeton, NJ

Testing Facility: Food and Drug Research Labs., Inc.
Waverly, NY

Title of Report: A Teratology study with AC6,601 in rabbits.

Author(s): Joseph C. Siglin, Kenneth A. Voss, Peter J. Becci

Report Issued: February 28, 1985 Study completed 10/15/84

Special Review Criteria

A. Materials

1. Test Compound: Malathion, Description: clear brown to colorless liquid, Lot #: AC 4661-38, Purity: 92.4%

   Contaminants: Not indicated.

2. Test Animals: Species: Rabbit, Strain: New Zealand White, Age: young, mature, Weight: 3.3 kg
   Source: New York State Rabbit Development, Hartwick, NY

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B. Study Design

The study design is based in part upon the results obtained in a range-finding study (Study No. 8170, February 28, 1985, MRID 152569). In the range-finding study, five rabbits (NZW-inseminated females) per group were exposed by the oral route to malathion in corn oil at doses of 25, 50, 100, 200, and 400 mg/kg body weight during days 6 to 18 of gestation. Mortality rates of 40 percent and 80 percent were observed in the 200 and 400 mg/kg dose groups, respectively. Additional toxic responses in the two high dose groups including salivation and/or tremors at the time of death. There were no deaths or other outward signs of toxicity noted at doses of 0 to 100 mg/kg. There were no fetal abnormalities observed at any dose.

As a result of the range-finding study, the dosages of malathion selected for the complete teratology study were 0, 25, 50, and 100 mg/kg body weight.

1. Animal Assignment - Animals (pregnant does) were assigned 20/group to the following test groups:

		Test Solutions	
Test Group	Treatment Level (mg/kg bwt)	Malathion Concentration (mg/mL)	Dosage Volume (mL/kg bwt)
A	corn oil	0	1.5
B	25	16.7	1.5
C	50	33.3	1.5
D	100	66.7	1.5

Each mated doe received a single daily oral dose of the vehicle (corn oil) or malathion dissolved in corn oil on days 6 to 18 of gestation.

2. Compound Preparation: A stock solution of the test material was prepared by dissolving malathion in corn oil at a concentration of 66.7 mg/mL (high dose). The remaining test solutions (mid and low dose) were prepared by serial dilution of the stock solution with corn oil. Test solutions were stored at 0 to 5 °C and warmed to room temperature prior to use.

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Experimental Procedures

All animals were individually housed in wire mesh cages and were fed and watered ad libitum. Animal Feed A, certified diet (Zeigler Bros., Gardner, PA), was utilized. (The following is paraphrased or quoted from pages 8 to 11 of the actual study.)

Following acclimation, male-female matings (1:1 pairings) were allowed. Observed copulation was designated as day 0 of gestation. Males were restricted to a single successful mating per day. Each mated female was given 200 IU of human chorionic gonadotropin by intravenous injection (ear vein). Bred does were randomly assigned to one of the four experimental groups.

Each doe was administered via gastric intubation a single daily oral dose of the vehicle (corn oil) or malathion dissolved in corn oil on days 6 to 18 of gestation. (Note: According to the Guidelines day 0 corresponds to the day of mating; compound is supposed to be administered on days 7 to 19 of gestation.) All doses were administered in a volume of 1.5 mL/kg body weight, based on body weight on gestation day 6.

"Does were observed twice daily (at least 5 hours apart) for mortality. Detailed observations for outward signs of toxicity, either physical or behavioral, were conducted once daily.

"Individual body weight was measured on days 0, 6, 12, 15, 18, 24, and 29 of gestation. Body weight gain was individually calculated for days 0 to 6, 6 to 12, 6 to 18, 18 to 29, and 0 to 29. Corrected body weight (body weight minus gravid uterus weight) and corrected body weight gain were individually calculated for pregnant does sacrificed at study termination (gestation day 29).

"Does showing signs of abortion were immediately sacrificed by intracardiac injection of sodium pentobarbital and subjected to complete gross necropsy. The urogenital system of each animal was examined in detail for possible abnormalities and reproduction data (listed below) were obtained where possible. Does dying spontaneously were examined in this same manner. Surviving does were euthanized (i.c. sodium pentobarbital) on day 29 of gestation and subjected to complete gross necropsy. The urogenital system of each female was examined in detail for possible abnormalities. The ovaries and uterus were excised, the uterus was weighed and its contents then examined. The following data were recorded for each pregnant female:

- Number of corpora lutea.
- Number and position of implantation and resorption sites.