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

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OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Identification No. 057701-5
Development Toxicity Study with AC 6,601 (Malathion) in Rats

Project No.: 9-2118
Tox Chem No.: 535
Record No.: 251422

FROM: Brian Dementi, Ph.D., D.A.B.T Brian Dementi 8/31/9-
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THRU: Roger Gardner, Acting Section Head 5/1/91
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You will find appended the Data Evaluation Report for the ident developmental toxicity study of AC 6,601 in the rat. This study sat the Series 83-3 (Teratology) Guideline requirement for AC 6,601

Attachment:

001 of 23

Reviewed by: Brian Dementi, Ph.D., D.A.B.T. Brian Dementi 8/31/89
Section I, Toxicity Branch I - IRS (H7509C)
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DATA EVALUATION REPORT

Study Type: Developmental Toxicity, Rat

Tox Chem No.: 535
MRID No.: 411609-01

Record No: 251422

Test Substance: AC6,601

Synonyms: Malathion; phosphorodithioic acid, S-[1,2-bis (ethoxycarbonyl)ethyl] O,O-dimethyl ester

Study No. 971-88-142

Sponsor: American Cyanamid Company
Princeton, NJ

Testing Facility: Argus Research Laboratory, Inc.
Perkasie, PA

Title of Report: A Development Toxicity Study with AC6,601 in Rats

Author: Elizabesth A. Lochry, Ph.D.

Report Issued: April 5, 1989

Classification: Core - Guideline

Conclusions:

As evaluated in rats according to current guidline requirements for developmental toxicity (Seris 83-3), at doses of 0 (vehicle) 200, 400 and 800 mg/kg/day, AC6,601 did not elicit any adverse developmental effects at any dose. Hence, for developmental toxicity NOEL > 800 mg/kg/day.

As evidenced by dam weight gain deficits and reduced feed intake at 800 mg/kg/daty, maternal toxicity LEL = 800 mg/kg/day; NOEL = 400 mg/kg/day.

Thus there was no evidence of developmental toxicity at doses below or even equal to that which elicited maternal toxicity.

A. Materials

1. Test Compound - AC 6,601

Description:	clear yellow oil
Lot No.:	AC 6015-136 B
Purity:	94%
Contaminants:	The study report does not contain a certificate of analysis which would reveal the complete chemical composition of the test material.

2. Test Animals:

Species:	rat
Strain:	Charles River Crl:CD^{tm}(SD)BR
Age:	Approximately 80 days at Day 0 of presumed gestation (71 days at receipt in laboratory).
Weight:	212-276 on day 0 of presumed gestation
Source:	Charles River Breeding Laboratories, Inc., Raleigh, NC

B. Study Design (the following is quoted or paraphrased from pages 18-27 of the study)

Following male/female cohabitation periods, healthy (presumed pregnant) female rats were assigned in groups of 25 to each of four study groups, consisting of one control and three dose groups. The presumed pregnant females were housed in individual cages. Since dams were terminated prior to delivery, nesting materials were not added to cages. The dams were fed and watered ad libitum throughout the study.

Batches of AC 6,601 test solutions, 400 ml each, were formulated in corn oil at concentrations of 0, 40, 80 and 160 mg/g. Technical solutions of AC 6,601 thus prepared were administered (5 ml/kg) orally once daily to dams via gavage in order to achieve the dosages of 0 (vehicle), 200, 400 and 800 mg/kg day for groups I-IV, respectively. Dosages were adjusted daily for changes in body weights. [NOTE: results of actual analyses of the AC 6,601 batch preparations performed by the sponsor are reported in TABLE I, p. 221 of this submission.]

Viability of rats was noted at least twice daily throughout the study. Observations for clinical signs of test substance effect, abortion and/or viability were also made several times each day during the dosage period (days 6 through 15 of preumed gestation). These observations were made once daily during the post-dosage period (days 16 through 20 of presumed gestation).

Body weights were recorded at least once weekly prior to mating and on day 0 and daily during days 6 through 20 of presumed gestation.

Food consumption was recorded on days 0 through 6 and 6 through 20 of presumed gestation.

On Day 20 of presumed gestation, all rats were sacrificed by carbon dioxide asphyxiation. The abdomen of each rat was opened, corpora lutea in each ovary were counted, and the intact uterus was excised, weighed and examined for pregnancy, number and placement of implantations, early and late resorptions and live and dead fetuses.

The thoracic and abdominal cavities of each dam were examined for gross lesions. Reproductive organs (ovaries, uterus and vagina) and tissues with gross lesions were preserved in neutral buffered 10% formalin for possible future evaluation.

"Each fetus was removed from the uterus, placed in an individual container and individually identified with a tag. Each fetus was subsequently weighed and examined to identify sex and gross external alterations. Live fetuses were then sacrificed by carbon dioxide asphyxiation.

"Approximately one half[a] of the fetuses in each litter were fixed in Bouin's solution and examined for soft tissue alterations using a variation of Wilson's sectioning technique (4). The remaining fetuses in each litter were eviscerated, cleared, stained with alizarin red S(5) and examined for skeletal alterations. Late resorptions were examined to the extent possible[b]. [Footnotes: a - "One externally normal 200 mg/kg/day dosage group fetus (4031-17) and two externally normal 400 mg/kg/day dosage group fetuses from the same litter (4064-10,11) were lost following gross external examination, precluding further evaluation."; b - "Two late resorptions occurred in this study. One control group late resorption was a cojoined parasitic twin. Because of the uniqueness of this specimen it was preserved intact in Bouin's solution. Autolysis precluded evaluation of the other late resorption (from an 800 mg/kg/day dosage group litter) and it was

discarded." p. 23; see Attachment I (copy of study references) for identification of numerical footnotes]

"Female rats that were found dead were examined for cause of death. The pregnancy status and uterine and ovarian contents were recorded. Maternal tissues with gross lesions were fixed in neutral buffered 10% formalin for possible future evaluation. Viscera that appeared normal were discarded." pp. 23-24

Statistical analyses were performed in accordance with a schematic as outlined in the study report (p. 25), a copy of which is appended. (Attachment II)

"Maternal body weight, gravid uterine weight and feed consumption averages (g/day and g/kg/day), as well as litter averages for percent male fetuses, fetal body weight, fetal ossification sites and percent fetal alterations were analyzed using Bartlett's Test of Homogeneity of Variances([10]) and the Analysis of Variance([11]), when appropriate [i.e. when Bartlett's Test was not significant ($P \leq 0.05$)]. If the Analysis of Variance was significant ($P \leq 0.05$), then Dunnett's Test([12]) was used to identify the statistical significance of individual groups. If the Analysis of Variance was not appropriate (i.e., when Bartlett's Test was significant ($P \leq 0.05$)], the Kruskal-Wallis test([13]) was used when less than or equal to 75% ties were present; when more than 75% ties were present, the Fisher's Exact Test([14]) was used. In cases in which the Kruskal-Wallis Test was statistically significant ($P \leq 0.05$), Dunn's Method of Multiple Comparisons([15]) was used to identify the statistical significance of individual groups.

"The Analysis of Covariance ([16]) was used to evaluate average maternal body weight changes during days 0 to 6 of gestation and days 0 to 20[a] of gestation. This test was also used to evaluate changes in average maternal body weight during days 6 to 7, 9, 12, 16, 19 and 20[a] of gestation. The methods previously described for Bartlett's Test ([10]) and the Analysis of Variance ([11]), were used to evaluate maternal body weight change data on days 7 to 8 and 8 to 9 of gestation (intervals which occurred after initiation of dosage), and for evaluation of maternal body weight change data during the postdosage period.
[Footnote: a - "Includes statistical analyses of maternal body weight change intervals involving the corrected day 20 of gestation body weight values." p. 26; see Attachment I (copy of study references) for numerical footnotes]

"All other Caesarean-sectioning data were evaluated using the procedures previously described for the Kruskal-Wallis Test." pp.26-

Results

1. Clinical Signs/Necropsy Findings - No test substance-related deaths occurred during the course of the study. Clinical signs were observed only among animals tested at the highest dose, 800 mg/kg/day. The clinical signs included a significantly increased ($P \leq 0.01$) number of dams with urine stained abdominal fur, occurri in 5 rats of the group on a total of 140 days; and chromodacryorrhe and chromorhinorrhea observed in one dam.

There were no other dose-related clinical or necropsy findings among dams.

2. Maternal Body Weight - [For refer... purposes and discussing dam body weight changes, a copy of page... and 2 of Table 4B "Summa of Maternal Body Weight Data" is appended (Attachment III)]. Toxicology Branch concurs with the study author that biologically meaningful effects of AC 6,601 on maternal body weight were evident only for animals tested at the highest dose. These effects include statistically significant deficits in body weight gain (e.g. at day 6-9 and 6-12 of gestation) and a significant increase in dam body weight during the post dosing period (e.g. days 16-20), considered to be a rebound phenomenon. There were no remarkable body weight effects for the 200 and 400 mg/kg/day dose groups.

3. Maternal Food Consumption - [For reference purposes in discussi dam food consumption data, a copy of pages 1 and 2 of Table 5B "Summary of Maternal Feed Consumption", is appended (Attachment IV)]. Toxicology Branch again concurs with the study author to the end that significant effects (deficits) in dam feed consumption were observed only among those exposed at the highest test dose (e.g. days 6-12 and 9-12 of gestation). Maternal feed consumption during days 6-12 of gestation averaged 20.4, 20.8, 21.4 and 18.7 grams/day for the control, low mid and high dose test groups, respectively. As was true with respect to body weight gain effects there was a feed consumption rebound effect observed for the high dose group during the 16-20 post dosing period.

4. Cesarean Section and Fetal Litter Data - An inspection of summary data as presented in Table 6B (p. 52; Attachment V) and 7B (p. 53; Attachment VI) did not reveal any remarkable effects of dosing upon the incidences or the mean values for the following parameters: corpora lutea, implantations, litter size, live fetuse dead fetuses, resorptions, implantations, or live fetal body weight (male or female).

5. Fetal External, Soft Tissue and Skeletal Examinations - Inspection of data presented in Table 8B "Summary of Alterations observed in Fetuses (p. 54; Attachment VII); 9B "Summary of Fetal Gross Alterations" (p. 55; Attachment VIII); 10B "Summary of Fetal Soft Tissue Alterations" (p. 56; Attachment IX); 11B "Summary of Fetal Skeletal Alterations" (p. 57; Attachment X); and 12B "Summary of Fetal Ossification Sites" (p. 60; Attachment XI) leads Toxicology Branch to the conclusion that there were no remarkable adverse (negative) effects of dosing with AC 6,601. Certain of the parameters exhibited significantly less compromise in the dosed groups than in the control. For example, both litters and fetuses with any alteration observed were less numerou significantly so for the most part, in all dosed groups than in the control (p. 54), there were no gross alterations in any of the dosed groups and only one fetus from the dosed groups, that at the high dose, exhibited a soft tissue alteration (kidney, pelvis, slight dilation, unilateral) (p. 56). Two fetuses (two litters) in the high dose group exhibited a cervical rib, but this is not viewed as presenting any particular concern for the test substance (p. 57).

RIN 1244-00

Malathion Tox Review # 8384

Page_____ is not included in this copy.

Pages 8 through 23 are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

X FIFRA registration data.

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
