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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 005646

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MEMORANDUM

SUBJECT: Propachlor, pp. 524-310, 152, 153, 286, 328, 331
Rabbit Teratology Study, Accession No. 255758
Caswell No. 194

FROM: Stephanie P. April, Ph.D. Stephanie P. April 12/14/86
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and

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Toxicology Branch
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Compound: Propachlor Tox. Chemical: 194

Registration Nos.: 524-310/286/153/152 Registrant: Monsanto

Accession No.: 255758

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Action Requested:

Review the above-cited Rabbit Teratology Study, IRDC No. 401-190, Study No. IR-82-244.

Background:

This is a second teratology study to fulfill a data requirement for propachlor registration. The study was requested in a Propachlor Data Call-In Notice of January 19, 1984.

Data Gaps:

2 chronic rodent
1 chronic nonrodent
reproduction
battery of mutagenicity

Conclusion:

These data indicate these approximate values:

Maternal Toxicity NOEL = > 50 mg/kg/day
Developmental Toxicity NOEL = 5 mg/kg/day

Core Classification:

Supplementary pending the arrival of adequately presented historical data and individual maternal necropsy data. Also the company should define their specific classifications of malformations versus variations which major vessel variations were found.

005645

Reviewed by: Stephanie P. April, Ph.D. Stephanie P. April 12/26/86
Section III, Toxicology Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D. M van Gemert 12.23.86
Section III, Toxicology Branch (TS-769C)

DATA EVALUATION REPORT

Study Type: Rabbit Teratology Study

Accession Number: 255758

Test Material: Propachlor

Synonyms: Ramrod Herbicide

Study No.: IR-82-224, IRDC No. 401-190

Sponsor: Monsanto Agricultural Products Co.
St. Louis, MO 63167

Testing Facility: International Research and Development Corp.
Mattawan, MI

Title of Report: Teratology Study in Rabbits with Propachlor

Author and Study Director: Larry Miller, B.S., and James L. Schardein, M.S.

Report Issued: December 21, 1983

Conclusion:

Propachlor may be a developmental toxicant but individual fetal and genetic data are required for this evaluation.

All groups showed developmental toxicity based upon the presence of what the registrant terms the observed variations without maternal toxictiy; however, there is no significant increase in these effects from those found in the untreated control group.

Maternal Toxicity NOEL = >50 mg/kg/day
Developmental Toxicty NOEL = 5 mg/kg/day

Classification

Supplementary, pending the arrival of adequately presented historical data and individual maternal necropsy data as well as definitions and listing of individual fetal and genetic variations which were found by the litter for each doe.

Materials and Methods:

Test Material:

Technical propachlor, Lot No. MTRF-11-13C, purity 96.5 percent in vehicle control of Mazola Corn Oil 100 percent pure. The substance was mislabeled as arachlor on p. 4 of study with a note that the sponsor mislabeled the technical propachlor. It is properly identified on p. 00051 in appendix on Monsanto sample sheet.

Animals:

Eighty sexually mature 4 1/2 to 5-month-old female New Zealand White rabbits from Langshaw Farms were superovulated by i.v. injection of APL chorionic gonadotrophin 20 days prior to artificial insemination. Propachlor was administered on days 7 through 19 of gestation. Their weight range at gestation day 0 was 3.338 to 4.496 kg.

Methods:

Sixty-four pregnant[1/] female animals were divided into one control group and three treated groups (16 per group) which received 5, 15, or 50 mg/kg/day of freshly prepared propachlor in corn oil daily as 0.5 mL/kg on gestation days 7 through 19 by oral intubation.

Prior to treatment the animals were observed twice daily for mortality and changes in appearance and behavior. During treatment they were observed twice daily for mortality and once daily for clinical signs of toxicity. Body weights were recorded on day 0, 7, 13, 19, 25, and 29.

All surviving does were sacrificed on day 29 and fetuses removed by caesarean section. The uterus was weighed and the number and location of viable and nonviable fetuses, early and late resorptions, and the number of total implantations and corpora lutea were recorded. Gross necropsies were performed.

1/ The does were artificially inseminated at approximately 5 1/2 to 6 months of age at 3 weeks after superovulation by injection of 50 U.S.P. units of APL into marginal ear vein.

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The fetuses from the does that died on test were examined externally and preserved in 10 percent neutral buffered formalin. All fetuses were weighed and examined externally for gross morphological changes. Internal gross pathological examinations of the fetuses were performed as well as dissection of the heart and mid-coronal brain slices. The fetal findings were classified as malformations and genetic or developmental variations.

Statistical analyses were performed to compare treated groups to control at a level of significance of $p < 0.05$ or $p < 0.01$. The report states that the chi-square test criterion with Yates' correction for 2 x 2 contingency tables and/or Fisher's exact probability test as described by Siegel[2/] were used to compare the male to female sex distribution and the number of litters with malformations.

Also in the report are references to the use of the following tests:

1. Mann-Whitney U-test described by Siegel[2/] and Weil[3/] for the judgment of significance of difference.

2. Steel and Torrie[4/] description of Bartlett's test for homogeneity of variances and the appropriate t-test (for equal and unequal variances) using Dunnett's[5/] multiple comparison tables to evaluate the significance of differences.

2. Results

Maternal Observations:

Appearance and Behavior:

There were no meaningful differences from control in the treated groups.

2/ Siegel, S. (1956) Nonparametric Statistics for the Behavioral Sciences. McGraw-Hill, New York, NY.

3/ Weils, C.S. (1970) Selection of the valid number of sampling units and consideration of their combination in toxicological studies involving reproduction, teratogenesis or carcinogenesis. Food Cosmet Toxicol, 8:177-182.

4/ Steel, R.G.D.; Torrie, J.H. (1960) Principles and Procedures of Statistics. McGraw-Hill, New York, NY.

5/ Dunnett, C.W. (1964) New Tables for multiple comparisons with a control. Biometrics, 51:482-491.

Mortality: Ten does died while on test.

Table 1

No. of Deaths	Dose mg/kg (Day)
2	0 (25, 26)
3	5 (3, 12, 16)
3	15 (5, 18, 25)
2	50 (15, 24)

Eight of the above mortalities, including one control animal, had congested and/or consolidated lungs. In the treated groups this consolidation was often accompanied by the presence of cheesy, caseous and/or fibrous material adhering to the thoracic cavity and one or more of the organs contained therein. There was no treatment-related difference from control in the treated animals that could be detected from the necropsies.

Body Weights

All treated groups had slight fluctuations of maternal body weight from control at various intervals of treatment. No change occurring was outside of an expected range of body weight variations.

The adjusted body weights on day 29 (doe weight minus gravid uterus weight) were comparable in all groups.

Table 2

	Weights Day 29	
Dose	Day 29	Day 0
0 mg/kg/day	3781	3855
5 mg/kg/day	3920	3914
15 mg/kg/day	3821	3816
50 mg/kg/day	3903	3837

Symptoms

There were gross abnormalities respectively in 9/16, 10/16, 13/16, and 8/16 of the control, low-, mid-, and high-dose rabbit groups. Necropsy revealed congested lungs and foci on the lungs as well as nasal congestion in treated animals that aborted. The most frequent clinical abnormalities were nasal discharge (white or clear), hair loss (inguinal, axillary, and abdominal), ocular discharge and soft reduced amounts of fecal material. There were no treatment-related symptoms.

Caesarean Section Observation:

An increase in preimplantation loss (%) with a dose-related trend in all treated groups was reported as given below:

Table 3

Dose (mg/kg/day)	Preimplantation Loss %
0	24.8
5	36.5
15	42.5
50	46.2

At 15 and 50 mg/kg there was a moderate increase in mean postimplantation loss and a decreased number of viable fetuses when compared to the control group. Only at 15 mg/kg was the number of viable fetuses significantly decreased and the percent of postimplantation loss significant. There was no dose-related effect.

The reduced size of the average number of viable fetuses per litter is due to one doe in each group resorbing an entire litter yield; a significant decrease in viable fetuses occurred only in the 15 mg/kg group. The number of total implantations per doe was also reduced in the 15 and 50 mg/kg group.

Table 4

Dose (mg/kg)(day)	Group Mean % Postimplantation Loss	Litters/ Group	# Viable Fetuses/ per Doe
0	6.8	12	8.0
5	4.5	8	7.9
15	21.9	10	5.2*
50	16.3	13	5.9

* Significant difference from control group; $p > 0.05$.

The % postimplantation loss = $\frac{\text{Total no. viable fetuses} \times 100}{\text{Total no. implantations}}$

Table 5

Dose	No. of Does With One or More Resorptions	%	Total Resorptions (Late & Early)	%
0	5	42	7 (4+3)	6.8
5	2	25	3 (0+3)	4.5
15	7	70	15 (0+15)	20.5
50	9	69	16 (3+13)	16.3

The above table illustrates the percentage of does experiencing resorptions and the actual percentage of the resorptions at each dose.

These parameters were not different from control values in the 5 mg/kg group.

There was no dose-related effect of treatment on the litters per group. There was no significant difference between control and treated groups in numbers of corpora lutea, mean fetal weight, or fetal sex distribution. The NOEL for developmental toxicity was 5 mg/kg/day predominantly based upon early resorptions and post implantation loss. It can be clearly seen in Table 4 that there was a large increase in the Group Mean % postimplantation loss in the mid and high treatment groups. It can also be seen in Table 5 that in these mid and high dose groups there were increased %'s of resorption due to a large number of early resorptions which appear to be treatment related.

Fetal Morphological Observations:

All external, visceral, and skeletal malformations as well as genetic and developmental variations are summarized in the report. The fetuses from the two control animals who died on test were inadvertently discarded by a "technical error."

There were no reported malformations according to the registrant's definition in the control group; however the malformations present in the treated groups did not increase in a dose-related trend. The high dose showed a decrease in malformations in comparison with the mid dose group. As can be seen in Table 6 most of the malformations were found in the low and mid dose groups and were concentrated in the skeletal area. These were not statistically significant.

The reported variations according to the report were present in the control group as well as the treated groups in a non-dosed related trend with more variations in the control group rather than the treated in some cases. More information such as individual fetal and litter data is required to make a proper evaluation of these effects.

3. Discussion

As can be seen in Table 6 Propachlor had a possible effect on the occurrence of malformations in that at the mid-dose (15 mg/kg/day) which included a large number of various skeletal anomalies. The high dose shows no increase over control values in the number of malformations of any type than does the mid dose. There is no dose related trend for any of the malformations found. The company did not define what they considered to be a malformation versus a variation.

The "variations" in major vessels should be defined. The vertebral variations, the carpal flexure, and the thirteenth rib are of important consideration in the fetal morphological considerations but are also found in a large percentage of the control fetuses.

Based upon the distributions of the mortalities throughout the groups, the absence of clinical changes, and the similar postmortem findings in the survivors, it was concluded that propachlor did not affect the maternal mortality.

The abortions that occurred were not treatment related since there were no abortions in the contral and high dose groups and two at 5 mg/kg and one at 15 mg/kg. The reported increase in preimplantation loss with a dose-related trend could indicate that there were maternal health problems.

There was Developmental toxicity at 15 and 50 mg/kg

groups with an increase in postimplantation losses and thus a decrease in the number of viable fetuses which was statistically significant only at 15 mg/kg. This may be developmental toxicity since there was no specific maternal toxicity. The clinical signs observed were not listed with frequency per dose group and therefore a dose relationship could not be evaluated.

The historical control data should be presented as separate studies as well as summary data for a period of no greater than 2 years previously. Individual maternal necropsy data are necessary to evaluate the individual fetal malformation and developmental and genetic variation which is given by the litter. The route of administration and vehicle should be identified (for historical control).

Mortality due to presumed disease conditions was high in the study (final litters examined 12, 8, 10, 13), but an adequate number of litters remained in the high dose to evaluate possible effects. The results undoubtedly reflect an overriding incidence of maternal poor health.

A teratology NOEL cannot be used here according to the teratology S.E.M. Developmental toxicology is indicated when a substance causes variations or malformations below the maternal NOEL.

In Table 6, excerpted from the text of the report, the company reports no malformations in the control group, only variations which the company must define.

4. Conclusion:

The data indicate these approximate values:

Maternal Toxicity NOEL = > 50 mg/kg/day
Developmental Toxicity NOEL = 5 mg/kg/day

5. Classification:

Supplementary. Inadequately presented historical data as well as the lack of the individual data mentioned in the discussion.