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

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MAY 18 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: AZODRIN (Monocrotophos) - Rabbit Teratology Study
Accession No. 401023-01
EPA Registration No. 352-459

TB Project No. 7-0537
Caswell No. 377

FROM: Irving Mauer, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: William Miller/Gary Otakie, PM Team 16
Insecticide-Rodenticide Branch
Registration Division (TS-767C)

THRU: Judith W. Hauswirth, Ph.D., Acting Head
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant

E.I. du Pont de Nemours & Company (Haskell Labs), Wilmington, Delaware.

Request

Review and evaluate the following study, submitted in response to reregistration requirements (Toxicology Chapter for the Monocrotophos Registration Standard, dated April 2, 1985):

Developmental Toxicity Study of AZODRIN®
Insecticide (Technical) in New Zealand
White (NZW) Rabbits

performed by Argus Research Labs (Horsham, PA), Argus protocol 619-005 (Haskell Lab. Report No. 014-87), dated January 12, 1987.

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TOXICOLOGY BRANCH: DATA REVIEW

Reviewed by: Irving Mauer, Ph.D. 5-15-87 TB Project: 7-0537
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Through: Judith W. Hauswirth, Ph.D., Acting Head
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C) Judith W Hauswirth 5/15/87

Chemical: Monocrotophos (Azodrin) Caswell No.: 377
EPA Chem.: 058901

Study Type: Teratology - Rabbit

Citation: Developmental Toxicity Study of Azodrin® Insecticide (Technical) in New Zealand White (NZW) Rabbits

Accession No.: 401023-01

MRID No.: N/A

Sponsor: E.I. du Pont de Nemours & Co. (Haskell Lab)
Wilmington, DE

Testing Lab.: Argus Research Laboratories, Inc., Horsham, PA

Study No.: Argus Protocol 619-005/Haskell Lab. Rpt. No. 014-87

Study Date: January 12, 1987

TB Conclusions/Evaluation:

Core-Minimum Data. The test substance, given to pregnant NZW rabbits at daily doses of 0.1, 1, 3, and 6 mg/kg on days 6 through 18 of presumed gestation, produced severe maternal clinical toxicity and death at the HDT.

Minimal (nonsignificant) increases in resorptions, reduction in live fetal weight and maternal uterine weight were also found at the HDT. At 3 and 6 mg/kg, a rare fetal malformation was noted, namely agenesis of the intermediate lobe of the lung.

Maternal NOEL = 1 mg/kg/day
Maternal LEL = 3 mg/kg/day (fecal disturbances)
Developmental NOEL = 1 mg/kg/day
Developmental LEL = 3 mg/kg/day (agenesis of the intermediate lobe of the lung)
A/D ratio = 1/1 = 1.00

TB Conclusions

This study has been graded as CORE-MINIMUM DATA, with the following parameters assigned:

Doses tested: 0, 0.1, 1, 3, and 6 mg/kg/day.
Maternal NOEL = 1 mg/kg/day.
Maternal LEL = 3 mg/kg/day (fecal disturbances)
Developmental NOEL = 1 mg/kg/day.
Developmental LEL = 3 mg/kg/day (agenesis of intermediate lobe of the lung)
A/D ratio = 1.00

The detailed TB Data Review is attached.

Attachment

DETAILED REVIEW

Test Chemical:

Azodrin Technical (WRC Tox Sample No. 921,926), purity unstated, a reddish-brown solid, dissolved in sterile water for testing.

Procedures:

Procedures according to Agency GLP standards and FIFRA Testing Guidelines (1978) were followed (Appendix A). Briefly, following a preliminary (pilot) dose-selection study at seven closely spaced doses ranging from 0.1 to 5 mg/kg/day, artificially-inseminated (with sperm from 4 proven bucks of the same strain and source) female rabbits (20 per dosage group) were gavaged on days 6 through 18 of presumed gestation at daily doses of 0 (vehicle), 0.1, 1, 3, and 6 mg/kg, adjusted daily on the basis of the recorded body weights of the does. Daily observations were made for signs of clinical toxicity, abortion, premature delivery, body weight, and feed consumption. Cause of death was determined to the extent possible, and uterine contents of dead animals recorded. Does that aborted or delivered prematurely were examined in the same manner as cesarean-sectioned animals.

All survivors were sacrificed on day 29 of presumed gestation, ovaries removed and corpora lutea counted. The uterus of each animal was weighed and examined for pregnancy, number and placement of implantations, early and late resorptions, and live/dead fetuses. Fetuses were sexed, and body weight and any soft tissue/skeletal alterations recorded.

Results: Maternal Observations (Report Summary Tables 1 to 8, Report Individual Data Tables 15 to 20)

One rabbit at the 3 mg/kg/day dose died, whereas a significant number ($p < 0.01$) of does, 13 (65%), at 6 mg/kg/day (12 pregnant, 1 nonpregnant) were found dead, all deaths occurring after three to six dosages and was preceded by severe clinical toxicity ("excitatory/depressive" signs of OP toxicity, diarrhea, weight loss, and decreased feed consumption). The principal findings at necropsy, especially at the HDT, were gastrointestinal ulceration, enlarged gallbladders and/or pulmonary edema; all incidences were significantly different from controls (Table 1).

Among 16, 18, 17, 18, and 19 pregnancies at the 0 (vehicle), 0.1, 1, 3, and 6 mg/kg/day dosage groups, two 0.1 mg/kg, one 1 mg/kg and one 6 mg/kg rabbits aborted (between day 21 and 25 of gestation). The incidence of abortion was said to be within historical control limits and not dosage-dependent (although no background data for maternal abortions were presented in this report) (Table 1).

Table 1: Selected (Positive) Maternal Effects of Monocrotophos in Rabbits[1/]

	Dosage Groups (mg/kg/day)				
	0	0.1	1	3	6
Rabbits tested (N)	20	20	20	20	20
Rabbits pregnant (N)	16	18	17	18	19
Clinicals Observations:					
Died	0	0	0	1	13**
Aborted	0	2	1	0	1
Delivered	0	0	0	3	0
OP effects[2/]	0	0	0	0	5-20**
Fecal disturbances	4	3	4	6**	6-16**
Alopecia	6	5	8	9	1
Necropsy Observations:					
Fluid around mouth	0	0	0	0	7**
Inflated lungs	0	0	0	0	8**
Gastric ulceration	0	0	0	3	7*
Gastric (green) fluid	0	0	0	0	6*
Duodenal ulcers	0	0	0	0	10**
Anal tar-like substance	0	0	0	0	6*
Body Weight Change[3/] (kilograms)	+0.26	+0.25	+0.25	+0.26	-0.04**
Feed Consumption (g/kg/day)[3/]	34.4	34.9	33.3	33.4	29.6
Cesarean-Sections					
N	16	16	16	15	6
Corpora lutea	10.9	10.7	11.6	11.1	10.3
Implantations	8.6	8.6	10.1	8.3	9.0
Litter Size	8.0	7.7	9.6	7.8	7.5
Live (total)	128	123	153	117	45
(Per litter)	8.0	7.7	9.6	7.8	7.5
Dead (total)	0	0	1	0	0
(Per litter)	0	0	0.1	0	0

1/ Extracted from Tables 1 to 8 and 15 to 20 of the Final Report.
2/ Hypernea/decreased motor activity/impaired righting reflex/ataxia/excess salivation/fecal staining/rales/tremors/constricted pupils. Highest value chosen.
3/ Days 0 to 29.
* Significant at $p < 0.05$.
** Significant at $p < 0.01$.

Table 1: Selected (Positive) Maternal Effects of Monocrotophos in Rabbits[1/] (cont'd)

	Dosage Groups (mg/kg/day)				
	0	0.1	1	3	6
Rabbits tested (N)	20	20	20	20	20
Rabbits pregnant (N)	16	18	17	18	19
Resorptions:	0.6	0.9	0.5	0.5	1.5
Early (total)	9	7	3	4	2
(Per litter)	0.6	0.4	0.2	0.3	0.3
Late (total)	1	7	5	4	7
(Per litter)	0.1	0.4	0.3	0.3	1.2
Does with resorptions	5	8	5	5	3
Does with all implants resorbing	0	1	0	0	0
Uterine weight (g)	410.35	434.27	520.54	436.13	387.31

1/ Extracted from Tables 1 to 8 and 15 to 20 of the Final Report.
2/ Hypernea/decreased motor activity/impaired righting reflex/ataxia/excess salivation/fecal staining/rales/tremors/constricted pupils. Highest value chosen.
3/ Days 0 to 29.
* Significant at $p < 0.05$.
** Significant at $p < 0.01$.

Persistent fecal changes (diarrhea, dried feces and/or no feces) were recorded at both the 3 and 6 mg/kg/day groups, which was significantly different from controls at both dosages ($p < 0.05$, $p < 0.01$) (Table 1).

Very slight and insignificant decreased mean body weight gains (-0.01 kg to +0.16 kg, compared to control values of +0.2 to +0.21) were recorded in the 3 mg/kg/day group; body weight gain had recovered, however, by the end of the study (Table 1). By contrast, reduction in body weight gain was severe, persistent, and statistically significant ($p < 0.01$) at the HDT (Table 1).

Feed consumption was significantly decreased ($p < 0.05$ to $p < 0.01$) only at the HDT, markedly during the dosage period (days 6 to 18), but persistent though less marked during the postdosage period (days 19 to 29) (Table 1).

Since a total of four rabbits aborted among the five dosage groups, (two at 0.1 mg/kg, one at 1 mg/kg, and one at 6 mg/kg), three delivered spontaneously (all in the 3 mg/kg group), and 12 pregnant 6 mg/kg does died, day-29 cesarean sectioning observations were based on 16, 16, 16, 15, and 6 pregnancies. Minimal (nonsignificant) increases in mean number of total (early and late) resorptions or mean late resorptions, as well as slightly decreased uterine weights, were found only at the HDT (Table 1).

No other reproductive parameter was apparently affected by the test substance, including observations on corpora lutea, implantations, litter size, dead fetuses, or early resorptions.

Results: Fetal Data (Report Summary Report Tables 9 to 13; Report Individual Data Tables 22 and 23)

Mean fetal weight was slightly reduced, and the mean percent dead or resorbed conceptuses increased at the HDT, but neither value reached the level of statistical significance as compared to control values. Average litter weights were 38.71, 40.10, 38.22, 39.89, and 36.60 g for the five groups (0, 0.1, 1, 3, and 6 mg/kg); males averaged 38.09, 40.72, 38.62, 39.76, and 36.48 g per litter, and females, 37.95, 39.66, 37.93, 38.52, and 36.78 g per litter. Mean percent dead or resorbed conceptuses per litter was given as 8.5, 7.4, 5.5, 8.1, and 15.9 (Table 2).

Fetal sex ratio was apparently not affected by the test substance at the doses used, the mean percent of live male fetuses per total live fetuses being recorded as 48.0, 46.1, 52.7, 55.4, and 66.2 (Table 2).

No increase in frank malformations (i.e., irreversible defects) or developmental changes (i.e., reversible) were attributed by the authors to the administration of the test compound among totals of 128, 123, 154, 117, and 45 live day-29 cesarean-derived fetuses from the 16, 15, 16, 15, and 6 litters with fetuses (pregnancy 11638 at 0.1 had only early resportions). Totals of 10 (62.5%), 9 (60%), 9 (56.2%), 8 (53.3%), and 4 (66.7%) litters had fetuses with some congenital alteration among the five dosage groups (0, 0.1, 1, 3, and 6 mg/kg/day, respectively). The incidence of fetuses with alterations was 26 (20.3%), 16 (13.0%), 23 (15.0%), 15 (12.8%), and 7 (15.6%), respectively, and the mean percent fetuses affected per litter was 17.61, 11.70, 13.92, 10.42, and 13.92 (Table 2).

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Table 2. Selected Fetal Effects of Monocrotophos Treatment (Day 16 to 18) of Does[1/]

Observation	Dosage Groups (mg/kg/day)				
	0	0.1	1	3	6
Litters examined (N) on day 29	16	15[2/]	16	15	6
Implantations (per litter)	8.6	9.0	10.1	8.3	9.0
Live fetuses (per litter)	8.0	8.2	9.6	7.8	7.5
Litters with one/more live fetuses	16	15[2/]	16	15	6
Live fetal body weights (g/litter)	38.71	40.10	38.22	39.89	36.60
Male/female ratio	1.01	1.03	1.02	1.03	0.99
% Dead/resorbed conceptuses per litter	8.5	7.4	5.5	8.1	15.9
Live fetuses (N)	128	123	153	117	45
% Fetuses with any alterations/litter	17.61	11.70	13.92	10.42	13.92
Gross External/Soft Tissue Defects:					
Open eyelid	0	0	1	0	0
Runt	0	0	0	1	0
Thoracoschis/Gastroschisis	0	0	0	0	1
Subcorneal hemorrhage	0	0	1	0	0
Enlarged right atrium	0	0	0	0	1
Small pulmonary artery	1	0	0	0	0
Absent intermediate pulmonary lobe	0	0	0	1	3*
Skeletal Changes:					
Irregular ossification of nasals	2	2	1	1	0
Misaligned sutures	2	1	1	0	0
Incomplete ossification:					
(Fetuses)	11	6	10	3*	0*
(Per Litter)	6	4	5	3	0
Inter/intra-parietals	3	1	3	1	3
Irregular shape	1	0	0	0	0
Angulated hyoid (ala)	0	1	2	1	0
Associated Vertebral/ rib alterations	0	1	1	0	1
Fused ribs	0	2	0	0	1
Wavy ribs	0	0	0	0	1
Extra ribs	0	0	0	1	0

1/ Extracted from Tables 9 to 14, 22 and 23 of the Final Report.
2/ One contained only resorptions.
* Significantly different from control, $p < 0.05$.

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Table 2. Selected Fetal Effects of Monocrotophos Treatment (Day 16 to 18) of Does[1/] (cont'd)

Observation	Dosage Groups (mg/kg/day)				
	0	0.1	1	3	6
Skeletal Changes: (cont'd)					
Sternal manubrium	2	0	0	0	0
Sternebral variations	2	0	0	0	1
Duplicated xiphoid	0	0	0	0	1
Irregular scapula	0	0	1	0	0
Incomplete ossification of pelvic pubes	3	0	1	1	0

1/ Extracted from Tables 9 to 14, 22 and 23 of the Final Report.

Although the Report notes that dead fetuses, late resorptions, and delivered pups were excluded from the summary and statistical analysis, some of these were examined to the extent that autolysis and cannibalization did not preclude an evaluation. For example, it was possible to examine resorptions from one control litter (5 fetuses), two from the 0.1 mg/kg/day dosage groups (7 and 8), two from the 1 mg/kg/day group (5 and 12), two from the 3 mg/kg/day group (3 and 4), and one from the 6 mg/kg/day group (4 fetuses). In addition, one 1 mg/kg/day dose group dead fetus (from a litter of 7), seven 3 mg/kg/day day-29 spontaneously delivered pups (of which 5 were cannibalized), and one delivered pup plus nine fetuses in utero from the 3 mg/kg/day group were also evaluated. All specimens appeared normal within the limits of evaluation.

Three gross externally malformed fetuses were recorded, one each from the 1 (in a litter of 10), 3 (of 8), and 6 (of 2) mg/kg/day groups; there were no malformed fetuses in the control or 0.1 mg/kg/day groups. The 1 mg/kg/day group fetus had open eyelid, delayed ossification of the skull (open frontal surface, enlarged fontanelle), and delayed sternal ossification) (incompletely ossified manubrium). The 3 mg/kg/day liveborn fetus was a runt (weight, 12.93 g), and manifested skeletal changes consistent with its small size (delayed skull development, incomplete ossification of the first sternal center, no ossification of pelvic pubes). The single abnormal fetus from the 6 mg/kg/day group had thoracoschisis and gastroschisis. In addition, the right atrium and aorta were enlarged, the intermediate lobe of the lung was absent, the sternum was duplicated from the manubrium through the xiphoid process, and there were wavy ribs. No other gross external alterations were found in other fetuses of this study.

Soft tissue malformations were found in one control fetus (in a litter of 8), a 1 mg/kg/day fetus (of 1), a 3 mg/kg/day fetus (of 10) and three fetuses in two litters (of 2 and 4) in

the 6 mg/kg/day group (the Report, however, mentions only two fetuses in this group). The control fetus had an enlarged aorta and small pulmonary artery. The 1 mg/kg/day fetus had a subcorneal hemorrhage. The intermediate lobe of the lung was absent in the 3 mg/kg/day fetus and in three 6 mg/kg/day fetuses (significantly different from concurrent control, $p < 0.05$, but stated to be within the historical control range for this laboratory--presented as Appendix C of this Report; hence not considered compound-related). One of the three 6 mg/kg/day fetuses was described above as having also a gross external malformation (thoracoschisis and gastroschisis) (Table 2).

Skeletal alterations in some fetuses with other congenital defects have already been described above. An additional six fetuses from four 0.1 mg/kg/day litters were first identified as having vertebral malformations and/or other skeletal variations (three with hemivertebra and fused centra, or fused ribs, or enlarged skull fontanelle; three with fused or split ribs, and minor skull alterations) (Table 2).

One 1 mg/kg/day fetus had related thoracic vertebral and rib alterations plus an internasal. One 3 mg/kg/day fetus was found with an extra rib, and one 6 mg/kg/day fetus had fused ribs and delayed ossification of a thoracic vertebra (the arch).

Irregular or incomplete ossification of the fetal skull was recorded as the most common finding in this study, and stated to be a common occurrence in this strain of rabbits (as recorded in Appendix C of the Report). Such findings was reported in 18, 9, 5, and 3 fetuses of 8, 6, 7, 4, and 3 litters from the 0, 0.1, 1, 3, and 6 mg/kg/day dosage groups (see Table 2).

Finally, no dosage-dependent changes in the incidence of fetal ossification sites (20 sites examined) were recorded.

In summary, no gross fetal external, soft tissue or skeletal alteration was considered to be related to administration of Azodrin to pregnant rabbits.

Report Conclusion:

On the basis of these data, the authors consider the NOEL for maternal effects to be 1 mg/kg/day and for developmental effects as 3 mg/kg/day.

TB Evaluation: Core-Minimum Data. The study was well designed and conducted, and the results comprehensively reported. A full disclosure of Quality Assurance was included in the Report (as Appendix G) detailing regular inspections throughout the course of the study of both the procedures as well as raw data sheets and log books.

This reviewer agrees in general with the conclusions of the study authors, except in one respect. Agenesis (absence) of the intermediate (diaphragmatic) lobe of the lung is a rare fetal malformation in NZW rabbits, this laboratory recording only one instance among 2482 control fetuses (0.4%) in 336 litters (0.3%) in seven studies conducted between 1982 and 1985 (Appendix C of the Report). The present study records a significant increase (3 of 45 fetuses, 6.7%, $p < 0.05$), in six litters (33.3%) of the high dose group, 6 mg/kg/day, but only one (0.8% in the 15 litters (6.7%) at the next lowest dose 3 mg/kg/day (Table 2). TB considers both incidences to be compound related, in showing a definite trend for this malformation. Hence, the following parameters are assigned to the study:

Doses tested = 0, 0.1, 1, 3, 6 mg/kg/day
Maternal NOEL = 1 mg/kg/day
Maternal LEL = 3 mg/kg/day (fecal disturbances)
Developmental NOEL = 1 mg/kg/day
Developmental LEL = 3 mg/kg/day (agenesis of the intermediate lobe of the lung)
A/D ratio = 1/1 = 1.00

APPENDIX A

AZODRIN

Page_____ is not included in this copy.

Pages 13 through 29 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.

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