2-13-85

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

004306

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

February 13, 1985

SUBJECT: AZODRIN - Miscellaneous Data Submitted in Response to Data Call-In.
ID 201-157 Acc. #252075 CASWELL 377

TO: W. Miller/S. Torregrosa, PM 16
Registration Division (TS-767)

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

2-13-85

THRU: Jane E. Harris, Section Head
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769)

12/14/85

Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

Action Requested:

In response to the monocrotophos DCl, review and evaluate the following study submitted December 21, 1983 by Shell:

"Technical Azodrin® (SD 9129) Teratology Study in SD CD® Rats". Report date 11/1983; performed by ToxiGenics, Inc.; submitted to Shell Development Company; EPA Acces #252075.

TB Evaluation/Core:

This teratology study is considered adequate for regulatory purposes and is CORE classified as MINIMAL. The reviewers concur with the author's conclusions that technical AZODRIN was not teratogenic at the doses tested, and fetotoxic only at levels producing maternal toxicity. (See TB Review, attached.)

Attachment

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Original 2/21/85

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TB Review 2/1/85

STUDY TYPE: Teratology - Rat

Caswell #377
EPA Chem #058901 (201-157)

CITATION: "Technical Azodrin® (SD 9129) Teratology Study in SD-CD Rats," submitted January 23, 1984, by Shell.

ACCESSION/MRID: 252075/na

SPONSOR/TESTING LAB: Shell Development Co., Houston, TX/ ToxiGenics, Inc., Decatur, IL.

STUDY NO./DATE: ToxiGenics #450-1248; Shell Project #61533 (Protocol #WTP-219)/November 16, 1983

TEST MATERIAL: "Technical Azodrin (SD-9129), WRC Sample No. 55F" as supplied by Shell Chemical Co. (Denver) to the testing lab. Characterization, stability, chemical analysis and purity (% ai) were not indicated in the report; however, it was reported that: "The concentrations of all samples before and after dosing were within 10% of the normal concentration specified in the protocols."

QA/GLP: Statement was included in the report, signed by Antoinette Skelley (for Toxigenics QA director, Donald G. MacKellar), November 16, 1983, and by C.C. Lu for Shell, December 1, 1983.

PROCEDURES: Standardized procedures were utilized; a copy of M & M is attached (pp. 4-13 of the Report). Briefly, 26 young sexually mature virgin Charles River Crl:CD (SD)BR female albino rats per group were dosed orally by gavage with test material (in 5 ml DW/kg) on gestation days 6 through 15 at levels of 0, 0.3, 1.0 and 2.0 mg/kg/day, sacrificed on gestation day 20, and gravid uteri removed for the determination of numbers of implantation sites, resorptions and fetuses (viable and dead). Thoracic and abdominal organs were saved for examination, and apparently non-gravid uteri treated with ammonium sulfide solution to confirm pregnancy status. Litters were sexed, weighed and measured (crown-rump), and treated for examination of skeletal as well as visceral development (approx. 1/2 for each procedure). Standard statistical analyses were conducted (with dams or litters considered the experimental unit) for maternal reproductive parameters (corpora lutea, implan- sites, pre-implant loss, resorption sites, viable fetuses, post-implant loss, % implant sites per viable fetus), and for fetal values (sex ratio, mean weight, crown-rump length, mean % abnormal fetuses per litter and litters containing abnormals), reporting statistical differences at the 5% level.

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RESULTS: Maternal Data. All females survived to sacrifice except one gravid 2.0 mg/kg animal found dead on D-15; a "thinned glandular stomach which lacked mucosal convolutions" was observed at necropsy. Additionally, this high-dose group was reported to exhibit muscle tremors/twitching, listlessness, salivation, perianal staining, crusty eyes, staggered gait, lacrimation and crusty muzzles. None of these manifestations of OP toxicity were reported in either of the two lower dose groups (0.3, 1.0 mg/kg). No compound-related histopathological changes were apparently found among surviving females. Significant reductions in live body weight gain and postmortem carcass weights compared to controls were recorded for both the 1.0 and 2.0 mg/kg test groups on gestation days 12, 15 and 20; but no differences for gravid uterine weight in any test group. [See tabulation at the end of this review.]

Reproductive Effects: No statistically significant changes from control values were recorded in mean number of corpora lutea, implant sites, early or late resorption sites, or viable or dead fetuses for any treated group. [See tabulation at the end of this review.]

Fetal Data (and Malformations). Compared to control values, significant decreases in body weights and crown-rump lengths were recorded only for the high-dose group, while fetal sex ratios were comparable in all groups.

Except for incidental occurrences (8 fetuses from a single 0.3 mg/kg group dam with rotated appendages, "thickened chest," and short torso; unilateral "darker ... left eye" in one 1.0 mg/kg fetus), the investigators recorded no external structural aberrations which they considered resulted from test article administration. They did, however, find a statistically increased mean percent of runt fetuses [and litters -- see Report Table 7] for the mid- and high-dose groups, but which was not dose related.

The report recorded no "...consistent skeletal structure aberrations which appeared to be the result of Technical Azodrin (SD 9129)...." between any treated groups and controls. However, significant differences in skeletal development of the 2.0 mg/kg litters which the authors categorize as "...common variants" or "...incidental findings" were reported (e.g., incomplete ossification; 14 ribs). These included an incidence of 58.4% non-ossified sternebrae [in the text, but stated as "58.1%" in Report Table 8] vs. 28.8% in concurrent controls, but within the control range previously reported by this laboratory, 4.7% to 81% (Report Appendix J). Additionally, significant reductions in the mean percents of incompletely ossified skull bones (interparietal, occipital) were recorded in the 0.3 and 1.0 mg/kg group fetuses, but no change for the 2.0 mg/kg group.

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No statistical differences in mean percent of grossly "malformed" fetuses per litter or number of litters with malformed fetuses were recorded from fetal visceral examinations, according to the report. As with the skeletal findings, statistical differences were reported for some "common" developmental variants indicated as "incidental findings," such as large (or small) atria and increased renal pelvic cavitation. Thus, $p < 0.05$ increases were recorded in the mean percents of 0.3 and 1.0 mg/kg group fetuses with these variants (and the number of litters treated at 0.3 mg/kg), but not among high-dose group fetuses (or litters).

Other fetal findings (of low occurrence) reported in this study were considered by the sponsor and/or consultants as fixation artifacts (e.g., misshapen brain in one 1.0 mg/kg group fetus); or spontaneous genetic variants in this strain of rats, based upon historical data from WIL Labs (Attachment 4 of the Report), such as malformed and/or misshapen brain in one control fetus, three of 0.3 mg/kg, one of the 1.0 mg/kg and two of the 2.0 mg/kg group treated; or unrelated to dose, such as undescended testes in one 0.3 mg/kg fetus and two of the 2.0 mg/kg group, but none in controls or in the 1.0 mg/kg group. In any case, none of these reached a level of statistical significance. [See tabulation at the end of this review.]

The authors and sponsor concluded that: "No indication of any teratogenic effect was observed due to Azodrin treatment at the levels tested," the HDT of which produced significant maternal toxicity (as evidenced by redouced body weights and abnormal clinical signs) as well as fetotoxicity (lower fetal body weight and crown-rump length) but no gross histopathological lesions.

Discussion: This teratology study is considered adequate for regulatory purposes and is CORE classified as MINIMAL. The reviewers concur with the author's conclusions that technical AZODRIN was not teratogenic at the doses tested, and fetotoxic only at levels producing maternal toxicity.

Although no gross or histopathological lesions were found in any test group, this reviewer is satisfied that significant maternal OP toxicity (especially at the HDT) and death (one at the HDT) represented a dose level high enough to have compromised fetal development (weight, length, runting). The non-dose-related skeletal and visceral effects noted may also be considered minor variations, of little toxicologic significance.

MATERNAL NOEL = 0.3 mg/kg
MATERNAL LEL = 1.0 mg/kg (decreased body weight gain)
FETAL NOEL = 1.0 mg/kg
FETAL LEL = 2.0 mg/kg (runting; reduced fetal weight and length).
No TERATA at the HDT.

3/21/85

Summary of Maternal Effects of Azodrin Administration to SD-CD Rats During Pregnancy* (ToxiGenics Report #450-1248, Acc. No. 252075).

Dose Group:	0.0	0.3 mg/kg	1.0 mg/kg	2.0 mg/kg
No. Dams	25	24	24	25
Died	0	0	0	1
Observations (number):				
Alopecia	1	1	1	0
OP effects **	0	0	0	25
Pathology	0	0	1 (spleen nodules)	1 (unilateral uterine hypoplasia and dilated ovary)
BW gain (D-6 to 20; g):	126.4	118.4	111.1 (SIG)	79.8 (SIG)
Reproductive Data (mean values):				
Pregnant (survivors)	25	24	24	24
Corpora lutea	16.0	16.1	15.9	17.2
Implants	15.0	15.0	15.3	15.3
Resorptions (early)	1.2	0.6	1.2	0.9
(late)	0.04	0.0	0.0	0.0
Fetuses (live)	13.7	14.3	14.0	14.3
(dead)	0.0	0.0	0.0	0.0
% Pre-Impl. Loss	6.6	6.3	3.9	10.1
% Resorp. Sites	8.4	4.4	8.0	5.9
% Dead Fetuses	0	0	0	0
% Viable Fetuses	91.6	95.6	92.0	94.1

* Derived by the reviewer from Report Tables 1-9 and Appendices (SD's omitted; significance at $p<0.05$ indicated as: "(SIG)").

** OP = signs of organophosphate toxicity (muscular, salivation, lacrimation, etc.)

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Summary of Fetal Effects of Azodrin Administration to SD-CD Rats During Pregnancy* (ToxiGenics Report #450-1248, Acc. No. 252075).

Dose Group:	0.0	0.3 mg/kg	1.0 mg/kg	2.0 mg/kg
Number: Males	160	172	160	171
Females	183	172	177	173
Sex Ratio (Males %):	47.9	49.1	48.3	50.1
Weight, g (per litter):				
Males	4.0	3.7	4.1	3.5 (SIG)
Females	3.7	3.6	3.9	3.3 (SIG)
Crown-Rump, cm (per litter):				
Males	3.8	3.7	3.9	3.6 (SIG)
Females	3.7	3.7	3.7	3.5 (SIG)
External Observations:				
Hematoma (%)	5(1.4)	2(0.6)	1(0.3)	4(1.2)
Runts (%)	2(0.6)	5(1.6)	8(2.7)SIG	6(1.9) SIG
Total "ABN"(%)	0	8(2.1)	1(0.3)	0(0.0)
Visceral:				
Atria	3	10	8	6
Renal Cavitation	0	2	0	1
Malformed Brains	1	3	1	2
Undescended Testes	0	1	0	3
Total Findings (%)	4(2.5)	17(10.6)SIG	11(6.5)SIG	12(6.2)

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HED/TOX:JOB:95708:Mauer/Carletta:HED:21:eg:Kendrick:898-1270:2/5/85:Del.2/13/8
REVISED:JOB:95708:Mauer/Carletta:Kendrick:898-1270:2/15/85:Kim

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