4.12.82 PP-1166 TXR-1760

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

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OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP 0G2396 Amendment to EUP No. 7969-EUP-EU for the Herbicide 2-[1-(ethoxyimino)-butyl]-5 [2-(ethylthio) propyl]-3-hydroxy-2-cyclohexen-1-one (BAS: 9052 H; Trademarked Poast®). Accession No. 099537. Teratology Study in Rabbits.

TOX Chem No. 72A

FROM: Minnie R. Sochard, Ph.D. M. Sochard 4/12/82
Toxicology Branch/HED (TS-769)

TO: Robert Taylor, PM #25
Registration Division (TS-767)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch/HED (TS-769) 4/15/82 4/18/82

THRU: Orville E. Paynter, Ph.D.
Chief Toxicology Branch/HED (TS-769)

Petitioner: BASF Wyandotte Corporation
Parsippany, New Jersey

Study No. 18, teratology study in rabbits with the chemical NP-55 (BAS 9052H) has been amended. The teratogenicity NOEL is 160 mg/kg/day and the Core Classification upgraded to Guideline. A meaningful teratogenic evaluation could not be made at the next highest dosage level (480 mg/kg/day) due to severe maternal toxic effects. These effects severely stressed both dams and fetuses causing maternal mortalities, increased abortions, resorption, post-implantation losses and decreased numbers of litters and viable fetuses. A revised Eight Point Summary page and revised review of the study are attached.

Attachment

cc: Robert Coberly, TOX

OPP:HED:TOX: M.SOCHARD:sb 10/5/81 X70576 Rm. 807 CM #2 #m5
Re: 4/7/82

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Summary of Toxicity Data

Eight Point Free Standing Summary

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1. Summary of selected toxicology data considered in setting the tolerances:

a) Data on Technical NP-55

STUDY	RESULTS	TOX CATEGORY	CORE CLASSIFICATION
Acute Oral LD50, Rat	3.125 gms/kg - males 2.676 gms/kg - females	III	Guideline
Acute Dermal LD50, Rat	> 5.0 gms/kg, males & females	III	Guideline
Acute Inhalation LC50, Rat (4 hours)	6.03 mg/L, males 6.28 mg/L, females	III	Guideline
Primary Eye Irritation, Rabbit	No irritation	IV	Guideline
Primary Dermal Irritation, Rabbit	No irritation	IV	Guideline
Dermal Sensitization, Guinea Pig	Negative	-	Minimum
14-Week Mouse Feeding Study	NOEL = 300 ppm	-	Minimum
14-Week Rat Feeding Study	NOEL = 300 ppm	-	Guideline
26-Week Dog Feeding Study	NOEL = 120 ppm	-	Minimum
2-Year Mouse Feeding Study (1-Year interim report)	NOEL - Cannot be determined from the interim report; also, female 12 mos. blood chem. data absent.	-	Supplementary
2-Year Rat Feeding Study (1-Year interim report)	NOEL - Cannot be determined from the interim report; also, urinalysis absent from protocol.	-	Supplementary
Teratology Study, Rats	Teratogenicity NOEL: 250 mg/kg /day (highest dose tested), (Maternal toxicity NOEL = 40 mg/kg/day; maternal LEL = 100 mg/kg/day [significantly decreased adrenal weight]).	-	Guideline
Teratology Study, Rabbits	Teratogenicity NOEL 160 mg/kg/day, (Maternal toxicity NOEL = 160 mg/kg/day; Maternal LEL= 480 mg/kg/day [severe weight loss, 5/16 deaths, 6/16 abortions, reduction in number of litters and viable fetuses]).	-	Guideline

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Detailed Review of Study

18. Teratology Study in Rabbits (of NP-55) International Research and Development Corporation. May 23, 1980, Accession No. 099537, Tab. C18, pp. 1-33; Appendix I (no pagination); Appendix II (6 pp.) Plus Protocols; Appendix III (no pagination).

Protocol - Four groups of sexually mature virgin female New Zealand White rabbits (Langshaw Farms, Augusta, Mi.) aged 7 months, acclimated and free of parasitic coccidiae, each group consisting of 16 animals, were artificially inseminated and induced to ovulate. On days 6-28 of gestation, the four groups of rabbits were fed the following dosages of NP-55 by gavage, respectively, suspended in 0.5% carboxymethylcellulose as a vehicle in a constant volume of one ml per kg: 0 mg/kg (vehicle control), 40, 160 and 480 mg/kg. Animals were observed daily prior to and following treatment for mortality and pharmacotoxic signs to day 29 of gestation. Animals showing signs of abortion or premature delivery were sacrificed and examined for gross evidence of morphological changes on the day signs appeared. Intact fetuses were examined and preserved as well as those tissues deemed necessary to confirm other findings. Gross necropsy was performed on all animals not surviving to scheduled sacrifice to determine cause of death, with tissues preserved and fetuses examined and preserved as noted above. Maternal body weights were measured on days 0, 6, 12, 18, 24 and 29 of gestation. On day 29, surviving females were sacrificed by an overdose of sodium pentobarbitol in the marginal ear vein, the uterus excised and weighed and the fetuses removed. The number and location of viable fetuses, early and late resorptions and the number of total implantations and corpora lutea recorded. Thoracic and abdominal cavities were examined for gross morphological changes. Uteri of non-gravid appearing females were opened and preserved for examination of pregnancy status. Fetuses were weighed and examined for external malformations and variations, including palate and eye. Visceral malformations and variations and sexes were determined by dissection, including brain (mid coronal slice). The heart was dissected by the method of Staples. Eviscerated, skinned fetuses were fixed, cleared and stained with Alizarin Red S (method similar to that of Dawson) for skeletal examination. Statistical procedures compared treatment to control groups at a significance level of $P < 0.05$. Statistical analysis was used to compare male/female sex distribution, number of litters with malformations, number of early and late resorptions and post implantation loss. The mean number of viable fetuses, total implantations, corpora lutea and

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mean fetal body weights were compared by analysis of variance with appropriate supplementary tests to judge significance of differences.

Results - For maternal observations, there were no differences in appearance or behavior during the gestation period between treatment and control groups. A summary of deaths and abortions is abstracted in Table I. Cause of deaths prior to sacrifice of dams could not be determined. In addition to data in Table I, red fluid in the bladder was found in one of each of the 160 mg/kg and 480 mg/kg rabbits. One control and two 480 mg/kg rabbits had pale livers. Mean body weights of 40 mg/kg/day rabbits were similar to controls; weights of 160 mg/kg/day rabbits were slightly less than controls during test week one and days 18-24. The 480 mg/kg rabbits showed a severe loss in body weight during NP-55 administration and over the entire gestation period, with a concomitant decrease in mean uterine weight due to increased early resorptions. There were no statistically significant differences in mean numbers of viable fetuses, late or early resorptions, total implantations, corpora lutea, fetal sex distribution or mean body weight in the 40 or 160 mg/kg/day NP-55 groups. In the 480 mg/kg/day group, however, statistically significant decreases in mean viable fetuses and increases in numbers of early resorptions and post implantation losses were observed. The number of gravid females in this group was less than half of the other groups. Total corpora lutea numbers and implantations in the 480 mg/kg/day group were similar to controls, although mean fetal weights were slightly lower. Male/female ratios were virtually reversed in the high dose group (ca 33/67) compared with the controls (ca 60/40).

On examination of the fetuses, no significant differences were found between those of the 40 mg/kg or 160 mg/kg groups and controls in the number of litters with malformations. However, the 2 litters from the 480 mg/kg group did exhibit a variety of malformations. 100% (8 fetuses) had full 13th ribs and 27 presacral vertebrae were found in 5 fetuses (63%). The sample size of fetuses from the 480 mg/kg/day group was considered too small for appropriate comparison and evaluation for teratogenic effects. No teratogenic effects were seen in fetuses at dose levels of NP-55 of 160 or 40 mg/kg/day administered to dams during days 6-28 of gestation. However, evidence for a variety of random ~~teratogenic~~ effects was seen in two litters of the 480 mg/kg/day group. These were considered not significant but characteristic effects in rabbits due to ~~mild~~ stress in the mothers.

Teratogenicity NOEL = 160 mg/kg/day. At the next highest dose level (480 mg/kg/day) a meaningful teratogenic evaluation could not be made due to severe maternal effects. These toxic effects severely stressed both dams and fetuses causing maternal mortalities, increased abortions, resorption, post-implantation losses and decreased numbers of litters and viable fetuses.

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Maternal Toxicity NOEL = 160 mg/kg/day

Maternal LEL = 480 mg/kg/day (severe weight loss, 5/16 deaths, 6/16 abortions, reduction in number of viable litters and fetuses).

Core Study - Guideline

TABLE I

Maternal Observations For Animals Treated On Gestation Days 6-28

Dose Group - mg/kg	No. Animals and Day of Death	No. Animals and Day of Abortion	Comment
0 Group	1 (day 25) [a]	1 (day 25) 1 (day 27)	Day 25 Animal died and aborted
40 Group	0	1 (day 27)	
160 Group	1 (day 2)[ab]	0	
480 Group	1 (day 24), 1 (day 25) 3 (day 26)[ac]	1 each (day 19, 21,22,24,26,29)[d]	Day 26 animal died & aborted

a No cause of death determined
b Treatment not yet initiated
c Two of 5 animals showed black or brown foci on stomach mucosa
d Fetuses aborted day 29, treated & examined with those at study termination.

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