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

DEC -9 1992

009881

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: ID. No. I001965, Vancide TH , Historical Control Data to Upgrade Developmental Study in Rats

Tox. Chem. No.: 481B
DP Barcode #: D178562
D180071
Record No. : S418265
S420790

FROM: Melba S. Morrow, D.V.M. MSM 11/27/92
Review Section II, Toxicology Branch I
Health Effects Division (H7509C)

TO: Valdis Goncarovs/ John Lee, PM31
Registration Division (H7505C)

THRU: Karl P. Baetcke, Ph.D.
Chief,
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Health Effects Division (H7509C)

Karl P. Baetcke 12/7/92

CONCLUSIONS:

Based on the supplementary information provided for historical controls, the developmental toxicity study in rats (original MRID # 41865701) can be upgraded to core minimum. The developmental NOEL has been determined to be 75 mg/kg when Vancide Th was administered to pregnant female rats on gestation days 6 through 15. The developmental LOEL was 150 mg/kg based on statistically significant increases in the incidences of dilated renal pelvises ($p \leq 0.05$) and bilateral convoluted ureters ($p \leq 0.01$) when high dose animals were compared to concurrent controls.

A copy of the DER for the supplement is attached for your reference.

ACTION REQUESTED:

Review supplemental information.

Reviewed by: Melba S. Morrow, D.V.M. MSM 11/27/92
Section II, Tox. Branch I (H7509C)
Secondary Reviewer: Joycelyn E. Stewart, Ph.D. JES 12/07/92
Section II, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Developmental Toxicity - Rats (Supplement)

GUIDELINE #: 83-3

TOX. CHEM. #: 481B

MRID #: 423086-01, 423662-00 and 423662-01

TEST MATERIAL: Hexahydro-1,3,5-triethyl-s-triazine

SYNONYMS: Vancide TH

STUDY NUMBERS: Supplement to 240834

SPONSOR: R.T. Vanderbilt
Norwalk, Connecticut

TESTING FACILITY: Exxon Biomedical Sciences
East Millstone, New Jersey

TITLE OF REPORT: Developmental Toxicity Study in Rats with Vancide TH

AUTHORS: Bruce K. Beyer

REPORT ISSUED: April 26, 1991

CONCLUSIONS: Based on the information provided for historical controls, the study can be upgraded to core minimum. The developmental NOEL has been determined to be 75 mg/kg when Vancide TH was administered to pregnant rats on gestation days 6 through 15. The developmental LOEL is 150 mg/kg based on statistically significant increases in the incidences of dilated renal pelvises ($p \leq 0.05$) and bilateral convoluted ureters ($p \leq 0.01$) when compared to concurrent controls.

CLASSIFICATION: Minimum
TOX. CATEGORY: N/A

DISCUSSION: The registrant has provided historical control data to support their claim that fetal variations (which consisted of bilateral dilated renal pelvises, bilateral convoluted ureters and bilateral distended ureters) observed in a developmental toxicity study conducted in rats, are within the historical control range. Seven control groups, representing six separate studies and covering in-life dates from September 18, 1989 to

June 21, 1991, served as the historical control data base. The historical control data revealed that the variations in question occured at inconstant frequencies. Table I provides information on the fetal and litter incidences of dilated renal pelvises, bilateral convoluted ureters and bilateral distended ureters in each study. A range was determined from the historical control values for each parameter.

TABLE I
HISTORICAL CONTROL DATA

LESION INCIDENCE (%)

STUDY CODE #		Dilated renal pelvis	Convoluted ureters	Distended ureters
7	fetal inc.	3/184 (1.6)	16/184 (8.6)	20/184 (10.8)
	litter inc.	3/24 (12.5)	10/24 (42)	11/24 (45.8)
8	fetal inc.	6/127 (4.7)	19/127 (15)	27/127 (21.2)
	litter inc.	3/18 (17)	9/18 (50)	11/18 (61)
9	fetal inc.	11/190 (57)	26/190 (13.6)	29/190 (15.2)
	litter inc.	5/25 (20)	11/25 (44)	11/25 (44)
13	fetal inc.	0/121 (0)	1/121 (0.8)	1/121 (0.8)
	litter inc.	0/9 (0)	1/9 (11)	1/9 (11)
14	fetal inc.	11/174 (6.3)	11/174 (6.3)	12/174 (6.8)
	litter inc.	6/22 (40.9)	6/22 (40.9)	6/22 (40.9)
15a	fetal inc.	0/48 (0)	0/48 (0)	0/48 (0)
	litter inc.	0/5 (0)	0/5 (0)	0/5 (0)
15b	fetal inc.	1/31 (3.2)	0/31 (0)	0/31 (0)
	litter inc.	1/3 (33.3)	0/3 (0)	0/34 (0)

Historical control ranges for the different renal anomalies are as follows:

Dilated renal pelvises
fetal incidence: 0 - 5.7%
litter incidence: 0 - 40.9%

Bilateral convoluted ureters
fetal incidence: 0 - 15%
litter incidence: 0 - 50%

Bilateral distended ureters
fetal incidence: 0 - 21.2%
litter incidence: 0 - 61%

Table II represents data from the original report in which Vancide TH was administered at doses of 0, 10, 75 and 150 mg/kg to pregnant rats. The compound was administered on days 6 through 15 of gestation. In this supplemental report the percentages of fetuses and litters having specific variations has been determined in order to compare the results obtained in the initial study to those obtained in the historical controls.

TABLE II
FETAL AND LITTER INCIDENCES (%) OF RENAL ABNORMALITIES REPORTED IN THE ORIGINAL DEVELOPMENTAL STUDY IN RATS

Group (mg /kg)	Incidence	Variation		
		Dilated renal pelvis	Convoluted ureters	Distended ureters
Control (0 mg/kg)	fetal	6/186 (3.2)	8/186 (4.3)	5/186 (2.6)
	litter	6/24 (25)	4/24 (16.6)	3/24 (12.5)
Low Dose (10 mg/kg)	fetal	10/182 (5.4)	9/182 (4.9)	10/182 (5.4)
	litter	6/25 (24)	6/25 (24)	6/25 (24)
Mid Dose (75 mg/kg)	fetal	13/193 (6.7)	17/193 (8.8)	9/193 (4.6)
	litter	8/23 (34.7)	8/23 (34.7)	5/23 (21.7)
High Dose (150 mg/kg)	fetal	17/152 (11.1)	21/152 (13.8)	13/152 (8.5)
	litter	10/19 (52.6)	9/19 (47.3)	7/19 (36.8)

When fetal and litter incidences are compared to historical controls the values reported for the low dose group is within the historical control range for each of the three parameters. At 75 mg/kg, the fetal incidence of dilated renal pelvises is slightly higher than the historical control range; however, the litter incidence is within the historical control range. The values reported for bilateral convoluted ureters and for bilateral distended ureters in animals in the mid dose group are within the historical control ranges for both fetal and litter incidences.

In the original study (MRID 41865701), at the low and mid doses, there was only a positive trend and no statistically significant increases for both dilated renal pelvises and convoluted ureters. At the highest dose tested the increases were statistically significant for dilated renal pelvises ($p \leq 0.05$) and for bilateral convoluted ureters ($p \leq 0.01$) when compared to concurrent controls.

Based on the supplementary information provided for historical controls and using the litter as the experimental unit, the developmental toxicity study conducted in rats, the developmental NOEL is 75 mg/kg and the developmental LOEL is 150 mg/kg. The maternal toxicity NOEL remains unchanged at 75 mg/kg.

The original study (MRID # 418657-01) can be upgraded to core minimum.