



8EHQ-95-13325

INIT 02/13/95

TOXICOLOGY DEPARTMENT
P.O. BOX 12014, 2 T.W. ALEXANDER DRIVE
RESEARCH TRIANGLE PARK, N.C. 27709
(919) 549-2000 TELEFAX (919) 549-2925
INTERNATIONAL TELEX NUMBER 4999378 - ANSWERBACK APC RTP

8EHQ-0295-13325

A

February 6, 1995



88950000114

CERTIFIED MAIL
RETURN RECEIPT REQUESTED
P 253 155 588

OPPT Document Processing Center (7407)
ATTN: Section 8(e) Coordinator
Office of Pollution Prevention and Toxics (OPPT)
US Environmental Protection Agency
Washington, DC 20460

ORIGINAL

Contains No CBI

95 FEB 13 AM 8:11

RECEIVED

RE: TSCA Section 8(e) Notice

Dear Sir or Madam:

This notice is being submitted by Rhône-Poulenc Ag Company (RPAC) to the Environmental Protection Agency (EPA) in accordance with the provisions of Section 8(e) of the Toxic Substances Control Act (TSCA), 15 USC § 2607 (e).

We are submitting the results of several toxicity studies on RP 020630 [CAS number and name: 39807-15-3 and 3-[2,4-dichloro-5-(2-propynyloxy)phenyl]-5-(1,1-dimethylethyl)-1,3,4-oxadiazol-2(3H)-one]. This compound is being study for research and development purposes and is currently in development as a pesticide.

No claims of confidentiality are made for this submission.

Results from several toxicity studies are summarized in the following paragraphs.

Dogs: Two 28-day dietary studies were conducted and included levels ranging from 30 to 27,000 ppm. Dietary levels of 3000 ppm and higher produced decreases in food consumption and body weight gain. Dark yellow urine was noted sporadically at 3000 and 27,000 ppm. Statistically significant increases in alanine amino transferase and alkaline phosphatase along with pigment accumulation in the liver were observed at 800 ppm and higher. A 52-week study was initiated at dietary levels intended to achieve doses of 1, 5, and 50 mg/kg/day. This study was terminated early due to significant a decreases in food consumption and body weight gain. Statistically significant increases in alanine amino transferase and alkaline phosphatase and orange urine along with increased porphyrins in the urine were also noted at 50 mg/kg/day. Since this study was terminated early, histopathology was not performed.

Teratology: In a definitive developmental toxicity study, rats were administered doses of 20, 100, or 500 mg/kg/day (25 females/group) on gestation days 6 through 15 inclusive. At 500 mg/kg/day, maternal body weight gain was significantly lower than control for gestation days 16 through 20, but no effect on body weight was noted during the dosing period. A significant decrease in the mean number of live fetuses per litter and increases in the mean number of dead

3/1/95

fetuses per litter, late resorptions per litter, and percent post implantation loss were observed at 500 mg/kg/day. Fetal weights were significantly decreased at 100 and 500 mg/kg/day (see attached table). Significant increases in pale fetuses, dark amniotic fluid, spongy appearance of heart muscle (fixed fetuses only), fluid in abdominal and thoracic cavities, less than 5 caudal vertebrae, and incomplete ossification of nasal, frontal, parietal, and occipital bones were reported at 100 and 500 mg/kg/day. Increases in the incidences of edematous fetuses, abnormal shaped hearts, large anterior fontanelle, abnormal ossification of occipital bone, unossified inferior incisors, wavy ribs, abnormally ossified ribs, bent scapula, bent acromion, abnormally ossified atlas arch, and incomplete ossification of interparietal, tympanal, basisphenoid, basioccipital, sternbrae, vertebrae, pubic, ischium bones, and phalanges were also reported at 500 mg/kg/day. Many of these findings, particularly for the fetal skeletal evaluations, were previously observed in the preliminary developmental toxicity study in rats and reported to EPA under Section 8(e) on September 1, 1994. However, edematous fetuses at 500 mg/kg/day and indications of this effect at 100 mg/kg/day were not observed in the preliminary study.

A preliminary developmental toxicity study was conducted in rabbits at doses of 0, 50, 100, 250, and 500 mg/kg/day (10 females/group) administered on gestation days 6 to 18 inclusive. Spontaneous abortions occurred in two females at 250 mg/kg/day and in five females at 500 mg/kg/day. Statistically lower maternal body weight gains were observed at 250 and 100 mg/kg/day. Weights of male fetuses were statistically lower than control at all doses but without any dose-response relationship. Weights of female fetuses were also lower than control at all doses, but statistical differences were observed only at 50 and 500 mg/kg/day. No significant findings were noted in the external, visceral, and skeletal examinations of the fetuses.

Mice: Dietary levels of 200, 2000, and 7000 ppm were administered to CD-1 mice (10/sex/group) in both the 28-day and 90-day studies. No evidence of toxicity was observed during the in-life phases of either study. Microscopic evaluation showed hepatic centrilobular hypertrophy and hepatic accumulation of dark brown pigment at 2000 and 7000 ppm. The accumulation of pigment in the liver is consistent with a compound producing porphyruria.

Rats: In a four-week study, RP 020630 was administered to rats via dietary admixture at levels of 0, 600, 6000, or 20,000 ppm (5 rats/sex/group). No indications of significant toxicity were noted during the in-life phase of the study. At study termination, microscopic examination revealed a higher incidence of follicular hypertrophy in the thyroid at 6000 ppm in males and 20,000 ppm in males and females and hepatocellular hypertrophy at 20,000 ppm in females.

In an ongoing two year rat study with dietary levels of 0, 20, 50, 500, and 5000/10,000 ppm, an increase in urinary porphyrin level has been observed at the highest dose level after 7, 12, and 25 weeks of treatment. No change in urinary porphyrin has been observed in the other dose groups. The high dose level in this study was decreased from 10,000 to 5000 ppm in Week 10 after animals failed to gain any weight between Weeks 5 and 10.

Further questions regarding this submission may be directed to the undersigned at 919-549-2222.

Sincerely,



Glenn S. Simon, PhD, DABT
Director of Toxicology

Developmental Toxicity Study in Rats with RP 020630

SUMMARY OF LITTER DATA

OBSERVATIONS	DOSE LEVELS (mg/kg/day)				HISTORICAL CONTROL DATA 205 Litters/12 Studies	
	Control	20	100	500	Mean	Study range
Number of pregnant females	18	20		22		
Mean number of Corpora lutea per litter ± S.D.	19.6 ±2.03	19.8 ±2.40	20.1 ±2.44	21.0 ±3.10	17.8	14.3 → 20.3
Mean number of implantations per litter ± S.D.	18.2 ±1.62	17.7 ±4.30	17.5 ±2.59	17.4 ±2.68	15.0	9.6 → 19.0
Mean pre-implantation loss (%)	7.1	11.3	12.4	16.0	15.5	4.9 → 46.0
Mean number of live foetus per litter ± S.D.	16.9 ±2.10	15.8 ±4.99	15.9 ±3.23	7.5** ±4.67	13.8	9.3 → 17.9
Mean number of dead foetus per litter ± S.D.	0.0	0.0	0.3* ±0.73	2.3** ±2.64	0.03	0.0 → 0.1
Mean number of early resorptions per litter ± S.D.	1.2 ±1.26	1.5 ±2.48	1.1 ±0.97	1.6 ±1.40	1.0	0.3 → 1.7
Mean number of late resorptions per litter ± S.D.	0.0	0.3 ±1.12	0.2 ±0.52	5.9** ±4.50	0.04	0.0 → 0.1
Mean post-implantation loss (%)	6.8	9.7	9.7	56.9**	8.7	1.8 → 17.5
Mean body weight of male foetuses (g) ± S.D.	3.68 ±0.34	3.78** ±0.42	3.06** ±0.61	2.14** ±0.26	3.65	3.39 → 3.85
Mean placental weight of male foetuses (g) ± S.D.	0.66 ±0.11	0.66 ±0.11	0.60** ±0.10	0.54** ±0.10	0.68	0.57 → 0.78
Mean body weight of female foetuses (g) ± S.D.	3.48 ±0.34	3.57** ±0.37	3.04** ±0.54	2.09** ±0.25	3.33	3.24 → 3.63
Mean placental weight of female foetuses (g) ± S.D.	0.62 ±0.10	0.63 ±0.10	0.59** ±0.09	0.53** ±0.07	0.81	0.57 → 0.74
Foetus sex ratio (%) Males : Females	75 131:174	105 162:154	90 150:167	159 102:64	93 1370:1461	65 → 141 40:62 → 38:27

* = Significant at a level of 0.05

** = Significant at a level of 0.01



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

Glenn S. Simon, Ph.D., DABT
Director of Toxicology
Rhône-Poulenc
P.O. Box 12014
2 T.W. Alexander Drive
Research Triangle Park, North Carolina 27709

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

APR 18 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requests".

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan
Terry R. O'Bryan
Risk Analysis Branch

Enclosure

13325A



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contains at least 50% recycled fiber

Triage of 8(e) Submissions

Date sent to triage: APR 19 1995

NON-CAP

CAP

Submission number: 13325A

TSCA Inventory: Y N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX GTOX
STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

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entire document:	0	1	2
pages	<u>1,2</u>		pages <u>1,2</u>
Notes:	<u>3</u>		
Contractor reviewer:	<u>FOR</u>		Date: <u>4/3/95</u>

CECATS DATA: Submission # BEHO 0295-13325 SEQ. A

TYPE: INT SUPP FLWP

SUBMITTER NAME: Rhone - Potlenc

Ag Company

SUB. DATE: 02/06/95 OTS DATE: 02/13/95 CSRAD DATE: 03/01/95

CHEMICAL NAME: 1,3,4-oxadiazol-2(3H)-one, 3-[3,4-dichloro-5-(2-propoxyloxy)phenyl]-5-(1,1-dimethylethyl)- CAS# 39807-15-3 ← RP 020630

INFORMATION REQUESTED: FLWP DATE: _____

- 0501 NO INFO REQUESTED
 - 0502 INFO REQUESTED (TECH)
 - 0503 INFO REQUESTED (VOL ACTIONS)
 - 0504 INFO REQUESTED (REPORTING RATIONALE)
- DISPOSITION:
0639 REFER TO CHEMICAL SCREENING
 0678 CAP NOTICE

VOLUNTARY ACTIONS:

- 0401 NO ACTION R/P RPT'D
- 0402 STUDIES PLANNED (INDIC HW AY)
- 0403 NOTIFICATION OF WORK R/OUTLINE
- 0404 LABEL/MSDS CHANGED
- 0405 PROCESS/ANDLING CHANGED
- 0406 APP USE DISCONTINUED
- 0407 PRODUCTION DISCONTINUED
- 0408 CONFIDENTIAL

INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C
0201 ONCO (HUMAN)	01 02 04	0216 EPICLIN	01 02 04	0241 IMMUNO (ANIMAL)	01 02 04
0202 ONCO (ANIMAL)	01 02 04	0217 HUMAN EXPOS (PROD CONTAM)	01 02 04	0242 IMMUNO (HUMAN)	01 02 04
0203 CELL TRANS (IN VITRO)	01 02 04	0218 HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243 CHEM/PHYS PROP	01 02 04
0204 MUTA (IN VITRO)	01 02 04	0219 HUMAN EXPOS (MONITORING)	01 02 04	0244 CLASTO (IN VITRO)	01 02 04
0205 MUTA (IN VIVO)	01 02 04	0220 ECO/NOVA TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	0221 ENV. OCCUREL/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0208 REPRO/TERATO (ANIMAL)	01 02 04	0222 EMER INCI OF ENV CONTAM	01 02 04	0247 DNA DAM/REPAIR	01 02 04
0209 NEURO (HUMAN)	01 02 04	0223 RESPONSE REQUEST DELAY	01 02 04	0248 PROD/USE/PROC	01 02 04
0210 NEURO (ANIMAL)	01 02 04	0224 PRODCOMP/CHEM ID	01 02 04	0251 MSDS	01 02 04
0211 CHR. TOX (HUMAN)	01 02 04	0225 REPORTING RATIONALE	01 02 04	OTHER	01 02 04
0212 ACUTE TOX. (ANIMAL)	01 02 04	0226 CONFIDENTIAL	01 02 04		
0213 SUB ACUTE TOX (ANIMAL)	01 02 04	0227 ALLERG (HUMAN)	01 02 04		
0214 SUB CHRONIC TOX (ANIMAL)	01 02 04	0228 ALLERG (ANIMAL)	01 02 04		
0215 CHRONIC TOX (ANIMAL)	01 02 04	0229 METAB/PHARMACO (ANIMAL)	01 02 04		
		0240 METAB/PHARMACO (HUMAN)	01 02 04		

IRIAGE DATA: NON-CEL INVENTORY Ongoing Review Species Species RTDX Toxicological Concern: Use: Production:

CAS SR NO YES (DROPPED) YES (DROPPED) NO (CONTINUE) M55, RAT MIED HIGH R: D Pesticide

IM TIRAMINI

URGENT Non - Se gavage, locally not 500 mg/kg - see Babbain, see in live tissues, see in

gavage, locally not 500 mg/kg - see Babbain, see in live tissues, see in
acute - abatement of 250 + 500 mg/kg, see BIV at 100 + 250 mg/kg, no sig effects on lactation.
100 mg/kg - normal effects on fetal malformation + weight.
200 mg/kg - 100% for developmental toxicity.

CECATS DATA: 02915-13225 SEQ. A

INFORMATION REQUESTED: FLWP DATE:

VOLUNTARY ACTIONS:

TYPE: (RT) SUPP FLWP
 SUBMITTER NAME: Rhone - Potlenc
Ag Company

0501 NO INFO REQUESTED
 0502 INFO REQUESTED (TECH)
 0503 INFO REQUESTED (VOL ACTIONS)
 0504 INFO REQUESTED (REPORTING NATIONAL F)
 DISPOSITION:
 0505 REFER TO CHEMICAL SCREENING
 0506 CAP NOTICE

0501 AND ACTION RI PART II)
 0502 STUDIES PLANNED WITHIN 90 DAY
 0503 INTERCATION IN WORK R (1111) M
 0504 LABELS AND (11ANK) S
 0505 PROCESS AND (11ANK) S
 0506 APP USE DISCONTINUED
 0507 PRODUCTION DISCONTINUED
 0508 CONFIDENTIAL

SUB DATE: 02/06/95 ORS DATE: 02/13/95 CERAD DATE: 03/01/95

CHEMICAL NAME: 1,3,4-oxadiazol-2(3H)-one, 3-[3,4-dichloro-5-(2-propoxyloxy)phenyl]-5-(1,1-dimethylethyl)-
CASE 39807-15-3 ← RP 020630

INFORMATION TYPE:	PEC	INFORMATION TYPE:	PEC	INFORMATION TYPE:	PEC
0201 ONCO (HUMAN)	01 02 04	0216 EPICLIN	01 02 04	0241 INGENEO (ANIMAL)	01 02 04
0202 ONCO (ANIMAL)	01 02 04	0217 HUMAN EXPOS (PROD CONTAM)	01 02 04	0242 BRUNING (HUMAN)	01 02 04
0203 CELL TRANS (IN VITRO)	01 02 04	0218 HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243 CHEMISTS PROP	01 02 04
0204 MUTA (IN VITRO)	01 02 04	0219 HUMAN EXPOS (MONITORING)	01 02 04	0244 CLASTO (IN VITRO)	01 02 04
0205 MUTA (IN VIVO)	01 02 04	0220 BOVAQUA TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	0221 ENV OCCURENCE/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0207 REPRO/TERATO (ANIMAL)	01 02 04	0222 EMER ENCI OR ENV CONTAM	01 02 04	0247 DNA DAMAGE/ PAR	01 02 04
0208 NEURO (HUMAN)	01 02 04	0223 RESPONSE REPORT DELAY	01 02 04	0248 PRODUSE/PROC	01 02 04
0209 NEURO (ANIMAL)	01 02 04	0224 PROD/COMP/CHRM ID	01 02 04	0251 HARDS	01 02 04
0210 ACUTE TOX (HUMAN)	01 02 04	0225 REPORTING RATIONALE	01 02 04	OTHER	01 02 04
0211 CHR TOX (HUMAN)	01 02 04	0226 CONFIDENTIAL	01 02 04		
0212 ACUTE TOX (ANIMAL)	01 02 04	0227 ALLERG (HUMAN)	01 02 04		
0213 SUB ACUTE TOX (ANIMAL)	01 02 04	0228 ALLERG (ANIMAL)	01 02 04		
0214 SUB CHRONIC TOX (ANIMAL)	01 02 04	0229 METAPHARMACO (ANIMAL)	01 02 04		
0215 CHRONIC TOX (ANIMAL)	01 02 04	0230 METAPHARMACO (HUMAN)	01 02 04		

NON-CELL INVENTORY: YES
 ONGOING REVIEW: YES (OR PREFERRED) RET, DOE
 SPECIES: MUS, RAT
 TOXICOLOGICAL CONCERN: LOW
 CAS SR NO: IN PROGRESS
 REPORT: HIGH
 USE: R: D
 PRODUCTION: pesticide

STOX

UNTESTED NON - COE 1. Dogs fed during lunch from 30 to 2700ppm for 28 days, showed decreased body weight gain at 3000 ppm, pigment accumulation at 800 ppm & 1500 ppm. Dogs 52 weeks study at 1, 5, 50 mg/kg under laminated, PhO NoAEL. Mice studies 28 and 90 days fed during lunch 8, 200, 2000 and 7000. Mice showed hepatic accumulation of dark pigment and hepatic sublobular hyperplasia. The NoAEL is 200 ppm. Rats 28 days dietary study 800, 500, 5000 or 2000 ppm, finding increased hyperplasia in the liver at higher doses and hepatocellular hyperplasia at the highest dose. The NoAEL 500 ppm.

CECATS DATA: Submission # BEHO 0295-1325 SEQ. A

TYPE (INT) SUPP FLWP
 SUBMITTER NAME: Rhone - Polenc
Ag Company

INFORMATION REQUESTED: FLWP DATE: _____
 0501 NO INFO REQUESTED
 0502 INFO REQUESTED (TECH)
 0503 INFO REQUESTED (VOL ACTIONS)
 0504 INFO REQUESTED (REPORTING RATIONAL F)
 DISPOSITION:
0639 REFER TO CHEMICAL SCREENING
 0678 CAP NOTICE

VOLUNTARY ACTIONS:
 0401 (NO ACTION REPORTED)
 0402 STUDIES PLANNED/IN PROGRESS
 0403 NOTIFICATION OF WORKING RESULTS
 0404 LABEL/MSDS CHANGES
 0405 PROCESS/PLANNING CHANGES
 0406 APP USE DISCONTINUED
 0407 PRODUCTION DISCONTINUED
 0408 CONFIDENTIAL

SUB. DATE: 02/06/95 OTS DATE: 02/13/95 CSRAD DATE: 03/01/95

CHEMICAL NAME: 1,3,4-oxadiazol-2(3H)-one, 3-[2,4-dichloro-5-(2-propoxyloxy)phenyl]-5-(1,1-dimethylethyl)-

CAS# 39807-15-3 < RP 020630

INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C
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0203 CELL TRANS (IN VITRO)	01 02 04	0218 HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243 CHEM/PHYS PROF	01 02 04
0204 MUTA (IN VITRO)	01 02 04	0219 HUMAN EXPOS (MONITORING)	01 02 04	0244 CLASTO (IN VITRO)	01 02 04
0205 MUTA (IN VIVO)	01 02 04	0220 BOO/AQUA TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	0221 ENV. OCCUREL/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0208 REPRO/TERATO (ANIMAL)	01 02 04	0222 EMER INCI OF ENV CONTAM	01 02 04	0247 DNA DAM/REPAIR	01 02 04
0209 NEURO (HUMAN)	01 02 04	0223 RESPONSE REQUEST DELAY	01 02 04	0251 PROD/USE/PROC	01 02 04
0210 NEURO (ANIMAL)	01 02 04	0224 PRODCOMP/CHEM ID	01 02 04	0299 OTHER	01 02 04
0211 ACUTE TOX (HUMAN)	01 02 04	0225 REPORTING RATIONALE	01 02 04		
0212 CHR. TOX. (HUMAN)	01 02 04	0226 CONFIDENTIAL	01 02 04		
0213 ACUTE TOX (ANIMAL)	01 02 04	0227 ALLERG (HUMAN)	01 02 04		
0214 SUB ACUTE TOX (ANIMAL)	01 02 04	0228 ALLERG (ANIMAL)	01 02 04		
0215 CHRONIC TOX (ANIMAL)	01 02 04	0229 METAB/PHARMACO (ANIMAL)	01 02 04		
		0240 METAB/PHARMACO (HUMAN)	01 02 04		

IMAGE DATA: NON-CBI INVENTORY

ONGOING REVIEW

SPECIES

TOXICOLOGICAL CONCERN:

USE:

PRODUCTION:

CAS SR NO NO

YES (DROPPREFERR) RAT, DOG
 NO (CONTINUE) MSS, RAT

LOW MED

R+D
Pesticide

IN TUMORI
UNCLASSIFIED Non-CBI

HIGH

SATOX

8 (E) -13325A

M/M/H/L/L/L

Low
SUBACUTE ORAL TOXICITY IN DOGS IS OF ~~MEDIUM~~ CONCERN, ~~BASED ON~~ PIGMENT ACCUMULATION IN LIVER AND INCREASES IN ALANINE AMINO TRANSFERASE AND ALKALINE PHOSPHATASE AT 800 PPM (20 MG/KG/DAY) AND HIGHER. DOSAGE (DIET, 28 DAYS) WAS 30 PPM TO 27,000 PPM (1 MG/KG/DAY TO 675 MG/KG/DAY, GROUP SIZE NOT REPORTED). NO MORTALITIES OCCURRED. LEVELS OF 3000 PPM (75 MG/KG/DAY) AND ABOVE PRODUCED DECREASES IN FOOD CONSUMPTION AND BODY WEIGHT GAIN.

Observations include
~~stet~~
ORAL DEVELOPMENTAL TOXICITY IN RATS IS OF ~~MEDIUM~~ CONCERN, ~~BASED ON~~ A SIGNIFICANT INCREASE IN NUMBER OF DEAD FETUSES IN ~~TREATMENT~~ GROUP. DOSAGES WITH 25 DAMS/GROUP (GAVAGE ON DAYS 6-15 OF GESTATION) WERE 20, 100, AND 500 MG/KG/DAY. NO MATERNAL DEATHS WERE REPORTED. A LOWER BODY WEIGHT GAIN WAS SEEN AT 500 MG/KG/DAY ON DAYS 16-20 OF GESTATION. AT 100 MG/KG/DAY AND 500 MG/KG/DAY, FETAL SKELETAL EVALUATION INDICATED INCOMPLETE OSSIFICATION OF NASAL, FRONTAL, PARIETAL, AND OCCIPITAL BONES WITH LESS THAN 5 CAUDAL VERTEBRAE. SIGNIFICANT DECREASES IN FETAL WEIGHTS AND IN PALE FETUSES, DARK AMNIOTIC FLUID, SPONGY APPEARANCE OF THE HEART MUSCLE AND FLUID IN THE ABDOMINAL AND THORACIC CAVITIES. INCREASES IN THE INCIDENCE OF EDEMATOUS FETUSES, ABNORMAL SHAPED HEARTS, LARGE ANTERIOR FONTANELLE, ABNORMAL OSSIFICATION OF THE OCCIPITAL BONE, UNOSSIFIED INFERIOR INCISORS, WAVY RIBS, ABNORMALLY OSSIFIED RIBS, BENT SCAPULA, BENT ACROMION, ABNORMALLY OSSIFIED ATLAS ARCH, AND INCOMPLETE OSSIFICATION OF THE INTERPARIETAL, TYMPANAL, BASISPHENOID, BASIOCCIPITAL, STERNEBRAE, VERTEBRAE, PUBIC, ISCHIUM BONES, AND PHALANGES WERE ALSO REPORTED AT 500 MG/KG/DAY. *rhe 500 mg/kg*

ORAL DEVELOPMENTAL TOXICITY IN FEMALE RABBITS IS OF HIGH CONCERN. DOSAGES (GAVAGE ON DAYS 6-18 OF GESTATION) WITH 10 DAMS/GROUP WERE 50, 100, 250, AND 500 MG/KG/DAY. NO MATERNAL MORTALITY OCCURRED. SPONTANEOUS ABORTIONS OCCURRED AT 250 MG/KG/DAY (2/10) AND AT 500 MG/KG/DAY (5/10) AND STATISTICALLY LOWER MATERNAL BODY WEIGHT AT THESE TWO DOSE LEVELS. MALE FETAL WEIGHTS WERE LOWER THAN CONTROLS AT ALL DOSE LEVELS AND FEMALES WERE LOWER AT 50 MG/KG/DAY AND 500 MG/KG/DAY.

SUBACUTE ORAL TOXICITY IN RATS IS OF LOW CONCERN. DOSAGES (DIET, 28 DAYS, 5/SEX/GROUP) WERE 600 PPM (30 MG/KG/DAY); 6000 PPM (300 MG/KG/DAY); AND 20,000 PPM (1000 MG/KG/DAY). NO MORTALITY OR TOXICITY SIGNS WERE OBSERVED. MALES AT 6000 PPM AND ABOVE AND FEMALES AT 20,000 PPM EXHIBITED FOLLICULAR HYPERTROPHY IN THE THYROID. HEPATOCELLULAR HYPERTROPHY WAS SEEN IN FEMALES AT 20,000 PPM.

SUBACUTE/SUBCHRONIC ORAL TOXICITY IN CD-1 MICE IS OF LOW CONCERN. DOSAGES (DIET, 28 DAYS AND 90 DAYS, 10/SEX/DOSE) WERE 200 PPM (24 MG/KG/DAY); 2000 PPM (240 MG/KG/DAY); AND 7000 PPM (840 MG/KG/DAY). NO MORTALITY OR SIGN OF TOXICITY WERE OBSERVED. AT 2000 PPM (240 MG/KG/DAY) AND 7000 PPM (840 MG/KG/DAY), MICROSCOPIC EVALUATION SHOWED HEPATIC CENTRILOBULAR HYPERTROPHY AND HEPATIC ACCUMULATION

OF DARK BROWN PIGMENT.

SUBACUTE/SUBCHRONIC ORAL TOXICITY IN RATS IS OF LOW CONCERN. DOSAGES (DIET, 25 WEEKS) WERE 20 PPM (1 MG/KG/DAY); 50 PPM (3 MG/KG/DAY); AND 5000/10,000 PPM (250/500 MG/KG/DAY). NO MORTALITIES OCCURRED. THE HIGH DOSE GROUP WAS DECREASED FROM 10,000 PPM TO 5000 PPM (500 MG/KG TO 250 MG/KG) IN WEEK 10, AFTER ANIMALS FAILED TO GAIN WEIGHT. AN INCREASE IN URINARY PORPHYRIN LEVEL WAS OBSERVED AT THE HIGHEST DOSE LEVEL AFTER 7, 12, AND 25 WEEKS OF TREATMENT. GROUP SIZE WAS NOT REPORTED. THIS IS AN ONGOING TWO YEAR STUDY.

8(E)-13325A

NAME(S):

1,3,4-OXADIAZOL-2(3H)-ONE, 3-[2,4-DICHLORO-5-(2-PROPYNYLOXY)PHENYL]-5-(1,1-DIMETHYLETHYL)-/RP 020630

CAS #:

039807-15-3

STUDY TYPE:

RTOX/CTOX/STOX/SBTOX

TOX CONCERN:

M(CTOX)/M(RTOX)/M(STOX)

DOGS - 28 DAY STUDY AT 30 TO 27000 PPM (DIETARY) DECREASED WEIGHT AT 3000 PPM. DOGS 52 WEEKS STUDY AT 1, 5, AND 50 MG/KG/DAY (DIETARY), TERMINATED BECAUSE OF REDUCED BODY WEIGHT GAIN. DEVELOPMENTAL STUDY IN RATS AT 20, 100 OR 500 MG (DIETARY) HAD EDEMATOUS FETUSES AT THE 2 HIGH DOSE GROUPS. DECREASED WEIGHT GAINS IN RABBIT FETUSES AT ALL DOSES, 50, 100, 250 AND 500. IN MICE 28 AND 90 DAY STUDIES SHOWED CENTRILOBULAR HYPERTROPHY AT THE HIGH DOSE. RATS 28 DAY STUDY AT 600, 6000, 20000 HAD LIVER AND THYROID LESIONS AT 2 HIGH DOSE GROUPS. RTOX: PRELIMINARY STUDY, RABBITS - ABORTIONS AT 250 AND 500 MG/KG, DECREASE BODY WEIGHT AT 100 AND 250 MG/KG NO SIGNIFICANT EFFECTS ON FETUSES GAVAGE

PROD:

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