4-14-70

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

000418

Date: April 14, 1970

Reply to Attn of:

Subject: Stam, 3',4'-dichloropropionanilide [and its metabolites] residue tolerance request: 10.0 ppm rice bran, rice polishings, and other mill fractions; 6.0 ppm rice hulls; 2.0 rough rice; 0.1 ppm poultry meat by-products (negligible): 0.05 ppm eggs, milk, fat meat and other meat by-products from beef and dairy cattle, and meat from poultry (negligib[illegible]

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PESTICIDE PETITION NO. OFO-932

Rohm and Haas Company
Independence Mall West
Philadelphia, Pa. 19105
(AF 24-037)

TO: Division of Regulations and Petitions Control (BF-320)

Petition toxicity data provided in support of the safety of the requeste[illegible] residue tolerances included the following.

Acute Toxicity:

LD_{50} rats - oral

Tech. grade Stam	1.384 g/kg
Stam F-34	1.87 ml/kg ✓

LD_{50} dogs - oral

Tech. grade Stam	1.217 g/kg ✓

Dermal toxicity rabbits tech. Stam; in 10% corn oil, 10 ml/kg for 24 hours to clipped skin - no toxic effects. ✓

Subacute rat feeding study: Tech. grade of Stam F-34.

10 ppm
33
100
330
1000
5000

Groups of albino rats, 10 of each sex in each group, were fed 0, 0.01, 0.033, 0.10, 0.33, 1.0 or 5.0% Stam F-34 diets for 3 months.

Observations for effects included:

1. Weekly body weights.
2. F[illegible] consumption measurements during a three day period in 13[illegible] week.
3. [illegible] crit, [illegible], total and differ[illegible] [illegible] of each sex in each group [illegible] end of the feeding period.
4. [illegible] samples from 5 of each sex in each [illegible] tests for protein and sugar.

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PC[illegible]

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5. Necropsy at termination.

   a. Gross examination for compound related organ and tissue changes.
   b. Liver, kidney, heart, spleen, and testes weighed.

6. Microscopic examination of heart, lung. liver, kidney, spleen, GI tract, bladder. bone marrow, s. muscle, skin, brain, thyroid adrenal, and pancreas of all survivors in all groups.

Results:

5% group - all dead by the 3rd week.
1% diet group -
1 male and 1 female dead during the 11-12 week.

Slightly reduced hematocrit and hemoglobin values.

Slightly increased liver/bw ratios.

Lessened growth.

0.33% diet group - lessened growth.
0.1% diet group - lessened growth.
→ 0.033 and 0.01% groups - effects absent.

Two-year Dog feeding study (Med. Coll. of Va. 1964)

Groups of purebred beagle dogs, 2 of each sex in each group were fed 0, 100, 600, or 4000 ppm Stam F-34 diets for two years.

Observations for effects included:

1. Weekly body weights.
2. Daily food consumption measurements.
3. Hematology. initially and at 3 month intervals included hematocrits, hemoglobin, total and differential leucocyte count
4. Urine tests for sugar and protein was done at the same interval as the hematology.
5. Liver function tests included bromsulphalein, SGOT, and SAP were run during the 24th month.
6. [illegible]

   a. [illegible] and organs for compound related [illegible].
   b. [illegible] testes weighed.

   [illegible] liver, kidney, spleen, [illegible] muscle, lymph nodes, bone [illegible] pancreas, adrenal [illegible].

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Results: 4000 ppm group

Depressed weight gains (stated to be related to decreased food intake).

Slightly increased SGOT and SAP values.

600 and 100 ppm groups - Effects not revealed by observations.

Two-year rat feeding study: (Med. Coll. of Va. 1962):

Groups of Wistar strain albino rats, 25 of each sex in each group, were fed 0, 100, 400, or 1600 ppm Stam F-34 diets for two years.

Observations for effects included:

1. Weekly body weights.
2. Food consumption measured during 3 day periods at the beginning of the 1st, 3rd, 6th, 12th and 24th month.
3. Hematology including hematocrits, hemoglobin, total and differential leucocyte counts were done at 3 month intervals.
4. Urine examination for sugar and protein was done at three month intervals.
5. Necropsy at termination.
   a. Examination of tissues and organs for compound related effects.
   b. Heart, liver, spleen, kidney, and gonads weighed.
6. Microscopic examination of heart, liver, lung, spleen, GI tract, kidney, urinary bladder, thyroid, adrenal, pancreas, gonads, pituitary, skeletal muscle, skin, bone marrow, and brain.

Results: 1600 ppm group, depressed body weight gain, increased mortality (males only - after 20 months), lessened food intake, slightly lowered hematocrits and hemoglobin amounts.

100 and 400 ppm groups - compound related effect not revealed by observations.

Three generation rat reproduction study (Med. Coll. of Va. 1966).

Groups of Wistar strain albino rats, 20 of each sex in each group were fed 0, 100, 400, or 1600 ppm Stam diets during the production of 3 generations. Each female was bred to her own diet group to produce two litters in each generation. Breeding was maintained to provide the gestation, fertility, viability and lactation values. Ten of each sex in each group of the F3b litters were [illegible] heart, bladder, lung, liver, kidney, spleen, GI tract, bone marrow, skeletal muscle, skin, brain, pituitary, thyroid, adrenal, pancreas, and gonads were examined microscopically.

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TABLE OF INDEXES

Diet Level	Litter	First Gener.	Second Gener.	Third Gener.	First Gener.	Second Gener.	Third Gener.
		F E R T I L I T Y			G E S T A T I O N		
		1st	2nd	3rd	1st	2nd	3rd
0	a	100	85	100	95	100	100
0	b	78	63	75	100	100	93
100	a	95	90	95	100	94	100
100	b	67	84	100	100	94	95
300	a	100	95	95	100	100	100
300	b	63	85	84	92	88	100
1000	a	95	90	100	100	100	100
1000	b	83	70	85	100	100	100
		V I A B I L I T Y			L A C T A T I O N		
0	a	91	90	96	73	82	75
0	b	86	86	93	94	98	92
100	a	99	97	99	86	89	82
100	b	97	99	95	98	91	85
300	a	88	98	93	81	80	89
300	b	90	96	99	98	98	93
1000	a	90	98	98	85	83	93
1000	b	98	96	90	97	96	90

Compound related organ and tissue changes were not found in the examined F_{3b} weanlings.

A one-thousand ppm diet was demonstrated to be a no-effect in this reproduction study.

Toxicity data summary:

Demonstrated no-effect levels.

Dogs two years 600 ppm diets
Rats two years 400 ppm diets

Three generation rat reproduction study 1000 ppm

CONCLUSION:

Petition toxicity data appear to support the safety of the requested residue tolerances. However, we will hold our final recommendation in abeyance pending the evaluation of DOP on the question of metabolites in the residue. DOP should also comment on the potential soil buildup of azobenzene.

Dr. G. E. Whitmore
Division of Toxicology
Petitions Review Branch (BF-148)

INIT:HBlumenthal

cc: BF-148
BF-1[illegible]
BF-[illegible]
[illegible]
[illegible]
PP [illegible]

GEW:[illegible]

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