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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: MAR 5 1982
MAR 5 1982

SUBJECT: Teratogenicity of FMC 5462 in Rabbits. (Acc No. 246792, Reg. No. 279-2306, Caswell No. 420)

FROM: George Z. Ghali, Ph.D.
Review Section IV
Toxicology Branch, HED (TS-769)

TO: George La Rocca
Product Manager No. 15
Registration Division (TS-767-C)

THRU: Christine F. Chaisson, Section Head
Review Section IV
Toxicology Branch, HED (TS-769)

Registrant: FMC Corporation
Agricultural Chemical Group
Philadelphia, Pa. 19103

Action Requested:

Review and evaluation of a rabbit teratology study on FMC 5462 (Endosulfan).

Conclusion and Recommendations:

1. The test chemical is not teratogenic under the experimental conditions.

2. Maternal toxicity was evident at 1.8 mg/kg/day (HTD) as manifested by the labored breathing and tonic convulsions of pregnant animals in this group. The NOEL for maternal toxicity is considered to be 0.7 mg/kg/day.

3. The study is adequate and conforms to standard testing procedures as outlined in the proposed Guideline (1978) except for the fact that no positive control group was included and food and water consumptions were not reported.

4. This study is classified as Core-minimum.

Review

Testing Laboratory:

Raltech Scientific Services, Madison, Wisconsin. Report No. A-79-370, dated July 27, 1981.

Test Animal:

Young adult New Zealand white rabbits, obtained from Hoppers Unlimited, Verona, Wisconsin and acclimated for 4 weeks.

Procedure:

pregnant rabbits were given the test chemical at the rate of 0.3, 0.7 or 1.8 mg/0.5 ml corn oil/kg maternal body weight/day by oral gavage on days 6-28 of gestation. The control group received corn oil only. Each treatment group consisted of 20 mated rabbits. When mortality was observed at the highest dose level, six more mated rabbits were added to this group. Maternal weights were recorded at day 0 (first day of treatment and at 6-day intervals thereafter and at the time of sacrifice. Animals were observed twice daily throughout the test period for any toxic signs, abnormalities in activity and appearance, morbidity and mortality. On day 29 of gestation, the dams in each group were sacrificed by euthanatization with carbon dioxide, and the entire reproductive tract was removed including both ovaries. Ovaries were examined for abnormalities and the number of corpora lutea was recorded. Uterus was examined, weighed and fetuses were removed

The number of live and dead fetuses, early and late resorptions, implantation sites were recorded.

All viable fetuses were sexed, measured, weighed, grossly examined, and examined for visceral abnormalities. Freehand sections were made of the heads of one half of the fetuses to permit gross examination of the eyes palate, nasal septum and brain. All fetuses were prepared for skeletal examination and evaluated for bone alignment, degree of ossification, and abnormalities.

Results:

A. Maternal Observations:

Four animals in the 1.8 mg/kg group died on gestation days 7, 10, 21 and 29. The first three are thought to be due to improper oral gavage. The probable cause of death for the last one was not established, but gross and histopatological examinations revealed a pale appearance of the liver and kidneys in addition to vacuolization of the hepatocyes. Two animals in the control and one in the middle dose level showed nasal congestion. In the highest dose level, four animals showed a noisy and rapid breathing, hyperactivity and convulsions.

There were no statistically significant difference in group mean body weights between the treated and control groups throughout the duration of the experiment.

Ascites was observed in approximately equal proportions in all groups.

At necropsy, the number of pregnant animals were 18, 17, 19, and 24 in the control, low, middle and high dose respectively. All pregnant females had viable litters, with the exception of the animal in the high dose level which died on test and had nine late resorptions.

There were no statistically significant differences in the mean number of corpora lutea, implantation efficiency, litter size, sex ratio, mean fetal length and weight, or in the number and percent of live and resorbed fetuses. Furthermore, there were no dead fetuses in the treatment groups. Three of the four animals which died on test had normally developing implants at necropsy.

B. Fetal Data:

No gross external abnormalities were observed in any of the fetuses in any treatment group except for two fetuses from one litter in the middle dose group had a kinked tail.

Two fetuses from separate litters in the control group had cleft palate and hemmorhagic vitreous humor.

One fetus from the control group and six fetuses from two litter in the hign dose group had the left carotid artery arising from innominate.

Four fetuses from one litter in the middle dose group had enlarged auricles, another fetus with an accessory left subclavian artery.

The authors stated that common skeletal variation and minor skeletal anomalies were present in all groups and included: bent scapular spine, unossified, misaligned, and fused sternebrae, rudimentary ribs, extra ribs, fused ribs, interrupted ossification of a rib, 27 presacral vertebrae, fused caudal vertebrae, and unossified tail. Examination of the data indicated that these variations and other minor anomalies occurred throughout all groups in a non-treatment related pattern. Other than that, no major skeletal malformations were observed in any group.

Toxicology Branch/HED Review

To: G. LaRocca, PM #15

Registration No(s).:

Pesticide Petition No(s).: 7E1940

Caswell No(s).: 420

Chemical(s): Endosulfan

RAC(s) - tolerance(s): See attached list.

Inert(s) cleared 180.1001:

% of ADI occupied: Existing: 140.10 Resulting: 140.11

Resulting % increase in TMRC: < 1%

Attached (?): ADI printout: YES/NO; TOX "one-liner": YES/NO; DER: YES/NO

Existing regulatory actions against registration:

RPAR status: No

New Data: No new toxicological data submitted.

Data considered in setting the ADI: Chronic feeding study in dogs showing NOEL of 0.75 mg/kg.

Data gaps: See attached memo from George Ghali to Hoyt Jameson (3-23-82).

Recommendation: Reject request for tolerance of 0.1 ppm on raspberries.

Comments: This rejection is not based on incremental risk assessment. Rather, the request is rejected due to the existing intake estimate of 140% ADI and to the numerous significant data gaps.

NOV 12 1982

Reviewer: Paul R. Gamer Date: 10-8-82

Section Head: C.J. Chaisson 11/10/82

File last updated 10/8/82

ACCEPTABLE DAILY INTAKE DATA

DOG mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day/60kg
0.750	30.00	100	0.0075	0.4500

Published Tolerances

CROP	Tolerance	Food Factor	mg/day/1.5kg
Apples(2)	2.000	2.53	0.07590
Apricots(3)	2.000	0.11	0.00337
Artichokes(4)	2.000	0.03	0.00090
Beans(9)	2.000	2.04	0.06120
Broccoli(19)	2.000	0.10	0.00307
Brussel Sprouts(20)	2.000	0.03	0.00090
Cabbage,sauerkraut(22)	2.000	0.74	0.02207
Cauliflower(27)	2.000	0.07	0.00215
Celery(28)	2.000	0.29	0.00858
Cherries(30)	2.000	0.10	0.00307
Collards(37)	2.000	0.08	0.00245
Cucumbers,inc pickl(46)	2.000	0.73	0.02177
Eggplant(53)	2.000	0.03	0.00090
Grapes, inc raisins(66)	2.000	0.49	0.01472
Kale(75)	2.000	0.03	0.00090
Lettuce(84)	2.000	1.31	0.03924
Melons(92)	2.000	2.00	0.06009
Mustard Greens(99)	2.000	0.06	0.00184
Nectarines(100)	2.000	0.03	0.00090
Peaches(114)	2.000	0.90	0.02698
Pears(116)	2.000	0.26	0.00766
Peas(117)	2.000	0.69	0.02085
Peppers(120)	2.000	0.12	0.00368
Pineapple(123)	2.000	0.30	0.00889
Plums,inc prunes(125)	2.000	0.13	0.00399
Pumpkin,inc squash(131)	2.000	0.11	0.00337
Spinach(150)	2.000	0.05	0.00153
Strawberries(152)	2.000	0.18	0.00552
Summer Squash(155)	2.000	0.03	0.00090
Sunflower(156)	2.000	0.03	0.00090
Tomatoes(163)	2.000	2.87	0.08624
Turnip Greens(166)	2.000	0.03	0.00090
Water Cress(166)	2.000	0.03	0.00090
Wintersquash(171)	2.000	0.03	0.00090
Cottonseed (oil)(41)	1.000	0.15	0.00225
Milk&Dairy Products(93)	0.020	28.62	0.00858
Sugar,cane&beet(154)	0.500	3.64	0.02729
Carrots(24)	0.200	0.48	0.00144
Corn,sweet(40)	0.200	1.43	0.00429
Sweet Potatoes(157)	0.200	0.40	0.00120
Meat, red(90)	0.200	10.81	0.03244
Almonds(1)	0.200	0.03	0.00009
Filberts(58)	0.200	0.03	0.00009
Macadamia nuts(87)	0.200	0.03	0.00009
Mustard Seed(185)	0.200	0.03	0.00009
Pecans(118)	0.200	0.03	0.00009

Potatoe 127)	0.200	5.43	0.01628
Rape Seed(1o6)	0.200	0.03	0.00009
Safflower(141)	0.200	0.03	0.00009
Walnuts(167)	0.200	0.03	0.00009
Blueberries(18)	0.100	0. 3	0.00005
Barley(8)	0.100	0.03	0. 0005
Oats(102)	0.100	0.36	0.00054
Rye(140)	0.100	0.03	0.00005
Wheat(170)	0.100	10.36	0.01554
Tea(1o2)	0.100	0.07	.00011

MPI	TMRC	% ADI
0.4500 mg/day/60kg	0.6080 mg/day/1.5kg	135.12

****

Unpublisned,Tox Approved 4E1430

CROP	Tolerance	Food Factor	mg/day/1.5kg
Coffee(36)	2.000	0.75	0.02238

MPI	TMRC	% ADI
0.4500 mg/day/60kg	0.6304 mg/day/1.5kg	140.10

****

Current Action 7E1940

CROP	Tolerance	Food Factor	mg/day/1.5kg
Raspberries(135)	0.1o0	0.03	0.00005

MPI	TMRC	% ADI
0.4500 mg/day/60kg	0.6305 mg/day/1.5kg	140.11

****