UNITED STAT. ENVIRONMENTAL PROTECTIO AGENCY
WASHINGTON, D.C. 20460

CASWELL#167B

APR 29 1980

002700

OFFICE OF TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 100-EUP-66 & 100-EUP-65, PP#9G2230, CGA-72662 (N-Cyclopropyl-1,3,5-triazine-2,4,6-triamine) feedthrough larvicide in poultry: topical for poultry, beef cattle, sheep and hog manure (including feedlots). DATA submittal in response to Toxicology Branch review 11/9/79.

FROM : Robert B. Jaeger
Toxicology Branch, HED (TS-769)

TO : Franklin Gee
Product Manager#17
Registration Division (TS-767)

THRU : M. Adrian Gross, Chief
Toxicology Branch, HED (TS-769)

Petitioner: Agricultural Division
CIBA-GEIGY Corp.

Petition No.: 9G2230
100-EUP-65 and 66

Temporary Tolerance: 0.1 ppm - meat, fat, and meat by-product of beef cattle, sheep and hogs.

0.2 ppm - eggs and meat, fat and meat by-products of poultry.

Supporting Data:

Acute Oral LD_{50} (Rat) = 3387 mg/kg (Technical)
Mutagenicity Tests (Technical)

Ames Test - negative at highest dose tested - 2025 ug/0.1 ml

Micronucleus Test - negative at highest dose test 8 g/kg

90-Day Subchronic Oral Dosing Study (Dog) -

NOEL = 300 ppm
LEL = 1000 ppm (based on increase in relative liver weight for males

002700

90-Day Subchronic Oral Dosing Study (Rat) -

NOEL = 30 ppm
LEL = 300 ppm (based on decrease in relative liver weight for males)

Teratology (Rat) (Technical) - negative for teratogenicity at high dose of 600 mg/kg

6-Month Caged Layer Feeding Study (Leghorn Chickens) - NOEL = 50 ppm (effects on hatchability and rearing were not evaluated).

Ciba-Geigy has submitted additional data and statistical analyses requested in Toxicology Branch review, same subject as above, dated 11/9/79.

The following data (Acc.#099272) were reviewed:

1) Mutagenicity (Cytogenic Study) - Nucleus Anomaly Test in Somatic Interphase Nuclei (Chinese Hamster) - Bone Marrow Cells

This test is considered a micronuleus test which follows a generally accepted procedure for such evaluation discribed by W. Schmidt. A few differences are noted from that of Schmidt (e.g., 1000 bone marrow cells per se versus 1000 polychromatic erythrocytes). None of those differences are known to detract from the significance of the observation obtained.

Acute Oral LD_{50} (Chinese Hamster) 8000 mg/kg; Doses tested in the micronucleus were 2, 4 and 8 g/kg.

CGA-72662 was not determined to be mutagenic by this test procedure.

2) Teratology Study - Rat
(IRDC, 12/21/79, 382-070)

Test Substance: CGA-72662 Technical

Species: Charles River COBS CD Rats

Age: 13 weeks

Mating: 1M to 1F; observation of copulatory plug (day 0)

Dose Group: 25F/dose - 0, 100, 300, 600 mg/kg

2

Administration: day 6 to 19 of gestation (oral)

Delivery: day 20 by C Section

002700

Maternal Observations: Daily for clinical signs and mortality

Body Weights - days 0, 6, 9, 12, 16, 20

C-Section Observations -

Uterus excised and weighed prior to removal of fetuses.

and location of viable and nonviable fetuses, early/later resorptions

total implants and C.L.

Abdominal and thoracic cavities/organs grossly examined.

Fetal Observations: Weighed, examined for external malformation, and sexed.

1/3 placed in Bouin's fixative for visceral examination (Wilson).

2/3 fixed in alcohol, placed in KOH and stained with Alizarin Red S for skeletal exam (Dawson).

Results:

Maternal: 100 mg/kg - oral discharge; soft stools

300 mg/kg - red nasal discharge; clear oral discharge; hair loss; soft stools

600 mg/kg - red nasal discharge; clear oral discharge; increased activity; matted and stained haircoat; (anogenital area); soft stools, hair loss

Body Weight: 100 mg/kg - no difference

300 mg/kg - slightly reduced

600 mg/kg - moderately reduced

002700

C-Section: No differences observed in the mean number of viable fetuses, late/early resorptions, post-implantation loss, total implantation, C.L. or fetal sex distribution.

300 mg/kg - mean fetal body weight slightly reduced

600 mg/kg - statistically significant decrease in mean fetal body weight

Fetal Observations: No malformations in the 100 and 300 mg/kg/day groups.

No statistical significance in the malformations in the 600 mg/kg/day group when compared to control.

(NOTE: 3 fetuses with cartilage anomaly noted in 600 mg/kg group; laboratory stated this anomaly has occurred before in a control group - unpublished data. This data however, was not indicated in Appendix III, Historical Control Data)

Increases in # of litters and fetuses with "developmental variation" in all treatment groups -

100 & 300 mg/kg - very slight increase in reduced ossification of skull and unossified sternebrae.

600 mg/kg - definite increase in unossified sternebrae.

The following chart [illegible] be used for comparison of fi[illegible]gs:

002700

Group	Findings: Skull (reduced ossification)	Sternebrae#5 and #6 (Unossified)	Other Sternebrae Unossified	Cartilage Anomaly
Historical Control				
Fetal(%)	1.3	12.5	7.4	Indicated, but not reported/ recorded.
Litter(%)	8.0	46.2	4.9	
Control				
Fetus(%)	0	21.4	0.9	0
Litter(%)	0	75.9	8.7	0
100 mg/kg				
Fetus(%)	0.9	29	2.3	0
Litter(%)	4.5	86.4	18.2	0
300 mg/kg				
Fetus(%)	0.4	33.2	2.1	0
Litter(%)	4.0	88	16	0
600 mg/kg				
Fetus(%)	0.9	76.3	10.7	0.9
Litter(%)	8.3	95.8	45.8	4.2

When the data obtained were compared to the historical data, it is noted that the 600 mg/kg dose demonstrates significant differences from the control data in the area of reduced ossification (skull, sternebrae, etc.). While the number of fetuses effectd at the lower doses is not significant, significantly more litters are effected. The conclusion reached is that CGA-72662 is not teratogenic to Charles River COBS CD Rats at levels up to and including 600 mg/kg/day for the period of major organogenesis. There were however, slight to moderate maternal effects (other than teratogenic) noted at all levels.

Classification: CORE-Minimum Data

002700

3) 6-Month Caged Layer Safety Study with CGA-72662 (performed by Dr. W.L. Beane, Poultry Physiologist, V.P.I. and S.U., Blacksburg, Va.)

Substance: CGA-72662

Species: Adult White Leghorn Chickens

Number/Sex: 80F, 32M

Dose: 0, 5, 25, 50 ppm (in the diet)

Duration: 26 weeks

Groups: 4 groups of 5F and 2 groups of 4M each were placed on each of the four (4) diets - (20F, 8M per dose)

Observations: Body weights/feed consumption - biweekly

Egg production - daily

Egg traits - weekly

Birds observed daily for untoward behavioral response, mortality, etc.

Gross exam on all birds terminally.

Organ weights - heart, spleen, liver, adrenal, testes

Results: There were no apparent effects on:

- egg production (#eggs laid)
- egg weight
- specific gravity (eggs)
- shell thickness
- shell weight
- mortality
- organ weights (those determined)
- body weight (male or female)

Some difference were noted in feed consumption for the 50 ppm group from week 8 to 26 (males); females were not similarly effected.

6

002700

Conclusion:

While there were no apparent effects on egg production or laying, per se, the hatching and rearing of young chicks was not observed. Toxicology Branch noted that this data was needed (11/9/79) and we have not changed from our previous decision. The registrant should please submit this required data.

Another difficulty with the study, as submitted, is that the identity of the test substance is not specifically identified with respect to concentrations, e.g. technical, 40%, formulation, etc. The registrant must submit this information in order for this study to be considered in support of subject EUP.

The submittal of the above data, in addition to the statistical analyses of the 90-Day Rat data, are in answer to questions raised by Toxicology Branch on 11/9/79 and discussed with the Registrant on 2/14/80. At this meeting on 2/14/80 Toxicology Branch had agreed to delete the requirement for a broiler chicken feeding study in response to the fact that the product will not be used for broilers. It was further agreed that the reproduction study (rodent) would be submitted when available, but that completed teratology studies be reviewed immediately. Review of the data submitted is sufficient, except as noted in the laying chicken feeding study (reviewed above).

I requested our Toxicology Branch statistician review the statistical data and information submitted by Ciba-Geigy. My instructions to him were to review only male liver and liver to body weight measurements by the statistical methods used by Ciba-Geigy. I asked that he please determine which test was the most appropriate for the data presented and what NEL did it support or not support. He determined that Dunnett's Test is the most appropriate test and that significant differences occur at the 300 ppm level for liver to body weight ratios. Therefore, 30 ppm is the NEL for the effect noted - namely, decreased liver weight in male rats. Such a finding is similarly supported by the Student's t-test ($p < 0.056$ at 30 ppm). It is therefore concluded that a NEL has been determined for the 90-Day Rat Subchronic Oral Study previously reviewed by Toxicology Branch (11/9/79) and that it now constitutes a CORE: Minimum Study. As previously stated to Ciba-Geigy personnel (2/14/80) Toxicology Branch does not consider liver to brain weight ratios appropriate measures of relative weight effects of specific organs in lieu of organ-to-body-weight measurements. Therefore, liver-to-brain weight ratios did not impact on Toxicology Branch's decision with respect to the finding of a NEL for subject study.

Toxicology Branch concludes that sufficient toxicity data have been submitted in support of subject EUP, and that renewal or continuance of this EUP and its associated tolerances is contingent upon the findings from the 2-year rat feeding study presently underway. It was noted, however, that the dose levels selected for the 2-year rat study may not have been properly selected (i.e. 50, 1000, and 3000 ppm) and that there is a "quantum" jump between the low dose and the medium dose levels selected.

C. Trick
4/10/80
4/14/80

1