11-9-1979

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

002687 Cancelled 1678

DATE: November 9, 1979

SUBJECT: 100-EUP-65 and 66, 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).

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

TO: Franklin Cee
Product Manager#17

Petitioner: Agricultural Division
CIBA-GEIGY Corp.

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

Temporary Tolerance: 0.2 ppm - meat, fat, and meat by-products of beef cattle, sheep and hogs

0.6 ppm - eggs and meat, fat, and meat by-products of poultry

Recommendation

Do not grant the EUP's and associated temporary tolerances.

Data Required in Support of EUP's

1. 90-Day Subchronic Oral Dosing Study in a Rodent - demonstration of a NEL.
2. Teratology Study - one species.
3. Reproduction Study (Rodent) - evaluation at least up through the first generation submitted.
4. Mutagenicity Screen - (a) Chromosome (cytogenic)
5. Broiler Chicken Feeding Study - 8-week feeding study (preferably in drinking water) at exaggerated dose; 25 broilers.
6. Laying Chicken Feeding Study - reproduction study to include rearing, laying, and hatching (to cover 4-week growth period after hatching); day one to 4 months; evaluation of egg production; exaggerated dose; 10 hens for each of 2 roosters.
7. Submit copies of the proposed labels.

EPA 1320-6 (REV. 3-76)

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Data Review

Accession No. 098384

A. Technical Grade CGA 72662

(N-Cyclopropyl-1,3,5-triazine-2,4,6-triamine)

Acute Oral LD_{50} (rat) 1/11/78

LD_{50} = 3387 (2524-4547) mg/kg

Rat: Tif:RAIF (SPF) strain

Sex: M/F

Body wt: 160-180 gr.

Acclimatization period: 4 days

Temp./Humidity: 22 ± 1° C; 55 ± 5%

Light/Dark: 10 hours light/day

Food/Water: ad libitum (fasted overnight)

Housing: Grouped 5/cage

Treatment: oral intubation

Doses (mg/kg): 1000, 1670, 3590, 4640, 6000

Animals/dose: 5M/5F

Observation period: 14 days

Toxic signs: sedation, dyspnea, exophthalmos, abnormal posture (curved position), ruffled fur

Gross Necropsy: all animals

Results: No gross organ changes seen.

Classification: CORE Minimum

Acute Oral LD_{50} (Mouse) 6/12/78

LD_{50} = 2029 (1472-2707) mg/kg

Mouse: Tif:MAG (SPF) strain

Sex: M/F

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Body wt: 20-30 gr.

Acclimatization: 4 days

Temp./Humidity: 22 ± 1° C; 55 ± 5%

Light/Dark: 10 hours light

Food/Water: ad libitum (fasted overnight)

Housing: Grouped 5/cage

Treatment: Oral intubation

Doses (mg/kg): 600, 1000, 2150, 3590, 4640, 7750

Animals/dose: 5M/5F

Observation period: 14 days

Toxic signs: sedation, dyspnea, abnormal posture (curved position), ruffled fur.

Gross necropsy: All animals

Results: No gross organ changes seen

Classification: CORE Minimum

1/11/78

Acute Oral LD_{50} (Rabbit)

LD_{50} = 1467 (1012-2127) mg/kg

Rabbit: Himalayan

Sex: M/F

Body wt: 1.0 to 2.1 kg

Acclimatization: 4 days

Temp./Humidity: 22 ± 1° C; 55 ± 5%

Light/Dark: 10 hours light

Food/Water: ad libitum (fasted overnight)

Housing: individually

Treatment: oral intubation

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Doses (mg/kg): 600, 1000, 2150, 3000

Animals/dose: 5M/5F

Observation period: 14 days

Toxic signs: sedation, abnormal posture (curved position), ruffled fur; also tremor, ataxia, salivation

Gross Necropsy: all animals

Results: partially congested organs and bloated gut (dead animals); no gross organ changes in killed animals.

Classification: CORE Minimum

Acute Dermal LD_{50} (Rat) 1/11/78

LD_{50} > 3100 mg/kg

Rat: Tif:RAIF (SPF) strain

Sex: M/F

Body wt: 180-200 gr.

Acclimatization: 4 days

Temp./Humidity: 22 ± 1° C; 55 ± 5%

Light/Dark: 10 hours light

Food/Water: ad libitum

Housing: individually

Treatment: 60 sq. cm. on back clipped free of hair 24 hr. prior to treatment; test material evenly dispersed with syringe and covered with an occlusive dressing.

Dressing removed after 24 hrs. and skin cleaned with lukewarm water.

Doses (mg/kg): 2150, 3170

Animals/Dose: 5M/5F

Observation period: 14 days

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Toxic signs: dyspnea, abnormal posture (carved position), ruffled fur; no local irritation

Gross Necropsy: All animals

Results: No gross changes observed

Classification: CORE Guidelines

Acute Intraperitoneal LD_{50} (Rat)

Not reviewed

Eye Irritation (Rabbit) 3/16/78

No irritation produced

Rabbit: Himalayan

Sex: M/F

No. of animals: 6

Body wt: 1.5 to 2 kg.

Acclimatization: 4 days

Temp./Humidity: 22 ± 1° C; 55 ± 5%

Light/Dark: 10 hours light

Food/Water: ad libitum

Housing: individually

Treatment: 0.1 g into conjunctival cul-de-sac of one eye of each rabbit; lids held closed for 1 second. 3/6 rabbits' eye washed 30 seconds after instillation (10 ml water).

Scoring: day 1, 2, 3, 4, 7 with a slit-lamp (Re: Draize); individually scores.

Tox Cat: IV

Classification: CORE Minimum

Skin Irritation (Rabbit) 3/16/78

P.I. Index = 1.1/8.0

mild irritant

Rabbit: Himalayan

Sex: M/F

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No. of animals: 6

Body wt: 1.5 to 2 kg

Acclimatization: 4 days

Temp./Humidity: 22 ± 1° C; 55 ± 5%

Light/Dark: 10 hours light

Food/Water: ad libitum

Housing: individual

Pretreatment: entire back and flank clipped free of hair 48 hours prior to treatment; immediately before treatment the left flank was abraded.

Treatment: gauze patches (2.5 x 2.5 cm) with test material applied to abraded and non-abraded skin areas in quantities of 0.5 g. Patches were occluded with impermeable damming. Dressing removal after 24 hours exposure.

Scoring: immediately and 48 hours after patch removal.

< 2 = mild

2-6 = moderate

>6 = severe

Well defined to moderate erythema and edema in abraded skin at 24 hours, slight in non-abraded; negative at 72 hours after application in both.
Tox Cat: III
Classification: CORE Minimum

Skin Sensitization (Guinea Pig) 7/27/78

Non-Sensitizing by T. Maurer Optimization Method (1975).

Guinea Pig: Pirbright white

No. of Sex: 10M/10F

Body wt: 400-450 gr.

Temp./Humidity: 22 ± 1° C; 55 ± 5%

Light/Dark: 10 hours light

Food/Water: ad libitum

Housing: individually

Induction Phase: intradermal injection every other day for a total of 10 injections (0.1% suspension in 0.9% physiological saline). First day 0.1 ml administered to right flank and back; subsequent injections to back only. Second and third week test material administered in Complete Freund's Adjuvant (1:1).

Challenge Phase: 14 days after last injection, a challenge of 0.1 ml (0.1% in 0.9% physiological saline) administered intracutaneously.

Scoring: reactions were recorded 24 hours after each induction injection and challenge injection. The 2 largest perpendicular diameters (in mm) and the increase in the skin-fold thickness (in mm) were measured and multiplied to give "reaction volume" (in ul) for each reading. The mean volume plus one S.D. of the induction reactions observed in the first week represented the skin irritation "threshold." Any reaction greater represented a "positive" reaction.

Occlusion: 10 days after the intracutaneous challenge injection, a subirritant dose (1% in vaseline) was applied epicutaneously under occlusive dressing and held in place 24 hours.

Results: the intradermal and epicutaneous doses failed to elicit sensitization reactions.

Classification: CORE Minimum

Mutagenicity Test - Salmonella/Mammalian Microsome 12/11/78

Ames Test

Bacteria used: TA 98, TA 100, TA 1535, and TA 1537 strains of Salmonella typhumurium.

With and without activation mixture of rat liver microsomes and co-factors.

Test Concentration: 25, 75, 225, 675 and 2025 ug/0.1 ml in DMSO.

Negative Control: DMSO

Positive Controls:

TA 1535 - N-methyl-N'-nitro-N-nitrosoguanidine 3 and 5 ug/0.1 ml phosphate buffer

TA 1537 - 9(5) aminoacridine hydrochloride monohydrate, 25, 5[illegible] 100 ug/0.1 ml DMSO

TA 98 - daunoblastin, 2.5, 5, 10 ug/0.1 ml phosphate buffer

TA 100 - 4-nitroquinolin-N-oxide, 0.0625, 0.125, 0.25 ug/0.1 ml phosphate buffer

Activation mixtures tested with TA 1535 and cyclophosphamide, 100, 250 ug/0.1 ml phosphate buffer.

3 Petri dishes per strain per group for exp. with and without activation.

Positive controls - 2 Petri dishes per strain per group

Plates incubated 48 hours at 37°C in darkness

Results: no evidence of induction of point mutations of the test substance or its metabolites in certain strains of S. typhimurium.

Classification: CORE Minimum

Accession No. 098383

B. 0.3% Premix 245-18

Acute Oral LD_{50} (Rat) 5/10/79

LD_{50} > 5033 mg/kg

Rat: Sprague-Dawley

No. & Sex: 5M/5F per dose

Dose: 5033 mg/kg in corn oil

Body wt: 200-230 g.

Acclimatization period: one week

Food/Water: ad libitum (fasted 16 hrs prior to test)

Housing: individually

Treatment: oral intubation

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Observation period: 14 days

Toxic signs: piloerection (males)

Gross Necropsy: all animals

Results: no gross effects; no deaths

Classification. CORE Guidelines

Acute Dermal LD_{50} (Rabbit) 5/18/79

LD_{50} > 2004 mg/kg

Rabbit: New Zealand Albino

Body wt: 2.5-3.7 kg

No. & Sex: 5M/5F per dose

Dose level: 2004 mg/kg

Food/Water: ad libitum

Housing: individual

Pretreatment: 24 hours prior, trunk clipped; approximately 30% of total body surface; each animal was abraded (2 long. and 2 perp. epidermal abrasions) into S.C. (horny layer).

Treatment: test material applied to backs of animals (evenly) and occluded for 24 hours. At the end of exposure period, wraps removed and exposed skin areas wiped clean.

Observation peiod: 14 days

Toxic signs: erythema and edema, diarrhea, few feces, little urination, one death

Gross Necropsy: all animals

Results: discoloration of G.I. contents; red fluid in abdominal cavity.

Edema: grade 3 in 24 hours, clear in 5 days

Erythema: grade 2 in 24 hours, clear in 7 days

Classification: CORE Guidelines

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Eye Irritation (Rabbit) 4/27/79

Mildly irritating

Rabbit: New Zealand Albino

No.: 9

Housing: individual

Acclimatization: one week

Food/Water: ad libitum

Eyes preexamined

Treatment: 100 mg undiluted material placed in the right conjunctival cul-de-sac of each rabbit; lids held shut for 1 second and released. 3/6 washed 30 seconds after instillation for 1 minute duration.

Scoring: Draize; 24, 48, 72 hours and 4 and 7 days after treatment.

Results: Unwashed: 13/110; clear in 7 days; primarily chemosis/redness; although 2/6 grade 1 iritis by 24 hrs. No corneal involvement.

Washed: 6/110; clear in 7 days; chemosis/redness slightly less than unwashed; no corneal involvement.

Classification: CORE Guidelines

Skin Irritation (Rabbit) 5/10/79

Slightly irritating

Rabbit: New Zealand Albino

No. & Sex: 3M/3F

Acclimatization: one week

Housing: individually

Food/Water: ad libitum

Pretreatment: 24 hrs prior, trunks were clipped free of hair (area 5 in. x 7 in.); there were 2 abraded and 2 intact areas per rabbit.

Treatment: 0.5 g in saline applied beneath a 1" x 1" sq. gauze patch. Patches were occluded. Patches removed after 24 hr exposure. Backs of animals were wiped with clean cloth to remove residual test material.

Scoring: 30 minute after patch removal exposed areas were scored; again at 72 hrs. after treatment. (Draize)

Intact: 1.20/8.0

Slightly irritating

Abraded: 1.54/8.0

Slightly irritating

Combined: 1.42/8.0

Slightly irritating

Results:

Intact: very slight erythema and edema - 6/6

Abraded: well defined erythema and edema - 4/6

No other toxic symptoms observed.

Classification: CORE Guidelines

Accession No. 098383

C. 5% SOO FL790350

Acute Oral LD_{50} (Rat) 5/16/79

LD_{50} (male) 5000 mg/kg (slope = 20.68)

(female) 3470 mg/kg (slope = 1.43)

Combined = 3860 mg/kg (slope = 2.12)

Rat: SD

No. & Sex: 5M/5F per dose

Dose: 2285, 2967, 3858, [illegible]11, 6514 mg/kg

Bodt wt: 200-300g

Acclimatization: one week

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Food/Water: ad libitum (fasted 16 hr. prior)

Housing: Individually

Treatment: oral intubation

Observationperiod: 14 days

Toxic signs: Salivation, polyuria, hypothermia, tremors, swollen nose, nasal discharge, prolapse of penis, lacrimation, epistasis, diarrhea, chromodacryorrhea, piloerection, ptosis, exophthalmos, dilated pupil, rapid breathing, constricted pupil, ataxia, activity decrease, loss of righting reflex, difficult and labored breathing, lethargy, death.

Gross Necropsy: All animals. Discoloration of liver, stomach and intestinal mucosa, prostate, adrenal glands, pancreas, mesenteric lymph nodes. Heart small and hard (very narrow cavities). Testes drawn into abdominal cavity.

Pronounced serosal blood vessels. No abdominal fat. Lumps on kidney and liver. Enlarged spleen, adrenal glands and liver (also brittle)

Small testes

Mass surrounding penis

Liver adhered to other tissues

Classification: CORE Guideline

Acute Dermal LD_{50} (Rabbit) 5/31/79

LD_{50} > 2004 mg/kg

Rabbit: New Zealand Albino

Body wt: 2.4-3.2 kg

No. & Sex: 5M/5F per dose

Dose: 2004 mg/kg

Food/Water: ad libitum

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Acclimatization: one week

Housing: individual

Preconditioning: 24 hrs. prior, trunk clipped, approx. 10% of total body surface; each animal was abraded (2 long and 2 perp. epidermal abrasions) into S.C. (horny layer).

Treatment: test material applied to backs of animals (evenly) and occluded for 24 hrs. At the end of exposure period, wraps removed and exposed skin wiped clean.

Observation period: 14 days

Toxic signs: erythema (0.70) and edema (0.23), diarrhea, decreased activity, dilated pupil, little or no urine, small, few or no feces, death.

Gross Necropsy: All Animals

Discoloration of kidneys, intestinal mucosa G.I. tract distended and adhered to other tissues

Irregular surface of kidneys.

Foam in colon

Classification: CORE Guidelines

Eye Irritation (Rabbit) 4/27/79

Mildly irritating

Rabbit: New Zealand Albino

No.: 9

Housing: Individually

Acclimatization: one week

Food/Water: ad libitum

Eye precondition

Treatment: 0.1 ml undiluted material placed in the right conjunctival cul-de-sac of each rabbit; lids held shut for one second and released. 3/6 washed 30 seconds after instillation for one minute duration.

Scoring: Draize; 24, 48, 72 hours and 4 and 7 days after treatment.

Results:

Unwashed: 9.3/110 mildly irritating (redness, chemosis, discharge)

Washed: 8.7/110 mildly irritating (redness, chemosis, discharge)

Classification: OECD Guideline

Skin Irritation (Rabbit) 4/27/79

Sligtly irritating

Rabbit: New Zealand Albino

No. & Sex: 3M/3F

Acclimatization: one week

Housing: Individually

Food/Water: ad libitum

Pretreatment: 24 hrs. prior, trunks were clipped free of hair (area 5 in. x 7 in.); there were 2 abraded and 2 intact areas per rabbit.

Treatment: 0.5 ml undiluted test material applied beneath a 1" x 1" sq. gauze patch. Patches were occluded. Patched removed after 24 hrs. exposure. Backs of animals were wiped with clean cloth to remove residue test material.

Scoring: 20 minutes after patch removed exposed areas were scored; again at 72 hrs. after treatment (DRAIZE).

Intact: 0.92/8.0

slightly irritating

Abraded: 1.17/8.0

slightly irritating

Combined: 1.05/8.0

slightly irritating

Classification: Supplementary (individual animal scores not included)

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Accession No. 098385

D. 90-Day Subchronic Oral Toxicity Study in Purebred Beagle Dogs (Tech.) 6/19/79 (IRDC)

Animal: Beagle Dog ,

No. & Sex: 4M/4F in each low and medium dose group

6M/6F in high dose and control

Doses: 0, 30, 300, 1000, 3000 ppm

Recovery Group: 2M/2F in high dose and control groups retained on study for a 4-week compound - withdrawal period.

Route of Administration: in the diet

Observation: ophthalmoscopic and physical examination - pretest, 4, 8 and 12 weeks; and 17 weeks (withdrawal dogs only).

laboratory tests (hematology, biochem, and urinalysis) - pretest, 4, 8 and 12 weeks; and 17 weeks/withdrawal dogs only).

individual body wt. and food consumption recorded weekly.

individual signs of toxicity or mortality observed daily.

Gross Necropsy: all dogs

Histopathology: all dogs

organs weighed: liver, spleen, kidneys, heart, brain, gonads, adrenals, thyroid, pituitary

tissues micro: adrenal, aorta (thoracic), bone marrow, brain, cecum, colon, esophagus, gall bladder, gonads, heart, kidneys, liver, lungs, cervical and mesenteric lymph nodes, mammary gland, skeletal muscle, pancreas, thyroid, peripheral nerve (sciatic), pituitary, prostate, salivary gland, skin, small intestine (duodenum, jejunum, ileum), spinal cord, spleen, sternum, stomach, trachea, urinary bladder, uterus, and gross lesions.

Results:

Ophthalmoscopy - performed with binocular indirect ophthalmoscope after 1% Tropicamide solution was placed in eyes to dilate the pupil. No difference between control and treated animals.

Laboratory Tests - (pretest, 29, 58, 85 dogs, and at 118 days for withdrawal dogs).

Hematology: hemoglobin, hematocrit, total erythrocyte count, total and differential leucocyte counts, prothrombin time.

Females - no compound-related effects

Males - a significant decrease ($p < 0.01$) in RBC, Hb and Ht at 3000 ppm in wks 58 and 85. Values were not significantly different at 118 weeks.

Other hematologic values were within normal variation; with the exception of control #281 with significantly increased total leucocyte count and segmented neutrophils and decreased lymphocytes throughout test.

Biochemistry: blood glucose, BUN, SAP, SGOT, SGPT, total cholesterol, total protein.

No significant differences observed other than a slightly increased SAP in males at the 3000 ppm at all measurement intervals. Also, Table 11 for males and females is incorrectly summarized for the enzyme evaluations.

According to the individual data for Table 16, the 118-day value for 0 ppm and 3000 ppm groups is incorrectly summarized in Table 11. (i.e. 118-day values for males are really the values obtained from females; and conversely values reported for females are actually the values obtained from males. For example, 0 ppm male. 118-day SAP value reported as 60 should actually be 99; 0 ppm female 118-day SAP value reported as 99 should actually be 60).

Urinalysis: pH, glucose, protein, bilirubin, ketone, microscopic examination of sediment.

No differences between control and test groups.

Gross Necropsy:

Mode of death - I.V. Sod. pentobarbital, and exsanguination.

No compound-related lesions observed under gross necropsy.

Organ Weight Changes: The relative liver weight for males was significantly greater than control at the 1000 ppm ($p < 0.025$) and 3000 ppm levels ($p < .01$). Females did not show this effect for liver. However, the relative kidney weight for both sexes at 3000 ppm was significantly greater than contol ($p < .05$ for males, $p < .025$ for females). These comparisons were made using the Student's t-Test.

Body Weight Changes: There was no clear dose related effect on body weight. Females were affected to a greater extent than males, showing less weight gain at the 3000 ppm level than controls. Males were affected slightly at 3000 ppm but not significantly different from 30 or 300 ppm levels (i.e. weight gain for 1000 ppm males was the same as controls).

Females (wk - 1 to + 13)

0	30	300	1000	3000
+1.7	+2.6	+1.5	+1.3	+0.8

Males (wk - 1 to + 13)

0	30	300	1000	3000
+2.2	+1.9	+1.7	+2.2	+1.4

Histopathology

Histopathology was unremarkable and there were no compound-related effects on any of the tissues sectioned.

Conclusion

The NOEL for this study is 300 ppm based on the increase in relative liver weight for males at the 1000 ppm and 3000 ppm levels. They were significant at $p < 0.025$ and $p < 0.1$ respectively.

Classification: CORE Minimum

Accession No. 098385

E. 90-Day Subchronic Oral Toxicity Study in Albino Rats (Tech.) 6/19/79 (IRDC)

Animal: Charles River CD Albino Rats

No. & Sex: 110M/110F, 20 rats/sex/group (additional 5 rats/sex/group for control and high dose groups - so called "Recovery Group").

Doses: 0, 30, 300, 1000, 3000 ppm

Route of Administration: in the diet

Observations:

ophthalmoscopic exam

conducted pretest and terminal (also at 16 wks for recovery group)

general signs of toxicity and mortality

observed twice daily

individual body weight and food consumption

determined weekly

laboratory tests (hematology, biochemistry, urinalysis) - day 29, 61 and 86 (urine collected day 83 and 89);

Recovery group at 118 days as well.

Gross Necropsy: all rats

Histopathology: all rats

organs weighed: liver, kidneys, testes, heart, spleen, brain.

tissues micro:

high dose and control - adrenals, aorta, bone marrow, brain, cecum, colon, esophagus, eye, gonads, Harderian gland, heart, kidney, liver, lung, cervical and mesenteric lymph nodes, mammary gland, skeletal muscle, optic nerve, pancreas, parathyroid and thyroid, peripheral nerve (sciatic), pituitary, prostate, salivary gland, skin, small intestine (duodenum, jejunum, ileum), spinal cord, spleen, sternum, stomach (cardiac, fundus, pylorus), trachea, thymus, urinary bladder, uterus, and gross lesions.

low and mid dose - liver, kidney, heart and gross lesions.

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Results:

Ophthalmoscopy - performed with binocular indirect ophthalmoscope after 1% tropicamide solution was placed in the eye to dilate the pupil. No differences between control and treated animals were noted.

Laboratory Tests:

Hematology: total platelet count, erythrocyte counts, total and differential leucocyte counts, hematocrit, hemoglobin, prothrombin time. No compound-related effects were noted.

Biochemistry: Calcium, potassium, SLDH, direct and total bilirubin, albumin, globulin, SGOT, SGPT, SAP, BUN, fastedblood glucose, total cholesterol, total protein. No compound-related effects were noted other than a dose-related decrease in calcium (mg/100 ml) for males, significant at 1000 and 3000 ppm. All the determinations were within normal limits.

Urinalysis: description of appearance, measurement of volume, pH, specific gravity, and qualitative tests for protein, glucose, ketones, bilirubin and urobilinogen; and microscopic examination of sediment. No compound-related effects noted.

General Behavior, Appearances, Survival - No compound-related effects noted. Survival was not affected by treatment.

Gross Necropsy: Mode of death - euthanitized by CO_2 asphyxiation and necropsied.

No compound-related lesions noted.

Organ weight changes:

The following relative organ weight change was considered significant compound related effects:

Relative Heart

Male - significant increase at 1000 and 3000 ppm

Relative Testes

Significant increase at 1000 and 3000 ppm.

Relative Liver

Male - significant decrease (Student t-Test)

30	$p < .05$
300	$p < .01$
1000	$p < .01$
3000	$p < .01$

(Absolute liver weights were also significantly decreased at all dose levels; $p < .05$)

The females did not demonstrate any clear compound-related effect except at the high dose in some instances.

Body Weight Changes

The following changes in body weight are noted:

Dose	Male	Female
0	438	267
30	431(-1.6)	270(+1.1)
300	458(+4.6)	264(-1.1)
1000	419(-4.3)	254(-4.9)
3000	410(-6.4)	236(-11.6)

The adverse effects noted at 3000 ppm for both sexes can be associated with a decreased food consumption. However, the organ: body weight effects noted (liver) for males is considered compound-related since food consumption was not altered, body weight changes did vary between gains and losses, and yet absolute organ weight (liver) was significantly decreased in both circumstrances.

Histopathology

There were no compound-related effects on any of the tissues examined.

Conclusion

The NOEL for this study has not been demonstrated. The significant decrease in relative and absolute liver weight for males at all levels fed, even though laboratory evaluation (hemat., biochem.) and both gross and histopathology examination failed to substantiate adverse effects, is justification for a thorough evaluation in this species. The rat is apparently the more sensitive species tested (rat vs. dog). "The weights of the livers were depressed more, in proportion to body weight, than would have been expected by chance; indicative of potential deleterious effect on this organ" (Weil, C.S. "Significance of organ-weight changes in food-safety evaluations", pp. 445, in: Francis J.C. Roe, ed. Metabolic Aspects of Food Safety, (1970).

Classification: CORE-Minimum

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Written