7-19-77 RU-611 TXR-4832

Chlordane

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 004832 174

DATE: July 19, 1977

SUBJECT: File Symbol 5535-RNU; Gro-Well Chlordane Termite Control. J. & L. Adikes, Inc., Jamaica, New York.

FROM: Toxicology Branch

TO: Timothy A. Gardner, Product Manager 15

This liquid formulation contains 46% technical chlordane in 49% petroleum distillates.

Applicant seeks to register this product for use exclusively in termite control.

ACUTE ORAL TOXICITY

Technical Chlordane; study by University of Illinois, July, 1968
Batch 8079, female rats LD_{50} = 249 mg/kg; males LD_{50} = 320 mg/kg
Batch 1009, female rats = 240 mg/kg; males = 300 mg/kg

Technical Chlordane; IRDC study, October, 1968, male rats
Batch 1009; LD_{50} = 442 mg/kg

Experimental Sample	A	LD_{50} = 442 mg/kg
"	B	332 mg/kg
"	C	365 mg/kg
"	D	442 mg/kg
"	E	590 mg/kg
"	F	487 mg/kg
"	G	536 mg/kg
"	H	502 mg/kg
"	I	521 mg/kg

"AG" Chlordane, IRDC Study, September, 1971; Male rats; LD_{50} = 389 mg/kg

Chlordane Technical, IRDC Study, August, 1974
Male Rats LD_{50} = 627 mg/kg
Female Rats = 431 mg/kg
Combined male & female rats; LD_{50} = 522 mg/kg

VEL-3857 Chlordane Deactivated; IRDC Study, April, 1975
Male rats - LD_{50} = 3709 mg/kg
Female rats - = 4068 mg/kg
Combined male & female rats; LD_{50} = 3885 mg/kg

Chlordane 4EC (#3232-58); IRDC Study, February, 1976
Male rats - LD_{50} = 583.9 mg/kg
Female rats - = 532.4 mg/kg
Combined male & female rats; LD_{50} = 557.5 mg/kg

INFORMATION WHICH MAY REVEAL IMPURITIES HAS BEEN DELETED.

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004832

ACUTE ORAL TOXICITY (cont.)

Chlordane Technical, IRDC Study in Mice, November, 1971
Male Mice; LD_{50} = 309.7 mg/kg
Female Mice; LD_{50} = 279.1 mg/kg

Alpha Gamma Chlordane; Industrial Bio-Test Study, May, 1970
Male & Female combined; LD_{50} = 232.9 mg/kg (rats)

Technical Chlordane, Analytical Reference Standard, IRDC Study, August, 1970
Male rats; LD_{50} = 315 mg/kg

Alpha Gamma Chlordane, 94% purity; Male rats, LD_{50} = 232 mg/kg

Technical Chlordane Analytical Reference Standard, IRDC Study, July, 1972
Group I rats (157-180 grams); male rats LD_{50} = 27[illegible] mg/kg
female rats LD_{50} = 301 mg/kg; combined male & female LD_{50} = 287 mg/kg
Group II rats (82-108 grams); male rats LD_{50} = 13[illegible] mg/kg
female rats LD_{50} = 191 mg/kg; combined male & female LD_{50} = 159 mg/kg

ACUTE INHALATION TOXICITY

Alpha Gamma Chlordane. Study by IRDC, October, 1974
Male rats: LC_{50} = 746 mg/liter; Female rats: LC_{50} = 800 mg/liter
Combined male & female: LC_{50} = 800 mg/liter

Technical Chlordane Analytical Reference Standard. Study by IRDC. Jan. 16, 1973.
Male Rats: LC_{50} = greater than 200 mg/liter. Not a toxic substance by inhalation route.

Chlordane 4 EC. Study by IRDC, February 16, 1976. Male and female rats.
No mortality at 2 mg/liter; 100% mortality over 6 days at 200 mg/liter.
A toxic, but not highly toxic, material by the inhalation route of administration.

Chlordane technical. Study by IRDC, August, 1974, in male & female rats, at concentration of 200 mg/liter. 5 male rats died within 9 days; 5 female rats survived the 14-day observation period. Chlordane technical is a toxic, but not highly toxic material by the inhalation route of administrati[illegible]

ACUTE DERMAL TOXICITY - RABBITS

Study by IRDC, February, 1976. LD_{50} greater than 2000 mg/kg. Not a toxic substance by dermal route of administration.

Study by IRDC, August 9, 1974. LD_{50} greater than 200 mg/kg and less than 2000 mg/kg. A toxic but not highly toxic substance by the dermal route of administration.

004832

PRIMARY SKIN IRRITATION - RABBITS

Study by IRDC, February 16, 1976. Primary Irritation Score = 2.83.
Not a primary skin irritant nor a corrosive substance.

Chlordane Technical. Liquid. Study by IRDC, August 9, 1974.
Primary irritation score = 2.2. A moderate irritant to the skin, but not a primary skin irritant nor a corrosive substance.

Alpha gamma chlordane, solid. Study by IRDC, September 16, 1971.
Primary irritation score = 3.1. Not a primary skin irritant.

EYE IRRIGATION STUDY - RABBITS

Study by IRDC, February 16, 1976.

5 minute wash: Not an eye irritant or a corrosive substance.
24-hour wash: An extremely irritant substance to the eye; not a corrosive substance.

Chlordane Technical (liquid). Study by IRDC, August 9, 1974.
5 minute wash: An extremely irritating substance
24-hour wash: An extremely irritating substance.

Alpha gamma chlordane (solid). Study by IRDC, September 16, 1971.
Unwashed: Total score 12.9 at 24 hours. Very slight corneal opacity at 24 & 48 hours in one animal.
Material is an eye irritant.

CHLORDANE 30-DAY RANGE-FINDING STUDY IN MICE. By IRDC, December 14, 1971.
Chlordane given to male and female mice in feed at 5, 10, 25, 50, & 100 ppm.
Food consumption values and increases in body weight were similar for all groups. No mortality was observed.
Pathologic findings included hepatomegaly in the 100 ppm males and females, and in 50 ppm males. Microscopically, increased size of liver parenchymal cells occurred in male mice at the 10, 25, 50, & 100 ppm levels and in female mice at the 50 and 100 ppm levels.

CHLORDANE 3-GENERATION REPRODUCTION STUDY IN ALBINO RATS. By Dr. L. Ingle, University of Illinois, July 21, 1947.

No gross lesions attributable to chlordane were seen in F3b pups at weaning.

Microscopic lesions in 3 pups dying from chlordane intoxication included marked cytoplasmic valuolation with partial or complete migration of granules toward the cell membrane, and cell hypertrophy prominent in the central and mid-zoned region of lobules. Vacuolation was in most instances accompanied by cytoplasmic margination in the same cells. (Possibly a natural reponse to increase in cell volume and no reduction in quantity of cytoplasmic materials or alteration of cell functions.)

004832

TECHNICAL CHLORDANE TERMINAL RESIDUE 5-MONTH REPRODUCTION STUDY IN CHICKENS. Conducted by Bio/Tox Research Laboratories, October, 1971

Technical chlordane terminal residues were fed for 5 months to 3 male and 15 female chickens at each of the following levels: 0.0, 0.1, 0.3, and 1.0 ppm. Total egg production, body weights, average egg weights, percent hatchability, and progeny viability showed no treatment related differences. Feed consumption was constant for each treatment group. Daily observations revealed no abnormal behavior nor toxic symptoms. All birds survived the treatment duration and appeared to be in good health at the time of sacrifice.

AND CHRONIC

1-HYDROXYCHLORDENE: ACUTE/ORAL TOXICITY IN RATS. Study by Dr. L. Ingle, Univ. of Illinois; October 18, 1965.

Acute Oral Toxicity in Rats: LD_{50} greater than 4.6 grams/kg.
CHLORDENE: LD_{50} = greater than 2.025 grams/kg.
OXYCHLORDENE: LD_{50} = 26.1 mg/kg.
CHLORDENE CHLORHYDRIN: LD_{50} = 2.078 grams/kg.

Incorporation of 1-hydroxychlordene into the diets of albino rats at levels of 2000, 100, 500, 250, 100, and 00.0 parts per million for 224 days produced the following results:

1. Growth and food consumption were normal at all levels.
2. Quantity of test compound ingested suggests that cumulative toxicity is not of significance. Possibly the compound is either degraded and eliminated or eliminated unchanged.
3. A one generation reproduction study involving a limited number of rats showed no adverse effects on fertility, litter size, litter weight, or survival and growth of young at any feeding level
4. Mortality among rats of all groups was low and no real differences existed.
5. At 224 days, necropsy revealed no gross pathology. The test compound cannot be considered as possessing carcinogenic properties when fed to rats for 224 days.
6. Histopathology of all visceral organs after 224 days of feeding was negative, except for the slight changes noted which were also observed in the control rats. A conservative conclusion is that the cellular alteration seen at the 2000 and 1000 ppm feeding level, although a possibility, cannot be considered as a significant pathological change. The same conclusion can be made with regard to hepatic cell enlargement.

90-DAY SUB-ACUTE TOXICITY OF ALPHA AND GAMMA CHLORDANE IN BARROWS. Study by Bio Toxicological Research Associates; January, 1970.

200 pound barrows were fed 300 ppm alpha or gamma chlordane daily for 90 days. At time of slaughter, no visible gross pathology was observed in any of the six pigs. During the course of study, no adverse effects or signs of toxicity were noted in any of the treated pigs.

CHRONIC TOXICITY OF ALPHA & GAMMA CHLORDANE IN MALE & FEMALE RATS. Study by University of Illinois, 1970.

20 male and 20 female rats received chlordane in diets daily for 2 years at the following levels:

Alpha chlordane: 5, 15, 25, and 35 ppm.
Gamma chlordane: 15, 25, 35, and 75 ppm
Alpha & gamma chlordane in 1:1 ratio: 5, 15, 25, 35, and 50 ppm

Alpha chlordane: No abnormalities in weight gains were observed with the possible exception of alpha chlordane fed male rats at 35 ppm where poor diet acceptance resulted in loss of weight to these animals. This was not interpreted as a toxic response. Slight retardation of growth, again due to poor diet acceptance, among females at 35 ppm indicated earlier in the series was erased later.

Gamma chlordane: Growth was essentially normal for males and females at all dietary levels.

Alpha + gamma chlordane in 1:1 ratio: Growth was essentially normal for males and females at all dietary levels.

FOOD CONSUMPTION: was less than that for controls for alpha chlordane males at 35 ppm. Variations among females at various feeding levels of alpha chlordane seem to be not related to dosage.

There was no significant difference in deaths among any groups at any level. A number of deaths were due to respiratory infections and not dose related.

ORGAN WEIGHT: Weights of hearts, kidneys, and liver were all within a normal range and showed no significant deviation from that of controls.

BLOOD: ALL blood analyses and tests were within the normal range and showed no particular or significant difference from control rats. None of the tests for hematocrit, hemoglobin, erythrocyte count, leucocyte count, blood urea nitrogen, blood glucose, serum alkaline phosphatase, or glutamic-pyruvic transaminase suggested detectable organ inflammation.

URINE: All tests and examinations were within the normal range, and not significantly different from those of controls. Tests and examinations show the urinary system to be functioning normally.

PATHOLOGY: Necropsy revealed no evidence of gross pathology with the exception of two control males and one male receiving alpha + gamma chlordane at 25 ppm. These three rats showed large fibro-adenomas.

With alpha chlordane, no micropathology was observed at 5 and 15 ppm which could be considered related to alpha chlordane. Two males and one female at 5 ppm and one male at 15 ppm showed evidence of chronic respiratory disease. At 25 ppm minimal compression of sinusoids due to slight hepatic cell hypertrophy were noted. No other liver cell alterations including cytoplasmic margination were observed. At 35 ppm the above noted sinusoid compression was slight to moderate. All other organs were normal except for the above noted respiratory infections.

Gamma chlordane: All organs for rats at all dietary levels except liver of those at 75 ppm were normal. A male and a female at 75 ppm showed chronic respiratory disease, but this was considered not to be chlordane related. At 75 ppm a few hepatic cells in the centrolobular region showed cytoplasmic homogeneity and some showed perinuclear vacuolation. These observations were considered to be slight in relation to all cells in the sections. Hepatic cell hypertrophy was minimum and not significantly different from that of controls. Other organs were normal.

Alpha & Gamma Chlordane 1:1 Ratio: Livers from rats at 35 & 50 ppm showed slight cytoplasmic homogeneity of hepatic cells in central & midzonal regions. Also slight cytoplasmic margination was observed at 50 ppm. Other organs were normal except for lungs of one female at 15 ppm and one at 35 ppm which showed evidence of respiratory disease. Again, this was not considered to be caused by the test compounds.

ALPHA & GAMMA CHLORDANE CONCLUSION: The study strongly supports the conclusion that when ranked in order of toxicity to rats, alpha chlordane is first (most toxic), followed by the combination of alpha & gamma chlordane, and finally gamma chlordane. Furthermore, the chemicals, whether alone or in combination, produced cell alterations only at the higher feeding levels over the two year period.

TWO-YEAR CHRONIC TOXICITY STUDY IN THE BEAGLE DOG. Study by IRDC

Twenty-six male and 26 female young purebred beagle dogs were fed chlordane at levels of 0.3, 3.0, 15.0, or 30 ppm. A 12-month interim report (October, 1965) showed no compound-related gross pathologic lesions in any dogs necropsied. Organ weights of treated dogs also were within the normal range. At 72 weeks, four dogs at 30 ppm were returned to the control diet for the remainder of the study. Our Dr. Mary Quaife reviewed data at the completion of the two year study. (The data were submitted for review by FDA's Advisory Committee on Chlordane Tolerances.) The data demonstrated no effects due to chlordane on behavior, appearance, mortality, body weight, or food consumption.

Concerning histopathology, changes which were considered to have possibly been compound-related were found only in the dogs from the 30 ppm dosage group and consisted of brown granular pigment in the cytoplasm of the epithelium of the renal convoluted tubules and in the liver parenchymal cells. Similar pigment is not uncommonly found in the kidneys of control dogs; however, it was felt that the quantities seen here were greater than found in controls.

Increased liver weight relative to body weight occurred at 2 years in all dogs at 30 ppm, in 4 of 8 at 15 ppm, and in all 4 dogs, formerly at 30 ppm, which had been withdrawn from chlordane dosage at 72 weeks on test. Likewise, compound-related increases in relative liver weight were seen in both a male and a female dog at 30 ppm, killed at 1 year.

Microscopic examination of tissues in dogs killed at 2 years showed compound-related changes only in the liver. They occurred in 5 of 6 dogs at 15 ppm, in 3 of 3 dogs at 30 ppm, and in all 4 dogs which had been removed from chlordane 8 months before end of 2-year feeding period. Liver changes consisted of enlargement of centrolobular hepatocytes with vacuolation and margination of coarse cytoplasmic granules. Oil-red-O-stained frozen sections of liver did not show lipid in the ballooned hepatocytes. Nor was there necrosis. Lesions appeared to be equally severe in dogs in the 15 ppm, 30 ppm, and withdrawn-from-30 ppm groups. One (of 2) dogs at 30 ppm, killed at one year, had lesions as described plus some liver cells with cytoplasmic hyaline bodies.

004832

No-effect level in dogs: 3 ppm
Effect level in dogs: 15 ppm. Effect consisted of compound-induced microscopically detectable lesions in livers of a majority of dogs killed after 2 years feeding of chlordane at 15 ppm. Liver hypertrophy also occurred.

EIGHTEEN-MONTH ORAL CARCINOGENIC STUDY IN MICE. By IRDC, December 14, 1973.

Chlordane was administered to 100 male and 100 female mice at dosage levels of 5, 25, and 50 ppm. Liver nodules or masses which were classified histologically as hepatomas occurred in 5 mice from the untreated control group, 54 mice from the 250 ppm 2-Acetamidofluorene group, and 6, 12, and 4 mice, respectively, from the 5, 25 and 50 ppm chlordane feeding groups. This lesion was characterized by a usually well differentiated adenomatous proliferation of small cells resembling hepatocytes but with slightly more basophilic cytoplasm and a higher nucleus-cytoplasm ratio. The mode of growth was expansive as was the hyperplastic nodule or infiltrative, displacing adjacent normal parenchyma.

Statistical analysis failed to show a significant increase in incidence of hepatoma in any of the groups fed chlordane when compared to the untreated control group. Incidence of nodular hyperplasia at the 25 and 50 ppm levels was significantly increased (p=less than 0.01) over control levels in male and female mice. While incidence of hepatoma was lower in the 50 ppm group than in the untreated control group, it should be noted that earlier deaths, probably from chlordane toxicity, had markedly reduced the population at 50 ppm; hence a far smaller number of mice was actually on study in this group during the portion of their life span when they would be most apt to develop neoplasia.

MUTAGENICITY: Work by M. J. Ashwood-Smith, J. Trevino, and R. Ring, supported by a Canadian National Research Council grant, demonstrated that chlordane is non-mutagenic in bacteria.

CHLORDANE PILOT RABBIT TERATOLOGY STUDY: By IRDC, December, 1971 004832

Four rabbits were treated at each dosage level from the 6th through the 18th day of gestation: 1, 5, 10, 25, & 50 mg/kg/day. Cesarean sections were done on the 28th day of gestation. Two rabbits at the 25 mg/kg/day dosage level showed ataxia and cachexia during latter days of gestation. Three rabbits at the 50 mg/kg/day dosage level showed ataxia, tremors, head jerks or convulsions during the period of compound administration. The number of rabbits delivering prior to term was 2, 3, and 1 at the 10, 25, and 50 mg/kg/day dosage levels respectively. Most rabbits in the control group and at the 1 and 5 mg/kg/day dosage levels maintained or gained body weight. Most of the rabbits at the 10, 25, and 50 mg/kg/day dosage levels maintained or showed losses in body weight.

On the basis of findings at necropsy examination, does from the 1 and 5 mg/kg/day levels were considered free of compound effect of a severity which would preclude satisfactory reproductive performance.

004832

Registrations of chlordane for certain uses were suspended in notices dated July 29, 1975; December 12, 1975; December 24, 1975; and January 19, 1976. Not included in the suspended uses was the use through subsurface ground insertion for termite control. In the statement of findings (FR Feb. 19, 1976) it was recognized that any soil (and consequently, water) residues of chlordane which might be found are most likely the result of chlordane applications for control of lawn and garden pests -- a use now suspended.

RECOMMENDATION: Based on data supplied to Toxicology Branch, and as per order of the Administrator in exempting use of chlordane for termite control from the chlordane registration suspension order, Toxicology Branch has no objection to registration of subject product for termite control in accordance with the proposed labeling supplied.

Roland A. Gessert

Roland A. Gessert, D.V.M.
Toxicology Branch

RE for OEP 8/12/77

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PAGES 9 THROUGH 11 ARE NOT INCLUDED. THOSE PAGES CONSISTED OF DRAFT LABELING