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001956

CONSUMER PROTECTION AND ENVIRONMENTAL HEALTH SERVICE

January 3 1969

JAN 3 1969

Mr. Kenneth B. Nash
Pesticides Regulation Division
Agricultural Research Service
U. S. Department of Agriculture
Washington D. C. 20250

Reg. No. 100-8
Referral Date - 10/6/67

Dear Mr. Nash:

The additional toxicological data on Bacteriostat CH 3565 (2,4,4'-trichloro 2 hydroxy-diphenylether) which was received from you on December 4, 1968, in connection with the above listed Reg. No. has been reviewed.

We have no objection to the continued registration of this label.

Sincerely,

Lamar B. Dale, Jr., Ph.D.
Pharmacologist
Registration Section
Pesticides Program

LBDale:mw

LBDale:mw
December 26, 1968

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DATA SUMMARY

Subacute Dermal Toxicity (New-born Beagle)

21 days - No untoward effects

Repeated Insult Patch Test (Human)

No irritation, fatigue or sensitization

Acute Intravenous Toxicity (Mouse)

Hexachlorophene = LD_{50} 18 mg/Kg

CH 3565 = LD_{50} = 19 mg/Kg

Acute Intravenous Toxicity (Rat)

CH 3565 = LD_{50} = 29 mg/Kg

Hexachlorophene = LD_{50} = 14.7 mg/Kg

Acute Intravenous Toxicity (Male Rat)

LD_{50} = 29.9 mg/Kg

Acute Intravenous Toxicity (Female Rat)

LD_{50} = 28.3 mg/Kg

Acute Subcutaneous Toxicity (Female Rat)

LD_{50} = CH 3565 = > 14,700 mg/Kg

Hexachlorophene = 76.5 mg/Kg

Temosept IV = 88% mg/Kg

18 Month Carcinogenic Study

Not a skin carcinogen

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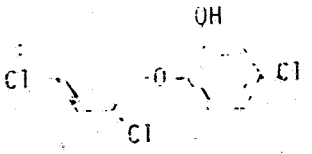
C01956

2,4,4'-Trichloro-2'-hydroxy diphenylether Bacteriostat CH 3565

Structural Formula :



Emperical Formula : $C_{12}H_7O_2Cl_3$

Physical Form : Solid

Use : Germicide

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LBD...:bjc
December 24, 1968

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2,4,4'-Trichloro-2'-hydroxy diphenyl ether
Bacteriostat CH 3565

Subacute Dermal Toxicity in New Born Beagles

Two litters of 1 week old beagle pups were utilized in this study. The litters were not evenly divided as to sex. One litter of pups served as the test group, the other group served as the treated control group.

The test material was made into a 0.1 solution with 5% ivory soap in distilled water. The test group of pups were immersed in this solution which was kept at body temperature for 30 seconds each day, 5 days per week for 3 weeks. The treated control groups were immersed in a 5 ivory soap solution in distilled water in the same manner.

The following parameters were measured:

body weights

food consumption

body length measurements

survival

behavioral reactions

skin reactions (macroscopic)

hematology

gross and microscopic examinations.

The test and control groups did not reveal any significant differences in the above parameters. In this study, bacteriostat CH 3565 in a 0.1 solution in 5% ivory soap did not produce any significantly different results than 5% ivory soap solution.

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Acute Aerosol Inhalation Toxicity Studies on Personal Deodorant Product F and Personal Deodorant Product G

Product F consist of CH 3565-0.10%, isopropyl palmitate 1.00%, ethanol SD-40-48.90%, Freon 12/114, 60/40-50.00%. Product G was identical in composition to Product F with the exception that it contained no CH 3565.

Two groups of 10 albino rats (5 male, 5 female) were exposed, in an inhalation chamber, to a total of 10 aerosol sprays during a period of 5 consequtive hours. The average amount of test material released per spray was 14.5 gm for product F and 14.1 gm for product G.

At the end of each test period, all animals exhibited generalized inactivity and weakness. The effects were slightly less pronounced among animals exposed to the aerosol of product G. No deaths, adverse body weight effects or gross pathologic alterations were observed among any test animals.

Repeated Insult Patch Test (Human)

In order to determine if the material was capable of irritating the skin of humans, repeated insult patch tests were carried out on 56 human volunteers (21 males, 35 females) of the following samples: wool containing 7200 ppm bacteriostat CH 3565, wool control, nylon containing 18,900 ppm bacteriostat CH 3565, and nylon control.

The test material was applied to a predesignated site on the upper arm of each subject and covered with gauze. The gauze, in turn, was covered with polypropylene, the edges of which were then affixed to the skin with tape.

At the end of 24 hours, the patches were removed. The contact sites were examined and observations were scored.

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Following removal, the contact sites were left untreated and uncovered and

allowed to rest. At the end of the rest period, they were reexamined to ascertain whether there were any changes.

The choice of contact site for the second and subsequent applications depended on the condition of the previous site after the rest period. If no irritation was observed at this time, the test material was reapplied to the same site. If irritation was observed at this time, the test material was applied to a new site.

The patches were applied on Mondays, Wednesdays, and Fridays. They were removed after 24 hour contact periods on Tuesdays, Thursdays and Saturdays. Rest periods of 24 hours following the Tuesday and Thursday removals and 48 hours following the Saturday removals.

After removal of the last application preceeding the challenge, the sites were examined immediately and once daily for at least 2 days.

The challenge was applied to the original contact site after 14 days of no contact with the test material. The challenge application was terminated after 24 hours. The sites were examined for immediate reactions which, if present were graded and recorded. These sites were reexamined 24 and 48 hours later for delayed reactions.

The material may be considered safe to use in contact with the skin in so far as primary irritation, fatiguing or sensitization are concerned.

Acute Intravenous Toxicity (Mouse)

Twenty male and female mice were divided into 3 groups and received single intravenous injections of bacteriostat CH 3565 in graded doses.

The animals were then returned to their cages and observed for 14 days for mortality and/or toxic effects.

The symptoms observed consisted of slight cramps, slight exophthalmos, ataxia, ventral decubitus, generalized twitching, dyspnea, somnolence and apnea.

The intravenous LD_{50} was found to be 19 mg/kg.

Acute Intravenous Toxicity (Rat)

Twenty-five male and female albino rats were divided into 5 groups of 5 animals each and received graded intravenous doses of bacteriostat CH 3565. The animals were observed for 8 days for mortality and/or toxic effects. The symptoms shown were the same as observed in mice.

The acute intravenous LD_{50} of bacteriostat CH 3565 in albino rats was found to be 29 mg/kg.

Acute Intravenous Toxicity - Hexachlorophene (Rat)

Twenty male and female albino rats were divided into 4 groups of 5 animals and received divided intravenous doses of hexachlorophene. The animals were observed 8 days for signs of toxicity and/or mortality.

The symptoms observed were the same as observed in the administration of bacteriostat CH 3565 to albino rats. The acute intravenous LD_{50} of hexachlorophene in albino rats was found to be 14.7 mg/kg.

Acute Intravenous Toxicity (Male Rats)

The acute (14 day) LD_{50} for male albino rats was found to be 29.9 mg/kg body weight with confidence limits (95) of 26.0-34.4 mg/kg body weight.

The dosage levels tested ranged from 20-40 mg/kg body weight.

Body weight changes in the groups with a mortality rate of 50% or less were comparable to the controls. Death was preceeded by opisthotonic convulsions and blood urine was observed in the surviving animals. Necropsy examinations were unremarkable except for occasional tail necrosis in the surviving animals.

Acute Intravenous Toxicity (Female rats)

The acute (14 day) LD_{50} for female albino rats is 28.3 mg/kg body weight with confidence (95%) of 24.8-32.3 mg/kg body weight. The dosage levels tested ranged from 20-40 mg/kg body weight.

Body weight changes in the groups with a mortality rate of 50% or less were comparable to the controls.

Death was preceeded by opisthotonic convulsions and blood urine was observed in surviving animals. Necropsy examinations were unremarkable except for occasional tail necrosis and lung congestion in the surviving animals at and greater than the 25 mg/kg dosage level.

The Acute Subcutaneous Toxicity of 3 compounds In Female Albino Rats

Female albino rats weighing from 200-250 gm were used in the study.

The test compounds were dissolved in 95% alcohol and administered subcutaneously at the following dosage levels: bacteriostat CH 3565-4640, 6810, 1000, 14700 mg/kg; hexachlorophene-46.4, 68.1, 100.0, 147.0, 215.0 and 316.0 mg/kg; Temasept IV-6810, 8260, 1000, and 1200 mg/kg.

Five rats were used at each dosage level. The volume administered was maintained constant at 2-3 ml/kg body weight at all dosage levels.

The rats were observed for pharmacodynamic and/or toxic signs and mortality for 5 hours immediately following administration of the compound, and at least once daily thereafter for a period of 14 days. All rats were necropsied and examined for evidence of gross pathology at the termination of the observation period.

The LD_{50} of bacteriostat 3565 was found to be greater than 14, 700 mg/kg. The LD_{50} of hexachlorophene was found to be 76.5 (58.6-99.7) mg/kg; the LD_{50} of Temasept IV was found to be 8870 (7430-10,600) mg/kg.

Chronic Toxicity (18 month Study of the Carcinogenic Potential of Bacteriostat CH 3565 in Mice)

An 18 month carcinogenic study was conducted employing Charles River CD-1 Swiss white mice. The study utilized an untreated control group, treated control group (acetone), positive control group (9,10-dimethyl-1,2-benzanthracene, 0.01% in acetone) and test groups I and II (0.5 and 1.0% bacteriostat CH 3565 in acetone respectively). Applications of 0.1 ml of the respective solutions were applied to the interscapular regions 3 times weekly.

The results showed that 0.5 and 1.0% acetone solutions of the test material are not carcinogenic. In addition, no abnormal findings were noted with respect to body weights, food consumption, behavioral and skin reactions, mortality, gross and microscopic pathology and tumor formation in either test group. Only one of the tumors noted grossly (test group I female) was identified as a squamous cell carcinoma. Findings for test group animals were comparable to those of the untreated and treated control group animals.

Significant findings noted in the positive control group consisted of

increased mortality and 100% skin tumor formation. The tumors were described as squamous cell carcinomas ranging from moderately well differentiated to undifferentiated. In addition the skin of the positive control animals showed a severe erythema, eschar formation, and edema at the site of tumor development. All other parameters for this group were normal.