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September 30, 1970

Mr. Henry S. Bussey, Head
Registration Procedures Section
Pesticides Regulation Division
Agricultural Research Service
U. S. Department of Agriculture
Washington, D. C. 20250

Reg. Nos. 100-491 & 100-502
Referral Date - 7/3/70

Dear Mr. Bussey:

The additional toxicological data on Irgasan DP 300 and Bacteriostat CH 3565 [5-chloro-2-(2,4-dichlorophenoxy)phenol] which were received from you in connection with the above listed Reg. Nos. have been reviewed.

We have no objection to continued registration at this time.

Sincerely,

David L. Greenman, Ph.D.
Pharmacologist
Pesticide Registration Branch
Division of Pesticide Chemistry
and Toxicology
Office of Pesticides

cc:
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BF-219/THHarris
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Product Name	:	Bacteriostat 3565 Irgasan DP 300
USDA Reg. Nos.	:	100-491 100-502
Active Ingredient	:	5-chloro-2-(2,4-dichloro-phenoxy)phenol (2,4,4'-trichloro-2-hydroxy-diphenylether)
Use	:	Processing or Manufacturing use only
Company	:	Geigy Industrial Chemicals

DATA SUMMARY

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I. Excretion (Human)

Over 5 day period: 65.4% of injected dose in urine
20.6% in feces
Half-life ~ 10 hours

II. Percutaneous Absorption (Human)

Applied to forearm in soap solution: about 8.9% absorbed in 2⁴ hrs.

III. Use in Hospital Laundries

No adverse reactions in 200,000 patients contacting laundry.

One laundry worker became sensitized to formulation.

IV. Fertility and General Reproduction Performance (Rat)

Males

Slight body weight gain suppression over first 14 days oral administration of 50 and 100 mg/KG/day.

4/10 died during the first 80 days of administration at 100 mg/KG/day dose.

Fertility index-same as controls.

No unusual reactions.

Females

Body weight gains normal.

1/10 on 50 mg/KG/day died during parturition.

1/10 on 100 mg/KG/day died during lactation.

No apparent effect on mating, fertility or lactation indices or on incidence of pregnancy and parturition or on gestation time.

No unusual behavior.

14th day of gestation - number of corpora lutea, implantation sites or number of fetuses not affected.

Slightly more resorption sites.

Progeny

More stillborn pups in 50 mg/KG/day group.

Viability and weights of pups during lactation - no effect.

No gross external abnormalities at birth or weaning.

V. Teratological Study (Rat)

1/124 of fetuses from rats receiving 100 mg/KG/day was esternally malformed.

No effect on gross external, internal or skeletal development of remainder.

No effect on body weight of treated adults or progeny.

No deaths or unusual reactions in adults.

VI. Teratological Study (Rabbit)

Treated Pregnant Females

Body weight gain depressed during treatment.

No deaths or unusual reactions.

No effect on corpora lutea or implantation sites.

Increase in resorption sites, especially at 100 mg/KG/day.

Progeny

No effect on 24 hr. viability or body weights.

2% of pups receiving from 50 mg/KG/day group show gross abnormalities

Contrast this $\bar{c}$ 35% for positive controls (thalidomide) and 0 for untreated controls and 100 mg/KG/day group.

No apparent effect on skeletal or internal development.

VII. Perinatal and Postnatal Performance (Rat)

Treated Female Adults

No effect on body weight

No deaths or unusual reactions

Progeny

No effect on litter size, number of stillborns viability or body weights during lactation.

SUMMARY

This product exhibits certain toxic effects during prolonged oral administration at daily doses about 1/50 the acute oral LD_{50}. Male rats especially appear to be sensitive to the product. Suppression of body weight gains were noted and several animals died. Weight suppression was also noted in pregnant rabbits. The data indicated an increased resorption of implanatation sites in both pregnant rats and rabbits, but other aspects of reproductive performance seemed normal. Teratological studies were negative. In view of the slow percutaneous absorption and the usage pattern this product appears to pose no great hazard.

Excretion (Human)

Three male volunteers were intravenously injected with 1μCi of ring labeled ^{14}C-CH 3565 (S.A. = 2.75 μCi/mg). Total urine and fecal samples were collected for 5 days and analyzed for ^{14}C content.

Over the 5 day period 65.4% of the ^{14}C was recovered in urine 20.6% in feces. The half-life, as shown by urinary excretion was about 10 hours.

Percutaneous Absorption (Human)

^{14}C-CH 3565, suspended in a solution of Ivory soap was applied to a 13 cm^2 area of the forearm of each of 6 males. Amounts applied were 60 $\mu g/cm^2$ of soap and 4 $\mu g/cm^2$ of CH 3565. The site of application was left unwashed and unprotected for 24 hours. Urine was collected for a 5 day period and analyzed for ^{14}C.

Based on the previous excretion study it was calculated that 8.9% of the CH 3565 was absorbed percutaneously.

Use in Hospital Laundries

Five hospital laundries in Switzerland have used a formulation containing 20% Irgasan DP 300. The formulation was added to rinse stage at an equivalent concentration of CH 3565 of 250 ppm. All laundry staff and patients were watched by the hospital dermatologists for possible adverse reactions. No adverse reactions were reported for any of 200,000 patients who came in contact with the treated laundry. One out of 234 laundry workers studied was sensitized to the formulation. Whether the

patient was sensitized to CH 3565 was not determined.

Fertility and General Reproductive Performance (Rat)

Three groups of Charles River albino rats (total of 90) were used. Controls received corn oil, T-I animals 50 mg/KG/day and T-II animals 100 mg/KG/day of CH 3565 as a 10% (w/v) solution in corn oil. Test solutions were given orally by means of a syringe equipped with a ball-tipped intubation needle. Solutions were prepared fresh daily. Males were treated daily starting at 40 days of age. Females received daily treatments starting at 86 days of age (two weeks prior to mating). Animals were maintained on a basic stock ration and water ad libitum. At 100 days of age animals were mated by grouping 2 females with one male. The day of mating was determined by the presence of sperm in the vagina. Half of the females were autopsied on the 14th day of pregnancy. The remainder stayed on treatment until weaning of the offspring.

Body weight gain was suppressed in both T-I and T-II males during the first 14 days of treatment. Subsequently only T-II animals showed weight gain suppression. Throughout the treatment period CH 3565 had no effect on body weight of females. Four out of 10 of the T-II males died, one during the first 60 days of treatment, the remainder during the period of mating. One out of 10 of the T-I females died during parturition and one of the T-II females died during lactation, subsequent to the death of her pups. No unusual behavioral reactions were noted in any of the animals. The fertility index of surviving animals of both

sexes was not different from controls. In both treatment groups indices of mating and lactation, incidence of pregnancy and parturition and gestation times were essentially the same as controls although 1 out of 20 T-I females failed to become pregnant. The number of implantation sites, corpora lutea and fetuses did not greatly differ between control and treated animals autopsied on day 14 of gestation although the number of resorption sites was somewhat higher in both groups treated with CH3565. Females of group T-I delivered more stillborn pups than controls, but T-II animals delivered no stillborn pups. Percent survival and body weights of pups at days 1, 4, 12 and 21 of lactation were not significantly different for controls and treated groups. Physical examination and pathologic studies revealed no abnormalities at birth or weaning of pups.

Teratological Study (Rat)

Sixty Charles River rats, determined to be pregnant by vaginal examination, were divided into 3 equal groups and administered test solutions orally as in the Fertility and General Reproduction Performance study. Controls received corn oil, T-I animals 50 mg/KG/day and T-II animals 100 mg/KG/day of CH 3565 on days 6 through 15 of pregnancy. Body weights were recorded on day 6, 9, 12, 15 and 20 of gestation and animals were killed by etherization on day 20. Fetal viability was determined by visual examination of spontaneous movement and color. Fetuses were externally examined for the following abnormalities; HYDROENCEPHOLY, EXENCEPHALY, MENINGOENCEPHALOCELE, SIMPLE MENINGOCELE, ANOPHTHALMIA, MICROPHTHALMIA, CLEFT LIP,

manbidle or palate, oblique facial cleft, micrognathia, ear abnormalities of size, shape or position, size or position of limbs, number and disposition of digits, umbilical hernia, gastroschisis, myelomeningocele, spina bifida and scoliosis.

Two-thirds of the fetuses of each group were evaluated for skeletal development (alizarin staining-Hurley). Internal development of the remaining fetuses was evaluated using the free-hand razor blade section technique (Wilson).

Body weight data for pregnant females and progeny were no different for controls and treated animals. There were no deaths or unusual reactions among adults. At day 20 of gestation the number of corpora lutea, implanatation sites, resorption sites and viable fetuses were essentially the same for all groups. One out of 124 fetuses from the T-II group show gross external abnormalities with numerous abnormalities of skeletal development. Gross external, internal and skeletal examination of the remaining progeny revealed no apparent differences between controls and treated animals.

Teratological Study (Rabbits)

A total of 60 New Zealand female albino rabbits were divided into 4 groups, two test groups (T-I and T-II) an untreated (C) and a thalidomide-treated positive control (PC) group. Test material was given via gelatin capsule daily from the 6th through 18th day of gestation. Controls received an empty gelatin capsule. Group T-I received 50 mg/KG/day and T-II 100mg/KG/day of CH 3565. Group PC received 75 mg/KG/day of thalidomide. All

animals received 2 mg/KG of luteinizing hormone intravenously and were then inseminated with 0.5 cc of diluted semen from proven bucks. Inseminated does were housed separately throughout the test. Does were weighed on days 0, 6, 9, 12, 15, 18 and at sacrifice (day 29 of gestation). Immediately after removal from the chorion viable young were thoroughly examined, weighed and placed in an incubator at 37°C. Viability was noted at hourly intervals for 7 hours and again after 24 hours. All young including those dead at the time of caesarian section were examined carefully by dissection to detect differences in size, shape and orientation of major organs and blood vessels. Skeletal tissue was examined by a modification of the Alizarin staining method of Hurley.

Body weight gains were somewhat depressed in pregnant animals during but not folicwing the period of treatment. There were no deaths or unusual behavioral reactions in these animals. At autopsy (day 29 of pregnancy) the number of corpora lutea and implantation sites were no different in control and treated animals but there was a significant increase in the number of resorption sites, particularly in group T-II. Viability and weights of fetuses were similar to controls in both treated groups. Two grossly abnormal pups (2.1% of total pups) were seen in the T-I group. One exhibited double talipomanus, the other spina bifida. Nearly 35% of the positive controls showed gross abnormalities while the C and T-II groups had none. Fetal skeletal and internal development showed no apparent difference from controls.

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Perinatal and Postnatal Performance (Rat)

Sixty pregnant rats (Charles River) were divided into a control and two test groups. Controls received corn oil, T-I rats received 50 mg/KG/day and T-II rats 100 mg/KG/day of CH 3565 in corn oil by oral administration. Solutions were given daily from the 15th day of gestation through the weaning of the litter. Daily records of body weight mortality and reactions were made. All animals were allowed to deliver and carry their litters through weaning. Records of progeny number, survival, reactions and body weight were kept.

Among the adults no deaths or unusual reactions were noted. Body weight gains were no different for treated and control animals.

Litter size, number of stillborn pups, number cannibalized, number of pups born viable, as well as viability and body weights at days 1, 4, 12 and 21 of lactation were similar for all groups.