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September 25, 1969

001958

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

Reg. No. 100-RT
Referral Date - 8/29/69

Dear Mr. Bussey:

The toxicological data on 2,4,4'-Trichloro-2-hydroxydiphenyl ether has been reviewed.

We have no objection to the registration of this label.

Sincerely,

Robert D. Coberly
Biologist
Division of Pesticide Registration

cc:
PS-1
PS-2
PS-300
PS-300/THHarris
PS-300/RBDoberly/mw
September 25, 1969
TOX FILE

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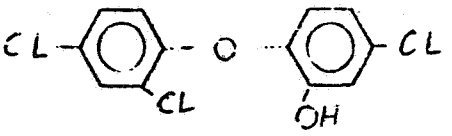
RDCoberly/ccw
9/29/69

001958

Chemical Name	:	2,4,4'-Trichloro-2'-Hydroxydiphenyl ether
Chemical Structure	:	
Empirical Formula	:	$C_{12} H_7 O_2 Cl_3$
Molecular Weight	:	289.5
Melting Point	:	54-57° C
Odor	:	Slightly aromatic
Appearance	:	White to off-white
Physical State	:	Crystalline powder
Purity	:	97% minimum
Vapor Pressure	:	4×10^{-6} mm Hg at 20° C
Thermal Decomposition	:	280-290° C
Use	:	Bacteriostat
Company	:	Geigy

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BACT 3565

Guinea Pig Photosensitization (CH-3565)	:	The test material is not a photosensitizer.
Phototoxicity (Human?)	:	No reaction.
Photoallergy (Human?)	:	No reaction.
14 Dat Rat Dermal (CH-3565)	:	Does not appear to have any effect on the skin.
Mice Reproduction Study (GP 41'353)	:	Dosage levels tested were 10, 50, and 100 mg/KG. Increase mortality (4/21) body wt retardation, reduction of mean pup weight and low litter weight was noted at 100 mg/KG. An increase in young with bipartite and/or asymmetrical sternebrae.

BACT 3565

Rabbit Pregnancy Study (GP41353)	:	Levels tested were 10, 25, and 50 mg/KG. Some embryonic affect was noted at 50 mg/KG.
4 and 13 Week Baboon Oral (GP 41353):		Dosage levels of 1.0, 10, 30, and 100 mg/KG/day were tested for four weeks. A level of 3.0 mg/KG/day was tested for 13 weeks. No mortality noted. One female at 100 mg/KG/day became angry and aggressive. No other effects were noted.
13 Week Rabbit Oral (GP 41353)	:	Dosage levels tested were 3.0, 30, and 150 mg/KG/day. Effects noted at 30 and 150 mg/KG/day which could have been result of lowered body resistance to infection.
13 Week Rat Oral (GP 41353)	:	Levels tested were 125, 250, 500, and 1000 mg/KG/day. Body wt inhibition noted in males at 500 and 1000 mg/KG. Liver pathology noted in all dosage levels. No effect level is less than 125 mg/KG/day.
91 Day Dog Oral (GP 41353)	:	Levels tested were 25,50, 100, and 200 mg/KG/day. Dose related diarrhea was noted in all animals. SAP values were greater than the control value for all test groups. Some SGOT and SGPT high values were noted. Low PCV, Hb and RBC values were recorded. Bile salts noted. Jaundice was noted and was dose related. No effect level is less than 25 mg/KG/day.

Rat and Rabbit Dermal Absorption	:	Moderately well absorbed thru the skin.
Human Dermal Absorption	:	Major metabolite was the glucuronide of the active ingredient. Absorption was poor.
Human Dermal Absorption	:	Major metabolite in the urine was the glucuronide. Absorption appears to be poor.
Human Dermal Absorption	:	Sample was poorly absorbed. Excreation was via urine and feces. Major metabolite was the glucuronide.

SUMMARY

This chemical does not appear to have a phototoxic or photoallergic dermal response in humans. The chemical is absorbed, but not readily, and is degraded mainly to the glucoronide within 24 hrs and excreated by both the urine and feces.

Prolonged consumption of the chemical has a definite pathological effects on the liver and hemopoietic activity at levels down to 50 mg/KG/day.

BACT 3565

PHASE I

Guinea Pig Photosensitization (CH-3565)

Exactly 0.05 mL of a 2% (w/v) absolute alcohol solution of the test material or TCSA (positive control material) was applied daily to the prepared sites on each animal for five consecutive days. After each application the animals were irradiated with ultra violet rays for 15 minutes using a sun lamp from a distance of 18 inches. Reactions were recorded 24 hours after each exposure.

After a rest period of ten days, the animals received three challenge applications of 0.05 mL of a 0.1% (w/v) solution of the test material for positive control material. Ultra violet irradiation for 15 minutes followed each challenge application and readings for erythema were made on the next day.

After the skins of the Guinea pigs appeared normal, they were shaven on the flanks and treated with a 0.2% (w/v) solution of the test material in a 8.0% (w/v) solution of Ivory soap for a total of three applications. The solutions were applied under gauze which were kept in contact with the skin for one hour. Ultra violet irradiation for 15 minutes followed each application and skin readings were made 24 hours after each treatment.

Results:

The challenge applications of the test material in the form of 0.1% solution in olive oil produced an increase in the intensity of erythema. The re-challenge applications of the test material which were made at a concentration of 0.2% in Ivory soap did not produce a reaction of any kind.

The positive control compound produced erythema in both the olive oil and Ivory soap.

PHASE II

Exactly 0.05 mL of absolute alcohol was applied to the prepared site on each animal in exactly the same manner as in Phase I. After a rest period of ten days, each animal received one application of 0.05 mL of olive oil and three applications of 0.05 mL of a 0.1% (w/v) solution of the test material in olive oil. Ultra violet irradiation for 15 minutes followed each challenge application. Readings for erythema were made the next day.

Results:

After the challenge application of olive oil, there was Grade 1 erythema in all animals. After the challenge application of the test material in olive oil, there was the same amount of erythema.

Comment

It appears the olive oil produces the same amount of erythema as the combination product of olive oil and the test material.

PHASE III

Three test groups consisting of six Guinea pigs each received a treatment of exactly 0.05 mL of a 2% solution of the test material dermally. The preparation was applied daily for five days to each animal. The animals were ultra violet-irradiated after each application. Skin readings were made for erythema after each application. After a rest period of ten days

the animals received three challenge applications of 0.05 mL of a 0.1% solution of the test material in olive oil. Two of the groups were carried along with the test group. The first one was treated with TBS and the second one with hexachlorophene. The skin sites of the animals insulted with hexachlorophene had not returned to normal and were allowed to rest for an additional seven days before receiving the three challenge applications.

In addition to the three or four mentioned test groups two treated control groups were also employed. These animals received daily exposure to 0.5 mL of absolute alcohol or Virginia press olive oil. After each application the animals were ultra violet-irradiated.

After a second rest period of three days the test groups were insulted with another three challenge application of 0.05 mL of 0.1% solution of the test material in olive oil on the original site. At the same time a challenge application of 0.05 mL of 0.2% of the test material in a solution of 8.0% Ivory soap was made on one flank and a challenge application of 0.05 mL of Ivory soap on the other flank. The animals originally insulted with olive oil received three challenge applications of 0.05 mL of a 0.1% solution of the test material in olive oil on the original site.

Results:

When challenge applications of the test material as a 0.1% solution in olive oil was applied erythema was noted. Re-challenge with these materials in the form of 0.2% solutions and 8.0% Ivory soap produced no reactions.

When the animals insulted with absolute alcohol were challenged with olive oil or the test material in olive oil there was erythema. Re-challenge of these animals with the test material in Ivory soap produced no reactions.

Animals which had been insulted with olive oil were challenged with olive oil and the test material in olive oil with erythema being noted in both cases. Re-chalenge with the test material in Ivory soap produced no reactions.

Phototoxicity (Human?)

Ten healthy adult white males were studied in this test. The test material as a 2.5% in petrolatum was applied to scotch tape stripped skin and to normal skin for one hour. The sites were then irradiated with Xenon ultra violet light equivalent to about one hour in the mid-day summer sunlight. Readings were made at 4 and 24 hours.

Results:

None of the ten subjects showed a reaction differing from the control site.

Photoallergy (Human?)

In this study the test material was applied to the same site for 5-48 hour intervals under occlusion in a concentration of 10% in petrolatum. Immediately after each application the site was exposed to solar stimulating ultra violet light from the Xenon lamp. Two weeks later a new site was photopatch tested in the same way.

esults:

one of the 25 subjects showed a reactiond differing from the control site.

l Day Rat Dermal (CH-3565)

iis study was set up in three groups with ten animals per group. The rst grcup had their backs shaved and depilated. The second group had ieir backs shaved and the skin burned with 90° water. The third group d their skin burned with 90° water but was not treated until three weeks ter being burned. A single 2.0 mL application of each test formulation re made daily for 14 days. The material was applied evenly over the tire wound area or an equivalent area in the control animals. Half the imals were males and half were females.

e test material was applied as a 3% W/V in oil. Hexachlorophene and Tuasal) were used in the other two test groups.

sults:

: Group 1 animals (shaved and depilated) showed 100% survival when tested :h the test material. The Hexachlorophene group showed 100% mortality. : Tuasal 100 showed 40% mortality.

alized areas of superficial skin irritation were observed randomly among treated animals and those which received oil based formulations. Dried od around the eyes and nose was a frequent finding among the non treated mals as well as those treated with the test material. No other unusual sistent findings were observed among the groups which received the test erial. However the other two groups showed signs of muscular weakness thargy.

he group 2 animals (scald-burned) showed 30% deaths. No noticeable dermal hanges were noted. The presence of dried blood around the eyes and nose as frequently noted among all groups. Muscular weakness and lethargy ere the principle observations recorded for all rats regardless of sex.

he group 3 animals (granulation tissue exposed) showed only 10% deaths. t termination of the study the burned wounds appeared to be healing. In eneral the animals treated with the test material appeared to recover qually well as compared to the control animals.

ice Reproduction Study (GP 41'353)

wenty-one female mice were tested per dosage level of 10, 50, and 100 mg/KG. he mice were allowed to mate over night before they were allocated to the est groups. The day of mating was considered day 0 of pregnancy. Dosing ommenced on day 1 and continued daily up to and including day 16 of pregnancy.

n day 17 the mice were killed by cervical dislocation and the uterine ontents examined immediately to determine the number of biable young, umber of resorption sites, litter weight, and fetal abnormalities.

esults:

ere were one and four deaths at 50 and 100 mg/KG respectively. A dose lated retardation of weight increase was noted among the test animals. wever this difference did not proceed to significance. Food consumption was comparable for all groups. The pregnancy rate was comparable r all groups.

gained, the relationship to treatment was doubtful; no other effects as assessed by daily observation, food consumption and pregnancy rate were apparent. Treatment did not adversely effect litter parameters, as assessed by litter size and fetal loss, litter and mean pup weights, when mean B values were considered but when animals showed total litter loss were included all groups showed increased fetal loss and consequently lower litter size.

Treatment did not adversely effect embryonic and fetal development, as assessed by the incidence of major malformations, minor abnormalities and the majority of skeletal variants was uneffected by treatment, the only significant effect observed being the presence of a higher proportion of 13 ribbed pups at 50 mg/KG.

4 and 13 Week Baboon Oral (GP 41353)

The dosage levels of 1.0, 10, 30, and 100 mg/KG/day were used for the 4 week study. Two, six, and two baboons were used respectively. Six were tested for 13 weeks at 3.0 mg/KG/day. The animals were dosed orally once a day for seven days a week. The hematology studies consisted of erythrocyte sedimentation rate, packed cell volume, hemoglobin, total red cell count, total white cell count, differential white cell count, reticulocyte count, platele count and prothrombin index.

The biochemistry studies consisted of plasma urea, true glucose, total serum proteins, serum alkaline phosphatase, serum glutamic pyruvic transaminase and serum bilirubin. Urinalysis studies were also conducted.

Results:

There were no deaths during the dosing period. One female receiving the dosage level of 100 mg/KG/day showed a marked change in behavorial pattern from the second week of dosing. The animal became very agitated and appeared to be angry and aggressive until sacrifice at four weeks. No other clinical signs were observed among the animals.

The body weight gained between the test and control animals was comparable. Also the test material had no adverse effect on the food consumption.

No evidence of any toxic damage to the eyes was recorded during the period of observation. The hematology and the biochemical laboratory results of the test and control animals were within normal limits as was the urinalysis.

A microscopic examination of the tissues taken from the animals which were sacrificed at four weeks showed no evidence of toxic damage. The liver and kidney weights of these animals were within normal limits. Also, no macroscopic abnormalities could be associated with the test material.

13 Week Study - The sacrifice after 13 weeks showed no macroscopic abnormalities. The liver and kidney weights revealed no abnormal findings. The microscopic examination of the tissues revealed no evidence of toxic damage.

13 Week Rabbit Oral (GP 41353)

Three males and three females were tested per dosage level of 3.0, 30, and 150 mg/KG/day. The animals were observed for daily food consumption, water consumption, clinical symptoms and body weight. Hematology observations

included thrombocytes, RBC, PCV, WBC, reticulocytes and total and differential counts. The biochemistry observation included urea, sugar, sodium, potassium, SGOT, SGPT, SAP, and serum proteins. Urinalysis was also done.

A full gross autopsy was made of all animals including those which died during the study. Organ weights were recorded for the adrenals, gonads, heart, kidneys, liver, lungs, and spleen. When necessary and whenever possible microscopic examination was made of the bladder, bone marrow, colon, lymph-node, pancreas, skin, small intestine, stomach, thymus, thyroid, eye, tongue, uterus or prostate.

Results:

The control animals and the low level animals (3.0 mg/KG/day) appeared to be normal throughout the observation period.

Neutrophilia was noted at different intervals in three females on the 150 mg/KG/day dosage level. These findings do not appear significant as for the one of the following reasons either the following determination of neutrophils was found to be within normal range or in the case where neutrophilia was diagnosed it was moderate. Also one animal in this group in addition to neutrophilia showed lekocytosis.

Two animals of the 30 mg/KG dosage level also showed neutrophilia and/or lymphopenia. The reviewer does not place any significance on these findings in relation to the action of the test material.

The gross autopsy showed evidence of pleurisy in one animal of the 3.0 mg/KG group; pulmonary infection in three animals of the 30 mg/KG/day group, and three animals of the 150 mg/KG group.

No noticeable pathology was noted in the control and the 3.0 mg/KG/day animals. In the 30 mg/KG/day animals three rabbits (two females and one male) showed edema with necrosis in the lungs.

The high level animals showed four animals with lung lesions consisting of edema with or without necrosis of the lung tissue.

Remarks:

In all groups there is evidence of nephritis or nephrosis. Livers show a mononuclear infiltration into some portal areas.

Lungs generally show a moderate peribronchial lymphoid reaction. All of these findings occur regularly in this strain of rabbit. In groups 3 and 4 the lung lesions are marked in most cases. Similar lesions are not seen in the low level (3.0 mg/KG/day) or the control animals.

Most of the important changes and abnormal values that have been noted have resulted from pulmonary infection. These are marketly more predominant in the groups 3 (30 mg/KG/day) and group 4 (150 mg/KG/day). It appears possible that these two dosage levels may have a tendency to reduce resistence to low grade pulmonary infection.

13 Week Rat Oral (GP 41353)

Twelve males and twelve females were tested per dosage level of 125, 250, 500, and 1000 mg/KG/day. The hematology studies consisted of PCV, Hb, WBC, total and differential counts. The biochemistry investigations included urea, sugar, sodium, potassium, SGPT, SGOT, SAP, and serum protein. Urinalysis was also done.

A full autopsy was made on all animals. The following organs were weighed; adrenals, gonads, kidneys, spleen, heart, lung, liver. Microscopic examination was conducted on all of these tissues and also of the bladder, bone marrow, colon, lymph-node, pancreas, skin, small intestine, stomach, thymus, thyroid, tongue, eye, and uterus or prostate.

Results:

The body weight gain of the male animals receiving the dosage levels of 500 and 1000 mg/KG/day were significantly lower than those of the corresponding control animals. The body weight gain of the females on these dosage levels was somewhat less than the controls but not significantly so. Also the food consumed by the male animals at these dosage levels was significantly lower than the corresponding control male food consumption. These same male animals also had a higher water consumption during the study.

Four rats died and three were killed during the course of the study in the 1000 mg/KG/day dosage level. The only other death occurred at the 125 mg/KG dosage level.

The livers in all dosed groups showed pathological lesions which appear dose related. Kidneys also show lesions particularly in the high level animals where nephrosis is more severe than in the lower dosage levels; small infiltrations of monouclear cells occur in all groups.

91 Day Dog Oral (GF 41353)

Three males and three females were tested per dosage level of 25, 50, 100, and 200 mg/KG/day. Hematology studies included PCV, Hb, RBC, thrombocytes;

ESR, reticulocytes, WBC. The biochemistry data included urea, sugar, sodium, potassium, SGOT, SGPT, SAP, and serum proteins. Urinalysis was also conducted. At termination of the study a full autopsy was conducted on each animal. Fourteen tissues from each animal were weighed at termination of the study. A microscopic examination was made of these fourteen tissues as well as seven others. The individual tissues are listed in the report.

Results:

It appears that four animals died at the 200 mg/KG dosage level and two animals died at the 100 mg/KG/day level.

Diarrhea was noted in all test groups, the severity and frequency appeared to be dose related. Jaundice was very marked in all except one of the animals that did not survive the full period of the study. The severity of the icterus also tended to be dose related.

At 30, 60, and 91 days the SAP values for the test groups were higher than the corresponding control group. In the three animals from which terminal samples were examined at 33, 43, and 62 days respectively SAP values were abnormally high and, as with most of the others showing severe toxic effects, abnormally high values were recorded for SGOT and SGPT, as well as ESR and reticulocytes. Abnormally low PCV, Hb and RBC values were recorded.

Urinalysis abnormalities were mainly confined to evidence of liver dysfunction as indicated by the presence of bile salts in those animals that had obvious clinical evidence of toxic effects.

Gross autopsy revealed evidence of liver disruption only in those animals that had been clinically effected; otherwise there were a few findings of gastro-enteric hemorrhages.

The livers of the 100, 50, and 25 mg/KG/day animals were heavier than the corresponding control animals. The pancreas of the 200 and 100 mg/KG/day animals was heavier than the corresponding control animals. The 200 mg/KG/day animals had heavier kidneys than the control or 25 mg/KG/day animals. The 100 mg/KG/day animals had heavier kidneys than the corresponding control animals. The adrenals of the 200 and 100 mg/KG/day animals was heavier than the corresponding control animals. The male gonads of the 100 mg/KG/day group were lighter than the corresponding controls. The uterus of the 100 and the 25 mg/KG/day animals was lighter than the corresponding control animals.

Histological findings showed that five livers of the animals receiving 200 mg/KG/day showed pathological changes ranging from severe to very mild. The findings in the 100 mg/KG/day animals showed very active bone marrows (both in test and placebo dog). In many animals showing severe liver damage, the bone marrow is hyperplastic; in addition a number of the spleens contained hemopoietic foci.

The animals receiving 50 mg/KG/day showed five cases of severe liver damage in which the animals had immature blood cells present in the lung.

The animals receiving 25 mg/KG/day showed focal interstitial nephritis. In two dogs there was some increase of pigment (lipofuscin) in the conboluted epithelium of the kidneys.

Comments:
Apart from the severe liver damage, there appears to be increased hemopoietic activity in many bone marrows. This suggest an increase in the turn over of blood cells with consequent marrow response.

Rat and Rabbit Dermal Absorption

An ointment as well as a tincture was tested in rats, and the ointment only in rabbits. The tincture represented a 0.2% solution of the test material in 50% ethanol and water. The ointment contained 3% of the active substance, and its based consisted mainly of water (68%) and glycerol stearate (15%). Portions of hair on the back of each animal was removed. Urine and feces were collected during at least 48 hours. A single animal was used in each experiment.

Exactly 0.5 mL of the tincture which was applied to one rat contained 1.0 mg of the technical material. Exactly 32.2 mg of the ointment which contained 0.967 mg of the test material was applied to one animal also.

Exactly 0.890, 0.917, and 0.907 mg of the test material was applied to the three test rabbits respectively.

Results:

The recovery data on the rat which was tested with the tincture showed 0.67% recovery in the urine and 22.4% recovery in the feces at the end of 48 hours.

The recovery data on the rat receiving the ointment showed a 1.6% recovery in the urine and a 21.9% recovery in the feces at 48 hours.

The rabbit which received the dosage of 0.890 mg of the test material showed a 48.1% recovery in the urine and approximately 1.0% recovery in the feces. The rabbit receiving the dosage of 0.917 mg of the active ingredient showed a recovery of 25.9% in the urine and 1.4% in the feces at 48 hours. At 96 hours this animal showed a total recovery of 28.7% in the urine and 2.2% in the feces.

The animal which received the dosage of 0.907 mg of the active ingredient showed a 27.5% recovery in the urine and a 1.3% recovery in the feces at 48 hours. At 96 hours this animal showed a total recovery of 29.7% in the urine and 1.7% in the feces.

Comment

The material appears to be moderately well absorbed through the skin.

Human Dermal Absorption

Exactly 1.08 gm of ointment, equivalent to 31.74 mg of active ingredient, of which 1.82 mg was radioactive was applied to a single human patient. Urine and feces was collected for 72 hours and analyzed for the active ingredient plus its metabolites.

Results:

Exactly 70.1% of the radioactivity was found in the dressing and cleansing material upon removable of the test patch. In addition to this the test patch itself contained a total of 0.65% of the radioactivity. At the end of the 72 hour period the urine contained 2.2% of the radioactive test material applied, and the feces contained 0.42%. The first 12 hours sample of the urine was accidentally discarded.

Assay of the radioactivity in the blood yielded values of background magnatude. The concentrations of the test material and metabolites were definitely below 0.001 mg/100 mL.

The metabolite studies showed that the major portion of the activity present in the urine was identified as the glucuronide of the starting material.

Human Dermal Absorption

Exactly 1.042 gm of ointment containing 30.33 mg of active ingredient of which 23.79 mg were active was placed on the flexor side of the left forearm of a 75 year old female suffering from mild cardiac insufficiency. I assume day of exposure was one time only.

Results:

Exactly 99.1% of the radioactive material was found in the dressing and cleansing material used to remove the test material. Another 0.335% of the active ingredient was found in the test patch. Of the test material absorbed the urine showed 2.16% at 72 hours and the feces showed 0.62%.

Determination of the radioactivity in the blood revealed values at the level of the background. The concentrations of the test material and its metabolites were definitely below 0.001 mg/100 mL.

The metabolite studies indicate nearly all of the substance found in the urine was in the form of the glucuronide.

It appears that absorption was poor.

Human Dermal Absorption

Exactly 0.9348 gm of ointment containing 27.25 mg of active ingredient of which 1.452 mg was radioactive was placed on the arm of a human female subject. No medication was given 48 hours before the beginning of the experiment. The ointment was applied to a 8 by 8 cm area of skin on the right elbow. The treated site was covered for 24 hours. Urine and feces were collected in daily portions over a 72 hour period. Seven days after the end of the experiment another 24 hour sample of urine and feces was analyzed. Blood samples were taken at 1, 3, 5, 9, and 24 hours post treatment.

Results:

Exactly 68.91% of the radioactivity material was found in the dressing and cleansing material. Another 0.478% of the radioactive material was found in the patches.

At 24 hours 3.5% of the radioactive dose applied was recovered from the urine. The feces for this 24 hour period was not recorded. At 72 hours 6.0% of the original radioactive sample was recovered from the urine and 2.0% recovered from the feces. Samples taken at day 9 and day 10 contained approximately 0.05% of the radioactive sample.

Assay of the radioactivity in the blood yielded values of the level of the background. The blood concentrations of the test material and its metabolites were below 0.001 mg/100 mL.

Metabolite studies which were carried out with the urine during the first 24 hours post treatment showed it to contain 10% of the active ingredient,

91.3% of the glucuronide and 3.2% of the sulfate. At 48 hours the urine showed 17.3% of the starting material, 81.6% of the glucuronide and 0.3% of the sulfate.