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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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10/5/82

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Casual# 652C

TO: Adam Heywood, PM #17
Registration Division (TS-767)

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Toxicology Branch, HED (TS-769)

SUBJECT: Experimental Use Permit For Florida Use of the Carbamate R_O 13-5223 of Maag Agrchemicals on 40 Tons of Peanut Seeds. Warehouse Use of 0.16 lbs a.i. Total.

Identifying Number: 35977-EUP-R
Action Code: 700
Accession Numbers: 247925 and 247926
Record Number: 73962

MRID 109379 - 109396, 130371
MRID 109321 - 109333

Purpose

Maag Agrochemicals, Vero Beach, Florida is requesting a EUP for an October, 1982 application of 0.16 lbs a.i. R_O 13-5223 onto a 40 ton peanut seed lot in a single trial.

Metabolism, AChE suppression, acute oral, inhalation, dermal, eye, and mutagenicity studies have been submitted by Maag in support of the proposed EUP.

Recommendations

Sufficient data has been submitted by the Registrant to provide adequate safety for the proposed use. This is true if RCB classifies the use as a "non-food" use. With the provision that inhalation exposure does not exceed a 4-hour exposure of $\geq$ 0.5 mg/L of air, Tox recommends for the immediate granting of the proposed EUP.

change with attach. J.W. Kelly

Conclusions

1. ^{14}C - R_O 13-5223 is rapidly cleared (in what form is not known) from the rat and apparently does not accumulate in any organ after a single dose.

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2. Flyhead AChE activity was uneffected by $R_0$13-5223 at a concentration as high as $2.5X10^{-4}$M. As a carbamate R_o 13-5223 does not effect AChE and thus will likely not pose a neurological problem to man.

3. Technical R_o 13-5223 (97-98% a.i.) showed a low degree of toxicity by the oral route with LD_{50} > 10,000 mg/kg.

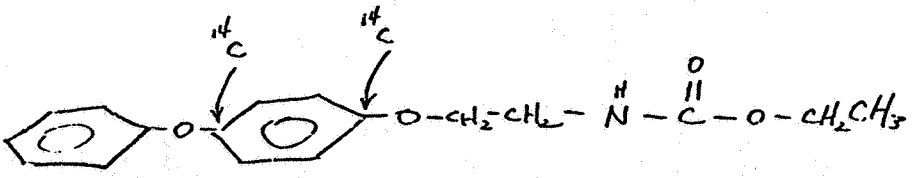
4. The inhalation studies on R_o 13-5223 powder and aerosol were performed at too low exposure concentrations to rule out even Category II toxicity. These studies indicate low levels of inhalation exposure produce no adverse affects. Since the formulation is [redacted] the proposed application rate is to be low (0.16 lbs a.i./40 tons of seeds) the exposure is expected to be low. Tox defers to EFB as to applicator exposures. Should these exposures be low (0.5 mg/L) then Tox has no objections to granting the EUP.

5. The dermis and eye of test animals were not affected by R_o 13-5223 even at relatively large exposures. Thus, potential or real exposures by these routes are not anticipated to pose a problem to man.

6. The Ames reverse mutation assay, the S. Cervisiae D-7 crossing over, mitotic gene conversion, reverse mutation assay, and the point mutation in Chinese Hamster V 79 lung cell line at the HGRPT locus assay were performed. All three tests performed were negative for mutagenicity.

Metabolism of ^{14}C-R_o13-5223 in Fullinshorfer Albino Rats

Ethyl [2-(p-phenoxyphenoxy-1.4-^{14}C) ethyl carbamate was administered at a single dose in rape oil@ 50 mg/kg body weight at a specific activity = 11.3 X 10^6 dpm/mg. The rats (5 males and 5 females) were dosed once by intubation only clearance was measured in urine, feces, and selected tissues by following total radioactivity.



^{14}C-R_o-13-5223

Most of the radioactivity excreted in urine and feces (60-80%) was cleared quickly in 24 hours. The total recovery of label at 96 hours was 90-92% with 61-65% in feces and 26-28% in urine. None of the tissues examined for radioactivity showed persistent residues. For instance, the percentage found in each organ of the applied dose was: plasma (.002), RBC (<.001, brain (.001), liver (.025), kidney (.002), heart (<.001), muscle (<.001), spleen (<.001), bone (<.001), gonads (<.001), fat (<.005), intestine (.04-.12), and stomach (.002).

The Agency concurs with Maag that R_o 13-5223 clears rapidly in the rat and does not accumulate in any organ tested. These data are supplemental to the total metabolism studies necessary to describe R_o 13-5223 metabolisms in test animals. Further studies which measure possible metabolites of R_o 13-5223 in the excetia should be conducted. Repeated dose studies should be done to see if repeated exposure to the parent R_o 13-5223 leads to any deterious metabolite which that might be persistent or bioaccumulate in a specific organ.

Study Classification: Supplemental

Acetyl Cholinesterase Activity in the House Fly Musca Domestica

Because of R_o 13-5223 is a carbamate, it is of interest to test the acetylcholinesterase activity of R_o 13-5223. An *in vitro* test was performed with R_o 13-5223 and housefly head AcHE suppression.

Primacarb was used as a control to inhibited AChE whereas the test substance R_o 13-5223 at 2.5×10^{-4}M and 2.5×10^{-5}M in the enzyme mixture did not.

It is concluded that R_o 13-5223 will not likely cause synaptic disturbance at the AChE locus. Further, in the acute oral studies animals observed for two weeks, after dosing, showed no neural disorders or pathologic neural behavior patterns.

Study Classification: Core-Minimum

Acute Oral Studies

Technical (97-98% a.i.) R_o 13-5223 was tested by gavage for oral acute toxicity (one dose), and it was found in one study the LD $_{50}$ > 10,C00 mg/kg (rat) and in another study LD $_{50}$ > 16,800 mg/kg (rat). Still another study in the mouse showed the LD $_{50}$ >8000 mg/kg.

A formulation of R_0 13-5223 (10.3% a.i. [redacted] showed LD $_{50}$ > 10,000 mg/kg. The formulation likely to be marketed [redacted] was not tested for acute oral toxicity.

To further underscore the low degree of toxicity of R_0 13-5223, the i.p. dosage LD $_{50}$ = 9220 mg/kg. Another study using a single dose (up to 10,000 mg/kg by gavage) and monitoring for 14 days showed two (2/5) females rats died showing gastric distress with crystals (presumed to be test substance) in the gastrointestinal tract. The rest of the rats lived and were sacrified at day 14 and necropsied. Histopathology showed splenic hemopoiesis in most of the treated animals.

Study Classification: Core Guideline (All acute oral studies).

Acute Inhalation Studies - Technical

Two types of 4-hour exposures in two separate experiments were performed: (1) R_0 13-5223 dusting with an average chamber concentration of 0.26g/m^3 (97% technical) of which 32.5% was respirable (<5 um a.d.), and (2) R_0 13-5223 aersol exposure with an average aersol concentration of 0.48g/m^3 of which 94.5% was respirable. The dust groups (10 of each sex) was compared to an air control and the aerosol group (10 of each sex) was compared to a vehicle control. The concentrations obtained were stated by Dr. Clark of Huntington Research Centre (performing contractor) to be the highest concentrations obtainable with the equipment used. Animals were observed for 14 days and then sacrificed for pathology.

Results show no deaths in dust or aerosol groups (or in controls). The dust group showed licking and excessive

salivation in the first 30 minutes fo exposures with eye closure and lacrimation at 1 1/2 hours exposure. The aerosol group also showed licking of the mouth and excessive salivation during the first 1 1/2 hours, and then, they were apparently normal thereafter. During the 14 day period the dust group showed brown straining of the fur for 2-10 days and in the aerosol group brown straining of fur and a dark nasal discharge 1 day after exposure which cleared by day 5.

There were no body weight changes in the dust or aerosol groups. The lung weight to body weight ratio was invariant. No macroscopic organ abnormalities were observed as there was no compound-related microscopic pathology in either exposure group.

The study was well conducted in all respects except: no dose response was established and the dose utilized was not high enough to rule out inhalation effects. The highest dose should be > 5mg/liter. This inhalation experiment should be repeated with a number of treatment groups and high dose ≥ 5mg/liter.

Study Classification: Supplemental

Acute Inhalation Studies - Formulation [redacted]

This study on 10.3% a.i. (w/w) started on 3/16/82 at Research and Consulting Co. Ldt., Itingen, Switzerland and the sponsor was Hollmann-LaRoche. Two groups of 2221 and 3052 mg/m^3 (gravimelrically determined) were aersol tested and compared to vehicle control Wistar Rats. Exposure was for four hours in 100 l. chambers at a flow rate of 600 l. air/hour and a pressure of 3 atm. Observation was for 14 days post-treatment.

No deaths, body weight changes, organ weights or gross morphology or microscopic or histologic alterations were noted with 10.3% a.i. [redacted] aerosol exposures.

It should be noted as in the previous inhalation experiment, that high enough a.i. concentrations were not achieved in the experiment in order to assess inhalation effects. The highest concentration 3052 mg/m^3 = 3052 mg/1000 L= 3.05 mg/L X .103 (% a.i.) = 0.31 mg/L which could not ever rule out Category II toxicity.

Study Classification: Supplemental

Acute Dermal Irritation Studies

In this study (11/15/79) on 10 males and 10 females, test compound (from a 40% a.i. solution in corn oil on shaved dorsal area) at 2000 mg/kg was applied and patch occluded for 24 hours. Following exposure the R_0 13-5223 was rinsed off and rats were observed for 14 days.

No dermal irritation was observed in males or females during the 14 days. There were no significant gross, behavioral, or histopathologic dose related changes noted.

Formulated (10.3% a.i.) $R_0$13-5223 showed no dose-related effects with applications of 1000, 3000, and 5000 mg/kg.

These data indication a Category 4 dermal toxicity.

Study Classification: Core-Minimum

A primary skin sensitization test was run on Guinea pigs. A induction dose (single) of .025 ml of 100%, 30%, 10% and 3% a.i. was applied to a 2 cm^2 area of flank skin (6-8 pigs per group). The applications were repeated daily for three weeks. On days 21 and 35 the colateral flank was treated with a challenge dose of R_0 13-5223. R_0 3-5223 was well tolerated and no allergic reactions reactions occured at 24 hours or 48 hours after challenge.

Study Classification: Core-Guidelines

Acute Eye Irritation

Rabbits were tested with 0.1 ml of 10% and 30% a.i. technical solutions in two eye irritation tests. Some mild redness was seen at first which subsided quickly by 24 hours. There were no corneal opacity or ulcerations, no iris involvement, nor any chemosis present.

A formulation of R_0 13-5223 (10.3% (w/w) [redacted] was also tested on 2/12/82. The test substance was applied undiluted at 0.1 ml. Some redness was seen in the first hour after administration that was both transitory and mild.

Study Classification: Core-Minimum

Ames Test

Mutagenicity Studies

Both test both spot Ames test (at 2400ug/disc) and a quantititative Ames test (at 37.5, 75, 150, 300 ug/plate) were found to be negative for revertant to wild type under the influence of R_0 13-5223. These negative results were demonstrated in strains TA-1535, TA-1537, TA-1538, TA-98 and TA-100 and were done in the presence and absence of rat liver activation mix (S-9) The posative control cyclophosphamide (100 ug/plate) showed remarkable enhancement of His revertants in TA 1535 (control 15-39 to cyclophosphamide 257-318 colonies). Thus, no mutagenic effects were seen in the Ames test.

Study Classification: Acceptable

Recombination in Saccharomyces Cervisiae Strain D_7

S. Cervisiae D_7 was dosed with 0.017, 0.040, 0.17 and 0.40 mg R_0 13-5223/ml for 3 hours. No crossing over was observed at the ade 2 locus. No mitotic gene conversion was observed at the trp 5 locus. No reverse mutation was observed at the ile 1 locus. These results constitute no mutagenic effects on the three genetic marker loci in strain D_7.

Thus, no genetic damage was observed when R_0 13-5223 was interacted with S. Cervisial strain D_7.

Study Classification: Acceptable

Point Mutation in a Mammalian Cell Line-Chinese Hamster Lung Cells.

R_0 13-5223 was tested on Lung Chinese Hamster cells in culture so to determine the mutation in the hypoxanthine guanine phosphoribosyl transferase (GHPRT) locus in the

specific cell line V 79. Normally V 79 cells will die when challenged with 8-azaguanine (AG) because this compound enters the nucleotide pool, becomes incorporated into nucleic acids, leading to cell death. However, when test compound mutates the HGPRT locus so as the cell becomes AG resistant (noted by AG^r) then V 79 cells survive because AG is not incorporated in to V 79 nucleic acids and therefore no cell killing. This foward mutation assay measures an increased number of colonies which clone from AG^r cells in the treatment media.

R_o 13-5223 (5 hour treatment) was cytotoxic with and without S-9 mix where R_0 13-5223 was tested at 0, 1, 5, and 25 ug/ml. Cell survival was reduced to less than 1/3 but which recovered by the time of AG challenge. Another experiment at 0, 25, 50, and 100 ug/ml showed cell survival (200 cells seeded) to go from 179 (0, control) to 9 (at 100 ug/ml). These cells were recovered consequently when AG challenge was made.

In neither experiment were AG^r cells induced by R_o 13-5223 at the HGPRT locus. On the other hand, positive controls EMS and AAF (with S-9) showed remarkable forward mutations in the HGPRT locus to AG^r thereby showing the sensativity of the Chinese Hamster V 79 cells to mutation in the HGPRT genomic region. Thus, R_0 13-5223 has been found not to be mutagenic in Chinese Hamster Lung cells, line V 79.

Study Classification: Acceptable

Mutagenesis Summary: R_o 13-5223 was negative when tested by GLP in the Ames Test (Salmonella 1535, 1537, 1538, 98, 100), S. Cervisiae D_7, and Chinese Hamster V 79 cells with and without S-9 activation rat liver mix.

J. W. Holder 9/30/82
M. for CSD 10/05/82

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TS-769:James W. Holder:gjd:557-1450:Rm:800:9/28/82