8-31-84

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

003989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Brodifacoum, Rodenticide

TO: William H. Miller PM-16
Registration Division (TS-767)

8/31/84

FROM: Robert P. Zendzian PhD. Head
Review Section III
Toxicology Branch
HED (TS-769)

THROUGH: William Burnam, Chief
Toxicology Branch

Compound Brodifacoum

Formulation TALON-G Rodenticide Pellets

Registration #10182-LI

Accession #250077, 245704 & 252894

Tox Chem #114AAA

Registrant ICI Americas Inc.

Action Requested

The Registrant requests an amendment of the registration of Talon-G to allow outdoor use against commensal rodents.

Recommendation

Toxicology Branch recomments that the amendment be denied. The Branch further recommends that additional testing of brodifacoum be required and that no further registration be approved until they are completed. Tests required are, 1)an antidotal study in dogs, 2)a special metabolism study to evalate the long half-life and potential for bioaccumulation. and 3) an additional teratology study(s).

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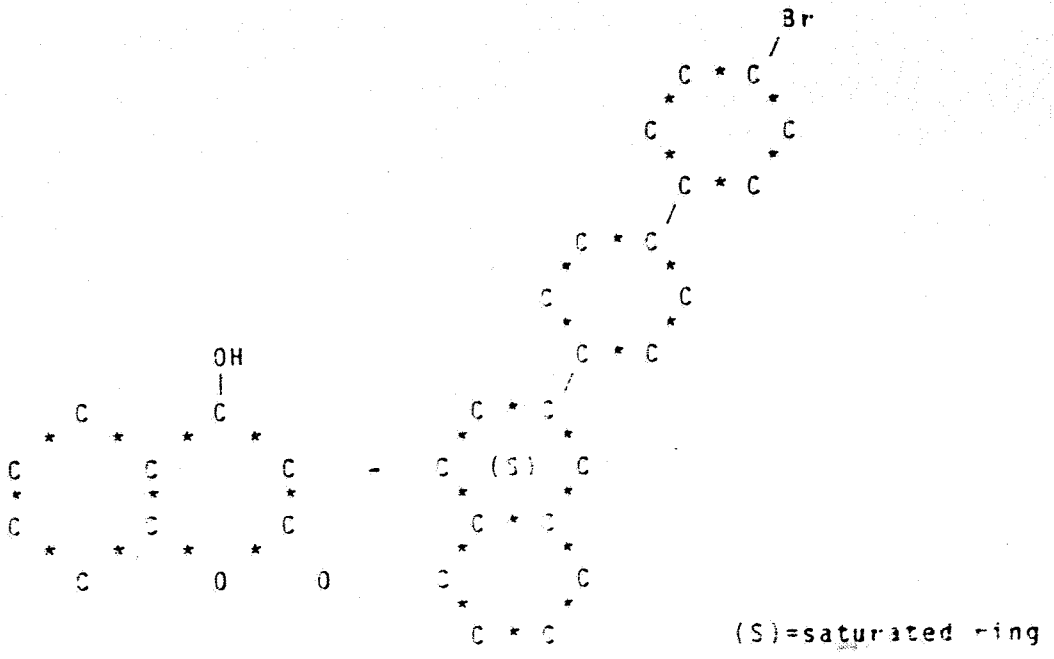
Brodifacoum is a highly toxic anticoagulant which has a demonstrated half-life in mammalian species of at least six months. This property can lead to one or more of three extremely serious adverse toxic effects. 1. Bioaccumulation can be expected to occur so that toxic responses can occur at intervals between doses as great as six months. 2. Under conditions of stress tissue stored compound can be mobilized and toxicity occur months after dosing. 3. An individual acutely poisoned with this compound will require treatment of extensive duration compared to commonly known anticoagulants of this type such as warfarin.

Chemistry

3-[3-(4'-bromo-[1,1'-diphenyl]4-yl)-1,2,3,4-tetrohydro-1-napthalenyl]4-hydroxy-2H-1-benzopyran-2-one



Background

Brodifacoum is an extremly toxic anticogulant rodenticide which functions as a vitamin K antagonist. The original toxicity data on the technical material, a 0.25% liquid concentrate and a 0.0005% w/v pellet dosage formulation were summerized in an EPA memo by R.A. Gessert (8/2/78). The acute oral toxicity of the technical material is as follows.

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Male Rat LD_{50} 0.27mg/kg
Mouse LD_{50} 0.4mg/kg
Rabbit LD_{50} 0.29mg/kg
Cat LD_{50} 25mg/kg
Guinea pig LD_{50} 2.87mg/kg
Dog LD_{50} 0.25 to 1mg/kg
Sheep LD_{50} 25mg/kg

Gassert's comment on the antidotal study submitted with the toxicity data is quoted in full as follows:

"Antidote Studies: Vitamin K_1 is antidotal. The minimum dose of Vitamin K_1 required to antidote a massive acute dose of the rodenticide lies between 10 and 20 mg/kg."

Without information on the experimental animal used, the dose of compound, the dose(s) of Vitamin K_1 and the criteria for effectiveness utilized it is imposible to use the statemert in the Gessart memo as a basis for treatment.

Subsiquently Doherty (9/12/78) approved an EUP for a 0.005% bait formulation for use in orchards on the basis of acute studies submitted with the request.

Doherty (10/19/78) recommended approval of a registration of the 0.005% bait formulation on the basis of the data reviewed in his 9/12/78 memo.

Doherty (10/4/79, two memos) reviewed the label for technical and 0.25% concentrate brodifacoum and noted the lack of teratology studies on the compound.

Doherty (6/18/80) reviewed rat and rabbit teratology studies on the technical material. Both studies were negative.

For the rat study Doherty concluded;

"This study is Core Minimum. No positive control was included. The raw data are not included and data are in summary tables only."

For the rabbit study Doherty concluded;

"This study is Core Minimum. No positive control was included. The data are presented in summary tables only. No raw or individual animal data as (sic) presented."

The studies were improperly classified, a lack of individual animal/litter data in teratology reports make them impossible to review and the studies should have been classified invalid.

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Biscardi (7/7/81) reviewed an antidotal study in the beagle dog. Since all dogs dosed with Brodifacoum were treated with the antidote vitamin K_1, it was impossible to determine if a toxic dose of the anticoagualant had been given. Therefore, it was impossible to determine if vitamin K_1 has protected against any toxic effect. Dr Biscardi classified this study invalid.

Additional Information

The Registrant has submitted the following additional studies which have been reviewed with the noted conclusions. DERs are attached.

Citation

Brodifacoum: Absorption, Excretion and Tissue Retention in the Rat. H. Bratt & P. Hudson, Imperial Chemical Industries Ltd. CTL/P/462, Jun 20, 1979.

Conclusion

Following an oral dose of 0.25mg/kg, brodifacoum is almost completely absorbed and only very slowly excreted in the urine. The half-life is estimated as 150-200 days with at least 50% of the retained radioactivity represented by the parent compound.

Citation

WBA 8119: Acute Oral Toxicity, G.R. Parkinson, Central Toxicology Laboratory, Imperial Chemical Industries Ltd, CTL/P/216 (revised). Jan 1976

Conclusion

Acute oral toxicity in dogs was between .25 and 1.0 mg/kg and in cats about 25mg/kg.

Citation

The Acute Oral Toxicity of WBA 8119 to the Domestic Pig D.B. Ross, Huntingdon Research Center, Report No. SRX/2/7670 Jan 27,1976.

Conclusion

The LD_{50} was estimated as between 0.5 and 2.0 mg/kg.

Citation

PP 581: Acute Oral Toxicity to Sheep, G.R. Parkinson, Central Toxicology Laboratory, Imperial Chemical Industries Ltd, CTL/P/258. Sept 1976

Conclusion

LD_{50} was estimated as in excess of 25mg/kg.

Discussion

The coumerin type anticoagulants, as exemplified by Warfarin, have properties that make then particularly useful as rodenticides. A single properly chosen dose is not lethal to the rat or nontarget organisms such as dogs, cats or children. Repeated daily dosing by the rat is lethal. The safety to nontarget organisms lies in the small likelyhood that they will ingest several doses of the anticoagulant at frequent enough intervals to produce toxic effects. This is a function of the half-life of Warfarin, between one and two days, which promotes bioaccumulation at shorter intervals and makes bioaccumulation impossible at longer intervals. In addition the treatment of this type of toxicity, with vitamin K and blood transfusions, is well established and usually successful.

Brodifacoum differs from warfarin in that it is considerably more toxic, a single feeding of the bait formulation will kill a rat, and it has a half-life that is at least 50 times longer. The treatment of brodifacoum toxicity has not been experimentally established but one may expect that it would require an extremely expended duration compared to warfarin.

For these reasons it is necessary to have a fuller understanding of the metabolism of the compound. A proposed protocol for the metabolism of rodenticides in enclosed which will provide the information required.

An antidotal study in dogs is required with proper controls. The study should include at least 2 animals/sex/group. Groups should consist of, 1)Treated with an acutely lethal dose. 2) Treated with an acutely lethal dose and then treated with antidotal doses at 24 hour intervals until the group one animals have died. 3)Treated with an acutely lethal dose and then treated with antidotal doses starting when toxic signs are observed and continued until complete recovery. Blood coagulation parameters should be followed on all animals.

The teratology studies submitted raise serious questions since warferin and several other coumerin type antivitamin

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anticoagulents are teratogenic. Warfarin has been demonstrated to be teratogenic in humans. In general all antivitamins are teratogenic under proper experimentl conditions. Since the detailed results of the teratology studies were not submitted it is impossible to properly review the studies. At least one additional teratology study is required in a species which has been shown to be sensitive to warfarin.

Enclosure

Metabolism Studies for Rodenticides, Proposed by Robert P. Zendzian PhD, Pharmacologist, Toxicology Branch, July 1984

References

Gessert, R., MEMO 10182-EUP-10. TALON RODENTICIDE. Brodifacoum. Original New Anticoagulant Rodenticide. Vitamine K_1 Antagonist. ICI Americas, Inc. Wilmington, Delaware. Aug 2, 1978

Doherty, J,. MEMO, Experimental Use Permit Application for Evaluation of TALON anticoagulant Rodenticide for Use Against Microtus in Orchards. Caswell No. 114AAA, 10108-EUP-12, Sept 12, 1978

Doherty, J,. MEMO, EPA Registration No. 10182-EA, (Rodenticide Pellets) and 10182-ER (Rodenticide Bait Pack), Oct 19, 1978

Doherty, J,. MEMO, EPA File No. 10182-EO, Brodifacoum 90.0% Technical. Oct 4, 1979.

Doherty, J,. MEMO, EPA File Symbles 10182-EN/EA/ER/EL/EU/EG/EE. Products Containing 0.005% Brodifacoum. Oct 4, 1979

Biscardi, S., MEMO, A One Month Anticoagulant Antidote Study in Beagle Dog FINAL REPORT. Jul 7, 1981.

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Metabolism Studies for Rodenticides

Introduction

This study is designed to determine the persistance and potential for bioaccumulation of rodenticides in the mammalian species. A rodenticide which persists in the body of a nontarget organism presents a significant danger in that it offers the possibility for chronic poisoning with long intervals between doses and can significantly increase the duration and complexity of treatment required in cases of acute poisoning.

When Required

This study is required for the initial registration of all rodenticides.

Materials

An analytically pure sample of the rodenticide isotopically-labeled in a portion of the molecule that will be indicative of the presence of the molecule in the organism should be used. Labeling may not be needed if specific and sensitive physical-chemical methods exsist for identifying the compound.

Young adult male and female rats of a commonly used strain are the species of choice. Other mammalian species may be used for particular compounds but a specific rational for this choice must be supplied.

Methods

1) Route. The oral route should be used unless another route of exposure is expected to occur in accidental exposure. In some cases it may be necessary to study more than one route.

2) Dose. A single oral dose at one-tenth the LD_{50} is recommended. The dose should not be expected to produce mortality. Since the oral LD_{50} of compounds in the rat often differs by sex a different mg/kg dose may be necessary for each sex.

3) Number of Animals. At least five males and five females should be used.

4) Observation period. Animals should be maintained, individually in metabolism cages for seven days or until 90+ percent of the dose is excreted, whichever comes first. Animals are killed at the end of the observation period.

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5) Collection and analysis of excreta. Expired air, urine and feces should be collected at suitable intervals during the observation period and analyzed quantitatively for the test material. Intervals of 4, 8, 12 and 24 hours, 1.5, 2, 3, 4, 5, 6 and 7 days are suggested. Expired air need not be collected if data is available to show lack of excretion by this route during the first 24 hours after dosing.

6) Tissue distrobution. At sacrifice, the quantity of labeled material remaining in bone, brain, fat, gonads, heart, kidney, liver lungs, muscle, spleen, other tissues which may be expected to retain the particular compound and residual carcass will be determined.

7) Metabolism. Identification of metabolites is not required unless significant bioretention occurs. Essentially if the half-life exceeds 48 hours or accumulation occurs in a particular organ, analysis should be performed to determine the quantity of active rodenticide retained.

8) Additional determinations. Blood kinetics are not usually required but may be useful if bioretention occurs.

Reporting

Reports should provide the information required in the Pesticide Assessment Guidelines, Subdivision F, Series 80-5 Reporting of data and Series 85-1 Metabolism study.

Proposed by

Robert P. Zendzian PhD
Pharmacologist
Toxicology Branch HED

July 1984

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Data Evaluation Report

Compound Brodifacoum

Citation

Brodifacoum: Absorption, Excretion and Tissue Retention in the Rat. H. Bratt & P. Hudson, Imperial Chemical Industries Ltd. CTL/P/462, Jun 20, 1979.

Reviewed by 2/25/80

Robert P. Zendzian PhD
Pharmacologist

Core Classification Supplementary

Tox Catagory N/A

Conclusion

Following an oral dose of 0.25mg/kg brodifacoum is almost completely absorbed and only very slowly excreted in the urine. The half-life is estimated as 150-200 days with at least 50% of the retained radioactivity represented by the parent compound.

Materials

Brodifacoum, analytical grade, 96% pure, cis:trans ratio 64.6:35.6

Brodifacoum, uniformly labeled on the phenyl ring of the coumarin moiety as individual isomers, mixed one to one for administration.

Hydroxycoumarin analytical grade

Adult male rats (190-210gm) Alderly Park specific pathogen-free strain (Wister-Derived).

Methods

1) Three rats were dosed orally with 14-C brodifacoum (6.6 uCi/kg; 0.25mg/kg) and urine and feces collected individuallily at 24 hour intervals for 10 days. At termination the rats were killed and abdominal fat, kidneys, heart, liver and residual carcasses collected for analysis.

2) Three rats were dosed orally with 14-C brodifacoum (6.6 uCi/kg; 0.25mg/kg) and killed 10 days after dosing. Blood (2ml) was collected for analysis by cardiac puncture. Pancreas and spleen were also collected.

3) Three rats were dosed orally with 14-C brodifacoum (6.9 uCi/kg: 0.5mk/kg) and urine and feces collected at 24 hour intervals for 5 days.

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4) Three rats were dosed orally with 14-C brodifacoum (7.2 uCi/kg: 1.5mg/kg) and urine and feces collected at 24 hour intervals for 5 days.

5) One rats was dosed orally with 14-C brodifacoum (6.6 uCi/kg: 0.25mg/kg) and expired air collected for 48 hours.

6) The bile ducts were cannulated on three rats. After recovery from anesthesia the rats were dosed orally with 14-C brodifacoum (6.6uCi/kg; 0.25mg/kg) and the bile collected at 24 hour intervals for 48 hours.

7) Three rats (80-90gm body weight) were given a single oral dose of 14-C brodifacoum (6.6uCi/kg; 0.25mg/kg)/. A single rat killed, quick frozen, block embedded and sectioned (longitudinal saggital sections) for whole body autoradiography 1, 5 and 10 days after dosing.

8) Twenty-four rats were dosed orally with 14-C brodifacoum (6.0uCi/kg; 0.21mg/kg) and killed in groups of 3 at 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hours after dosing. Blood (2 ml) was taken by cardiac puncture. Blood was also collected from 3 untreated rats.

9) Six rats were dosed orally with 14-C brodifacoum (6.0uCi/kg; 0.21mg/kg) and killed in groups of 3 at 10 and 17 hours after dosing. Blood (2 ml) was taken by cardiac puncture.

Samples of urine, feces, bile and extracts from various organs were analysed for metabolites by several chromatographic procedures

Results Results are numbered as in the methods section above.

1) Following an oral dose of 0.25mg/kg, the mean precent of dose excreted in the urine was 1.31 after 10 days with the highest excretion on day one (0.88) and excretion stabalizing on days 5 to 10 at 0.02 to 0.04 %/day. In the feces the mean percent of dose after 10 days was 11.01 with the highest excretion on day 2 (4.70%). Fecal excretion decreased throughout the 10 day collection period.

The mean percent of dose remaining in various tissues after ten days was abdominal fat 3.29, liver 22.84, kidney 0.78, heart 0.10 and residual carcass 50.82.

2) Following an oral dose of 0.25mg/kg, the mean precent of dose persent in tissues after 10 days was pancreas 2.33, spleen 0.16 and blood 0.05.

3) Following an oral dose of 0.5mg/kg, the mean percent of dose excreted in the urine was 2.34 after 5 days with the highest excretion on day one (2.05%). In the feces the mean

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percent of dose after 5 days was 30.75 with the highest excretion on day one (14.95%). One rat died on day four and the remaining two on day five.

4) Following an oral dose of 1.5mg/kg, the mean percent of dose excreted in the urine was 2.81 after 5 days with the highest excretion on day one (2.01). In the feces the mean percent of dose after 5 days was 42.56 with the highest excretion on day two (16.23%). All three rats died on day on day five.

5) Following a single oral dose of 0.25mg/kg to one rat no radioactivity was detected in expired air over 48 hours.

6) Following an oral dose of 0.25mg/kg, the mean precent of dose excreted in the bile was 0.55 for the first 24 hours and 0.77 for the second with a total of 1.36.

7) Following an oral dose of 0.25mg/kg, whole body autoradiograms at one, five and ten days post dose showed that the highest concentrations of radioactivity were present in the liver, pancreas and salivary glands with activity also present in the gastric mucosa, intestinal mucosa, vertebrae, nasal mucosa, kidneys, adrenals, menim=nges, fat and skins.

8 & 9) Mean blood concentrations of brodifacuom (ng equilivants /ml of blood) following a single oral dose of 0.21mg/kg are given in the following table taken from table 4 of the report. Actvity was less than the limit of detection (1.1 ng eq/ml) on day 17.

Hrs after dosing	0.25	0.50	1.0	2.0	4.0	6.0	8.0	10.0	17.0	24.0	240.0
ng eq/ml	2.8	2.2	4.4	5.9	10.1	15.4	16.1	13.1	5.7	5.7	1.3

Analysis for metabolites showed that 50% or more of the retained radioactivity was represented by the parent compound.

Discussion

The dose of 0.25mg/kg brodifacoum administered in most of these experiments approximates the LD_{50} in the male rat. The compound is almost completely absorbed and only very slowly excreted. The half-life is estimated as 150-200 days with at least 50% of the retained radioactivity represented by the parent compound. This extensive half-life indicates a serious potential for cumulative toxicity.

This study satisfies the Guideline requirements for a single high oral dose in male rats.

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Data Evaluation Report

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Compound Brodifacoum. WBA 8119

Citation

WBA 8119: Acute Oral Toxicity, G.R. Parkinson, Central Toxicology Laboratory, Imperial Chemical Industries Ltd, CTL/P/216 (revised). Jan 1976

Reviewed by 2/23/90
Robert P Zendzian PhD
Pharmacologist

Core Classification Supplementary

Tox Catagory I

Conclusion

Acute oral toxicity in dogs was between .25 and 1.0 mg/kg and in cats about 25mg/kg.

Materials

WBA 8119 (brodifacuom)

Female beagle dogs (8-12kg)

Male and female cats (2-3kg)

Methods

Compound was dissolved in polyethylene glycol 300 and administered orally by gravage. Animals were observed for 4 weeks. Necropsies were performed on all animals killed in extremis or at termination. Doses used and results are shown in Tables 1 & 2.

Results

Table 1. Female dogs

	Dose (mg/kg)			
	0.25	1.00	1.00	4.00
(no. died/no. treated)	0/2	2/2	2/2	2/2

LD 50 estimated as between 0.25 and 1.0 mg/kg

Toxic signs appeared at about six days in the fatalities consisting of subdued behavior, loss of appetite, pale, respiratory difficulties, hypothermia, blood in feces and minor external hemorrhages. Necropsy of animals killed in extremis revealed heamorrhages, particularly in the neck and thorax.

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Table 2. Male and Female Cats

	Dose (mg/kg)			
	5.00	10.00	25.00	50.00
(no. died/no. treated)	0/2	0/2	1/2	0/2

LD_{50} estimated at 25mg/kg

The animal that died was not necropised. Animals at 50mg/kg showed subdued behavior and loss of appetite at about two weeks but were normal at 4 weeks.

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Compound Brodifacoum. WBA 8119

Citation

The Acute Oral Toxicity of WBA 8119 to the Domestic Pig
D.B. Ross, Huntingdon Research Center, Report No. SRx/2/7670
Jan 27,1976.

Reviewed by 3/31/82
Robert P. Zendzian PhD
Pharmacologist

Core Classification Supplementary

Tox Catagory I

Conclusion

The LD_{50} was estimated as between 0.5 and 2.0 mg/kg.

Materials

WB 8119 (brodifacuom)

Large white pigs from a local pig breeder.

Methods

Compound was administered orally by gravage in polyethlene glycol 300. Two animals per dose were dosed at 0.5, 1.0, 2.0, 5.0 or 10 mg/kg. Animals were observed for 21 days. Animals were sacrificed in extremis or at terminatioin and necorpsied.

Results

All animals died except one at 0.5 and two at 1.0 mg/kg. Deaths occured 3 to 18 days postdose. LD_{50} was estimated as between 0.5 and 2.0 mg/kg. Animals appeared normal until about four hours before death when some loss of muscle function and mild convulsions were observed. Bleeding from the nose, ears and rectum was observed immediately prior to death. Necropsy revealed signs of internal bleeding in the animals that died.

Compound Brodifacoum, PP 581

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Citation

PP 581: Acute Oral Toxicity to Sheep, G.R. Parkinson, Central Toxicology Laboratory, Imperial Chemical Industries Ltd, CTL/P/258. Sept 1976

Reviewed by 2/13/84
Robert P. Zendzian PhD
Pharmacologist

Core Classification Supplementary

Tox Catagory Could not be determined

Conclusion

LD_{50} was extimated as in excess of 25mg/kg.

Materials

PP 581 (brodifacuom)

Castrated sheep (30-35kg)

Methods

Compound was administered orally by drench, in polyethylene glycol, to two sheep at 25mg/kg. Animals were observed for three weeks and then necropsied.

Results

No toxic effects were observed. LD_{50} was extimated as in excess of 25mg/kg.

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