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Section II, Toxicology Branch II (H7509C)

DATA EVALUATION REPORT I

STUDY TYPE: Antidotal - Dog

MRID NO: 420075-01

TOX. CHEM. NO. 112701

TEST MATERIAL: Brodifacoum

SYNONYMS: Talon

STUDY NUMBER(S): PD0646

SPONSOR: ICI Americas Inc.
Agricultural Products
Wilmington, DE 19897

TESTING FACILITY: ICI Central Toxicology Laboratory
Alderley Park, Macclesfield
Cheshire, UK

TITLE OF REPORT: Brodifacoum: Antidote Study in Dogs

AUTHOR(S): Hopkins, M. N.

STUDY COMPLETED: 27 June 1991

CLASSIFICATION: Acceptable as an antidotal study. There is no specific guideline data requirement for antidotal studies. However, the findings of this study are part of the toxicological data base for brodifacoum and may be taken into consideration in any regulatory decision the Agency may make regarding this active ingredient.

CONCLUSIONS:

1. Each dog in a group of 4 male beagles received a single oral dose of 5 mg/kg brodifacoum. Prothrombin times for each of the dogs were then monitored over a period of 5 weeks. "Doses of 2 mg/kg vitamin K_1 were administered to dogs by the intramuscular route whenever their prothrombin times were elevated to levels consistent with a life-threatening effect on coagulation." Individual dogs required 12-15 vitamin K_1 treatments in the period from days 2 to 29 post-dosing.

2. From previous information received by the Agency, the acute oral LD_{50} in dogs for brodifacoum is between 0.25 and 1.0 mg/kg. All four dogs survived to the end of this study (5 weeks after the test material was administered), although there were bodyweight losses in 3/4 of the animals.

3. It is concluded that the vitamin K_1 treatments were effective in preventing mortality which would have resulted from spontaneous hemorrhaging in these animals, and that the findings of this study are in agreement with material previously received by the Agency (several studies in Acc. No. 251781, reviewed in document 003568; also a study - MRID and/or Acc. No. unavailable - conducted by Bio/Dynamics, and reviewed by S. Biscardi, document 003742, dated July 7, 1981). It is noted that the statement is made in a memorandum (document no. 003568) dated February 1, 1984 that: "the pharmacological effect of warfarin by inhibiting vitamin K_1 epoxide reductase appears similar for brodifacoum, acenocoumarol and difenacoum."

4. While vitamin K_1 is an effective treatment following brodifacoum poisoning, there still remains the possibility of incidents involving pets or small children in which it is not known or realized that ingestion of brodifacoum has occurred, and this possibility remains a concern to the Agency.

5. The findings of this study indicate that measurable amounts (although apparently insufficient to cause hemorrhagic symptoms) of brodifacoum are still present in the dog liver at 35 days after dosage. Further, two of the four dogs had weight losses of more than 1 kg over the observation period, and the weight losses were continuing to worsen at the end of the study. These findings are of additional concern.

6. The study is classified as acceptable as an antidotal study on brodifacoum.

A. MATERIALS:

1. Test compound: Brodifacoum, identified as an off-white powder, with a batch no. RS/143/C, and a CTL Reference Number of Y00052/029. The purity is reported as 96.8% w/w. The test substance was stored at room temperature.

2. Antidote: From p. 11: "Vitamin K_1 (KONAKION$_{10}$, Roche Products Limited, Dunstable, Bedfordshire, UK) was obtained as a 10mg/ml solution, for use as an antidote."

3. Test animals: From p. 11: Four male beagle dogs, 11-12 years old, from the colony maintained at ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, UK. From information on p. 28 two of the dogs had been born on 29 June, 1984, and the other two on 23 July, 1984 (p. 10: "The in-life phase of the study was conducted between 24 June 1985 and 12 August 1985.").

B. STUDY DESIGN:

1. Dosage selection: From p. 10: "The dosage of brodifacoum used in this study was selected because it was found to be lethal to dogs in a previous study conducted at CTL..." According to information in the Tox one-liners, the dog oral LD_{50} for brodifacoum is between 0.25 and 1.0 mg/kg. There is no indication within the text as to the basis or rationale for the 2 mg/kg vitamin K_1 dose (by intramuscular injection).

2. Experimental design: From p. 12: "The study comprised a group of four males, each given a single oral dose of brodifacoum at 5 mg/kg bodyweight before feeding. The dose was administered in gelatin capsules of 9 ml capacity...and was calculated based on the most recent bodyweight (to the nearest 0.5 kg) and allowing for known purity (96.8% w/w)."

"Following dosing the animals were monitored for anti-coagulant effect by regular determination of prothrombin time and kaolin-cephalin time. When coagulation times were found to be elevated to potentially life threatening values, vitamin K_1 (2 mg/kg) was given by intramuscular injection to maintain haemostasis."

3. Statistics: There is no indication that any statistical methods or analyses were used.

4. There is a signed and dated "Statement of GLP Compliance" on p. 3 of the report.

C. METHODS AND RESULTS:

1. Observations: From p. 13: "The dogs were observed at least twice daily for gross clinical and behavioural abnormalities. Daily records of faecal consistency were made."

"In addition, dogs were given a full clinical examination by a veterinarian in week -1 and prior to termination. The examination included cardiac and pulmonary auscultation."

Results:

From p. 14: "There were no unscheduled deaths during the study."

"Dog No. 3 appeared to be thin and slightly dehydrated from Week 2 of the observation period. Poor body condition was noted at the pre-termination veterinary examination. There were no other significant clinical observations."

"Administration of brodifacoum had no effect on faecal consistency in this study."

2. Body weights: From p. 13: "All dogs were weighed weekly, before feeding, throughout the pre-experimental period, on the day of dosing and thereafter at weekly intervals during the observation period."

   Results: From p. 14: "Two dogs...showed a progressive loss in bodyweight during the 5-week observation period of between 1.2-1.4 kg. The body weight of the two remaining dogs was generally unaffected." Refer also to appended p. 1.

3. Food consumption:

   From p. 12: "The dogs received 350 g of LABORATORY DIET A... an expanded dry diet, at approximately 10:00 am daily..." From p. 13: "Food residues were recorded daily prior to giving the next meal and any residual food discarded..."

   Results:

   From p. 15: "Food consumption was unaffected in this study." However, no quantitative data are provided in the report.

4. Coagulation times:

   From p. 13: "Jugular vein blood samples were taken from all animals before dosing, 24 hours after dosing and at regular intervals during the observation period."

   "At each time-point, 2 ml of blood was taken into tubes containing 0.11M trisodium citrate as anticoagulant, and prothrombin time and kaolin-cephalin time were measured to monitor the extent of the anticoagulant effect. The latter was performed only as a back-up to the prothrombin time."

Results: From p. 15: "All animals showed prolonged prothrombin times within 2 days of dosing with brodifacoum, and vitamin K_1 therapy was necessary in all animals by the third day of the observation period. The increases in prothrombin time were controlled by administration of vitamin K_1, although this was necessary for 3-4 weeks before normal haemostasis was restored."

Refer to appended pages 2 and 3 for data as to individual prothrombin times and when vitamin K_1 was administered.

5. Terminal investigations:

From p. 14: "On completion of the observation period, all dogs were killed with an overdose of sodium pentobarbitone... given intravenously, but not exsanguinated. The thoracic and abdominal cavities were opened and their contents examined. The liver of each animal was removed, weighed (without the gall bladder) and frozen whole for analysis of tissue residue of brodifacoum..."

Results: Refer to appended page 4 for terminal liver weights, and brodifacoum residues (expressed in terms of mg/kg liver). From the data in appended p. 4, calculations can be made as to the total amounts of brodifacoum which were present in individual livers at termination:

	Terminal Liver weight (g)	Brodifacoum residue (mg/kg liver)	Total amount of Brodifacoum in liver (mg)
#1	416	1.29	0.537
#2	340	1.32	0.449
#3	339	1.23	0.417
#4	491	1.37	0.673

From the body weight data, calculations can be made as to the total initial dosage of brodifacoum that each animal received and the amount present in the livers as a percentage of the initial dosage:

	Initial body weight (kg)	Total dosage Brodifacoum (mg)	Brodifacoum in liver as % of initial dose
#1	14.2	71	0.76
#2	13.0	65	0.69
#3	10.8	54	0.77
#4	15.9	79.5	0.85

If the oral LD_{50} for brodifacoum in dogs is 1 mg/kg (the information that the Agency has received indicates that it is between 0.25 and 1 mg/kg) then the dogs at 35 days still had a level of brodifacoum within their livers equal to 3.45-4.25% of the oral LD_{50} dose.

D. DISCUSSION:

Each dog in a group of 4 male beagles received a single oral dose of 5 mg/kg brodifacoum. Prothrombin times were then monitored over a period of 5 weeks. "Doses of 2 mg/kg vitamin K_1 were administered to dogs by the intra-muscular route whenever their prothrombin times were elevated to levels consistent with a life-threatening effect on coagulation." Individual dogs required 12-15 vitamin K_1 treatments in the period from days 2 to 29 post-dosing.

From previous information received by the Agency, the acute oral LD_{50} in dogs for brodifacoum is between 0.25 and 1.0 mg/kg. All four dogs survived to the end of this study (5 weeks after the test material was administered), although there were weight losses in 3/4 of the animals.

It is concluded that the vitamin K_1 treatments were effective in preventing mortality which would have resulted from spontaneous hemorrhaging in these animals, and that the findings of this study are in agreement with previous material received by the Agency (several studies in Acc. No. 251781, reviewed in document 003568; also a study - MRID and/or Acc. No. unavailable - conducted by Bio/Dynamics, and reviewed by S. Biscardi, document 003742, dated July 7, 1981). It is noted that the statement is made in a memorandum (document no. 003568) dated February 1, 1984 that: "the pharmacological effect of warfarin by inhibiting vitamin K_1 epoxide reductase appears similar for brodifacoum, acenocoumarol and difenacoum."

However, while vitamin K_1 has been shown to be antidotal, there remains the possibility of incidents involving pets or small children in which it is not known or realized that ingestion of brodifacoum has occurred and for which treatment would be delayed; this remains a concern to the Agency. Also, the findings of this study indicate that measurable amounts (although apparently insufficient to cause hemorrhagic symptoms) of brodifacoum are still present in the dog liver at 35 days after dosage. Further, two of the four dogs had weight losses of more than 1 kg over the observation period, and the weight losses were continuing to worsen at the end of the study.

Overall, the study is classified as acceptable as an antidotal study. There is no specific guideline data requirement for antidotal studies. However, the findings of this study are part of the toxicological data base for brodifacoum and may be taken into consideration in any regulatory decision the Agency may make regarding this active ingredient.

Page ___ is not included in this copy.

Pages 7 through 10 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

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_____ The product confidential statement of formula.

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