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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

APR 25 1997

MEMORANDUM

SUBJECT: HED Chapter of the Reregistration Eligibility Decision Document (RED) for Brodifacoum (Case No.: none)

FROM: John C. Redden, M.S.
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

THRU: Karen Whitby, Ph.D., Chief
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and
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4/25/97

TO: Lois Rossi, Division Director
Special Review and Reregistration Division (7508W)

Please find attached the Human Health Assessment for the Brodifacoum Reregistration Eligibility Decision Document (RED).

HED recommends that reregistration of brodifacoum be contingent on measures to mitigate risks, especially to children. In addition, HED is requesting a requirement on the label that PCOs wear waterproof gloves when handling this chemical. This would help to prevent accidental oral ingestion and dermal exposure to brodifacoum by occupational workers.

II. EXECUTIVE SUMMARY

HED recommends that reregistration of brodifacoum be contingent on measures to mitigate risks, especially to children. In addition, HED is recommending a requirement on the label that PCOs wear waterproof gloves when handling this chemical. This would help to prevent accidental oral ingestion and dermal exposure to brodifacoum by occupational workers.

HED has identified a variety of possible risk mitigation measures, that may reduce the number and severity of accidental brodifacoum exposures to children and pets.

- Require that all homeowner use products (non RUPs) be sold, distributed, and applied in tamper resistant bait stations. These stations may be disposable or rechargeable. A PCO would have to refill a rechargeable bait station, as homeowners would not have access to loose baits.

- Require that all baits which are not sold and distributed in tamper resistant bait stations be designated restricted use products.

- Require that all RUPs, including loose baits and place packs have labeling specifying that they must be put in tamper resistant bait stations when applied in any residential setting and other areas where children could be present (schools, recreations areas, etc.).

- *It is suggested that the Registration Division develop a less stringent standard for a* bait station (than tamper-resistant bait station) that would decrease the chances that a child would be able to obtain the bait from the station. This would be a less expensive station that would deter a child from obtaining the bait, and would not necessarily be considered "tamper resistant," but would offer some deterrent.

- Require the addition of Bitrex at 10 ppm to all brodifacoum products sold for use in a residential setting. Bitrex may not deter all children from eating bitrex-containing products. Also domestic pets may still consume the products at the recommended concentration of Bitrex. The concentration of Bitrex cannot be raised, because this will deter consumption by rodents. Also, domestic pets (especially dogs) may eat bitrex-containing products at the suggested concentration of 10 ppm. Based on information supplied by various registrants a concentration of bitrex greater than 10 ppm may deter concumption of these products by rodents. If this option is chosen, HED is recommending efficacy studies on the reformulated product. Note a detailed discussion of the Bitrex option can be found in the HED Diphacinone RED Chapter.

- Consider changing the shape, color, and texture of baits to make them less desirable to children or pets. Registrants/manufacturers should be encouraged to

research alternative designs for baits which could reduce child exposures. If this option is chosen, HED is recommending efficacy studies on the formulated product.

- It may be that there are already some existing anticoagulant rodenticide end-use products which, by their packaging, appearance and/or composition, are significantly less attractive to children than other such products. Any information that the Agency could receive from the registrants regarding this possibility could be taken into consideration.

- Require that a dye that stains the mouth, urine and feces of children and domestic pets be in all baits used in a residential setting. This measure will enable a responsible party, the parent, physician or veterinarian by looking at the stool or child's mouth to determine, if ingestion had taken place.

III. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

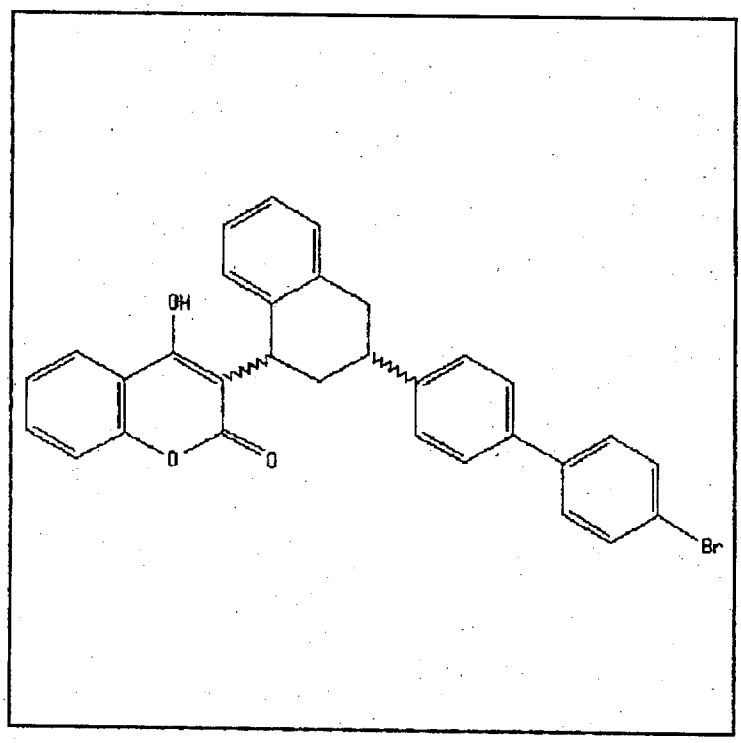
As brodifacoum is a non-food use pesticide, this section will be provided by the Registration Division.

1. Identification of Active Ingredient

Chemical Name: Brodifacoum

PC Code: 112701

Structure



B. Human Risk Assessment

Brodifacoum is an anticoagulant rodenticide with terrestrial and residential non-food uses. The data requirements for this chemical are similar to those of the other anticoagulant rodenticides. At present, the available toxicological database for brodifacoum is adequate and will support reregistration. A 21-day dermal study in rats (Guideline 82-2) is a data gap, and is required as confirmatory data.

1. Hazard Assessment

a. Acute Toxicity

Results of the acute toxicity studies conducted with technical brodifacoum are summarized below in Table 1:

Table 1. Acute Toxicity Values of Technical Brodifacoum.

Route	Species	Results	Toxicity Category
Oral	Rat	LD_{50} (M) = 0.418 mg/kg LD_{50} (F) = 0.561 mg/kg	I
Dermal	Rabbit	LD_{50} (M) = 5.21 mg/kg LD_{50} (F) = 3.16 mg/kg	I
Inhalation	Rat	LC_{50} (M) = 4.86 μg/L LC_{50} (F) = 3.05 μg/L	I
Eye Irritation[a]	Rabbit	Some minor eye irritation, clearing by day 7.	III
Skin Irritation[a]	Rabbit	Unlikely to cause anything more than mild irritation; the high toxicity (note the dermal LD_{50} values above) precludes necessity for testing the technical for dermal irritation potential.	-
Dermal Sensitization[a,b]	Guinea Pig	Non sensitizer	N/A

[a] Not required for TGAI, however, presented here for informational purposes.
[b] Conducted on the 0.25% Brodifacoum Formulation Concentrate; see below.

In an oral LD_{50} study in which technical brodifacoum (96.1%) was administered as a suspension in polyethylene glycol 300 to rats, there were no mortalities or signs of toxicity in males or females at 0.25 mg/kg, nor in males at 0.35 mg/kg (females were not tested at this dose level). However, 5/5 males and 1/5 females died following dosage at 0.5 mg/kg, and 5/5 females died following dosage at 0.75 mg/kg (males were not tested at this dose level). Signs of toxicity at 0.5 and 0.75 mg/kg included pallor, bleeding from the nose and/or rectum and/or other sites. Deaths occurred in the period from 3-8 days after dosing. Post mortem examination of those animals which died or were sacrificed in extremis and/or

showed signs of bleeding revealed the presence of free or clotted blood in the abdominal and/or thoracic cavity. Discoloration or pallor of a number of organs was also observed. These findings are consistent with the known anticoagulant activity of brodifacoum. The LD_{50} is calculated to be 0.418 mg/kg for males (95% confidence interval between 0.35 and 0.5 mg/kg) and 0.561 mg/kg for females (95% confidence interval 0.472-0.667 mg/kg). These results place brodifacoum in Toxicity Category I (MRID 42687501) by the oral exposure route.

In a dermal LD_{50} study with rabbits brodifacoum technical (95.6%) was applied as a suspension in corn oil (500 mg/kg), olive oil (10 mg/kg), or polyethylene glycol 600 (1 mg/kg), with 24-hour occluded dermal exposure. At 500 mg/kg, all the males were euthanized in extremis on days 5-6, and all females between days 5 and 8. At 10 mg/kg, 4/5 males were found dead or were euthanized in extremis between days 7 and 11, and 5/5 females between days 6 and 8. The animals which died or were euthanized showed signs of extreme toxicity consistent with anticoagulant activity (pallor, bleeding/bruising, breathing abnormalities) immediately prior to death. There were practically no signs of skin irritation in any of the animals. The dermal LD_{50} of brodifacoum technical was calculated to be 5.21 mg/kg (95% confidence interval 1.95-13.8 mg/kg) for males, and 3.16 mg/kg (95% c.i. 1.00-10.00 mg/kg) for females. These results place technical brodifacoum in toxicity category I (MRID 42232101) in terms of dermal toxicity potential.

In an inhalation LC_{50} study in rats, groups of young adult Wistar-derived rats, 5/sex, were exposed (nose only) for 4 hours to aerosols of brodifacoum (96.1% a.i.) generated from an acetone solution. The mean particulate concentrations were 0.82, 1.88, or 4.96 μg/L; corresponding brodifacoum concentrations were 0.69, 1.72 or 4.40 μg/L. The mass median diameters were 0.80, 0.89 and 0.68 μm, and the geometric standard deviations were 3.09, 1.91 and 2.54, respectively. Animals were observed for 14 days after exposure. Mortalities (accompanied by symptoms consistent with anti-coagulant activity) occurred on days 4-6 in 3/5 males and 5/5 females exposed to highest concentration (4.96 μg/L). The inhalation LC_{50} for males = 4.86 μg/L (based on particulate concentration), and for females = 3.05 μg/L. Brodifacoum technical (96.1%) is in toxicity category I (inhalation LC_{50} at or below 50 μg/L) based on the LC_{50} values in both sexes (MRID 43110501).

In an eye irritation study in rabbits, aliquots of 100 mg technical brodifacoum (92.5%) were instilled in the conjunctival sac of the left eye in each of 9 New Zealand white rabbits. Three of the rabbit eyes were irrigated for one minute with lukewarm tap water starting 30 seconds after instillation of the test material. In some of the rabbits, there was subsequent iritis and/or slight redness of the conjunctivae with slight chemosis and discharge; with all irritation clearing by day 7. Brodifacoum technical (92.5%) is in toxicity category III in terms of eye irritation potential (MRID 00066938). However, it is noted that because of the high toxicity of brodifacoum, absorption of any significant amount of the technical material by the ocular exposure route might result in mortality (and the animals in this study were followed for only 7 days after exposure). Technical brodifacoum is in toxicity category III in terms of its ocular irritation potential.

There are no dermal irritation studies on technical brodifacoum. Because of the relatively high toxicity, dermal exposure to undiluted (or mixtures containing a relatively high percentage of) technical brodifacoum would probably be fatal (the dermal LD_{50} of brodifacoum technical in rabbits is given above as 5.21 mg/kg for males, and 3.16 mg/kg for females).

Because of the high toxicity of technical brodifacoum, end-use products (mostly containing 0.005% brodifacoum) are usually manufactured from a formulation containing 0.25% brodifacoum. Results of the acute toxicity studies conducted with brodifacoum Formulation Concentrate are summarized below in Table 2:

Table 2. Acute Toxicity Values of Brodifacoum Formulation Concentrate (0.25%)

Route	Species	Results	Toxicity Category
Oral	Rat	LD_{50} (M) = 163 mg/kg LD_{50} (F) = 152 mg/kg	II
Dermal	Rat[a]	LD_{50} (M) > 2000 mg/kg LD_{50} (F) > 2000 mg/kg	III
Skin Irritation	Rabbit	Test material stained the skin pink at application site, but no indication of an inflammatory response	IV
Dermal Sensitization	Guinea Pig	Evaluation complicated by pink staining at the application site, but no evidence of a sensitization response.	N/A

[a]Study conducted with rats; however, rabbits may be a more sensitive species

In an acute oral toxicity study (MRID No. 44021701), groups of fasted, young Alpk:APfSD (Wistar-derived) rats, 5/sex were given a single oral dose of brodifacoum Formulation Concentrate (active ingredient: brodifacoum: label declaration 0.25%; analytical concentration 0.259%) in deionized water at doses of 50, 200, or 500 mg/kg (males), and doses of 100, 150 or 200 mg/kg (females), and were subsequently observed for 14 days.

LD_{50} Males = 163 (95% C.I.: 97-275) mg/kg
Females = 152 (95% C.I.: 132-175) mg/kg
Combined = not reported

Brodifacoum Formulation Concentrate (0.25%) is in TOXICITY CATEGORY II based on the oral LD_{50} in both sexes.

Animals which died or subsequently showed symptoms were generally normal through day 4; symptoms (decreased activity, pallor, piloerection, stains around nose) in some animals were observed only on the day of (or the day before) death. Some rats which were found dead had shown no previous signs of toxicity. Mortalities occurred 4-7 days after dosing. Necropsy findings in rats which died included pallor of the kidney, liver, lung, pancreas and spleen, and clotted and/or free blood in the thymus and/or thoracic cavity, consistent with the anticoagulant activity of brodifacoum. There were no consistent effects on body weight.

In an acute dermal toxicity study (MRID No. 44021702), a group of five male and two groups each with five female young adult Alpk:APfSD (Wistar-derived) rats received a single 24-hour occluded dermal exposure to 2000 mg/kg undiluted brodifacoum formulation Concentrate (active ingredient: brodifacoum: label declaration 0.25%; analytical concentration 0.259%). At 24 hours the application site was cleansed with cotton swabs. In order to prevent ingestion of any residual material, rats were fitted with collars which were kept in place until day 4 for the males and first group of females, and throughout the observation period for the second group of females. The animals were observed for 14 days following removal of the occlusive dressings. 1/5 males and 2/10 females died on days 7-9 with symptoms consistent with anticoagulant activity; one of the dead females was reported to have chewed and partly removed the dressing.

Dermal LD_{50} Males > 2000 mg/kg
Females > 2000 mg/kg
Combined > 2000 mg/kg

Brodifacoum formulation concentrate (0.25%) is in TOXICITY CATEGORY III in terms of dermal toxicity potential, based on the dermal LD_{50} values in both sexes. It is noted that this study was conducted with rats, which may be a less sensitive species than rabbits, which are usually used in dermal toxicity studies.

Among the survivors, one female showed bruising at the application site on days 10-15. Necropsy findings (pallor of the brain, liver, lung, pancreas and/or spleen) for animals which were euthanized in extremis were consistent with anti-coagulant activity of brodifacoum. Survivors all gained weight.

In a primary dermal irritation study (MRID No. 44021703), a group of six female young adult rabbits (New Zealand white), weights ranging from 3940-4290 g, each received a single 4-hour occluded dermal exposure to 0.5 ml of undiluted brodifacoum formulation concentrate (0.25% a.i.), with scoring for dermal irritation within the first hour after removal of the occlusive wrap, and at 1, 2 and 3 days. There was slight edema only in one rabbit, and that was within one hour following exposure, but the test material stained the skin pink at the application sites, preventing full assessment of erythema. However, subsequent histopathological examination of application and unexposed skin sites showed no indications of an inflammatory response associated with exposure to the test material.

Brodifacoum formulation concentrate (0.25%) is in TOXICITY CATEGORY IV in terms of dermal irritation potential, based on the lack of any significant irritation (slight edema observed in only one animal within one hour following exposure, and lack of inflammatory response observed in histopathological examination.

In a dermal sensitization study (MRID 44021704) with brodifacoum formulation concentrate (0.25% a.i.), administered at challenge undiluted and as 30% and 10% w/v suspensions in deionized water, young adult Crl:(HA)BR male guinea pigs were tested using the method of Buehler.

There were no indications of a sensitization reaction, although evaluation was complicated by pink staining at the application sites. Skin samples were examined histopathologically, with no indications of a significant inflammatory response. In this study, brodifacoum formulation concentrate (0.25% a.i.) is not a dermal sensitizer.

b. Subchronic Toxicity

The Agency has no record that any subchronic toxicity studies on brodifacoum have been received and/or reviewed; however, it is noted that there are a number of multiple-dose studies that the Agency has received (including a special study (Brodifacoum: Blood Kinetics Study in the Pregnant Rat, MRID 42641902, see below), that include prothrombin time measurements which appear to be the most sensitive indicator of toxicity for the anticoagulants.

Because of the potential for non-purposeful dermal exposure, and to more accurately assess the margins of exposure associated with potential incidental exposure, a 21-day dermal toxicity study, (Guideline 82-2) is required (as confirmatory data; however, the current toxicological data base is sufficient for the purposes of this RED). **Such a study should include prothrombin and activated partial thromboplastin time measurements, including pre-exposure, as well as on days 7, 14 and 21 of exposure.**

c. Chronic Toxicity/Carcinogenicity

There are no chronic toxicity and/or carcinogenicity studies on brodifacoum. Given the exclusively non-food uses (and the negative findings in the mutagenicity studies), no chronic and/or carcinogenicity studies are required.

d. Developmental Toxicity

In a developmental toxicity study (MRID 00052443, with additional data in MRID 40307202) brodifacoum (92.5%) was administered to 30 Alderley Park, Wistar-derived

mated female rats/dose level by gavage in 10% v/v ethanol:water at dose levels of 0 (vehicle only), 0.001, 0.01 or 0.02 mg/kg/day from days 6 through 15 of gestation.

There was blood in the uteri of one 0.01 and three 0.02 mg/kg females. This was considered to be possibly related to the administration of brodifacoum. There were no indications of any dose-related developmental effects associated with exposure to brodifacoum at doses up to and including 0.02 mg/kg/day. The dose level of 0.02 mg/kg/day is considered adequate, based on the occurrence of 100% mortality at a nominal value of 0.05 (analytical value of 0.35) mg/kg/day in a preliminary study, and blood measurements in a special study (Brodifacoum: Blood Kinetics Study in the Pregnant Rat, MRID 42641902, see below).

The rat maternal toxicity NOEL is 0.001 mg brodifacoum/kg/day (based on the equivocal finding of blood in the uteri of one 0.01 and three 0.02 mg/kg females).

The rat developmental NOEL is 0.02 mg brodifacoum/kg/day (HDT).

This developmental toxicity study in the rat is classified as Acceptable (Guideline) (83-3a), and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3(a)) in the rat.

In a special study (MRID 42641902) mixtures of unlabeled brodifacoum (98.7%) and radiolabelled brodifacoum (radiochemical purity >95%) were administered to Alderley Park, Wistar-derived mated female rats by gavage at nominal doses of 0.0125 mg/kg (Group A: 24 rats, starting on day 1 of gestation, with sacrifice by exsanguination of 3 rats on days 1, 3, 5, 7, 9, 11, 13, 16) or 0.02 mg/kg (Group B: 15 rats, starting on day 7, with sacrifice of 3 rats on days 7, 9, 11, 13 and 16). The test material was administered as a suspension in polyethylene glycol 600. Terminal blood samples were analyzed for brodifacoum levels.

The following mean ng equivalents of brodifacoum/gram of maternal blood were observed: Group A (0.0125 mg/kg/day, days 0-16): day 1: 0.560; day 3: 0.924; day 5: 1.556; day 7: 1.809; day 9: 2.015; day 11: 2.795; day 13: 2.168; day 16: 3.396. Group B (0.02 mg/kg/day, days 7-16): day 7: 0.691; day 9: 1.362; day 11: 3.087; day 13: 2.427; day 16: 4.488.

The relative proportions of mean blood brodifacoum levels in group B rats as compared to group A rats were the following: Day 7: 0.382; Day 9: 0.666; Day 11: 1.10; Day 13: 1.12; and Day 16: 1.32.

In this study there was a steady increase of blood brodifacoum levels with continued dosage of both 0.0125 mg/kg/day and 0.02 mg/kg/day, consistent with findings of a previously reviewed metabolism study (MRID 00080235), in which three rats given a single oral dose of 0.25 mg labeled brodifacoum still retained a mean of 77.73% of the initial dose (mean total label recovery was 91.51%) after 10 days. The combination of

high toxicity and body accumulation of brodifacoum would have eventually resulted in mortalities at these dosage levels at some time after 16 days.

The study is classified as Acceptable (Nonguideline) as it is not a required guideline study. It is acceptable for the purposes for which it was intended as a special study, and the findings adequately justify the dosing schedule and doses used in the rat developmental toxicity study (MRID 00052443 and 40307202; summarization in MRID 92195013).

In a developmental toxicity study in rabbits (MRIDs 00052442 and 40307201) brodifacoum (92.5%) was administered to 15 mated female Dutch rabbits/dose level by gavage in 5% v/v ethanol:water at dose levels of 0 (0.5% v/v aqueous Tween 80), 0 (5% v/v aqueous ethanol, the vehicle used with brodifacoum), 0.001, 0.002 or 0.005 mg brodifacoum/kg/day from days 6 through 18 of gestation.

Ten of the 15 rabbits receiving 0.005 mg/kg/day died or were humanely euthanized; all were found to have internal hemorrhage. Nine of these does had loss of blood (in some cases heavy) from the vagina. All of the implants of one doe (#47; euthanized on day 16) in the 0.005 mg/kg/day group are reported to have had a hemorrhagic appearance, but otherwise there were no indications of any dose-related developmental or toxic effects associated with exposure to brodifacoum at doses up to and including 0.005 mg/kg/day. Because only three litters (and only 20 fetuses) were available from the 0.005 mg/kg/day group at 29 days (and taking into consideration the hemorrhagic appearance of the implants of #46), the NOEL for fetal toxicity is 0.002 mg/kg/day, and the LOEL is 0.005 mg/kg/day. The only possible indication of toxicity in the 0.002 mg/kg/day does was the occurrence of a small hemorrhage beneath the lid of one eye on gestation day 14 in one rabbit (#44) which was not pregnant, but a similar finding was not reported for the 0.005 mg/kg/day females.

In addition, the prothrombin time was significantly increased at 0.005 mg/kg/day on day 20 relative to controls (to 26.5 [seconds?] from 14.5) in a preliminary range-finding study.

The following table shows the prothrombin time measurements (presumably in seconds) on day 20 in a preliminary range-finding study.

Table 3. Prothrombin Time in the Preliminary Developmental Toxicity Range-Finding Study in the Rabbit (Day 20)

	Control	0.001 mg/kg/day	0.005 mg/kg/day
Mean	14.5	17.4	26.5**
SD	2.0	-	5.1

No. of samples	4	1	3

** Statistically significant at the 1% level (Student's t-test) compared with the control group

Data extracted from appendix 1 of MRID 00052442 (p. 31)

The rabbit maternal NOEL is 0.002 mg brodifacoum/kg/day. The LOEL is 0.005 mg/kg/day (based on 75% mortality associated with hemorrhage in pregnant females at this dose level). The developmental toxicity NOEL is 0.002 mg/kg/day, as only 3 litters (with a total of 20 fetuses) were available for evaluation at 0.005 mg/kg/day), and it is reported that all of the implants from a 0.005 mg/kg/day doe which was euthanized on day 16 had a hemorrhagic appearance.

This developmental toxicity study in rabbits is classified as Acceptable (Guideline) (83-3b).

e. Reproductive Toxicity

A 2-generation reproduction toxicity study is not required for brodifacoum as there are no food uses associated with this active ingredient, and there would not be any significant (in terms of frequency, magnitude, or duration) human exposure associated with its uses.

f. Mutagenicity

In a Salmonella typhimurium (Ames) assay which was conducted with and without metabolic activation (S9 from rat liver) in replicate studies, doses ranged from 1.6 - 5000 μg/plate in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538. Additional testing was carried out using a dose range of 0.064 - 200 μg/plate with and without S9 in strains TA1538 and TA100. The test material was delivered to the test system in dimethyl sulfoxide. Compound insolubility was seen at 5000 μg/plate +/- S9. Cytotoxicity was observed for the majority of the strains at ≥40 μg/plate -S9 and ≥1000 μg/plate +S9.

In the first trial, there was a 14.6x increase in revertants (relative to the mean control value) for strain TA1538 at the highest dose level (5000 μg/plate, with precipitation of the test material) -S9; however, replicate plating indicated these colonies were not protrophic mutants and an increased incidence of revertants in this strain and at this dose level was not observed in the second trial. **It is concluded then that there was no evidence that brodifacoum induced a mutagenic response in any strain at any nonactivated or S9-activated dose level.** This study (MRID 41563301) satisfies the Guideline requirement (84-2) for a Salmonella typhimurium (Ames) reverse mutation assay.

In a mouse micronucleus assay (MRID 41563302), groups of five male and five female C57BL/6J mice received single intraperitoneal injections of 0.187 or 0.30 mg/kg brodifacoum (96%) in corn oil; these doses represented 50 and 80% of the 7-day median lethal dose respectively. Mice were sacrificed at 24, 48 and 72 hours postadministration and harvested bone marrow cells were examined for the incidence of micronucleated polychromatic erythrocytes (MPEs).

No deaths or other signs of toxicity were reported, and there was no evidence of target cell cytotoxicity; however, 70% of the mice administered 0.5 mg/kg in a preliminary study died. The positive control induced the expected high yield of MPEs in males and females. **Brodifacoum did not induce a clastogenic and/or aneugenic effect in either sex at any dose or sacrifice time.** This study (MRID 41563302) satisfies Guideline requirements (84-2) for an in vivo chromosomal aberration assay.

The two studies cited above (MRID 41563301 and 41563302) satisfy the mutagenicity data requirements for an anticoagulant. Overall, these results indicate brodifacoum has little, if any, genotoxic activity.

g. Metabolism

In the first part of a metabolism study (MRID 44021705) brodifacoum, 3-[3-(4'-bromo-[1,1'-biphenyl]-4-yl)-1,2,3,4-tetrahydro-1-naphthalenyl]-4-hydroxy-2H-1-benzopyran-2-one, radiochemical purity >98%, radiolabelled (^{14}C) in the benzene ring of the benzopyran, was administered to 3 previously bile-duct cannulated Crl:CD(SD)BR strain male rats as a single oral administration at a nominal dose level of 10 mg/kg body weight, well above the LD_{50} value of 0.3 mg/kg. The rats had been predosed with vitamin K_1 in their drinking water, but showed symptoms of anticoagulant toxicity before sacrifice at 48 hours. Bile, urine and feces were collected at pre-dose, 6, 12, 24, and 48 hr post-dose, and radioactivity was determined in these samples, as well as in the livers and residual carcasses. The metabolite profiles of ^{14}C-brodifacoum in bile and bile extracts were examined by chromatographic and spectroscopic techniques.

Total mean recovery of radioactivity was 102.9 ± 8.1%. Recovery from feces (presumably unabsorbed brodifacoum) was 36.11 ± 8.83%; from liver was 14.79 ± 0.41; from the residual carcass: 42.85 ± 5.06%. The mean from bile (all 3 animals) was 6.40 ± 5.45%, but one rat had poor bile flow, possibly from blockage in the cannula; the two remaining animals had a mean 9.53% of the label in bile.

The major (and only identified) metabolite of brodifacoum in bile was the glucuronide (attachment to the 4-hydroxy moiety of brodifacoum), which accounted for 39.43 to 77.28% of the total radioactivity in individual bile samples, while brodifacoum represented 0.00 to 24.95% of the total activity. Further characterization appeared to split the glucuronide peak into 2 components, and while the cis:trans ratio of parent material was 70:30, the ratio in the

glucuronide was reversed (30:70). One unidentified metabolite (region 10) ranged from 1.59 to 21.7% total radiolabel.

Although only one metabolite (the glucuronide) is identified, it is the parent compound which is of toxicological concern, and the registrant has adequately demonstrated in previously submitted studies (refer to MRIDs 00080235 and 42007502) that a high proportion of unmetabolized compound is retained, particularly in the liver.

In a second study (*in vitro* perfusion, also in MRID 44021705) the lower vena cava of a single male rat was ligated; the hepatic portal vein was then cannulated and the liver was cleared of blood and the bile duct cannulated. The liver was perfused, and, after equilibration, ^{14}C-brodifacoum, at a dose of 10 mg/kg, was added to the main perfusate reservoir; bile and perfusate were collected at pre-dose, 1 minute (perfusate only), 1, 2, 3, 4 and 6 hr post-dose. The radioactivity present in bile, perfusate, terminal perfusate supernatant, supernatant filtrate and liver was determined. There was 74.32% recovery after 6 hours, with 59% of the total in perfusate, and 15.19% in liver. Metabolite profiling was attempted, but no metabolites were identified. All radioactivity in the perfusate supernatant was bound to perfusate proteins, with no activity being measured in the aqueous filtrate.

In a metabolism study (MRID 42007502) groups of male rats received single oral doses of ^{14}C-labeled brodifacoum at different dose levels (Group 2: 0.02 mg/kg; Group 3: 0.15 mg/kg; Group 4: 0.35 mg/kg), and blood was taken from 1-3 rats/group at various intervals following this dosage. The following Kaolin Cephalin Time (KCT) and Prothrombin Time (PT) measurements were made:

Table 4. Kaolin Cephalin and Prothrombin Time in a Metabolism Study in Male Rats

	Group 2 0.02 mg/kg		Group 3 0.15 mg/kg		Group 4 0.35 mg/kg	
	Clotting times (seconds)		Clotting times (seconds)		Clotting times (seconds)	
Time after Dosing	KCT	PT	KCT	PT	KCT	PT
6 hr	-	-	-	-	ND	14.3 ± 1.7
12 hr	-	-	-	-	ND	20.7 ± 3.7
18 hr	-	-	-	-	43.7 ± 2.1	37.2 ± 5.4
24 hr	14.9[a] ±4.2	13.0[a] ±1.8	15.8 ± 4.8	13.0 ± 1.1	58.9 ± 7.6	95.5 ± 2.7
48 hr	-	-	-	-	113.7±10.6	147.6± 6.9
72 hr	-	-	-	-	92.8 ±49.4	39.7 ±19.4
96 hr	-	-	-	-	32.3 ± 7.2	18.8 ± 2.0
Day 8	-	-	-	-	21.3[a]± 2.4	15.8[a]± 1.2
Day 14	-	-	14.0 ± 1.1	14.3 ± 0.2	15.4 ± 4.5	17.4 ± 0.5
Day 28	14.9[a] ±1.1	12.7[a] ±0.3	21.3 ± 2.9	13.6 ± 0.6	20.2 ± 2.9	13.4 ± 0.4
Day 56	-	-	16.2[a]± 2.4	12.7[a]± 0.6	19.6[a]± 2.2	13.3[a]± 0.2
Day 84	-	-	-	-	17.2 ± 2.9	12.5 ± 0.4
Week 13	14.1[a] ±1.1	15.4[a] ±0.6	16.5 ± 1.4	13.8 ± 0.2	-	-
Week 26	-	-	12.3*	16.1*	-	-
Week 39	16.6 ± 4.3	13.5 ± 1.2	15.0 ± 1.7	13.8 ± 0.5	-	-
Week 52	-	-	15.6 ± 6.2	12.7 ± 1.2	-	-
Week 65	16.7 ± 3.3	13.5 ± 0.8	18.0 ± 3.2	13.2 ± 0.5	-	-
Week 78	-	-	18.6 ± 1.3	12.8 ± 1.2	-	-
Week 91	16.8 ± 2.0	14.6 ± 0.4	19.8 ± 2.2	15.1 ± 1.5	-	-
Week 104	14.7 ± 3.0	11.1 ± 1.0	13.2 ± 0.5	10.9 ± 0.6	-	-

The standard deviation (SD) is derived from data obtained with 3 animals per group.
* = single value only.
a = 2 values only
ND = not determined
Table taken from p. 26 of MRID 42007502.

The results given above clearly show an increase in clotting time in rats which had received a single oral dose of 0.35 mg/kg. Assuming the effect was manifested as a doubling of the normal clotting time (to approximately 30 seconds for kaolin cephalin and/or prothrombin times), effects were evident as soon as 18 hours after dosage, and were still present at 96 hours post-dosage.

In addition, the metabolism study in MRID 42007502 demonstrates that considerable amounts of the radiolabel are retained in the liver following dosage.

Table 5: Percentage of radioactivity retained in the liver following single-dose administration of ^{14}C Brodifacoum

Time after dosing	Group 2 (0.02 mg/kg) Mean SD	Group 3 (0.15 mg/kg) Mean SD	Group 4 (0.35 mg/kg) Mean SD
Day 1	47.33 ± 10.87	29.71 ± 4.40	28.92 ± 1.79
Week 4	39.16 ± 3.50	37.07 ± 1.94	23.47 ± 1.21
Week 8	-	30.86 ± 4.23	23.00 ± 0.09
Week 12	-	-	21.24 ± 3.19
Week 13	34.01 ± 2.49	31.74 ± 5.13	-
Week 39	20.33 ± 0.42	22.02 ± 2.83	-
Week 65	15.97 ± 2.33	15.36 ± 3.03	-
Week 91	10.57 ± 1.08	12.39 ± 3.08	-
Week 104	11.78 ± 0.97	11.74 ± 1.64	-

Table from data on pages 30-32 of MRID 42007502.

It is concluded that overall there is sufficient metabolism data (including excretion, distribution, retention half-life and amounts retained within different organs). This metabolism study in the rat then, when taken with previously submitted metabolism studies (in MRIDs 00080235 and 42007502) is classified as acceptable; and the combination of these studies is adequate to satisfy the 85-1 data (metabolism study) guideline requirement.

In an antidotal study (MRID 42007501) four male beagle dogs each received a single oral dose of 5 mg/kg brodifacoum (96.8%). Prothrombin times for each of the dogs were then monitored over a period of five 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. All four dogs survived to the end of this study (5 weeks after the test material was administered). However, based on elevations in prothrombin time, vitamin K_1 had to be administered to one dog on day 29; this dog had also been treated with vitamin K_1 on days 23 and 24 as well as on previous occasions, and the last prothrombin time measurement for this dog was on day 34. The possibility exists that this dog would have required additional vitamin K_1 treatments after day 34.

While vitamin K_1 has been shown to be an effective treatment following brodifacoum ingestion, there still remains the possibility of incidents involving pets or small children in which it is not known or realized that ingestion has occurred until it is too late for effective treatment. This possibility remains a concern to the Agency.

Examination of the accepted labels for a number of brodifacoum-containing products indicates that although many include a statement similar to the following: "For Human Cases: Vitamin K_1 is antidotal at doses of 10-20 mg (not mg/kg). Repeated treatments may need to be given for up to 30 days (based on monitoring of prothrombin times)" others specify that: "For human cases, vitamin K_1 is antidotal... Repeated doses may need to be given up to two weeks (based on monitoring of prothrombin times)." Where appropriate, revisions should be made specifying monitoring of prothrombin times for at least 30 days after ingestion (and if prothrombin times are elevated at any point during this period, monitoring should be continued after 30 days).

h. Neurotoxicity

Neurotoxicity studies are not required for anticoagulants. In addition, the available toxicity database does not indicate that brodifacoum is not neurotoxic.

i. Other Toxicological Considerations

None.

2. Dose/Response Assessment

a. Reference Dose (RfD)

The HED Reference Dose (RfD)/Peer Review Committee evaluated the toxicological data on brodifacoum and recommended that no chronic oral RfD be established.

b. Carcinogenic Classification and Risk Quantification

There are no carcinogenicity studies on brodifacoum. Given the exclusively non-food uses (and the negative findings in the mutagenicity studies), no chronic and/or carcinogenicity studies are required. Therefore, a cancer risk assessment is not appropriate.

c. Other Toxicological Endpoints

Since no dermal absorption data are available, 100% dermal absorption for brodifacoum is assumed. The toxicity endpoints for the short- and intermediate-term occupational risk assessments are based on the maternal and developmental toxicity NOEL of

2 μg/kg/day (LOEL = 5 μg/kg/day) observed in a developmental study in rabbits (MRIDs 00052442 and 40307201).

3. Dietary Exposure and Risk Assessment/Characterization

a. Dietary Exposure (Food Sources or Accidental Poisoning)

Brodifacoum is a non-food use pesticide. Therefore, it is unlikely that there will be any exposure to brodifacoum via food sources. However, accidental poisonings are possible.

Although this is a non-food use chemical, an acute dietary risk assessment was recommended because of the high acute oral toxicity (LD_{50} = 0.42 mg/kg) and the severity of the maternal toxicity observed in developmental toxicity studies with rats and rabbits. The Committee decided to use the developmental toxicity study in rabbits since this species was shown to be more sensitive than rats. In recommending this dose/endpoint, the Committee noted that although the deaths may not have been due to a single dose (exposure), this NOEL/endpoint was used because of the lack of a complete data base as well as the severity of the effects seen in this study.

The endpoint for accidental acute dietary poisoning is a maternal NOEL of 0.002 mg/kg/day; at 0.005 mg/kg/day (LOEL) 10 of 15 rabbits died or were sacrificed and all were found to have internal hemorrhage.

b. Dietary Exposure (Drink Water Source)

Brodifacoum is a non-food use pesticide, and the use pattern does not have the potential to result in ground or surface water contaminations (see EFED Chapter).

c. Dietary Risk Assessment and Characterization

Brodifacoum is a non-food use pesticide. Therefore, it is unlikely that there will be any exposure to brodifacoum via food sources.

4. Occupational and Residential Exposure and Risk Assessment/Characterization

a. Occupational and Residential Exposure

i. Summary of Use Patterns and Formulations

Brodifacoum 3-[3-(4-bromo[1,1-biphenyl]4-yl)-1,2,3,4-tetra-hydro-1-napthalenyl]4-hydroxy-2H-1-benzophyran-2-one is a rodent control agent. It is a warfarin-like compound (but more toxic) that acts as an anticoagulant and is formulated as meal bait, paraffinized pellets, rat and mouse bait ready-to-use place packs, and paraffin blocks, cakes, and slabs. All products contain 0.005 percent active ingredient.

Brodifacoum is currently registered for the control of rodents in and around farm structures, households, and domestic dwellings, uncultivated agricultural and nonagricultural areas, commercial transportation facilities, industrial areas, in sewage systems, aircraft, ships, boats, railway cars, and food processing, handling, and storage areas and facilities. Application may be made as frequently as is necessary. Both general use and restricted use brodifacoum products are currently registered.

Baits and bait packs are placed at 15 to 30 foot intervals for rats and 8 to 12 foot intervals for mice. When bait blocks are used in sewage systems, wire is used to secure blocks above the high water mark. The rate of application is 16 ounces of product per 15 foot interval for rats and 2 ounces per 8 to 12 foot interval for mice. According to labels, all baits are to be placed out of the reach of children, pets, domestic animals and nontarget wildlife, or in tamper resistant bait stations. Bait stations must be resistant to destruction by dogs and by children under 6 years of age, and must be used in a manner that prevents children from reaching into bait compartments and obtaining bait. If bait can be shaken from stations when they are lifted, stations must be secured or otherwise immobilized. Baits may be loaded into bait stations by hand (place packs, cakes, blocks, and slabs), or by using a scoop for loose baits (meal baits, grain baits) and pellets.

Occupational-use products and homeowner-use products

At this time some products containing brodifacoum are intended primarily for homeowner use and some are intended primarily for occupational use.

ii. Handler Exposures & Assumptions

HED has determined that there is a potential exposure to applicators or other handlers during typical use-patterns associated with brodifacoum. Specifically, EPA is concerned about potential dermal and inhalation exposures to handlers during the loading and application of brodifacoum.

Based on the use patterns and potential exposures described above, six major handler exposure scenarios were identified for brodifacoum: (1) placing bait packs; (2) loading bait boxes or bait stations with meal bait, grain bait, bait pellets, or other food-based bait from larger containers; (3) breaking paraffinized slabs, cakes, and blocks into pieces and placing the pieces at bait stations; (4) securing large paraffin blocks at bait stations in sewers; (5) applying bait by hand; and (6) applying bait (e.g., pellets) in broadcast treatments using ground equipment.

It is unclear from labels and other available information (1) the extent to which it is necessary, due to size or design of packages, for handlers to directly handle or contact the bait during bait station loading (which may result in dermal exposures) ; or (2) the extent to which it is possible for dusts associated with meal baits, grain baits, or pellets to result in

inhalation exposure to handlers during bait station loading. Although the vapor pressure of brodifacoum is relatively low (9.8×10^{-7} Torr), HED is concerned about potential inhalation of particulates, fine particles and dusts associated with baits which could be inhaled resulting in ingestion/oral exposure.

Calculations of daily exposure to pesticidal active ingredients by handlers are used to assess risk to those handlers. There are no handler exposure data available for the use patterns associated with brodifacoum mixing, loading, and application.

iii. Post-Application Exposures & Assumptions

EPA has determined that there is a potential for exposure to homeowners and others following applications of brodifacoum, particularly in residences. EPA has concerns about possible post-application exposures if (1) baits are not placed out of reach of children or are not placed in tamper-resistant bait stations, as specified in labeling; (2) baits are available to homeowners in packages which are not tamper resistant and could be accessible to children prior to application; and (3) baits are brightly colored or packaged in a way in which they could be appealing to children or mistaken by children for food or candy.

iv. Mixer/Loader/Application Exposure Assessment

There are no exposure data currently available for calculating risks to handlers resulting from exposures to brodifacoum.

v. Post-Application Exposure Assessment

There are no data currently available to address post-application exposure for brodifacoum.

b. Occupational and Residential Risk Assessment/Characterization

i. Risk from Dermal and Inhalation Exposures

There are no exposure data currently available for calculating risks to handlers resulting from exposures to brodifacoum. However, EPA has several concerns about the risks to handlers of brodifacoum products, particularly commercial handlers (1) handling large quantities of product, (2) handling dusty, non-paraffinized products, or (3) applying products by hand. These concerns are based on (1) very high acute toxicity, (2) potentially high dermal absorption, and (3) and absence of exposure data for all scenarios considered.

HED recommends that all labels for occupational-use products require commercial handlers to wear waterproof gloves while handling all brodifacoum formulations that are not

contained in a tamper-resistant bait station or in place packs. This would reduce dermal exposure to brodifacoum and diminish the potential oral exposure that could result from hand-to-mouth transfer. Though no exposure data are available, EPA believes that both tamper-proof bait stations and place packs are options that also greatly reduce the potential for dermal contact with brodifacoum.

In addition, HED recommends that occupational handlers (commercial applicators) wear protective eyewear and a dust/mist respirator when handling non-paraffinized brodifacoum formulations, such as meal or grain-based baits, unless those formulations are contained in tamper-resistant bait stations or place packs. The eyewear and respirator would reduce the possibility of inhalation and ingestion of dusts resulting from the pouring and application of these products and reduce the potential ocular absorption that could result from contact with such dusts.

Because the vapor pressure of brodifacoum is low (9.8×10^{-7} Torr), the potential for risk resulting from inhalation of brodifacoum vapors is not a significant concern despite a very low LC_{50} (4.86 mg/L).[3] However, if fine particles become airborne during the handling of brodifacoum baits and/or tracking powder, individuals may inhale these particles. Because these particles also could potentially be ingested, such exposure would contribute to the individual's risk resulting from accidental ingestion/oral exposure.

ii. Risk From Post-Application Exposures

There are no data currently available to address post-application exposure for brodifacoum. The group most at risk would be children less than 6 years old. Only the following rough calculations are possible.

The dose a 10 kilogram child would receive from a 43 gram place pack of brodifacoum at 0.005% active ingredient is

43 grams X 1000 mg/gram = 43000 mg
43000 mg X .00005 = 2.15 mg technical a.i. in a 43 gram pack
2.15 mg / 10 kg = 0.215 mg/kg
MOE = NOEL / Exposure; NOEL = 0.002 mg/kg
MOE = 0.002 mg/kg / 0.215 mg/kg = 0.009

This exposure would result in a Margin of Exposure of less than 1. Poison specialists conclude that a child in one bite would consume approximately 5 grams. Using 5 grams in the above equation results in a Margin of Exposure that is still less than 1 (0.08).

HED recommends that measures to mitigate these potential risks be considered. HED has identified the following possible risk mitigation measures that, if implemented individually or in combination, would likely reduce the humber and severity of accidental exposures to children and pets.

HED has identified a variety of possible risk mitigation measures, that may reduce the number and severity of accidental brodifacoum exposures to children and pets.

- Require that all homeowner use products (non RUPs) be sold, distributed, and applied in tamper resistant bait stations. These stations may be disposable or rechargeable. A PCO would have to refill a rechargeable bait station, as homeowners would not have access to loose baits.

- Require that all baits which are not sold and distributed in tamper resistant bait stations be designated restricted use products.

- Require that all RUPs, including loose baits and place packs have labeling specifying that they must be put in tamper resistant bait stations when applied in any residential setting and other areas where children could be present (schools, recreations areas, etc.).

- It is suggested that the Registration Division develop a less stringent standard for a bait station that would decrease the chances that a child would be able to obtain the bait from the station. This would be a less expensive station that would deter a child from obtaining the bait, and would not necessarily be considered "tamper resistant," but would offer some deterrent.

- Require the addition of Bitrex at 10 ppm to all brodifacoum products sold for use in a residential setting. Bitrex does not deter all children from eating bitrex laden products. Also domestic pets may still consume the products at the recommended concentration of Bitrex. The concentration of Bitrex cannot be raised, because this will deter consumption by rodents. If this option is chosen, HED is recommending efficacy studies on the formulated product. Note a detailed discussion of the Bitrex option can be found in the HED Diphacinone RED Chapter.

- Consider changing the shape, color, and texture of baits to make them less desirable to children or pets. Registrants/manufacturers should be encouraged to research alternative designs for baits which could reduce child exposures. If this option is chosen, HED is recommending efficacy studies on the formulated product.

- It may be that there are already some existing anticoagulant rodenticide end-use products which, by their packaging, appearance and/or composition, are significantly less attractive to children than other such products. Any information that the Agency could receive from the registrants regarding this possibility could be taken into consideration.

- Require that a dye that stains the mouth, urine and feces of children and domestic pets be in all baits used in a residential setting. This measure will enable a responsible

party, the parent, physician or veterinarian by looking at the stool or child's mouth to determine, if ingestion had taken place.

iii. Restricted Entry Interval

Brodifacoum has no restricted entry interval requirement.

iv. Incident Reports

Young children experience excessive exposures to anticoagulant rodenticides. Based on 13,000 such exposures reported to Poison Control Centers in 1995, the total estimated exposures yearly would be 31,000. An analysis of pesticide ingestion in 1989 in children less than six years of age compared the number of ingestion to the number of containers reported in U.S. homes in 1990. When 83 active ingredients were ranked, the top 5 products responsible for childhood ingestion per 1,000 containers were all anticoagulant rodenticides. Brodifacoum ranked second with 4.2 exposures per 1,000 container. This ratio for brodifacoum was 105 times higher than the median for all pesticides. Table 6 provides a breakdown by age and medical outcome for all long-acting anticoagulant exposures reported to poison Centers from 1985 through 1992. Note that only 54% of all cases received follow-up to determine medical outcome.

TABLE 6: AAPCC data on accidental exposures to long-acting anticoagulants 1985-92 (8 year period). Total exposures = 55,145 (6,893 per year)

Age group (years)	Number	Percent
< 6	52,126	94.5
6-17	984	1.8
> 17	1,659	3.0
Unknown	376	0.7
Total	55,145	100.0

Medical outcome	Number	Percent
None	28,223	94.1
Minor	1,658	5.5
Moderate	85	0.28
Major	15	0.050
Death	1	0.003
Total	29,982	100.0

Minor: Minimal symptoms with no residual disability (e.g., mild gastrointestinal symptoms, skin irritation, drowsiness).

Moderate: Symptoms are more pronounced, prolonged, or more of a systemic nature than minor symptoms with no residual disability. Usually some form of treatment is indicated. Examples include: high fever, disorientation, hypotension which rapidly responds to treatment and isolated brief seizures.

Major: Symptoms are life-threatening or result in residual disability or disfigurement. Examples include patients who require intubation plus mechanical ventilation, who sustain repeated seizures, cardiovascular instability, or coma.

A large percent receive health care treatment, though 99 percent of these exposures experience no or only minor ill effects. Reports in the scientific literature suggest that the amount of health care received is excessive and that most exposures could be treated at home. Typically 37% of rodenticide cases reported to Poison Centers seek treatment in a health care facility compared to only 23% for all pesticides. Based on rough estimates of the cost of health care supplied by the U.S. Consumer Product Safety Commission, the total

emergency health care and related costs from anticoagulant rodenticides is $8.6 million. This compares to an estimated $79 million spent by consumers yearly for rodenticides.

Pets (primarily dogs) exposed to anticoagulants accounted for over 5,000 incidents in 1987 according to the University of Illinois National Animal Poison Control Center. The anticoagulant rodenticides are a cause of serious and costly poisonings in domestic animals, especially dogs. Secondary poisoning through consumption of poisoned rodents is also a concern. Although most of the reports to the NAPCC were for exposure only and clinical signs were not evident, there still may be significant cost to the pet owner in diagnostic tests and monitoring.

Of nontarget animals exposed to commensal rodenticides dog incidents account for more than 80% of the reported cases. Four thousand rodenticide-related inquiries a year (1986-1988) were made to the Illinois Animal Poison Information Center. Asymptomatic exposures of animals may go undetected as pets and livestock generally are not watched as closely as children. For animal exposures reported in 1987, the animal's owner typically was the source of the rodenticide. Most of these exposures were accidental and occurred in or around human residences. It is reasonable to expect that if the pesticide is in or around the residence that children could also be exposed.

HED believes that the number of pet incidents will go down if brodifacoum and other rodenticides are in tamper-resistant bait stations.

Interested parties outside of the Agency have suggested other approaches for insuring better bait protection by nonprofessional users. Many of these suggestions involved reclassification of products and/or special packaging requirements. Therefore, HED is suggesting a number of options which may help prevent unintentional exposure to children and pets.

Table 7 tabulates suicide attempts in adults, from anticoagulant rodenticides that resulted in prolonged prothrombin time and clinical signs of bleeding. HED notes that in most of the cases cited the exposure (mg/kg), is much less than the LD_{50} of diphacinone, but the exposure (mg/kg) is about twenty times greater than the NOEL. The estimated hazardous dose for the superwarfarin-type anticoagulant rodenticides, such as brodifacoum, in humans can be estimated by examining these cases. Intentional ingestion by adults have been reported for brodifacoum, diphenacoum, and chlorphacinone where the actual amount ingested was known (see Table 7). From these ingestions (all in adults) it is possible to estimate the dose that is associated with frank clinical signs (bleeding of gums, nose bleeds, blood in urine, and others) and prolonged prothrombin time. Cases are grouped in Table 7 to show that the estimated low dose to result in confirmed clinical poisoning would range from about 0.11 to 0.36 mg/kg for adults for a number of anticoagulants, including 6 cases involving brodifacoum. Children may be more or less sensitive than adults.

Table 7: Suicide attempts in adults resulting in prolonged prothrombin time and clinical signs of bleeding

lowest reported dose (abstract only, brodifacoum)	0.014 mg/kg (Outlier)
three other low dose cases (3-10 packets, brodifacoum 2 cases, diphenacoum 1 case)	0.11-0.36 mg/kg
Four medium dose cases (4-36 packets, brodifacoum 3 cases, diphenacoum 1 case)	1.07-1.43 mg/kg
High dose case (chlorphacinone)	8.93 mg/kg

1) Data are from the open literature (see References).
2) HED has assumed each adult weighs 70 kg.

Poisoning specialists estimate the risks to children by assuming a one year old child weighing 10 kg would get one swallow (approximately 5 grams). This provides an estimated dose of 500 mg/kg. For brodifacoum and other anticoagulants formulated at 0.005% active ingredients, the dose would be 0.025 mg/kg. Therefore, the margin of exposure from the lowest dose causing clinical effects in adults (0.1 mg/kg) to the dose of a child consumed one swallow (0.1/0.025) would be 4 (see Table 7 above). Available evidence indicates that most accidents are related to improper use rather than to improper storage and that accidents of both types are preventable.

The Agency has concluded that the large numbers of exposure incidents provide evidence that current policies for promoting bait protection have not been sufficient and, therefore, that tougher, more explicit policies are needed.

According to available information, pest control operators traditionally used stations of the sorts which the Agency has previously described as "inadequate." These include weak stations made of cardboard or thin plastic, and sturdier stations which do not inhibit spillage or reach-in access to baits.

Nonprofessional users (i.e., the "general public") often apply baits in open containers or in ready-to-use, non-protective, packaging. Bait stations typically are not offered for sale at the outlets where nonprofessional users buy rodenticides. Attempts to market ready-to-use (bait-filled) protective rodenticide bait stations to the general public have not been reported as commercially successful ventures. Ready-to-use bait stations that have been tested generally have been found not to be completely "tamper-resistant". Improvements to such units probably would add to their retail prices and put them at further competitive disadvantages relative to baits sold "loose," in cardboard boxes, or in plastic placepacks.

Adding bittering agents to rodenticides should be considered to prevent children from making repeated ingestion. Use of a dye on the bait that leaves a noticeable color on the tongue would assist caretakers to find out whether a child found with a rat bait actually

ingested some of the bait. A variety of other changes in packaging design (shape, color, texture) might affect the attractiveness of these products to children and pets. Manufacturers should be encouraged to test new designs that could significantly reduce their products attractiveness to children. These three steps should be considered to reduce the need for expensive health care and reduce the likelihood of ingesting a toxic dose.

40 CFR § 152.170 Criteria for restriction to use by certified applicators states: "...when used in accordance with label directions, or widespread and commonly recognized practice, the pesticide may cause significant subchronic, chronic or delayed toxic effects on man as a result of single or multiple exposures to the product ingredients or residues."

HED believes that requiring, as one potential option, "tamper-resistant bait stations" would be consistent with 40 CFR § 157.22 Criteria for Child-Resistant Packaging which states:

> "(6) The pesticide or device has such characteristics that, based upon human toxicological data, use history, accident data or such other evidence as is available, the Agency determines there is serious hazard of accidental injury or illness which child-resistant packaging could reduce: and (b) Use criterion. The product's labeling either directly recommends residential use or reasonably can be interpreted to permit residential use."

v. Data Requirements

Handler Studies

Handler exposure studies are not required at this time, but may be required pending the outcome of discussions between EPA and the registrant.

Post-Application Studies

Post-application exposure studies are not required at this time, but may be required pending the outcome of discussions between EPA and the registrant.

IV. RISK MANAGEMENT AND REREGISTRATION DECISION

deferred pending risk management decisions by SRRD.

V. ACTIONS REQUIRED BY REGISTRANTS

deferred pending risk management decisions by SRRD.