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No. 88

BROMADIOLONE

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CLASSIFICATION:

Primary use: Rodenticide

Secondary use: None

Chemical group: Coumarin

1.0 GENERAL INFORMATION

1.1 **COMMON NAME:** bromadiolone (BSI, E-ISO, F-ISO); broprodifacoum (Republic of South Africa).

1.1.1 **Identity:**

IUPAC name: 3-[3-(4'-bromobiphenyl-4-yl)-3-hydroxy-1-phenylpropyl]-4-hydroxycoumarin.

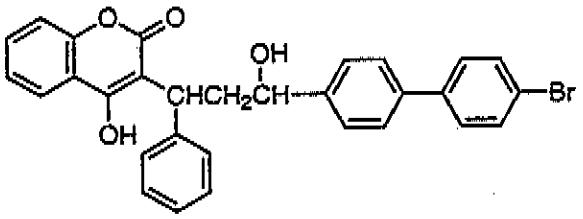
CAS name: 3-[3-[4'-bromo(1,1'-biphenyl)-4-yl]-3-hydroxy-1-phenylpropyl]-4-hydroxy-2-*H*-1-benzopyran-2-one.

CAS registry number: 28772-56-7.

Molecular formula: $C_{30}H_{23}BrO_4$

Relative molecular mass: 527.4

Structural Formula:



Synonyms and trade names: Apobas; Bromard; Bromatrol; Bromone [R]; Bromorat; Canadien 2000[R]; Contrac [R]; Contrax [R]; Deadline; Hurex; Lanirat; LM 637; Maki[R]; Morfaron; Musal; Ramortal; Ratimon; Ratimus [R]; Rodine-C; Slaymor; Super-Caid [R]; Sup'operats [R]; Termus; Topidon.

1.2 **SYNOPSIS:** Bromadiolone is very toxic for all mammalians. A single dose may cause death in rodent species. The anticoagulant effect can be successfully countered by vitamin K_1 administration.

1.3 SELECTED PROPERTIES

1.3.1 **Physical characteristics**: The technical material (97% pure) is an odourless, yellow-white powder. A mixture of the two diastereoisomers melts at 200 - 210 °C.

Solubility (at 20 °C):

19	mg/litre water
8.2	g/litre ethanol
10	g/litre acetone
25	g/litre ethyl acetate
750	g/litre dimethylformamide

1.3.2 **Stability**: Stable under recommended application and storage conditions. Stable below 200 °C.

1.3.3 **Vapour pressure**: Negligible (0.002 mPa at 20 °C).

1.4 AGRICULTURE, HORTICULTURE AND FORESTRY

1.4.1 **Common formulations**: Available as baits, concentrates, tracking powders and in paraffin blocks. Formulations include dusts (0.1%), solutions (0.25%), pellets, particulates and solids (0.005%). Also available is a mixed formulation with sulphaquinoxaline.

1.4.2 **Pests controlled**: Rats and mice, including those resistant to first generation anticoagulants.

1.4.3 **Use pattern**: To be used in tamper-proof baited traps filled with sufficient fresh bait to provide an uninterrupted supply for 10-15 days. Concentrated products should be diluted with bait material as directed by the manufacturer. May be used in permanent bait stations or used periodically. May be used outdoors, in non-food storage areas and in food processing plants, but only where food or feeds, their handling equipment or packaging materials are never open or exposed.

1.4.4 **Unintended effects**: Poultry are sensitive to this rodenticide. Failure to adhere to manufacturers' recommendations or careless placement and design of traps may allow poisoning of non-target species, primary through consumption of bait and secondary through consumption of poisoned rodents.

1.5 PUBLIC HEALTH PROGRAMMES

1.5.1 **Common formulations**: See Section 1.4.1.

1.6 HOUSEHOLD USE

1.6.1 **Common formulations**: Available as 0.005% formulations pre-mixed with baits in pellet and particulate form and in solid formulations.

1.6.2 **Susceptible pests**: Mice and rats.

1.6.3 **Use pattern**: According to manufacturers' instructions on evidence of infestation.

1.6.4 **Unintended effects**: Poisoning of pets and other non-target species is possible if baits are not used or placed as recommended.

2.0 TOXICOLOGY AND RISKS

2.1 TOXICOLOGY - MAMMALS

2.1.1 **Absorption route**: Absorbed from the gastrointestinal tract, from intact skin, and the respiratory system.

2.1.2 **Mode of action**: Bromadiolone is vitamin K antagonist. The main site of its action is the liver, where several of the blood coagulation precursors under vitamin K dependent post translation processing take place before they are converted into the respective procoagulant zymogens. The point of action appears to be the inhibition of K_1 epoxide reductase.

2.1.3 **Excretion products**: The major route of elimination in different species after oral administration is through the faeces. The liver is the main organ of accumulation. Bromadiolone has been found in the liver as an unchanged parent compound. Elimination from the liver is biphasic with an initial rapid phase of 2-8 days and a slower phase with half-life of 170 days.

2.1.4 **Toxicity, single dose:**

Oral LD_{50}

Rat	1.1 mg/kg b.w.
Mouse	1.8 mg/kg b.w.
Rabbit	1 mg/kg b.w.
Dog	> 10 mg/kg b.w. (MTD)
Cat	> 25 mg/kg b.w. (MTD)

Dermal LD_{50}

Rabbit	9.4 mg/kg b.w.

Death due to multiple internal haemorrhages were observed four days or more following administration of a lethal dose to rats, mice and rabbits.

In rabbits an oral dose of 0.1 mg/kg b.w. resulted in an 80% depression of prothrombin activity within three days of administration.

Bromadiolone is non-irritant to the skin and a slight irritant to the eye.

2.1.5 **Toxicity, repeated dose:**

The five-day oral LD_{50} for SD Norway rat was reported to be 0.12 mg/kg b.w./day and 0.07 mg/kg b.w./day for wild strain.

In rabbits, oral administration of 0.05 mg/kg b.w./day for three weeks maintained prothrombin activity at 20% of the pretreated value. The inhibition was apparent within 48 hours. A temporary, but complete, restoration of activity was achieved by a single intravenous dose of 3 mg vitamin K_1/kg b.w., administered whilst bromadiolone dosing continued.

The maximum tolerated 5-day oral dose of bromadiolone was considered to be 25 mg in pigs (large white strain) weighing 25 kg.

2.1.6 **Dietary studies:**

Short-term: After 45 oral daily doses of 0.5 mg bromadiolone, no change in the prothrombin time in pigs was observed.

Long-term: No published information available.

Teratogenicity: Bromadiolone was given orally to four groups of 25 female rats from day 6 to 15 of pregnancy at doses 0, 17.5, 35 and 70 μg/kg b.w./day. Maternal toxicity occurred at the higher dose levels. There was no evidence of embryotoxiciy or teratogenic effects at any dose level. A similar absence of effects was reported in a study on rabbits treated orally with daily doses of either 2, 4 or 8 μg/kg b.w./day on days 6 to 18 of pregnancy, although there was maternal toxicity at the highest dose level.

Mutagenicity: Bromadiolone was tested in teh Salmonella reverse mutation assay at concentrations ranging from 10 to 3330 μg per plate on strains TA 1535, TA 1537, and TA 1538. No evidence of mutagenic effect was found either with or without metabolic activation.

Bromadiolone did not induce forward mutations in Chinese hamster ovary cells either with or without metabolic activation.

In a mouse micronucleus test at four dose levels from 50 to 400 μg/kg bromadiolone did not induce micronuclear changes in bone marrow polichromatic erythrocytes.

2.1.7 **Supplementary studies of toxicity**: No published information available.

2.2 TOXICOLOGY - MAN

2.2.1 **Absorption route**: No published information available. Data available for other mammalian species show that bromadiolone may be absorbed from the gastrointestinal tract, from the skin, and from the lung.

2.2.2 **Dangerous doses**: No published information available.

2.2.3 **Observations on occupationally exposed workers**: No published information available.

2.2.4 **Observations on exposure of the general population**: No published information available.

2.2.5 **Observations on volunteers**: No published information available.

2.2.6 **Reported mishaps**: Accidental bromadiolone poisoning was reported in two children, resulting in prolonged disturbance in blood coagulation processes. Descarboxyprothrombin levels were increased in both cases by 27% and 29.9%, respectively (normal, as a non-detectable level). A case of bromadiolone ingestion with a bleeding in a 27-year old female has also been reported.

2.3 TOXICITY TO NON-MAMMALIAN SPECIES

2.3.1 **Fish**:

LC_{50} - 96 hour	Rainbow trout	1.4 mg/litre

2.3.2 **Birds**:

Oral LD_{50}	Quail	1600 mg/kg b.w.

Poultry are sensitive to bromadiolone. A bolus oral dose of 1.25 mg/Leghorn hen/day, for 10 days, killed 2/10 hens. A dose of 2.5 mg/hen/day for 30 days killed eight of the 10 hens tested.

2.3.3 **Other species**: No published information available.

3.0 FOR REGULATORY AUTHORITIES - RECOMMENDATIONS OF COMPOUND

3.1 RECOMMENDED RESTRICTIONS ON AVAILABILITY

[For definition of categories see the "Introduction to Data Sheets".]

Concentrate (0.25%) - Category 1.

Bait formulation (0.005%) - Category 5.

3.2 TRANSPORTATION AND STORAGE

Formulation in category 1: Should be transported and stored in clearly labelled, rigid, leakproof containers away from food and feedstuffs, their containers and packaging materials. Storage should be under lock and key, secure from access by children and other unauthorized persons.

Formulations in category 5: The resemblance of many formulations to food and feedstuffs necessitates particular care when handling these formulations. For this reason the conditions stipulated above should also be applied to this category.

3.3 HANDLING

All formulations: Handling of technical material or powder concentrates will

require full airfed protection and an impervious suit, suitable for wash-down. Operations with liquid concentrations will require PVC or nitrile-rubber gloves, armlets and apron with a face shield and rubber boots. Impermeable gloves must be worn at all times during the handling of these formulations. Additionally eye protection should be worn when handling liquid formulations.

3.4 DISPOSAL AND/OR DECONTAMINATION OF CONTAINERS

All formulations: Decontamination of containers for re-use should not be permitted. The containers and remaining residues should be burned. Disposal according to national regulations.

3.5 SELECTION, TRAINING AND MEDICAL SUPERVISION OF WORKERS

Formulations in category 1: Workers suffering from active liver or blood clotting disorders should be excluded from contact. Account should be taken of the workers' ability to follow instructions for the handling and placement of this rodenticide. Regular determination of prothrombin times is recommended.

Formulations in category 5: A warning to minimize contact and ensure careful placement of the baits and traps is essential.

3.6 ADDITIONAL REGULATIONS RECOMMENDED IF DISTRIBUTED BY AIRCRAFT

No recommended aerial application reported.

3.7 LABELLING

Formulation in Category 1 - Minimum cautionary statement:

DANGER - POISON

(Skull and cross bones insignia)

Bromadiolone is an anticoagulant and may cause haemorrhaging. It is very toxic by inhalation, contact with the skin and by ingestion. Keep away from unauthorized persons and domestic animals. Wear impermeable gloves. face-shield, rubber boots and an impervious suit. Keep out of lakes, streams or ponds.

Formulations in category 5: Minimum cautionary statement:

"WARNING- POISON"

Bromadiolone is an anticoagulant and may cause haemorrhaging if swallowed or following skin contact. Keep out of the way of food and feeds, their packaging and handling materials and keep out of reach of children and pets. Wear impermeable gloves during handling. Avoid mouth and skin contact. Wash splashes or spillage from skin or eyes immediately. Wash hands before smoking or eating and after using the product. This product is toxic to wildlife and pets; ensure that traps and baits are not accessible to non-target species. Pre-mixed or prepared baits may resemble food or feedstuffs. Care should be taken at all times to ensure that such formulations cannot become mistaken for food or feed.

3.8 RESIDUES IN FOOD

Since this rodenticide is not intended for direct application to growing crops, no residues in plant foodstuffs are expected. Even if the bait is spilled, it will not be taken up by plants.

4.0 PREVENTION OF POISONING IN MAN AND EMERGENCY AID

4.1 PRECAUTIONS IN USE

4.1.1 General: Bromadiolone is an anticoagulant, highly toxic to rodents and highly toxic to other mammals. A lengthening of the blood clotting time may be seen after ingestion or dermal absorption of the compound. The action is a specific inhibition of prothrombin synthesis and can be effectively counteracted by vitamin K_1. The low concentration of bromadiolone present in most formulations decreases the hazard of these products and symptoms may not be present following exposure.

4.1.2 Manufacture and formulation - TLV: No published information available. Precautions must be taken to avoid inhalation, oral or dermal exposure to bromadiolone or its formulations.

4.1.3 Mixers and applicators: Persons associated with bromadiolone mixing and use should wear impermeable gloves. Workers using liquid formulations should additionally wear eye protection. Splashes or spillages should be washed immediately from the eyes or skin. Hands must be washed immediately after use and before smoking or eating.

4.1.4 Other populations likely to be affected: With careful attention to usage, handling and disposal practices other populations should not be exposed to bromadiolone. Users must be particularly careful to ensure that the baits can never be mistakenly used as food or feed stuffs.

4.2 ENTRY OF PERSONS INTO TREATED AREAS

Unprotected persons may enter the areas where baits have been placed immediately after their placement. However, where such placements cannot be made totally secure from tampering they must be identified and access by unauthorized persons must be prevented.

4.3 DECONTAMINATION OF SPILLAGE AND CONTAINERS

Decontamination of containers for re-use should not be permitted. Empty containers and unused formulations should be burned. Spillage of liquid formulations should be contained with absorbent material. This material, or spillage of solid formulations, should be collected and burned. Residues should be removed from the spillage site by washing with detergent and water. Impermeable gloves should be worn for all of these procedures.

4.4 EMERGENCY AID

4.4.1 **Early symptoms of poisoning**: The main features of bromadiolone poisoning are excessive bruising, nose and gum bleeding and blood in urine and faeces in the less severe cases, and bleeding from several organs within the body leading to shock and possibly death in the more severe cases. The onset of the signs of poisoning may not be evident until a few days after ingestion.

4.4.2 **Treatment before person is seen by physician, if symptoms appear following exposure**: The person should stop work immediately and remove contaminated clothing. The affected skin should be washed with soap and water. If the compound has entered the eyes they should be flushed with water. Following ingestion of the compound medical assistance should be sought immediately. Vomiting may be induced in the fully conscious patient if ingestion of the formulation has occurred in the preceding 2-3 hours.

5.0 FOR MEDICAL AND LABORATORY PERSONNEL

5.1 MEDICAL DIAGNOSIS AND TREATMENT IN CASES OF POISONING

5.1.1 **General information**: Bromadiolone is an anticoagulant rodenticide of high toxicity to most mammals. It may be absorbed from the gastrointestinal tract and from the skin. In patients with blood clotting impairment or liver diseases, or following exposure to large amounts of bromadiolone, blood clotting may be disturbed. Coumarin-type compounds may also cause capillary fragility.

5.1.2 **Symptoms and signs**: Poisoned victims may show evidence of excessive blood loss. The lengthened prothrombin time is usually apparent within 24 hours and reaches a maximum of 36-72 hours after exposure.

5.1.3 **Laboratory**: The prothrombin time should be determined. There is a lengthening of this time at doses below those necessary to cause haemorrhage. The extended clotting time may indicate the extent of the poisoning, but may also be affected by an intrinsic deficiency of clotting factors in the patient's blood.

5.1.4 **Treatment**: All suspected poisonsed patients should receive medical attention immediately. If poisoning is recent (within 2-3 hours) gastric lavage has been recommended. Repeated administration of activated charcoal is useful. Vitamin K_1 (phytomenadione) is the specific antidote of choice. Dosage is dependent on coagulation parameters, mainly prothrombin time.

If the patient is bleeding severely, 25 mg of vitamin K_1 (phytomenadione) should be given by slow intravenous injection. Prothrombin time should be checked at 3-hourly intervals in severe cases and after 8-10 hours in less severe cases. If no improvement occurs, vitamin K_1 injection should be repeated. In moderate to minor cases of poisoning, vitamin K_1 may be given in lower doses.

Whole blood, fresh frozen plasma or factor concentrate should be used in cases of acute severe bleeding in order to rapidly restore the blood clotting factors.

5.1.5 **Prognosis**: The prognosis for a complete recovery is good. Mild depression of the blood clotting process will spontaneously overcome as new clotting factors are synthesized. Severe poisoning is successfully treated by vitamin K_1 administration.

5.1.6 **References to previously reported cases**: Two poisoned children (described in 2.2.6) were treated with vitamin K_1. The first child rapidly recovered after treatment with high-dose intravenous factor IX-prothrombin complex and vitamin K_1. The clotting profile became normal on the third day after admission. The second child gave a poor response to 10 mg intravenous vitamin K_1, and the dose was increased to 20 mg.

5.2 SURVEILLANCE TESTS

Determination of the prothrombin time (Quick's One Stage Test) by the use of test kits or following the method described in: Quick AJ (1935), *J. Biol.* Chem. **109**:73. Many haematology texts also cite the method, e.g. Dacie JV and Lewis SM (1963), Practical Haematology, Churchill Ltd., London.

5.3 LABORATORY METHODS

5.3.1 **Detection and assay of compound and residues**: HPLC analysis with fluorescence detection:

Hunter K (1985), J Chromatog **321**,(2):255-72;
Hunter K (1983), J Chromatog **270**:267-76 and 277-83.

5.3.2 **Other tests in case of poisoning**: Determination of prothrombin time (see 5.2).

REFERENCES

The Pesticide Manual, A World Compendium (10th edition 1994), Tomlin, C., ed. British Crop Protection Council, 20 Bridport Road, Thornton Heath, CR4 7QG, U.K.

WHO (1995), Environmental Health Criteria No. 175, Anticoagulant Rodenticides. UNEP/ILO/WHO, Geneva, 121 pp.

WHO (1995), Health and Safety Guide No. 94, Bromadiolone. UNEP/ILO/WHO, Geneva, 28 pp.

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