

## REVIEW ARTICLE

# TOXIC POTENTIAL OF SUPERWARFARIN: BRODIFACOUM

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Received 31<sup>st</sup> December 2013.

Revised 12<sup>th</sup> February 2013.

Published 8<sup>th</sup> March 2013.

### Summary

Brodifacoum, a commercially available, long-acting anticoagulant rodenticide, is a highly toxic compound. Structurally it is similar to warfarin, but it is many times more potent, with the ability to cause severe bleeding in humans. Most of the health hazards of brodifacoum are associated with accidental ingestion. Superwarfarin intoxication may have no signs or symptoms other than bleeding at various sites. Brodifacoum has the potential to be used as a chemical warfare agent because of its high potency and long duration of action.

*Key words: anticoagulant; brodifacoum; superwarfarin; health risk; agent of opportunity; possible terrorist agent*

### INTRODUCTION

Brodifacoum is a potent, second-generation anticoagulant pesticide that has been successfully used in cereal baits in New Zealand for rodent eradication. Anticoagulant rodenticides of brodifacoum type derived from warfarin are referred to as “superwarfarins” (Sharma, Bentley, 2005; Pavlu et al., 2006; Fang et al., 2012). Superwarfarins are commercially available, long-acting anticoagulant rodenticides

many times more potent than warfarin and many of them have the capacity to cause severe bleeding problems that may last for months in humans (Gunja et al., 2011; Subban et al., 2012).

Most of the exposures to superwarfarins are accidental. However, this group of long-acting anticoagulants may be used as chemical warfare agents due to their high potency and long duration of action. The capability of terrorists to misuse these commercially available poisons is dependent upon the availability of large amounts of highly concentrated product, the target population and its vulnerability, and a method of effective delivery and dissemination (EPA, 2005; Murphy and Lugo, 2009). Today there is a greater risk than ever before that extremist/terrorist groups may use industrial or household chemical substances to harm, kill, or terrorize society because these substances are easy to obtain and conceal.

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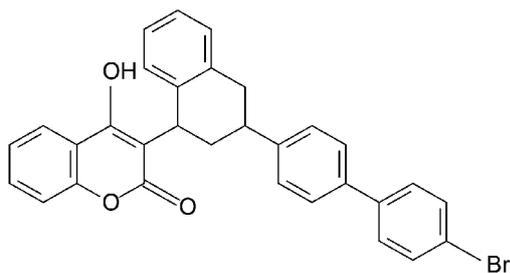
## CLASSIFICATION OF BRODIFACOUM

Brodifacoum was first introduced in 1977 by the British company Sorex, and then marketed by the Imperial Chemicals Incorporated Plant Protection Division. This pesticide has been available in several countries for the control of a wide range of rodent pest species. It was at the time of its introduction the only anticoagulant rodenticide to produce 100% mortality in most rodent species after only a 24 h dose (Chalermchaikit et al., 1993).

## Chemistry

Brodifacoum (CAS Numer 56073-10-0; molecular weight 523.42) is a brominated hydroxycoumarin derivative with the chemical name 3-(3-(4'-bromo(1,1'-biphenyl)-4-yl)-1,2,3,4-tetrahydro-1-naphthalenyl)-4-hydroxycoumarin. The name brodifacoum is partially an acronym of the chemical name: bro – di (instead of bi), – f (instead of ph), – a from naphthyl) and coum obviously from coumarin. It is one of the most potent superwarfarin anticoagulant rodenticides (Fig. 1) developed.

Pure brodifacoum is an off-white to fawn-colored powder with the melting point at 230 °C and a solubility of 3.8 µg/L in water, 20 g/L in acetone, 3 g/L in chloroform, and 0.6–6 g/L in benzene. Its logP (octanol-water) is 8.17. Brodifacoum is a very stable compound (Jin et al., 2007) that persists with no loss of activity - after exposure to direct sunlight- for 30 days (Chalermchaikit et al., 1993).



**Figure 1.** Structure of brodifacoum, a highly toxic superwarfarin and possible terrorist agent.

## Toxicokinetics

Brodifacoum is well absorbed from the gastrointestinal tract (Vandenbroucke et al., 2008) with peak plasma concentrations occurring within 12 hours of ingestion. In humans, serum brodifacoum levels were detectable over a seven-

month period post-ingestion. Five days after admission, the serum brodifacoum concentration was 1302 ng/ml and then gradually decreased until day 209 when it became undetectable. Brodifacoum elimination showed a first order kinetic and a 56-day half-life (Olmos, López, 2007). Binding to plasma proteins may slow distribution and prolong half-life (Bruno et al., 2000).

The metabolism and elimination of the trans-isomer were more rapid than that of the cis-isomer. The elimination is biphasic with an initial rapid phase of three days and a slower phase of 120 to 130 days. The major route of elimination after oral administration is via the feces. The urine is only a minor route of elimination (Watts et al., 1990, Watt et al. 2005).

## Toxicodynamics

The mechanism of action of all anticoagulant rodenticides is similar to that of warfarin, specific inhibition of vitamin K1 epoxide reductase (Breckenridge et al., 1985). In the coagulation cascade, some of the clotting factors must bind calcium ions to be activated. The Ca<sup>2+</sup>-binding ability of these clotting factors requires carboxylation of their glutamyl residues. This carboxylation step uses vitamin K1 hydroquinone as a cofactor. The carboxylase reaction converts vitamin K1 hydroquinone to its epoxidic form. In the normal physiological cycle, the epoxide is reduced to the original vitamin K1 by the vitamin K1 epoxide reductase. Superwarfarin rodenticides produce their effect by interfering with vitamin K1 epoxide reductase, resulting in the depletion of vitamin K1 and subsequently in the impairment of the synthesis of the pro-coagulant factors II, VII, IX, and X and that of the anti-coagulant proteins C and S (Craciun, 1998).

## Toxicity

Brodifacoum is highly toxic to mammals and birds. A number of non-target mammal and bird species have been contaminated with brodifacoum, either directly through consuming baits, or indirectly through secondary poisoning (Eason et al. 2002). Experimental toxicity data for brodifacoum obtained in laboratory animals using different routes of application and incidentally obtained data for humans are summarized in Table I. Vitamin K1 epoxide reductase is a polymorphic enzyme, which explains the differences in sensitivity to warfarin type agents.

**Table 1.** Overview Toxicity Test Types of Brodifacoum in different organisms.

Organism	Test Type *	Route	Reported Dose	Source
cat	LD <sub>50</sub>	oral	25 mg/kg	Pesticide Manual 1991
chicken	LD <sub>50</sub>	oral	4.5 mg/kg	Pesticide Manual 1991
dog	LD <sub>50</sub>	oral	0.25mg/kg	Pesticide Manual 1991
mouse	LD <sub>50</sub>	oral	0.29 mg/kg	Pesticide Manual 1991
rat	LD <sub>50</sub>	oral	0.16 mg/kg	Pesticide Manual 1991.
rat	LD <sub>50</sub>	skin	200 mg/kg	Pesticide Manual 1991.
rat	LC <sub>50</sub>	inhalation	0.5 mg/m <sup>3</sup> /4 hr	Pesticide Manual 1991
duck	LD <sub>50</sub>	oral	2 mg/kg	Pesticide Manual 1991
domestic animals (goat/sheeps)	LDLo	oral	3 mg/kg	Godfreyab, 1984
gerbil	LD <sub>50</sub>	oral	1mg/kg	Mathur, Prakash, 1981
red-necked wallaby ( <i>Macropus rufogriseus</i> )	LD <sub>50</sub>	oral	1.3 mg/kg	Godfreyab, 1984
guinea pig	LD <sub>50</sub>	oral	2.8 mg/kg	Pesticide Manual 1991
rabbit	LD <sub>50</sub>	oral	0.20 mg/kg	Godfreyab, 1984
rabbit	LDLo	skin	2.5 mg/kg	National Technical Information Service. Vol. OTS0545460
mammal (species)	LD <sub>50</sub>	oral	1.32 mg/kg	Godfreyab, 1984
man	TDL <sub>0</sub>	oral	0.12 mg/kg	Sheen et al., 1994 Jones et al., 1984
man	TDL <sub>0</sub>	Oral	0.167 mg/kg	Hoffman et al., 1988
women	TDL <sub>0</sub>	oral	0.172 mg/kg	Morgan et al., 1996

\* LD<sub>50</sub> = The median lethal dose , TDL<sub>0</sub> = Lowest Published Toxic Dose

### Clinical effects

Clinical signs are usually delayed for 24–36 hours post-ingestion until the preformed clotting factors are depleted. Since preformed anti-coagulant proteins (C & S) have shorter half-lives than the pro-coagulant factors II, VII, IX, and X it is possible to observe in the immediate phase post-exposure an increased generation of microthrombi and even tissue necrosis).

Clinical signs and symptoms of acute intoxication by brodifacoum in humans range from a mild tendency to bleed in less severe poisoning cases to severe coagulopathy. Mild bleeding tendencies are often recognized as nose or gum bleeding, hemoptysis, ecchymosis, bloody or melenotic stools, hematuria, abdominal or flank pain, enhanced bruising, or ventral hematomas. Severe bleeding may lead to shock and death. Internal and external bleeding are the most frequent clinical manifestations of acute intoxication by brodifacoum, followed by

tachycardia, hypotension and multiple organ failure due to blood loss and insufficient perfusion and oxygenation. The onset of the signs and symptoms of poisoning may not be evident until a few days after exposure (Berny et al., 1995; Braithwaite, 1982; Munday and Thompson, 2003; Moery and Pontius. 2009; Wu et al. 2012 Corke, 1997; Casner, 1998; Baker et al., 2002; Olmos and López, 2007).

The great majority of reported human exposures are in children under the age of six due to accidental or unintentional ingestion (Osterhoudt and Henretig, 2003). Intentional suicidal ingestion of large amounts of brodifocoum conveys a great risk for its severe toxicity and mortality and these patients should be referred to a healthcare facility for examination and treatment if needed (Ingels et al., 2002).

### Analytical methods

A number of analytical methods were developed for detecting brodifacoum and other anticoagulant

rodenticides in various matrices. Early fluorimetric methods were used to detect warfarin in serum (Vesell and Shively, 1974; Welling et al., 1970) and HPLC method was performed for brodifacoum (Koubek et al., 1979; Hoogenboom et al., 1983). Brodifacoum may be detected down to concentration about 1 ng/mL of serum and 1 ng/g of liver (Chalermchaikit et al., 1993; Felice and Murphy, 1989). Another HPLC method for detecting brodifacoum in serum and liver using difenacoum as the internal standard has been reported (O'Bryan and Constable, 1991). There is also a method for the simultaneous detection of five superwarfarin rodenticides in human serum (Kuijpers et al., 1995).

### **ACCIDENTAL POISONINGS**

The 1995 annual report of the American Association of Poison Control Center Toxic Exposure Surveillance System reported more than 13,000 poisonings with hydroxycoumarin compounds (Litovitz et al., 1996). In 2004, the number of exposures to superwarfarin had increased to 16,054 (Watson et al., 2005). Accidental poisonings are fairly common in the world (Cao et al., 2012) and brodifacoum was involved in a large percentage of these poisonings (Palmer et al., 1999; Berry et al., 2000).

The great majority of adult exposures to brodifacoum are due to deliberate acute or chronic surreptitious ingestion. Long-acting anticoagulants such as brodifacoum produce rapid and persistent bleeding due to hypoprothrombinemia (Berry et al., 2000). Bleeding disorders may persist for many months. The severity of the intoxication depends on the amount of brodifacoum ingested, preexisting comorbidity, and co-ingestion of other toxic substances (Palmer et al., 1999; Walker and Beach, 2002). Fatalities are usually due to intentional suicidal ingestion of large amounts.

### **GENERAL TREATMENT AND RECOMMENDATIONS**

Accidental ingestion of small amounts of brodifacoum usually do not require any medical intervention or routine follow-up laboratory studies. Gastric decontamination has no effect on the clinical outcome after "taste" amounts are ingested by

children (Shepherd et al., 2002). In cases of suspected terrorist acts, massive misuse, intentional criminal, or any deliberate intentional suicidal ingestion, or when the amount ingested is either a large amount, or cannot be determined, the patient should be referred to a healthcare facility for clinical and laboratory assessment and treatment if necessary (Manoguerra and Cobaugh, 2005).

Induction of emesis has been recommended for children with a history of accidental ingestion of small amounts of brodifacoum, if it can be performed within one hour of ingestion (Katona and Wason, 1989). Emesis is contraindicated in patients with a bleeding disorder, particularly those under treatment with anticoagulants, or with a history of chronic, long-acting anticoagulant ingestion. Gastric lavage is recommended within the one to two hours post-ingestion window. The administration of activated charcoal is preferred when large amounts were ingested. Protection of the airways is -as always- necessary (Golej et al., 2001).

Vitamin K1 is the specific antidote and should be administered to any patient with a prolonged prothrombin time (Tsutaoka et al., 2003).

### **TERRORIST MISUSE OF BRODIFACOUM AS AGENT OF OPPORTUNITY**

Today there is a greater risk than ever before that extremist/ terrorist groups may use industrial or household chemical substances to harm, kill, or terrorize civil society. These toxic commercial and industrial chemicals stored in large quantities are considered "Agents of Opportunity" because they are readily commercially available. A large number of them exist and they include the superwarfarins. Although superwarfarins are classified as compounds in the Low Toxicity Group, they may be used to harm and terrorize people through the ingestion of contaminated food and/or water. Ingestion of superwarfarins may go unnoticed when these are mixed with food, because signs or symptoms are often delayed. Consequently, the victims may not associate the ingestion with the coagulopathy. Moreover, superwarfarin intoxication may have no initial signs or symptoms other than the appearance of blood in stools and urine.

The ingestion of small amounts of brodifacoum may not cause any bleeding problems. Ingestion of greater amounts provides increased risk of severe bleeding in 36 to 48 hours. The coagulopathy may last several weeks to months despite vitamin K1

treatment. Inhibition of synthesis of vitamin K1-dependent clotting factors may also occur following repeated ingestion of small amounts making these agents insidious (Murphy and Lugo, 2009).

## CONCLUSIONS

Brodifacoum has been marketed in several countries for the control of a wide range of rodent pest species. Brodifacoum is highly toxic to mammals and birds. (Radi and Thompson, 2004). While most of the health hazards for humans are associated with accidental ingestion of brodifacoum, the compound has the potential to be misused by terrorists. Intoxication can cause prolonged bleeding that is sometimes fatal.

## ACKNOWLEDGMENTS

This work was supported by the long-term organization development plan (University Hospital, Hradec Kralove, Czech Republic).

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