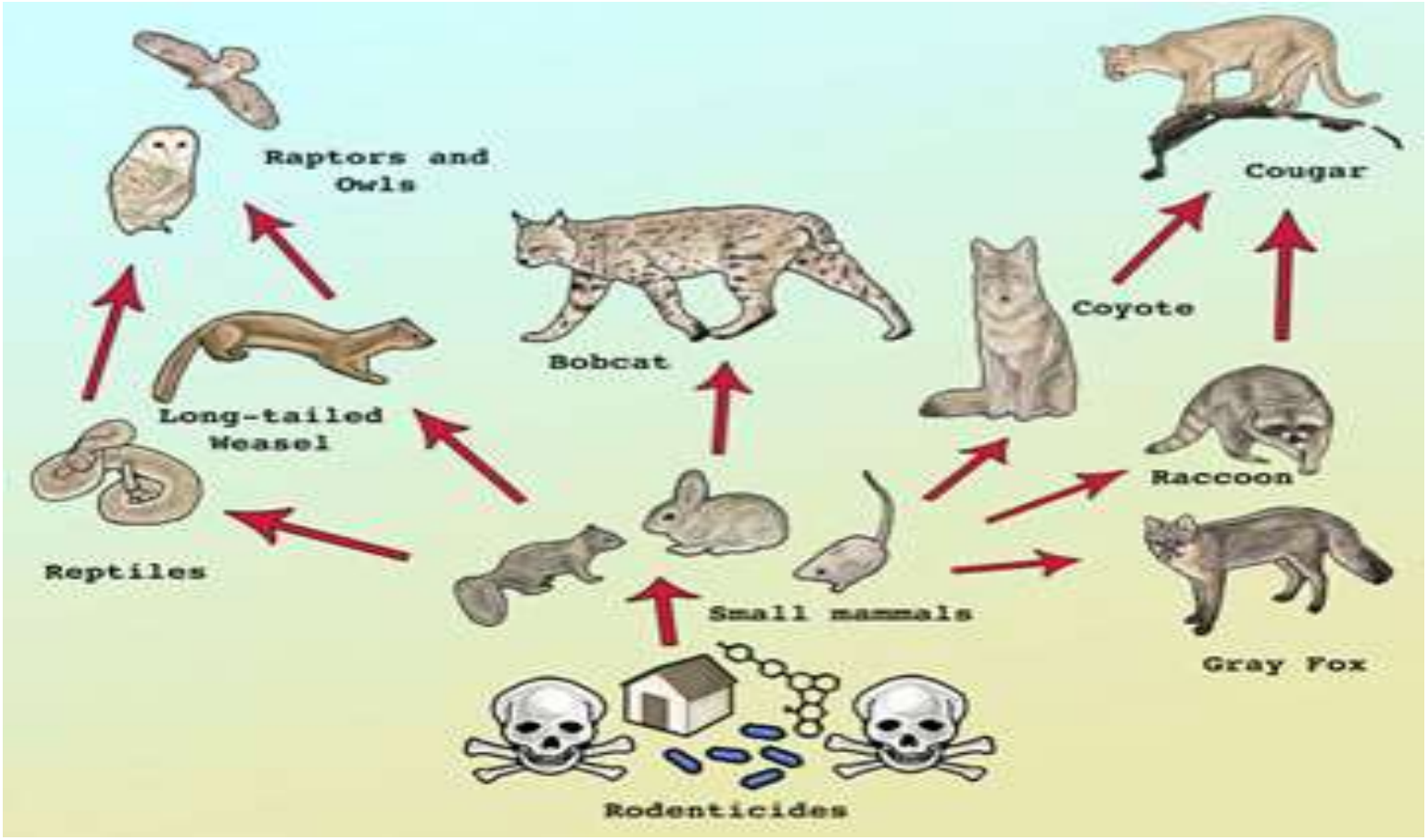
Anticoagulant rodenticides



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Introduction

- The origin of oral anticoagulant therapy and anticoagulant rodenticides traces back to investigations of moldy sweet-clover poisoning in the 1920s.
- This disease of cattle in Wisconsin was characterized by high mortality and internal bleeding.
- Investigations revealed that the diseased cattle had been fed moldy sweet-clover hay
- Anticoagulant pesticides are used widely in agricultural and urban rodent control.
- The emergence of warfarin-resistant strains of rats led to the introduction of a new group of anticoagulant rodenticides variously referred to as 'superwarfarins', 'single dose' or 'long-acting'.
- Anticoagulant rodenticide ingestion is a common toxicity in dogs. That the clinical signs are delayed and an antidote is readily available makes this a unique toxicity in regards to diagnosis and treatment.
- The following is a recommendation for a clinical approach to rodenticide toxicity based on the way rodenticides interact with the coagulation system and the timeline of events that occur following ingestion of a toxic dose.

Background

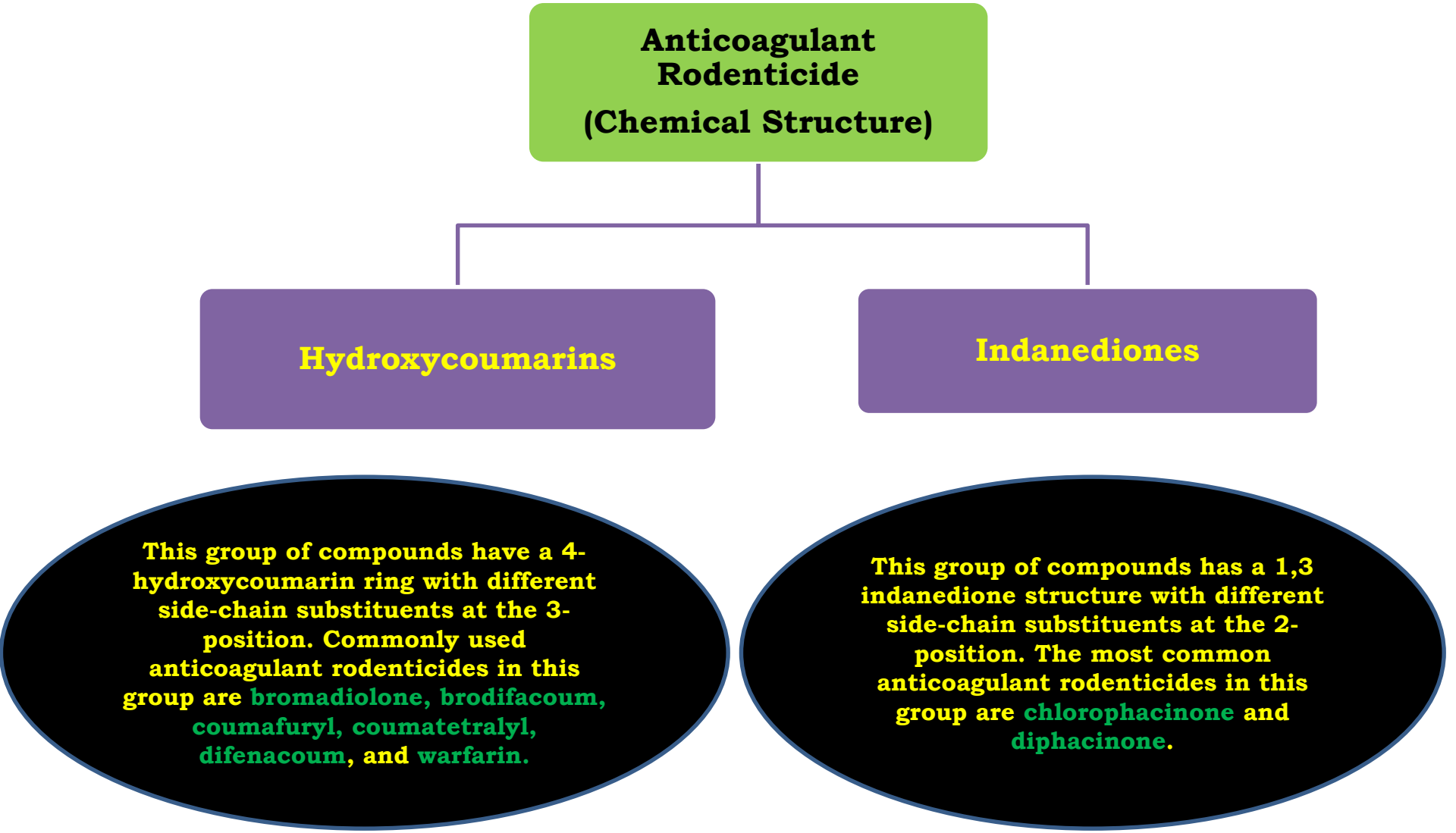
- In the **1940**s, a small British pharmaceutical company suggested that dicoumarol might have rodenticidal properties.
- Trials carried out by **Armour** and **Barnett** (1950) confirmed the idea and started the era of anticoagulant rodenticides.
- **Warfarin** was the first **anticoagulant rodenticide** introduced into the market shortly after World War II and became widely used in many countries.
- Other anticoagulant compounds with potency similar to that of warfarin were also synthesized. These early anticoagulant rodenticides have often been called "**first-generation anticoagulant rodenticides**."
- These first-generation compounds generally have moderate toxicity, with acute LD50 values ranging from **10 to 50 mg/kg body wt.** (Table 48.1).
- The first-generation compounds often needed continuous bait exposure for rodent control.

TABLE 48.1 The oral LD_{50} values (mg/kg body wt.) of some anticoagulant rodenticides

Animals	Bromadiolone	Brodifacoum	Difenacoum
Rat (acute)	0.65	0.27	1.8
Rat (chronic)	(0.06–0.14) x 5	(0.05–0.08) x 5	0.15 x 5
Mouse	0.99	0.4	0.8
Rabbit	1.0	0.2	2.0
Pig	3.0	10.0	80.0
Dog	10.0	3.5	50.0
Cat	25.0	25.0	100.0
Chicken	5.0	10.0–20.0	50.0
Guinea pig	2.8	–	–
Opossum	–	0.17	–
Sheep	–	10.0	100.0

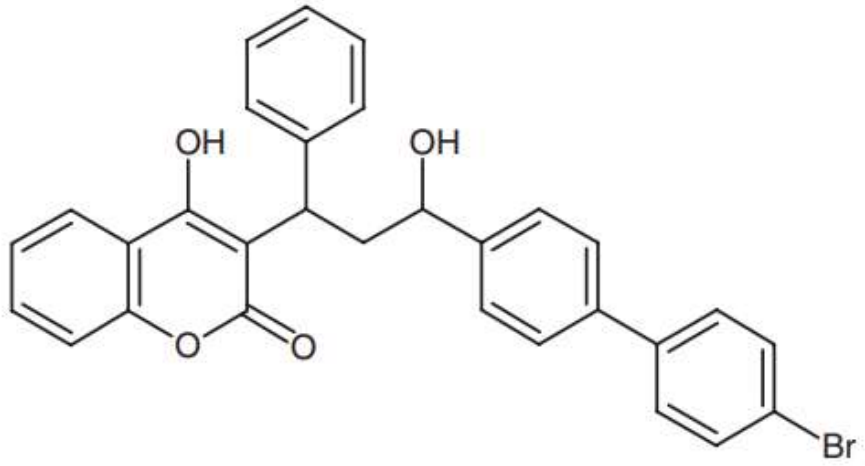
Chemical Structure

- Anticoagulant rodenticides are also categorized by chemical structure. The chemical structure of the currently marketed products fits in one of two chemical classes:

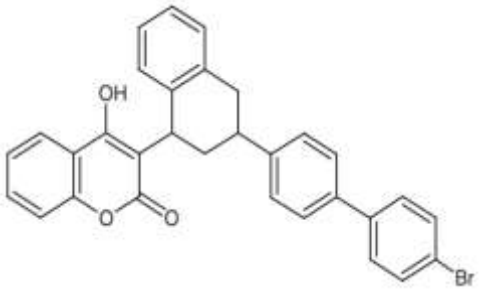


1.) Bromadiolone

- {3-(3-(4'-bromobiphenyl-4-yl)-3-hydroxy1-phenylpropyl)-4 hydroxycoumarin} was synthesized and marketed by the French company Lipha SA during the mid-1970s.
- Bromadiolone is considered more palatable to rodents than most other anticoagulants.
- Its concentration in baits is usually 50 ppm (Chalermchaikit et al., 1993). Although bromadiolone is considered a "second-generation anticoagulant rodenticide", some resistance problems have been reported with **Rattus norvegicus** and **Mus musculus** in the UK and Denmark (Rowe et al.,1981).

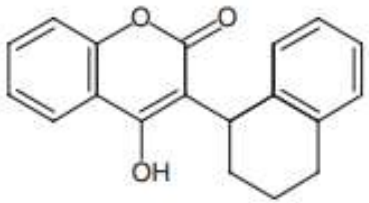


2.) Brodifacoum



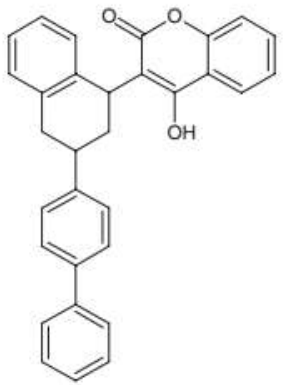
- Brodifacoum{**3-(3-(4'-bromobiphenyl-4-yl)-1,2,3,4tetrahydronaphth-1-yl)-4-hydroxycoumarin**} is one of the newer and more potent second-generation anticoagulant rodenticides.
- Brodifacoum has been marketed in several countries for the control of a wide range of rodent pest species.
- It is the only anticoagulant rodenticide found to produce 100% mortality in most rodent species after only a 24-h dose .
- Brodifacoum was effective against warfarin-resistant rats and mice in 1984, but the possibility of resistance has been raised (Lund, 1984).
- However, dogs are susceptible and are commonly exposed to potentially toxic quantities of brodifacoum .

3.) Coumatetralyl



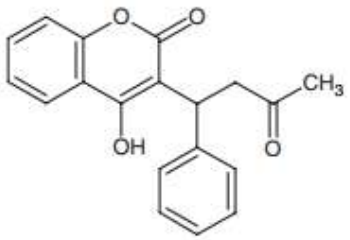
- Coumatetralyl {3-(alpha-tetralyl)-4-hydroxycoumarin} was introduced by Bayer AG with the trademark name of Racumin. It has been used for commensal control in many countries.
- Pure coumatetralyl is a colorless powder which is stable at temperatures below 150°C. Its solubility is 20–50 g/l in propan-2-ol, 50–100 g/l in methylene dichloride, and 4 mg/l in water.
- German anticoagulant, introduced in 1952, and is used at 0.025–0.05% in baits. Its toxicity is considered equal to warfarin for R. norvegicus but slightly less efficient against M. musculus. The chronic LD50 in R. norvegicus is 1.4 mg/kg for five repeated doses.
- Cats and dogs seem to be almost as susceptible as rats, with dogs being killed by 2 mg/kg for five repeated doses and cats by 10 mg/kg for four repeated doses.

4.) *Difenacoum*



- Difenacoum {3-(3-p-diphenyl-1,2,3,4-hydronaphth-1-yl)-4-hydroxycoumarin} was synthesized in the UK and marketed in 1975 by Sorex Ltd. under the trademark “Neosorexa”, and by ICI Plant Protection Division under the trademark “Ratak” as a 0.005% pelleted bait, and as a wax block.
- Pure difenacoum is an off-white powder with a solubility of greater than 50 g/l in acetone, 600 mg/l in benzene, and less than 10 mg/l in water.
- It is more toxic than warfarin, but less palatable. Difenacoum is still effective against many populations of warfarin-resistant rats (Desideri et al., 1979), but resistance may be developing in the UK .

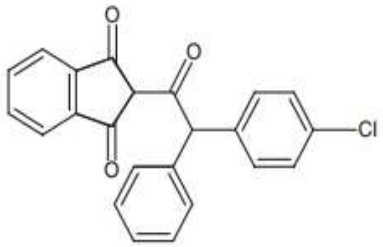
5.) *Warfarin*



- Warfarin {3-(a-acetonylbenzyl)-4-hydroxycoumarin} was the first anticoagulant rodenticide introduced shortly a Warfarin {3-(a-acetonylbenzyl)-4-hydroxycoumarin} was the first anticoagulant rodenticide introduced shortly after World War II after development by the Wisconsin Alumni Research Foundation.
- Warfarin is still used widely, especially for the control of R. norvegicus in areas where resistance has not developed.
- Warfarin is formulated as dry bait (0.005–0.05%) as well as a liquid bait, based on the sodium salt, and a tracking dust (0.5–1.0%). It is generally applied as the S-isomer, which has a toxicity 10 times greater than the R-isomer.
- Warfarin is sometimes combined with an antibacterial agent, sulfaquinoxaline, in order to reduce the bacterial production of vitamin K in the rat intestine, but the effectiveness of this combination has not been proven.

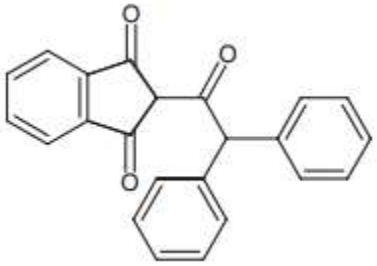
2.) Indanedione group

A.) Chlorophacinone



- Chlorophacinone {2-(alpha-4-chlorophenyl-a-phenylacetyl)-1,3-indandione} was first introduced during the mid- 1960s by Lipha S.A. of France, at concentrations of 0.05% in baits and 0.2% in tracking dust.
- Chlorophacinone does not induce “baitshyness” and is compatible with cereals, fruits, roots, and other potential bait substances.
- Its acute LD50s in R. norvegicus is about 20.5 mg/kg which is less toxic than warfarin, but it has a stronger initial effect on rats and mice.
- For control of house mice populations, a prolonged feeding period is needed. Chlorophacinone is not effective against warfarin-resistant rodents .

B.) Diphacinone



- Diphacinone (2-diphenylacetyl-1,3-indandione) is an old anticoagulant rodenticide, introduced by Vesicol Chemical Corp. and the Upjohn Co. It has been produced and usedprimarily in the US as a 0.005% dry or liquid bait.
- Pure diphacinone is a yellow powder which is very soluble in chloroform (204 g/kg), toluene (73 g/kg), xylene (50 g/kg), and acetone (29 g/kg), but sparingly soluble in water (0.30 g/l).
- It will decompose in water due to sunlight.
- It is more toxic than warfarin to rats, mice, and dogs, but its palatability is somewhat lower.
- Diphacinone is not effective against warfarin-resistant rodents.
- The anticoagulant rodenticides are marketed to have efficacy against a number of target pest species. These species are listed below by chemical compounds.

Target Species

❖ **Brodifacoum**

- One day of feeding on a 0.005% brodifacoum or difenacoum bait is successful in controlling the lesser bandicoot rat (Bandicota bengalensis) in Burma (Brooks et al., 1980).
- Within 3 days, a 0.005% brodifacoum bait gave complete control of golden hamsters (Mesocricetus auratus) resistant to 0.005% warfarin and difenacoum.
- A number of different rodenticides have been tested for efficacy against rodents incucumber (Cucumis sativus) plantings.

❖ **Bromadiolone**

- Bromadiolone has been effective against warfarin-resistant rats and mice. It is effective against the Norway rat (R. norvegicus).
- Bromadiolone residues have been examined in tissues of Arvicola terreteris and coypu (Myocastor coypus) after field use.
- Its effects on the breeding performance of house mice have also been investigated.

❖ **Chlorophacinone**

❖ The efficacy of chlorophacinone against mice, voles, and squirrels has been established. At a 25-ppm bait concentration, chlorophacinone is more effective than coumachlor in controlling common mice (M. musculus) in Egypt).

❖ It can control common voles (Microtus arvalis) , palm squirrels (Funambulus pennanti) (Mathur and Prakash, 1980), and house mice (M. musculus).

❖ **Coumafuryl**

- Coumafuryl is more effective on R. rattus, R. norvegicus, and B. bengalensis than fumarin and warfarin when used in liquid form.
- It was effective in controlling the cotton rat (Sigmodon hispidus) at concentrations used to control R. rattus and R. norvegicus), and Mastomys natalensis.

❖ **Diphacinone**

- Diphacinone has been shown to control rats, vampire bats, B. bengalensis, and coyotes.

❖ **Difenacoum**

- Fifty percent of male mice exposed to 0.5 mg difenacoum/kg body wt. died within 9 days, whereas no female mice died.
- Norway rats (R. norvegicus) fed 25 ppm difenacoum bait for 5, 10, or 20 days had whole carcass residues of 0.52–0.74 mg/kg body wt. with the higher amount being present after the longer feeding period.

❖ **Warfarin**

- The efficacy of warfarin has been evaluated against squirrels (Chambers and Chambers, 1983) and a host of other species.

Non Target Species

- Unfortunately non-target species may also be exposed to anticoagulant rodenticides.
- Anticoagulant rodenticides are a potential hazard to all species of mammals and birds
- The **environmental, avian, and wildlife** species so exposed are summarized briefly before the discussion of non target exposure in humans and domestic animals below.

❖ **Environmental**

- Anticoagulant rodenticides may be detected in **water, soil, and invertebrates**. A method of detecting warfarin in water has recently been reported, perhaps since anticoagulant rodenticides are used in **rice paddies** and accidental discharges of brodifacoum bait may occur in fresh water or a marine environment (Primus et al., 2005).
- The toxicity of anticoagulant rodenticides in soil may be related to the portion not bound to humic acid. Testing for the halogenated biphenyl side chain has been suggested as a way to determine soil exposure to rodenticides.
- Diphacinone has been detected in snails and slugs in Hawaii. It ranged from 0.8 to 2.5 ppm in Oxychilus sp. snails, from 1.3 to 4.0 in Deroceras laeve slugs, and up to 1.8 ppm in Limax maximus slugs .

❖ **Wildlife**

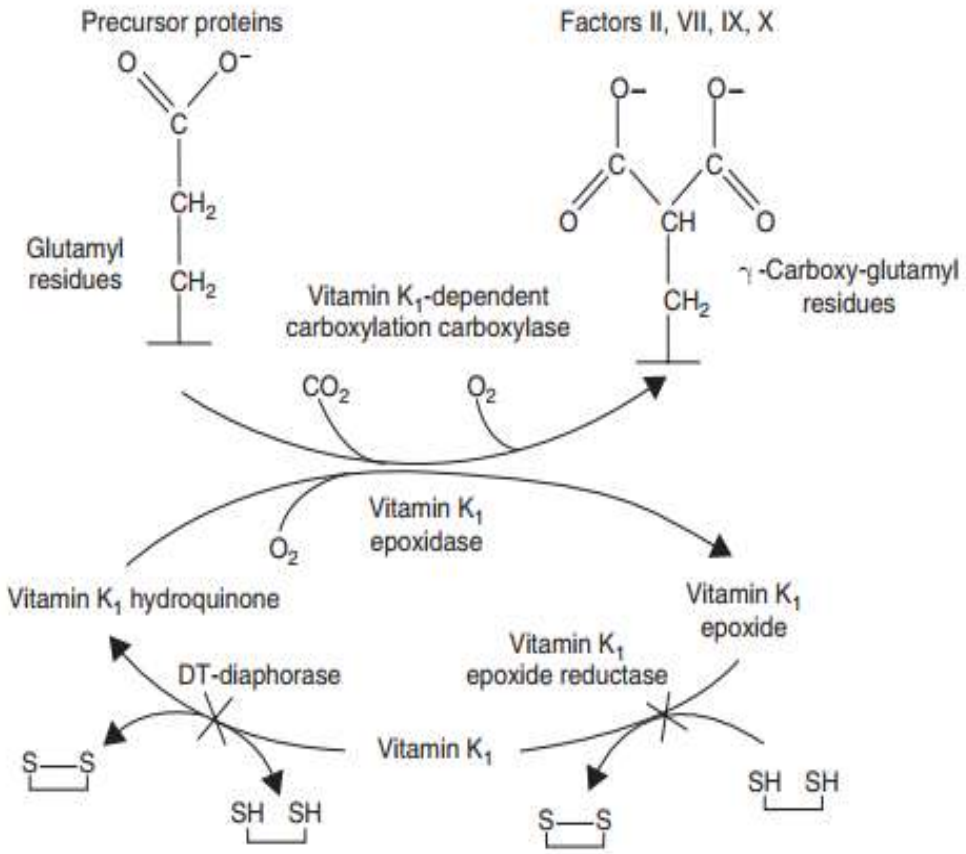
- Anticoagulant rodenticides have been detected in polecats and mink in the wild.
- Recently, difenacoum and bromadiolone were detected in 35% of male (13 of 37) and 38% of female (5 of 13) polecats (Mustela putorius) collected in England and Wales in areas where the baits had been used.
- Spatial and temporal residues in polecats in Britain have also been reported.A previous study found difenacoum in 7 of 24 livers .
- In France, populations of the free-ranging European mink (Mustela lutreola) have declined. Investigators found bromadiolone and chlorophacinone residues in the livers of four species of free-ranging mink and raised the question of the risk to European mink from anticoagulant rodenticides.
- See also the risks of brodifacoum in non-target birds and animals.
- Secondary poisoning of fox after broadcast of anticoagulant rodenticides for voles has been proposed. Bromadiolone toxicosis of coypu has also been reported.

❖ **Avian**

- Anticoagulant rodenticide toxicosis of birds has been reported throughout the United States, and in Australia. Brodifacoum and difenacoum residues have been detected in a number of non-target avian species.

❖ Offspring of turkey vultures (Cathartes aura) died after being fed brodifacoum-poisoned mice in a zoo setting. Similar residues have been detected in other carnivorous birds including Dacelo novae-guinae and Tockus deckeni.

Mechanism of action



- The mechanism of action of all anticoagulant rodenticides is similar to that of warfarin, i.e. inhibition of vitamin K1 epoxide reductase.
- In the coagulation cascade, the clotting factors II, VII, IX, and X must bind calcium ions to be active in clot formation.
- The Ca2-binding ability requires converting glutamyl residues on these clotting factors to -carboxyl glutamyl residues by the process of carboxylation.
- This carboxylation uses vitamin K1 hydroquinone as a cofactor. This vitamin-K-dependent carboxylase reaction converts vitamin K1 hydroquinone to its epoxide form, vitamin K1 2,3-epoxide.

- In the normal cycle, vitamin K1 2,3-epoxide is reduced to the original vitamin K1 (phylloquinone) by enzyme epoxide reductase, and is thus recycled (Figure 48.1).
- Anticoagulant rodenticides produce their effect by interfering with the enzyme vitamin K1 epoxide reductase, resulting in the depletion of vitamin K1 and subsequently impairing the synthesis of normal clotting factors II, VII, IX, and X .
- Clinical coagulopathy soon follows the depletion of vitamin K1 in the liver.

Toxicokinetics

❖ Bioavailability

- Most anticoagulant rodenticide toxicoses occur after oral exposure. However, a diphacinone-induced coagulopathy has been reported after dermal exposure to a liquid preparation.
- A quite unusual case is exposure to brodifacoum after donation and transplantation of multiple organs.
- The oral bioavailability of warfarin, chlorophacinone, and bromadiolone were estimated at 79%, 92%, and 88% respectively, in sheep. These anticoagulants degraded by about 15% over 24 h in rumen extracts (Berny et al., 2006).
- The bioavailability of warfarin is influenced by dietary protein (Barber and Colvin, 1980).

❖ Distribution

- Sixty percent of 14C labeled diphacinone is eliminated in feces and 10% in urine over 4 days in mice and 8 days in rats. Tissue distribution indicated that liver had the most 14C activity, with the lowest amounts in brain, muscle, blood, and fat.
- The disposition and pharmacodynamic properties of brodifacoum have also been characterized in rats. Similarly, 30% of 14C labeled flocoumafen is eliminated in feces and less than 3% in urine within 3 days in rats. About 60% of 14C flocoumafen is liable to beta-glucuronidase and most radioactivity is found unchanged in the liver.
- Elimination is biphasic with rapid phase of 5 days, then a prolonged phase of 100 days in Japanese quail.

❖ Elimination

- The different chemical structures give different elimination kinetics for the various anticoagulant rodenticides. Elimination kinetics is estimated from human or animal clinical cases in many instances.
- Such cases are presented for the 4-hydroxycoumarins warfarin, brodifacoum, difenacoum,bromadiolone, difethialone, and chlorophacinone.
- Warfarin has a terminal half-life of 5.6 0.7 h with a mono-exponential decay. Brodifacoum and difenacoum have a bi-exponential decay of 60 1.9 and 83 10 h, respectively, in rabbits.
- Although an estimated median half-life of brodifacoum elimination has been estimated to be 2.4 days in 7 dogs, the data may reflect the first elimination phase.
- Plasma half-life for brodifacoum was xxx in a zzz.

• Duration

- Despite reported elimination half-lives, the duration ofanticoagulant effect provides an indication of the clinically relevant treatment times.
- Brodifacoum and difenacoum cases seem to have the longest duration of anticoagulant effect in animals and humans.
- Duration of treatment has also been reported for bromadiolone and chlorophacinone cases, and pindonedosed sheep. A patient exposed to bromadiolone had to be treated for 6 months.

Toxicity

Occurrence	Dose
❑ Anticoagulant rodenticides are the most common rodenticide exposure of dogs and the most common toxin seen in many US veterinary practices. ❑ Dogs suspected of anticoagulant rodenticide poisoning in the Netherlands had brodifacoum (19), bromadiolone (14), difenacoum (8), difethialone (6), and chlorophacinone (1) ❑ Assessment of potential toxicity of pindone for domestic animals has also been made.	❑ **Humans:** A 25-year-old man attempted suicide by eating four 42-g boxes of 0.005% brodifacoum bait and succeeded in developing a coagulopathy. ❑ Rodenticides may be more toxic when repeatedly ingested over several days than when an equal amount is consumed in a single feeding ❑ Susceptibility may be greater in hypo prothrombinemic juveniles or animals with malabsorption syndromes. ❑ Also the concurrent administration of highly protein-bound drugs, e.g. phenylbutazone, aspirin, or disease states, such as chronic renal disease may increase the susceptibility of individuals to anticoagulant rodenticide poisoning

Diagnosis

- A clinical diagnosis of anticoagulant rodenticide poisoning is most often dependent on a history of exposure, or clinical signs, evidence of a coagulopathy, and response to vitamin K1 therapy. The most pragmatic approach for determining the specific anticoagulant rodenticide involved is to read the product package. This approach alone is not definitive because as much as 25% of anticoagulant rodenticide intoxicated dogs do not have the anticoagulant in serum the owners suspect (Murphy).
- Diagnostic approach to the bleeding patient has been described.
- A diagnostic protocol should utilize more than one coagulation test, since it is necessary to differentiate rodenticide poisoning from other coagulopathies, such as disseminated intravascular coagulopathy, congenital factor deficiencies, hyperviscosity syndromes, platelet deficiencies or functional defects, von Willebrand's disease, and canine ehrlichiosis.
- Hypovitaminosis K associated bleeding has been reported in cats with malabsorption syndrome.

Summary

- This group includes the second generation 4-hydroxycoumarins brodifacoum, bromadiolone, difenacoum, flocoumafen and the indanedione derivatives chlorophacinone and diphacinone.
- Most cases of anticoagulant rodenticide exposure involve young children and, as a consequence, the amounts ingested are almost invariably small.
- Intentional ingestion of anticoagulant rodenticides, particularly of the long-acting variety, and occupational exposure due to poor hygiene, may result in impairment of coagulation and clinically System. significant sequelae.
- Virtually any organ may be the site of haemorrhage and many, if not most, patients have evidence of bleeding from more than one when examined.
- If active bleeding occurs, prothrombin complex concentrate (which contains factors II, VII, IX and X) 50 units/kg or recombinant activated factor VII 1.2–4.8mg,. or fresh frozen plasma 15 mL/kg (if no concentrate is available) and phytomenadione 10mg intravenously (100 μg/kg bodyweight for a child) should be given.

THANK YOU