



Pesticide Fact Sheet

Name of Chemical: Difenacoum
Reason for Issuance: New Rodenticide
Date Issued: September 2007

Description of Chemical

Common Name	Difenacoum
Chemical Name:	3-[3-(1,1'-biphenyl)-4-yl]-1,2,3,4-tetrahydro-1-naphthalenyl]-4-hydroxy-2H-1-benzopyran-2-one CAS) 3-[3-(1,1'-biphenyl)-4-yl]-1,2,3,4-tetrahydro-1-naphthalenyl]-4-hydroxy-2H-1-benzopyran-2-one (IUPAC)
EPA Chemical Code:	119901
Chemical Abstracts Service (CAS) Number:	56073-07-5
Chemical Class:	4-hydroycoumacin class of anticoagulants
Registrations:	Difenacoum Technical EPA Reg. No. 47629- 12 Difenacoum Rat and Mouse Pellets, 0.005% EPA Reg. No. 47629- 14
Pesticide Type:	Rodenticide
Mode of Action:	Disrupt clotting ability of blood (anticoagulant)
Route of Exposure:	Ingestion
Registrant	Woodstream Corporation

I. USE PATTERN AND FORMULATIONS

Difenacoum belongs to the 4-hydroxycoumarin class of anticoagulants and is a pesticide intended to control commensal rodents (Norway rat, roof rat, and house mice) in and around buildings and inside of transport vehicles. In Europe, it has been marketed as a "second generation anticoagulant", a designation that it shares with brodifacoum, bromadiolone, and difethialone (rodenticides first registered in the United States in 1980's or 1990's). First generation anticoagulants are warfarin and its sodium salt, diphacinone and its sodium salt, and chlorophacinone (rodenticides first registered in the 1950's, 1960's, or 1970's). Difenacoum's route of exposure is by ingestion, and its mode of action is the disruption of the clotting of the blood. European countries have registered this rodenticide since the 1970's.

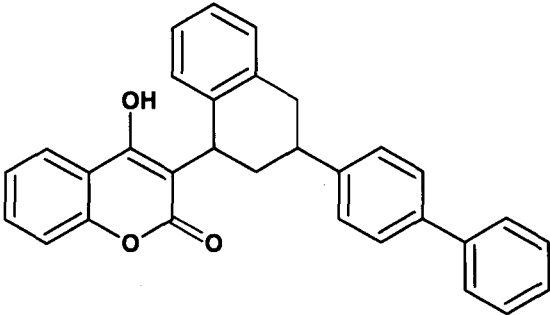
The registrant, Woodstream of Lilitz, Pennsylvania, has two initial registrations, a Difenacoum Technical, EPA Reg. No. 47629-12 and Difenacoum Rat and Mouse Pellets, EPA Reg. No. 47629-14, as a loose pellet formulation at 0.005% (50 ppm).

Table 1. Summary of Proposed Directions for Uses of Difenacoum.				
Formulation [EPA Reg. #]	Method of Application	Use Sites	Application Rate	Timing of Application
For Control of Norway Rats, Roof Rats, and House Mice				
Difenacoum Rat and Mouse Pellets (0.005% a.i.) #47629-14	By hand, spoon, and ready-to-use place packs	In and around periphery of homes; industrial, commercial and public buildings; transport vehicles (trains, ships, airplanes); and alleys. All baits are to be placed out of the reach of children, pets, domestic animals, and non- target wildlife, or in tamper-resistant bait stations.	Rats: 3 to 7 ounces of bait per placement (15-30 feet intervals) Treating borrows: 1 to 2 ounces of bait applied with spoon Mice: 0.5 to 1 ounce of bait per placement (8-12 feet intervals)	Highest bait consumption is expected to occur on the first day or two after treatment. Continue baiting until all signs or evidence of rodent activity have ceased.

II. SCIENCE FINDINGS

1. Chemical Nomenclature and Physical/Chemical Properties:

Table 2 presents the nomenclature of Difenacoum, and Table 3 presents the physical/chemical characteristics of Difenacoum:

Table 2. Difenacoum Nomenclature.	
Chemical Structure	
Common Name	Difenacoum, diphenacoum
Molecular Formula	C ₃₁ H ₂₄ O ₃
Molecular Weight	444.5
IUPAC Name	3-(3-biphenyl-4-yl-1,2,3,4-tetrahydro-1-naphthyl)-4-hydroxycoumarin
CAS Name	3-[3-(1,1'-biphenyl)-4-yl-1,2,3,4-tetrahydro-1-naphthalenyl]-4-hydroxy-2H-1-benzopyran-2-one
CAS Registry Number	56073-07-5
Technical Product	Difenacoum Technical (99.0% w/w, EPA Registration No. 47629-12)
End-use Product	Difenacoum Rat and Mouse Pellets (0.005% w/w), EPA Registration # 47629-14
Chemical Class	Anticoagulant Rodenticide

* Not yet registered.

Table 3. Physicochemical Properties of Technical Grade Difenacoum.		
Parameter	Value	Reference
Melting Point/Range	211.0 – 215.0°C (98.7% w/w)	MRID 46750965
pH	Not available	
Relative Density (20.5°C)	1.27 (98.7% w/w)	
Water Solubility (20°C)	<0.05 mg/L at pH 4 1.7 mg/L at pH 7 61 mg/L at pH 9	
Solvent Solubility (g/L at 20°C)	Acetone 7.6 Propan-2-ol 1.5 Ethyl acetate 3.7 Toluene 1.2 Methanol 1.2 Hexane 0.01 Dichloromethane 19.6	

Table 3. Physicochemical Properties of Technical Grade Difenacoum.				
Parameter		Value		Reference
Vapor Pressure (25°C)		6.7 x 10 ⁻⁹ – 5.4 x 10 ⁻¹⁴ Pa		
Dissociation Constant (pK _a)		4.5		
Octanol/Water Partition Coefficient (Log[P _{OW}])		7.6		
UV/Visible Absorption Spectrum				
Wavelength of peak (nm)	310.6	259.4		
Absorbance	0.267	0.664		
Molar Extinction Coefficient	17,100	46,600		

2. Toxicology Summary

Tables 4 (Acute Toxicity Profile – Difenacoum) and Table 5 (Subacute, Chronic, Other Toxicity Profile – Difenacoum) summary the toxicological studies that support Woodstream's initial registrations.

Table 4 Acute Toxicity Profile – Difenacoum				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral – rat	46750935	LD ₅₀ = 1.8 mg/kg (♂) (95% C.I. = 1.5-2.1 mg/kg)	I
870.1100	Acute oral – rat	46750936	LD ₅₀ = 2.6 mg/kg (♀) (95% C.I. = 2.1-3.7 mg/kg)	I
870.1100	Acute oral – rat and mouse	46766206	LD ₅₀ (cis) Male Rats = 1.17 mg/kg, Female Rats = 1.625 mg/kg Male Mice = 0.45 mg/kg Female Mice = 1.0 mg/kg LD ₅₀ (trans) Male Rats = 7.33 mg/kg, Female Rats = 6.0 mg/kg Male Mice = 1.181 mg/kg Female Mice = 2.75 mg/kg	I
870.1200	Acute dermal – rat	46750938	LD ₅₀ = 63 mg/kg (♀) (95% C.I. = 34-85 mg/kg)	I
870.1300	Acute inhalation – rat	46750939	LC ₅₀ =>0.003646 mg/L (♂+♀)	I
870.2400	Acute eye irritation – rabbit	46750940	1/3 conjunctival irritation immediately after. No positive irritation at 24-hours.	IV
870.2500	Acute dermal irritation – rabbit	46750941	No irritation at the 24-hour observation.	IV
870.2600	Skin sensitization – guinea pig	46750942	Not a sensitizer	N/A

Table 5 Subchronic, Chronic and Other Toxicity Profile – Difenacoum			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
Non-guideline	6-Week oral toxicity (dog)	46750944 (1994) Acceptable/nonguideline 0, 0.01, 0.025, 0.05, 0.1, 0.2 mg/kg/day	NOAEL = Not determined LOAEL = 0.01 mg/kg/day based on changes in blood coagulation, particularly increased prothrombin time beginning on day 30. All animals exposed to ≥ 0.025 mg/kg/day were sacrificed early due to increased coagulation times and/or clinical evidence of hemorrhage.
870.3100	90-Day oral toxicity (rat)	46766207 (1991) Unacceptable /guideline 0, 0.01, 0.02/0.09, 0.03 mg/kg/day	NOAEL = Cannot be determined LOAEL = Cannot be determined No effect on coagulation at 0.01 mg/kg/day This study was classified unacceptable due to inadequate number of animals/sex/dose. There were no surviving males after day 78. The dose level for the 0.02 mg/kg/day animals was increased to 0.09 mg/kg/day on Day 65 (F) or 66 (M). Hematology data are not available for the low dose group.
870.3700a	Prenatal developmental in rodents (rat)	46766208 (1994) Acceptable/guideline 0, 0.01, 0.03, 0.09 mg/kg/day	Maternal NOAEL = 0.03 mg/kg/day Maternal LOAEL = 0.09 mg/kg/day based on vaginal bleeding and increased kaolin-cephalin time. Developmental NOAEL = 0.09 mg/kg/day Developmental LOAEL = Not observed
870.3700b	Prenatal developmental in non-rodents (rabbit)	46750947 (1994) Acceptable/guideline 0, 0.001, 0.005, 0.015 mg/kg/day	Maternal NOAEL = 0.005 mg/kg/day Maternal LOAEL = 0.015 mg/kg/day based on changes in blood coagulation (increased prothrombin and kaolin-cephalin times). All animals in the 0.015 mg/kg/day group were sacrificed to prevent or minimize fatal maternal hemorrhage. Developmental NOAEL = 0.015 mg/kg/day Developmental LOAEL = Not observed
870.5100	Gene mutation – bacterial reverse mutation assay	46750948 (1995) Acceptable/guideline	Negative.
870.5100	Gene mutation – bacterial reverse mutation assay	46766209 (1986) Acceptable/nonguideline	Negative.
870.5300	Gene mutation – <i>in vitro</i> mammalian cell gene forward mutation assay	46750952 (1995) Acceptable/guideline	Negative.

Table 5 Subchronic, Chronic and Other Toxicity Profile – Difenacoum			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.5375	Cytogenetics - <i>in vitro</i> mammalian cell chromosome aberration test	46750950 (1995) Acceptable/guideline	Positive for chromosomal aberrations in cultured human lymphocytes with and without S9 activation, with a variable dose-response.
870.5375	Cytogenetics - <i>in vitro</i> mammalian cell chromosome aberration test	46766210 (1986) Acceptable/guideline	Positive for chromosomal aberrations in Chinese hamster lung cells with and without S9 activation, with a variable dose-response.
870.5395	Cytogenetics – mammalian erythrocyte micronucleus test (rat)	46766211 (1996) Acceptable/guideline	Negative.
870.5395	Cytogenetics – mammalian erythrocyte micronucleus test (mouse)	46766212 (1987) Acceptable/guideline	Negative.
870.5550	Other effects – unscheduled DNA synthesis in mammalian cells in culture	46773601 (1996) Acceptable/guideline	Negative.
870.5550	Other effects – unscheduled DNA synthesis in mammalian cells in culture	46766214 (1990) Acceptable/guideline	Negative.
870.7485	Metabolism and pharmacokinetics (rat)	46766216 (1996) Acceptable/guideline 0.051 or 0.54 mg/kg	<p>Groups of 4 female SD rats were given a single oral gavage dose of radiolabelled difenacoum.</p> <p>Absorption: Rapid; reached mean peak blood level for each dose group 4 hours after dosing.</p> <p>Distribution: Radioactivity was present in all tissues examined. At necropsy (168 hours), the majority of the unexcreted dose was present in the <u>liver</u> (37.6%/20.6% mean radioactivity from administered low/high dose), with smaller amounts in the <u>carcass</u> (17.2%/13.5%; low/high dose), the <u>GI tract</u> (4.0%/2.7%; low/high dose), and <u>pancreas</u> (1.1%/1.2%; low/high dose).</p> <p>Metabolism: Absorbed difenacoum is extensively metabolized, with both parent compound and up to 4 metabolites present in the liver at 7 days after dosing. In the liver, 4 metabolites were found in low dose animals and 2 metabolites were found in high dose animals. Both the parent compound and two of the hepatic metabolites are eliminated in the faeces within the first 24 hours, along with a polar metabolite(s).</p> <p>Elimination: At 24 hours, 17.7%/19.8%</p>

Table 5 Subchronic, Chronic and Other Toxicity Profile – Difenacoum			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
			(feces), 1.4%/1.2% (urine), and 0.36%/0.06% (expired CO ₂) of the radioactivity from the administered low/high dose, respectively, was recovered. By 168 hours, 39.9%/50.9% (feces) and 1.9%/1.44% (urine) of the radioactivity from the administered low/high dose, respectively, was recovered.

Table 5 Subchronic, Chronic and Other Toxicity Profile – Difenacoum			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485	Metabolism and pharmacokinetics (rat)	46766215 (2002) Acceptable/nonguideline 0.57 mg/kg (<i>cis</i> isomer) or 0.55 mg/kg (<i>trans</i> isomer)	<p>Groups of 4 female SD rats were given a single oral gavage dose of radiolabelled <i>cis</i> or <i>trans</i>-difenacoum.</p> <p>Absorption: Reached plateau in plasma 8-24 hours after dosing, followed by slow elimination phase. Peak blood level of the <i>cis</i>-isomer (0.21 µg equiv/ml) was approximately 2.5 times greater than the <i>trans</i>-isomer (0.08 µg equiv/ml) at 8 hours.</p> <p>Distribution: Radioactivity was present in all tissues examined. At 96 hrs, the highest levels were found in the <u>liver</u> (19-22% of the administered dose of <i>cis</i>-isomer; 22-29% <i>trans</i>), <u>carcass</u> (13.9-16.3% <i>cis</i>; 11.9-13.5% <i>trans</i>), <u>pancreas</u> (1.2-1.8% <i>cis</i>; 1.3-1.4% <i>trans</i>), and <u>GI tract</u>, including stomach, intestines, cecum, and content (4-4.2% <i>cis</i>; 3.1-4.3% <i>trans</i>).</p> <p>Metabolism: Not investigated in this study.</p> <p>Elimination: Within 96 hours, the radioactivity was recovered mostly in the <u>feces</u> (41% of the administered dose of <i>cis</i>-isomer; 44.5% <i>trans</i>), with small amounts in <u>urine</u> (0.5% <i>cis</i>; 0.6% <i>trans</i>).</p>
870.7485	Metabolism and pharmacokinetics (rat)	46750957 (1987) Acceptable/nonguideline 1.2 mg/kg	<p>32 male Alpk:AP rats were given a single oral gavage dose of radiolabelled difenacoum and were sacrificed in groups of three at 1, 4 and 8 days, and 2, 4, 8, 12 and 26 weeks after dosing.</p> <p>Absorption: The concentration of radioactivity in the blood and tissues was highest 24 hours after dosing, which was the earliest measurement.</p> <p>Distribution: The highest concentration of radioactivity, expressed as % of the dose, was found in the liver (42%), followed by the pancreas (0.48%), kidney (0.22%), and salivary glands (0.09%), with lower concentrations in the blood and fat. Whole body autoradiography showed that radioactivity levels were similarly distributed and not significantly reduced (except for the GI tract) at 5 days after dosing.</p> <p>Metabolism: The <i>cis:trans</i> ratio of difenacoum in the liver at 24 hours was 64:36, while the ratio of administered difenacoum was 44:56, which suggests that the <i>trans</i>-isomer was being preferentially metabolized or eliminated. Five metabolites were found in the liver, accounting for 53% of the total radioactivity in the liver extract, but these were not identified.</p> <p>Elimination: Elimination from the liver was biphasic, with a rapid phase during days 1-8 accompanied by a reduction in clotting factor</p>

Table 5 Subchronic, Chronic and Other Toxicity Profile – Difenacoum			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
			<p>synthesis ($t_{1/2}$ = 3 days), followed by a slower terminal phase during days 28-182 ($t_{1/2}$ = 118 days). Similar biphasic elimination was found in the kidney and salivary glands, but not the pancreas. The relative rate of elimination was liver, fat, and blood > kidney > salivary glands > pancreas.</p>
870.7485	Metabolism and pharmacokinetics (species)	44742901 (1992) Unacceptable/guideline	<p>Irrespective of dose, most of an orally administered radiolabeled fenazaquin was in rat excreta (89.5-107.7%) at 168 hours with approximately 20% of the radiolabel in urine. After initial uniform distribution, about 0.5-1.6% of the dose was in the carcass and below 0.04% of the dose in each tissue. There was no radiolabel in the expired air and no evidence for bioaccumulation. Based on excretion and tissue residue data, bioavailability is conservatively estimated at about 20% of an administered dose.</p> <p>Non-metabolized fenazaquin was higher in feces (1.0-15.0% of administered dose) than in urine (below 0.5% of dose) and some of the major metabolites were identified including AN-1 (urine) in addition to the fecal metabolites F-1, F-2 and F3. The metabolic pathway of fenazaquin involved cleavage of the ether bond, resulting in the formation of the respective alcohol (4-OH quinazoline metabolite) and carboxyl acid (AN-1) derivatives. Other biotransformation reactions included oxidation of one of the methyl groups on the alkyl side chain to produce either an alcohol (F-1) or carboxylic acid (F-2) metabolites. Finally, hydroxylation at the O-ether alkyl moiety of F-1 or the 2-position of the quinazoline ring of F-2 resulted in F-1A and F-3 metabolites, respectively.</p>

2. Environmental Fate Summary

Difenacoum bait consists of blue-green cylindrical pellets. It has very low solubility and low vapour pressure, but is very persistent.

Table 6 summarizes the environmental fate studies supporting Difenacoum.

Table 6. Fate and Transport Parameters for Difenacoum.

<i>Parameter</i>	<i>Value</i>	<i>Comments</i>
Hydrolysis $t_{1/2}$ (days)	Stable 1000 80	pH 5 pH 7 pH 9
Aqueous Photolysis $t_{1/2}$ (days)	0.14 0.34 0.30	pH 5 pH 7 pH 9
Atmospheric Photolysis $t_{1/2}$ (days)	0.087	N/A (low vapor pressure, solid bait placed on ground)
Aerobic Soil $t_{1/2}$ (days)	439	
Aerobic Aquatic $t_{1/2}$ (days)		<i>not provided</i>
Anaerobic Soil $t_{1/2}$ (days)		<i>not provided</i>
Anaerobic Aquatic $t_{1/2}$ (days)	Stable	after 49 days
Log K_{oc}	2.1 – 2.3	
Log K_{oc}	6.45	Calculated from K_{ow}

3. Environmental Effects Summary

A. Primary Terrestrial Hazards Studies

Table 7 summarizes acute oral toxicity studies on difenacoum for the Northern bobwhite and mallards.

Table 7. Acute oral toxicity of difenacoum to Northern bobwhite and mallards.

Species	% ai	LD ₅₀ (mg/kg bw)	Observation period (days)	Study date	MRID no.
Northern bobwhite (<i>Colinus virginianus</i>)	91.1	66 (56 ♀; 140 ♂)	28	1980	46750922
Mallard (<i>Anas platyrhynchos</i>)	94.6	>2000	21	1996	46750921

Table 8 summaries sub-acute dietary toxicity studies on Difenacoum for mallards and the ring-necked pheasant.

Table 8. Sub-acute dietary toxicity of difenacoum in mallard and ring-necked pheasant.

Species	% ai	LC ₅₀ (ppm)	Observation period (days)	Study date	MRID no.
Mallard (<i>Anas platyrhynchos</i>)	91.1	18.9	40	1980	46750926
Ring-necked pheasant (<i>Phaisianus colchicus</i>)	96.5	57	19	2000	46766204

Table 9 summaries feeding tests conducted on difenacoum and other anticoagulant rodenticides.

Table 9. Adverse Effects of Difenacoum and Other Anticoagulant Baits Fed to Adult Leghorn Chickens for up to 15 Days (adapted from Lund 1981)

Anticoagulant	Avg. intake per bird ^a		Mortality	Adverse effects
	Bait (g)	ai (mg/kg)		
Difenacoum (50 ppm)	611 (458-835)	19 (13.5-28.3)	2/4	loss of appetite; hemorrhage from day 5
Brodifacoum (50 ppm)	362 (252-443)	10.5 (7.1-15.0)	4/4	death from day 6
Bromadiolone (50 ppm)	496 (329-684)	12 (5.9-16.9)	2/4	loss of appetite; hemorrhage from day 6
Warfarin (250 ppm)	922 (584-1232)	149 (132-171)	0/3	none

^a range is given in parentheses

Table 10 summarizes a chronic toxicity on difenacoum to the Japanese quail.

Table 10. Chronic toxicity of difenacoum in Japanese quail.

Species	% ai	NOAEC (ppm)	Observation period (days)	Study date	MRID no.
Japanese quail (<i>Coturnix coturnix japonica</i>)	96.7	>0.100	140	2005	46799101

Table 11 summarizes the acute oral toxicity test on Difenacoum to the laboratory rat.

Table 11. Acute oral toxicity of difenacoum to the laboratory rat.

Species	% ai	LD ₅₀ (mg ai/kg)	Observation period (days)	Study date	MRID no.
Laboratory rat (<i>Rattus norvegicus</i>)	98.7	1.8 ♂ 2.6 ♀	14	1995	46750935 46750936

Table 12 summaries a chronic/developmental toxicity test on Difenacoum to the laboratory rat and rabbit.

Table 12. Chronic/developmental toxicity of difenacoum to the laboratory rat and rabbit.

Species	% ai	LOAEL/NOAEL (mg ai/kg-bw/day)	Exposure/ Observation period (days)	Study date	Effects Observed
Rabbit (<i>Oryctolagus cuniculus</i>)	98.5	Maternal: 0.015 / 0.005 Fetus: 0.015 (highest dose tested)	Days 8-20 post mating	1994	Increased coagulation time in dams at 0.015 dose level. No fetal effects observed.
Laboratory rat (<i>Rattus norvegicus</i>)	98.2	Maternal: 0.09/0.03 Fetus: 0.09 (highest dose tested)	Days 7-16 post mating	1994	Vaginal bleeding and increased kaolin-cephalin time in dams at 0.09 dose level. No fetal effects observed.
Laboratory rat (<i>Rattus norvegicus</i>)	NR ¹	0.1/0.03	Exposure = 90 days	NR	Dosed at 0.03, 0.1, 0.2 mg ai/kg bw/day. 10% death (males) and increase in prothrombin time and thrombin time (males and females) at medium dose. 55% mortality, increase in thrombin and prothrombin time in females, signs of toxicity at high dose.

¹Not Reported.

B. Aquatic Hazards Studies

All aquatic freshwater fish and invertebrate tests show Difenacoum to be very highly toxic to those species. This active is also toxic to algae.

Table 13 summaries freshwater acute toxicity tests on Difenacoum.

Table 13. Acute toxicity of difenacoum to freshwater fish.

Species	% ai	LC ₅₀ (ppb)	Exposure duration (h)	Study date	MRID no.
Rainbow trout (<i>Oncorhynchus mykiss</i>)	96.3	64	96 (renewal after 48 h)	1995	46750919
Bluegill sunfish (<i>Lepomis macrochirus</i>)	96.3	258	96 (renewal after 48 h)	1995	46750920

Table 14 summaries freshwater invertebrate toxicity tests on Difenacoum.

Table 14. Acute toxicity of difenacoum to aquatic invertebrates.

Species	% ai	EC ₅₀ (ppb)	Exposure duration (h)	Study date	MRID no.
Waterflea (<i>Daphnia magna</i>)	61.4% <i>cis</i> 38.6% <i>trans</i>	520	48	1991	46750918
	96.3	610	48	1995	46750917

Table 15 summaries a toxicity test on Difenacoum to algae.

Table 15. Toxicity of difenacoum to aquatic plants.

Species	% ai	EC ₅₀ / NOAEC (ppb)	Exposure duration (h)	Study date	MRID no.
Green alga (<i>Selenastrum capricornutum</i>)	96.3	320 / 250 (growth curve)	72	1995	46750929
	61.4% <i>cis</i> 38.6% <i>trans</i>	≥ 2500 (growth curve)	96	1991	46766205

C. Secondary Hazards Studies

The Agency reviewed several secondary hazard studies on birds and mammals (or their summaries) and found evidence that difenacoum, like related anticoagulants, are capable of producing toxicity effects secondarily.

Table 16 summaries adverse effects of difenacoum and other anticoagulants to barn owls exposed to rats fed toxic bait.

Table 16. Adverse Effects of Difenacoum and Other Anticoagulants to Barn Owls Exposed To Rats Fed Bait (adapted from Mendenhall and Pank 1980)

Anticoagulant	Days exposed	No. tested/ no. dead	Sublethal effects Observed
<i>Second-generation anticoagulants:</i>			
Difenacoum (50 ppm)	1 3 6 10	1/0 2/0 1/0 2/0	the 3 owls offered rats for 6 or 10 days survived but all hemorrhaged (1 severely)
Brodifacoum (50 ppm)	1 3 6 10	1/0 2/2 1/1 2/2	none reported in the lone survivor
Bromadiolone (50 ppm)	1 3 6 10	1/0 2/0 1/0 2/1	none reported
<i>First-generation anticoagulants:</i>			
Diphacinone (50 ppm)	10	2/0	none reported
Chlorophacinone (50 ppm)	10	2/0	none reported
Fumarin (250 ppm)	10	2/0	none reported

Table 17 summaries another barn owl study (Gray et. Al, 1992) showing adverse effects of difenacoum and other anticoagulants to barn owls exposed to mice fed toxic bait.

Table 17. Secondary toxicity in Barn Owls (Gray et al. (1992) .

			Residue Concentration (mg/kg)		
Survival Status	Anticoagulant consumed (µg/day)	Cumulative consumption (mg/kg owl bw)	Liver	Fat	Muscle
Difenacoum (50 ppm):					
Survived (n=3)	36 – 128	1.6 – 5.5	0.06 – 0.14	<0.01	0.01
Died (n=1)	101	3.7	0.25	0.01	0.01
Brodifacoum (50 ppm):					
Survived (n=3)	52 – 99	1.9 – 3.3	0.55 – 0.69	<0.01 – 0.01	0.02
Died (n=1)	133	5.5	1.67	0.13	0.04
Flocoumafen ^a (50 ppm):					

Survived (n=2)	39 – 43	1.8 – 1.9	0.51 – 0.52	0.01	0.04 – 0.06
Died (n=2)	56 – 85	2.2 – 2.8	0.57 – 0.70	0.07 – 0.08	0.05 – 0.06

^aFlocoumafen is not registered in the U.S.

In studies with **mammals**, Shore et al. (2003) present data on residues in polecats (*Mustela putorius*) accidentally killed on roads in England. Livers were analyzed for residues of second-generation anticoagulant rodenticides, including difenacoum, bromadiolone, flocoumafen, and brodifacoum. Of 100 carcasses collected for all three studies between 1992 and 1999, 31 contained residues of at least one second-generation anticoagulant. Difenacoum was the most prevalent compound, having been detected in 26 animals.

D. Characterization of Toxicokinetics

Absorption, distribution and excretion of difenacoum are similar to that reported for other second-generation anticoagulants (brodifacoum, flocoumafen, bromadiolone). Difenacoum appears to be well absorbed following oral administration.

- Difenacoum is slowly eliminated. Urinary and fecal excretion during a 7-d period after dosing of female rats, fecal and urinary excretion accounted for only 57 and 39%, respectively, of a dose of 0.05 and 0.54 mg/kg of [¹⁴C]-difenacoum. Excretion was greatest during the 24 h period after dosing and was very slow thereafter.
- Difenacoum and/or its metabolites are widely distributed in body tissues. The concentration of radioactivity was above the limit of detection in all 15 tissues analyzed in excretion studies, with highest concentrations found in the liver and pancreas.
- The concentration in fat was relatively low. Difenacoum is highly lipophilic, but that does not significantly affect tissue distribution due to a high affinity for specific binding sites in tissues.
- Elimination from tissues is biphasic, with an initial rapid phase during the first few days after dosing followed by a very slow phase. The slow elimination from tissues is consistent with the slow fecal elimination found during an excretion study.
- The *trans*-isomer is either less well absorbed or more rapidly eliminated from rats than is the *cis*-isomer, though the differences are not great.
- Difenacoum is partly excreted in feces as metabolites, and metabolites also constitute part of the residue in liver. Neither the extent of fecal excretion nor the proportion of metabolites in faeces is dose dependent, but the proportions of difenacoum and its metabolites in liver are both dose and time dependent.

E. Incidents in United Kingdom

Table 18 illustrates the potential for difenacoum to affect a wide range of nontarget organisms secondarily.

Table 18. Wildlife incidents involving difenacoum recorded in the UK's Wildlife Incident Investigation Scheme.

Year	No. Incidents ¹	Species Involved ²
2006	36 ³	cat, stoat, weasel, dog, buzzard, kestrel, barn owl, red kite, fox, ferret, pigeons, peacock
2005	15	buzzard, kestrel, red kite, badger, fox, grey squirrel, rat, bantam chicken, cat, dog, goose
2004	20	blackbird, buzzard, crow, house sparrow, red kite, sparrowhawk, badger, fox, pony, cat, dog
2003	11	crow, dove, red kite, badger, rabbit, cat, dog
2002	24	buzzard, feral pigeon, red kite, fox, cat, dog
2001	8	Buzzard, red kite, badger, pine marten
2000	15	buzzard, red kite, badger, fox, cat, dog
1999	19	buzzard, house sparrow, red kite, tawny owl, fox, cat, dog
1998	9	buzzard, pheasant, dog, cat

III. HUMAN HEALTH EFFECTS RISK ASSESSMENT

A. Toxicological Doses and Endpoints for Difenacoum in Human Risk Assessments

Table 19 summarizes the toxicological doses and endpoints for difenacoum in non-occupational human health risk assessments.

Table 19. Toxicological Doses and Endpoints for Difenacoum for Use in Non-Occupational Human Health Risk Assessments.				
Exposure/Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations)	Dietary endpoints were not selected because difenacoum is strictly a non-food use chemical.			
Chronic Dietary (All Populations)	Dietary endpoints were not selected because difenacoum is strictly a non-food use chemical.			
Incidental Oral (Episodic)	NOAEL = 0.005 mg/kg/day	UF _A = 10x UF _H = 10x	Residential LOC for MOE = 100	Developmental toxicity study in rabbits LOAEL = 0.015 mg/kg/day based on changes in blood coagulation (increased prothrombin and kaolin-cephalin times).
Dermal (Short-Term)	NOAEL = 0.005 mg/kg/day Dermal absorption rate = 4%	UF _A = 10x UF _H = 10x	Residential LOC for MOE = 100	Developmental toxicity study in rabbits LOAEL = 0.015 mg/kg/day based on changes in blood coagulation (increased prothrombin and kaolin-cephalin times).
Inhalation (Short-Term)	NOAEL = 0.005 mg/kg/day Default inhalation absorption rate = 100%	UF _A = 10x UF _H = 10x	Residential LOC for MOE = 100	Developmental toxicity study in rabbits LOAEL = 0.015 mg/kg/day based on changes in blood coagulation (increased prothrombin and kaolin-cephalin times).
Cancer	Classification: N/A			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 20 summarizes the toxicological doses and endpoints for difenacoum in occupational human health risk assessments.

Table 20. Summary of Toxicological Doses and Endpoints for Difenacoum for Use in Occupational Human Health Risk Assessments.				
Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal (Short-Term)	NOAEL= 0.005 mg/kg/day Dermal absorption rate = 4%	UF _A = 10x UF _H = 10x	Occupational LOC for MOE = 100	Developmental toxicity study in rabbits LOAEL = 0.015 mg/kg/day based on changes in blood coagulation (increased prothrombin and kaolin-cephalin times).
Inhalation (Short-Term)	NOAEL= 0.005 mg/kg/day Default inhalation absorption rate = 100%	UF _A = 10x UF _H = 10x	Occupational LOC for MOE = 100	Developmental toxicity study in rabbits LOAEL = 0.015 mg/kg/day based on changes in blood coagulation (increased prothrombin and kaolin-cephalin times).
Cancer	Classification: N/A			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

B. Residential Exposure and Risk

Since difenacoum is strictly a non-food use rodenticide and since, based on its physicochemical properties, no measurable concentrations of difenacoum are expected in drinking water, only residential exposure could be included in an aggregate assessment. Therefore, a separate aggregate risk assessment was not conducted.

1. Residential Handlers Exposure and Risk

An assessment for mixer/loader scenarios was not performed, since both formulations (pellets and place packs) are considered “ready-to-use”. Since the dermal and inhalation endpoints are the same, dermal and inhalation doses were combined to calculate a total MOE for applicator scenarios. All applicator scenarios resulted in total MOEs greater than the level of concern (MOEs ≥ 100) at the baseline level, as indicated in Table 21.

Table 21. Residential Handler Short-term Exposure and Risk for Difenacoum At Baseline (No Gloves).

Scenario	Use Site	Dermal Unit Exposure (mg/lb) ^a	Inhalation Unit Exposure (mg/lb) ^a	Application Rate ^b (lb ai/site)	Site Treated ^c (sites/day)	% Dermal Absorption	Dermal Dose ^d (mg/kg/day)	Dermal MOE ^f	Inhalation Dose ^e (mg/kg/day)	Inhalation MOE ^g	Total MOE ^h
Applicator											
Difenacoum (0.005% a.i.) pellets Reg.# 47629-XX	In and around homes, commercial, industrial and public buildings; rat burrows	103.77	0.47	0.0000218 (7 oz prod, = 794 pellets)	2	4	2.6E-6	1900	2.9E-7	17,000	1700
Difenacoum (0.005% a.i.) placepacks Reg.# 47629-XX	In and around homes, commercial, industrial and public buildings			0.0000094 (3 oz place pack)		4	1.1E-6	4500	1.26E-7	40,000	4100

a. PHED Version 1.1 Scenario 17: Granular Bait Dispersed by Hand; Dermal unit exposure (baseline- no gloves) = $5.67 + 62 + (3.61/0.1) = 103.77$

b. Application Rate based on proposed registered label for Difenacoum .

According to registrant one pellet weighs 0.25 grams. 1 ounce (28.35 g)/0.25 g = 113 pellets; 113 x 7 ounces = 794 pellets/7 oz

c. Number of bait sites set, treated per day

d. Short-term Dermal Dose (mg/kg/day) = [Rate (lb ai/A) x UE (mg /lb ai) x Sites Treated (A/day)] x % dermal absorption / BW (70 kg)

e. Short-term Inhalation Dose (mg/kg/day) = [Rate (lb ai/A) x UE (mg /lb ai) x Sites Treated (A/day)] / BW (70 kg)

f. Short-term Dermal MOE = [Dermal NOAEL (0.005 mg/kg/day)]/ Dermal Dose (mg/kg/day)

g. Short-term Inhalation MOE = [Inhalation NOAEL (0.005 mg/kg/day)] / Inhalation Dose (mg/kg/day)

h. Total MOE = NOAEL (0.005 mg/kg/day) / Dermal Dose (mg/kg/day) + Inhalation Dose (mg/kg/day)

2. Postapplication Dermal Exposure

EPA did not conduct a separate quantitative an adult, short-term, postapplication dermal exposure (adult clean-up and bait disposal) assessment because is would be similar to the to applicator exposure (adult bait application).

EPA did not conduct a quantitative child, short-term dermal postapplication exposure assessment because, although incidental child dermal contact could occur, EPA does not consider this exposure to be a routine behavior on a regular basis. It considers this exposure to be an episodic event.

3. Postapplication Episodic Incidental Ingestion of Bait

- EPA considers ingestion of granules to be an episodic event and not a routine behavior. EPA conducted this risk assessment because of the high incidence of episodic oral exposures (>15,000/year) for existing rodenticides on the market. Difenacoum Rat and Mouse Pellets pose the risk of incidental ingestion of pellets. The episodic oral MOE for incidental ingestion of granules by children is 0.3. Even though the Agency's level of concern is exceeded for episodic ingestion of difenacoum by children, the human health risk from the use of difenacoum will not be significantly different compared to other registered rodenticides with similar use patterns and mode of action. Additionally, the product label will include directions for application of the bait in areas inaccessible to children and pets

Table 22. Postapplication Exposure and Risk for Incidental Ingestion of Granules of Difenacoum.					
Scenario	IgR (g/day)	F	CF1 (mg/g)	Dose ^a (mg/kg/day)	MOE ^b
Difenacoum Rat and Mouse Pellets Reg No 47629-XX	5	0.00005	1000	0.016667	0.3

^a Dose = IgR x F x CF1 ÷ BW

^b MOE = NOAEL (0.005 mg/kg/day)/Dose

C. Occupational Exposure and Risk

1. Handlers Exposure and Risk

All Difenacoum applicator scenarios resulted in MOEs that are not of concern (MOEs ≥ 100).

2. Postapplication Exposure and Risk

All postapplication scenarios resulted in MOEs that are not of concern at the baseline level (MOEs ≥ 100).

IV. ECOLOGICAL FATE AND EFFECTS RISK ASSESSMENT

A. Potential Primary Risks

Acute Risk to Birds – Using the mallard LC₅₀ of 18.9 ppm, the dietary RQ for difenacoum bait formulated at 50 ppm is 2.6. This value exceeds the acute avian LOCs of 0.1 for listed species and 0.5 for non-listed species. These LOCs are also exceeded if the ring-necked pheasant LC₅₀ of 57 ppm is used; this value results in an RQ of 0.88. These RQ values indicate a concern for acute risk to birds resulting from primary exposure.

The dietary RQ exceeds the acute LOC for perching birds of a wide range of weights, often after one day. EPA concludes that if birds are exposed via direct consumption of bait, acute risk to birds is likely. These findings concur with those of the Rapporteur Member State in the draft CA Report.

Chronic Risks to Birds – EPA has concluded that there is a chronic risk is a concern for birds, although there is uncertainty with the actual calculated RQ value.

Acute Risks to Wild Mammals – EPA's comparative risk assessment for the rodenticide cluster used 25-g and 100-g rodents and 1000-g mammals to estimate the dose, amount of bait, and number of pellets needed to provide one LD₅₀ dose. These values are also used here, along with 15-g and 35-g rodents, in keeping with standard EFED procedures in estimating acute risk to wild mammals. In all cases, the dose-based RQ is above the acute risk LOCs for listed (LOC = 0.1) and non-listed (LOC = 0.5) mammals. Based on these numbers, acute risk is presumed for wild mammals that would consume bait directly. These results agree with the findings presented by the Rapporteur Member State in the CA Report.

Chronic Risks to Wild Mammals – The CA Report uses the 90-day rat repeated-dose toxicity test NOAEC to calculate chronic risk to wild mammals. EFED policy is to use a mammalian teratogenicity study if a two-generation rat reproduction study is not available. EFED concludes that chronic risk resulting from primary exposure to difenacoum is a concern for wild mammals. These findings agree with those of mammalian chronic risk due to primary exposure in the CA Report.

2. Potential Secondary Risks to Birds and Non-Target Mammals

The potential for risk to birds and non-target mammals resulting from secondary exposure to second-generation anticoagulants was identified in EFED's comparative risk assessment. Since difenacoum is a second-generation anticoagulant, there is sufficient

reason to expect that avian and mammalian risk will result from secondary and tertiary exposure to difenacoum.

The feeding studies with barn owls provide the best evidence that predatory birds will be affected by anticoagulant properties of difenacoum if they feed on contaminated animals. They also provide further evidence that difenacoum is similar to bromadiolone in terms of secondary risks and that information from other second-generation anticoagulants provides further evidence of the potential risk.

Similar types of feeding studies with mammals are not available for difenacoum, but studies were also presented that demonstrate difenacoum exposure in carnivorous mammals found killed along roadsides or trapped on game farms. Difenacoum is retained in the liver of birds for some time.

Incidents involving birds and difenacoum in the UK also indicate the potential for difenacoum to cause risk from secondary exposure. Predatory, scavenging, and/or omnivorous birds are included among the bird species associated with difenacoum in the UK incident reports, indicating the occurrence of secondary exposure and its effects on wildlife. The CA determined that acute and chronic risk is possible due to secondary poisoning.

3. Relationship of Difenacoum Toxicity to First- and Second-Generation Anti-Coagulants

EPA compared difenacoum to other anticoagulants based on acute toxicity, hepatic half-life, and avian and mammalian RQs. They concluded that the toxicity of difenacoum to most taxa is more similar to the second-generation anticoagulants than to the first-generation anti-coagulants. The liver half-life of difenacoum is also very consistent with those of the other second-generation anticoagulants.

Table 23. Difenacoum compared to other anticoagulants based on acute toxicity, hepatic half-life, and avian and mammalian RQs.

	2 nd Generation Anti-Coagulants				1 st Generation Anti-Coagulants		
	Difenacoum ¹	Brodifacoum	Bromadiolone	Difethialone	Diphacinone	Chlorophacinone	Warfarin
<i>Acute Toxicity</i>							
Mallard LD ₅₀	>2000	0.26	nd	nd	3158	Nd	620
Bobwhite LD ₅₀	66	nd	138 - 170	0.26	>400	258	>2150
Mallard LC ₅₀	19	2.0	158 - 440	1.4	906	172	890
Bobwhite LC ₅₀	nd	0.8	38	0.56	>5000	56	625
R-n. Pheasant LC ₅₀	57	nd	nd	nd	nd	Nd	nd
Rat LD ₅₀	1.8 - 2.6	0.4 - 0.6	0.6 - 0.8	0.3 - 0.8	2 - 7	3 - 11	2.5 - 680
Mouse LD ₅₀	0.8	0.4	1.7	0.5 - 1.3	2 - 340	1 - 17	4 - 40
Rbow trout LC ₅₀ (ppb)	64	15	240	51	2600	450	88,000
Bluegill LC ₅₀ (ppb)	258	25	3000	75	7500	710	>16,000
Daphnid EC ₅₀ (ppb)	520	980	240 - 2000	4	1800	640	>17,000
<i>Rat hepatic half-life(days)</i>	128	113 ² - 350	170 - 318	74 - 126	3 ²	Nd	26 ²

¹All values based on studies summaries in the difenacoum dossier provided by the registrant or in the CA Report. The studies that produced these values have not been subjected to standard EFED data evaluations.

²Fisher et al. 2003.

V. EFFICACY

Difenacoum has been used in Europe for over 30 years, and targets the same commensal rodent species (Norway rat, roof rat, and house mouse) proposed for the U.S. registration. European and US field data was submitted in support of the registration. The Registration Division also confirmed with Dr. Bobby Corrigan, a nationally known expert on rodent control, that there will be little if any difference in the efficacy of difenacoum on "European" rodents compared to "American" rodents.

Rats and mice are serious public health pests since they are hosts for vector transmitted diseases such as plague, murine typhus and Lyme disease. As an anticoagulant, difenacoum will not provide a new mode of action but it does provide a new bait formulation as a tool for rodent control. Since bait acceptance is critical to the efficacy of rodenticides, difenacoum bait provides the applicator with another choice of formulation which may prove to be more attractive to rodent pests in some situations.

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DISCLAIMER: The information presented in this Pesticide Fact Sheet is for informational purposes only and may not be used to fulfill data requirements for pesticide registration and reregistration.

APPENDIX I:

GLOSSARY OF TERMS AND ABBREVIATIONS

ADNT	Acute delayed neurotoxicity
a.i.	Active Ingredient
aPAD	Acute Population Adjusted Dose
ARI	Aggregate Risk Index
BCF	Bioconcentration Factor
CAS	Chemical Abstracts Service
ChE	Cholinesterase
ChEI	Cholinesterase inhibition
cPAD	Chronic Population Adjusted Dose
%CT	Percent crop treated
DAT	Days after treatment
DEEM-FCID	Dietary Exposure Evaluation Model - Food Consumption Intake Database
DNA	Deoxyribonucleic acid
DNT	Developmental neurotoxicity
DIT	Developmental immunotoxicity
DWLOC	Drinking Water Level of Comparison.
EC	Emulsifiable Concentrate Formulation
EEC	Estimated Environmental Concentration. The estimated pesticide concentration in an environment, such as a terrestrial ecosystem.
EPA	U.S. Environmental Protection Agency
FQPA	Food Quality Protection Act
GLC	Gas Liquid Chromatography
GLN	Guideline Number
LC₅₀	Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm.
LD₅₀	Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
LOAEL	Lowest Observed Adverse Effect Level
LOAEC	Lowest Observed Adverse Effect Concentration
LOC	Level of Concern
LOD	Limit of Detection
LOQ	Limit of quantitation
mg/kg/day	Milligram Per Kilogram Per Day
mg/L	Milligrams Per Liter

MOE	Margin of Exposure
MRID	Master Record Identification (number), EPA's system of recording and tracking studies submitted
MTD	Maximum tolerated dose
NA	Not Applicable
NOEC	No Observable Effect Concentration
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Effect Level
NOAEC	No Observed Adverse Effect Concentration
NPDES	National Pollutant Discharge Elimination System
OP	Organophosphate
OPP	EPA Office of Pesticide Programs
OPPTS	EPA Office of Prevention, Pesticides and Toxic Substances
PAD	Population Adjusted Dose
PAG	Pesticide Assessment Guideline
PAM	Pesticide Analytical Method
PHED	Pesticide Handler's Exposure Data
PHI	Preharvest Interval
ppb	Parts Per Billion
PPE	Personal Protective Equipment
ppm	Parts Per Million
PRZM/	
EXAMS	Tier II Surface Water Computer Model
RAC	Raw Agriculture Commodity
RBC	Red Blood Cell
RED	Reregistration Eligibility Decision
REI	Restricted Entry Interval
RfD	Reference Dose
SCI-GROW	Tier I Ground Water Computer Model
SF	Safety Factor
TGAI	Technical Grade Active Ingredient
UF	Uncertainty Factor
µg	micrograms
µg/L	Micrograms Per Liter
µL/g	Microliter per gram
USDA	United States Department of Agriculture
WPS	Worker Protection Standard

APPENDIX II:

Citations Considered to be Part of the Data Base Supporting the Registration of Difenacoum

- 35806 Mendenhall, V.M.; Pank, L.F. (1979) Secondary Poisoning of Owls by Anticoagulant Rodenticides. (U.S. Fish and Wildlife Service, Patuxent and Denver Wildlife Research Centers, unpublished study)
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- 46750903 Russell, S. (1996) Difenacoum: Determination of Physico-chemical Properties: Final Report. Project Number: 355/7/1014, 355/7. Unpublished study prepared by Corning Hazleton (Europe). 60 p.
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