INFOTOX (Pty) Ltd

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Retrieval and scientific interpretation of ecotoxicological information

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Report Compiled for
2022 Environmental Science ZA (Pty) Ltd (Envu)

Derogation Risk Assessment Report for FINALE® and RODILON® Rodenticides Containing Difethialone, a CMR Substance of Concern (Reproductive Toxicity Hazard)

Product trade names:

FINALE® Rat and Mouse Wax Blocks (L9643)

FINALE® Rat and Mouse Pellets (L9711)

RODILON® Rat and Mouse Wax Blocks (L5356)

INFOTOX Report No 001-2025 Rev 3.0

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31 March 2025

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WCA van Niekerk PhD QEP (USA) Pr Sci Nat (Environmental Science)
Managing Director

31 March 2025

Internal review:

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Expertise and Declaration of Independence

This report was prepared by INFOTOX (Pty) Ltd ("INFOTOX"). Established in 1991, INFOTOX is a professional scientific company, highly focused in the discipline of ecotoxicological risk assessment. Both occupational and environmental human health risks, as well as risks to ecological receptors, are addressed.

Dr Willie van Niekerk, Managing Director of INFOTOX, has BSc, Hons BSc and MSc degrees from the University of Potchefstroom and a PhD from the University of South Africa. He is a Qualified Environmental Professional (QEP), certified by the Institute of Professional Environmental Practice (IPEP) in the USA (No 07960160), and a registered Professional Natural Scientist (Pr Sci Nat, Environmental Science, No 400284/04). Dr Van Niekerk has specialised in chemical toxicology and human health risk assessments, but he has experience in many other areas in the disciplines of analytical and environmental sciences.

Dr Marlene Fourie has BSc and Hons BSc degrees from the University of Stellenbosch and MSc and PhD degrees from the University of Pretoria. Her field of specialisation is reproductive biology/toxicology. Dr Fourie also has an MSc-degree in epidemiology from the University of Pretoria. Following positions as Medical Natural Scientist at the Andrology Unit, Department of Urology, University of Pretoria and the Pretoria Academic Hospital from 1987 to 2001, she joined INFOTOX as a Medical Biological Scientist. Dr Fourie has conducted many health risk assessments and projects relating to the health status of communities. She is a registered Professional Natural Scientist (Pr Sci Nat, Toxicological Science, No 400190/14). Dr Fourie has completed the Globally Harmonised System (GHS) course *Classifying and Labelling Chemicals According to the UN GHS*, presented by the United Nations Institute for Training and Research (UNITAR) in 2017, with previous experience in GHS classification since 2010.

This specialist report was compiled for 2022 Environmental Science ZA (Pty) Ltd (Envu). We do hereby declare that we are financially and otherwise independent of 2022 Environmental Science ZA (Pty) Ltd (Envu).

Signed on behalf of INFOTOX (Pty) Ltd, duly authorised in the capacity of Managing Director:

Willem Christiaan Abraham van Niekerk

31 March 2025

Executive Summary

This document is a risk assessment report supporting an application for derogation for the restricted use of FINALE® and RODILON® registered solid rodenticide products, namely pellets and wax blocks, containing the active ingredient difethialone. The wax bock and pellet formulations are supplied to professional pest control operators ("PCOs") and to the general public.

The FINALE® and RODILON® rodenticides are identified as substances of concern due to classification as reproductive hazards category 1B according to the Globally Harmonized System of Classification and Labelling of Chemicals ("GHS"). The classification is due to the active ingredient difethialone, which is classified in GHS reproductive toxicity category 1B (H360D), indicating a hazard to the development of the unborn child ("D").

Product names, registered suppliers and Act 36 of 1947 registration numbers:

Product	Act 36 of 1947 registration numbers	Registered manufacturer / supplier / distributer
FINALE® Rat and Mouse Wax Blocks	L9643	2022 Environmental Science ZA (Pty) Ltd.
FINALE® Rat and Mouse Pellets	L9711	2022 Environmental Science ZA (Pty) Ltd.
RODILON® Rat and Mouse Wax Blocks	L5356	2022 Environmental Science ZA (Pty) Ltd.

Intended product use:
Solid anti-coagulant rodenticide products for use as follows:

Product	Use (according to label)
FINALE® Rat and Mouse Wax Blocks	… effective against warfarin resistant rats and mice. For use on the farm and industrial premises (outside buildings, warehouses and stores).
FINALE® Rat and Mouse Pellets	A highly active anticoagulant bait for control of the Norway rat (*Rattus norvegicus*), roof rat (*Rattus rattus*) and house mouse (*Mus musculus*). For indoor use in normal in-premises locations protected from weather or dampness.
RODILON® Rat and Mouse Wax Blocks	Active anticoagulant in block form for control of the Norway rat, roof rat and house mouse. Effective against warfarin resistant rats and mice. For use in the home, on the farm, in public health and industrial premises.

The human health risk assessments presented here are based on internationally-accepted human health risk assessment principles and methods. The health and ecological risk assessment guidance of the following major international regulatory agencies is followed:

- The 2016 Norwegian CA Assessment Report on Difethialone with a view to the renewal of the approval of difethialone as an existing active substance, in product-type 14 under the Biocidal Products Directive (Commission Directive 2007/69/EC), provided for in Article 14 of the Biocidal Product Regulation (EU) No 528/2012 (BPR).
- The 2007 Norwegian CA Assessment Report on Difethialone, Product-type 14 (Rodenticides), under Directive 98/8/EC concerning the placing (of) biocidal products on the market. Dated 21 June 2007.
- The 2016 US Environmental Protection Agency ("USEPA") Registration Review Scoping Document for Difethialone.
- The 2011 USEPA report on the Pesticide Effects Determinations of difethialone on certain non-target species.
- The 2020 USEPA Draft Human Risk Assessment for Registration Review of Anticoagulant Rodenticides Chlorophacinone, Diphacinone and its Sodium Salt, Brodifacoum, Bromadiolone, Difenacoum, Difethialone.

Human health risk assessment

The scope of the solid rodenticide human health risk assessment ("HHRA") is determined by the registered product use. The purpose is to evaluate the risks of reproductive/developmental toxicity effects in persons exposed to difethialone in the identified products listed above. Since developmental effects are the only health endpoints (aside from mortality) for which dose-response values are available in toxicological studies, there is no other choice but to base acceptable exposure levels of males and children on this health endpoint as well. Therefore, the absence of a risk to health in general, and specifically the absence of a risk to the developing foetus, is implied by a finding of "acceptable exposures" or "acceptable risks".

The following human exposure scenarios were identified for assessment:

- Primary dermal exposure of non-professionals (domestic users) and professional PCOs handling, placing, refilling and disposing of unused pellet and wax block baits.
- Secondary human exposures are assessed as:
    - Accidental dermal contact of adult non-professionals with the product in the use phase, or with potential product residues on dead or dying rodents.
    - Accidental exposure of infants/toddlers transiently mouthing or chewing on bait. Dermal exposure is not assessed separately, because regulatory agencies generally accept that potential dermal exposure of toddlers/infants is covered by the oral exposure assessment.

Adult difethialone pellet rodenticide users, whether PCOs or domestic users, are not at risk of a health effect, including effects on the development of the foetus in case of pregnant females, whether gloves are worn or not. However, this can never be used to negate the need for recommending the use of gloves while handling pellets, as discussed in the following paragraphs.

Provided that gloves are worn, PCOs handling FINALE® and RODILON® wax blocks are not at risk of a health effect, including effects on the development of the foetus in case of pregnant females. Dermal exposure of PCOs not wearing gloves would be unacceptable, particularly while applying blocks. Cleaning of bait boxes and disposal of left-over bait and dead rodents are not associated with a risk to health, whether gloves are worn or not.

The FINALE® and RODILON® wax blocks risk assessment for domestic users, assumed not to wear gloves, demonstrates that primary exposure while applying bait and cleaning up bait stations are not associated with a risk to health.

The above finding of the absence of a risk to health, in some scenarios, when gloves are not worn, does not invalidate the need for gloves. Gloves also protect against potential secondary exposure while handling dead rodents and against diseases carried by rodents. As recommended on the label, gloves should be worn while handling bait, cleaning up or removing dead rodents.

Secondary exposure without wearing gloves, of adult bystanders accidentally touching bait products, or disposing of left-over bait or dead rodents, or cleaning up bait dragged from bait stations by foraging rodents, is not associated with a risk to health.

An unacceptable risk of a health effect associated with secondary exposure is identified for children accidentally mouthing or chewing on pellets or wax blocks with 0.0025% difethialone.

The risks to health can be limited by clear communication of the pesticide applicator (professional or domestic) to such bystanders, and by following label instructions to keep the bait out of reach of children and uninformed persons.

Regardless of the precautionary measures followed, any noted contact of a child with a rodenticide should be brought to the immediate attention of a medical professional, without exception. All product labels must clearly display the contact details of a local/national poison centre.

Environmental (ecological) risk assessment

Secondary exposure in mammals and birds of prey describes the ingestion, by natural predators in the environment, of dead or dying target animals, that is, rats or mice in the case of rodenticide formulations. The general conclusions of international regulatory assessments based on available toxicity values in predatory birds and non-target predatory mammals is that secondary risks to mammalian and avian predators cannot be excluded. However, mitigation measures such as limiting access by non-target organisms and frequent inspections to search for and correctly dispose of rodent carcasses can limit the risk of secondary poisoning of non-target animals.

Responsible product application and care, with clear instructions on product labels and safety data sheets ("SDSs") to prevent contamination of waterways, should limit aquatic contamination to negligible. Therefore, no risk assessment for secondary poisoning through the aquatic food chain is required, and also no risk assessment for non-mammalian or non-avian terrestrial organisms.

The effects versus societal needs/benefits balance

There is no question that there is a legitimate societal need for cost-effective, relatively inexpensive rodenticides, considering the serious and potentially lethal human diseases, e.g., hantavirus, typhus and the bubonic plague, that are spread by mice and rats. Furthermore, rodent plagues imply a burden of economic costs of property, food and crop damage and spoilage.

Continued access to cost-effective rodenticides can be approached as an issue of environmental justice. The balance of societal need and benefits, versus the overt poisonous nature of the product, is always to be considered regarding any regulatory decisions to limit access to rodenticides. This is particularly important to socio-economically disadvantaged communities. Such communities bear a double burden of more frequent rodent infestations, with concomitant exposure to diseases spread by rodents, possible rat-bite injuries to infants, damage to property and food spoilage and contamination, and limited resources to use other, non-poisonous solutions.

Restricted use applied for

The restricted use applied for is according to the intended product use:

- A highly active anticoagulant bait for control of the Norway rat, roof rat and house mouse. Effective against warfarin resistant rats and mice.
- FINALE® Rat and Mouse Wax Blocks are for use on the farm and industrial premises (outside buildings, warehouses and stores).
- FINALE® Rat and Mouse Pellets are for indoor use in the home, on the farm and industrial premises, in locations protected from weather or dampness.
- RODILON® Rat and Mouse Wax Blocks are for use in the home, on the farm, in public health and industrial premises.

Mitigation measures

As recommended on the FINALE® and RODILON® product labels, gloves should be used by all users, PCOs and domestic users, while handling bait, while cleaning up and while disposing of left-over bait and dead rodents.

International regulatory agencies tend to recommend bait box use, in particular for domestic users or for application in the domestic scenario. Bait boxes are not recommended or obligated on the labels of the assessed FINALE® pellets and wax blocks formulations, but the user is instructed to "*Place …* the product … *in a covered bait station to prevent access by children and domestic*

animals". "*Bait boxes or other special containers*" are "*strongly recommended"* on the RODILON® wax blocks label. The method of risk calculation recommended in international guidance followed in this report does not include consideration of whether bait boxes are used or not. Therefore, the use of bait boxes will not change the risk assessment.

It is clear that bait boxes add an extra layer of protection for bystanders, pets and non-target animals, but it is not recommended that bait boxes should be made mandatory, because this will imply and added cost premium to the user. Considering the argument for the continued availability of lower cost, but effective, rodenticides to especially lower-income consumer groups, a blanket measure to make bait box use compulsory is not appropriate. However, bait box use in domestic settings should be encouraged.

Bait box use by PCOs should also not be made compulsory, because it is not always necessary, not always practical, and also not always the most effective method of application.

The complete set of mitigation measures recommended in Section 9.3 of this report must be adhered to.

Support for the restricted use application

The balance of societal need and benefits, versus the overt toxic nature of the product, is always to be considered regarding any regulatory decisions to limit access to rodenticides. This is particularly important to socio-economically disadvantaged communities. Such communities bear a double burden of more frequent rodent infestations, with concomitant exposure to diseases spread by rodents, possible rat-bite injuries to infants, damage to property and food spoilage and contamination, and limited resources to use other, non-poisonous solutions.

When the above mitigatory measures are applied, accidental poisoning of bystanders, children, pets and non-target animals can be effectively limited. Therefore, the applications for derogation of the products assessed in this report are supported, provided that recommended mitigation measures are effectively implemented.

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List of Abbreviations

AEL	Acceptable exposure level
BCFs	Bioconcentration factors
BW	Body weight
CMR	Carcinogenicity, mutagenicity, and reproductive toxicity
EC	European Commission
EC50	The concentration of a compound resulting in a half-maximal response, e.g., immobilisation of invertebrates or inhibition of algal growth
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemical's
ECHA	European Chemicals Agency
ErC50	The aqueous concentration of a test substance resulting in a 50% reduction in growth rate of aquatic organisms
EU	European Union
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
HEEG	Human Exposure Expert Group
HHRA	Human health risk assessment
IPCS	International Programme on Chemical Safety
KABAM	Aquatic bioaccumulation model
K_{oc}	Partition coefficient organic carbon-water
K_{ow}	Octanol-water partition coefficient
LD50	The dose (mg/kg body weight) of a chemical that is lethal to 50% of exposed experimental animals
LC50	Lethal concentration 50, the concentration required to kill half of a group of aquatic test animals
LOAELs	Lowest-observed-adverse-effect levels
LOC	Level of concern
MOE	Margin of exposure
NOAELs	No-observed-adverse-effect levels
NRC	US National Research Council
OECD	Organisation for Economic Co-operation and Development
OPPT	USEPA Office for Pollution Prevention and Toxics
PCOs	Pest control operators
PNECs	Predicted no-effect concentrations
POD	Point of departure
PPDB	Pesticide Properties Database
PPE	Personal protective equipment
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SDSs	Safety data sheets
FGARS	First generation anticoagulant rodenticides
STOT RE	Specific target organ toxicity (repeated exposure)
TNsG	Technical Notes for Guidance
TRA	Targeted Risk Assessment
UF	Uncertainty factors

UFA	Uncertainty in extrapolating animal data to humans
UFH	Variation in susceptibility among the members of the human population
UF_{Sev}	Additional factor for severity of effects.
USEPA	United States Environmental Protection Agency

List of Terms

Acute toxicity	Adverse effects following oral or dermal administration of a single dose of a substance, or multiple doses given within 24 hours, or an inhalation exposure of 4 hours.
Anticoagulants	Chemical substances that decrease the clotting of blood, which, at sufficient blood concentrations, can cause excessive bleeding.
Carcinogenicity	Substance that causes cancer.
Derogation	An exemption from or relaxation of the consideration of this product for removal from the market due to it being considered a CMR product of concern.
Developmental toxicity	Any developmental malformation of the foetus, caused by a toxic substance. that is caused by the toxicity of a chemical or pathogen.
Environmental Fate	Behaviour in or movement of a chemical substance after having been released to the environment. The behaviour in or movements through the environmental compartments of air, soil and water, and the preferred final destiny compartment(s) are described.
Epidemiology	Study of the determinants, occurrence, and distribution of health and disease in a defined population.
Exposure assessment	Identification of environmental pathways, potentially exposed groups, routes of direct and indirect exposure, and estimates of concentrations and duration of exposure.
Genotoxicity	Damage to the cell genes, which may result in mutations.
Mutagenicity	Property of chemical agents to induce genetic mutation.
Neurotoxicity	Ability of a chemical to cause damage or malfunction of the neurological system.
Receptors	People/organisms exposed to the substance of interest.
Registrar	Registrar of the fertilisers, farm feed, agricultural remedies and stock remedies Act, 1947 (Act 36 of 1947) in the Department of Agriculture, Land Reform and Rural Development.
Reproductive toxicity	A substance or agent that can cause adverse effects on the reproductive system, causing the inability to reproduce offspring.
Risk characterisation	Integration of the components described above. The risk characterisation will also provide a review of documented human exposure incidents
Routes of exposure	Inhalation, ingestion, and dermal contact
Surrogate	A chemical with properties, including potential toxicity, that are likely to be similar to another substance of interest for which little information about the properties and/or toxicity are known. “Transferring” the known properties of the surrogate to that of the uncharacterised substance is known as the “bridging principle”, or “read-across” for the purposes of hazard and risk assessment.
Target organ toxicity	The effects on the organ impacted by a hazardous substance
Teratogenic	Causing defects in a developing foetus
Uncertainty review	Identifies the nature and, when possible, the magnitude of the uncertainty and variability inherent in the characterisation of risks

1 Introduction

1.1 Products identification

This document is a risk assessment report supporting an application for derogation for the restricted use of the registered solid rodenticide products listed below.

Report prepared for:		
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All products in Table 1.1.1 contain the rodenticide active substance difethialone, which has been identified as a reproductive toxicity hazard.

Table 1.1.1: Assessed products.

Product	Act 36 of 1947 registration numbers	Registered manufacturer / supplier / distributer
FINALE® Rat and Mouse Wax Blocks	L9643	2022 Environmental Science ZA (Pty) Ltd.
FINALE® Rat and Mouse Pellets	L9711	2022 Environmental Science ZA (Pty) Ltd.
RODILON® Rat and Mouse Wax Blocks	L5356	2022 Environmental Science ZA (Pty) Ltd.

1.2 Regulatory context

In a document circulated to “All Regulatory Holders” on 14 April 2022, the Registrar: Act 36 Of 1947, of the Department of Agriculture, Land Reform and Rural Development (“Registrar” and “The Department”) refers to an assessment that was carried out at the international level to determine risks to human health due to exposure to active ingredients and their formulations that meet the criteria of carcinogenicity, mutagenicity, and reproductive toxicity (“CMR”) categories 1A or 1B according to the Globally Harmonized System of Classification and Labelling of Chemicals (“GHS”). The Department then stated that “*the assessment identified the need to reduce risks to human health associated with such products*”.

Category 1A covers substances that are known to be CMR, mainly according to human evidence. Category 1B covers substances presumed to be CMR based on data from animal studies.

The Registrar stated his intention to "*prohibit the use of ingredients and their formulations that meets* (sic) *the criteria of CMR categories 1A or 1B of the GHS as from 01 June 2024*".
However, in exceptional circumstances, the Registrar may grant registration of an implicated agricultural remedy when it can be demonstrated that:

"a) The risk to humans, animals or the environment from exposure to the active substance in an agricultural remedy, under realistic worst-case conditions of use, is negligible" (and other conditions not relevant to this INFOTOX report).

In February 2024, the Registrar issued a Guideline for the Application for a Derogation for an Agricultural Remedy Identified as a Substance of Concern.

This INFOTOX report deals with the assessment of risk to humans, animals and the environment, associated with the use of the rodenticide products indicated in Section 1. Specific attention is given to the risk of reproductive toxicity effects in occupational workers.

2 Background to human health risk assessment

2.1 The health risk assessment paradigm

A significant factor in the Organisation for Economic Co-operation and Development (OECD 2021) guidance document on key considerations for the identification and selection of safer chemical alternatives deals with the likelihood of exposure (human and ecological). OECD recommended that routes of exposure to a hazardous chemical that are unlikely, based on measured exposure data or physical-chemical properties of the substance of concern, should be excluded from the assessment. More correctly, the statement should refer to pathways of exposure (air, soil, water, and sediment), and routes of exposure (inhalation, ingestion, and dermal contact).

This recommendation of the OECD (2021) takes the assessment a step further from the hazard data of chemicals represented in the GHS, to the level where the potential for exposure of humans and ecological receptors is assessed, and through accounting for the toxicology of a substance or formulation, the level of risk is determined. This is aligned with the observations and recommendations of Karamertzanis et al. (2019).

Karamertzanis et al. (2019) evaluated the impact on classifications of carcinogenicity, mutagenicity, reproductive and specific target organ toxicity after repeated exposure in the first ten years of implementation of the REACH[1] regulation. The authors highlighted that classification for carcinogenicity, mutagenicity, reproductive toxicity, and specific target organ toxicity (repeated exposure) ("STOT RE") triggers several obligations for manufacturers, importers, and professional users.

Karamertzanis et al. (2019) then stated:
"*In addition to such consequences under other legislations* (sic)*, registrants are required to carry out exposure assessment and risk characterisation for substances that are classified and, hence, classification under REACH is a trigger for risk assessment for human health."*

[1] Registration, Evaluation, Authorisation and Restriction of Chemicals.

OECD (2021) referred to the European Centre for Ecotoxicology and Toxicology of Chemical's ("ECETOC")[2] Targeted Risk Assessment ("TRA") tool for calculating the risk of exposure from chemicals to workers, consumers, and the environment. This illustrates the logic of basing the final decision about the safety of a chemical or formulation on health risk assessment, rather than only on hazard identification, as represented in the GHS.

The original paradigm for regulatory human health risk assessment ("HHRA") in the USA was developed by the US National Research Council (NRC 1983). This model has been adopted and refined by the US Environmental Protection Agency ("USEPA") and other international agencies as published under the International Programme on Chemical Safety (IPCS 1999; IPCS 2010), and is widely used for quantitative human health risk assessments.

Figure 2.1.1 illustrates the health risk assessment paradigm in a simple diagram.

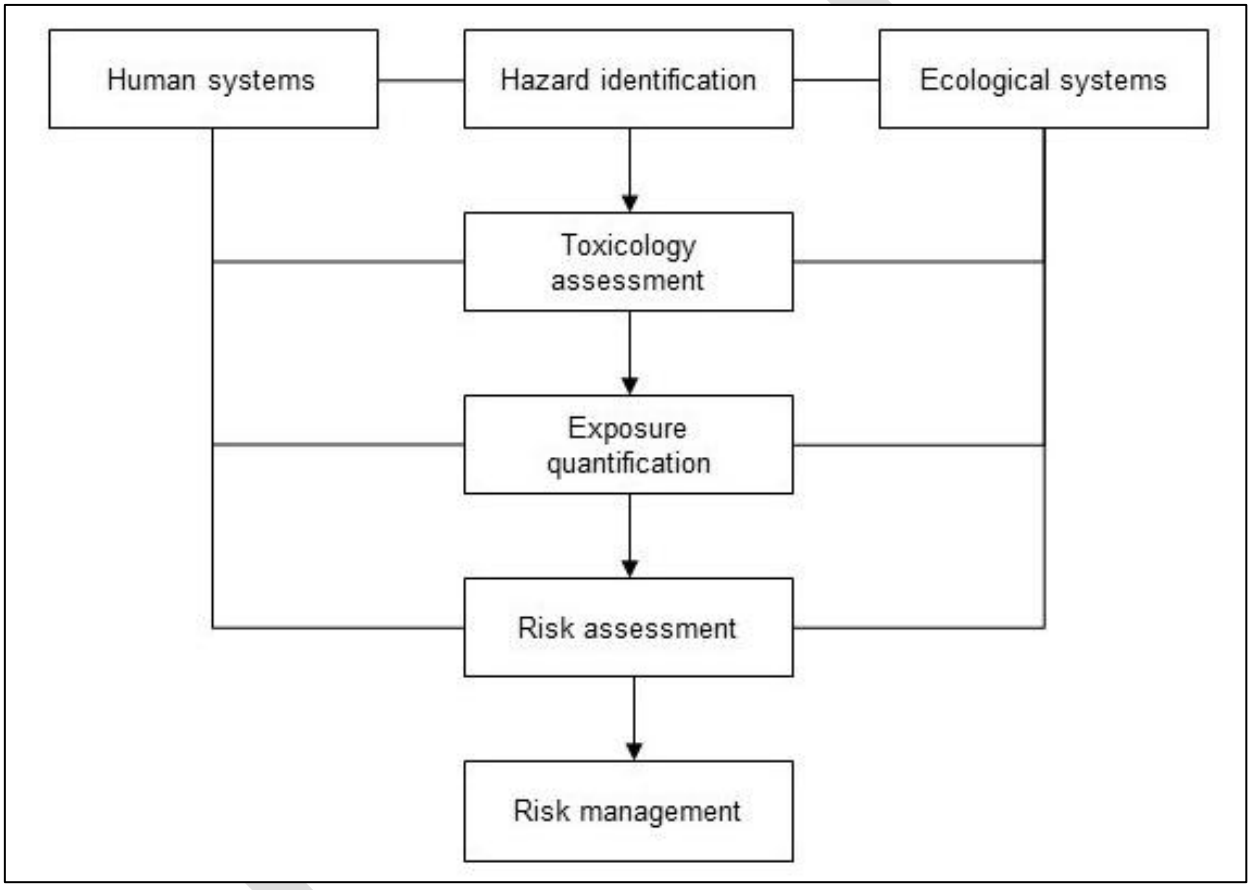


Figure 2.1.1: The holistic health risk assessment paradigm.

It is shown in this INFOTOX report that exposure assessment and health risk quantification are essential steps in managing health risks associated with hazardous chemicals.

2.2 Human health risk assessment methodology

The human health risk assessment ("HHRA") paradigm divides human health risk assessment into several logical steps, as illustrated in Figure 2.2.1. All of these are not fully applicable to the toxicological risk assessment for the purpose of derogation of rodenticides:

[2] http://www.ecetoc.org/tools/targeted-risk-assessment-tra/.

- **Hazard assessment** is the identification of the chemical constituent of concern and the hazard it poses, in this case reproductive/developmental toxicity hazards of difethialone. This is discussed in Section 3.
- **Dose-response assessment** (toxicological assessment) addresses the relationship between levels of uptake and the manifestation of adverse effects (reproductive/developmental toxicity). Toxicological information from available reproductive/developmental studies and applied standard risk assessment methodologies are used to derive a point of departure ("POD") and acceptable exposure level ("AEL") or acceptable operator exposure level ("AOEL") for HHRA purposes, by applying appropriate uncertainty factors and safety factors for infants and children, referring to dose through the routes of exposure. The AEL is the exposure dose that is accepted as not associated with a risk to human health. The derived toxicological values will be protective specifically against potential reproductive/developmental effects of the product. This ensures compliance with the Guideline for the Application for a Derogation for an Agricultural Remedy Identified as a Substance of Concern, issued by the registrar: Act 36 of 1947, in February 2024.

- **Exposure assessment considers** the identification of environmental pathways, potentially exposed groups, routes of direct and indirect exposure, and estimates of concentrations and duration of exposure. A conceptual model of application practices and exposure pathways and routes applicable to the identified receptors was constructed to guide the exposure assessment for the health risk assessment.

  The HHRA considers the following potential <u>occupational exposure</u> scenarios:
  - The oral, dermal and inhalation routes of exposure of professional pest control rodenticide applicators.

  <u>Residential exposure</u> scenarios are assessed, because the rodenticides are for sale in retail outlets catering to the general public:
  - Assuming that non-professionals might not be diligent users of personal protective equipment ("PPE"), the exposure of domestic users (non-professionals) handling rodenticides without gloves, that is, dermal exposure, is assessed.
  - The normal procedure recommended on product labels is to place rodenticides for residential exposure out of reach of children, and away from food products or places where food may be stored or prepared. E.g., label instructions are: "*Set bait stations where these will be inaccessible to children and domestic animals*".
  - Nonetheless, accidental mouthing or ingestion of bait by infants/toddlers are assessed.

- **Risk characterisation** involves the integration of the components described above. The risk characterisation also provides a review of documented human exposure incidents, if available.

- **Uncertainty review** identifies the nature and, when possible, the magnitude of the uncertainty and variability inherent in the characterisation of risks.

The human health risk assessments presented here are based on internationally-accepted human health risk assessment principles and methods. The health and ecological risk assessment guidance of the following major international regulatory agencies is followed:

- The Norwegian CA Assessment Report on Difethialone with a view to the renewal of the approval of difethialone as an existing active substance, in product-type 14 under the Biocidal Products Directive (Commission Directive 2007/69/EC), provided for in Article 14 of the Biocidal Product Regulation (EU) No 528/2012 (BPR) (Norwegian CA 2016).

- The Norwegian CA Assessment Report on Difethialone, Product-type 14 (Rodenticides), under Directive 98/8/EC concerning the placing (of) biocidal products on the market. Dated 21 June 2007 (Norwegian CA 2007).
- The US Environmental Protection Agency ("USEPA") Registration Review Scoping Document for Difethialone (USEPA 2016).
- The USEPA (2011a) report on the Pesticide Effects Determinations of difethialone on certain non-target species.
- The USEPA (2020) Draft Human Health Risk Assessment for Registration Review of Anticoagulant Rodenticides Chlorophacinone, Diphacinone and its Sodium Salt, Brodifacoum, Bromadiolone, Difenacoum, Difethialone.

3 Hazard identification

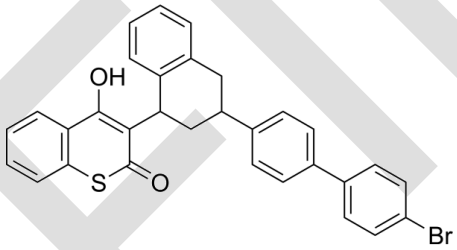
3.1 The need for GHS classification

Internationally, there is a demand for safer chemicals and technologies, and it is appropriate to utilise information in the GHS as a starting point. This INFOTOX report relates specifically to active ingredients and their formulations that meet the criteria of CMR categories 1A or 1B in the GHS. Information in the GHS represents hazard data, not information on risk.

3.2 Difethialone CMR hazard classification

Difethialone is a second-generation anticoagulant rodenticide ("SGAR"). It is a derivative of benzothiopyranone, which is similar to 4-hydroxycoumarin, the backbone of most SGARs (McGee et al. 2020).

Active ingredient identification

 **Difethialone**	**CAS #:** 104653-34-1 **Mol. formula:** $C_{31}H_{23}BrO_2S$ **Molecular weight:** 539.5 g/mol **ISO common name:** difethialone

The GHS hazard classification identifying the product as a CMR hazardous substance of concern, is: Reproductive toxicity category 1B (H360D); "D" indicating a hazard of developmental effects (effects on the growing foetus) (Table 3.2.1).

Table 3.2.1: CMR GHS classification of difethialone.

Hazard class and category code	Hazard statement code	Hazard statement	Signal word	Pictogram
Carcinogenic	Not classified	Not applicable	Not applicable	Not applicable
Mutagenic	Not classified	Not applicable	Not applicable	Not applicable

Reproductive Toxicity Cat. 1B	H360D	May damage the unborn child	Danger	
Classification according to the European Chemicals Agency ("ECHA" online); harmonised European Union ("EU") classification.				

GHS Category 1B criteria for substance classification:

- Presumed human reproductive toxicant - largely based on evidence from experimental animal studies.
- Animal studies provide clear evidence of an adverse effect on fertility or on foetal development in the absence of other toxic effects.
- If other toxic effects were present, the adverse effects on reproduction must have been regarded as not secondary to the toxic effects.

Table 3.2.2 presents the difethialone concentrations of the rodenticide products included in this assessment report. All products are mixtures of more than one chemical substance. None of the other constituent substances have been classified as CMR hazards. The complete compositions are not provided here, in order to protect proprietary information, but have been made available to the Registrar of Act 36 of 1947, in confidence, at the time of the application for registration.

Table 3.2.2: Concentrations of difethialone in the rodenticide products.

Formulation components	Active ingredient content	
	g/kg	% w/w
Pellets		
FINALE® Rat and Mouse Pellets	0.025	0.0025
Block form		
FINALE® Rat and Mouse Wax Blocks	0.025	0.0025
RODILON® Rat and Mouse Wax Blocks	0.025	0.0025

Hazard classification identifying products as CMR substances of concern:
Difethialone is assigned the H-code H360D; "D" indicating developmental effects (effects on the growing foetus). The hazard classifications of FINALE® and RODILON® rodenticide products have been dealt with in the existing product registrations.

The difethialone classification presented in Table 3.2.1 is according to the Summary of Classification and Labelling presented by the European Chemical Agency ("ECHA") (ECHA online). The *Reproductive toxicity hazard, category 1B (H360D)* is associated with a "*Specific Concentration limit*" of *Repr. 1B; H360D: C ≥ 0.003 %* according to the harmonised GHS classification relevant to Annex VI of European Community Regulation (EC) No 1272/2008 (CLP Regulation). The implication of the "*specific concentration limit"* is that the FINALE ® and RODILON® rodenticide products, assessed in this report, should be classified as a GHS Category 1B Reproductive toxicity hazard, based on the relevant concentrations of difethialone in the products (Table 3.2.2). The listed products are assigned the H-code H360D because the concentrations of difethialone are sufficient to justify the reproductive toxicity classification (≥ 0.003 % mass) according to the ECHA classification limit for chemical mixtures containing difethialone.

It is understood that the South African classification regulations actually refer to the GHS as presented in the latest revised edition of the UN "Purple Book". It is further understood that the Purple Book refers only to the concentration limit of 0.1%. Technically the concentrations of difethialone in the FINALE® and RODILON® products do not meet the criteria for classification of the rodenticide products according to the Purple Book. However, the decision to apply for derogation is motivated by the strict classification according the ECHA specific concentration limit.

4 Environmental fate and behaviour

4.1 Difethialone in air

Difethialone is not considered readily volatile and is not expected to partition into the atmosphere to a significant extent, due to:

- Low vapour pressure less than 1.3×10^{-5} Pa (22.6°C).
- Henry's law constant less than 1.8×10^{-2} $Pa.m^3.mol^{-1}$

The predicted poor partitioning into air was supported by low levels of volatilisation observed in aerobic soil metabolism studies. Furthermore, a very short atmospheric half-life (approximately 2 hours) is theoretically predicted; therefore, atmospheric transport is also unlikely (Norwegian CA 2016 and USEPA 2011a).

4.2 Difethialone in water

Difethialone is poorly/slightly soluble in water (Norwegian CA 2016, USEPA 2011a and Lewis et al. 2016), at 0.39 mg/litre.

Difethialone is hydrolytically stable, with variously reported half-lives (Norwegian CA 2016, USEPA 2011a):

- 154 to 211 days at pH 5, 7 and 9 (USEPA 2011a).
- Norwegian CA (2016):
  - pH 5: > 1 year
  - pH 7: 175 days
  - pH 9: 155 days

However, difethialone is rapidly photodegradable in water, with half-lives (DT_{50}) of less than or close to 60 minutes (23 to 62 minutes), in a pH range of 5 to 9, depending on the water temperature (USEPA 2011a and Norwegian CA 2016).

Abiotic degradation studies in water indicate the formation of multiple components, but none has been chemically identified (Norwegian CA 2016).

Difethialone is not readily biodegradable in water (Norwegian CA 2016), with less than 6% biodegradation within 28 days in standardised tests.

According to the USEPA (2011a) bioaccumulation in fish is expected, due to its estimated log of the octanol/water partition coefficient (log K_{ow}) of 9.82. A slightly lower log K_{ow} of 6.29 at pH 7.3 and ambient temperature is listed by the Norwegian CA (2016). Lewis et al. (2016) also listed difethialone as a substance with a high potential for bioconcentration, with a BCF of 39 974 litre/kg.

4.3 Difethialone in soil

The organic carbon-water partition coefficient ("K_{oc}") in soil indicates the mobility of a chemical in soil, that is, the propensity of a chemical substance to bind to the organic matter present in soil. A high Koc value is associated with a strong bond to the soil particles, and thus less mobility (less likely to move, or leach, through soil). A lower Koc value indicates chemical mobility, and faster leaching rates through soil. A higher Koc can thus also indicate potential accumulation of a chemical in soil over time, under conditions of continuous addition to soil, but such conditions are not applicable to rodenticides.

Lewis et al. (2016) lists a very high K_{oc} of 54 000 000 litre/kg, based on which it is concluded that difethialone is essentially non-mobile in soil. The USEPA (2011a) listed a much lower value of 555 litre/kg wet weight, but also concluded that the compound was immobile, based on studies in four types of soil. The Norwegian CA (2016) is in agreement regarding immobility in soil, based on Freundlich soil adsorption coefficients, normalised for organic carbon content ($K_f$oc) of 1.0×10^8 to 5.3×10^9 litre/kg for soil adsorption.

The practical implication of the low difethialone concentrations in rodenticides, the low rodenticide application rates and the high tendency of the substance to absorb to soils, is that difethialone is unlikely to leach through soil, unlikely to contaminate groundwater, and that the potential for surface runoff, contaminating surface water, is low.

4.4 POP classification

According to the Norwegian CA (2016) difethialone has a high bioaccumulation potential in mammals/birds. The average aerobic biodegradation half-life in soil is 635 days at a temperature of 20°C, which exceeds the criteria for persistence (>120 days) and can be classified as very persistent (>180 days). However, since atmospheric transport of difethialone is unlikely (Section 4.1), the substance does not meet all criteria for classification as a persistent organic pollutant (“POP”).

4.5 Summary

The environmental fate concerns regarding difethialone are summarised in Table 4.5.1.

Table 4.5.1: Summary of environmental fate concerns for difethialone.

Concern	Notes
Volatilisation	Not volatile
Aquatic bioconcentration/ bioaccumulation	Not readily biodegradable in aquatic systems. Although stable to hydrolysis, difethialone is highly susceptible to photolysis. Bioaccumulation in fish is expected.
Persistence in soil	Highly absorbent to soil, is essentially immobile. The long aerobic biodegradation half-life in soil indicates persistence in soil, but difethialone is not classified as a POP, because atmospheric transport to soils and water bodies is unlikely.
Groundwater contamination	Low potential, is immobile in soil.
Sediment contamination	Insufficient information
Residues of concern	No major metabolites found
References: Norwegian CA (2016) and USEPA (2011a)	

5 Environmental assessment

5.1 Primary vs secondary exposure

Primary exposure of non-target species, that is, direct contact with and ingestion of the rodenticide, is not expected, since the usual rodenticide label instructions are to place the bait out of reach of animals. However, the use of bait boxes is not mandatory, although the labels refer to "covered bait stations"; therefore, attention is given to primary exposure and risk assessments conducted by the reviewed regulatory authorities (e.g., the Norwegian CA 2016).

Secondary exposure in mammals and birds of prey describes the ingestion, by natural predators in the environment, of dead or dying target animals, that is, rats or mice in the case of solid difethialone formulations.

The assessment of secondary exposure where predators have access to dead or dying rodents is not trivial. One approach to the study of secondary exposures of predators requires field studies conducting detail experimental examinations, e.g., of the stomach content of predators. The experimental data are then incorporated into complex probabilistic risk assessments. However, these complex assessments do not guarantee sufficient evidence to support definitive conclusions, since important uncertainties and data gaps tend to remain.

5.2 Toxicity to rodents and non-target species

Mammals

As expected, difethialone is "*very highly toxic"* to mammals in an acute oral exposure scenario (USEPA 2011a). A rat LD50 value of 0.4 to 0.8 mg/kg-bw is reported for difethialone by the Norwegian CA (2016) for the assessment of acute primary exposure (ingestion of the bait) of mammals. The USEPA (2011a) had used a similar rat acute oral LD50 of 0.55 mg/kg-bw for environmental risk assessment purposes.

Birds

The avian acute toxicity LD50 of difethialone in the bobwhite quail is 0.264 mg/kg-bw (Norwegian CA 2016). This value was also used by the USEPA (2011a) for the assessment of secondary risks to predatory birds, and was also used for the assessment of risks to reptiles. The bobwhite quail short-term dietary (5 days feeding) LC50 of difethialone is 0.560 mg a.i./kg food (Norwegian CA 2016). The Norwegian CA (2007) cites an unreferenced secondary poisoning dietary study with barn owls, which indicates that excretion/metabolism during the 56-day observation period was low and that ingested difethialone in rats is readily available to the owls.

Reproductive toxicity studies in birds were waived, based on animal welfare considerations, but a difethialone reproductive toxicity NOEC of 0.01 mg/kg food was determined, based on read-across from an avian reproduction NOEC for difenacoum (Norwegian CA 2016).

The above information supports the USEPA (2011a) conclusion that difethialone is considered "*very highly toxic"* to birds on an acute oral and subacute dietary exposure basis.

Aquatic compartment

Difethialone's toxicity to organisms in the aquatic compartment is judged as high (Lewis et al. 2016 and Norwegian CA 2007) as reflected in the following Norwegian CA (2016) toxicity data:

- Fish (*Oncorhynchus mykiss*) 96 hours LC50 = 51 µg/litre.

- Invertebrates (*Daphnia magna*) 48-hours immobilisation EC50 = 4.4 µg/litre.
- Algae (*Selenastrum capricornotum*) 72-hours growth rate inhibition ErC50 > 180 µg/litre.

Despite the highly toxic nature of difethialone, the likelihood of a risk to the aquatic compartment was considered very low by the Norwegian CA (2007), based on a comparison of the most sensitive EC50 (4.4 µg/litre for daphnia) and the predicted environmental concentration ("PEC") of difethialone in the aquatic compartment, associated with difethialone rodenticide use.
Secondary poisoning through the aquatic food chain is not assessed in this risk assessment report, because responsible product application and care, with clear product label and SDS instructions to prevent contamination of waterways, should limit aquatic contamination to negligible.

The activated sludge microorganisms 3-hours EC50 for microbial respiration inhibition is more than 100 mg/litre sludge, which greatly exceeds the solubility limit (0.39 mg/litre) of difethialone in water (Norwegian CA 2007). Therefore, the risk of difethialone inhibition of biological sewage treatment processes is negligible.

Terrestrial invertebrates
The acute toxicity of difethialone to earthworms is considered low (Lewis et al. 2016). The difethialone LC50 for exposure of *Eisenia fetida* for 14 days is more than 1 000 mg/kg dry soil, that is, 885 mg/kg wet weight. Observed mortality at this level was 23% (Norwegian CA 2007 and 2016).

Effects on honeybees and other beneficial arthropods were thought not relevant to the rodenticide use of difethialone and were not assessed by the Norwegian CA (2016).

5.3 Environmental assessments by international regulatory authorities

The USEPA (2011a) concluded that the primary route of dissipation/transport of difethialone through the environment might be through consumption of the bait product by target species that do not die immediately after feeding. The affected rodents may move to fairly distant places before dying, during which time secondary exposure of predatory animals occur, as explained in Section 5.1.

The USEPA (2011a) assessed the potential for adverse effects of difethialone rodenticide use on a non-target rodent species, a small fox species and a predatory snake species in terms of:
- Direct toxic effects through primary and secondary exposure on:
  - Survival.
  - Reproduction.
  - Growth of individuals.
- Indirect effects, namely:
  - Reduction of food sources, and/or
  - Modification of the habitat.

In summary, the USEPA (2011a) found a risk of adverse effects on:
- Snakes and reptiles through direct toxic effects associated with secondary rodenticide exposure.
- Small and larger mammals through direct and indirect effects.

These results can likely be extrapolated to most other predatory species that include rodents in their diets.

The Norwegian CA (2007) conclusions are similar to the USEPA. A high risk of primary and secondary poisoning to non-target mammals and birds is identified for difethialone rodenticides. Moreover, the substance can be considered as a potential "PBT" substance (persistent, bioaccumulative and toxic) and as a "vPvB" (very bioaccumulative, very persistent). Therefore, the CA advised that rodenticides containing difethialone have to be handled with great caution and proper measures to protect people and the environment should be in place when such products are used.

The European Commission (EC 2017) decision document for the approval of difethialone for use in biocidal products of product-type 14 (rodenticides) also mentioned concerns in relation to instances of primary and secondary poisoning, even where restrictive risk management measures are applied.

Therefore, it is fair to conclude that secondary exposure risks to non-target terrestrial and avian species cannot be excluded. Reasons to support the continued use of rodenticides with the difethialone active ingredient are presented in Section 9.2.

6 Human health and toxicological review

6.1 Pertinent human health effects

Difethialone is an SGAR, as explained previously, a second-generation repeated-dose anticoagulant rodenticide. Anticoagulent rodenticides are structurally similar to vitamin K, allowing disruption of the normal blood clotting mechanisms by inhibiting enzymatic vitamin K regeneration (Norwegian CA 2017). The result of biochemical interference is an increased bleeding tendency and, eventually, haemorrhage and death. The chemical "backbone" involved in the toxic effect of difethialone is benzothiopyranone, which is similar to 4-hydroxycoumarin, the backbone of most SGARs (McGee et al. 2020).

According to the 2022 Annual Report of the American Association of Poison Control Centers ("AAPCC"), more than 3 000 anticoagulant rodenticide ingestion incidents were reported in the United States; approximately half of these in children younger than 6 (cited by Isackson and Irizarry 2024). Similar data are not available for South Africa, but the US data show that incident numbers can be significant.

Detailed recent data are not easily accessible, but the Office of Chemical Safety and Pollution Prevention of the USEPA (2022a) has performed an updated analysis of exposure incidents reported to both the USA Incident Data System ("IDS") and the AAPCC. Reviewing AAPCC data, a 46% decline in child rodenticide exposures was found from 2011 to 2017. In both databases, SGAR incident reports had declined over time. The number of SGAR incidents reported to the IDS during the time period 2008 to 2018 had decreased by 79% and the number reported to AAPCC by 70% from 2004 to 2017.

Considering occupational exposure incidents, 21 were reported to the NIOSH SENSOR-Pesticides database from 2011 to 2015, 9 to the Californian database from 2012 to 2016, and 2 in the IDS (2015 to 2019). Overall, the USEPA (2022a) found a low frequency of 21 occupational incidents from 2011 to 2015, for all types of anticoagulant rodenticides, of which 15 cases involved zinc phosphide. Of the 21 occupational cases, 1 case was high in severity, 5 cases were moderate in severity, and 15 cases were low in severity. Ten cases sought care in an ER or hospital; and 11 cases contacted poison control for treatment and guidance (all 11 cases that contacted poison control were low in severity).

The health effect most frequently reported by the occupational cases was nausea, followed by altered taste (metallic or chemical taste), vomiting, upper respiratory pain/irritation, and shortness of breath. These symptoms are relevant to acute (single) exposure incidents. The severity statistics and the nature of the observed health effects demonstrate that proper training of pesticide applicators and the use of personal protective equipment are effective management tools limiting occupational exposure risks.

Similarly updated European incident data were not provided, but the Norwegian CA (2007 and 2016) noted that many incidents of human poisoning, both accidental and intentional, of anticoagulant rodenticides have been reported in literature, but only one published case report of difethialone intoxication (Norwegian CA 2016).

According to current knowledge, difethialone has no endocrine disrupting properties (Norwegian CA 2016).

6.2 Routes of absorption

Oral absorption
Difethialone is rapidly and extensively absorbed by rats, and the Norwegian CA (2007 and 2016) assumed a 100% absorption rate for risk assessment purposes.

Dermal absorption
The Norwegian CA (2016) calculated an in vivo human dermal absorption of 4% for the difethialone substance, by combining rat in vivo data and rat:human in vitro data. Absorption rates from product formulations were not available, but the 4% absorption rate was accepted as a reasonable worst-case value for use in rodenticide products risk assessments.

Inhalation
Difethialone has a very low volatilisation potential, as predicted from its physical-chemical properties (low vapour pressure and low Henry's law constant, Section 4.1). Therefore, it is not expected to be present in the atmosphere in significant quantities when applied in solid form. The potential for inhalation exposure is thus low, but if inhalation exposure should take place, e.g., to dusts, a default absorption value of 100% is assumed (Norwegian CA 2007).

Distribution, accumulation, elimination and bio-transformation
Distribution to body organs has been demonstrated, with the highest levels occurring in the liver. Thus, difethialone has the potential to bioaccumulate in the liver, and is slowly removed, with an experimental half-life in the liver in the region of 18 weeks for both males and females (rat study, Norwegian CA 2016). Approximately 10% of the administered dose was still present in the liver at the end of the six-month observation period. Elimination was exclusively in the faeces as unchanged parent material and no major metabolites were identified.

6.3 Toxicological studies

The Norwegian CA (2007) reported the following acute toxicity information:

- Lowest acute oral LD50:
  - Male rat: 0.55 mg/kg-bw.
  - Mouse: 1.29 mg/kg-bw.
  - Less toxic to dogs (11.8 mg/kg-bw) and cats (≥ 16 mg/kg-bw).
  - Pigs: 2.0 to 3.0 mg/kg-bw.

- Dermal LD50 in rats: 6.5 mg/kg-bw.

- Inhalation in rats, nose only, for 4 hours: LC50 ≥ 5.0 µg/litre air but < 19.3 µg/litre air.

None of the rat or mice acute oral studies investigated sublethal effects.

The repeated exposure (90-day) oral toxicity values for haemorrhagic effects associated with difethialone, reported by the Norwegian CA (2007) are:
- Rat:
  - LOAEL = 4 µg/kg-day.
  - NOAEL = 2 µg/kg-day.
- Dog:
  - LOAEL = 20 µg/ kg-day.
  - NOAEL = 10 µg/ kg-day.

Maternal toxicity effects of haemorrhages and mortality were reported by the Norwegian CA (2016) from developmental toxicity studies, with the following toxicity values:
- Rat maternal NOAEL ≥ 50 µg/kg-day.
- Rabbit maternal LOAEL = 10 µg/kg-day.
- Rabbit maternal NOAEL = 5 µg/kg-day.

In the developmental toxicity studies, the dosing period is usually:
- Rats: females from 2 weeks before mating to 4 days after delivery, typically a period of 40 to 55 days.
- Rabbits: females typically for around 28 days of gestation.

Reproductive and developmental toxicity

The decision by the European authorities to classify difethialone as a developmental toxicity hazard (H360D) needs some background discussion. According to the Norwegian CA (2007 and 2016), embryotoxic or teratogenic effects were not observed in studies conducted in the rat and rabbit, and no effects on the developing foetus were seen in either species.

The embryofoetal toxicity values reported by the Norwegian CA (2016) are:
- Rat NOAEL ≥ 50 µg/kg-day.
- Rabbit LOAEL > 10 µg/kg-day

A multigeneration study was not required, based on the high risk of death by haemorrhage from the natural events of reproduction and parturition, nullifying the study objective in any case, and based on the absence of potential long-term exposure of the public population.

Although the developmental toxicity studies with difethialone in rat and rabbit failed to indicate developmental toxicity, difethialone has the same chemical active group and the same well-known mode of action by which warfarin, also an anticoagulant anti-vitamin K (“AVK”) substance, causes teratogenicity in humans. The Norwegian CA (2016) reported that ECHA’s Risk Assessment Committee (“RAC”) evaluated data available for warfarin and difethialone and, relying on a weight-of-evidence approach, concluded that difethialone should be classified as a developmental toxicity hazard (H360D).

Neurotoxicity, genotoxicity and carcinogenicity

Aside from blocking regeneration of vitamin K in the liver, no other pharmacologic activity has been established for difethialone. In line with this, the Norwegian CA (2016) reported that various

screening tests for potential pharmacological activity were conducted, in which no antianginal[3] activity; no antihypertensive activity; no sedative activity; no anticonvulsant activity; no antidepressant activity; no antispasmodic activity and no analgesic, anti-inflammatory or gastric antiacid activities were found. The absence of particularly sedative, anticonvulsant and antidepressant effects and the absence of any clinical signs of neurotoxicity in rodent and dog toxicity tests support the conclusion that difethialone shows no neurotoxic effects (Norwegian CA 2007).

Difethialone was not mutagenic in a standard range of in vitro and in vivo tests. Regarding potential carcinogenicity, such effects have not been reported in humans on long-term warfarin administration regimes. Since warfarin and difethialone are closely related, difethialone is not expected to be carcinogenic and animal carcinogenicity tests were not demanded by international regulatory authorities registering difethialone for use as a rodenticide (Norwegian CA 2007 and 2016).

7 Approaches to rodenticide health risk management

7.1 USEPA human health risk management strategy

The USEPA overall risk management strategy is to limit potential non-target exposures. This strategy is followed because the available hazard and toxicity profile for the rodenticides informed the pivotal conclusion that *any* potential exposure may result in adverse effects and potential risks of concern; therefore, quantitative risk assessments are not required or conducted. Rather, the USEPA determined that labelled uses of these products should be modified, as needed, to assure that occupational and non-occupational dermal and inhalation exposures are limited as far as possible. The occupational mitigation measures most recommended are the use of suitable PPE.

7.2 The European Union approach to human health risk management

7.2.1 Solid rodenticide application practices

The Norwegian CA (2007 and 2016) based difethialone exposure assessments on the EU Technical Notes for Guidance ("TNsG"), compiled in 2007 by the European Chemicals Bureau ("ECB" 2007). The TNsG provides indicative exposure values for a range of generic exposure scenarios discussed in the TNsG, amongst these for European Union ("EU") Product Type 14: Rodenticides.

The TNsG assumes a general rule that rodenticides are formulated, sold (packaged) and applied (placed) in such a way that humans and non-target animals should not be exposed. Bait stations in which the rodenticide is to be placed should protect people and non-target animals from exposure. Nevertheless, the TNsG considers primary exposure to the rodenticide applicator. This is relevant to the solid formulations assessed in this report.

The TNsG (ECB 2004) describes the use of bait stations, including bait boxes (box-like bait stations) for solid rodenticide products as follows:

[3] Angina, or angina pectoris, is chest pain or discomfort that occurs due to an insufficient oxygen supply to the heart, caused by narrowed or blocked coronary arteries (the heart's blood supply). Antianginal drugs relieve angina symptoms and prevent future attacks by addressing the imbalance between the heart's oxygen supply and demand.

- These boxes/stations, especially when tamper-proof, are used to prevent human contact with the rodenticide.
- Several application methods are available, such as merely hiding the rodenticide under a cover, to prevent or at least diminish contact after placing, or placing the rodenticide in a pipe, long enough to prevent contact with the bait. More elaborate enclosed bait boxes, which have holes for the rodents to enter, are available.
- Boxes/stations should be placed in such a way that bystanders, such as children, and non-target animals, cannot reach the bait. However, contamination of the bait boxes' surroundings with rodenticide from spillage caused by the rodents, or due to the rodents' contaminated urine, faeces and carcasses, is possible.

Wax bait wedges, rounds or blocks
- Wax bait wedges, rounds or blocks are usually placed in bait boxes.

Pellets
- May be used indoors and outdoors, and can be placed in larger, unenclosed surfaces.
- May be placed directly into rodent burrows/holes with a spoon or small shovel. In this case, the burrows/holes may be covered to prevent access by children and non-target animals such as pets and birds.
- The surroundings may be contaminated with the rodenticide from spillage by rodents.

7.2.2 Solid rodenticide exposure variables

The TNsG (ECB 2007) distinguishes an application, use and disposal phase, based on handler use patterns, for exposure assessment purposes.

Application phase:
The TNsG (ECB 2007) identified the most prominent handler exposure scenarios, based on formulation use patterns:
- Placing of bait boxes.
- Loading of bait boxes or bait stations with wax blocks/rounds/wedges/pellets from larger containers, by transfer of bait from the product packaging to the bait station.
- Securing large paraffin blocks at bait stations in sewers.
- Applying bait by hand, or placing pellets directly into rodent burrows/holes with a spoon or small shovel.

The TNsG summarises exposure data gathered largely in the Nordic countries, compiled for the application phase (Table 7.2.2.1). The amounts presented in the table are according to the formulated products for which data were collected. Substantiated product- and scenario-specific data are preferred, but the TNsG exposure data may be used when actual measured data are not available.

Table 7.2.2.1: TNsG-based exposure variables for solid rodenticide application.

Formulation	Amount per application	Handling duration	Event frequency (per day)		Days per year	
			Normal	Worst case	Normal	Worst case
Professional applicator (PCO)						
Wax blocks	250 g	5 min	4	8	55	220
Pellets, impregnated grain	150 to 400 g	5 min	4	16	55	220
Bait station placing*	40 g	As above	2 x bait stations, 4 times per year			

Formulation	Amount per application	Handling duration	Event frequency (per day)		Days per year	
			Normal	Worst case	Normal	Worst case
Non-professional applicator/domestic or general public users						
Wax blocks	20 to 40 g	<5 min	1	1	1	20
Pellets, impregnated grain	25 to 50 g	<5 min	1	2	1	20
Bait station placing*	40 g	As above	2 x bait stations, 4 times per year			
*Likely of bait stations supplied with loaded bait, which is not the norm in South Africa.						

Post-application use phase:

- The baiting period, when the biocidal product is available for consumption by the target organism.
- Rodenticides are usually confined to areas with a minimum of human access. Bait-boxes in private and industrial areas are assumed locked off to prevent contact.
- Primary exposure duration and frequency variables are based on PCOs and domestic/general public users attending the feeding stations and replacing/adding new baits.
- The largest number of bystanders are exposed in this phase, e.g., unaware workers, usually accidentally or by curiosity. Children may be similarly exposed if application was in the home area.
- Exposure of adults is mainly by dermal contact and that of children by dermal and possible oral contact, through transient mouthing of the bait product.

Table 7.2.2.2: TNsG-based exposure variables during the concentrate post-application use phase.

Formulation	Amount per application	Handling duration	Event frequency (per day)		Days per year	
			Normal	Worst case	Normal	Worst case
Professional applicator (PCO)						
Wax blocks	250 g	<5 min	1/7	1	110	220
Pellets, impregnated grain	150 to 400 g	<5 min	1 to 2	16	110	220
Non-professional applicator/domestic or general public users						
Wax blocks	20 to 40 g	<5 min	1	1	1	20
Pellets, impregnated grain	25 to 50 g	<5 min	1	1	1	20

Disposal phase:

- Bystander exposure includes possible contact of the general public, or unaware workers, with dead rodents or spilled bait.
- PCOs and non-professionals (general public users) are assumed to remove/clean the bait box, which may result in handling of surplus formulated product. Default exposure variables are presented for each assessed formulation in Scenario 8.
- Disposal activities include cleaning up and disposal of rodenticide dragged away from the bait station by rodents. Disposal should include handling of carcasses, which may have residues of the active substances on the skin or having bled on the floor. However, it appears that dead rats and mice often are swept up with a broom, together with other refuse (ECB 2007), implying that dermal contact might not be extensive.
- Brooming may give rise to dust containing the active substance, which may give rise to exposure by the inhalation route.

7.2.3 Toxicity values and human health risk calculations

Regulatory authorities derive limit values protecting the health of humans; that is, exposure levels or dose values that are not expected to result in adverse effects on health of the general population, including sensitive individuals and children.

Since developmental effects are the only health endpoints (aside from mortality) for which dose-response values are available in toxicological studies, there is no other choice but to base acceptable exposure levels of males and children on this health endpoint as well. Therefore, the absence of a risk to health in general, and specifically the absence of a risk to the developing foetus, is implied by a finding of "acceptable exposures or risks".
The Norwegian CA (2016) conducted human health risk calculations using systemic Acceptable Exposure Levels ("AELs") for difethialone presented in Table 7.2.3.1. The AEL is the exposure dose that is accepted as not associated with a risk to human health. Since difethialone is not volatile, significant levels in air are unlikely. From this, it follows that the most relevant modes of exposure for operators and consumers are by dermal contact or oral absorption.

The subchronic exposure scenario is not usually assessed by regulatory agencies, since it is not considered applicable to the most frequent rodenticide use scenarios, which are of an acute rather than a continuous subchronic exposure nature. Neither the TNsG (ECB 2004 and 2007) nor the HEEG (2012) includes directions for the assessment of repeated subchronic exposure of PCOs or domestic users.

Table 7.2.3.1: Summary of difethialone AELs.

*Point of departure (POD)	Uncertainty Factors	AEL	Study and toxicological effects
Acute exposure			
NOAEL administered = 0.005 mg/kg-day	UF_A= 10 UF_H= 10 UF_{Sev} = 3 Total UF= 300	1.7 x 10^{-5} mg/kg-day	Rabbit (most sensitive species) teratogenicity study maternal NOAEL. Maternal toxicity: haemorrhages, mortality. Norwegian CA (2016).
Subchronic exposure (medium term)			
NOAEL administered = 0.002 mg/kg-day	UF_A= 10 UF_H= 10 UF_{Sev} = 3 Total UF= 300	7.0 x 10^{-6} mg/kg-day	The lowest NOAEL from a 90-days repeated dose study with rats (2 µg/kg bw) based on haemorrhagic effects. Norwegian CA (2007 and 2016).
Chronic exposure			
Long-term toxicity studies were waived, in the interests of animal welfare and because of the observed severity of the toxic effects in the available rat, pig and dog 90-days repeated dose studies. The subchronic exposure AEL is accepted as applicable to chronic exposure (Norwegian CA 2016).			
*Point of Departure (POD): Data point derived from dose-response data, used to extrapolate risks associated with lower environmentally relevant human exposures. NOAEL: no-observed-adverse-effect level. LOAEL: lowest-observed-adverse-effect level. UF: uncertainty factor. UFA: extrapolation from animal to human (interspecies). UFH: potential variation in sensitivity among members of the human population (intraspecies). UF_{Sev}: additional factor for severity of effects.			

Dose calculations are done as recommended by the TNsG (ECB 2004 and ECB 2007). For this purpose, dermal absorption was assumed as presented in Section 6.2 (4%) and a default body weight of 60 kg. The systemic dose is expressed as a percentage of the AEL, and the risk of a health effect is deemed unacceptable if the systemic dose is approximately 100 per cent, or more, of the AEL. Detailed calculations are presented for each difethialone bait formulation assessed in Section 8.

In short, based on the TNsG (ECB 2004), the systemic dose is calculated with Equation 7.2.3.1.

Systemic dose (mg/kg-day) = Systemic exposure (mg/day) / body weight (kg) Equation 7.2.3.1

Systemic exposure is calculated with simplified Equation 7.2.3.2:

Systemic exposure = Exposure per event x events per day Equation 7.2.3.2

Where:

Systemic exposure	Systemic exposure per day (mg/day).
Exposure per event	Calculated as explained in Section 8 for the different product formulation types.
Events per day	Number of events per day; that is, estimated or default number of application- or clean-up events per day.

8 Human health risk assessment of solid rodenticides containing difethialone

8.1 FINALE® Rat and Mouse Pellets

8.1.1 Exposure assessment

Approach

Table 3.2.2 presents the percentage by mass of difethialone in each solid formulation product, showing a concentration of 0.025 g/kg (0.0025 % w/w) in the FINALE® Rat and Mouse pellets to be assessed in this report. The Norwegian CA (2007 and 2016) also assessed a pellet bait containing 25 ppm (0.0025 % w/w) difethialone, which is thus directly applicable to the FINALE® Rat and Mouse pellet formulation registered in South Africa.

The Norwegian CA (2016) described the bait as a ready-to-use rodenticide (mixing not required) for use by professionals and the general public "in and around buildings". Default exposure values were from the TNsG (ECB 2007). The harmonised exposure assessment approach for anticoagulant rodenticides, proposed by the Human Exposure Expert Group ("HEEG") of the EC Joint Research Centre Institute for Health and Consumer Protection was used (HEEG 2012). The HEEG provides guidelines towards a harmonised approach to biocide exposure assessment for industry and competent authorities including the number of manipulations in the assessment of anticoagulant rodenticides applicable to professional pesticide applicators. Data determined in a PCO survey by the European Chemical Industry Council, referred to as the CEFIC study (not referenced by the Norwegian CA), which included decanting, loading/placement and clean-up of bait, were also used where applicable.

The Norwegian CA (2016) summarised the exposure assumptions for human dermal exposure to difethialone in pellet baits as presented in Table 8.1.1.1.

Table 8.1.1.1: List of scenarios assessed by the Norwegian CA for a pellet rodenticide.

Scenario	Exposed group	Primary or secondary exposure and scenario description
Application and post application (includes clean-up and disposal)	Professional (PCO)	Primary exposure - decanting of pellet bait, loading of bait station and emptying and disposing of bait stations (including bait boxes). Frequency of daily use: • Pellets used in and around buildings. • Maximum 79 bait points treated/day plus clean-up: remains of 16 bait points collected. • Note: the HEEG (2012) default number of pellets bait points is 63, but the conservative value of 79 bait points will be used for FINALE® pellet calculations. • Remains = 90 g (rats) or 60 g (mice) pellets per bait station. • Level of protection: Gloves (90 % exposure reduction).
	Non-professional: domestic/general public	Primary exposure - Loading of bait station and emptying and disposing of bait stations (including bait boxes). Frequency of daily use: • Pellets used in and around buildings. • Maximum 5 bait points treated/day plus remains of 5 bait points collected. • Remains mass cleaned up assumed equal to that of PCOs: Assumed as for PCOs = 90 g (rats) or 60 g (mice) pellets per bait station. • Level of protection: gloves (90 % exposure reduction).
Ingestion/ mouthing	General public	• Infants ingesting 10 mg bait (TNsG default for bait treated with repellent). • Also, infants ingesting 5 g bait (TNsG: estimate by Poison Information Specialists). • Scenario concerning handling of dead rodents is not presented as it is considered as unrealistic.

Although the Norwegian CA (2007 and 2016) assessment is directly applicable to the FINALE® Rat and Mouse pellet formulation registered in South Africa, it is noted that the assessment accounted only for dermal exposure and not inhalation exposure, which is usually also accounted for in other pellet bait risk assessments by international regulatory agencies. The Finnish CA (2008) conducted a health risk assessment, reviewed by EFSA (2008) for professional users (occupational scenario) and for non-professional users (residential/farm/domestic scenario), based on a pellet formulation containing difenacoum, which included dermal and pellet dust inhalation exposure. Therefore, the FINALE® pellet formulation assessment presented in this report will account for inhalation exposure as well.

Since calculations of dermal exposure doses were not presented by the Norwegian CA, the example of the Finnish CA (2008) pellet and pellet dust dermal and inhalation exposure calculations will be followed. Exposure factors used by the Finnish CA were based on the CEFIC exposure study for grain bait, considered a worst-case analogy to pellet baits. However, updated HEEG (2012) exposure factors will be used as far as possible for the FINALE® pellet assessment, and referenced accordingly. Difethialone-specific dermal and inhalation absorption factors will be used.

Primary exposure: PCOs

Oral exposure of PCOs is not expected, since good hygiene measures are routinely given on SDSs, e.g., washing before eating or smoking.

The results of the exposure calculations for PCOs are presented in Table 8.1.1.2. Finnish CA (2008) example calculations were followed, but with difethialone-specific and HEEG (2012) values as applicable.

Table 8.1.1.2: PCO difethialone exposure: pellet bait decanting, loading and clean-up.

Scenario and exposure variable description	Dermal exposure (75th percentile)	Inhalation exposure (75th percentile)
Default values		
Mass of pellets per bait point	50 to 75 g; use 75 g for calculations	
Total mass of pellets used per day	75 g x 79 manipulations (see "loading, placement" below) = 6.0 kg (rounded)	
Concentration of difethialone in product (Table 3.2.2)	0.0025%	0.0025%
Body weight (kg)	60	60
Inhalation rate (m^3/hr)	-	1.25
Absorption rate of difethialone (Section 6.2)	4%	100%
Decanting		
Manipulations per day (per 3 kg of product) (HEEG 2012)	1 event	1 event
Manipulations per day for 6 kg of pellets	2 events	2 events
Minutes per event (HEEG 2012)	-	3
Minutes for 2 events (6 kg of pellets per day)	-	3 x 2 = 6 minutes
Air concentration of product while decanting (mg product/m^3) (HEEG 2012)	-	9.62 mg/m^3 during a decanting event
Inhalation rate (m^3 air/hour) (not specified in the Finnish CA (2008) report, but implied in the calculations)	-	1.25
Amount of product on hands/forearms (mg) per 3 kg manipulation (HEEG (2012) average for ≤ 4 manipulations)	93.01	-
Adjusted amount of product on hands/forearms (mg) for 6 kg of pellets decanted (HEEG (2012) formula)	[(93.01 mg)/3 kg] x 6 kg = 186.0	-
Difethialone dose (mg/kg-day) (without PPE)	3.1×10^{-6}	5.0×10^{-7}
Difethialone dose (mg/kg-day) (wearing gloves)	3.1×10^{-7}	-
Loading, placement		
Manipulations per day (bait points treated/day, Table 8.1.1.1)	79	Negligible inhalation exposure
Amount of product on hands/forearms per manipulation (mg) (HEEG (2012) average for > 4 manipulations)	2.04	
Total amount of product on hands/forearms	161.2	
Difethialone dose (mg/kg-day) (without PPE)	2.7×10^{-6}	
Difethialone dose (mg/kg-day) (wearing gloves)	2.7×10^{-7}	
Clean-up		
Manipulations per day (clean-ups/day, Table 8.1.1.1)	16	Negligible inhalation exposure
Amount of product on hands/forearms per manipulation (mg) (HEEG (2012) average for > 4 manipulations)	3.79	
Total amount of product on hands/forearms	60.6	
Difethialone dose (mg/kg-day) (without PPE)	1.0×10^{-6}	
Difethialone dose (mg/kg-day) (wearing gloves)	1.0×10^{-7}	
Sums of difethialone exposure		
Difethialone dose (mg/kg-day) (without PPE)	6.8×10^{-6}	5.0×10^{-7}
Difethialone dose (mg/kg-day) (wearing gloves)	6.8×10^{-7}	-
Total difethialone dose without PPE (mg/kg-day)	$6.8 \times 10^{-6} + 5.0 \times 10^{-7} = 7.3 \times 10^{-6}$	
Total difethialone dose with PPE (mg/kg-day)	$6.8 \times 10^{-7} + 5.0 \times 10^{-7} = 7.3 \times 10^{-7}$	
Difethialone dermal exposure/day = 0.0025% (difethialone w/w) x (product exposure / manipulation) x number of manipulations x dermal absorption factor.		

Scenario and exposure variable description	Dermal exposure (75th percentile)	Inhalation exposure (75th percentile)
Difethialone inhalation exposure/day = 0.0025% (difethialone w/w) x air concentration of product (mg product/m³) x activity minutes per day x inhalation rate x inhalation absorption factor.		

Primary non-professional exposure: general public/domestic exposure

- PPE use is not included in the calculations, because it is assumed that that non-professionals might not be diligent users of PPE.
- Calculations were performed with assumptions related to rat control activities, and no separate calculations were considered necessary to assess exposure in mice control campaigns, in which bait sizes are smaller.
- The Norwegian CA (2016) did not assess the scenario of handling of dead rodents because this was considered unrealistic.
- Oral exposure of adult users is considered negligible.

Calculations for non-professionals were repeated as for PCOs, but using the applicable exposure factors for non-professionals, and are presented in Table 8.1.1.3.

Table 8.1.1.3: Domestic users difethialone pellet bait exposure: decanting, loading and clean-up.

Scenario and exposure variable description	Dermal exposure (75th percentile)	Inhalation exposure (75th percentile)
Default values		
Mass of pellets per bait point (FINALE® Rat and Mouse Pellets label)	50 to 75 g; use 75 g for calculations	
Total mass of pellets used per day (FINALE® Rat and Mouse Pellets)	75 g x 5 manipulations (see "loading, placement" below) = 0.375 kg (rounded to 0.5 kg for exposure calculations)	
Concentration of difethialone in product (Table 3.2.2)	0.0025%	0.0025%
Body weight (kg)	60	60
Inhalation rate (m³/hr)	-	1.25
Absorption rate of difethialone (Section 6.2)	4%	100%
Decanting		
Manipulations per day (per ≤ 3 kg of product) (HEEG 2012)	1 event	1 event
Manipulations per day for 0.5 kg of pellets	1 event	1 event
Minutes per event (HEEG 2012)	-	3
Air concentration of product while decanting (mg product/m³) (HEEG 2012)	-	9.62 mg/m³ during a decanting event
Inhalation rate (m³ air/hour) (not specified in the Finnish CA (2008) report, but implied in the calculations)	-	1.25
Mass of product on hands/forearms (mg) per 3 kg manipulation (HEEG (2012) average of ≤ 4 manipulations)	93.01	-
Adjusted amount of product on hands/forearms (mg) for 0.5 kg of pellets decanted (HEEG (2012) formula)	[(93.01 mg)/3 kg] x 0.5 kg = 15.5	-
Difethialone dose (mg/kg-day) (without PPE)	2.6×10^{-7}	2.5×10^{-7}
Difethialone dose (mg/kg-day) (wearing gloves)	Assumed not using gloves	-
Loading, placement		
Manipulations per day (bait points/day, Table 8.1.1.1)	5	Negligible inhalation

Scenario and exposure variable description	Dermal exposure (75th percentile)	Inhalation exposure (75th percentile)
Amount of product on hands/forearms per manipulation (mg) (HEEG (2012) average for > 4 manipulations)	2.04	exposure
Total amount of product on hands/forearms	10.2	
Difethialone dose (mg/kg-day) (without PPE)	1.7×10^{-7}	
Difethialone dose (mg/kg-day) (wearing gloves)	Assumed not using gloves	
Clean-up		
Manipulations per day (clean-ups/day, Table 8.1.1.1)	5	Negligible inhalation exposure
Amount of product on hands/forearms per manipulation (mg) (HEEG (2012) average for ≤ 4 manipulations)	4.52	
Total amount of product on hands/forearms	22.60	
Difethialone dose (mg/kg-day) (without PPE)	3.8×10^{-7}	
Difethialone dose (mg/kg-day) (wearing gloves)	Assumed not using gloves	
Sums of difethialone exposure		
Difethialone dose (mg/kg-day) (without PPE)	8.1×10^{-7}	2.5×10^{-7}
Difethialone dose (mg/kg-day) (wearing gloves)	Assumed not using gloves	-
Total difethialone dose without PPE (mg/kg-day)	$8.1 \times 10^{-7} + 2.5 \times 10^{-7} = 1.1 \times 10^{-6}$	
Total difethialone dose with PPE (mg/kg-day)	Assumed not using gloves	
Difethialone dermal exposure/day = 0.0025% (difethialone w/w) x (product exposure / manipulation) x number of manipulations x dermal absorption factor. Difethialone inhalation exposure/day = 0.0025% (difethialone w/w) x air concentration of product (mg product/m³) x activity minutes per day x inhalation rate x inhalation absorption factor.		

Secondary exposure: mouthing by infants/toddlers

- The ingestion and mouthing of any rodenticide bait by an infant/toddler is generally viewed as "*an exceptional scenario, which may occur accidentally*".
- The risk of oral exposure is minimised by addition of a bittering agent (as for FINALE® Rat and Mouse Pellets) and by an appropriate covering of baits (e.g. by use of a bait station), which is recommended for FINALE® Rat and Mouse Pellets.
- Based on the TNsG (ECB 2007) consumption of up to 5 g is assumed if no bait boxes are used and no bittering agent is added.
- The minimised accidentally ingested amount is expected to be 10 mg per mouthing event, since it is likely that that the bittered bait will be spit out and not swallowed. This value is used for the FINALE® Rat and Mouse Pellets calculations, because a bittering agent is included.
- Inhalation exposure is considered not relevant for secondary exposure scenarios, since decanting of bait is not a secondary exposure activity.
- The Finnish CA (2008) conducted a health risk assessment, reviewed by EFSA (2008) for professional users (occupational scenario) and for non-professional users (residential/farm/ domestic scenario), based on a pellet formulation presented by an applicant for registration. Although the pellet formulation contained difenacoum, the example calculations are applicable to other pellet rodenticides and the EFSA review has found calculations acceptable. Ingestion of baits is considered as the worst case, while dermal contact is assumed to be minor compared to oral exposure; is viewed as covered by the oral exposure assessment, and thus excluded from the calculations. This assumption is also followed for the difethialone risk assessment.
- The default body weight of an infant/toddler is 10 kg.

- The adopted oral absorption rate of difethialone is 100% (Section 6.2).
- The difethialone content of the FINALE® Rat and Mouse Pellets is 0.0025 weight %.

Systemic exposure of an infant/toddler for the scenario of accidental ingestion by transient mouthing is calculated according to the Finnish CA (2008) method, with values adjusted for FINALE® Rat and Mouse Pellets:

- $Exposure_{oral}$ = Ingested amount x difethialone content x oral absorption / body weight
- = (10 mg x 0.0025% x 100%] / 10 kg
- = 2.5×10^{-3} mg/kg-bw

8.1.2 Pellets risk assessment

The risk calculations are conducted by comparing the calculated difethialone exposure doses (Section 8.1.1) to the acute AEL (Table 7.2.3.1) of 1.7×10^{-5} mg/kg-day. The calculation of risks is summarised in Table 8.1.2.1. Exposure doses less than 100 per cent of the AEL are acceptable.

Exposure and risk calculations are based on PPE use premises as indicated. It was considered that non-professional users would not necessarily wear gloves and exposure and risks were calculated accordingly. A dermal protection factor of 90%, when wearing gloves, was factored in the calculations for PCOs, as was done by the Norwegian CA (2016). Inhalation exposure and risk calculations were done based on the assumption that the PCOs and the general public (non-professionals) would not be using respiratory protection.

Table 8.1.2.1: Difethialone pellets: primary exposure health risks of PCOs and non-professionals.

Route of exposure / activity	Exposure dose mg/kg-day			Risk = (Dose/AEL)%		
	Dermal	Inhalation	Sum	Dermal %	Inhalation %	Sum %
PCO: <u>without</u> gloves, no respiratory protection						
Decanting pellets	3.1×10^{-6}	5.0×10^{-7}	3.6×10^{-6}	18.24	2.95	21.18
Loading pellets	2.7×10^{-6}	Insignificant	2.7×10^{-6}	15.80	Not applicable	15.80
Cleaning phase	1.0×10^{-6}	Insignificant	1.0×10^{-6}	5.95	Not applicable	5.95
Total if all activities on one day	6.8×10^{-6}	5.0×10^{-7}	7.3×10^{-6}	39.98	2.95	42.93
PCO: <u>with</u> gloves, no respiratory protection						
Decanting pellets	3.1×10^{-7}	5.0×10^{-8}	3.6×10^{-7}	1.82	0.29	2.12
Loading pellets	2.7×10^{-7}	Insignificant	2.7×10^{-7}	1.58	Not applicable	1.58
Cleaning phase	1.0×10^{-7}	Insignificant	1.0×10^{-7}	0.59	Not applicable	0.59
Total if all activities on one day	6.8×10^{-7}	5.0×10^{-8}	7.3×10^{-7}	4.00	0.29	4.29
Non-professional (general public, domestic user): without gloves, no respiratory protection						
Decanting pellets	2.6×10^{-7}	2.5×10^{-7}	5.1×10^{-7}	1.52	1.47	2.99
Loading pellets	1.7×10^{-7}	Insignificant	1.7×10^{-7}	1.00	Not applicable	1.00
Cleaning phase	3.8×10^{-7}	Insignificant	3.8×10^{-7}	2.22	Not applicable	2.22
Total if all activities on one day	8.1×10^{-7}	2.5×10^{-7}	1.1×10^{-6}	4.74	1.47	6.21
AEL_{acute} = 1.7×10^{-5} mg/kg-day						

The risk calculations demonstrate that dermal exposure of professionals not wearing gloves or respiratory equipment would be acceptable. However, this finding does not mean that gloves need not be worn using the pellet bait, since gloves also protect against possible secondary exposure while handling dead rodents and against diseases carried by rodents. As recommended on the label, professionals should wear gloves at all times while handling bait, while cleaning up and while handling dead rodents.

The risk assessment for non-professionals, assumed not to wear gloves, demonstrates that exposure while applying bait and cleaning up bait stations are not associated with a risk to health. However, this finding does not negate the need for gloves, because gloves also protect against possible secondary exposure while handling dead rodents and against diseases carried by rodents. As recommended on the label, non-professionals should also wear gloves at all times while handling bait, cleaning up or removing dead rodents.

The above scenarios of handling bait while not wearing gloves also accounts for the secondary accidental exposure of bystanders, that is, uninformed persons, touching the bait while in use, or touching or cleaning up bait that has been dragged about by rodents. Since the risks associated with handling the bait while not using gloves are acceptable for the general public, risks associated with secondary accidental dermal exposure would also be acceptable.

In the case of secondary exposure, an unacceptable risk is identified for children accidentally mouthing or chewing on pellets with 0.0025% difethialone:

- Difethialone dose: 2.5×10^{-3} mg/kg-bw (see Section 8.1.1).
- $Risk_{infant/toddler} = (Dose_{infant/toddler})/AEL$
- $= (2.5 \times 10^{-3}$ mg/kg-bw$)/(1.7 \times 10^{-5}$ mg/kg-bw$) \times 100$
- > 1 000%

Therefore, specific risk mitigation measures are required to prevent exposure to children and are discussed Section 9. In any case, any noted contact of a child with rodenticide bait should be brought to the immediate attention of a medical professional, without exception.

With regard to indirect (secondary exposure) to pellet baits in use, a health risk related to adults in contact with dead rodents, due to pellet residues on fur, is considered of low relevance. Rather, gloves are recommended when handling dead rodents, in order to prevent contact with rodent-borne diseases; therefore, exposure to pellet bait residues on rodent fur is considered negligible.

In conclusion, considering primary exposure during the application of FINALE® Rat and Mouse Pellets, with or without gloves, are not associated with unacceptable health risks, whether used by professionals or non-professionals. This does not sanction product use or clean-up without gloves, and recommendations to wear gloves should remain on labels.

8.2 Wax blocks

8.2.1 Exposure assessment

Primary exposure of users occurs during the intended use of the wax blocks, described as follows: "*An active rodenticide anticoagulant bait in block form for the control of the roof rat, Norway rat and house mouse"*.

The difethialone content in the blocks/wax products is 0.025 g/kg (0.0025 % w/w). The Norwegian CA (2007 and 2016) also assessed a block bait containing 25 ppm (0.0025 % w/w) difethialone, which is thus directly applicable to the FINALE® and RODILON® wax block formulations registered in South Africa.

The Norwegian CA (2016) described the bait as a ready-to-use rodenticide (mixing not required) for use by professionals and the general public "in and around buildings" and "in sewers". Default exposure values were from the TNsG (ECB 2007) and the harmonised exposure assessment approach for anticoagulant rodenticides (HEEG 2012). Data determined in the CEFIC study, which included loading/placement and clean-up of bait, were also used by the Norwegian CA where applicable.

The dermal route is the only route applicable to primary exposure of PCOs and non-professionals handling rodenticide blocks. Inhalation exposure is not expected (HEEG 2012). The Norwegian CA (2016) summarised the exposure assumptions for human dermal exposure to difethialone in block baits as presented in Table 8.2.1.1.

Table 8.2.1.1: List of scenarios assessed by the Norwegian CA for a wax block rodenticide.

Scenario	Exposed group	Primary or secondary exposure and scenario description
Application and post application (includes clean-up and disposal)	Professional (PCO)	Primary exposure - loading of bait station and emptying and disposing of bait stations (including bait boxes). Frequency of daily use: • Blocks used in and around buildings. • Maximum 79 bait points treated/day plus clean-up: remains of 16 bait points collected. • Note: the HEEG (2012) default number of wax blocks bait points is 60, with 15 being cleaned up per day per PCO, but the conservative values of 79 bait points and 16 clean-ups will be used for FINALE® wax blocks calculations. • Level of protection: Gloves (90 % exposure reduction).
	Non-professional: domestic/general public	Primary exposure - Loading of bait station and emptying and disposing of bait stations (including bait boxes). Frequency of daily use: • Blocks used in and around buildings. • Maximum 5 bait points treated/day plus remains of 5 bait points collected. • Level of protection: Gloves (90 % exposure reduction)
Ingestion/ mouthing	General public	• Infants ingesting 10 mg bait (TNsG default for bait treated with repellent). • Also, infants ingesting 5 g bait (TNsG: estimate by Poison Information Specialists). • Scenario concerning handling of dead rodents is not presented as it is considered as unrealistic

Equations for the calculation of dermal exposure doses were not presented by the Norwegian CA. Therefore, calculations for the FINALE® and RODILON® wax block assessments were performed with the default values presented by the Norwegian CA, HEEG (2012) exposure factors and following ECB (2007) and HEEG (2012) guidance.

The primary exposure calculations for professional users are presented in Table 8.2.1.2. The assessment parameters are as follows:

- Default exposure values were as presented in Table 8.1.1.1, with HEEG (2012) exposure factors where indicated.
- Calculations were done with product-specific information where available, e.g., the amount of bait to be used per bait point.

- The skin is the main exposure route and professional users are assumed to wear protective gloves.
- A default body weight of 60 kg for an adult, which is lower than the default of 70 kg often used, e.g., by the USEPA (2011b). The lower body weight results in a conservative (higher) dose estimate, and thus a higher risk estimate.
- Dermal absorption value of 4% (Section 6.2) is used.
- The skin is the main exposure route. Inhalation exposure is not expected (HEEG 2012). Primary oral exposure of pest control operatives is not expected, since good hygiene measures are routinely recommended on SDSs, e.g., washing before eating or smoking.

The primary exposure calculations for non-professional users are also presented in Table 8.2.1.2. The assessment parameters are as follows:

- Default exposure values were as presented in Table 8.1.1.1, with HEEG (2012) exposure factors where indicated.
- Calculations were done with product-specific information where available, e.g., the amount of bait to be used per bait point.
- Non-professionals:
  - Are assumed not to use wax blocks on a daily basis.
  - The skin is the main exposure route. Inhalation exposure is not expected (HEEG 2012). Primary oral exposure is not expected, since precautionary hygiene measures are presented on the label, e.g., "*wash hands after handling*", etc.
  - Non-professional users are assumed not to diligently wear protective gloves, even though it is recommended on the label.
- A default body weight of 60 kg for an adult, which is lower than the default of 70 kg often used, e.g., by the USEPA (2011b), resulting in a conservative (higher) dose and risk estimate.
- Dermal absorption value of 4% (Section 6.2) is used.
- The skin is the main exposure route. Inhalation exposure is not expected (HEEG 2012). Primary oral exposure is not expected, since washing of hands after use, and other safety measures against accidental hand-to-mouth transfer are recommended on the label.

Secondary exposure of an adult occurs when adults accidentally touch wax blocks, or clean up wax block debris without knowing that it contains a hazardous rodenticide. It is assumed that dermal exposure will not be more than calculated for a non-professional intentionally applying or cleaning up the product. Thus, risks associated with non-professional use is an adequate estimate, and likely an overestimate, of accidental adult exposure. Calculations are not repeated.

Secondary exposure: mouthing by infants/toddlers

- The ingestion and mouthing of any rodenticide bait by an infant/toddler is generally viewed as an exceptional scenario, which may occur accidentally.
- The risk of oral exposure is minimised by addition of a bittering agent (as for FINALE® and RODILON® blocks) and by an appropriate covering of baits (e.g. by use of a bait station), which is recommended for FINALE® and RODILON® blocks.
- Based on the TNsG (ECB 2007) consumption of up to 5 g is assumed if no bait boxes are used and no bittering agent is added.
- The minimised accidentally ingested amount is expected to be 10 mg per mouthing event, since it is likely that that the bittered bait will be spit out and not swallowed. This value is used for the FINALE® and RODILON® blocks calculations, because a bittering agent is included in the product.
- Inhalation exposure is considered not relevant for secondary exposure scenarios.

- The Finnish CA (2008) conducted a similar exposure assessment for a bait with difenacoum, and accepted that the potential dermal exposure of toddlers/infants is covered by the oral exposure assessment. This assumption is also followed for the difethialone risk assessment.
- The default body weight of an infant/toddler is 10 kg.
- The adopted oral absorption rate of difethialone is 100% (Section 6.2).
- The difethialone content of the FINALE® and RODILON® blocks is 0.0025 weight %.

Systemic exposure of an infant/toddler for the scenario of accidental ingestion by transient mouthing is calculated according to the Finnish CA (2008) method, with values adjusted for FINALE® and RODILON® wax blocks:

- $Exposure_{oral}$ = Ingested amount x difethialone content x oral absorption / body weight
- = (10 mg x 0.0025% x 100%] / 10 kg
- = 2.5 x 10^{-3} mg/kg-bw

Table 8.2.1.2: Difethialone wax block primary exposure assessment.

Scenario and exposure variable description	PCOs dermal exposure	Non-professionals; general public/domestic users
Default values		
Concentration of difethialone in product	0.0025%	0.0025%
Body weight (kg)	60	60
Dermal absorption rate of difethialone	4%	4%
Wax block loading scenario (mixing phase not applicable to wax blocks): FINALE® and RODILON® blocks		
Number of bait blocks/bait point	4 blocks (product label) = number of contacts/bait point	
Block mass of FINALE®	12 blocks = 500 g (retail information page); 42 g/block	
Block mass of RODILON®	42 g/block	
Indicative product exposure (dermal) per block	27.79 mg / 5 blocks (20 g each) = 5.56 mg/contact (HEEG 2012)	
FINALE® and RODILON® dermal product exposures per block	*5.56 mg/contact	
Dermal product loading / bait point	5.56 mg x 4 blocks	5.56 mg x 4 blocks
Number of bait points loaded / day	79 (Table 8.2.1.1)	5 (Table 8.2.1.1)
Total product exposure (dermal)	5.56 mg/contact x 4 contacts x 79 bait points = 1 756 mg	5.56 mg/contact x 4 contacts x 5 bait points = 111 mg
Difethialone exposure/day (dermal)	0.044 mg/day	0.003 mg/day
Difethialone absorbed/day (dermal)	1.76 x 10^{-3} mg/day	1.11 x 10^{-4} mg/day
Difethialone systemic dose (no gloves)	2.93 x 10^{-5} mg/kg-day	1.85 x 10^{-6} mg/kg-day
Systemic dose (gloves, 10% penetration)	2.93 x 10^{-6} mg/kg-day	Assumed not using gloves
Clean-up scenario: FINALE® and RODILON® wax blocks		
Number of bait points cleaned up / day	16	5
Exposure to product / cleaning (default)	**5.7 mg/box cleaned (HEEG 2012)	
Total product exposure (dermal)	91.2 mg/day	28.5 mg/day
Difethialone exposure/day (dermal)	0.0023 mg/day	0.0007 mg/day
Difethialone absorbed/day (dermal)	9.12 x 10^{-5} mg/day	2.85 x 10^{-5} mg/day
Systemic dose (no gloves)	1.52 x 10^{-6} mg/kg-day	4.75 x 10^{-7} mg/kg-day
Systemic dose (gloves, 10% penetration)	1.52 x 10^{-7} mg/kg-day	Assumed not using gloves

Total difethialone dose without PPE (mg/kg-day)	$2.9 \times 10^{-5} + 1.5 \times 10^{-6} = 3.1 \times 10^{-5}$	$1.9 \times 10^{-6} + 4.7 \times 10^{-7} = 2.3 \times 10^{-6}$
Total difethialone dose with PPE (mg/kg-day)	$2.9 \times 10^{-6} + 1.5 \times 10^{-7} = 3.1 \times 10^{-6}$	Assumed not using gloves

* The **default indicative dermal value** is used for FINALE® and RODILON® wax blocks calculations, despite the FINALE® and RODILON® block masses being 42 g versus the 20 g default of the HEEG. The HEEG (2012) guidance states that the size of a bait block is ignored and the indicative dermal exposure to the products is valid for blocks with different sizes. This is probably because the skin surface area in contact with a wax block does not increase linearly according to the increase in block mass.
Difethialone exposure/day (dermal) = Total product exposure (dermal) x difethialone content (0.0025%).
Difethialone absorbed/day (dermal) = Difethialone exposure/day x dermal absorption rate (4%).
Difethialone systemic dose = (Difethialone absorbed/day)/60 kg body mass.
** The number of disposed blocks per bait box are not considered for the clean-up phase (HEEG 2012).

8.2.2 Wax blocks risk assessment

The risk calculations are conducted by comparing the calculated difethialone exposure doses (Section 8.2.1) to the acute AEL (Table 7.2.3.1) of 1.7×10^{-5} mg/kg-day. Exposure doses less than 100 per cent of the AEL are considered acceptable. The calculation of risks is summarised in Table 8.2.2.1.

The risk calculations for PCOs demonstrates that dermal exposure of professionals not wearing gloves would not be acceptable, particularly while applying blocks. The risk of PCOs wearing gloves is acceptable. Cleaning of bait boxes are not associated with a risk to health, whether gloves are worn or not. However, this finding does not mean that gloves need not be worn while cleaning up, since gloves also protect against possible secondary exposure while handling dead rodents and against diseases carried by rodents. As recommended on the label, PCOs should wear gloves at all times while handling bait, while cleaning up and while handling dead rodents.

The risk assessment for non-professionals, assumed not to wear gloves, demonstrates that exposure while applying bait and cleaning up bait stations are not associated with a risk to health. However, this finding does not negate the need for gloves, because gloves also protect against possible secondary exposure while handling dead rodents and against diseases carried by rodents. As recommended on the label, non-professionals (general public, domestic users) should also wear gloves at all times while handling bait, cleaning up or removing dead rodents.

In the case of secondary exposure, an unacceptable risk is identified for children accidentally mouthing or chewing on wax blocks with 0.0025% difethialone. Specific risk mitigation measures are required to prevent exposure to children and are discussed Section 9. In any case, any noted contact of a child with rodenticide bait should be brought to the immediate attention of a medical professional, without exception.

Table 8.2.2.1: Difethialone wax blocks health risks of primary and secondary exposure.

Route of exposure	Dermal exposure dose (mg/kg-day) (all adult)		Risk = (Dose/AEL) % AEL_{acute} (mg/kg-day) = 1.7 x 10^{-5}			
	PCOs	Non-professionals	PCOs	Acceptable Yes/No	Non-professionals	Acceptable Yes/No
Primary exposure: application of FINALE® and RODILON® wax blocks						
Without gloves	2.93 x 10^{-5}	1.85 x 10^{-6}	172%	No	10.9%	Yes
With gloves	2.93 x 10^{-6}	Assumed not to wear gloves	17%	Yes	Assumed not to wear gloves	
Primary exposure: clean-up of FINALE® and RODILON® wax blocks						
Without gloves	1.52 x 10^{-6}	4.75 x 10^{-7}	8.9%	Yes	2.8%	Yes
With gloves	1.52 x 10^{-7}	Assumed not to wear gloves	0.9%	Yes	Assumed not to wear gloves	
Total dose, assuming all activities on one day (worst-case) (FINALE® and RODILON® wax blocks)						
Without gloves (mg/kg-day)	3.08 x 10^{-5}	2.33 x 10^{-6}	181.1	No	13.7	Yes
With gloves (mg/kg-day)	3.08 x 10^{-6}	Assumed not to wear gloves	18.1	Yes	Assumed not to wear gloves	
Secondary exposure: accidental mouthing by infants/toddlers						
Oral exposure dose = 2.5 x 10^{-3} mg/kg-day		**Risk = (Dose/AEL) %** > 10 000%		**Acceptable? Yes/No** No		

In summary, it is reasonable to conclude that the difethialone exposures of professional and non-professional users of the FINALE® and RODILON® wax blocks assessed in this report are acceptable and without a risk to health, provided that professionals wear gloves while using the blocks. Non-professionals should also be encouraged to wear gloves, which would also protect against diseases carried by rodents.

With regard to secondary exposure to wax blocks in use, a risk to infants transiently mouthing or chewing on wax blocks would be associated with a risk to health, but is not likely to occur commonly, because the taste deterrent (bittering agent) included in the formulation will cause the child to spit out any chewings. Nonetheless, preventative measures recommended on the label, such as keeping the product out of reach of children, must be adhered to.

Secondary exposure of adult bystanders accidentally touching or cleaning up wax blocks dragged about by rodents is expected to be not more than that calculated for non-professionals not wearing gloves while handling the product. Therefore, secondary risks to adult bystanders, without gloves, would be acceptable, since risks to non-professionals not wearing gloves are also acceptable.

9 Discussion

9.1 Summary of risks associated with solid rodenticide formulations

The HHRA results presented in this report, concerning the use of FINALE® rodenticide bait pellets and the FINALE® and RODILON® wax blocks formulations registered in South Africa, are summarised with regard to primary exposure to professional PCOs and non-professional rodenticide users (general public/domestic users), and regarding secondary exposure of adults and

infants/toddlers in accidental contact with rodenticides. Contact with rodenticide on the fur of dead rodents is sometimes viewed as a potential exposure scenario to PCOs, domestic users and bystanders (unaware members of the general public, including children). Although the TNsG (ECB 2007) includes this scenario, it is not included in the HEEG (2012) and the Norwegian CA (2007 and 2016) viewed the scenario as "unrealistic". Therefore, the scenario is not included in the FINALE® and RODILON® wax blocks assessments. On the outside chance that this might happen, the degree of exposure can be viewed as equal to that of accidental contact with bait.

Pellet baits

- Exposures and risks in the expected handling scenarios are acceptable for the PCOs and non-professional/domestic users. Non-professional users were assessed assuming that gloves are not worn.
- Secondary exposure is acceptable for adults in accidental dermal contact with the bait product.
- Infants/toddlers transiently mouthing or chewing on pellets are at risk. However, this is not likely to occur commonly, because the taste deterrent (bittering agent) included in the formulation should cause the child to spit out the pellets. Nonetheless, the use of tamper-proof bait boxes should be recommended in the household setting.

Wax blocks

- Exposures of PCOs in the wax blocks application phase are unacceptable if gloves are not worn. Wearing gloves are associated with an acceptable risk to health. Health risks are acceptable during the clean-up phase, whether gloves are worn or not.

- Non-professionals applying bait and cleaning up bait stations are not at a risk to health due to difethialone exposure, whether gloves are worn or not.
- An unacceptable risk is shown for infants/toddlers accidentally mouthing or chewing wax blocks.

9.2 The risks versus societal needs/benefits balance

There is no question that there is a legitimate societal need for cost-effective, relatively inexpensive rodenticides, considering the serious and potentially lethal human diseases, e.g., hantavirus, typhus and bubonic plague, that are spread by mice and rats. Furthermore, rodent plagues imply a burden of economic costs of property, food and crop damage and spoilage.

The USEPA (2022b) approached this need is an issue of environmental justice*, "the fair treatment and meaningful involvement of all people, regardless of race, color, national origin, or income, in the development, implementation, and enforcement of environmental laws, regulations, and policies*". In particular, care is taken with low-income populations who are particularly vulnerable to mouse and rat infestations that are most common in housing for lower socio-economic populations.

Other control measures, e.g., rodent exclusion, can be recommended as an alternative to the use of poisoned bait, but can be expensive and/or time-consuming, and thus not practical, for low-income households and in multi-family dwellings. Furthermore, the USEPA (2022b) points out that "*rodent prevention methods often rely on support from the entire community and may be more difficult in communities with a higher population density or with a lower quality of services (e.g., in areas with poor waste management services)*". In these instances, rodent control measures such as mechanical trapping and use of rodenticides may have a higher benefit to these populations relative to more affluent populations.

The poorest populations may thus experience a greater degree of rodent infestations and consequently may be disproportionately overburdened by exposure to the diseases transmitted by rodents. Clearly, the poor may be most affected by severe restrictions on the use of rodenticides, and particularly of second-generation anticoagulant rodenticides, which are cost-effective and currently fairly accessible in general hardware stores and in large supermarkets. Therefore, economically and socially disadvantaged populations may be disproportionately affected by availability or use restrictions of such rodenticides. Undesirable effects would include cost increases or reduction in rodent control, with subsequent detrimental health effects.

Considering the societal need and benefit of continued access to second-generation anticoagulant rodenticides, it is more advantageous to society to rather adopt these as important tools in an integrated pest management approach to the control of rodent infestations. Therefore, in balance, while identifying risks of concern to the environment, the USEPA (2022b) "*acknowledges that there are many benefits associated with these active ingredients and supports the continued registration of these active ingredients*".

The EC (2017) renewed the approval of difethialone for use in rodenticides, subject to compliance with certain specifications and conditions. The European Commission (EC 2017) renewed the approval of difethialone for use in biocidal products of product-type 14 (rodenticides), subject to compliance with certain specifications and conditions. The expiry date of the approval was recently extended to 31 December 2026 (EC 2024).

The main reasons for approval were:

- Rodents can carry pathogens that are responsible for diseases which can pose serious dangers for human or animal health.
- Non-chemical rodent control methods such as mechanical-, electrical- or glue traps may not be sufficiently efficient and also not necessarily more humane than rodenticides with difethialone as an active substance.
- Effective rodent control cannot rely on non-chemical controls or prevention methods only and currently relies largely on the use of anticoagulant rodenticides. Therefore, difethialone is considered essential to ensure appropriate rodent control.
- It was concluded that the use of difethialone rodenticides would prevent or control a serious danger to human and animal health. Non-approval could lead to insufficient rodent control, not only causing significant negative impacts on human or animal health or the environment, but also other economic and social consequences.
- Risks to human health, animal health or the environment arising from use of products containing difethialone can be mitigated; therefore, the non-approval of difethialone as an active substance would have a disproportionate negative impact on society in comparison to the risks arising from the use of the substance.

Nonetheless, the USEPA and the EC strongly argues for mitigation measures provided as clear label instructions, to ensure that use in accordance with the label directions "*will not generally cause unreasonable adverse effects on the environment taking into account the economic, social, and environmental costs and benefits of the use of any pesticide*". Mitigation measures, including as proposed by international regulating entities, are presented in Section 9.3.

9.3 Proposed mitigation measures

Wearing of gloves

The finding of acceptable health risks, even while not wearing gloves in some scenarios, does not mean that gloves need not be worn, since gloves also protect against potential secondary exposure

while handling dead rodents and against diseases carried by rodents. As recommended on the FINALE® and RODILON® wax blocks product labels, gloves should be used at all times while handling bait, while cleaning up and while handling dead rodents.

Tamper-proof bait boxes for application

International regulatory agencies tend to recommend bait box use, in particular for domestic users or for application in the domestic scenario. Bait boxes are not recommended or obligated on the labels of the assessed FINALE® pellets and wax blocks formulations, but the user is instructed to "*Place …* the product … *in a covered bait station to prevent access by children and domestic animals"*. "*Bait boxes or other special containers*" are "*strongly recommended"* on the RODILON® wax blocks label. The method of risk calculation recommended in international guidance followed in this report does not include consideration of whether bait boxes are used or not. Therefore, the use of bait boxes will not change the risk assessment.

It is clear that bait boxes add an extra layer of protection for bystanders, pets and non-target animals, but it is not argued that bait boxes should be made mandatory, because this will imply and added cost premium to the user. Considering the argument for the continued availability of lower cost, but effective, rodenticides to especially lower-income consumer groups, a blanket measure to make bait box use compulsory is not appropriate. However, bait box use in domestic settings should be encouraged.

Bait box use by PCOs should also not be made compulsory, because it is not always necessary, e.g., in spaces not accessible by bystanders, pets, or non-target animals. Bait boxes are not always practical, e.g., in tight spaces such as sewers and roof spaces. Bait boxes are also not always the most effective method of application, e.g., outdoor spaces where it is more effective to place bait not in a bait box, but under cover, such as under a piece of corrugated iron, or in a piece of pipe, around grain storage silos, or near farm animal feed stores or places where agricultural livestock are fed, or in sapling plantations.

Other measures

The following measures include those generally proposed by international regulatory agencies to protect man, animals and the environment:

- Where possible, prior to the treatment inform any possible bystanders (users of the treated area and their surroundings) about the rodent control campaign.
- Consider preventive control measures (e.g. plug holes, remove potential food and drinking as far as possible) to improve product intake and reduce the likelihood of reinvasion.
- Baits must be unattainable to children, pets or other non-target animals in order to minimise the risk of poisoning.
- The FINALE® pellets and wax blocks labels recommendation to apply bait in a covered bait station, and the "*strongly recommended"* RODILON® instructions to use "*bait boxes or other special containers"*, must remain on the labels, to prevent access by children and domestic animals.
- Any noted contact of a child with any type of rodenticide should be brought to the immediate attention of a medical professional, without exception.
- The bait stations should be visited at least every 2 to 3 days at the beginning of the treatment and at least weekly afterwards. The purpose of visits is:
    - To check whether bait stations are intact (bait boxes intact or bait stations still adequately covered).
    - To clean up bait dragged out of the bait box/station by rodents.

    - To search for and remove dead rodents, in order to reduce the risk of secondary human exposure and secondary poisoning of non-target animals.
- Do not use the product as permanent baits for the prevention of rodent infestation or monitoring of rodent activities. It is noted that pulse baiting is generally authorised for rodenticides that contain difethialone.
- Remove the remaining product at the end of treatment period.
- When placing bait points close to or in water drainage systems, ensure that bait contact with water is avoided.
- Outdoor bait must be protected from rain. Place the baiting points in areas not liable to flooding.
- For outdoor use, baiting points must be covered and placed in strategic sites to minimise the exposure to non-target species.
- The product information (i.e., label and/or leaflet) shall clearly show that, if PCOs should deploy bait boxes, these should be properly labelled with the following information:
    - "*do not move or open*";
    - "*contains a rodenticide*";
    - product name or Act 36 of 1947 registration number;
    - active substance(s) and
    - "*in case of incident, call a poison centre* (*insert national phone number*)".
- Carcass removal instructions:
    - While wearing gloves, collect and properly dispose of visible carcasses of target pests or non-target animals.
    - Place carcasses in leakproof plastic bags or other suitable containers and dispose of in the trash or dispose of according to the label disposal instructions.
    - Carcasses buried on site must be buried a minimum of 45 cm below the ground surface, preferably deeper.
- All carcasses must be disposed of in a way inaccessible to wildlife, to prevent secondary poisoning of predatory animals.
- Wearing gloves while handling rodenticides must be recommended on all labels.

10 Conclusions

In support of the application for derogation regarding the restricted use of the registered solid rodenticide products, identified as substances of concern due to the reproductive toxicant properties of the rodenticide ingredient difethialone, the human health risk assessment results lead to the following conclusions:

- Since developmental effects are the only health endpoints (aside from mortality) for which dose-response values are available in toxicological studies, there is no other choice but to base acceptable exposure levels of males and children on this health endpoint as well. Therefore, the absence of a risk to health in general, and specifically the absence of a risk to the developing foetus, is implied by a finding of “acceptable exposures or risks”.

- Adult users of FINALE® Rat and Mouse Pellets and FINALE® and RODILON® Rat and Mouse Wax Blocks, whether professional PCOs or non-professionals, wearing gloves, are not at risk of a health effect, including on the development of the foetus in case of pregnant females.

- For some of the solid bait products, in some cases, acceptable risks are also demonstrated for adults not wearing gloves, e.g., non-professionals handling and using pellets and wax blocks. However, this can never be used to negate the need for recommending the use of gloves on product labels. Recommending the use of gloves is a protective measure for all bait users. Gloves also protect against diseases carried and spread by rodents.

- Infants/toddlers chewing on solid bait products are at risk of a health effect. Transient mouthing may also result in a risk to health. However, accidental exposure of bystanders, specifically children, can be limited by clear communication of the professional pesticide applicator to such bystanders, and by following label instructions to place the bait station out of reach of children and uninformed persons.

- Regardless of the precautionary measures followed, any noted contact of a child with a rodenticide should be brought to the immediate attention of a medical professional, without exception. All product labels must clearly exhibit the contact details of a local/national poison centre.

- A risk of detrimental environmental effects cannot be excluded in the case of primary bait exposure of non-target animals, or secondary exposure of non-target animals to contaminated dead or dying pray, because of the overt toxicity of the anti-coagulant active ingredient difethialone. Therefore, it is of primary importance that all possible mitigation measures recommended in Section 9.3 should be followed to limit environmental exposure.

- The restricted use applied for by the suppliers of rodenticides containing difethialone is according to the intended product use:
  - An anti-coagulant poison for control of the Norway rat, roof rat and house mouse.
  - FINALE® Rat and Mouse Pellets are for use in the home, on the farm and industrial premises, in locations protected from weather or dampness.
  - FINALE® Rat and Mouse Wax Blocks are for use on the farm and industrial premises (outside buildings, warehouses and stores).
  - RODILON® Rat and Mouse Wax Blocks are for use in the home, on the farm, in public health and industrial premises.

- With application of the recommended mitigation measures, accidental exposure of bystanders, children, pets and non-target animals can be effectively limited.

- The balance of societal need and benefits, versus the overt toxic nature of the product, is always to be considered regarding any regulatory decisions to limit access to rodenticides. This is particularly important to socio-economically disadvantaged communities. Such communities bear a double burden of more frequent rodent infestations, with concomitant exposure to diseases spread by rodents, possible rat-bite injuries to infants, damage to property and food spoilage and contamination, and limited resources to use other, non-poisonous solutions.

- The application for derogation of the products assessed in this report is supported, provided that recommended mitigation measures are effectively implemented.

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