INFOTOX (Pty) Ltd

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Retrieval and scientific interpretation of ecotoxicological information

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Report Compiled for: Regulatory Aspects

Derogation Risk Assessment Report for TOMCAT® All-weather Blox (L5524) a Solid Anticoagulant Rodenticide Containing Bromadiolone, a CMR Substance of Concern (Reproductive Toxicity Hazard)

INFOTOX Report No 018-2025 Rev 4.0

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30 April 2025

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30 April 2025

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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 Regulatory Aspects. We do hereby declare that we are financially and otherwise independent of Regulatory Aspects.

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

Willem Christiaan Abraham van Niekerk

30 April 2025

Executive Summary

This document is a risk assessment report supporting an application for derogation for the restricted use of TOMCAT® All-weather Blox, containing the active ingredient bromadiolone, supplied to professional pest control operators ("PCOS") and to the general public.

TOMCAT® All-weather Blox is identified as of concern due to classification as a reproductive toxicity hazard category 1B according to the Globally Harmonized System of Classification and Labelling of Chemicals ("GHS"). The classification is due to the active ingredient ("a.i.") bromadiolone, which is classified in GHS reproductive toxicity category 1B (H360D), indicating a hazard to the development of the unborn child ("D").

Product name, registered supplier, Act 36 of 1947 registration number and a.i. concentration.

Product	Act 36 of 1947 registration number	Registered manufacturer / supplier / distributer	Bromadiolone concentration
TOMCAT® All-weather Blox	L5524	MC Pharma (Pty) Ltd	0.05 g/kg = 0.005 % (w/w)

Intended product use:
The product use description is: an anti-coagulant bait for the control of rats and mice. "*For use in the garden, home, by farming community, industries, PCOs and public health*".

The occupational and residential 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 United States Environmental Protection Agency ("USEPA"), particularly documents produced by the Office of Chemical Safety and Pollution Prevention during 2016 and 2022.
- The Swedish Competent Authority ("CA") acting as the Rapporteur Member State of the European Community ("EC") to carry out the assessment report evaluating bromadiolone as a rodenticide, with the view of satisfying regulatory requirements for placing biocidal products on the market, submitted by the Swedish CA 30 May 2008, revised 16 December 2010.

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 bromadiolone in TOMCAT® All-weather Blox. Since developmental effects are the only health endpoints (aside from mortality) for which short-term 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 systemic risk to health in general, and specifically the absence of a risk to the developing foetus (developmental effects), is implied by a finding of "acceptable exposures or risks".

The following human exposure scenarios were identified for assessment:

- Primary exposure of professional PCOs, non-professionals and domestic users handling, placing, refilling and disposing of unused bait and dead rodents.
- Secondary human exposures are assessed as:
    - Accidental contact of bystanders (adults or children) with the rodenticides while in use.
    - Contact by adults (general public) with dead or dying rodents.
    - Accidental exposure of infants/toddlers transiently mouthing or chewing on bait.

The human health risks associated with using TOMCAT® All-weather Blox are characterised as follows:

- Unacceptable health risks are not foreseen for professional operators applying blocks on a daily basis, while wearing gloves. Assuming the use of gloves by professionals is acceptable in the light of clear product label instructions to this effect. A risk of harm to health is not indicated.
- Non-professionals are not expected to wear protective clothing or to use gloves. Calculated risks based on this assumption are acceptable. There is thus not a risk of harm to health.
- Bystanders accidentally touching bait residues, or dead rodents, are not at a risk to health.
- A risk to health is indicated for infants and toddlers ingesting the bait, but the bittering agent included in the block formulation should prevent extended mouthing and chewing on the bait. Nonetheless, this finding emphasises the application of safety measures recommended on the label to keep the bait away from children, which should prevent exposure and risks.

Acceptable risks were demonstrated for adult non-professional users not wearing gloves. However, this cannot 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, and also protects against diseases carried by rodents.

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.

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 bromadiolone 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 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 environmental 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 by the suppliers of TOMCAT® All-weather Blox is according to the intended product use:

- An anti-coagulant bait for the control of rats and mice.
- "*For use in the garden, home, by farming community, industries, PCOs and public health*".

The application for derogation of TOMCAT® All-weather Blox assessed in this report is supported, provided that recommended mitigation measures are implemented.

Mitigation measures
The following mitigatory label and/or leaflet instructions should be included:

Prior to bait application:
- Where possible, prior to the treatment inform any possible bystanders (e.g. users of the treated area and their surroundings) about the rodent control campaign.
- Consider preventive control measures (e.g., plug holes, remove potential food as far as possible) to improve product intake and reduce the likelihood of reinvasion.

Bait application instructions:
- The use of gloves is highly recommended when handling bait products and dead rodents.
- The use of adequate tamper-resistant bait boxes is highly recommended. Bait box use in domestic settings should be encouraged and the TOMCAT® All-weather Blox label should recommend the use of bait boxes in homes or where public access is likely.
- If the use of bait boxes is not practical, baiting points must be covered and placed in strategic sites to minimise the exposure to non-target animals and to uniformed bystanders.
- Precautions, e.g., keeping the product away from children and pets, and other directions for use on the product label must be followed. Baits must be unattainable to children, pets or other non-target animals in order to minimise the risk of poisoning.
- When placing bait points close to water drainage systems, ensure that bait contact with water is avoided.
- Protect bait from atmospheric conditions (wind and rain). Place the baiting points in areas not liable to flooding.

Precautions during use and disposal (clean-up)
- Bait stations should be visited at least every 2 to 3 days at the beginning of the treatment and at least weekly afterwards, in order to check whether the bait is accepted, bait boxes are intact or that bait stations are still adequately covered, as is practical, and to remove rodent bodies and bait that might have been removed or spilled from the bait station by rodents.
- Search for and remove dead rodents at frequent intervals during treatment.
- 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.
- Remove the remaining product at the end of treatment period. Clear disposal instructions must be provided on the label.
- Do not use the product as a permanent bait for the prevention of rodent infestation or monitoring of rodent activities.

Other precautions
- Any noted contact of a child with a rodenticide bait should be brought to the immediate attention of a medical professional, without exception.

Specific labelling recommendations
- The product information (i.e., label and/or leaflet) shall clearly show that:

- The product should be used in "*in tamper resistant bait boxes*", or in otherwise "*adequately covered bait stations"*.
- 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)*".
- Wearing gloves while handling bait and dead rodents must be emphasised on all labels.

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. Due to these cost concerns, the use of a bait box cannot be made obligatory for domestic or general public users, but recommendations to use bait boxes must be placed on all labels.

The application for derogation of the products assessed in this report is supported, provided that recommended mitigation measures are 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
HHRA	Human health risk assessment
IPCS	International Programme on Chemical Safety
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
SGARS	Second 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 Product identification

This document is a risk assessment report supporting an application for derogation for the restricted use of the registered solid rodenticide product TOMCAT® All-weather Blox.

Report prepared for:		
Name	Regulatory Aspects on behalf of rodenticide manufacturers / retailers	
Contact details	Physical address	63 Glover Avenue, Doringkloof, Centurion, 0157
	Postal address	As physical address
	E-mail address	hannelie@regspecs.co.za

TOMCAT® All-weather Blox is registered to MC Pharma (Pty) Ltd, Act 36 of 1947 registration number L5524. It is an anticoagulant rodenticide with active ingredient ("a.i.") bromadiolone, a reproductive toxicity hazard. The product is a wax block formulation for in- and outdoor application.

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."*

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.

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

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

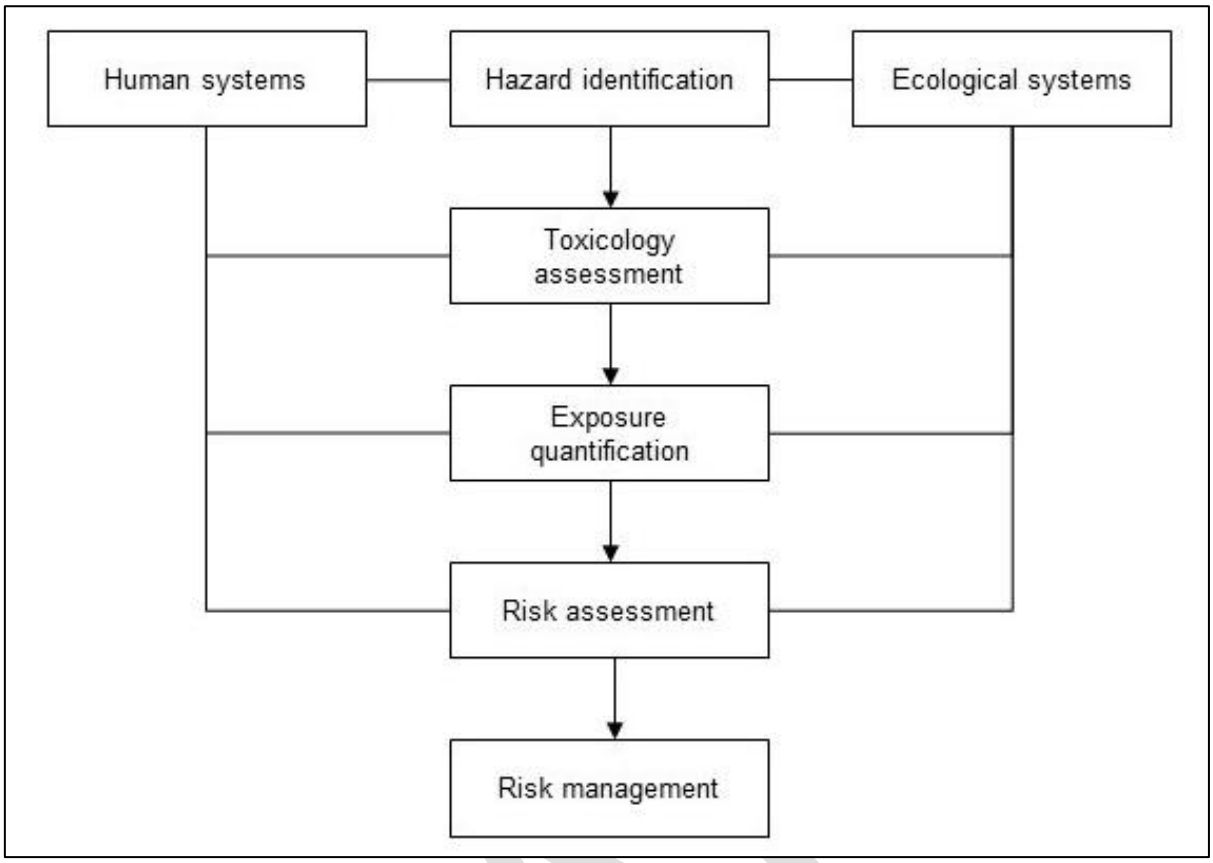

Figure 2.1.1: The holistic health risk assessment paradigm.

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:

- **Hazard assessment** is the identification of the chemical constituent of concern and the hazard it poses, in this case reproductive/developmental toxicity hazards of bromadiolone. 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") or acceptable exposure level ("AEL"), and level of concern ("LOC") for the HHRA purposes, by applying appropriate uncertainty factors and safety factors for infants and children, referring to dose through the routes of exposure. 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. Health risks may also be assessed following the margin of exposure ("MOE") approach. The MOE approach is basically a comparison of the calculated exposure dose and the toxicity limit value for a specific health effect, referred to as the health effect endpoint.

- The calculated MOE is compared to the level of concern ("LOC"), also referred to as a benchmark MOE. The LOC is the margin of exposure between the calculated exposure and the POD that indicates a risk of health effects associated with the calculated exposure. Each POD is associated with a specific numerical LOC value. Therefore, if a calculated MOE is higher in value than the LOC associated with the POD used for the MOE calculation, a risk to health under the assessed exposure conditions is highly unlikely and excluded for all practical purposes. However, if the calculated MOE is lower than the associated LOC, a risk to health cannot be excluded.

- **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 focuses on the following occupational user exposure scenarios:
  - The oral, dermal and inhalation routes of exposure of pest control operators ("PCOs").

  Residential user exposure 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: "*Always make sure that baits are placed out of the reach of children and non-target 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.

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 Bromadiolone CMR hazard classification

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

Active ingredient identification

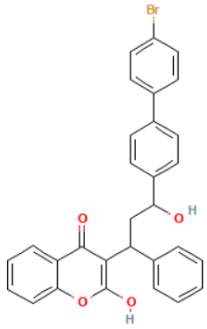 **Bromadiolone**	**CAS #:** 28772-56-7 **Mol. formula:** $C_{30}H_{23}BrO_4$ **Molecular weight:** 527.4 g/mol

Table 3.2.1: CMR GHS classification of bromadiolone.

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 EU classification.				

GHS Category 1B criteria for substance classification:

- Presumed human reproductive toxicant - largely based on evidence from experimental animals.
- 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.

The bromadiolone concentration of TOMCAT® All-weather Blox is:

- 0.05 g/kg
- 0.005 % (w/w)

TOMCAT® is a mixture of more than one chemical substance, but none of the other constituent substances has been classified as a CMR hazard. The complete composition is not provided here, in order to protect proprietary information, but has been made available to the Registrar of Act 36 of 1947, in confidence, at the time of the application for registration.

TOMCAT® All-weather Blox is assigned the H-code H360D because the concentration of bromadiolone is sufficient to justify the reproductive toxicity classification (≥ 0.003 % w/w, according to guidance of the European Chemical Agency ("ECHA") (ECHA online) on the harmonised classification of chemical mixtures containing bromadiolone. 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 concentration of bromadiolone in TOMCAT® All-weather Blox (0.005%) satisfies the reproductive toxicity classification criterium (≥ 0.003 % w/w), according to ECHA guidance and should be classified as a GHS Category 1B Reproductive toxicity hazard.

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 concentration of bromadiolone in TOMCAT® All-weather Blox does not meet the criterium for classification 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 Bromadiolone in air

Bromadiolone in solution or in solid formulations is not expected to partition into the atmosphere to a significant extent, due to:

- Vapour pressure far less than 1×10^{-6} Pa.
- Henry's law constant less than 2.18×10^{-3} $Pa.m^3.mol^{-1}$, the value above which volatilisation from an aqueous solution is expected:
  - Estimates of 4.25×10^{-4} $Pa.m^3.mol^{-1}$ and 8.99×10^{-7} $Pa.m^3.mol^{-1}$ reported by the Swedish CA (2010).
  - 5.55×10^{-5} $Pa.m^3.mol^{-1}$ (USEPA 2016a).

Bromadiolone is expected to rapidly photolyse and photodegrade (DT_{50} = 2 hours) and thus not expected to persist in air (Swedish CA 2010).

4.2 Bromadiolone in water

The solubility of bromadiolone in water is limited to moderate. Reported values are:

- 1.21 mg/litre at pH 7 (25°C) (USEPA 2016a).
- 3.43 mg/litre at 25°C (pH not provided) (USEPA 2020a).
- Increasing the pH increases solubility (Swedish CA 2010):
  - Highest solubility of 180 to 1 200 mg/litre at pH 9 to 10 and 20°C.
  - Approximately 0.1 mg/l at pH 4 to 5, 20°C.
  - 2.48 to 18.4 mg/l at pH 7, 20°C.
- The University of Hertfordshire Pesticide Properties DataBase ("PPDB", Lewis et al. 2016) lists a solubility of 18.4 mg/litre at 20°C, interpreted as "moderate" solubility in water.

The aqueous hydrolysis DT_{50} at 20°C and pH 7 is 30 days, interpreted as indicating moderate persistence (Lewis et al. 2016) and the likely stability (USEPA 2020a) of bromadiolone in environmental water bodies.

The log of the octanol/water partition coefficient (log K_{ow}) at pH 7 and 20°C is listed as:

- 6.8 (Swedish CA 2010).
- 4.07 (Lewis et al. 2016).
- 4.07 (USEPA 2020a).

The log K_{ow} values indicate a relatively high propensity to accumulate in lipid-like environments as opposed to a watery environment, that is, bromadiolone is lipophilic and hydrophobic. Bromadiolone will thus be able to penetrate cell walls with relative ease and is likely to accumulate in the fatty deposits of exposed organisms.

The PPDB (Lewis et al. 2016) considered bromadiolone's bioconcentration factor ("BCF") of 867 litre/kg in fish as reaching the threshold for concern. The USEPA (2020a) reported a BCF of 1 658 (unitless) and the Swedish CA (2010) calculated values of 339 to 575 (unitless), based on the log K_{ow}. Both authorities interpreted the BCFs as reflecting the potential of bromadiolone to bioconcentrate.

4.3 Bromadiolone in soil

The organic carbon 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.

The Swedish CA (2010) concluded that bromadiolone should strongly adsorb to soil, since KOC values ranged between 1 563 and 41 600 ml/g, which corresponds to slightly mobile to non-mobile according to the classification index used. The theoretical classification was supported by laboratory soil column leaching and aged leaching studies submitted to the CA, which indicated that bromadiolone and any potential degradation products are not likely to move through the soil profile and are unlikely to reach groundwater in significant quantities.

The USEPA (2016a) cited a bromadiolone half-life of 128 days in soil, from an unpublished study, and concluded that it can generally be considered immobile, except in soils of low organic matter and clay, such as sand, based on data from other unpublished studies. The PPDB (Lewis et al. 2016) interpreted the organic-carbon normalized Freundlich distribution coefficient ("K_{foc}") of 1 636 as indicating slight mobility in soil. The potential for groundwater contamination should thus be low.

4.4 Summary

The USEPA (2020a) has summarised the environmental fate concerns for bromadiolone as presented in Table 4.4.1.

Table 4.4.1: USEPA summary of environmental fate concerns for bromadiolone.

Concern	Yes	No	Notes
Aquatic bioconcentration/ bioaccumulation	Possible		Relatively high log K_{ow} and fish BCF (see Section 4.2).
Groundwater contamination		X	Low mobility in soil (see Section 4.3).
Sediment contamination		X	Potential exposure is assumed negligible based on the use pattern (USEPA 2016a).
Persistence in the environment	Moderately persistent		Due to relatively long half-life in soil, slight mobility in soil (Section 4.3) and potential bioconcentration in fish (Section 4.2).
Residues of concern	Bromadiolone (parent)		Due to persistence of the parent, environmentally and in-vivo.
Secondary exposure of non-target animals/birds/fish etc.	X		-
Volatilisation		X	Not volatile (see Section 4.1)

5 Environmental assessment

5.1 Bromadiolone toxicity to non-target species

5.1.1 Mammals

As can be expected of a rodenticide ingredient, bromadiolone is very highly toxic to mammals, as reported by the Swedish CA (2010) and the USEPA (2020a) from various sources:

- Acute oral LD50s of 1.31 and 0.56 to 0.84 mg/kg-bw (Swedish CA 2010) and 0.6 mg/kg-bw (USEPA 2020a).
- NOAEL from a 90-day subchronic test with rabbits was 5 x 10^{-4} mg/kg-day.
- NOAEL from a 90-day subchronic test with rats fed difethialone was 2 x 10^{-3} mg/kg-day and accepted as representative of the subchronic toxicity of bromodialone, since "*difethialone is at least as toxic as bromadiolone*" (Swedish CA 2010).
- NOAEL from a 2-generation study with rats was 0.035 mg/kg-bw and the LOAEL 0.070 mg/kg-bw (USEPA 2020a).

From the above subchronic studies, the Swedish CA proposed the following predicted no-effect concentrations ("PNECs"):

- $PNEC_{oral\text{-}mammals}$ = 5.6 x 10^{-6} mg/kg-day from the rabbit study.
- $PNEC_{oral\text{-}mammals}$ = 2.2 x 10^{-5} mg/kg-day from the rat study.

5.1.2 Birds

Bromadiolone is acutely toxic to birds, indicated by the following numbers reported by the Swedish CA (2010) and the USEPA (2020a):

- LD50 value of 138 mg/kg-bw for bobwhite quail (Swedish CA 2010). This is similar to a value of 170 mg/kg-bw cited by the USEPA (2020a) from an unpublished study, also of bobwhite quail.
- Lowest LC50 in food was 62 mg bromadiolone/kg food with bobwhite quail and 28.9 mg/kg food in partridge (Swedish CA 2010). The USEPA (2020a) reported an LC50 of 37.6 mg/kg diet from an unpublished bobwhite quail study.

Dietary studies reviewed by the Swedish CA (2010) lead to:

- Conclusion that the dietary NOEC for birds is possibly lower than 19 mg/kg food.
- A drinking water NOEC of 0.26 mg/litre drinking water or 39 µg/kg-day was reported in a 6-week (42 days) reproduction study in Japanese quail.
- The food NOEC was 0.1 mg/kg food in a longer 20-week (140 days) study, equivalent to 0.01138 mg/kg-day.
- A secondary toxicity study in the great horned owl provided an LD100 (all perished) of 0.056 mg/kg-day.

From the above, the Swedish CA proposed the following PNECs:

- $PNEC_{oral\text{-}birds}$ = 1.3 x 10^{-3} mg/kg-day from the 42-day study (8.7 x 10^{-3} mg/litre in drinking water).
- $PNEC_{oral\text{-}birds}$ = 3.8 x 10^{-4} mg/kg-day from the 140-day study (3.3 x 10^{-3} mg/kg food).
- Secondary poisoning $PNEC_{oral\text{-}birds}$ = 1.9 x 10^{-4} mg/kg-day (7.5 x 10^{-4} mg/kg food).

5.1.3 Aquatic environment

Bromadiolone is toxic to organisms in the aquatic compartment, as demonstrated by the aquatic toxicity data from the Swedish CA (2010) and the USEPA (2020a), summarised in Table 5.1.3.1.

Table 5.1.3.1: Aquatic toxicity of bromadiolone.

Exposure study	Species	Toxicity value	Reference
Acute	Freshwater fish: Rainbow trout	96-hr LC50 = 1.4 mg/litre NOAEC ≤ 0.46 mg/litre LOAEC < 0.46 mg/litre	USEPA (2016a)
Acute	Freshwater fish: Rainbow trout	96-hr LC50 = 2.86 mg/litre	Swedish CA (2010)
Acute	Freshwater fish: Rainbow trout	96-hr LC50 > 8.0 mg/litre	Swedish CA (2010)
Acute	Freshwater fish: Bluegill sunfish	96-hr LC50 = 3.0 mg/litre NOAEC = 1.3 mg/litre LOAEC = 2.2 mg/litre	USEPA (2016a)
Acute	Freshwater invertebrate: *Daphnia magna*	48-hr EC50 = 0.24 mg/litre NOAEC = 0.088 mg/litre LOAEC = 0.19 mg/litre	USEPA (2016a)
Acute	Freshwater invertebrate: *Daphnia magna*	48-hr EC50 = 2.0 mg/litre NOAEC = 1.2 mg/litre LOAEC = 1.8 mg/litre	USEPA (2016a)
Acute	Freshwater invertebrate: *Daphnia magna*	48-hr EC50 = 5.79 mg/litre	Swedish CA (2010)
Acute	Freshwater invertebrate: *Daphnia magna*	48-hr LC50 = 2.0 mg/litre	Swedish CA (2010)
Growth inhibition (72-hours)	Algae	ErC50 = 1.14 mg/litre EbC50 = 0.17 mg/litre	Swedish CA (2010)
Sewage sludge/ respiration inhibition	Sewage treatment plant microorganisms	EC50 = 132.8 mg/litre EC50 = 31.6 mg/litre	Swedish CA (2010)
LC50: water concentration at which 50% lethality is observed, relative to the control. EC50: water concentration at which 50% immobility is observed, relative to the control. ErC50: 50% reduction in growth rate relative to the control. EbC50: 50% reduction in biomass relative to the control.			

5.1.4 Terrestrial invertebrates

Earthworms

The USEPA (2016a) concluded that evidence suggest that toxicity to earthworms may occur and that the exposure pathway for exposure is complete for certain types of invertebrates. The USEPA cited a study demonstrating bromadiolone toxicity to earthworms, with a 14-day LC50 of more than 4.74 mg/kg soil (Liu et al. 2015, cited by USEPA 2016a and 2020a).

The Swedish CA (2010) also considered earthworms as a representative species of terrestrial invertebrates and cited a 14-day bromadiolone LC50 of 8.4 mg/kg wet weight ("ww") soil and a NOEC of 918 mg/kg ww soil, from which a $PNEC_{soil}$ of 0.918 mg/kg ww was calculated. As an alternative, motivated by the availability of test data on only one terrestrial invertebrate, the Swedish CA (2010) used equilibrium partitioning calculations to calculate a a PNECsoil of 0.099 mg/kg ww from the available daphnia toxicity data (Table 5.1.3.1).

The Swedish CA (2010) concluded that the PNECsoil value derived from the equilibrium partitioning calculations is more realistic and used the value of 0.099 mg/kg ww soil in environmental risk assessments.

Honey bees

Exposure of honey bees is not expected by the USEPA (2020a), given the expected rodenticide use patterns. Toxicity data on honey bees was not available, but was also not required by the USEPA, due to the lack of expected exposure. The Swedish CA (2010) also considered rodenticide exposure of honey bees as not relevant.

5.2 Environmental risk assessment

5.2.1 Persistence, bioaccumulation and toxicity (PBT)

The Swedish CA (2010) concluded that bromadiolone is "not readily biodegradable" in water and is persistent in soil, while the USEPA (2020a) concluded that it is possibly moderately persistent in the environment. Both authorities agreed that bioaccumulation is potentially of concern in fish. The Swedish CA (2010) was also concerned about wildlife. It is considered potentially toxic based on results from short-term toxicity data on aquatic organisms (Swedish CA 2010). Thus, environmental contamination with bromadiolone presents a potential risk to the environment in general (specifics are addressed in the following sections). Therefore, it is clear that measure need to be taken to prevent environmental contamination.

5.2.2 Bromadiolone metabolites and degradates

Breakdown products (degradates) of bromadiolone were identified in an unpublished aerobic soil metabolism study cited by the USEPA (2016a). However, the degradation products were not considered of concern for the environmental risk assessment, because the main risk concern is primary exposure from direct consumption of bait products and secondary exposure from consumption of prey that ingested bait. Contamination of soil and water from use of bait products is expected to be minimal. Therefore, bromadiolone remains the residue of concern (USEPA 2016a).

5.2.3 Primary vs secondary environmental exposure

Primary exposure

Primary exposure of non-target species is defined as direct contact with and ingestion of the applied rodenticide, that is, of TOMCAT® All-weather Blox deployed outdoors. The label instructions are to place the blocks in such a way that it is not accessible to animals and birds, e.g., under loose boards or tiles. The product is thus not intended for broadcast application in the environment, but for application at specific problem sites. Nonetheless, the use of bait boxes is not specifically recommended on the product label and primary exposure remains of concern in any case, since target animals can drag concealed blocks out into the open.

The USEPA (2020a) assessed the risks of primary bait consumption to birds and mammals, on single and on multiple days and found:

- Birds were not at risk in case of single day consumptions, but were at risk in case of multiple day consumptions.
- Mammalian risks of concern are indicated in case of single and multiple days consumption.

The Swedish CA (2010) similarly concluded:

- Birds are not at risk of acute primary poisoning, but for mammals the situation is more uncertain.

- Long-term risk assessment for bait containing bromadiolone in and around buildings (as is applicable to TOMCAT® All-weather Blox) found very high risks for long-term primary poisoning of both mammals and birds.

However, the Swedish CA (2010) is correct in pointing out that long-term consumption of sufficient quantities of bromadiolone bait is generally not realistic and that risks associated with long-term exposure should be regarded strictly as worst case.

Exposure to terrestrial invertebrates is not expected if bait is enclosed in tamper-proof bait stations, but exposure is possible in other application scenarios. Primary exposure of terrestrial invertebrates is not indicated as of particular concern by the USEPA (2020a).

Due to the expected solid rodenticide use patterns, primary exposure of aquatic organisms is not expected by the USEPA (2020a) or the Swedish CA (2010).

In conclusion, mammals are most likely at risk of harm due to acute primary rodenticide ingestion. Both the USEPA (2020a) and the Swedish CA (2010) recommended mitigation by risk management principles, given further attention in Section 9.2.

5.2.4 Secondary exposure

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. Both the Swedish CA (2010) and the USEPA (2020a) consider bromadiolone as of concern with regard to secondary exposure. The USEPA (2020a) listed environmental incident data supporting this concern.

Bromadiolone used for control of rodents in sewers may end up in sewage treatment plants (“STPs”), where it might inactivate the microorganisms in sewage sludge, with negative effects on the breakdown of organic material. The Swedish CA (2010) assessed this possibility and concluded that the risks of this occurring with bromadiolone used for control of rodents in sewers is acceptable.

Responsible product application and care, with clear product label and SDS instructions 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 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, as found in an SGARs study example evaluated by the USEPA (USEPA 2005).

The general conclusions of 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 (Swedish CA 2010 and the USEPA 2020a) and both authorities recommended mitigation by risk management principles, given further attention in Section 9.2.

6 Human health and toxicological review

6.1 Pertinent human health effects

Bromadiolone is a second-generation single-dose anticoagulant rodenticide. It disrupts the normal blood clotting mechanisms by preventing regeneration of vitamin K, which inhibits activation of blood clotting factors. The result of biochemical interference is an increased bleeding tendency and eventual haemorrhage and death (Swedish CA 2010). The chemical "backbone" involved in the toxic effect is 4-hydroxycoumarin, which is present in the chemical structure of some of the most common rodenticides, such as brodifacoum, bromadiolone, coumatetralyl, coumafuryl, and difenacoum (Murphy and Lugo 2015).

The USEPA (2020b) studied incident records of rodenticide exposures (not necessarily ingestion, and not necessarily resulting in death). The total number of rodenticide incidents slightly decreased from 198 incidents in 2009 to 146 incidents reported in 2018, and incidents specifically with second generation anticoagulant rodenticides ("SGARS"), such as bromadiolone, had decreased by 79 per cent from 164 incidents in 2009 to 34 incidents in 2018. Similar data are not available for South Africa, but the USEPA data show that incident numbers can be described as moderate.

Overall, the USEPA 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). This demonstrates that proper training of pesticide applicators and the use of personal protective equipment are effective management tools limiting occupational exposure risks.

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 (USEPA 2020b).

6.2 Routes of absorption

Oral absorption

The Swedish CA (2010) reported studies showing rapid and extensive absorption by the oral route in rats. Oral absorption was more than 70% (71 to 77%) based on carcass, urinary- and biliary excretion. The USEPA (2016b) did not propose an oral absorption rate value.

Dermal absorption

The USEPA (2016b) concluded that the dermal absorption of bromadiolone is likely less than 10%, based on a weight of evidence approach but chose a dermal absorption value of 10% as a conservative estimate based on the available data.

The Swedish CA (2010) reported the following values:

- Blocks: 1.6%, as a worst-case assumption if the formulation is not in wax.
- Wax block products dermal absorption was estimated at 0.32%.
- A worst-case value of 0.36% was obtained from an in vitro study on a representative wax block formulation containing 0.005 % bromadiolone that was used for risk assessments by the Swedish CA (2010).
- Wearing gloves is assumed to reduce the exposure of hands by 90% (Swedish CA 2010).

The in vitro study on a representative wax block formulation containing 0.005% bromadiolone, reported by the Swedish CA (2010), is directly applicable to TOMCAT® All-weather Blox, of which the bromadiolone concentration is also 0.005% (see Section 3.2). Therefore, the worst-case value of 0.36% obtained from the in vitro study should be used for dermal exposure health risk assessments of TOMCAT® All-weather Blox.

Inhalation

The USEPA (2016b) considers bromadiolone end-use product bait block formulations, such as TOMCAT® All-weather Blox, as having limited potential for inhalation exposure, since bromadiolone in solid preparations has a very low volatilisation potential. This is based on the low vapour pressure of bromadiolone (see Section 4.1). Neither the USEPA (2016b) nor the Swedish CA (2010) had proposed an inhalation absorption factor for bromadiolone.

6.3 Toxicological studies

Metabolism (in mammals) is limited. The sole major metabolite identified was as a hydroxylated analogue of bromadiolone. Significant toxicological effects were not shown for any of the metabolites identified for hydroxy coumarin-derived rodenticides; therefore, the toxicologically relevant chemical species is bromadiolone (Swedish CA 2010). The USEPA (2016b) concluded that bromadiolone does not appear to produce a toxic metabolite produced by other substances. This excludes a common mechanism of toxicity finding and negates the need to adjust toxicological PODs for such an eventuality.

Distribution and excretion: Accumulation of bromadiolone in the liver is commonly described. The liver half-life is approximately 318 days and on study reported that 33% to 48% of the oral dose was retained in laboratory rodents 7 days post dose, mainly in liver. It is excreted relatively slowly and almost entirely via the bile and faeces (Swedish CA 2010).

The USEPA (2016b) describes a rat study in which 0.2 µg/kg-bw was administered as a single dose, in order to study retention in the liver. A biexponential excretion pattern was found, with a liver half-life of 17 days in phase I and 318 days in phase 2. The results were interpreted as indicating a substantial retention of bromadiolone in the liver “for a long time” (USEPA 2016b).

Acute toxicity data presented by the Swedish CA (2010) and the USEPA (2016b) are presented in Table 6.3.1.

Table 6.3.1: Acute toxicity of bromadiolone in mammals.

Species	Exposure study	Toxicity value	Reference
Rat	Oral acute	LD50 between 0.56 and 0.84 mg/kg-bw	USEPA (2016b)
Rat	Oral acute	Two sources: • 1.31 mg/kg-bw (male and female combined); 95% confidence limits 1.17 to 1.49 mg/kg-day • LD50 between 0.56 and 0.84 mg/kg-bw	Swedish CA (2010)
Rabbit	Dermal acute	LD50 = 1.71 mg/kg-bw	USEPA (2016b) and Swedish CA (2010)
Rat	Dermal acute	LD50 = 23.31 mg/kg-bw	Swedish CA (2010)
Rat	Inhalation acute	LC50 = 0.43 µg/litre air	Swedish CA (2010)
Rat	Inhalation acute	LD50 = 0.43 mg/kg-bw	USEPA (2016b)

Repeated dose toxicity data presented by the Swedish CA (2010) and the USEPA (2016b) are presented in Table 6.3.2.

Table 6.3.2: Repeated dose toxicity of bromadiolone in mammals.

Species	Exposure study	Toxicity value	Reference
Rat	20-day oral gavage	NOAEL < 6.4 µg/kg-day, not established LOAEL = µg/kg-day based on external and internal haemorrhage, anorexia and polydypsia	USEPA (2016b)
Rat	90-Day oral repeated dose	NOAEL = 2.5 µg/kg-day	Swedish CA (2010)
Rabbit	90-Day oral repeated dose	NOAEL = 0.5 µg/kg-day	Swedish CA (2010)
Rat	Oral: Developmental toxicity	Maternal: • NOAEL = 35 µg/kg-day • LOAEL = 70 µg/kg-day based on vaginal bleeding in the treated dams Developmental: • NOAEL = 70 µg/kg-day • LOAEL = not established	USEPA (2016b)
Rabbit	Oral: Developmental toxicity	Maternal: • NOAEL = 4 µg/kg-day • LOAEL = 8 µg/kg-day based on vaginal bleeding in the treated dams Developmental: • NOAEL = 8 µg/kg-day • LOAEL = not established	USEPA (2016b)
Rabbit	Oral: Developmental toxicity	Maternal: • NOAEL = <2 µg/kg-day • LOAEL = 2 µg/kg-day *Developmental: • NOAEL = 2 µg/kg-day • LOAEL = 4 µg/kg-day	Swedish CA (2010)
Polydypsia: abnormal urge to drink fluids at all times. *The Swedish CA (2010) had mistakenly reversed the NOAEL and LOAEL values.			

Reproductive and developmental toxicity

The USEPA (2016b) referenced the unpublished rat and rabbit prenatal exposure studies summarised in Table 6.3.2. These prenatal developmental studies did not indicate a concern for either toxicity or susceptibility in the offspring.

The Swedish CA (2010) reported the same data as provided by the USEPA for rats and rabbits. Both authorities referenced studies for which data protection is claimed. The authors are referenced by the Swedish CA, but not by the USEPA, but it is concluded that the same data source was probably used. In addition, the Swedish CA (2010) referenced a rabbit teratogenicity study showing severe foetal malformations at maternally toxic levels of bromadiolone, but concluded that the effects may have been due to generalised toxicity and not specifically to effect of bromadiolone. Reference is also made to guideline embryotoxic and teratogenic studies in which bromadiolone tested negative (no embryotoxic or teratogenic effect).

In spite of these findings, based on the structural similarity of bromadiolone to warfarin, and the same mode of action, bromadiolone is considered a possible developmental toxicant. The Swedish CA (2010) refers to a Commission Working Group of Specialised Experts on Reproductive Toxicity that had in 2006 "*unanimously recommended that all AVK[3] rodenticides should collectively be regarded*

[3] AVK = Antivitamin K

as human teratogens due to the structural similarity to and the same mode of action as the known developmental toxicant warfarin".

Neurotoxicity, genotoxicity and carcinogenicity

Neurotoxic effects were not observed in any of the toxicological studies reviewed by the Swedish CA (2010) or the USEPA (2020b). The Swedish CA (2010) also concluded that focused neurotoxicity studies would be scientifically unjustified based on animal welfare grounds, and on the fact that the well-known vitamin K-inhibition pathway did not indicate the involvement of the nervous system.

Bromadiolone displayed no mutagenic activity in a standard battery of genotoxicity tests (USEPA 2020b) and the Swedish CA (2010).

The Swedish CA (2010) concluded that long-term carcinogenicity studies were not considered technically feasible and concern about possible non-genotoxic carcinogenic effects are not justified from the available repeated-dose or a two-generation study on rats. Bromadiolone is also devoid of chemical structures known to be associated with possible carcinogenicity. The USEPA (2020b) also concluded that carcinogenicity studies are not necessary, since long-term exposures are not anticipated for non-food-use chemicals such as SGARs. Thus, there is not concern about possible carcinogenicity.

7 Approaches to rodenticide health risk management

7.1 USEPA human health risk management strategy

The USEPA (2020b) accepted that anticoagulant pesticides are extremely acutely toxic by all routes of exposure. Therefore, the USEPA did not aim to derive toxicity values, such as reference concentrations or acceptable daily intakes, as a basis for an overall human health risk assessment and risk management strategy for bromadiolone or the other anticoagulants. The USEPA waived further human health data requirements, and did not require any additional toxicological data, since it was concluded that additional data would not inform or impact the overall 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, a quantitative risk assessment was not conducted or required as a necessity

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

Exposure to bromadiolone in rodenticides was calculated by the Swedish CA (2010) according to the recommendations in the Technical Notes for Guidance ("TNsG") on Human Exposure to Biocidal Products, compiled by the European Chemicals Bureau ("ECB") of the European Commission ("EC") in 2002 (ECB 2002), which was later updated (ECB 2007). The TNsG provides indicative exposure

values for a range of generic exposure scenarios discussed in the TNsG, amongst these 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, and the use of bait boxes is usually recommend. In case bait boxes are not practical, the bait station must be covered in order to prevent access by non-target animals and unaware bystanders.

Rodenticide users

The TNsG (ECB 2007) distinguishes two main types of users, namely:

- Users in contact with the biocidal product as a consequence of their professional life. In this assessment of products registered in South Africa, "professional" users are viewed as occupationally exposed PCOs:
  - Industrial users: involved in manufacturing, handling and/or packaging of actives or products in industry. These are not applicable to the health risk assessments presented in this report.
  - Professional users: those using end-products in their professional capacity. In South Africa, the term Pest Control Operators ("PCOs") is applicable and PCOs are required to be registered in South Africa. PCOs are relevant to the health risk assessments presented in this report.
  - Professional users are sometimes assessed according to sub-categories of "trained" and "untrained" professionals. An example of an "untrained" professional would be a person managing orchards or plantations where rodenticides are used to protect young saplings from rodents stripping the bark. In the case of untrained professional users, at least a basic knowledge of the associated hazards, PPE use and the interpretation and implementation of safety instructions on product labels and SDSs is assumed.

- Non-professional users (consumers): "*member of the general public who may primarily be exposed to biocides by using a consumer product*" (ECB 2007). In the case of the rodenticides assessed in this report, the "*consumer product*" referred to is a rodenticide product accessible to lay persons, sold in shops where the product is accessible to the general public.
  - According to the TnsG the consumer is "*unlikely to take informed measures to control exposure and to follow exactly the instructions for using the biocidal product*".
  - The non-professional use pattern is expected to involve a lower frequency and/or duration of use.

Exposure terminology

Primary and secondary exposure scenarios are distinguished in the TNsG (ECB 2007):

- Primary exposure "*occurs to the individual who actively uses the biocidal products, i.e. the user*". The user may be a professional at work or a non-professional, that is, a consumer (see previous definitions of professionals and non-professionals).

- Secondary exposure "*may occur after the actual use or application of the biocidal product*". The TNsG further differentiates between professional user secondary exposure as:
  - *Intentional secondary* exposure, that is, any secondary exposure incurred during a worker's regular employment duties, e.g., a carpenter exposed to wood dust impregnated with a biocide.
  - *Incidental secondary* exposure scenarios not necessarily incurred during employment but resulting from the professional use of a biocide, e.g., home laundering of contaminated work clothes.

- The ECB (2007) concluded that, in most instances, secondary exposure scenarios are best assessed using the methodology for non-professional users (consumers).

Intentional secondary exposure, as defined above, is not applicable to rodenticides, because the rodenticides are not applied to consumer products, or to surfaces to which persons (occupational or the general public) might subsequently be exposed.

While reviewing the human health risk assessments of EU competent authorities, it was apparent that the term "secondary exposure" was generally applied to bystanders in accidental contact with rodenticides, principally during the use- and disposal phases (see definitions below). Such accidental contact should, in any case, also account for the incidental secondary dermal exposure to contaminated clothing being laundered, because of the conservative (high-end) accidental exposure values that are used (see the exposure values descriptions provided below). The term "secondary exposure" is applied accordingly in this solid rodenticide human health risk assessment report, meaning accidental contact of adult or child bystanders with the product.

Secondary exposure also includes inappropriate contact with dead rodents or left-over bait, e.g., a bystander cleaning up dead rodents or left-over or spilled bait, dragged away from the bait station by rodents. Secondary exposure of bystanders is assessed and the risks are reported numerically, or relative to the primary exposures and risks of PCOs.

Rodenticide use phases

The TNsG (ECB 2007) distinguishes the following phases, based on handler use patterns:

- Application,
- Use, and
- Disposal phases.

In the case of solid rodenticides, the product "as supplied" is applied during the application and use phase. The use exposure variables are thus similar. A smaller mass of rodenticide might be applied during the use phase, but, for ease of presentation in this report, exposure and risks during the application and use phases are assumed similar. Risks indicated for the "application phase" are thus also valid for the "use phase", although it might, in an unknown proportion of cases, slightly overestimate exposure during the "use phase". This is of little practical importance, because the rodenticide label instructions do not prescribe the application of different masses during the use phase.

Some disposal phase activities, such as cleaning up and disposing of spilled bait and dead rodents, might also be applicable during the use phase, but are not considered separately in the "use" phase. The conservative disposal phase exposure variables are viewed as sufficiently representative of exposure during clean-up and disposal activities in the use phase.

The TNsG (ECB 2007) phase descriptions are:

Application phase:

- Transfer of bait from the product packaging to the bait station. The place where the bait is dispensed ("placed") is referred to as the bait station.
- Several bait station constructs are possible, 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 bait contact by scavenger or predatory non-target animals, or application of the solid bait in a secure, tamper-proof bait box.
- The most prominent handler exposure scenarios, based on formulation use patterns, are:
  - Placing of bait boxes.

- Loading of bait boxes or bait stations with grain bait, bait pellets or wax blocks/rounds/wedges from larger containers.
- Securing large paraffin blocks at bait stations in sewers.
- Applying bait by hand.

Use phase (after application):

- This is 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. The TNsG assumes that bait-boxes in private and industrial areas are "locked off" to prevent contact, but this assumption is not applied in the risk assessment of products registered in South Africa.
- As stated before, it is assumed that activities and exposure during this phase is not much different from the application and disposal phases. Primary user exposure is thus not specifically assessed during the use phase, because exposures during the application and disposal phase are applicable to these activities during the use phase.
- The largest number of bystanders are exposed in this phase, e.g., unaware workers, adults and children in the vicinity, usually accidentally or by curiosity. Bystander exposure includes possible contact of the general public, or unaware workers, with dead rodents or spilled bait, assessed mainly as part of the disposal (clean-up) phase.
- Human exposure could be by accidental touching (dermal contact) and, in the case of children, by transient mouthing or chewing of bait.

Disposal (clean-up) phase:

- Final inspection of rat holes, bait points, drain and sewerage, as professionals decide when to stop the local campaign, and are assumed to remove/clean the bait stations, which may result in exposure.
- Normally, the same person applies the rodenticide, disposes of empty packaging, collects residues and dead rodents, and empties containers for disposal.
- Bystander exposure includes possible contact of the general public, or unaware workers, with dead rodents or spilled bait.
- Professionals and non-professionals are assumed to remove/clean the bait box, which may result in handling of surplus formulated product.
- Disposal activities include cleaning up and disposal of rodenticide dragged away from the bait station by rodents.
- 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 will be minimal.

8 Human health risk assessment of TOMCAT® All-weather Blox

8.1 Bromadiolone concentrations of assessed bait products

The bromadiolone concentration of TOMCAT® All-weather Blox is 0.05 g/kg (product label), that is, 0.005 % (w/w) (see Section 3.2). The bromadiolone concentration is equal to that of the wax blocks formulations assessed by the Swedish CA (2010) and the USEPA (2016b). Although the updated USEPA (2020b) approach has shifted to strengthening management without recalculating human health risks, the 2016 exposure assessments (USEPA 2016b) are still applicable. Both authorities have fully assessed the occupational professional (PCOs) and non-professional

(domestic/residential users) uses and exposure scenarios for wax blocks with a bromadiolone concentration of 0.005% w/w. Therefore, these assessments are directly applicable to the assessment of TOMCAT® All-weather Blox, provided that the use scenarios are comparable. These are compared in Section 8.2.

8.2 Solid rodenticide application practices and exposure variables

Occupational exposure to bromadiolone in rodenticides was calculated by the Swedish CA (2010) according to the TNsG recommendations, using “indicative exposure values” for a range of generic exposure scenarios discussed in the TNsG, and also measured exposure values from “operator exposure studies” presented to the Swedish CA (2010).

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, which is applicable to TOMCAT® All-weather Blox assessed in this report.

The TNsG (ECB 2007) describes the use of bait stations, including bait boxes (box-like bait stations) for solid rodenticide products as follows:

- 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.
- These boxes/stations, especially when tamper-proof, are used to prevent human contact with the rodenticide.
- 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.

The exposure variables derived from the sources described above are also used for the exposure assessments of South African products, since exposure values are generic according to the use and application scenario, and because similar South African values are not available.

The intended uses of wax bait blocks described by the USEPA (2016b) and the Swedish CA (2010) are compared to uses of TOMCAT® All-weather Blox, as far as uses are described on the product label (Table 8.2.1). Recommended application practices are compared in Table 8.2.2. Treatment of rats usually requires more blocks per station (placement point) and are presented in Table 8.2.2. TOMCAT® All-weather Blox sizes are assumed in the region of 10 to 28 g, which is referred to by the USEPA (2016b) as “mini-blocks”, and comparable to the block sizes of 20g generally referred to by the Swedish CA (2010).

Table 8.2.1: Intended uses of wax blocks in exposure and health risk assessments.

Scenario	Swedish CA (2010)	USEPA (2016b)	TOMCAT® All-weather Blox
Occupational/professional use	Yes	Yes	Yes
Consumer/residential/non-professional use	Yes	No	Yes
Inside and around buildings, residences, waste dumps, industrial and commercial buildings, agricultural and public buildings	Yes	Yes	Yes
Sewers	Yes	Yes	Not specifically mentioned, but also not excluded.

Table 8.2.2: Wax blocks application practices.

Scenario	Swedish CA (2010)	USEPA (2016b)	TOMCAT® All-weather Blox
Block sizes (general)	20 g	10 to 28 g	10 g (TOMCAT® product information from internet consumer product information)
Blocks per placement (label instructions)			
Occupational/professional and consumer/residential/ non-professional	2 to 10	28 (highest number recommended)	4 to16
Bait points manipulated per day: defaults for risk calculations			
Occupational/professional use	Placed: 60 Cleaned up: 15	Not calculated	Assumed according to defaults
Consumer/residential/non-professional use	Placed: 5 Cleaned up: 5	Not assessed	Assumed according to defaults

8.3 Toxicity values

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.

The USEPA (2020b) did not derive toxicity values, such as reference concentrations or acceptable daily intakes, as a basis for an overall human health risk assessment and risk management strategy for bromadiolone or the other anticoagulants, since it was accepted that anticoagulant pesticides are extremely acutely toxic by all routes of exposure. Therefore, the USEPA waived further human health data requirements, and did not require any additional toxicological data from commercial applicants seeking registration of rodenticide products for sale in the USA, since it was concluded that additional data would not inform or impact the overall risk management strategy. Nonetheless, the toxicity values for health risk calculations, presented in USEPA (2016b), are valid for risk calculations and are presented in Table 8.3.1.

The Swedish CA (2010) conducted human health risk calculations using systemic Acceptable Exposure Levels ("AELs") for bromadiolone presented in Table 8.3.2. The AEL is the exposure dose that is accepted as not associated with a risk to human health.

Table 8.3.1: Summary of toxicological doses and endpoints for bromadiolone human health risk assessment derived by the USEPA.

*Point of departure (POD)	Uncertainty Factors	LOC	Study and toxicological effects
Dermal short-term (1 to 30 days) and intermediate term (1 to 6 months)			
NOAEL = 4 µg/kg-day	UF_A= 10 UF_H= 10 Total UF= 100	LOC for MOE = 100	Prenatal developmental toxicity study in rabbit. LOAEL = 8 µg/kg-day, based on vaginal bleeding in dams. A dermal absorption factor of 10% is assumed for risk assessment purposes.
Source: USEPA (2016b). *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. UF_A: extrapolation from animal to human (interspecies). UF_H: potential variation in sensitivity among members of the human population (intraspecies). LOC: level of concern. MOE: margin of exposure.			

Table 8.3.2: Summary of bromadiolone AELs derived by the Swedish CA.

*Point of departure (POD)	Uncertainty Factors	AEL	Study and toxicological effects
Acute exposure			
LOAEL = 0.002 mg/kg-bw (2 µg/kg-day)	UF_A= 10 UF_H= 10 UF_{LOAEL} = 2 UF_{Sev} = 3 Total UF= 600 Correction for oral absorption: 70%	2.3×10^{-6} mg/kg-bw	Unpublished teratogenicity (developmental toxicity) oral exposure study in the rabbit showing severe foetal malformations following exposure to maternally toxic levels of bromadiolone.
Repeated exposure (medium and chronic)			
NOAEL = 0.0005 mg/kg-day (0.5 µg/kg-day)	UF_A= 10 UF_H= 10 UF_{Sev} = 3 Total UF= 300 Correction for oral absorption: 70%	1.2×10^{-6} mg/kg-day	Unpublished subchronic study in the rabbit, the most sensitive species. NOAEL of 0.5 µg/kg-bw based on prolonged prothrombin time at 1 µg/kg-bw (LOAEL).
Source: Swedish CA (2010). *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. UF_A: extrapolation from animal to human (interspecies). UF_H: potential variation in sensitivity among members of the human population (intraspecies). UF_{Sev}: additional factor for severity of effects. UF_{LOAEL}: using a LOAEL instead of a NOAEL.			

The PODs used by the Swedish CA (2010) are lower than that used by the USEPA (2016b). The total uncertainty factors (UFs) used by the Swedish CA are greater than that used by the USEPA by at least a factor of 3 (100 vs 300 and 600). These differences indicate that, given similar exposure assessments, the risks calculated according to the Swedish CA AEL (Table 8.3.2) will be higher (more conservative) than calculated with the USEPA POD and compared to the USEPA LOC.

8.4 Human exposure and health risk assessments

8.4.1 Exposure assessments

Routes of exposure

The Swedish CA (2010) assessed the potential routes of exposure as follows:

- Inhalation exposure:
  - Wax block formulations are generally non-dusty and bromadiolone is not volatile; therefore, the risk of inhalation exposure to bromadiolone for professional or amateur (residential) users is considered negligible.
  - For non-users (bystanders), the risk of inhalation exposure to residues during or after application is considered negligible.
- Dermal exposure:
  - Dermal exposure of users is likely to be limited to the hands during application.
  - Dermal exposure of other parts of the body of users is negligible.
  - For non-users (bystanders), risks of dermal exposure to residues are considered:
    - Low risks during application.
    - Unlikely after application, since bystanders are not likely to come into contact with products used in sewers or around buildings.
- Oral exposure:
  - Risk of professional or amateur users during use is considered to be low.
  - Dermal contamination may lead to oral exposure if hands are not washed properly after handling, but proper cautioning phrases on labels should limit this.
  - For non-users, risks during or after application is considered to be low.
- Children are potentially most at risk among the bystander group:
  - They may play inside or around buildings where baits are placed, or close to the floor where baits have been placed indoors.
  - Children or infants may be incidentally exposed by touching unprotected blocks (dermal exposure).
  - Product labels and good practice should advise users to prevent access to bait by children.
  - The risk for exposure will be very limited if products are applied in tamper resistant bait boxes.
  - Many products (including TOMCAT® All-weather Blox) contain a bittering agent to prevent infants from chewing and ingesting baits.

Occupational exposure

The USEPA (2016b) did not assess residential use scenarios, but arrived at the following conclusions regarding occupational exposure:

- The dermal and inhalation routes should be considered for activities such as filling and refilling bait stations, or distributing bromadiolone bait products into rodent burrows or sewers.
- Short-term occupational handler dermal and inhalation exposure to bromadiolone products formulated as blocks are considered negligible.
- Occupational post-application exposure is not expected from the registered bromadiolone rodenticides and use patterns. Occupational post-application activities, e.g., removing dead rodent carcasses, required the use of waterproof gloves as instructed on registered labels; therefore, exposures are expected to be negligible.

The Swedish CA (2010) is in agreement regarding negligible inhalation exposure (see the previous paragraphs), but considers the possibility of limited dermal exposure in the occupational use scenario.

Residential/non-professional/general public exposure

Swedish CA (2010) exposure assumptions specific to non-professional users (general public, use in residential settings) are:

- Non-professional users are untrained and cannot be expected to wear protective clothing.
- Use is occasional for a short time in a single day and unlikely to be repeated more than once a week.
- After use the remaining unused product is likely to be collected and disposed of in a controlled way, according to product labels.

Indirect/public bystander exposure

Swedish CA (2010) exposure assumptions are:

- For products applied in bait stations or outdoors, incidental exposure of adults and older children will be very limited and is expected mainly by dermal contact, if at all.
- Younger children/toddlers/infants playing indoors on the floor or outside around buildings are most at risk by:
  - Incidental dermal exposure.
  - Incidental oral exposure by chewing bait or touching their mouths with contaminated fingers.

8.4.2 Risk assessments

The USEPA (2016b) did not assess health risks due to exposure to bromadiolone in rodenticide baits, because the document was a scoping report for risks assessments that had been planned during the product registration review process.

With regard to potential aggregate exposure due to bromadiolone from different sources, e.g., food products, the USEPA indicated that aggregate exposure is not considered, since bromadiolone blocks are not intended to come into contact with food, drinks or beverages.

The Swedish CA (2010) conducted risks assessments by the comparison of calculated systemic exposure doses with the AEL values presented in Table 8.3.2. Exposure doses were calculated based on default values in EU Guidance documents, namely the June 2002 version of the TNsG (ECB 2002), and based on exposure values derived from submitted operator exposure studies. Dermal absorption was assumed as presented in Section 6.2 (0.3% for wax blocks; assuming 90% reduction of dermal exposure when using gloves) 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%, or more, of the AEL.

In short, the systemic dose is calculated with Equation 8.4.2.1.

Systemic dose (mg/kg-day) = Systemic exposure (mg/day) / body weight (kg) Equation 8.4.2.1

Systemic exposure is calculated with Equation 8.4.2.2:

Systemic exposure = Exposure per event x events per day Equation 8.4.2.2

Where:

Systemic exposure	Systemic exposure per work day (mg/day)
Exposure per event	mg/event
Events per day	Number of events per day (applying bait or cleaning up left-over bait).

8.4.3 Risk characterisation

The Swedish CA (2010) characterised the risks associated with the use of bromadiolone wax/paraffin bait blocks as follows:

- Occupational/professional use:
  - Professional operators applying blocks on a daily basis, while wearing gloves, are exposed to acceptable doses of bromadiolone.
  - Health risks were assessed by comparison with the repeated dose AEL of 1.2×10^{-6} mg/kg-day (Table 8.3.2) and were found acceptable.

- Non-professional residential use:
  - Acceptable exposure was estimated for non-professional operators applying bromadiolone blocks, on single occasions, in and around buildings to control rats.
  - Non-professionals are not expected to wear protective clothing; therefore, the estimations were for use without gloves.
  - Non-professional operators are not expected to apply the products on a daily basis and exposure dose comparisons were with the acute AEL of 2.3×10^{-6} mg/kg-day (Table 8.3.2).
  - Health risks indicated by comparison with the AEL are acceptable.

- Indirect exposure as a result of bait block use:
  - Incidental exposure will be very limited in case of products applied in bait stations or outdoors.
  - Accidental oral exposure doses of toddlers/infants ingesting 5 g or 10 mg of bait were calculated and compared with the acute AEL of 2.3×10^{-6} mg/kg-day (Table 8.3.2).
  - The comparisons indicated exposure doses in excess of the AEL by more than 1 000%, indicating that infants and toddlers ingesting the bait will be at risk.
  - However, the bittering agent should cause children to spit out the bait, limiting ingestion. Therefore, in practice the Swedish CA (2010) expects the margins of safety to be higher than calculated.
  - Product labels and good practice advice should mostly prevent access of children to the bait.

- Handling dead rodents:
  - Infants playing with dead rodents are considered an unlikely scenario.
  - Contamination of rodent fur by bromadiolone excreted in urine is expected to be negligible, since less than approximately 5% of radioactivity taken up by oral exposure is excreted into urine.
  - Bromadiolone contamination of rodent fur is thus expected to be negligible and consequently it will not be transferred to the hands to any significant extent.
  - Exposure of adults and children handling dead rodents is therefore assumed to be negligible.

8.5 TOMCAT® All-weather Blox risk characterisation

TOMCAT® All-weather Blox is comparable to the bromadiolone block formulations assessed by the USEPA (2016b) and the Swedish CA (2010) in the following details:

- The concentrations of bromadiolone are equal: 0.005%.
- Occupational exposure, as for a PCO, was assessed by both authorities.
- Residential exposure of members of the public, applying the bait blocks in their homes, was assessed by the Swedish CA (2010).

- Bystander or occupational post-application exposure was assessed by both authorities.
- Incidental oral exposure of toddlers/infants mouthing or chewing bait blocks was given specific attention by both authorities.

Exposure was assessed by both authorities, but only the Swedish CA calculated risks from quantified exposure doses. It is acceptable to extrapolate the result of the Swedish CA (2010) bromadiolone bait blocks risk assessment to TOMCAT® All-weather Blox, firstly given the similarities listed above. Secondly, the Swedish CA toxicity values for risk calculation (Table 8.3.2) are more conservative compared to the USEPA values (Table 8.3.1) with regard to the POD and the total UF applied to the POD to calculate the acceptable dose, which is the AEL in case of the Swedish CA (2010). Therefore, applying the Swedish CA assessment results to TOMCAT® All-weather Blox does not cause an underestimation of the rodenticide use health risks associated with the professional (PCO) or non-professional (residential/general public).

The human health risks associated with using TOMCAT® All-weather Blox are thus:
- Unacceptable health risks are not foreseen for professional operators applying blocks on a daily basis, while wearing gloves. Assuming the use of gloves by professionals is acceptable in the light of clear product label instructions to this effect. A risk of harm to health is not indicated.
- Non-professionals are not expected to wear protective clothing or to use gloves. Calculated risks based on this assumption are acceptable. There is thus not a risk of harm to health.
- Bystanders accidentally touching bait residues, or dead rodents, are not at a risk to health.
- A risk to health is indicated for infants and toddlers ingesting the bait, but the bittering agent included in the block formulation should prevent extended mouthing and chewing on the bait. Nonetheless, this finding emphasises the application of safety measures recommended on the label to keep the bait away from children, which should prevent exposure and risks.

Since developmental effects are the only health endpoints (aside from mortality) for which dose-response values are available in toxicological studies (Tables 8.3.1 and 8.3.2), 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”. Vice versa, unacceptable health risks indicate unacceptable risks of developmental effects.

9 Discussion

9.1 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 (2022) 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 (2022) 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 (2022) "*acknowledges that there are many benefits associated with these active ingredients and supports the continued registration of these active ingredients*".

However, 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 proposed by international regulating entities are presented in Section 9.2.

9.2 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 most 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 TOMCAT® All-weather Blox 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 and the TOMCAT® All-weather Blox label should recommend the use of bait boxes in homes or where public access is likely.

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.
- Precautions, e.g., keeping the product away from children, pets and directions for use on the product label must be followed. Baits must be unattainable to children, pets or other non-target animals in order to minimise the risk of poisoning.
- Any noted contact of a child with any type of rodenticide should be brought to the immediate attention of a medical professional, without exception.
- Labels should clearly recommend application in a bait box, or covered bait station, but this should not be made mandatory, as argued above.
- 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.
- Remove the remaining product at the end of treatment period. Clear disposal instructions must be provided on the label.
- When placing bait points close to or in water drainage systems, ensure that bait contact with water is avoided.
- 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 is recommended the TOMCAT® All-weather Blox label and must remain in place.

10 Conclusions

In support of the application for derogation regarding the restricted use of the registered solid rodenticide product TOMCAT® All-weather Blox label, identified as a substance of concern due to the reproductive toxicant properties of the rodenticide ingredient bromadiolone, 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". Vice versa, unacceptable health risks indicate unacceptable risks of developmental effects.

- Professional PCOs, assumed to use gloves, are not at risk of a health effect on the development of the foetus in case of pregnant females, or of other health effects such as interference with blood clotting mechanisms.

- Adult non-professional or general public bait blocks users, assumed not to use gloves, are not at risk of a health effect on the development of the foetus in case of pregnant females, or of other health effects such as interference with blood clotting mechanisms.

- The finding of acceptable risks for users not wearing gloves cannot 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, and also protects against diseases carried by rodents.

- Infants/toddlers mouthing or chewing on solid bait products are at risk of a health effect. 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 bromadiolone. Therefore, it is of primary importance that all possible mitigation measures recommended in Section 9.1 should be followed to limit environmental effects.

- The restricted use applied for by the suppliers of TOMCAT® All-weather Blox is according to the intended product use:
  - An anti-coagulant bait for the control of rats and mice.
  - "*For use in the garden, home, by farming community, industries, PCOs and public health*".

- When the recommended mitigation measures are applied, 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 TOMCAT® All-weather Blox assessed in this report is supported, provided that recommended mitigation measures are implemented.

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