Product Assessment Report

Bromadiolone Mixed Bait

(Ratata® rágcsálóirtó szer)

Product type:	**PT 14 (Rodenticide)**
Active substance:	**Bromadiolone (0.005% w/w)**
Type of application:	**Authorisation**
Authorisation number:	**HU-2013-PA-14-00038-0000**
Date of decision:	**„....." June 2013**
Date of expiry:	**30 June 2016**

Biocidal Product Assessment Report (PAR) related to Product Authorisation under Directive 98/8/EC
Product covered by this dossier:
Ratata® rágcsálóirtó szer HU-2013-PA-14-00038-0000

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1. General information about the product application

1.1 Applicant

Company Name:	Bábolna Környezetbiológiai Központ Kft.
Address:	Szállás u. 6.
City:	Budapest
Postal Code:	1107
Country:	Hungary
Telephone:	+36-1-4320-400
Fax:	+36-1-4320-401
E-mail address:	info@babolna-bio.com

1.1.1 Person authorised for communication on behalf of the applicant

Name:	Mr. János Szilágyi
Function:	registration division leader
Address:	Szallas u. 6.
City:	Budapest
Postal Code:	1107
Country:	Hungary
Telephone:	+36-1-4320-400
Fax:	+36-1-4320-401
E-mail address:	info@babolna-bio.com

1.2 Current authorisation holder[1]

Company Name:	Bábolna Környezetbiológiai Központ Kft.
Address:	Szállás u. 6.
City:	Budapest
Postal Code:	1107
Country:	Hungary
Telephone:	+36-1-4320-400
Fax:	+36-1-4320-401
E-mail address:	info@babolna-bio.com
Letter of appointment for the applicant to represent the authorisation holder provided (yes/no):	No (the applicant is the current authorisation holder)

1.3 Proposed authorisation holder

Company Name:	Bábolna Környezetbiológiai Központ Kft.
Address:	Szállás u. 6.
City:	Budapest
Postal Code:	1107
Country:	Hungary
Telephone:	+36-1-4320-400
Fax:	+36-1-4320-401
E-mail address:	info@babolna-bio.com

[1] Applies only to existing authorisations

Letter of appointment for the applicant to represent the authorisation holder provided (yes/no):	No (the applicant is the proposed authorisation holder)

1.4 Information about the product application

Application received:	21/June/2011
Application reported complete:	../../2013
Type of application:	Product authorisation – first authorisation
Further information:	–

2. Information about the biocidal product

2.1 General information

Trade name:	Bromadiolone Mixed Bait
Hungarian trade name:	Ratata® rágcsálóirtó szer
Manufacturer's development code number(s), if appropriate:	No code number assigned
Product type:	PT 14 (Rodenticides)
Composition of the product (identity and content of active substance(s) and substances of concern; full composition see confidential annex):	bromadiolone 0.005 w/w% IUPAC name: 3-[(1RS,3RS; 1RS,3RS)-3-(4'-bromobiphenyl-4-yl)-3-hydroxy-1-phenylpropyl]-4-hydroxycoumarin CAS: 28772-56-7 EC: 249-205-9 Minimum purity: 98.0 w/w%
Formulation type:	VIII.3 Solid formulation VIII.4. Other formulation (mixture of granules and flakes and crystals)
Ready to use product (yes/no):	Yes
Is the product the very same (identity and content) to another product already authorised under the regime of directive 98/8/EC (yes/no); If yes: authorisation/registration no. and product name: or Has the product the same identity and composition like the product evaluated in connection with the approval for listing of active substance(s) on to Annex I to directive 98/8/EC (yes/no):	No Differences in formulation type and non-active ingredients of formulation.

2.2 Information on the intended use(s)

Overall use pattern (manner and area of use):	VI.2 Covered application VI.2.1 In bait stations VI. 2.2 Other covering IV.1.1.2 Indoor use, no potential for contamination outdoors

	IV.1.2.2 Indoor use, no potential for contamination of food IV.2 Outdoor use

Target organisms:	I.1 *Rodentia* (Rodents) I.1.1 *Muridae* (Murids) I.1.1.1 *Rattus norvegicus* (Brown rat) I.1.1.3 *Mus musculus* (House mouse) all stages: II.1 Juveniles II.2 Adults all sexes, all strains, all locations, all territories, at any time of year
Category of users:	V.1 Non-professional / general public V.2 Professional V.3 Specialised professional
Directions for use including minimum and maximum application rates, application rates per time unit (e.g. number of treatments per day), typical size of application area:	For use against mice, commercially available bait stations (not refillable) or covered/protected bait points are authorised. For use against rats, only commercially available tamper resistant bait stations (prefilled or refillable) are authorised. For both rats and mice, the bait should be supplied in inner packs or units, each containing at most enough bait for one point (either rat or mouse). Bait stations/bait points are manually placed in the rodent infested area. Ideally trays and bait boxes should be fixed to the ground. The product is intended for use in domestic, industrial and commercial buildings including in and around farm buildings. For rat control: it is recommended to establish feeding points by every 7-10 m. Application rate: 0.2-0.25 kg bait/baiting points. For mice control: it is recommended to establish feeding places on every 5 m^2. Application rate: 0.05-0.1 kg bait/baiting points. In case of higher infestation double the number of feeding points. Check the bait every 4-7 days and replace the consumed bait with fresh ones. The elimination of all rodents is to be expected within 2-3 weeks, depending on the extent of the infestation and on the size of the area.
Potential for release into the environment (yes/no):	No
Potential for contamination of food/feedingstuff (yes/no)	No
Use Restrictions:	Do not use in sewers.

2.3 Information on active substance(s)

Active substance chemical name:	bromadiolone
CAS No:	28772-56-7
EC No:	249-205-9
Purity (minimum, g/kg or g/l):	98.0% w/w
Inclusion directive:	2009/92/EC
Date of inclusion:	2011.07.01.
Is the active substance equivalent to the active substance listed in Annex I to 98/8/EC (yes/no):	Yes
Manufacturer of active substance(s) used in the biocidal product:	
Company Name:	Dr Tezza srl
Address:	Via Tre Ponti
City:	S. Maria di Zevio
Postal Code:	37050
Country:	Italy

2.4 Information on the substance(s) of concern

The product does not contain any substances of concern.

2.5 Documentation

2.5.1 Data submitted in relation to product application

All data were produced in studies of acceptable quality. The studies are listed in Doc I. Appendix III.

2.5.2 Access to documentation

The applicant has submitted a letter of access, issued by representatives of the four companies in the Bromadiolone Task Force giving Bábolna Bioenvironmental Centre Ltd. and the other three members of the Task Force full and independent access to all the data included in the Bromadiolone Task Force submission in support of the Annex I listing of bromadiolone (Directive 2009/92/EC) in Directive 98/8/EC.

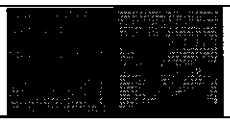
3. Classification, labelling and packaging

3.1 Classification and labelling

3.1.1 Harmonised classification of the active substance

Bromadiolone is not currently classified in Annex I of Council Directive 67/548/EEC or according to Annex VI of Regulation (EC) No. 1907/2006 (REACH). The following classification and labelling is proposed on the basis of available data resulting from the assessment of bromadiolone and is provided in the table below according to Directive 67/548/EEC. Additionally, the extrapolation of these proposals is also provided in the table below in accordance with Regulation (EC) 1272/2008.

Classification of the active substance, bromadiolone, according to Directive 67/548/EEC and CLP Regulation (EC) 1272/2008:

Symbol(s)		**Pictogram(s)**	
Indication(s) of danger	**T+** Very Toxic **N** Dangerous for the Environment	**Signal word(s)**	Danger
Risk phrases	**R26/27/28** Very toxic by inhalation, in contact with skin and if swallowed **R48/23/24/25** Toxic: Danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed. **R61** May cause harm to the unborn child **R50/53** Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment	**Hazard statements**	**H300** Fatal if swallowed **H310** Fatal in contact with skin **H330** Fatal if inhaled **H360D** Suspected of damaging the unborn child **H372** Causes damage to organs through prolonged or repeated exposure through inhalation **H400** Very toxic to aquatic life **H410** Very toxic to aquatic life with long lasting effects
Safety phrases	**S45** In case of accident or if you feel unwell, seek medical advice immediately. Show label where possible. **S53** Avoid exposure – obtain special instructions before use **S60** This material and its container must be disposed of as hazardous waste **S61** Avoid release to the environment. Refer to special instructions/safety data sheet.	**Precautionary statements**	**P201** Obtain special instructions before use **P273** Avoid release to the environment **P308 + P313** If exposed or concerned: get medical advise/attention **P314** Get medical advice/attention if you feel unwell **P501** Dispose of contents/container in accordance with national regulations

Bromadiolone is not classified as highly flammable and does not undergo self ignition below its melting point. It is not considered to be explosive or to have oxidising properties. There is no record that it has reacted with any storage container during many years of industrial production. It is concluded therefore, that there are no hazards associated with its physico-chemical properties under normal conditions of use.

3.1.2 Harmonised classification and labelling of the biocidal product

A proposal for the classification and labelling of Bromadiolone Grain Bait in accordance with Directive 1999/45/EC is presented below:

Symbol(s)	N/A
Indication(s) of danger	N/A
Risk phrases	N/A
Safety phrases	**S2** Keep out of the reach of children **S13** Keep away from food, drink and animal feedingstuffs **S20/21** When using do not eat, drink or smoke **S24** Avoid contact with skin **S35** This material and its container must be disposed of in a safe way **S 37** Wear suitable gloves **S46** If swallowed, seek medical advice immediately and show this container or label

A proposal for the classification and labelling of Bromadiolone Grain Bait in accordance with CLP Regulation (EC) 1272/2008 is presented below:

Pictogram(s)	N/A
Signal word(s)	N/A
Hazard statements	N/A
Precautionary statements	**P102** Keep out of the reach of children **P220** Keep away from food, drink and animal feedingstuffs **P262** Do not get in eyes, on skin or on clothing **P270** Do not eat, drink or smoke when using this product **P280** Wear protective gloves **P301 + 310** If swallowed: immediately call a poison centre or doctor/physician **P501** Dispose of contents/container in accordance with national regulations

3.2 Justification for the proposal

Bromadiolone technical concentrate is classified Xn; R21/22 and is present in the formulated product at 2.0% w/w. The remaining components of the formulated product are either not classified or are not present at concentrations requiring them to be taken into consideration for classification purposes (please refer to Annex Confidential Information).

The physico-chemical properties of the product do not require classification for physico-chemical hazard.

The available acute toxicity studies (see Section B6) confirm that the product does not require classification for acute health effects.

All components of the formulated product are either not classified or are not present at concentrations requiring them to be taken into consideration for classification purposes (please refer to Annex Confidential Information). No classification for environmental effects

is required.

3.3 Packaging

Category of user	Description	Packaging materials	Pack sizes/Net weight
Amateur user	20 g mixed bait sachet in a plastic baiting box	paper box	0.04 kg (2x20 grams bait sachets in 2 baiting boxes)
	90 or 200 g mixed bait in a plastic tray	paper box	0.18 kg (2 pcs of 90 g trays) 0.40 kg (2 pcs of 200 g trays)
	20 g bait sachet	paper box	0.10 kg (5 pcs)
	100 or 200 g bait in plastic bag	–	0.1 kg 0.2 kg
	100 or 200 g bait in plastic bag	paper box	0.2 kg (2x100 grams) 0.4 kg (4x100 grams) 0.4 kg (2x200 grams)
Professional user	90 or 200 g mixed bait in a plastic tray	paper box	4.32 kg (48 pcs of 90 g bait trays) 2.4 kg (12 pcs of 200 g bait trays) 4.4 kg (24 pcs of 200 g bait trays) 9.6kg (48 pcs of 200 g bait trays) 14.4 kg (72 pcs of 200 g bait trays) 19.2 kg (96 pcs of 200 g bait trays)
	20 g bait sachet	cardboard box	8 kg (400 pcs)
	– (bulk densitiy)	plastic bucket	4, 8, 12 kg
		paper barrel	30 kg
		paper bag	25, 40 kg

4. Summary of the product assessment

4.1 Identity related issues

The source of the active substance in the product is the same as that of the active substance included in Annex I of 98/8/EC.

The composition of the product is described in the Confidential Annex.

The product has not the same identity and composition as the product evaluated in connection with the approval for listing of active substance(s) on to Annex I of directive 98/8/EC. There are some differences in the formulation type and non-active ingredients of the formulation.

The product does not contain any substances of concern.

5. Physicochemical properties, storage stability and analytical methods

5.1 Physico-chemical properties and storage stability Bromadiolone Mixed Bait

Consists of : 70% Bromadiolone Loose Bait and 30% Bromadiolone Granule Bait

Property	*Method/Guideline*	*Result*	*Reference*
Physical state, appearance	OPPTS 830.6303	solid mixture of flakes, cylindrical granules and crystals	Study no: 484.191.3455 (GLP)
Colour	OPPTS 830.6302	Turquoise, natural light brown, light red and white mixtures	
Odour	OPPTS 830.6304	cereal like	
Explosive properties	justifications	The structure and physico-chemical properties of the ingredients **do not suggest any explosive, oxidising, flammable or autoflammable potential.** Widespread experimental and commercial use over many years has not shown any evidence of these activities.	
Oxidising properties			
Flash point			
Autoflammability			
pH-value	CIPAC MT 75.3	6.8 at 20°C	Study no: 484.191.3457 (GLP)
Acidity/alkalinity	justification	No need because pH is between 4 – 10	Study no: 484.191.3456 (GLP)
Relative density	EEC A.3, OECD 109	D_4^{20} : 1.335	Study no: 484.191.3458 (GLP)
Storage stability (I) (accelerated) Results of these studies are handled as seepage information for Bromadiolone Mixed Bait	CIPAC MT 46.3 Performed not with the Bromadiolone Mixed Bait but with its components Product consists of: 70% Bromadiolone Loose Bait and 30% Bromadiolone	Accelerated storage stability tests (54 ± 2°C, 14 days) were conducted with 2-2 batches of the components of the product. These studies support 2 years shelf life of Bromadiolone Mixed Bait. Difference of initial and final concentrations of the a.s. is cca. 2% in case of B. Loose Bait and	Bromadiolone Loose Bait batch No: KI/ 73217, KI/73212 and Bromadiolone Granule Bait batch No: KI/73213, KI/73218. In house validated HLC method of the applicant. Loose Validation : VJ-B-04-12

Property	*Method/Guideline*	*Result*	*Reference*
	Granule Bait	B. Granule Bait.	Granule Validation: VJ-B-06-12
Storage stability (II) (6 months at ambient temperature) Results of these studies are handled as seepage information for Bromadiolone Mixed Bait	Performed not with Bromadiolone Mixed Bait but with its components. This product consists of: 70% Bromadiolone Loose Bait and 30% Bromadiolone Granule Bait	6 months stability tests at ambient temperature with 2 -2 batches of the component of the product were conducted. Difference of initial and final concentrations of the a.s. is 3.84% in case of Bromadiolon Loose Bait and 2% in case of Bromadiolone Granule Bait.	Bromadiolone Loose Bait batch numbers: KI/73217, KI/73212 and Bromadiolone Granule Bait: KI/73213, KI/73218 In house validated HLC method of the applicant: Loose Validation: VJ-B-06-12 Granule Validation: VJ-B-04-12
Storage stability (III) (12, 18 and 24 months at ambient temperature in original packaging)	Performed with the Bromadiolone Mixed Bait: batch No: KI/77476	In case of the 12 and 18 months long stability tests the decrease of a.s. is: 5.88% Loss of bromadiolone in 24 months trial is: 7.84% Data from storage stability studies (I-III) demonstrate that the product has an acceptable shelf life of 2 years.	KI/77476 consists of : 70% KI/73217 +30% KI/73218 In house non-validated HLC method of the applicant.
Storage stability (IV)	Performed with the product Individual Palatability Mortality Trial Studies (*Mus musculus*)	after 1 year after 18 months after 24 months	Study no.: 121.007 121.071 131.024
Storage Stability (V)	Performed with the product Individual Palatability Mortality Trial Studies (*Rattus norvegicus*)	after 1 year after 18 months after 24 months	Study no.: 111.109 121.069 131.006
Storage stability – effects of light	justification	Storage and use do not result in exposure to sunlight	

Property	*Method/Guideline*	*Result*	*Reference*
Technical characteristics	justification	Not necessary as the product is a bait	
Compatibility with other products	justification	Not relevant as the product is not intended to be mixed with other products	
Surface tension	justification	Not applicable	
Viscosity	justification	Not applicable	
Particle size distribution	CIPAC MT 59 CIPAC MT 170	[> 500 µm]	Study No: 484.191.3459 (GLP)

Measurements and information submitted allow reliable assessment of the physico-chemical properties of Bromadiolone Mixed Bait. No physico-chemical hazard was identified, the product is not considered to be flammable. The physico-chemical properties of the product does not suggest any explosive, oxidising, flammable or autoflammable potential.

Storage stability tests listed above demonstrate that the product is stable for at least 2 years under ambient storage conditions.

5.2 Analytical methods

5.2.1 Determination of the active substance in the biocidal product Bromadiolone Mixed Bait

Bromadiolone Mixed Bait is formed from 70% Bromadiolone Loose Bait and 30% Bromadiolone Granule Bait.

No method is developed for determination of a.s. of Bromadiolone Mixed Bait however methods have been developed and validated for bromadiolone in products named: Bromadiolone Granule bait (nominal content: 50 mg a.s./kg) and Bromadiolone Loose Bait (nominal content: 50 mg a.s./kg).

These methods are accepted, concentration ($C_{Mixed\ Bait}$) **of bromadiolone in Bromadiolone Mixed Bait** and $SD_{Mixed\ Bait}$ of bromadiolone concentration can be expressed as follows

$C_{Mixed\ Bait} = 0.7 \times C_{Loose\ bait} + 0.3\ C_{Granule\ Bait}$

where

$C_{Loose\ bait}$ is bromadiolone concentration in product Bromadiolone Loose Bait

$C_{Granule\ bait}$ is bromadiolone concentration in product Bromadiolone Granule Bait

$\mathbf{C_{Mixed\ Bait} = 0.7 \times 45.9 + 0{,}3 \times 48.1 = 46.56}$

$(SD_{Mixed\ Bait})^2 = (0.7)^2 \times (SD_{Loose\ bait})^2 + (0.3)^2\ (SD_{Granule\ Bait})^2$

$(SD_{Mixed\ Bait})^2 = (0.7)^2 \times (1.22)^2 + (0.3)^2\ (0.901)^2$

$SD_{Mixed\ Bait} = \mathbf{0.895}$

$SD_{Loose\ bait}$ is standard deviation of bromadiolone concentration in product Bromadiolone Loose Bait (Study No.: 484.104.2853)

$C_{Granule\ bait}$ is standard deviation of bromadiolone concentration in product Bromadiolone Granule Bait (Study No: 484.104.2932)

5.2.1.1 Determination of the active substance in the biocidal product Bromadiolone Loose Bait from which Bromadiolone Mixed Bait contains 70%

A method has been developed and validated for the determination of bromadiolone in the product named: Bromadiolone Loose Bait (nominal content: 50 mg a.s./kg).

All validation parameters meet the acceptance criteria. Validation data demonstrate that the method is suitable for the determination of the active substance content in the formulation Bromadiolone Loose Bait. No analytical methods for determination of the impurities were tested for the formulated product since the formulation does not contain toxicologically or ecotoxicologically relevant impurities.

Test item:	Bromadiolone Loose Bait
Active substance (a.s.):	bromadiolone
Analytical method:	Reverse phase HPLC/UV detection at 265 nm
Specificity:	Yes, no interfering substances at retention time of bromadiolone; blank sample was analyzed
Calibration: (5 level, 3 parallel)	Five concentration levels in narrow range (8, 9, 10, 11 and 12 µg a.s./mL), three parallels on two different days from separate stock solutions; corresponding to 50 mg ± 20% a.s./kg i.e. 40 – 60 mg a.s./kg Loose Bait (80% to 120% of the nominal application rate are covered)
Linear range, correlation coefficient:	Detector response was proved to be linear in range: 8 – 12 µg a.s./mL R^2: > 0.99
Reinjection repeatability:	RSD%: 0.1 (7 injections from the same samples, 10 µg bromadiolone/ml) at two analytical occasions
Recovery:	Mean recovery: 99% only one concentration level (nominal concentration of the a.s. (50 mg a.s./kg), using five replicate determinations)
Accuracy:	≤ 3%
Precision:	< 3%
Limit of determination	not stated

Reference	Study No: 484.104.2853 (GLP)

Determination of active substance content of Loose bait

Number of measurements (n):	7
Mean of measurements:	45.9 mg
Standard deviation (SD):	1.22
RSD:	3%
Value of 95% confidence interval:	1.44
bromadiolone content:	**45.9 ± 1.44 mg/kg**
Reference	Study No: 484.104.2929 (GLP)

5.2.1.2 Determination of the active substance in the biocidal product Bromadiolone Granule Bait from which Bromadiolone Mixed Bait contains 30%

A method has been developed and validated for the determination of bromadiolone in the product named: Bromadiolone Granule Bait (nominal content: 50 mg a.s/kg).

All validation parameters meet the acceptance criteria. Validation data demonstrate that the method is suitable for the determination of the active substance content in the formulation Bromadiolone Granule Bait. No analytical methods for determination of the impurities were tested for the formulated product since the formulation does not contain toxicologically or ecotoxicologically relevant impurities.

Test item:	Bromadiolone Granule Bait
Active substance:	bromadiolone
Analytical method:	Reverse phase HPLC/UV detection at 265 nm
Specificity:	Yes, no interfering substances at retention time of bromadiolone; blank sample was analyzed
Calibration: (5 level, 3 parallel)	Five concentration levels in narrow range (8, 9, 10, 11 and 12 µg a.s./mL), three parallels on two different days from separate stock solutions; corresponds to 50 mg ± 20% a.s./kg i.e. 40 – 60 mg a.s./kg Granule Bait (80% to 120% of the nominal application rate are covered)
Linear range, correlation coefficient:	Detector response was proved to be linear in range: 8 – 12 µg a.s./mL R^2: 0.998 and R^2: 1.000
Reinjection repeatability:	RSD%: 0.1 and 0.2 (7 injections from the same samples,

	10 µg bromadiolone/ml) at two analytical occasions
Recovery:	Mean recovery: 98% (94 – 101%) only one concentration level (nominal concentration of the a.s. (50 mg a.s./kg), using five replicate determinations)
Accuracy:	≤ 2%
Precision:	≤ 3%
Limit of determination	not stated
Reference	Study No: 484.102.2856 (GLP)

Determination of active substance content of Granule bait

Number of measurements (n):	7
Mean of measurements:	48.10 mg
Standard deviation (SD):	0.901
RSD:	1.87%
Value of 95% confidence interval:	0.9
bromadiolone content:	**48.1±0.9 mg/kg**
Reference	Study No: 484.104.2932 (GLP)

5.2.1.3 Determination of the active substance in residues

None of the components of the Bromadiolone Mixed Bait product other than the active substance is considered to be of toxicological, ecotoxicological or environmental concern. Suitable analytical methods for the determination of residues of bromadiolone in soil, water, food, air and body fluids were evaluated and declared acceptable during Annex I inclusion. Analytical method for bromadiolone residues are listed below, see also Annex III.A 4.2.

5.2.2 Analytical methods for bromadiolone residues

Matrix	*Method, (LOQ)*
Soil	HPLC-MS, (LOQ: 0.22 µg/kg)
Water	HPLC-MS, (LOQ: 0.05 µg/L); LC-MS/MS for confirmation
Air	No method is required due to low vapour pressure of active substance and spray application is not used.
Body fluids and tissues	LC-MS/MS, (LOQ: 0.01 mg/L for blood, LOQ: 0.01 mg/kg for liver)

Food/feed of plant origin (cucumber, wheat, oilseed rape, whole lemon)	for monitoring purposes LC-MS/MS, (LOQ: 0.01 mg/kg)
Food/feed of animal origin (bovine liver)	for monitoring purposes LC-MS/MS, (LOQ 0.01 mg/kg)

5.3 Risk Characterisation for Physico-Chemical properties

As described in the Annex I inclusion dossier bromadiolone does not have hazardous physico-chemical properties. Since the non-active ingredients of Bromadiolone Mixed Bait do not exhibit hazardous physico-chemical properties, no such risk is expected during use and storage of the formulated product.

6. Efficacy of the biocidal product

6.1 Function/Field of use

Main Group: 3 – Pest control
Product type (PT): 14
Function: Rodenticide

6.2 Organisms to be controlled, products, organisms or objects to be protected and label claims

Target organisms:

- *Rattus norvegicus* (Brown rat, Norway rat)
- *Mus musculus* (House mouse)

Bromadiolone Mixed bait is intended to control rats and mice in domestic, industrial and commercial buildings including in and around farm buildings to protect human food and animal feedstuffs and for general hygiene purposes (pathogen transmission and direct property damage).

The draft product label makes the following claims:
„Control of rats and mice in and around domestic, industrial, commercial, institutional and agricultural buildings."

6.3 Effects on target organisms

As with other anticoagulants, bromadiolone is a vitamin K antagonist. It interferes with the regeneration of prothrombin, disturbing the normal blood clotting mechanism and causing an increased tendency to bleed. The main site of action is the liver, where several of the blood coagulation precursors undergo vitamin K dependent post translation processing before they are converted into the respective procoagulant zymogens. The specific point of action is thought to be the inhibition of K1 epoxide reductase. The anticoagulants accumulate and are stored in the liver until broken down. The plasma prothrombin (procoagulant factor II) concentration provides a suitable guide to the severity of acute intoxication and to the effectiveness and required duration of the antidotal therapy (vitamin K1).
Signs of poisoning in rodents and other mammals are those associated with an increased tendency to bleed leading ultimately to profuse haemorrhage. After feeding on bait containing

the active ingredient for 2-3 days the animal becomes lethargic and slow moving. Signs of bleeding are often noticeable and blood may be seen around the nose and anus. As symptoms develop the animal loses its appetite and will remain in its burrow or nest for increasingly long periods of time.
Death will usually occur within 4-5 days of ingesting a lethal dose and animals often die out of sight in their nest or burrow.

6.4 Method of application

6.4.1 Field of use:
IV.1.1.2 Indoor use, no potential for contamination outdoors
IV.1.2.2 Indoor use, no potential for contamination of food
IV.2 Outdoor use

6.4.2 User category:
V.1 Non-professional/General public

V.2 Professional

V.3 Specialised professional

The active substance in Bromadiolone Mixed Bait is the anticoagulant bromadiolone. The product is formulated as a ready-to-use mixed bait (mixture of 70% Bromadiolone Loose Bait and 30% Bromadiolone Granule Bait), containing 0.005% (50 ppm, 50 mg/kg) active ingredient. It is not diluted in any medium, mixed with other products, or sprayed, misted, dusted or applied to extensive areas as small particles. It is not applied to plants. The baits are made of solid pieces, which are placed directly near areas where rodents are frequent and where the baits are eaten directly by the target animals.

The product is placed in a bait station in such way that rats and mice can eat them. In situations where bait boxes cannot be used, the bait is covered in a way that non-target organisms cannot reach them.

Rodents eat the bait over one or more days and die typically 1-5 days later. Baiting points are inspected frequently and replenished when bait has been eaten. Dead rodents are removed for disposal in order to prevent them being eaten by non-target mammals and birds.

When no more bait is eaten and rodent activity stops, the remains of all bait are removed for disposal.

6.4.3 Baiting strategy
The treatment frequency of Bromadiolone Mixed Bait is 2-4 applications per year, 3-6 month apart. The amount of used product per application is usually 50-250 grams per baiting point. Bait points are placed typically every 4-10 m.

Application rate in and around buildings:
Professional user:
Against **rats**: 200-250 g (bulk) / baiting point (baiting box)
10-12 x 20 g sachet / baiting point (baiting box)
2 x 90 g or 1 x 200 g baiting tray / 7-10 m
Against **mice**: 50-100 g (bulk) / baiting point (baiting box)
1-5 x 20 g sachets / baiting point (baiting box)
1 x 90 g baiting tray / 5 m^2
Non-professional user:
Against **rats**: 4-5 x 20 g sachet / baiting point (baiting box)
2 x 90 g or 1 x 200 g baiting tray / 7-10 m
2x100 g or 1x200 g plastic bag / baiting point (baiting box) / 7-10 m
Against **mice**: 1-4 x 20 g sachets / baiting point (baiting box)
1 x 90 g baiting tray / 5 m^2
plastic baiting box / 5m^2
1x100 g plastic bag / baiting point (baiting box) / 5m^2

6.5 Mechanism of resistance

6.5.1 Biochemical resistance

The biochemical mechanism of warfarin resistance has been studied in four geographic strains of Norway rat. The mechanism appears to differ in each strain, but in each of them an altered form of K-epoxide reductase is involved. In two strains (Welsh and Hampshire) the reductase has both decreased activity and a decreased sensitivity to warfarin inhibition whereas in another two strains (Scottish and Chicago) it is reversibly inhibited by warfarin as compared to irreversible inhibition found in susceptible strains. There is some indication that decreased sensitivity of a second enzyme, vitamin K-quinone reductase, to warfarin inhibition may also be significant in certain strains. There appers to be a consensus amongst biochemists that the variants of at least one of these reductases, by their altered affinities for anticoagulants and vitamin K, and supplemented in some cases by subsidiary mechanisms such as faster microsomal clearance of the anticoagulant, are the biochemical basis of resistance in the Norway rat.
Studies of second generation anticoagulants like bromadiolone indicate that anticoagulant tolerance in resistant strains is affected by genotype, sex, vitamin K status and age and thus the mechanism is presumably more complex involving more genes than the vitamin K reducing gene.
This information is relevant for and can be extrapolated to bromadiolone.

6.5.2 Behavioural resistance

Several elements of behaviour such as neophobia and conditioned or unconditioned aversion to bait can help rodents to avoid ingesting a fatal dose and may explain treatment failures that cannot be accounted for by physiological resistance. The enhancement of such behaviour can constitute a novel defence mechanism and was termed behavioural resistance by Humphries

et al. (1992) working with mice. Similarly Brunton et al. cited enhanced neophobia in the Norway rats as an example of behavioural resistance.
This information is relevant for and can be extrapolated to bromadiolone.

6.6 Occurrence of resistance

Resistance to the first generation anticoagulants has been widely reported in both *Rattus norvegicus* and *Mus domesticus* since the late 1950's. The incidence of resistance to first generation anticoagulants in areas in which it is established is commonly 25-85%. Some degree of resistance to difenacoum and bromadiolone has been reported in the UK and Denmark and other European countries both for Norwegian rats and house mice but this is usually only found in certain populations of rodents highly resistant to first generation anticoagulants. Considerable doubt exists as to the significance of reports of resistance to second-generation anticoagulants and in the UK control failures with the second-generation products are increasingly being attributed to baiting problems rather than physiological resistance.
Resistance is of no importance when it is low compared to the field dosage rate of the anticoagulant. In the UK a small but apparently heritable decrease in susceptibility to brodifacoum was detected by means of laboratory tests with bait containing 10 ppm brodifacoum but was not known to have a practical effect on field control when using bait of standard concentration (50 ppm).
In contrast, in the same geographic location a 4x resistance to difenacoum was widely recognised as causing a control problem even thought such a low level of resistance would not usually be expected to affect control. Further studies suggested the presence of behavioural resistance. Subsequent investigations indicated that the control difficulty was not due to resistance but to the large size of the infestations and the competing attractions for the rats of cereal stored in the infested area.

6.7 Resistance management

The immediate aim of resistance management is to prevent or delay the development of resistance to a given anticoagulant while, as far as it is not counterproductive, permitting its continued use. The ultimate aim is to reduce or eliminate the adverse consequences of resistance.
The use of a suitable arsenal of alternative rodenticides is necessary for the management of resistance. Even out-moded compounds such as zinc phosphide were beneficial when anticoagulant resistance first appeared in the UK. The newer rodenticides to which resistance has not yet developed including the anticoagulants brodifacoum, flocoumafen and difethialone and the non-anticoagulants calciferol and bromethalin, all appear to have a role in resistance management. The most practical way to achieve this is first to stop using rodenticides to which the rodents are resistant and then to eliminate the resistant population by the exclusive use of non-selective or counter selective control techniques, both chemical and non-chemical.
Another strategy that consists of withholding or saving effective rodenticides while continuing to use a given anticoagulant until resistance exhausts its usefulness is sometimes put forward as a means of limiting the development of resistance. However it is generally accepted that this strategy is likely to accelerate the development and spread of resistance.

The applicant suggests and makes the following measures to prevent resistance:

1. Non-chemical control techniques (e.g. traps)
2. Preferential use of rodenticides and formulations to which resistance rarely develops.
3. Professional users are encouraged to monitor the infestation level prior the treatment. Babolna Bio has developed rodenticide (no bromadiolon) free extruded wax block for monitoring purposes.
4. Ensure the complete eradication of the target population whenever a rodenticide is used.
5. Campaigns should be recorded and the time between campaigns should be as long as possible.
6. The length of the campaign should be minimised, aiming at an optimal effect on the target rodents.
7. Unless under supervision of a pest control operator or other competent persons, do not use anticoagulant rodenticides as permanent baits.
8. Avoid the use of first generation anticoagulants, to which resistance develops relatively easily.
9. Rotation of second generation anticoagulants.
10. Maintain uncontrolled, susceptible populations in refugee from which emigration can occur.
11. Babolna Bio Ltd. periodically sends test samples (field collected tails of rats) to a German high technology (gene technology) laboratory. The results (Dr. Hans-Joachim Pelz, Federal Biological Research Centre for Agriculture and Forestry Institute for Nematology and Vertebrate Research) showed that the occurrence of resistant rats in Hungary is sporadic and it can be stated that the Hungarian rat population is generally not resistant to bromadiolone.
12. It is recommended that the label states that any instances of resistance have to be referred to the manufacturer of the active substance.

6.8 Evaluation of label claims

The potency of bromadiolone, a second-generation anticoagulant against commercial rodents is well documented. It is well known that both formulation type and age of the formulation can affect palatability and potency. This is particularly true in situations where a control programme is being carried out in a situation where there is an excess of highly attractive, alternative foodstuffs for the rodents to feed on. In this situation control can be extremely difficult to achieve simply because the target rodents do not eat the rodenticide bait preferring other foodstuffs in the vicinity. Because of the over-riding importance of palatability in the ultimate effectiveness of a bait it is normal during the development of bait formulations to carry out either laboratory choice tests or field trials to establish their effectiveness in controlling the target species.

Standard test protocols have been developed for the evaluation of baits. Laboratory test guidelines have been issued by the EPPO Standards PP1(2004) and TNsG on Product Evaluation (2009). The standard protocol compares the test bait with a highly palatable standard bait formulation for which the detailed composition and storage conditions are

clearly laid down (standard EPA meal). The test bait is considered effective when acceptance by the target species is not significantly less than 20% compared to the standard EPA meal and mortality in the test is not less than 90%.
The Bromadiolone Product Dossier Task Force has carried out extensive laboratory and semi-field trials on its Bromadiolone Mixed Bait (containing 0.005% w/w bromadiolone). Efficacy reports are presented for both of the laboratory and semi-field evaluation of this formulation against *Rattus norvegicus* and *Mus musculus*.
It can be concluded from the test results that the Bromadiolone Mixed Bait is sufficiently attractive to be effective in the control of rats and mice.
The following efficacy studies were carried out with Bromadiolone Mixed Bait:

Test product	Test organisms	Test system/Concentration applied/exposure time	Test conditions	Test results: effects, mode of action, resistance	Reference
Bromadiolone Mixed Bait	House mouse (*Mus musculus*) 10 laboratory bred wild animals (5 males, 5 females)	Laboratory test. Palatability – mortality trial study. Choice feeding test: fresh baits. 3-day pre-test normal diet (CRLT/N) intake assessment. 5 day bait feeding period and 6 day normal diet period. Unrestricted access to the test bait and to palatable and familiar alternative food (challenge diet – EPA STANDARD) during the 5-day test period. The quantity of food placed in each pot was *sufficient to meet each animal's daily needs.*	The animals were individually caged. Normal laboratory requirements: • temperature: 22 ± 2°C • relative humidity: min. 40% ± 10% • continuous change of air (ventilation) • 12-hour light-dark cycle	The mean acceptance o the test item was 30.9%. Total mortality was observed in both male and female mice. The mean time to death was 5.2 days. The efficacy was total: 100% in 7 days.	Biological Laboratory of Babolna Bio Ltd., Hungary 111.018

Test product	Test organisms	Test system/Concentration applied/exposure time	Test conditions	Test results: effects, mode of action, resistance	Reference
Bromadiolone Mixed Bait	House mouse (*Mus musculus*) 10 laboratory bred wild animals (5 males, 5 females)	Semi-field test carried out in a semi-field trial room (4 sqm). Palatability – mortality trial study. Choice feeding test: fresh baits. 3-day acclimatization period CRLT/N diet *ad libitum*. 3-day pre-test normal diet (CRLT/N) intake assessment. 5 day bait feeding period. Unrestricted access to the test bait and to palatable and familiar alternative food (challenge diet – EPA STANDARD) during the 5-day test period. The quantity of food was *sufficient to meet each animal's daily needs.*	Semi-natural conditions. Semi-field trial room: 3.1 x 1.18 m, airspace: 8. 34 m^3 Normal laboratory requirements: • temperature: 22 ± 2°C • relative humidity: min. 40% ± 10% • continuous change of air (ventilation) • 12-hour light-dark cycle	The mean acceptance of the test item was 29.2%. Total mortality was observed in both male and female mice. The mean time to death was 5.2 days. The efficacy was total: 100% in 7 days.	Biological Laboratory of Babolna Bio Ltd., Hungary 111.043
Bromadiolone Mixed Bait	Norway rat (*Rattus norvegicus*) 10 laboratory bred wild animals (5 males, 5 females)	Semi-field test carried out in semi-field trial rooms I and II. (total: 7,7 sqm). Palatability – mortality trial study. Choice feeding test: fresh baits. 3-day acclimatization period CRLT/N diet *ad libitum*. 3-day pre-test normal diet (CRLT/N) intake assessment. 5 day bait feeding period. Unrestricted access to the test bait and to palatable and familiar alternative food (challenge diet – EPA STANDARD) during the 5-day test period. The quantity of food placed in each pot was *sufficient to meet each animal's daily needs.*	Semi-natural conditions. Semi-field trial rooms: I.: 3.1 x 1.18 m, airspace: 8, 34 m^3 II.: 3.1 x 1.30 m, airspace: 9.19 m^3 Normal laboratory requirements: • temperature: 22 ± 2°C • relative humidity: min. 40% ± 10% • continuous change of air (ventilation) • 12-hour light-dark cycle	The mean acceptance o the test item was 45.1%. Total mortality was observed in both male and female mice. The mean time to death was 4.8 days. The efficacy was total: 100% in 5 days.	Biological Laboratory of Babolna Bio Ltd., Hungary 111.029

Test product	Test organisms	Test system/Concentration applied/exposure time	Test conditions	Test results: effects, mode of action, resistance	Reference
Bromadiolone Mixed Bait, after 1 year of storage	House mouse (*Mus musculus*) 10 laboratory bred wild animals (5 males, 5 females)	Laboratory test. Palatability – mortality trial study. Choice feeding test: aged baits. 3-day pre-test normal diet (CRLT/N) intake assessment. 5 day bait feeding period and 6 day normal diet period. Unrestricted access to the test bait and to palatable and familiar alternative food (challenge diet – EPA STANDARD) during the 5-day test period. The quantity of food placed in each pot was *sufficient to meet each animal's daily needs.*	The animals were individually caged. Normal laboratory requirements: • temperature: 22 ± 2°C • relative humidity: min. 40% ± 10% • continuous change of air (ventilation) • 12-hour light-dark cycle	The mean acceptance o the test item was 20.8%. Total mortality was observed in both male and female mice. The mean time to death was 6.2 days. The efficacy was total: 100% in 9 days.	Biological Laboratory of Babolna Bio Ltd., Hungary 121.007
Bromadiolone Mixed Bait, after 1 year of storage	Norway rat (*Rattus norvegicus*) 10 laboratory bred wild animals (5 males, 5 females)	Laboratory test. Palatability – mortality trial study. Choice feeding test: aged baits. 3-day pre-test normal diet (CRLT/N) intake assessment. 5 day bait feeding period and 6 day normal diet period. Unrestricted access to the test bait and to palatable and familiar alternative food (challenge diet – EPA STANDARD) during the 5-day test period. The quantity of food placed in each pot was *sufficient to meet each animal's daily needs.*	The animals were individually caged. Normal laboratory requirements: • temperature: 22 ± 2°C • relative humidity: min. 40% ± 10% • continuous change of air (ventilation) • 12-hour light-dark cycle	The mean acceptance o the test item was 47.2%. Total mortality was observed in both male and female mice. The mean time to death was 5.3 days. The efficacy was total: 100% in 8 days.	Biological Laboratory of Babolna Bio Ltd., Hungary 111.109

Test product	Test organisms	Test system/Concentration applied/exposure time	Test conditions	Test results: effects, mode of action, resistance	Reference
Bromadiolone Mixed Bait, after 1,5 years of storage	House mouse (*Mus musculus*) 10 laboratory bred wild animals (5 males, 5 females)	Laboratory test. Palatability – mortality trial study. Choice feeding test: aged baits. 3-day pre-test normal diet (CRLT/N) intake assessment. 5 day bait feeding period and 6 day normal diet period. Unrestricted access to the test bait and to palatable and familiar alternative food (challenge diet – EPA STANDARD) during the 5-day test period. The quantity of food placed in each pot was *sufficient to meet each animal's daily needs.*	The animals were individually caged. Normal laboratory requirements: • temperature: 22 ± 2°C • relative humidity: min. 40% ± 10% • continuous change of air (ventilation) • 12-hour light-dark cycle	The mean acceptance o the test item was 37.4%. Total mortality was observed in both male and female mice. The mean time to death was 5.5 days. The efficacy was total: 100% in 7 days.	Biological Laboratory of Babolna Bio Ltd., Hungary 121.071
Bromadiolone Mixed Bait, after 1,5 years of storage	Norway rat (*Rattus norvegicus*) 10 laboratory bred wild animals (5 males, 5 females)	Laboratory test. Palatability – mortality trial study. Choice feeding test: aged baits. 3-day pre-test normal diet (CRLT/N) intake assessment. 5 day bait feeding period and 6 day normal diet period. Unrestricted access to the test bait and to palatable and familiar alternative food (challenge diet – EPA STANDARD) during the 5-day test period. The quantity of food placed in each pot was *sufficient to meet each animal's daily needs.*	The animals were individually caged. Normal laboratory requirements: • temperature: 22 ± 2°C • relative humidity: min. 40% ± 10% • continuous change of air (ventilation) • 12-hour light-dark cycle	The mean acceptance o the test item was 47.5%. Total mortality was observed in both male and female mice. The mean time to death was 6.1 days. The efficacy was total: 100% in 8 days.	Biological Laboratory of Babolna Bio Ltd., Hungary 121.069

The classification of co-formulants does not give rise to concern with respect to repeated dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity and no classification based on these components is necessary.

7.3 Exposure assessment

Exposure assessment

Exposure path	Industrial use	Professional use	General public	Via the environment
Inhalation	Not applicable	Negligible	Negligible	Negligible
Dermal	Not applicable	Potentially significant	Potentially significant	Negligible
Oral	Not applicable	Negligible	Potentially significant/accidental	Negligible

The primary route of exposure to the active substance from formulation and use of the biocidal product is the dermal route. From use of the biocidal product, dermal exposure will be confined to the hands only. Inhalation exposure to the active substance during manufacture and use in the biocidal product is unlikely due to the low vapour pressure of the substance. During formulation inhalation exposure to dust produced from the dry mix may occur. However, the exposure during formulation is expected to be minimal due to operating in a closed system, where dust masks are stipulated as extra protection. Also, during the production every worker must wear protective glasses, plastic gloves, mask and overall. Exposure of manufacturing workers is governed by industrial legislation.

The following exposure assessment is based on studies and expert opinions regarding wax block baits. As an appropriate exposure model is not available, the authorizing Competent Authority deems that the material of the wax blocks tends to adhere to the skin more than the Mixed Bait, thus placing wax blocks represent higher risk and can be accepted as a worst case scenario for the Bromadiolone Mixed Bait.

7.3.1 Primary exposure
7.3.1.1 Professionals

Bromadiolone Mixed Bait is used by professionals in and around buildings for control of rats and mice. These users (e.g. from private companies and local authorities) are trained operators who handle rodenticides on a daily basis. They can be expected to wear protective clothing (gloves) when handling the products. After use, unused product is likely to be collected and disposed of in a controlled way.

Bromadiolone Mixed Bait contains granules, cereal flakes and crystals, bromadiolone is not volatile and the risk of inhalation exposure to the product for professional or amateur users during use is considered to be negligible. For the rodenticide which is placed in the bait station by hand, dermal exposure of users is likely to be limited to the hands only during application. Exposure of other parts of the body can be deemed as negligible. When applied properly, oral contact to the biocidal product is unlikely. It is possible however that dermal contamination may lead to oral exposure, if the hands are not washed properly after handling

Total systemic exposure to bromadiolone of professional operators applying and cleaning up Bromadiolone Mixed Bait in and around buildings is estimated at 0.0037 µg/kg bw/day and 0.0030 µg/kg bw/day when the product is used to control rats and mice, respectively, based on default values (see Appendix 1 for details). Based on extrapolation from an operator exposure study, exposure to bromadiolone of professional operators applying and cleaning up Bromadiolone Mixed Bait in and around buildings is estimated to 0.0004 µg/kg bw/day when the product is used to control rats and mice. Thus, in the operator exposure study in which operators carried out the same tasks, exposure was 10.8 % (rats) and 13.3% (mice) of the estimated exposure based on default values.

7.3.1.1 Summary of exposure of professional users

Field of use envisaged	Gloves	Total systemic exposure (µg/kg bw/day)	
		Default (TNsG)	Measured
In/around buildings for control of rats	Yes	0.0037	0.0004
	No	0.0370	0.0038
In/around buildings for control of mice	Yes	0.0030	0.0004
	No	0.0296	0.0038

Non-professionals

Non-professional users are assumed not to wear protective gloves (or other protective clothing) when handling the products. Non-professional users are expected to collect and dispose of unused or partly-used products. Otherwise the conditions for professionals regarding inhalation and body exposure also apply to non-professional users.

Table 7.3.1.2 Summary of exposure of non-professional users

Field of use envisaged	Gloves	Total systemic exposure (µg/kg bw/day)	
		Default (TNsG)	Measured
In/around buildings for control of rats	No	0.0038	0.0004
In/around buildings for control of mice	No	0,0038	0.0004

Total systemic exposure to bromadiolone of non-professional operators applying Bromadiolone Mixed Bait in and around buildings is estimated at 0.0038 µg/kg bw/day when the product is used to control rats or mice, based on default values. Based on extrapolation from an operator exposure study, exposure to active substance of non-professional operators applying the product in and around buildings is estimated to be 0.0004 µg/kg bw/day when the product is used to control rats and mice. Thus, in the operator exposure study in which operators carried out the same tasks, exposure was 9,5% both for rats and mice of the estimated exposure based on default values.

7.3.2 Secondary exposure

As discussed above (section 7.3.1.1), the risk of inhalation exposure to residues during or after application via the environment is considered to be negligible. Children could potentially be the group most at risk as they may play inside or around buildings where baits have been

Test product	Test organisms	Test system/Concentration applied/exposure time	Test conditions	Test results: effects, mode of action, resistance	Reference
Bromadiolone Mixed Bait, after 2 years of storage	House mouse (*Mus musculus*) 10 laboratory bred wild animals (5 males, 5 females)	Laboratory test. Palatability – mortalitiy trial study. Choice feeding test: aged baits. 3-day pre-test normal diet (CRLT/N) intake assessment. 5 day bait feeding period and 6 day normal diet period. Unrestricted access to the test bait and to palatable and familiar alternative food (challange diet – EPA STANDARD) during the 5-day test period. The quantitiy of food placed in each pot was *sufficient to meet each animal's daily needs.*	The animals were individually caged. Normal laboratory requirements: • temperature: 22 ± 2°C • relative humidity: min. 40% ± 10% • continuous change of air (ventilation) • 12-hour light-dark cycle	The mean acceptance o the test item was 24.5%. Total mortality was observed in both male and female mice. The mean time to death was 5.8 days. The efficacy was total: 100% in 9 days.	Biological Laboratory of Babolna Bio Ltd., Hungary 131.024
Bromadiolone Mixed Bait, after 2 years of storage	Norway rat (*Rattus norvegicus*) 10 laboratory bred wild animals (5 males, 5 females)	Laboratory test. Palatability – mortalitiy trial study. Choice feeding test: aged baits. 3-day pre-test normal diet (CRLT/N) intake assessment. 5 day bait feeding period and 6 day normal diet period. Unrestricted access to the test bait and to palatable and familiar alternative food (challange diet – EPA STANDARD) during the 5-day test period. The quantitiy of food placed in each pot was *sufficient to meet each animal's daily needs.*	The animals were individually caged. Normal laboratory requirements: • temperature: 22 ± 2°C • relative humidity: min. 40% ± 10% • continuous change of air (ventilation) • 12-hour light-dark cycle	The mean acceptance o the test item was 46.4%. Total mortality was observed in both male and female mice. The mean time to death was 5.5 days. The efficacy was total: 100% in 7 days.	Biological Laboratory of Babolna Bio Ltd., Hungary 131.006

7. Human health risk assessment

7.1 Effects assessment

7.1.1 Studies submitted and assessed at Annex I Inclusion

Table 7.1.1 Toxicokinetical studies

Route	Method, Guideline	Species, Strain, Sex, no./dose	Dose levels, Duration of exposure	Result
Oral (gavage)	OECD 417	SD rats, male and female, single low dose 4/sex, single high dose 3/sex, repeated low dose 4/sex	0.5 mg/kgbw/day (single dose) and 0.05 mg/kgbw/day (single dose) 0.2 mg/kgbw/day (repeated dose 14 days)	Oral absorption: 71-77%
Dermal *in vitro*	OECD 428	5 human skin samples (female)	Bait: saline 0.0025% Wax block: 0.005% (w/w)	Dermal absorption Bait: saline: 0.36% Wax block: 0.04%

Bromadiolone was absorbed fairly slowly after oral administration with peak levels noted at 4-8h post dose in all rats administered 0.5 or 0.05 mg/kg bw. The absorption was > 70 % of the administered dose based on urinary and biliary excretion and carcass amounts (GI excluded). The major route of excretion was via the faeces accounting for ca 50-60 % of the dose, whilst 1-5 % was excreted via urine. Bile investigations showed that biliary elimination plays a major role in the excretion. No parent bromadiolone was excreted in bile or urine. The main retention site was the liver (up to 48% of the dose, even 7 days after administration).

The ingredients of the biocidal product may influence the dermal penetration of the active substance, especially for a highly lipophilic substance, like bromadiolone. Available evidence suggests that formulation type strongly influences the absorption, i.e in liquids all of the amount of active substance present in the product is available for dermal absorption, while in solids only those present or near the contact zone. In case of the Bromadiolone the result of the solubilised granule formulation was chosen for risk assessment, and the authorizing Competent Authority deems that it represents a worst case even for solid formulation types with higher fat/oil contents than granules.

Based on an *in vitro* dermal absorption study of formulated active substance (granule bait (incorporated bromadiolone: 0.00255 w/w) homogenized in saline) a value of 0.36% was obtained that was used for the risk assessment of the product.

7.1.2 Studies submitted and assessed at product authorization

The product is a 70:30 mixture of two other products with identical active substance content, Bromadiolone Granule Bait and Bromadiolone Loose Bait. Acute studies are available for the two components (with very similar results), therefore, as synergistic or antagonistic effects are not expected, no new studies were conducted with Bromadiolone Mixed Bait.

Acute toxicity and irritation

Bromadiolone Loose Bait

Acute toxicity tests were conducted on the formulated product 'Bromadiolone Loose Bait' in studies meeting current guidelines.

Acute oral toxicity

No lethality and no clinical symptoms were observed at single oral dose of 2000 mg/kg bw of Bromadiolone Loose Bait.

The acute oral LD_{50} of the product is >2000 mg/kg bw. Consequently no classification according to Directive 67/548/EEC or CLP Regulation (EC) No 1272/2008 is warranted.

Table 7.1.2.1a. Acute oral and dermal toxicity

Route	Method, Guideline	Species, strain, sex, No./Group	Dose levels Duration of exposure	LD_{50}	Remarks	Reference
Oral	OECD 423 GLP	Rat: Crl:(WI)Br females; 3/group	2000 mg/kg bw	> 2000 mg/kg bodyweight	No deaths. No clinical signs or abnormalities noted at necropsy.	Kuthy, PM (2011a) Acute Oral Toxicity Study (Acute Toxic Class Method) of Test Item Loose Bait In Rats
Dermal	OECD 402 GLP	Rat: Crl:(WI)Br Preliminary study; 2 female per dose Main study; 5 Male & 5 female per dose	Preliminary study; 5, 50, 300, 2000 mg/kg bw. Main study; 2000 mg/kg bw. Exposure: 24h	> 2000 mg/kg bodyweight	No deaths. No clinical signs or abnormalities noted at necropsy. No signs of dermal irritation.	Kuthy, PM (2011b) Acute Dermal Toxicity Study of Test Item Loose Bait In Rats

Acute dermal toxicity

An acute dermal toxicity study was performed with test item Bromadiolone Loose Bait. A limit test was performed on the basis of the result of the preliminary study (there were no deaths in the preliminary study at 5, 50, 300 and 2000 mg/kg dose levels). A single group of male and female animals (n=5 animals/sex) was exposed to pulverised Bromadiolone Loose Bait at 2000 mg/kg bw by dermal route.

No mortality occurred during the study.

The acute dermal LD_{50} of the product is >2000 mg/kg bw. Consequently no classification according to Directive 67/548/EEC or CLP Regulation (EC) No 1272/2008 is warranted.

Acute inhalation toxicity

No test for inhalation toxicity is available. The product is formulated as cereal flakes and using mostly food grade materials, which are solid at room temperature and of low vapour pressure. The active substance is non-volatile as well. The loose bait is not friable or dusty such that airborne particles can be produced. They are therefore not respirable, do not product respirable particles, and do not produce respirable vapours.

Skin irritation and corrosivity

Bromadiolone Loose Bait is classified as not irritating to the skin and has not been classified into any category in the acute skin irritation test based on the criteria of directive 67/548/EEC or CLP Regulation (EC) No 1272/2008.

The product is not irritating to rabbit skin and is not classified into any category based on 67/548/EEC or CLP Regulation (EC) No 1272/2008 criteria.

Table 7.1.2.2a Skin irritation

Species	Method, Guideline	Average score 24, 48, 72 h		Reversibility (yes/no)	Remark	Reference
		Erythema	Oedema			
Rabbit	OECD 404 GLP	0 (0.00-0.00-0.00)	0 (0.00-0.00-0.00)	n/a	Not irritating	Kuthy, PM (2011c) Acute Skin Irritation Study of Test Item Loose Bait In Rabbits

Eye irritation

Table 7.1.2.3a Eye irritation

Species	Method	Score				Remark	Reference
		Cornea	Iris	Conjuctiva			
				Redness	Chemosis		
Rabbit	OECD 405 GLP	0 (0-0-0)	0 (0-0-0)	0.33 (0.33-0.33-0.00)	0 (0.00-0.00-0.00)	Not irritating	Kuthy, PM: Acute Eye Irritation Study of Test Item Loose Bait In Rabbits

The product was classified as not irritating for the eye and has not been classified into any category so it has no obligatory labelling requirement for eye irritation based on Directive 67/548/EEC and CLP Regulation (EC) No 1272/2008.

Skin sensitization

Table 7.1.2.4a Skin sensitization

Species	Method	Average score	Remark	Reference
Guinea pig	OECD 406 GLP	0.0	Non-sensitiser	Ståhl J: Skin sensitisation study of test item Loose Bait in guinea pigs

A skin sensitisation test was conducted on the formulated product 'Bromadiolone Loose Bait' in a study meeting current guidelines. The Buehler method was chosen because the biocidal product is an insoluble solid and the alternative guinea-pig maximisation method would involve intradermal injections of the test item.

The test item Bromadiolone Loose Bait was classified as a non-sensitiser. No classification according to Directive 67/548/EEC or CLP Regulation (EC) No. 1272/2008 is necessary.

The above mentioned studies are indicating a low risk of irritation and sensitisation following exposure to the product.

Bromadiolone Granule Bait

Acute toxicity tests were conducted on the formulated product 'Bromadiolone Granule Bait' in studies meeting current guidelines.

Acute oral toxicity

No lethality and no clinical symptoms were observed at single oral dose of 2000 mg/kg bw of Bromadiolone Granule Bait.

The acute oral LD_{50} of the product is >2000 mg/kg bw. Consequently no classification according to Directive 67/548/EEC or CLP Regulation (EC) No 1272/2008 is warranted.

Table 7.1.2.1b. Acute oral and dermal toxicity

Route	Method, Guideline	Species, strain, sex, No./Group	Dose levels Duration of exposure	LD_{50}	Remarks	Reference
Oral	OECD 423 GLP	Rat: Wistar females; 3/group	2000 mg/kg bw	> 2000 mg/kg bodyweight	No deaths. No clinical signs or abnormalities noted at necropsy.	Kuthy, PM (2011a) Acute Oral Toxicity Study (Acute Toxic Class Method) of Test Item Granule Bait In Rats
Dermal	OECD 402 GLP	Rat: Crl:(WI)Br Preliminary study; 2 female per dose Main study; 5 Male & 5 female per dose	Preliminary study; 5, 50, 300, 2000 mg/kg bw. Main study; 2000 mg/kg bw. 24 hours	> 2000 mg/kg bodyweight	No deaths. No clinical signs or abnormalities noted at necropsy. No signs of dermal irritation.	Kuthy, PM (2011b) Acute Dermal Toxicity Study of Test Item Granule Bait In Rats

Acute dermal toxicity

An acute dermal toxicity study was performed with test item Bromadiolone Granule Bait. Limit test was performed on the basis of the result of the preliminary study (there were no deaths in the preliminary study at 5, 50, 300 and 2000 mg/kg dose levels). A single group of male and female animals (n=5 animals/sex) was exposed to Bromadiolone Granule Bait at 2000 mg/kg bw by dermal route.

No mortality occurred during the study.

The acute dermal LD_{50} of the product is >2000 mg/kg bw. Consequently no classification according to Directive 67/548/EEC or CLP Regulation (EC) No 1272/2008 is warranted.

Acute inhalation toxicity

No test for inhalation toxicity is available. Active substance is of low vapour pressure at room temperature. The product is formulated as a granule bait using mostly food grade materials, which are solid at room temperature and of low vapour pressure. The granules are not friable or dusty such that airborne particles can be produced. They are therefore not respirable, do not product respirable particles, and do not produce respirable vapours.

Skin irritation and corrosivity

Bromadiolone Granule Bait is classified as not irritating for the skin and has not been classified into any category in the acute skin irritation test based on the criteria of directive 67/548/EEC or CLP Regulation (EC) No 1272/2008.

The product is not irritating to rabbit skin and is not classified into any category based on 67/548/EEC or CLP Regulation (EC) No 1272/2008 criteria.

Table 7.1.2.2b Skin irritation

Species	Method, Guideline	Average score 24, 48, 72 h		Reversibility (yes/no)	Remark	Reference
		Erythema	Oedema			
Rabbit	OECD 404 GLP	0 (0.00-0.00-0.00)	0 (0.00-0.00-0.00)	n/a	Not irritating	Kuthy, PM (2011c) Acute Skin Irritation Study of Test Item Granule Bait In Rabbits

Eye irritation

Table 7.1.2.3b Eye irritatiob

Species	Method	Score				Remark	Reference
		Cornea	Iris	Conjuctiva			
				Redness	Chemosis		
Rabbit	OECD 405 GLP	0 (0-0-0)	0 (0-0-0)	0.33 (0.33-0.00-0.66)	0 (0.00-0.00-0.00)	Not irritating	Kuthy, PM (2011c) Acute Eye Irritation Study of Test Item Granule Bait In

							Rabbits

The product was classified as not irritating for the eye and has not been classified into any category so it has no obligatory labelling requirement for eye irritation based on Directive 67/548/EEC and CLP Regulation (EC) No 1272/2008.

Skin sensitization

Table 7.1.2.4b Skin sensitization

Species	Method	Average score	Remark	Reference
Guinea pig	OECD 406 GLP	0.0	Non-sensitiser	Ståhl J: Skin sensitisation study of test item GRANULE BAIT in guinea pigs

A skin sensitisation test was conducted on the formulated product 'Bromadiolone Granule Bait' in a study meeting current guidelines. The Buehler method was chosen because the biocidal product contains insoluble materials and the alternative guinea-pig maximisation method would involve intradermal injections of the test item.

The test item Granule Bait was classified as a non-sensitiser. No classification according to Directive 67/548/EEC or CLP Regulation (EC) No. 1272/2008 is necessary.

The above mentioned studies are indicating a low risk of irritation and sensitisation following exposure to the product.

7.2 Critical endpoints and selection of the NOAEL/LOAEL

Active ingredient

Bromadiolone was absorbed fairly slowly after oral administration. The absorption was between 71-77% of the administered dose and approximately 20% unchanged bromadiolone was found in faeces. Therefore a correction for oral absorption of approximately 70% was made in the risk characterisation calculations. The absorbed bromadiolone was extensively metabolized. The major route of excretion was via the faeces with biliary elimination playing a major role in the excretion. No parent bromadiolone was observed in urine or bile. A large amount was retained in the animals 7 days post dosing, accounting for 33-48% of the dose, and was mainly retained in the liver..

The active substance bromadiolone acts by blocking the regeneration of vitamin K and thus interferes with the clotting cascade. Increasing levels of the active substance progressively reduce the capacity of the blood to form a clot at the site of injury, and death results from haemorrhage. Bromadiolone is acutely toxic by the oral, inhalation and dermal routes.

Bromadiolone is not a skin or eye irritant and is not a sensitiser. Repeated exposure leads to clinical signs consistent with increased clotting time and haemorrhagic events. The effects can be reversed by treatment with vitamin K if given in time.

The overall NOAEL for repeated dose effects is 0.5 µg/kg/day based on the absence of adverse effects in this dose group in the 90-day rabbit study.

The carcinogenicity study and the chronic toxicity study were waived. Performing long-term exposure studies is technically difficult when studying highly toxic substances such as bromadiolone, since dose levels, at which toxicity is identifiable but without rendering high levels of lethality, are hard to predict. Also, no genotoxic potential has been identified for bromadiolone in *in vitro* tests of genotoxicity. The closely-related substance warfarin has the same mode of action and has been used as a pharmaceutical in the treatment of clotting disorders for over forty years, with no indications of carcinogenicity or adverse effects on fertility following long-term use in humans.

The two-generation reproduction toxicity study is of low reliability. In this study, no clinical signs were seen in any dose group and no dose-related effects were reported. Therefore, reproductive effects following bromadiolone exposure can not be excluded based on the results from this study. However, since long term exposure studies are technically hard to perform for such highly toxic substances as bromadiolone, waiving of the study has been accepted.

The derivation of an acceptable level of exposure value for single use (AEL_{acute}) is based on the teratogenicity study in rabbits. The acute studies performed are not suitable for setting limit levels as they do not measure the most sensitive end-points. In the teratogenicity study no NOAEL for maternal toxicity could be set since there were bleedings in three animals in the lowest dose group. Therefore the LOAEL of 2 µg/kg bw has to be used. Using a safety factor of 600 (10 for interspecies and 10 for intraspecies variability, 2 for using LOAEL instead of NOAEL and an extra factor of 3 for severity of effects) results in an AEL_{acute} of 0.0023 µg/kg bw (also corrected for oral absorption of approximately 70%). This is considered a suitable AEL for non-professionals applying rodenticide baits on a single occasion and for indirect exposure.

To derive an AEL_{medium}, for repeated exposure, the subchronic study in rabbits is used. The NOAEL in this study is 0.5 µg/kg bw based on the prolonged prothrombin time seen at 1 µg/kg bw. With a safety factor of 300 this would lead to an AEL_{medium} of 0.0012 µg/kg bw (also corrected for oral absorption of approximately 70%). This AEL is suitable for repeated exposure of for example a professional pest control officer.

To set an $AEL_{chronic}$ the same NOAEL as for AEL_{medium} will be used as no chronic studies have been performed. The extra safety factor of 3 will apart from severity of effects also cover for the differences in exposure time.

Product formulation

Based on the submitted studies the two components of 'Bromadiolone Mixed Bait' was not found to be toxic via oral or dermal route. No classification according to Directive 67/548/ EEC or CLP Regulation (EC) No 1272/2008 is warranted for oral and dermal acute toxicity.

In acute dermal and eye irritation tests the product was not irritating to rabbit skin and eyes. The product was not found to have sensitising properties. Therefore no classification for skin irritation, eye irritation or sensitisation is necessary.

placed. Thus, it is important that product labels and good practice advise for users to prevent access to bait by children. However, as stated above bromadiolone is not volatile, and so in practice the risk of inhalation exposure to bromadiolone for all non-users is considered to be negligible. For non-users, the risk of dermal exposure to residues during application is considered to be small. After application, non-users are not likely to come into contact with Bromadiolone Mixed Bait used in and around buildings. Risk of oral exposure to residues during or after application is considered to be low. Children or infants may play close to the floor where baits have been placed indoors and could be incidentally exposed by touching unprotected baits. For products applied in tamper resistant bait boxes risk of exposure will be very limited. Bromadiolone Mixed Bait also contains a bittering agent to prevent infants from chewing and ingesting baits.

Where appropriate, exposure assessments are based on default values of EU Guidance documents. For oral exposure of infants/children two scenarios are made. One for infants with 10 mg product (default value for bait treated with repellent) and one for children with 5 g (TNsG on Human Exposure to Biocidal Products, User Guidance). Body weight is assumed to be 10 kg for infants and 15 kg for children.

Table 7.3.2 Summary of indirect exposure

Field of use envisaged	**Individual exposed**	**Total systemic exposure (µg/kg bw/day)**
In/around buildings for control of rats and mice	Infant	0.035
	Child	11.7

These values assume ingestion of poison bait; however 'Bromadiolone Mixed Bait' contains denatonium benzoate, a bittering agent which will reduce the likelihood of ingestion. Since the deterrent may not be completely effective in protecting against ingestion in all children, it is important that the product is kept out of the reach of children, and away from other non-target species, including pets and livestock, during storage and use.

7.4 Risk characterization

7.4.1 Primary exposure
7.4.1.1 Professional users

Exposure of professional operators applying Bromadiolone Mixed Bait on a daily basis, while wearing gloves, is acceptable. In the worst case scenario the exposure for use in and around buildings for control of rats is 308 % of AOEL and MOE is 95 when based on default values, which were changed to 33 % of AOEL and a MOE of 875 when based on measured values. In these estimations gloves are worn. The results are summarised in tables 7.4.1.1-1 and 7.4.1.1-2 below.

Table 7.4.1.1-1 Professional Users – Primary Exposure, in and around buildings against rats

Exposure Scenario (indicate duration)		Estimated Internal Exposure				Relevant NOAEL/LOAEL [µg/kg b.w/day] & Reference Value e.g: AEL (acute or medium or chronic)	AF MOE_{ref}	MOE	Exposure /AEL
		estimated oral uptake [µg/kg bw/day]	estimated inhalation uptake [µg/kg bw/day]	estimated dermal uptake [µg/kg bw/day]	estimated total uptake [µg/kg bw/day]				
Tier 1-Default (no PPE)	in and around buildings, against rats	negligible	negligible	0.0370	0.0370	0.5 µg/kg bw AEL_{medium} of 0.0012 µg/kg bw*	300	9.5	30.83
Tier 1-Measured (no PPE)	in and around buildings, against rats	negligible	negligible	0.0038	0.0038	0.5 µg/kg bw AEL_{medium} of 0.0012 µg/kg bw*	300	92.1	3.17
Tier 2-Default (Refinement, PPE or other RMM)	in and around buildings, against rats	negligible	negligible	0.0037	0.0037	0.5 µg/kg bw AEL_{medium} of 0.0012 µg/kg bw*	300	95	3.08
Tier 2-Measured (Refinement, PPE or other RMM)	in and around buildings, against rats	negligible	negligible	0.0004	0.0004	0.5 µg/kg bw AEL_{medium} of 0.0012 µg/kg bw*	300	875	0.33

Table 7.4.1.1-2 Professional Users – Primary Exposure, in and around buildings against mice

Exposure Scenario (indicate duration)		Estimated Internal Exposure				Relevant NOAEL/LOAEL [µg/kg b.w/day] & Reference Value e.g: AEL (acute or medium or chronic)	AF MOE_{ref}	MOE	Exposure /AEL
		estimated oral uptake [µg/kg bw/day]	estimated inhalation uptake [µg/kg bw/day]	estimated dermal uptake [µg/kg bw/day]	estimated total uptake [µg/kg bw/day]				
Tier 1-Default (no PPE)	in and around buildings, against mice	negligible	negligible	0.0296	0.0296	0.5 µg/kg bw AEL_{medium} of 0.0012 µg/kg bw*	300	13.5	21.58
Tier 1-Measured (no PPE)	in and around buildings, against mice	negligible	negligible	0.0038	0.0038	0.5 µg/kg bw AEL_{medium} of 0.0012 µg/kg bw*	300	92.1	3.17
Tier 2-Default (Refinement: PPE or other RMM)	in and around buildings, against mice	negligible	negligible	0.003	0.003	0.5 µg/kg bw AEL_{medium} of 0.0012 µg/kg bw*	300	135	2.17
Tier 2-Measured (Refinement: PPE or other RMM)	in and around buildings, against mice	negligible	negligible	0.0004	0.0004	0.5 µg/kg bw AEL_{medium} of 0.0012 µg/kg bw*	300	875	0.33

*Corrected for oral absorption of approximately 70%.

7.4.1.2 Non-professional users

Exposure of non-professional operators applying Bromadiolone Mixed Bait on a single occasion is acceptable. For use in and around buildings to control rats and mice the exposure was 165% AOEL and MOE was 368 for rats and mice based on default values. When the estimations were based on measured values the margins were even higher, 17% of AOEL and MOE of 3500. Since non-professionals can not be expected to wear protective clothing, the estimations are for use without gloves. Non-professional operators are not expected to apply Bromadiolone Mixed Bait on a daily basis and therefore comparisons with a repeated dose AOEL are not considered appropriate. The assessments are summarised in table 7.4.1.2 below.

Table 7.4.1.2 Non Professional Users – Primary Exposure, in and around buildings against rats and mice

Exposure Scenario (indicate duration)		Estimated Internal Exposure				Relevant NOAEL/LOAEL [µg/kg b.w/day] & Reference Value e.g: AEL (acute or medium or chronic)	AF MOE_{ref}	MOE	Exposure /AEL
		estimated oral uptake [µg/kg bw/day]	estimated inhalation uptake [µg/kg bw/day]	estimated dermal uptake [µg/kg bw/day]	estimated total uptake [µg/kg bw/day]				
Tier I-Default (no PPE)	in and around buildings, against rats	negligible	negligible	0.0038	0.0038	LOAEL 2.0 µg/kg bw AELacuteof 0.0023 µg/kg bw*	600	368	1.65
Tier I-Measured (no PPE)	in and around buildings, against rats	negligible	negligible	0.0004	0.0004	LOAEL 2.0 µg/kg bw AELacuteof 0.0023 µg/kg bw*	600	3500	0.17
Tier I-Default (no PPE)	in and around buildings, against mice	negligible	negligible	0.0038	0.0038	LOAEL 2.0 µg/kg bw AELacuteof 0.0023 µg/kg bw	600	368	1.65
Tier I-Measured (no PPE)	in and around buildings, against mice	negligible	negligible	0.0004	0.0004	LOAEL 2.0 µg/kg bw AELacuteof 0.0023 µg/kg bw	600	3500	0.17

*Corrected for oral absorption of approximately 70%.

** As the product also sold in Tamper Resistant Bait Boxes for mice control and the box can not be opened.

7.5 Secondary exposure

Children are potentially the group most at risk as they may play inside or around buildings where baits have been placed. Infants could be exposed orally by chewing bait or touching their mouth with contaminated fingers. The calculated MOE was 40 based on a default exposure value which assumes that infants will ingest 10 mg of bait and 0.12 when assuming that children will ingest 5 g bait. These values show that infants and children ingesting bait will be at risk. However, Bromadiolone Mixed Bait contains a bittering agent which would prevent ingestion of the baits. Therefore, in practice the margins of safety are expected to be higher than those calculated. It is also important that product labels and good practice advise users to prevent access to bait by children.

Approximately 5% of the radioactivity is excreted into urine of rats after oral exposure with [C^{14}]-bromadiolone. In addition no parent compound was detected in the urine by HPLC assessment. Therefore the amount bromadiolone present on the fur is expected to be negligible and consequently it will not be transferred to the hands to any significant extent. Exposure of adults and children to active substance by handling dead rodents (which is considered as an unlikely scenario) is therefore assumed to be negligible.

The fact that the identity of the metabolites in urine is unknown consequently means that their toxicity is unknown. Therefore persons handling dead rodents without gloves could be at risk (if it is assumed that the residues are of equal toxicity as bromadiolone), since they may potentially ingest urinary residues transferred to hands. However, it is deemed unlikely that adults would handle dead rodents without gloves and that infants would play with them. Still, as a worst case it could be assumed that an unattended child may handle a dead rodent. If a rat ingests 28g of bait (based on the palatability studies), it corresponds to 1.4 mg bromadiolone. According to metabolism study, the active substance excreted slowly, the majority of it leaves the body in 72 hours (and one-third still remains in the carcass). 70 µg (i.e. 5%) is excreted in 3*25 ml urine (usual urine volume of rats is 25-35 ml/day). A child weighing 15 kg must consume 36 µl rat urine to exceed the AEL_{acute} of 0.0023 µg/kg bw, which is an unlikely but not impossible scenario. Since the dead rodents as such also can be considered to have a negative impact on human health i.e due to spreading of germs and diseases, the above calculations can be seen as further showing the importance of active collection and disposal of dead rodents, from areas where bromadiolone is used and where children may be present.

Table 7.5 Indirect exposure of non users, as a result of use

Exposure Scenario (indicate duration)		Estimated Internal Exposure				Relevant NOAEL/LOAEL [µg/kg b.w/day] & Reference Value e.g: AEL (acute or medium or chronic)	AF MOE_{ref}	MOE	Exposure /AEL
		estimated dermal uptake [µg/kg bw/day]	estimated inhalation uptake [µg/kg bw/day]	estimated oral uptake [µg/kg bw/day]	estimated total uptake [µg/kg bw/day]				
Tier 1 (Worst Case) Short term scenario	in and around buildings, against rats and mice Non-users (adults, children and infants) will not be present during application. **Infants may ingest pieces of the mixed bait.**	negligible	negligible	0.035	0.035	LOAEL 2.0 µg/kg bw AELacuteof 0.0023 µg/kg bw*	600	40	15.2
	in and around buildings, against rats Non-users (adults, children and infants) will not be present during application. **Children may ingest pieces of the mixed bait.**	negligible	negligible	11.7	11.7	LOAEL 2.0 µg/kg bw AELacuteof 0.0023 µg/kg bw*	600	0.12	5087

*Corrected for oral absorption of approximately 70%.

7.6 Combined exposure

The active substance is used as a rodenticide only. Therefore there will be no additional exposure through use in other biocidal products. Only professionals use the product on a frequent basis and indirect exposure via the environment is almost negligible.

7.7 Conclusions of risk characterization

An acceptable exposure is estimated for professional operators applying Bromadiolone Mixed Bait on a daily basis, wearing gloves. In the worst case scenario exposure for use in and around buildings for control of rats is 308 % of the AOEL and the MOE is 95 when based on default values, which were changed to 33 % of AOEL and a MOE of 875 when based on measured values.

An acceptable exposure is estimated for non-professional operators applying Bromadiolone Mixed Bait on a single occasion. For use in and around buildings to control rats and mice the exposure was 165% of AOEL and MOE was 368 for rats and mice based on default values. When the estimations were based on measured values the margins were better: 17% of AOEL and MOE of 3500. Since non-professionals can not be expected to wear protective clothing, the estimations are for use without gloves. Non- professional operators are not expected to apply Bromadiolone Mixed Bait on a daily basis and therefore comparisons with a repeated dose AOEL are not considered appropriate.

Children are potentially the group most at risk as they may play inside or around buildings where baits have been placed. Infants could be exposed orally by chewing bait or touching their mouth with contaminated fingers. The calculated MOE was 40 based on a default exposure value which assumes that infants will ingest 10 mg of poison bait and 0.12 when assuming that children will ingest 5 g bait. These values show that infants and children ingesting bait will be at risk. However, Bromadiolone Mixed Bait contains a bittering agent which would prevent ingestion of the baits. Therefore, in practice the margins of exposure are expected to be higher than those calculated. It is also important that product labels and good practice advise users to prevent access to bait by children.

Approximately 5% of the radioactivity is excreted into urine of rats after oral exposure with [C14]-bromadiolone. No parent compound was detected in the urine by HPLC assessment. In a very worst case scenario, handling dead rodents could pose risk for children, but rat carcass as such can be considered to have a negative impact on human health i.e. due to spreading of germs and diseases and that scenario can be seen as further showing the importance of active collection and disposal of dead rodents from areas where bromadiolone is used and where children may be present.

8. Environmental Risk Assessment

The product contains substances that are mostly food-grade materials. The active substance is the most toxic constituent of the product. Denatonium benzoate might be a substance of concern based on its classification and environmental fate properties. However the concentration of denatonium benzoate in the rodenticide bait is very small (0.002 % v/v).

Therefore it can be accepted that the only substance of environmental concern is the active substance.

8.1. Fate and behaviour in the environment

The environmental fate and behaviour of the active substance bromadiolone has been evaluated during the assessment for Annex I inclusion.

Bromadiolone is not readily biodegradable. No hydrolysis was found at the investigated pH 7, and 9, so hydrolysis of bromadiolone is not expected to be a significant process in the environment.

In the soil degradation study (OECD 307) bromadiolone was tested on 4 different soil types. Degradation was detected during the test DT_{50} was between 5.8 and 23.6 days, DT_{90} was between 76 and 183 days at 20 °C. The main degradation product is the bromadiolone ketone.

Bromadiolone is strongly adsorbed to soil and Koc values range between 3530 and 41600 mL/g (mean value: 14770 mL/g), which corresponds to 'slightly mobile' to "non-mobile". Bromadiolone is unlikely to reach groundwater in significant amount due to its immobility in soil.

The rapid photolysis rate in air (t½ ca 2 hours), the low vapour pressure of bromadiolone and the low Henry's law constant together show that bromadiolone is not expected to volatilise to or persist in air in significant quantities.

Two fish bioconcentration studies were performed, but both failed. Therefore BCF was derived by calculation from log Kow, resulting in a BCF values of 339. It can be concluded that bromadiolone has a potential to bioaccumulation.

The formulation of bromadiolone in 'Bromadiolone Mixed Bait' has no impact on the route or rate of degradation of the active substance bromadiolone in the environment. So it was concluded that no additional studies involving the formulated product are required.

8.1.1. Effect assessment

Based on the results of toxicity studies, bromadiolone was found to be toxic to fish. In the test performed under static conditions the 96-hour LC_{50} was 2.86 for *Oncorhynchus mykiss*.

D. magna was the least sensitive, with a 48-hour EC_{50} of 5.79 mg/L.

Algae represented the most sensitive of the three aquatic trophic levels tested the 72-hour E_rC_{50} *Pseudokirchneriella subcapitata* was 1.14 mg/L.

Bromadiolone had no effects on earthworms at 1331 mg/kg dw, which is equal NOEC 918 mg/kg ww calculated for wet soil.

In the acute toxicity study to birds, Japanese quail were exposed to bromadiolone once and then observed for 14 days. This study was conducted to determine the lethal dose, but it also made it possible to determine effect concentrations at which birds did cower, which was found to be a dose dependent effect. The LD_{50} was 134 mg/kg bw on average for both sexes.

The dietary toxicity test to birds, as acute study with partridge resulted in an LC_{50} of 28.9 mg/kg food.

In the reproductive toxicity test bromadiolone was supplied via drinking water. It was difficult to determine any clear effects on reproduction in this study, but it showed effects on liver weight, spleen weight and testes weight. Effects on 14 day survival of the hatchlings were also found and there were indications on a decreased body weight gain of the adult birds. The NOEC was determined to be 0.26 mg/L drinking water (measured concentration).

Bromadiolone is acutely toxic to mammals with an acute oral rat LD_{50} of 1.31 mg/kg.

Three studies on secondary poisoning of birds by anticoagulant rodenticides are available. From the studies it may be concluded that the investigated rodenticides pose a high risk of secondary poisoning to owls and that consumption of 3 mice poisoned with the related substance brodifacoum caused lethality to barn owls. Lethal liver concentrations were found to be between 0.63 and 1.7 mg brodifacoum/kg fw. This correlates well with a field report where liver concentrations of dead hawks after a field trial were investigated and found to be on average 0.23 mg brodifacoum/kg fw.

8.1.2. PBT assessment
Bromadiolone is not readily biodegradable, has a relatively high bioconcentration factor and is toxic to both aquatic organisms and mammals. Thus, bromadiolone is considered as a potential PBT substance.

8.1.3. Exposure assessment
The environmental exposure assessment is based on the fact that the two components of Bromadiolone Mixed Bait, namely Bromadiolone Granule Bait and Bromadiolone Loose Bait are mixed in 70:30 ratio which does not alter the Bromadiolone concentration. The two components, Bromadiolone Granule Bait and Bromadiolone Loose Bait are also under authorization and the environmental exposure results of the two components had very similar results. Therefore the same method, default values were used with the environmental exposure assessment of Bromadiolone Mixed Bait as were used for the calculation of the component's exposure.

Bromadiolone Mixed Bait containing 50 mg bromadiolone/kg is used by professional and non-professional users in the control of rats and mice in and around building.

The product is not intended to be used in sewers, open areas and waste dumps, so there was no calculation for these compartments.

The summary of calculated PEC values used for risk assessment purposes are presented in the table below:

Scenario of proposed use (ESD worst case)	**PEC_{sw}**	**PEC_{stp}**	**PEC_{sed}**	**PEC_{soil} (mg/kg)**	**PEC_{grw} (mg/L)**
In/around buildings	Negligible	Negligible	Negligible	0.046	$1.77 \cdot 10^{-4}$

8.2. PEC in surface water, groundwater and sediment

The exposure to surface water or sediment following the use of the product in and around building is considered to be negligible. PEC in ground water is calculated in the soil section.

8.3. PEC in Air

The quantity of bromadiolone used is limited, the vapour pressure and the Henry's law constant is very low and bromadiolone is rapidly degraded in air. The PEC of bromadiolone in air is therefore considered to be negligible.

8.4 PEC in soil

Emissions to soil in the area influenced by each bait box by direct release, and the total emission per campaign by indirect release are summarized in the table below:

Scenario	**$Elocal_{soil}$ Direct release per campaign (mg/campaign)**	**$Elocal_{soil}$ Indirect release per campaign** (mg as/550 m^2)**	**PEC_{soil} = $Clocal_{soil}$ Total released (mg as/kg)**
ESD worst case	0.625	452	0.046
ESD typical (CEFIC)	0.19	136	0.014
Proposed use	0.625	452	0.046

* Emission by direct release from individual bait box

** Emission by indirect release per campaign

PEC groundwater was calculated according to equation 67 in TGD II, where it is assumed that PEC local groundwater equals to PEC local pore water in agricultural soils. The soil pore water concentration is calculated to be $1.77 \cdot 10^{-4}$ mg/L determined by the predicted bromadiolone concentration in local soil, the bulk density of the soil and the soil-water partitioning coefficient.

Due to the limited use of bromadiolone in campaigns that last for a limited time, usually three weeks, and that good management practice prescribes that both leftover feed and dead rodents are collected and disposed of in a secure way, the exposure to groundwater is likely to be negligible.

8.5. Non compartment specific exposure relevant to the food chain (primary and secondary poisoning)

The exposure to bromadiolone via direct consumption of the bait, i.e. primary poisoning, or indirectly via consumption of living or dead rodents that have been exposed to the bait, i.e. secondary poisoning to non-target birds and mammals is quantified in Section 8.6.4.

8.6. Risk characterisation

The risk assessment is performed for Bromadiolone Mixed Bait, i.e. solid Mixed Bait which contain 0.005 % of the a.i bromadiolone which equals 50 mg bromadiolone/kg. The product is intended for use in in and around buildings. The risk characterisation is based on the product information from the applicant, the Technical Guidance Document II (TGD II, 2003) and the EUBEES 2 emission scenario document (ESD) for biocides used as rodenticides (Larsen,

2003). The risk characterisation is performed by comparing the predicted no effect concentration (PNEC), with the predicted environmental concentration (PEC). Values for PNEC and PEC have been derived through calculations presented in detail in documents II-A and II-B, respectively. Considering the different ingredients in the product, only the active ingredient bromadiolone will cause risk for the environment and the risk characterisation is therefore only performed for bromadiolone.

When Bromadiolone Mixed Bait containing bromadiolone is used in and around buildings the risk assessment shows that the risks for the atmosphere, organisms in surface waters and the soil compartment are all acceptable. However, an unacceptable, although quite small risk for groundwater contamination was identified. It is unlikely that the calculation leading to this risk is realistic. The reasons for this are mainly that the worst case scenario describes a situation with contamination in highly localised areas of soil and no consideration is given to dilution when bromadiolone migrates downwards through soil layers. Furthermore, risk mitigation measures including good management practices in rodenticide use are likely to substantially reduce bromadiolone contamination to soil relative to the worst case exposure scenario.

8.6.1. Aquatic compartment

Fort he use of Bromadiolone Mixed Bait as a rodenticide product in and around buildings, risk assessment is only performed for groundwater since this is the only water compartment that can be contaminated.

Risk characterisation for groundwater:

Predicted concentration = $1.77 \cdot 10^{-4}$ mg/L

Permissible concentration = $1 \cdot 10^{-4}$ mg/L

The comparison above indicates a slight risk of groundwater contamination. However, the in and around buildings scenario is a true worst case scenario which describes the situation in very localised spots of soil, and no consideration is given to dilution when bromadiolone migrates through soil layers. Furthermore, risk mitigation measures including good management practices in rodenticide use are likely to substantially reduce bromadiolone contamination to soil relative to the worst case exposure scenario.

8.6.2. Atmosphere

Since bromadiolone will be used only locally and since it has a low vapour pressure and low Henrys law constant the concentration of bromadiolone in the atmosphere will be negligible. Therefore no risk assessment is performed for the atmosphere.

8.6.3. Terrestrial compartment

Bromadiolone can contaminate soil only through the use of Bromadiolone Mixed Bait (Ratata) in and around buildings. Bromadiolone contamination of soil around buildings will occur both from direct contamination when baits are deployed outdoors and from indirect contamination via dead bodies, urine and faeces from the target organisms. The worst case PECsoil which is the sum of the direct and indirect contamination was determined to 0.046 mg/kg (Doc II-B).

The $PEC/PNEC_{soil}$ was calculated to be 0.46 based on EPM PNEC 0.099 mg/kg and this indicates that the risk for soil organisms when bromadiolone is used around buildings is acceptable.

8.6.4. Non compartment specific effects relevant to the food chain (primary and secondary poisoning)

It has been shown in numerous scientific reports (Newton et al, 1997; Fournier-Chambrillon, et al 2004; Shore et al, 1999; Gillies and Pierce, 1999; Eason and Spurr, 1995) that non-target birds and mammals have been, and are continuously, exposed to second generation anticoagulant rodenticides in the environment. This exposure occurs most likely by consumption of living or dead rodents that have been poisoned by baits containing rodenticides (secondary poisoning). Moreover, year after year there are reports (Barnett et al, 2006) of accidents where non-target mammals have been poisoned by consumption of rodenticides (primary poisoning).

The risk of bromadiolone to non-target birds and mammals has been assessed according to the ESD and the TGD II. However, although bromadiolone has a potential to bioaccumulation, assessment of secondary poisoning through the aquatic food chain is not performed. The risk assessment indicates that there will be very low concentrations of bromadiolone in the aquatic compartment, and there was no risk identified of bromadiolone for surface water or sediment dwelling organisms. The justification for not performing an assessment of secondary poisoning via the terrestrial food chain is that secondary poisoning will be limited due to the small area that potentially is contaminated by bromadiolone around buildings and the limited number of earthworms inhabiting this area.

8.6.4.1 Primary poisoning

Non-target animals such as wild and domestic animals may come in contact with baits if the bait is incompletely protected or if bait stations have been damaged. Also well protected bait may be encountered by animals which are small enough to be able to reach the bait, and therefore may be subject to primary poisoning.

In the Tier 1 assessment of primary poisoning it is assumed that the whole day's food requirement is satisfied by consumption of mixed baits (granule bait and loose bait are mixed in 70:30 ratio), and therefore the concentration in food will be the same as the concentration of a.s. in the bait, 50 mg/kg. This is then compared to the long-term PNECs for birds and mammals. The resulting PEC/PNEC ratios in table below reveal a high risk for both birds and mammals of long-term primary poisoning.

Table 8.6.4.1-1: Long-term primary poisoning (Tier 1)

Organism group	Species/test	Results	Assessment factors	PEC (conc. in food, mg/kg)	PNEC (conc. in food)	PEC/PNEC
Long-term						
Birds	Japanese quail (*Coturnix coturnix japonica*) reproduction test 42 days	NOEC = 0.039 mg/kg bw/day 0.26 mg/L drinking water	30	50	0.0087 mg/L	5750
Mammals	Rabbit 90 days	NOAEL = 5 10^{-4} mg/kg bw/day	90	50	0.00019 mg/kg (1)	263000

1 calculated using conversion factor from Table 22 in the TGD.

In the Tier 2 acute qualitative risk assessment the daily uptake (ETE) of bromadiolone is compared with the effect data for birds and mammals. The effect value for birds is based on an acute study, rather than a short-term study as required for anticoagulant rodenticides according to the TNsG on data requirements, but since this endpoint value will be used for a qualitative assessment only. To refine the risk assessment the actual dose of bromadiolone consumed by the bird after one day/one meal ETE is calculated using the equation below (equation 19 in the ESD). When calculating the dose both the typical body weight of the animal (BW) and daily mean food intake (FIR) are considered. The calculations are performed in two steps where the avoidance factor (AV), the fraction of the diet obtained from the rodenticide treated are (PT) and the fraction of food type in the animals diet (PD) are all considered in accordance with the ESD. In the worst case calculations performed in the first step avoidance factors, fraction of the diet from treated areas and fraction of food type in diet are all set to the default value of 1. In the realistic worst case calculations, step 2, performed according to the ESD the AV = 0.9, PT = 0.8 and PD = 1. The results are presented in tables 8.6.4.1-2 and 8.6.4.1-3 below.

ETE = (FIR/BW)*C*AV*PT*PD (mg/kg bw*day) Eq. 19

Table 8.6.4.1-2

Non-target animal	Typical bodyweight (g)	Daily mean food intake (g dw/day)	Concentration of bromadiolone in bait (mg/kg)	ETE (mg/kg bw)	
				Step 1	Step 2
Dog	10 000[a]	456[b]	50	2.28	1.64
Pig	80 000 [a]	600 [a]	50	0.38	0.27
Pig, young	25 000 [a]	600 [a]	50	1.20	0.86
Tree sparrow	22 [a]	7.6 [a]	50	17.27	12.44
Chaffinch	21.4 [a]	6.42 [a]	50	15.00	10.8
Wood pigeon	490 [a]	53.1 [a]	50	5.42	3.90
Pheasant	953 [a]	102.7 [a]	50	5.39	3.88

a According to table 3.1 in the ESD
b Calculated from log FIR=0.822 log BW-0.629 according to equation on page 50 ESD

Table 8.6.4.1-3

Non-target animal	PECoral = ETE, concentration of bromadiolone after one meal (mg/kg)		LD50 (mg/kg bw/d)	PECoral higher than LD50 (y/n)	
	Step 1	Step 2		Step 1	Step 2
Dog	2.28	1.64	1.3	y	y
Pig	0.38	0.27	1.3	n	n
Pig, young	1.20	0.86	1.3	n	n
Tree sparrow	17.27	12.44	134	n	n
Chaffinch	15.00	10.8	134	n	n
Wood pigeon	5.42	3.90	134	n	n
Pheasant	5.39	3.88	134	n	n

The ETE values calculated for acute exposure for the worst case (step 1) and realistic worst case (step 2) are compared to the LD50 values in the table. This comparison indicates that birds are not at risk for acute primary poisoning; while the situation for mammals is more uncertain. Dogs are at risk and pigs are very close to being at risk.

The long-term risks of bromadiolone are determined by the expected concentrations (EC) in the animal after metabolism and elimination, which is regarded as PEC. The EC is calculated by using the actual dose of the substance consumed by a non-target animal each day (ETE) using the realistic worst case scenario (step 2), calculated above. When calculating the long-term risks, elimination and metabolism of the substance (El) have to be considered. According to the ESD, a default value of 0.3 for El can be used if no studies are submitted that show different.

Calculations are performed according to equation 20 in the ESD;

EC = ETE*(1-El) Eq. 20

The long-term PNEC values used for mammals and birds are those from rabbit and Japanese quail according to the calculations performed in Doc II-A section 4.2.4.2, and they are presented in the table below.

Table 8.6.4.1-4

Non-target animal	PEC = EC, concentration of bromadiolone after one day of elimination (mg/kg)	PNEC dose (mg/kg bw/day)	PEC/PNEC
Dog	1.15	0.0000056	205000
Pig	0.19	0.0000056	33900
Pig, young	0.60	0.0000056	107000
Tree sparrow	8.71	0.0013	6700
Chaffinch	7.56	0.0013	5800
Wood pigeon	2.73	0.0013	2100
Pheasant	2.72	0.0013	2100

The results of the PEC/PNEC calculations show that there are very high risks for long-term primary poisoning of both mammals and birds. The calculations are based on that bait is consumed only during one day and then eliminated from the animal, but it should also be

considered that an animal might consume bait again before the first dose is eliminated. On the other hand it should been taken into consideration that the actual doses are strictly worst case and that consumption of these quantities of bromadiolone bait by the non-target animals exemplified above are generally not realistic.

8.6.4.2 Secondary poisoning

Secondary poisoning of bromadiolone occurs when poisoned rodents are caught by predators and eaten by scavengers that hunt and forage around bromadiolone treated areas. It has been reported by Shore et al. (1999) that there is an increased hazard of exposure for predators during the winter months which might be caused by that there is less prey available in the winter season. It should also be considered that behaviour of poisoned rodents might change as presented in two reports referred to in the ESD. According to these reports more than half of the rats that died by rodenticide poisoning died away from cover. Moreover, it seemed as the rats changed their behaviour when still alive and were more active during the days than rats normally are and also spent more time unprotected above ground. Such behaviour can make them a more easy prey to predators and they are also more easily found by scavengers. It was found, when water voles were studied during a campaign that 38 % of them died above ground (Saucy et al, 2001, in ESD).

Calculations of the risk for secondary poisoning of scavengers and predators are done by determining the concentration of bromadiolone in their food, i.e. the poisoned rodents. This PECoral is then compared to the LC50 values presented in Doc II-A section 4.2.4.2 for a qualitative risk assessment in accordance with the decision from TM III-06. According to the ESD section 3.3.1 the consumption of rodenticides makes up at least 20 % of total consumptions in a choice test and could in a worst case be up to 100 %, whilst 50 % would be considered the normal situation. Therefore, in the calculations PD values are set to 0.2, 0.5 and 1.0. The FIR/BW quotient is a default value set to 0.1, i.e. it is assumed that the rats eat 10 % of their bodyweight each day. The avoidance factor (AV) is 1, which means no avoidance, since rats is their natural prey, and the fraction of diet (PD) obtained in the area is set to 1. The calculation is done according to equation 19 in the ESD;

ETE = (FIR/BW)*C*AV*PT*PD (mg /kg bw*day) Eq. 19

This equation gives the concentration of bromadiolone in the rat (PECoral) after a meal the first day. Considering the elimination rate and that the mean time to death is seven days the concentration in the rodents each day can be calculated by;

$$EC_n = \sum_{n=1}^{n-1} ETE \cdot (1 - EL)^n$$

Eq. 21

Table 8.6.4.2-1 Residues in target animals at specific point in times and varying bait consumptions

	Residues in target animal (mg/kg bw), with bait consumption in % of daily consumption (PD)		
	20%	50%	100 %
Day 1 after the first meal	1.0	2.5	5.0
Day 2 before new meal	0.7	1.8	3.5

Day 5 after the last meal	2.8	6.9	13.9
Day 7 mean time to death	1.4	3.4	6.8

The concentrations of bromadiolone in rats are at peak after consuming bait for 5 days; thereafter the concentrations in rodents are decreasing until day 7 due to excretion and metabolism of the rodenticide. The values from day 5 are used as PECoral. The effect data used for birds is the LD50 for Japanese quail of 134 mg/kg bw recalculated, using equation 77 in the TGD II and the conversion factor bw/dfi of 8 (domestic hen) from table 22 in the TGD II, which seems in good agreement with the actual food consumption noted in the study. The result is LC50 = 1070 mg/kg food, which seems rather high. The effect data used for mammals is the LD50 for the rat of 1.3 mg/kg bw recalculated, using the conversion factor bw/dfi of 20 from table 22 in the TGD II, resulting in an LC50 = 26 mg/kg food. Such recalculation does not follow the recommendations in the TGD II that data from acute studies where the test substance is administered as a dose should not be recalculated this way, but since the data will be used only in a qualitative assessment and the results will not be used in risk assessment. During the active substance evaluation it has been considered acceptable.

Table 8.6.4.2-2. Calculated PECs and recalculated LC_{50} values for mammals and birds.

	PEC Expected concentration in rodent (mg/kg) caught on day 5 after meal			**LC50 (mg/kg food)**
	PD = 0.2	**PD = 0.5**	**PD = 1**	
Mammals	2.8	6.9	13.9	26
Birds	2.8	6.9	13.9	1070

This qualitative assessment indicates no unacceptable risk for secondary poisoning of birds or mammals.

To assess the risk of long-term secondary poisoning to birds and mammals, the PEC in rodents after 5 days is used and compared to the long-term PNECoral for birds and mammals (Table 2.4.2.2.2-1). For birds, the PNEC value from the reproduction test is used, and for mammals the PNEC value calculated from the 90 day test with rabbits (see Doc II-A. section 4.2.4.2).

Table 8.6.4.2-3

	PNECoral (conc. in food)	**PECoral Bromadiolone conc. in target rodent (mg/kg bw), ESD default values**	**PEC/PNEC**
Birds	0.0087 mg/L	13.9	1600
Mammals	0.00019 mg/kg	13.9	73200

The PEC/PNEC ratios indicate very high risks for long-term secondary poisoning of birds and mammals by consumption of rodenticide poisoned rodents.

For the Tier 2 assessment the average food intake for each species and the average weight of the species have been considered, and the values are taken from table 3.5 in the ESD. The amount of a.i. consumed by the non-target animal is 13.9 mg/kg bw for rodents caught on day 5 and 16.6 mg/kg bw for resistant rodents caught on day 14, also assuming that the non-target animals feed to 50 % on the rodents, all in accordance with the ESD. By knowing the amount of a.i. consumed by the non-target animal and the weight of the animal the PEC

(concentration in non-target animal) after one day consumption of rodents can be calculated. The results are presented below in table 2.4.2.2.3-1.

Table 8.6.4.2-4

Species	Body weight (g)	Daily mean food intake (g/day)	Normal susceptible rodents caught on day 5		Resistant rodents caught on day 14	
			Amount a.i. consumed by non-target animal (mg)	Conc. in non-target Animal (mg/kg)	Amount a.i. consumed by non-target Animal (mg)	Conc. in non-target Animal (mg/kg)
Barn owl *(Tyto alba)*	294	72.9	0.51	1.7	0.61	2.1
Kestrel *(Falco tinnunculus)*	209	78.7	0.55	2.6	0.65	3.1
Little owl *(Athene noctua)*	164	46.4	0.32	2.0	0.39	2.3
Tawny owl *(Strix aluco)*	426	97.1	0.67	1.6	0.81	1.9
Fox *(Vulpes vulpes)*	5700	520.2	3.60	0.6	4.32	0.8
Polecat *(Mustela putorius)*	689	130.9	0.9	1.3	1.09	1.6
Stoat *(Mustela erminea)*	205	55.7	0.40	1.9	0.46	2.3
Weasel *(Mustela nivalis)*	63	24.7	0.17	2.7	0.21	3.3

The results of the PEC/PNEC calculations are presented in the table below. For birds the PNEC (dose) from the reproduction test is used, and for mammals the PNEC (dose) calculated from the 90 day rabbit test, as presented in Doc II-A section 4.2.4.2.

Table 8.6.4.2-5 Expected concentrations (PEC) in non-target animals after a single day of exposure and resulting PEC/PNEC ratios. PNEC values expressed as dose (mg/kg bw/day) are used in the calculations.

Species	PEC day 5 (conc. in food, mg/kg bw)	PNEC (dose, mg/kg bw/day)	PEC/ PNEC (day 5)	PEC day 14 (conc. in food, mg/kg bw)	PNEC (dose, mg/kg bw/day)	PEC/ PNEC (day 14)
Barn owl *(Tyto alba)*	1.7	0.0013	1300	2.1	0.0013	1600
Kestrel *(Falco tinnunculus)*	2.6	0.0013	2000	3.1	0.0013	2400
Little owl *(Athene noctua)*	2.0	0.0013	1500	2.3	0.0013	1800
Tawny owl *(Strix aluco)*	1.6	0.0013	1200	1.9	0.0013	1500
Fox *(Vulpes vulpes)*	0.6	0.0000056	110000	0.8	0.0000056	140000
Polecat *(Mustela putorius)*	1.3	0.0000056	180000	1.6	0.0000056	290000
Stoat *(Mustela erminea)*	1.9	0.0000056	340000	2.3	0.0000056	410000
Weasel *(Mustela nivalis)*	2.7	0.0000056	480000	3.3	0.0000056	590000

The worst case calculations according to the ESD show very high risks for secondary poisoning of bromadiolone to both birds and mammals. The concentrations in the rodents in principle need to be reduced with 3-6 orders of magnitude in order to bring down the risk for non-target animals to acceptable levels.

8.6.4.3 Conclusion

According to the calculations in accordance with the ESD and TGD II, the evaluated product with bromadiolone will cause unacceptable risks both for acute and long-term exposure and both for primary and secondary poisoning. The very high risk quotients indicate that birds and mammals that have rodents as prey or feed on carcasses of rodents are significantly threatened by the use of bromadiolone. These identified risks must be mitigated by applying all appropriate and available risk mitigation measures.

9. Measures to protect man, animals and the environment

9.1 Waste management

Dead rodents must be removed in parallel with the check control to prevent secondary poisoning and minimize public health hazard. The dead rodent carcasses should be collected with protective gloves in plastic bags turned inside out then it should be put in a second bag and knotted to close. The carcass in a double plastic bag should be placed in a closed waste container. Dispose of the packaging, remains of unused product and dead rodents to certified waste disposal operator. Where possible recycling of external uncontaminated packaging

material is preferred to disposal or incineration, otherwise, the remaining waste must be incinerated in a suitable incineration plant holding a permit delivered by the competent authorities or disposed of to a licensed waste disposal site.

9.2 Reducing the risks of primary and secondary poisoning of non-target animals:

1. Campaigns should be coordinated regionally to minimise the time of exposure for non-target animals that roam over large areas.
2. Site inspections should be made regularly whereby bait points should be checked and dead rodents removed.
3. After a campaign remaining bait should be removed.
4. The length of the campaign should be minimised, aiming at an optimal effect on the target rodents
5. Campaigns should be recorded and the time between campaigns should be as long as possible.

9.3 Emergency measures to protect the environment

The product must not penetrate the sewers, surface water, ground water and neighbouring areas. Methods for cleaning up: collect the product with mechanical means, store it in tight containers and dispose according to local legislation.

10.Proposal for decision

10.1 Proposal for decision

Bromadiolone Mixed bait is intended to control rats and mice in domestic, industrial and commercial buildings including in and around farm buildings to protect human food and animal feedstuffs and for general hygiene purposes (pathogen transmission and direct property damage).

As with other anticoagulants, bromadiolone is a vitamin K antagonist. It interferes with the regeneration of prothrombin, disturbing the normal blood clotting mechanism and causing an increased tendency to bleed. After feeding on bait containing the active ingredient for 2-3 days the animal becomes lethargic and slow-moving. Death will usually occur within 4-5 days of ingesting a lethal dose and animals often die out of sight in their nest or burrow.

Studies of second generation anticoagulants like bromadiolone indicate that anticoagulant tolerance in resistant strains is affected by genotype, sex, vitamin K status and age and thus presumably more complex involving more genes than the vitamin K reducing gene. The potency of bromadiolone, a second-generation anticoagulant against commercial rodents is well documented. Efficacy reports are presented for both laboratory and semi-field evaluation of this formulation against *Rattus norvegicus* and *Mus musculus*.

It can be concluded from the test results that the Bromadiolone Mixed Bait is sufficiently attractive to be effective in the control of rats and mice.

Physico-chemical hazard: the product is not considered to be fire hazard. Consideration of the physico-chemical properties of the product does not suggest any explosive, oxidising, flammable and autoflammable potential.

From the human health risk assessment of Bromadiolone Mixed Bait for the purpose of product authorization, the following conclusions could be drawn:

Health risks for the professional and non-professional users of the biocidal products are at an acceptable level if principles of good working practice are applied and use instructions on the label are respected. The accidental ingestion of baits poses a risk to infants. Adequate measures for protection and risk mitigation have to be applied during use.

Necessary issues accounted for in the product label:

S2	Keep out of the reach of children
S13	Keep away from food, drink and animal feedingstuffs
S20/21	When using do not eat, drink or smoke
S24	Avoid contact with skin
S35	This material and its container must be disposed of in a safe way
S46	If swallowed, seek medical advice immediately and show this container or label

10.2 Background to the decision

The active substance bromadiolone has been included in Annex I to the Biocidal Products Directive (BPD) for use in rodenticide products. The authorisation procedure for rodenticide products containing bromadiolone as an active substance is therefore reviewed in accordance with the prerequisites for authorisation according to the BPD. The applicant shall demonstrate with documentation that the biocidal product, when applying the common principles in Annex VI to the BPD, does not have physic-chemical hazard and any direct or indirect unacceptable effects on human or animal health or the environment and that it is effective for the intended use.

Physico-chemical hazard: the product is not considered to be fire hazard. Consideration of the physico-chemical properties of the product does not suggest any explosive, oxidising, flammable and autoflammable potential.

Anticoagulants used as rodenticides are non-selective, highly toxic substances. Second generation anticoagulant rodenticides (SGARs), such as bromadiolone, are also persistent with slow elimination from the body, and prone to accumulate in non-target species that consume poisoned rodents (secondary poisoning). Monitoring studies from several countries, including Sweden and Denmark have shown high levels of second generation anticoagulants, including bromadiolone, in predatory mammals, raptors and owls. The active substance bromadiolone is considered to be a potential PBT.

For these reasons, bromadiolone would normally not have been included in Annex I of the BPD. However, due to the fact that bromadiolone and other second generation anticoagulant rodenticides were considered essential for reasons of public health and hygiene they were nevertheless included in the Annex I of the BPD. The inclusion directive for bromadiolone contains specific provisions that shall be applied by the Member States at product authorisation. One of these specific provisions states that primary as well as secondary exposure of humans, non-target animals and the environment shall be minimized by considering and applying all appropriate and available risk mitigation measures.

Concerning the environmental risks all PEC/PNEC for primary and secondary poisoning are greater than 1. The product Bromadiolone Mixed Bait containing bromadiolone indicates unacceptable risks to non-target animals both for primary and secondary poisoning. Therefore, environmental risks should be considered primarily to non-target animals on the basis of available data for bromadiolone. These identified risks must be mitigated by applying appropriate and available risk mitigation measures. In spite of the environmental risks the benefits of the product preventing the epidemics causing by rodents should be evaluated crucial.

The Hungarian CA's view on second generation anticoagulant rodenticides (SGARs) containing bromadiolone as the active substance for use on the Hungarian market and implementation for the authorisation of Bromadiolone Mixed Bait is presented below.

1. USER CATEGORY

The Hungarian CA determines the following user categories for the product:

→ Non-professional users
→ Professional users

The decision of Hungary to authorise non-professional use was based in particular on the risk of a delay in treatment of household infestations due to the costs involved in hiring trained professionals, and the associated risks to public hygiene. In Hungary there is no well functioning infrastructure for deratisation with some exceptions i.e. Budapest.

It can be stated, that the product fulfils the specific provisions of the inclusion directive for bromadiolone:

→ The nominal concentration of the active substance in the product does not exceed 50 mg/kg and the product is a ready-to-use rodenticide.
→ The product contains an aversive agent (Bitrex®) and a dye.
→ The product is not in the form of and can not be used as tracking powder.
→ There are risk mitigation measures to apply, amongst others, there is an upper limit to the package size for non-professional users. The maximum weight of the packaging for non-professional users is 400 g.

The form of the packaging ensures the safety of the non-professional user. The product is available in bait stations or covered plastic trays only and is wrapped in teapaper bags.
The user guide provides detailed vocational instructions for the safe use of the product (for example safe way of placing the boxes/trays, waste management).

2. FIELD OF USE

The Hungarian CA determines the following fields of use for the product:

→ In and around buildings

The authorisation of this product both for non-professional and professional users only allows for use indoors and around buildings in the following areas:
The area of use „in and around buildings" shall be understood as the building itself and the area around the building that needs to be treated in order to deal with the infestation of the

building. The baits should be placed at strategic points as close to the treated building as possible. According to the emission scenario documents for rodenticides (Larsen, 2003), a rat normally travels an area averaging 30-50 meters in diameter. This suggests that baits must not be placed further away from the treated building than 50 meters when used against rats.
Other outdoor uses, such as landfills cannot be authorised, as the risk for secondary poisoning following such outdoor use are considered to be unacceptable.

3. TARGET ORGANISMS

The product is authorised only for use against house rats (*Rattus norvegicus*) and house mice (*Mus musculus*). Authorisation of this product does not allow use against non-target organisms.

4. BAITING STRATEGY

The Hungarian CA considers the use of tamper-resistant and secured bait boxes, disposable bait boxes, covered trays and other secure coverings as appropriate risk mitigation measures for nearly all conditions of use. Application of the above mentioned policy secures that rodents cannot remove the bait from the box, the risks for accidental exposure to children and non-target animals are expected to be substantially reduced.

APPENDIX 1 Detailed human exposure calculation

Exposure to professional users – in/around buildings for control of rats

Product and intended use	Exposure scenario	PPE	Inhalation uptake Exposure concentration (mg/m^3)	Dermal uptake Exposure concentration (mg/m^2)
'Bromadiolone Mixed Bait (Ratata)' In and around buildings for control of rats	Treating 63 and cleaning-up 16 bait points/day. Handling 19,75 kg product/day (Assume 3 minutes exposure per manipulation)	Gloves	Default values; Assumed in EU guidance to be 10^{-5} mg product/m^3	Default values; Assumed in EU guidance to be 1000 mg wax/day from handling 8 x 200 g baits/day, a total of 40 minutes handling/day.
			Measured values; Not measured. Found to be negligible (less than the LOQ) in pilot surrogate exposure study.	Measured values; Measured as 186 mg product/gloves (= arithmetic mean value) when making 10 manipulations loading bait boxes with Mixed Bait (Ratata)s. Measured as 51.2 mg product/gloves (= arithmetic mean value) when making 10 manipulations cleaning up bait boxes and disposing of unwanted Mixed Bait (Ratata)s.

1. EXPOSURE ASSESSMENT BASED ON DEFAULT VALUES	
Dermal Exposure	
Maximum biocidal product handled/day:	19,75 kg total
Default value for amount of wax dislodged:	1000 mg/1.6 kg handled
Amount of biocidal product dislodged:	1000 x (19,75 ÷ 1.6) = 12343,75 mg
Protective gloves:	Yes
Concentration of bromadiolone:	50 mg/kg
Amount of bromadiolone on gloves:	50 x 12343,75 ÷ 10^6 mg = 0,617 mg/day
Reduction in exposure from gloves:	90%
Amount of bromadiolone on skin:	0,617 x (10%) = 0.0617 mg/day
Dermal absorption of bromadiolone:	0.36%
Systemic exposure of bromadiolone:	0.000222 mg/day
Operator body weight:	60 kg
Systemic exposure:	0.00000370 mg/kg bw/day
Inhalation Exposure	
Systemic exposure of bromadiolone:	0.00001 mg/m^3 x 1.25 m^3/h x (79 x 3 min/d ÷ 60 min/h) x (50 mg ÷ 10^6 mg) = 2.47 x 10^{-9} mg/day
Operator body weight:	60 kg
Systemic exposure:	4.11 x 10^{-11} mg/kg bw/day (negligible)
Total Systemic Exposure (dermal + inhalation):	0.00000270 mg/kg bw/day **0.0037 µg/kg bw/day**
Total Systemic Exposure (without gloves):	0.00002703 mg/kg bw/day **0.0370 µg/kg bw/day**
2. EXPOSURE ASSESSMENT BASED ON MEASURED VALUES	
Dermal Exposure	
Measured value for amount of wax on gloves:	186 mg /10 manipulations during loading 51.2 mg /10 manipulations during disposal
Protective gloves:	Yes
Amount of biocidal product on gloves during loading:	186 x (63 manipulations/10 manipulations) = 1171,8 mg
Amount of biocidal product on gloves during disposal:	51.2 x (16 manipulations /10 manipulations) = 81,92 mg
Total amount of biocidal product on gloves:	1253,7 mg
Concentration of bromadiolone:	50 mg/kg
Amount of bromadiolone on gloves:	50 x 1192,8 ÷ 10^6 mg = 0,0627 mg/day
Reduction in exposure from gloves:	90%
Amount of bromadiolone on skin:	0,0627 x 10% = 0,00627 mg/day
Dermal absorption of bromadiolone:	0.36%
Systemic exposure of bromadiolone:	0.0000226 mg/day
Operator body weight:	60 kg
Systemic exposure:	0.000000376 mg/kg bw/day
Inhalation Exposure	
Systemic exposure of bromadiolone:	< LOQ (negligible)
Total Systemic Exposure (dermal and inhalation):	0.000000376 mg/kg bw/day **0.0004 µg/kg bw/day**

Total Systemic Exposure (without gloves):	0.000003761 mg/kg bw/day	**0.0038 µg/kg bw/day**

Exposure to professional users – in/around buildings for control of mice

Product and intended use	Exposure scenario	PPE	Inhalation uptake Exposure concentration (mg/m^3)	Dermal uptake Exposure concentration (mg/m^2)
'Bromadiolone Mixed Bait (Ratata)' In and around buildings for control of mice	Treating 63 and cleaning-up 16 bait points/day. Handling 15,83 kg product/day (Assume 3 minutes exposure per manipulation)	Gloves	Default values; Assumed in EU guidance to be 10^{-5} mg product/m^3	Default values; Assumed in EU guidance to be 1000 mg wax/day from handling 8 x 200 g baits/day, a total of 40 minutes handling/day.
			Measured values; Not measured. Found to be negligible (less than the LOQ) in pilot surrogate exposure study.	Measured values; Measured as 186 mg product/gloves (= arithmetic mean value) when making 10 manipulations loading bait boxes with Mixed Bait (Ratata)s. Measured as 51.2 mg product/gloves (= arithmetic mean value) when making 10 manipulations cleaning up bait boxes and disposing of unwanted Mixed Bait (Ratata)s.

1. EXPOSURE ASSESSMENT BASED ON DEFAULT VALUES	
Dermal Exposure	
Maximum biocidal product handled/day:	15,8 kg total
Default value for amount of wax dislodged:	1000 mg/1.6 kg handled
Amount of biocidal product dislodged:	1000 x 15,8 ÷ 1.6) = 9875 mg
Protective gloves:	Yes
Concentration of bromadiolone:	50 mg/kg
Amount of bromadiolone on gloves:	50 x 9875÷ 10^6 mg = 0.4938 mg/day
Reduction in exposure from gloves:	90%
Amount of bromadiolone on skin:	0.4938 x (10%) = 0.0494 mg/day
Dermal absorption of bromadiolone:	0.36%
Systemic exposure of bromadiolone:	0.0001778 mg/day
Operator body weight:	60 kg
Systemic exposure:	0.000002963 mg/kg bw/day
Inhalation Exposure	
Systemic exposure of bromadiolone:	0.00001 mg/m^3 x 1.25 m^3/h x (75 x 3 min/d ÷ 60 min/h) x (50 mg ÷ 10^6 mg) = 2.47 x 10^{-9} mg/day
Operator body weight:	60 kg
Systemic exposure:	4.11 x 10^{-11} mg/kg bw/day (negligible)
Total Systemic Exposure (dermal + inhalation):	0.00000296 mg/kg bw/day **0.0030 µg/kg bw/day**
Total Systemic Exposure (without gloves):	0.00002963 mg/kg bw/day **0.0296 µg/kg bw/day**
2. EXPOSURE ASSESSMENT BASED ON MEASURED VALUES	
Dermal Exposure	
Measured value for amount of wax on gloves:	186 mg /10 manipulations during loading 51.2 mg /10 manipulations during disposal
Protective gloves:	Yes
Amount of biocidal product on gloves during loading:	186 x (60 manipulations/10 manipulations) = 1171,8 mg
Amount of biocidal product on gloves during disposal:	51.2 x 15 manipulations = 81,92 mg
Total amount of biocidal product on gloves:	1253,7 mg
Concentration of bromadiolone:	50 mg/kg
Amount of bromadiolone on gloves:	50 x 1192,8 ÷ 10^6 mg = 0,0627 mg/day
Reduction in exposure from gloves:	90%
Amount of bromadiolone on skin:	0,0627 x 10% = 0,00627 mg/day
Dermal absorption of bromadiolone:	0.36%
Systemic exposure of bromadiolone:	0.0000226 mg/day
Operator body weight:	60 kg
Systemic exposure:	0.000000376 mg/kg bw/day
Inhalation Exposure	
Systemic exposure of bromadiolone:	< LOQ (negligible)
Total Systemic Exposure (dermal and inhalation):	0.000000376 mg/kg bw/day **0.0004 µg/kg bw/day**
Total Systemic Exposure (without gloves):	0.000003761 mg/kg bw/day **0.0038 µg/kg bw/day**

Exposure to non-professional users – in/around buildings for control of rats

Product and intended use	Exposure scenario	PPE	Inhalation uptake Exposure concentration (mg/m^3)	Dermal uptake Exposure concentration (mg/m^2)
'Bromadiolone Mixed Bait (Ratata)' In and around buildings for control of rats	Treating and cleaning-up 5 bait points/day. Handling 2 kg product/day (Assume 3 minutes exposure per manipulation)	None	Default values; Assumed in EU guidance to be 10^{-5} mg product/m^3	Default values; Assumed in EU guidance to be 1000 mg wax/day from handling 8 x 200 g baits/day, a total of 40 minutes handling/day.
			Measured values; Not measured. Found to be negligible (less than the LOQ) in pilot surrogate exposure study.	Measured values; Measured as 107 mg product/gloves (= arithmetic mean value) when making 5 manipulations loading bait boxes with Mixed Bait (Ratata)s. Measured as 24.9 mg product/gloves (= arithmetic mean value) when making 5 manipulations cleaning up bait boxes and disposing of unwanted Mixed Bait (Ratata)s.

1. EXPOSURE ASSESSMENT BASED ON DEFAULT VALUES	
Dermal Exposure	
Maximum biocidal product handled/day:	2 kg total (1 kg loading + 1 kg disposal)
Default value for amount of wax dislodged:	1000 mg/1.6 kg handled
Amount of biocidal product dislodged:	1000 x (2 ÷ 1.6) = 1250 mg
Protective gloves:	No
Concentration of bromadiolone:	50 mg/kg
Amount of bromadiolone on gloves:	50 x 625 ÷ 10^6 mg = 0.0625 mg/day
Reduction in exposure from gloves:	0%
Amount of bromadiolone on skin:	0.0625 x (100%) = 0.0625 mg/day
Dermal absorption of bromadiolone:	0.36%
Systemic exposure of bromadiolone:	0.000225 mg/day
Operator body weight:	60 kg
Systemic exposure:	0.00000375 mg/kg bw/day
Inhalation Exposure	
Systemic exposure of bromadiolone:	0.00001 mg/m^3 x 1.25 m^3/h x (10 x 3 min/d ÷ 60 min/h) x (50 mg ÷ 10^6 mg) = 3,12 x 10^{-10} mg/day
Operator body weight:	60 kg
Systemic exposure:	5,2 x 10^{-12} mg/kg bw/day (negligible)
Total Systemic Exposure (dermal + inhalation):	0.00000375 mg/kg bw/day **0.0038 µg/kg bw/day**
2. EXPOSURE ASSESSMENT BASED ON MEASURED VALUES	
Dermal Exposure	
Measured value for amount of wax on gloves:	107 mg /5 manipulations during loading 24.9 mg /5 manipulations during disposal
Protective gloves:	No
Amount of biocidal product on skin during loading:	107 mg
Amount of biocidal product on skin during disposal:	24.9 mg
Total amount of biocidal product on gloves:	131.9 mg
Concentration of bromadiolone:	50 mg/kg
Amount of bromadiolone on skin:	50 x 131.9 ÷ 10^6 mg = 0.00660 mg/day
Dermal absorption of bromadiolone:	0.36%
Systemic exposure of bromadiolone:	0.0000237 mg/day
Operator body weight:	60 kg
Systemic exposure:	0.000000396 mg/kg bw/day
Inhalation Exposure	
Systemic exposure of bromadiolone:	< LOQ (negligible)
Total Systemic Exposure (dermal and inhalation):	0.000000396 mg/kg bw/day **0.0004 µg/kg bw/day**

Exposure to non-professional users – in/around buildings for control of mice

Product and intended use	Exposure scenario	PPE	Inhalation uptake Exposure concentration (mg/m^3)	Dermal uptake Exposure concentration (mg/m^2)
'Bromadiolone Mixed Bait (Ratata)' In and around buildings for control of rats	Treating and cleaning-up 5 bait points/day. Handling 2 kg product/day (Assume 3 minutes exposure per manipulation)	None	Default values; Assumed in EU guidance to be 10^{-5} mg product/m^3	Default values; Assumed in EU guidance to be 1000 mg wax/day from handling 8 x 200 g baits/day, a total of 40 minutes handling/day.
			Measured values; Not measured. Found to be negligible (less than the LOQ) in pilot surrogate exposure study.	Measured values; Measured as 107 mg product/gloves (= arithmetic mean value) when making 5 manipulations loading bait boxes with Mixed Bait (Ratata)s. Measured as 24.9 mg product/gloves (= arithmetic mean value) when making 5 manipulations cleaning up bait boxes and disposing of unwanted Mixed Bait (Ratata)s.

1. EXPOSURE ASSESSMENT BASED ON DEFAULT VALUES	
Dermal Exposure	
Maximum biocidal product handled/day:	2 kg total (1 kg loading + 1 kg disposal)
Default value for amount of wax dislodged:	1000 mg/1.6 kg handled
Amount of biocidal product dislodged:	1000 x (2 ÷ 1.6) = 1250 mg
Protective gloves:	No
Concentration of bromadiolone:	50 mg/kg
Amount of bromadiolone on gloves:	50 x 625 ÷ 10^6 mg = 0.0625 mg/day
Reduction in exposure from gloves:	0%
Amount of bromadiolone on skin:	0.0625 x (100%) = 0.0625 mg/day
Dermal absorption of bromadiolone:	0.36%
Systemic exposure of bromadiolone:	0.000225 mg/day
Operator body weight:	60 kg
Systemic exposure:	0.00000375 mg/kg bw/day
Inhalation Exposure	
Systemic exposure of bromadiolone:	0.00001 mg/m^3 x 1.25 m^3/h x (10 x 3 min/d ÷ 60 min/h) x (50 mg ÷ 10^6 mg) = 3,12 x 10^{-10} mg/day
Operator body weight:	60 kg
Systemic exposure:	5,2 x 10^{-12} mg/kg bw/day (negligible)
Total Systemic Exposure (dermal + inhalation):	0.00000375 mg/kg bw/day **0.0038 µg/kg bw/day**
2. EXPOSURE ASSESSMENT BASED ON MEASURED VALUES	
Dermal Exposure	
Measured value for amount of wax on gloves:	107 mg /5 manipulations during loading 24.9 mg /5 manipulations during disposal
Protective gloves:	No
Amount of biocidal product on skin during loading:	107 mg
Amount of biocidal product on skin during disposal:	24.9 mg
Total amount of biocidal product on gloves:	131.9 mg
Concentration of bromadiolone:	50 mg/kg
Amount of bromadiolone on skin:	50 x 131.9 ÷ 10^6 mg = 0.00660 mg/day
Dermal absorption of bromadiolone:	0.36%
Systemic exposure of bromadiolone:	0.0000237 mg/day
Operator body weight:	60 kg
Systemic exposure:	0.000000396 mg/kg bw/day
Inhalation Exposure	
Systemic exposure of bromadiolone:	< LOQ (negligible)
Total Systemic Exposure (dermal and inhalation):	0.000000396 mg/kg bw/day **0.0004 µg/kg bw/day**

Indirect exposure

Product and intended use	Exposure scenario	Inhalation uptake Exposure concentration (mg/m^3)	Dermal uptake Exposure concentration (mg/m^2)	Oral uptake Exposure concentration (mg/event)
'Bromadiolone Mixed Bait (Ratata)' In and around buildings for control of rats	Non-users (adults, children and infants) will not be present during application. Infants may ingest part of the Mixed Bait (Ratata)	None	Not applicable	Assumed in EU guidance to be equivalent to 10mg wax (infants) for transient mouthing of poison bat treated with repellent
	Non-users (adults, children and infants) will not be present during application. Children may ingest part of the Mixed Bait (Ratata)	None	Not applicable	Poison specialists estimate that a child would consume up to approximately 5 grams in one bite. TNsG on Human Exposure to Biocidal Products (June 2002), User Guidance version 1, page 67.

1. EXPOSURE ASSESSMENT FOR INFANTS BASED ON DEFAULT VALUES	
Oral Exposure	
Default value for amount of product ingested:	10 mg
Concentration of bromadiolone:	50 mg/kg
Amount of bromadiolone ingested:	10 x 50 ÷ 10^6 mg = 0.00050 mg
Oral absorption of bromadiolone	70%
Systemic exposure of bromadiolone:	0.00035 mg/day
Body weight:	10 kg
Systemic exposure:	0.000035 mg/kg bw/day **0.035 µg/kg bw/day**
2. EXPOSURE ASSESSMENT FOR CHILDREAN BASED ON MEASURED VALUES	
Oral Exposure	
Default value for amount of product ingested:	5000 mg
Concentration of bromadiolone:	50 mg/kg
Oral absorption of bromadiolone	70%
Amount of bromadiolone ingested:	5000 x 50 ÷ 10^6 mg = 0.25 mg
Systemic exposure of bromadiolone:	0.175 mg/day
Body weight:	15 kg
Systemic exposure:	0.0117 mg/kg bw/day **11.7 µg/kg bw/day**