Annex V - Comparison of overall risks of anticoagulant active substances for human health, animal health and the environment (Question f)

Contents

1. Introduction

As part of the COM mandate[1], ECHA was requested to examine whether some anticoagulant active substances contained in rodenticide products would have a lower overall risk for human health, animal health and the environment than others (i.e. question (f) of the mandate). The following items were suggested as sources of information:

1) Primary and secondary poisoning data and reports on accidental poisoning;
2) Data on persistence in the environment (bioaccumulation, toxicokinetics data, persistence in target organisms, degradation in the environment);
3) Any other relevant and robust scientific information that could allow to conclude that a substance has a lower overall risk.

To examine these properties, hazard and exposure related information was collected from the following sources:

- Competent authority report (CAR) and Assessment Report of the initial approval
- Renewal Assessment Report (RAR)
- CLH Report and RAC Opinion
- EU Survey on poisoning data and accidental poisoning
- Literature data and monitoring reports

As a first step, toxicological and ecotoxicological endpoint data was gathered from the CAR and RAR documents. Information related to the classification was retrieved from the CLH documents and CLP database. A targeted literature review was conducted to complement the information available in the regulatory assessment documents.

An EU Survey was launched in February 2022 to consult the EU Poison Centres in order to collect information on anticoagulant rodenticides primary and secondary poisoning data and reports on accidental poisoning.

The Technical Guidance Note on Comparative assessment of biocidal products[2] (TGN-CABP) was applied as a guiding document. For instance, the key elements for Tier IA and Tier IB comparison in TGN-CABP were followed to identify the critical hazard properties for examination. In addition, the OECD Guidance on Key Considerations for the Identification and Selection of Safer Chemical Alternative[3] was used as a supportive document for consulting recommended practices and for the reporting of the outcome of the comparison.

Besides the objective to rank the individual anticoagulant rodenticide active substances in terms of their overall risks, an attempt was made to describe the differences of first generation anticoagulant rodenticides (FGARs) and second generation anticoagulant rodenticides (SGARs) at a group level.

The following of anticoagulant rodenticide active substances were covered in the analysis:

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[1] Mandate requesting an ECHA opinion under Article 75(1)(g) of the BPR on questions related to an EU comparative assessment of anticoagulant rodenticides. Ares(2021)3565732-31/05/2021. Available at: https://echa.europa.eu/documents/10162/3443005/mandate_opinion_request_anticoagulant_rodenticides_en.pdf/492f2e46-fcbb-3626-f695-9d1dd9d00dce?t=1636378792843

[2] Technical Guidance Note on comparative assessment of biocidal products (CA-May15-Doc.4.3.a-Final). Available at: https://circabc.europa.eu/w/browse/f39ab8d9-33ff-4051-b163-c938ed9b64c3

[3] OECD (2021), Guidance on Key Considerations for the Identification and Selection of Safer Chemical Alternative, OECD Series on Risk Management, No. 60, Environment, Health and Safety, Environment Directorate, OECD.

Active substance	Type
Chlorophacinone	FGAR
Coumatetralyl	FGAR
Warfarin	FGAR
Brodifacoum	SGAR
Bromadiolone	SGAR
Difenacoum	SGAR
Difethialone	SGAR
Flocoumafen	SGAR

2. Human Health

The Human Health (HH) section is structured as follows:

- Comparison at screening level including:
    - A comparison of the HH harmonized classification of the anticoagulant rodenticides, with focus on:
        - Acute Toxicity
        - Specific Target Organ Toxicity - Repeated exposure (STOT RE)
        - Reproductive Toxicity
    - A comparison based on hazard data from the List of Endpoints of Assessment Reports, with focus on:
        - Reference values
        - Acute Toxicity
        - Pharmacokinetic parameters
        - Repeated Dose Toxicity
        - Reproductive Toxicity – Developmental Toxicity
- Comparison of exposure and risk assessment including the Risk Mitigation Measures for users (trained professionals, professionals, and non-professionals) and for indirect exposure.
- EU Poison Centres data includes information on:
    - Human poisoning cases
    - Animal poisoning cases

2.1 Comparison – screening level

2.1.1 Comparison based on harmonised classification

The human health harmonised classification of the anticoagulant rodenticides is summarised in Tables 1, 2 and 3. Information from the RAC opinions and ECHA's dissemination website was used to compile these tables [1], [2], [3], [4], [5], [6], [7], [8].

Acute toxicity

Table 1 provides an overview of the Acute Toxicity classifications of the substances.

Throughout the human health section of this document, the substances were presented in the tables per alphabetical order within each group (FGARs vs. SGARs).

Table 1. Summary of classification for Acute toxicity

	Chlorophacinone	Coumatetralyl	Warfarin	Brodifacoum	Bromadiolone	Difenacoum	Difethialone	Flocoumafen
Type	FGAR			SGAR				
Acute Toxicity								
Oral	Cat. 1	Cat. 2		Cat. 1				
Dermal	Cat. 1	Cat. 3	Cat. 1					
Inhalation	Cat. 1	Cat. 2	Cat. 1					
Category code								
Oral	H300							
Dermal	H310	H311	H310					
Inhalation	H330							

FGAR: 1st generation anticoagulant rodenticide; SGAR: 2nd generation anticoagulant rodenticide.
H300 Fatal if swallowed; H310 Fatal in contact with skin; H311 Toxic in contact with skin; H330 Fatal if inhaled

All the substances are classified for Acute toxicity. While some differences can be seen in the classification categories per route of exposure, these differences are not significant enough to allow any ranking and/or the assignment in different hazard categories. For example, for acute oral toxicity, all substances are in category 1 or category 2, i.e. fatal if swallowed and triggering the same P-statements.

While coumatetralyl has a somewhat lower classification for acute dermal toxicity (category 3), it is also classified for acute oral toxicity category 2. In order to perform a ranking of hazards, it is more appropriate to consider the acute toxicity potential without considering each route of exposure separately.

In summary, no ranking is possible since the acute toxicity hazard is the same for all substances.

FGAR vs SGAR: All the SGARs are classified Acute Tox 1 (oral, dermal and inhalation). Some differences are seen in the FGARs, some of which are classified in lower categories. However, as all substances are "fatal if swallowed", no categorization/differentiation can be made between FGAR and SGAR based on this hazard.

It should be noted that these substances are designed to kill rodents and the intention of the SGARs was precisely to improve the efficiency of the products by having more potent substances than the FGARs.

See also Table 7 for an overview of the LD_{50}/LC_{50} values of the anticoagulant rodenticides (information from LoEP of RARs).

Specific Target Toxicity - Repeated exposure (STOT RE)

Table 2 provides an overview of the STOT RE classifications of the substances, including Specific Concentration limits (SCLs).

Table 2. Summary of classification for STOT RE

	Chlorophacinone	**Coumatetralyl**	**Warfarin**	**Brodifacoum**	**Bromadiolone**	**Difenacoum**	**Difethialone**	**Flocoumafen**
Type	FGAR			SGAR				
STOT RE								
	Cat. 1							
Category code								
	H372 (blood)							
SCLs								
Cat. 1 H372	C ≥ 0,1%	C ≥ 1%	C ≥ 0,5%	C ≥ 0,02%	C ≥ 0,005%	C ≥ 0,02%		C ≥ 0,05%
Cat. 2 H373	0,01% ≤ C < 0,1%	0,1% ≤ C < 1%	0,05% ≤ C < 0,5%	0,002% ≤ C < 0,02%	0,0005 % ≤ C < 0,005%	0,002% ≤ C < 0,02%		0,005% ≤ C < 0,05%

FGAR: 1st generation anticoagulant rodenticide; SGAR: 2nd generation anticoagulant rodenticide.
STOT RE: Specific Target Toxicity - Repeated Exposure.
H372 (blood) Causes damage to organs (state all organs affected, if known) through prolonged or repeated exposure (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard).
H373 May cause damage to organs (state all organs affected, if known) through prolonged or repeated exposure (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard).

All the substances are classified as STOT RE 1. While differences are seen in the SCLs of the substances, ranking the substances considering only this one hazard endpoint is not considered appropriate as the ranking should be on the overall hazard and not on separate endpoints.

FGAR vs SGAR: As noted above, all the anticoagulant rodenticides are classified as STOT RE 1. While SGARs at group level have lower SCLs than the FGARs, no clear categorization/differentiation can be made between FGARs and SGARs based on this hazard only.

Similar to acute toxicity, the differences in SCLs between the FGARs and SGARs also reflect the intention to have more potent/efficient SGAR biocidal products compared to the FGARs.

Reproductive toxicity

Table 3 provides an overview of the Reproductive Toxicity classifications of the substances, including Specific Concentration limits (SCLs).

Table 3. Summary of classification for Reproductive toxicity

Chlorophacinone	**Coumatetralyl**	**Warfarin**	**Brodifacoum**	**Bromadiolone**	**Difenacoum**	**Difethialone**	**Flocoumafen**
FGAR			SGAR				
Reproductive Toxicity (Repr.)							
1B		1A	1B				
Category code							
H360D							
SCLs							
C ≥ 0,003 %							

FGAR: 1st generation anticoagulant rodenticide; SGAR: 2nd generation anticoagulant rodenticide.
Repr. 1A: Known human reproductive toxicant; Repr. 1B: Presumed human reproductive toxicant.
H360D: Suspected of damaging the unborn child.

Based on the Reproductive Toxicity (Repr.) classification (including SCLs), no differentiation can be made between the different substances since they are all classified Repro. 1A or 1B with the same SCL, meeting the exclusion criteria.

When classifying and setting SCLs for developmental toxicity, a read-across and Weight of Evidence (WoE) approach was followed by RAC. The following extract from the RAC opinion of Bromadiolone [5] demonstrates the approach:

Based on the assumption that all AVK[4] rodenticides, including Warfarin and other anticoagulant coumarin pharmaceuticals (see below) share the same MoA, namely inhibition of vitamin K epoxide reductase (VKOR), the assessment of Bromadiolone includes consideration of the whole database for the AVKs. A weight of evidence assessment by RAC resulted in the conclusion that Bromadiolone has the capacity to adversely affect the human in utero development. Therefore, a classification with Repr. 1B is proposed with the reasoning given below:

- *Bromadiolone shares the same MoA as expressed by other anticoagulant AVK rodenticides and coumarin pharmaceuticals*
- *Warfarin and 2 other coumarin pharmaceuticals (acenocoumarol, phenprocoumon) have been shown to cause developmental toxicity in humans.*
- *One of the 2nd generation AVK rodenticides (Brodifacoum) has been shown to cause foetal effects in humans, possibly after one or a few exposures.*
- *For AVK rodenticides with a long half-life in the body, even single exposures might suffice to trigger developmental effects. However, such studies are normally not conducted and effects of single dose exposure cannot be detected in standard OECD TG 414 test whereas the repeated exposure may lead to maternal mortality with a steep dose-response relationship.*
- *The standard animal studies will not pick up all developmental toxicity effects of the AVK rodenticides, most notably the face and CNS malformations that are characteristic for Warfarin and other AVK coumarin pharmaceuticals.*
- *The most sensitive window for face malformations in humans is the first trimester. Thus, even if some AVK rodenticides may have a lower degree of placental transfer than Warfarin, this will not affect the face malformation hazard.*

Not all steps of the MoA in the target tissues liver and bone have been proven, thus introducing some uncertainty in the assessment. However, the RAC is of the opinion that the uncertainty is not sufficiently big to warrant a Repr. 2 classification.

Reliable evidence of an adverse effect on reproduction in humans, which is required for Repr. 1A, was not available for Bromadiolone, but a potential for human developmental toxicity is presumed based on the above stated weight of evidence assessment, and RAC thus proposes classification as Repr. Cat 1B, i.e. "presumed human reproductive toxicant".

Regarding the SCL setting, RAC noted the following:

As the other AVK rodenticides were equally or more toxic than Warfarin, it is not considered appropriate to apply the generic concentration limit for these substances (0.3%), but rather to base the SCLs on the SCL proposed for Warfarin. Thus, the RAC is of the opinion that the SCL for Warfarin can be used as a surrogate SCL for the other AVK rodenticides, resulting in a SCL of 0.003% for all AVK rodenticides, including Bromadiolone.

[4] AVK: anti-vitamin K

A similar rationale can be found in the RAC opinions for the other anticoagulant rodenticides.

Conclusion based on classification

In summary, all the anticoagulant rodenticides are classified for Acute Toxicity (all routes), STOT RE 1 and as Repro 1A or 1B (thereby meeting the exclusion criteria). Regarding the Acute Toxicity and STOT RE classifications, the differences between the substances are minor.

No ranking is possible between the active substances and no differentiation/categorization can be made between FGARs and SGARs at group level.

2.1.2 Comparison based on hazard data in the List of Endpoints

A comparison of the human health hazard profiles of the AVKs was performed by comparing the List of Endpoints (LoEPs) from the Assessment reports (ARs)/Renewal Assessment reports (RARs).

Reference Values

An overview of the reference values from the Renewal Assessment Reports LoEPs for the different anticoagulant rodenticides is provided in Table 4, Table 5 and Table 6.

The different reference values are provided in the tables. For Brodifacoum, two different values are indicated referring to two applicants (indicated as “A” and “B” in the tables below).

$AEL_{short\text{-}term}$

Table 4. Overview of the $AEL_{short\text{-}term}$ values from the RARs

Active substance	**$AEL_{short\text{-}term}$** (mg/kg bw/day)
Chlorophacinone	3.3×10^{-5}
Coumatetralyl	3.1×10^{-5}
Warfarin	-
Brodifacoum	A. 3.3×10^{-6} B. 6.67×10^{-6}
Bromadiolone	2.3×10^{-6}
Difenacoum	1.1×10^{-6}
Difethialone	1.7×10^{-5}
Flocoumafen	6.7×10^{-6}

- There is a 30-fold difference between the lowest and highest $AEL_{short\text{-}term}$ value (not set for warfarin).
- Within the SGARs, there is a 16-fold difference between the lowest and highest $AEL_{short\text{-}term}$ value.
- Within the FGARs, no significant difference was seen (no $AEL_{short\text{-}term}$ set for warfarin).

$AEL_{medium-term}$

Table 5. Overview of the $AEL_{medium-term}$ values from the RARs

Active substance	**$AEL_{medium-term}$** (mg/kg bw/day)
Chlorophacinone	1.7×10^{-5}
Coumatetralyl	1.7×10^{-5}
Warfarin	2×10^{-4}
Brodifacoum	A. - B. 6.67×10^{-6}
Bromadiolone	1.2×10^{-6}
Difenacoum	1.1×10^{-6}
Difethialone	7×10^{-6}
Flocoumafen	8.3×10^{-6}

- There is a 182-fold difference between the lowest and highest $AEL_{medium-term}$ value. Excluding Warfarin, there is a 16-fold difference between the lowest and highest $AEL_{medium-term}$ value.
- Within the SGARs, there is a 8-fold difference between the lowest and highest $AEL_{medium-term}$ value.
- Within the FGARs, there is a 12-fold difference between the lowest and highest $AEL_{medium-term}$ value.

$AEL_{long-term}$

Table 6. Overview of the $AEL_{long-term}$ values from the RARs

Active substance	**$AEL_{long-term}$** (mg/kg bw/day)
Chlorophacinone	1.7×10^{-5}
Coumatetralyl	-
Warfarin	2×10^{-4}
Brodifacoum	3.3×10^{-6}
Bromadiolone	1.2×10^{-6}
Difenacoum	1.1×10^{-6}
Difethialone	7×10^{-6}
Flocoumafen	8.3×10^{-6}

- There is a 182-fold difference between the lowest and highest $AEL_{long-term}$ value. Excluding Warfarin, there is a 16-fold difference between the lowest and highest $AEL_{long-term}$ value.
- Within the SGARs, there is a 8-fold difference between the lowest and highest $AEL_{long-term}$ value.
- Within the FGARs, there is a 12-fold difference between the lowest and highest $AEL_{long-term}$ value.

ADI and ARfD

Acceptable Daily Intake (ADI) was only derived for Brodifacoum (two values: A. 1 x 10^{-6} mg/kg bw/day; B. 3 x 10^{-6} mg/kg bw/day) and an Acute Reference Dose (ARfD) was only derived for Warfarin (6.7 x 10^{-2} mg/kg bw/day). No comparison is therefore possible for these reference values.

Conclusion based on Reference values

In summary, all anticoagulant rodenticides have very low reference values in the range of 10^{-4} to 10^{-6} mg/kg bw/day.

While some differences were observed between substances, it should be highlighted that the reference values are not directly comparable as the values depend on the way they were derived, including dose-spacing, methodology used in the toxicology studies and the database for each substance. Therefore, comparing the values does not allow concluding on differences in intrinsic toxic properties. Quantitative comparisons/rankings between substances are therefore not scientifically meaningful and could be misleading.

There are no clear differences in the hazard of the substances, as all substances are toxic with very low reference values (in the µg/kg bw range).

FGAR vs SGAR: At group level, no differentiation can be made between FGARs and SGARs when comparing the reference values.

Other Human Health endpoints from LoEP of RARs

From the LoEPs from the ARs/RARs, all anticoagulant rodenticides were considered as:

- Not irritant/corrosive for skin, eye or respiratory tract;
- Not skin sensitizers;
- Not genotoxic;
- Not neurotoxic.

Studies were waived for several endpoints, including respiratory sensitization, chronic repeated dose toxicity, carcinogenicity, (developmental) neurotoxicity, (developmental) immunotoxicity.

In the sections below, further information is provided on some human health endpoints where a possible differentiation between anticoagulant rodenticides could be made.

For example, as noted in the Coumatetralyl RAR (July 2016) [9]:

"Coumatetralyl (as a FGARs) and SGARs have different properties:

- *Acute toxicity profiles - with coumatetralyl having higher acute LD50 in rats and birds compared to SGARs,*
- *Pharmacokinetic parameters - with coumatetralyl displaying shorter hepatic elimination half-life in mice and rats and therefore lower accumulation and quicker elimination when compared to SGARs.*
- *Environmental and Physico-chemistry properties with FGARs showing lower potential of persistence and bioaccumulation when compared to SGARs"*

Acute Toxicity

Table 7 provides the LD_{50}/LC_{50} values from the LoEP of the RARs. The SGARs tend to show lower LD_{50} values than FGARs, mirroring the Acute Toxicity classifications.

A similar observation was noted in the Coumatetralyl RAR (July 2016) – see above extract. Several publications [10], [11] have also discussed the differences in toxicity, especially between FGARs and SGARs.

It should however be highlighted that LD_{50}/LC_{50} values are not directly comparable as such because they are linked to dose-spacing and methodology used in the toxicology studies. Therefore, these values cannot be directly compared in terms on inherent toxicity.

See also the Acute Toxicity classification presented in section 2.1.1.

Table 7. Overview of the LD_{50}/LC_{50} values of the anticoagulant rodenticides (information from LoEP of RARs)

	Chlorophacinone	**Coumatetralyl**	**Warfarin**	**Brodifacoum**	**Bromadiolone**	**Difenacoum**	**Difethialone**	**Flocoumafen**
	FGAR	FGAR	FGAR	SGAR	SGAR	SGAR	SGAR	SGAR
Rat LD_{50} oral in mg/kg bw (lowest)	3.15	15	5.62	A. 0.4 B. <5	C. 1.31 D. 0.56 - 0.84	1.8	0.4-0.8 (Dog: 11.81)	0.13-0.5
Rat LD_{50} dermal in mg/kg bw (lowest)	0.329	258	40	A. 3.16 B. 7.48	D. 1.71 (Rabbit: C. 23.31)	51.54	6.5	0.43-1.14
Rat LC_{50} inhalation in µg/L (lowest)	7.0 µg/L	39 µg/L/4h	< 5 µg/l/4 h	A. 3.05 µg/l B. No data	C. No data D. 0.43 µg/L	E. 3.65 - 5.85 µg/l/4 h, head-only F. 16.27-20.74 µg/l/4 h, nose only	Whole body ≤ 10.7 µg/l/4h Nose only ≥ 5.0 µg/l/4h but <19.3 µg/l/4h	0.6-7 µg/l

A., B. C. and D. in the table refers to different applicants. LoEP: List of Endpoints from Renewal Assessment Reports (RARs).

Pharmacokinetic parameters

The AR of Coumatetralyl reported that coumatetralyl displays shorter hepatic elimination half-life in mice and rats and therefore lower accumulation and quicker elimination when compared to SGARs.

Whenever available, the table from the coumatetralyl RAR was completed with PK information (liver half-life data) for the other anticoagulant rodenticides extracted from the ARs and/or literature data (in grey in Table 8). Pharmacokinetic (PK) and elimination data was also extracted from the ARs of the different anticoagulant rodenticides (see Annex 1: Extracts of PK information from ARs_CONF).

Table 8. Overview of the Pharmacokinetics parameters of the anticoagulant rodenticides (information from AR/RAR)

	Chlorophacinone	**Coumatetralyl**	**Warfarin**	**Brodifacoum**	**Bromadiolone**	**Difenacoum**	**Difethialone**	**Flocoumafen**
	FGAR	FGAR	FGAR	SGAR	SGAR	SGAR	SGAR	SGAR
Half-life LIVER Rat		55 day [17]		> 200 days [18]	318 days [19]	Long T1/2 and binding to the liver [20]	126 days [20]	215 days [21]
Half-life LIVER mouse	35.4 days [12]	15.8 days [12]	66.8 days [12]	307.4 days [12]	28.1 days [12]	61.8 days [12]	28.5 days [12]	93.8 days [12]
Additional information on potential for accumulation and elimination (from LoEP)	The blood half-life for elimination is 10 h. In a study dosing 1-1-4 mg/kg, the results indicate rapid absorption and relatively rapid metabolism in the liver and 100% elimination within four days. However, higher doses (2 mg/kg) showed that at 168 h excretion is incomplete with 8% of dose still present in the carcass.		Evidence of accumulation after repeated dose application (plasma half-lives ca. 40 - 163 h after administration of 2, 5 and 10 mg (study in humans). Most of the urinary excretion was complete within 2 days.					Yes, potential for accumulation

Table adapted from the Overall comparison table from the Coumatetralyl AR (July 2016) [22]. New information in comparison to the information in Coumatetralyl AR is highlighted in grey.

Several publications have also discussed the differences in PK, especially between FGARs and SGARs. For example:

As noted in Vandenbroucke (2008) [12]:

> *"The elimination half-lives in plasma for first-generation rodenticides were shorter than those for second-generation rodenticides.* ***Coumatetralyl, a first-generation product, had a plasma elimination half-life of 0.52 days. Brodifacoum, a second-generation product, showed a plasma elimination half-life of 91.7 days****. The* ***elimination half-lives in liver varied from 15.8 days for coumatetralyl to 307.4 days for brodifacoum****."*

Horak (2017) [10] noted:

> *"The affinity of different anticoagulant compounds for the binding sites, and different biotransformation pathways for isomeric forms or second-generation compounds containing bromine, sulfur or fluorine likely contributes to some notable differences in the toxicity, metabolism and excretion of first versus second-generation compounds and coumarin versus indandione compounds****. In general, second-generation anticoagulant rodenticides are more toxic with hepatic half-lives approximating 100–300 days, in contrast to first-generation compounds with hepatic half-lives in the range of 60 days or less.*** *The indandiones tend to have the shortest hepatic persistence. Excretion of second-generation compounds tends to occur mostly through feces, while first-generation compound excretion is largely in urine."*

As noted as well by Chetot et. al (2020) [13]:

> *"...****the differences in pharmacokinetic properties being at the origin of the classification of ARs into two generations, the second generation including highly efficient in a single dose[5] and highly tissue-persistent active substances*** [14] [15] [10], [16].*"*

And Chetot et al. 2020 [11]:

> *"Warfarin was also used as anticoagulant rodenticide (AR) since the 50's but was rapidly replaced by more potent VKA [18,19] named "super warfarin". Nowadays, the use of VKA is the main method implemented to control rodent populations worldwide. VKA used as AR have all the same mechanism of action and own the same central 4-OH-coumarin core. Nevertheless,* ***their pharmacokinetics properties and their efficiency are different*** *[20,21] and VKA used as AR are classified according to two generations, the* ***first generation molecules (warfarin, chlorophacinone, coumatetralyl…) requiring repeated ingestions to be lethal but being less tissue-persistent than second generation molecules (difenacoum, brodifacoum, flocoumafen, difethialone and bromadiolone), which are toxic after a unique ingestion."***

While this information supports that SGARs have a higher potential for bioaccumulation and slower elimination than FGARs, the half-life values can be impacted by the different methodologies applied in the respective studies, the range of doses used, etc. The values

[5] During commenting, it was noted that difenacoum is not claimed to be a single dose substance and efficacy studies to support such a claim has not been provided.

are therefore not directly comparable.

Repeated dose toxicity

An overview of the NOAEL values reported from the repeated-dose toxicity studies is provided in Table 9. Reviewing the effects and NOAEL values from the acute and sub-chronic repeated dose toxicity studies, the same mode of action is reported for all substances with an effect on blood coagulation with haemorrhage and prolonged blood clotting time. This is reflected in the classification of all anticoagulant rodenticides for Specific Target Organ Toxicity - Repeated Exposure (STOT RE 1) / H372 (blood).

The NOAELs for all substances are low (in the µg/kg bw range). The NOAEL values are not directly comparable between substances because they are linked to the way they were derived, including dose-spacing and methodology used in the toxicology studies. Therefore, these values cannot be directly compared in terms of intrinsic toxic properties.

Table 9. Overview of the NOAEL values from the repeated dose toxicity studies (information from AR/RAR)

	Chlorophacinone	Coumatetralyl	Warfarin	Brodifacoum	Bromadiolone	Difenacoum	Difethialone	Flocoumafen
	FGAR	FGAR	FGAR	SGAR	SGAR	SGAR	SGAR	SGAR
Repeated dose toxicity – short term								
Oral NOAEL in mg/kg bw/day (lowest)	-	-	extrapolation from human clinical use	-	-	-	-	0.0025 (rat)
Dermal NOAEL in mg/kg bw/day (lowest)	-	-	-	-	-	-	-	-
Inhalation NOAEL in µg/l/4h (lowest)	-	-	-	-	-	-	-	-
Repeated dose toxicity – subchronic								
Oral NOAEL (mg/kg bw/day)	0.005 (rat)	0.0068 (rat)	-	A. 0.001 (rat) B. 0.04 (rat)	C. 0.0025 (rat); 0.0005 (rabbit) D. 0.008 (dog)	0.03 (rat)	0.002 (rat) 0.01 (dog)	0.0025 (rat)
Dermal NOAEL (mg/kg bw/day)	0.08 (rabbit)	-	-	-	-	-	-	-
Inhalation NOAEL (µg/l/4h)	-	-	-	-	-	-	-	-
Repeated dose toxicity – chronic/long term								
Oral NOAEL (mg/kg bw/day)	-	-	Extrapolation from human clinical use	-	-	-	-	-

A., B. C. and D. in the table refers to different applicants. LoEP: List of Endpoints from Renewal Assessment Reports.

Reproductive toxicity - Developmental toxicity

An overview of the developmental toxicity data from the LoEP of the substances is provided in Table 10. Some differences are identified in the teratogenicity potential of the different anticoagulant rodenticides.

As mentioned in section 2.1.1, RAC considered a read-across and Weight of Evidence (WoE) approach when classifying the anticoagulant rodenticides for developmental toxicity Repro 1A or 1B.

Interestingly, Chetot et al. [13] noted that not all anticoagulant rodenticides are teratogenic. Using a neonatal exposure protocol, they reported that warfarin (FGAR) evokes skeletal deformities in rats, while bromadiolone (a SGAR) did not cause such effects. It was hypothesized that these differences in teratogenicity could be due to major differences in their fate after oral administration. Using a rat model, the exposure of fetuses or newborns was assessed by measuring the amount of AS found in the liver of the exposed mother (noting that in adults, anticoagulant rodenticides are preferentially located in the liver and are almost absent from other tissues) and compared it to the amount found in newborns/fetuses. Warfarin (FGAR), coumatetralyl (FGAR) and bromadiolone (SGAR) were detected in fetuses and newborns, demonstrating that these substances are able to cross the placental barrier and are excreted in milk. However, the transfer from dam to fetus varied among the substances; i.e. warfarin and coumatetralyl were roughly evenly distributed between the liver of the mother and the fetus while bromadiolone was found almost exclusively in the liver of the mother and in very small quantities in fetus. While the mechanism of action of these anticoagulant rodenticides is identical, the concentration on the site of action, i.e. the fetus, does not consistently reflect the exposure of the mother. While the authors suggest that the read-across approach used by RAC (leading to the classification of all anticoagulant rodenticides for Reproductive Toxicity category 1) could be challenged, they also acknowledge that further data (in particular pharmacokinetic) is needed on the individual substances.

Table 10. Overview of the Developmental toxicity endpoints (from LoEPs of AR/RARs)

	Chlorophacinone	**Coumatetralyl**	**Warfarin**	**Brodifacoum**	**Bromadiolone**	**Difenacoum**	**Difethialone**	**Flocoumafen**
Type	FGAR	FGAR	FGAR	SGAR	SGAR	SGAR	SGAR	SGAR
Reproductive toxicity - Developmental toxicity								
Doses (mg/kg bw/day)	Rabbit: 0; 0.005; 0.01; 0.025; 0.075	Rat: 0; 0.035; 0.07 or 0.14 Rabbit: 0; 0.0125; 0.025 or 0.05	Rat: 0.04; 0.08; 0.16; 0.32	A.Rat: 0.001; 0.01; 0.02 Rabbit: 0.001; 0.002; 0.005 B.Rat: 0; 0.01; 0.02; 0.04 Rabbit: 0; 0.001; 0.002; 0.004	C.Rabbit: 0; 0.002; 0.004; 0.008 D.Rabbit: 0; 0.002; 0.004 or 0.008 Rat: 0; 0.0175; 0.035 or 0.07	E.Rabbit: 0; 0.001; 0.005; 0.015 Rat: 0; 0.01; 0.03; 0.09 F.Rabbit; 0; 0.001; 0.005; 0.015 Rat: 0; 0.01; 0.03; 0.09	Rat: 0; 0.0125; 0.025 or 0.050 Rabbit: 0; 0.0025; 0.005; 0.01 or 0.02	Rabbit: 0; 0.001; 0.002 or 0.004 Rat: 0; 0.01; 0.02 or 0.04
Species/ Developmental target/ critical effect	See note 1 under the table	Rat: bleedings, symptoms of anaemia and mortality in dams Rabbit: internal and external bleedings and mortality in dams	See note 2 under the table	See note 3 under the table	Rabbit, rat	Rabbit: increased clotting time and hemorrhage in dams; **no clear developmental toxicity in fetuses** (some defects or skeletal variations observed without dose-dependence). Rat: Hemorrhages in dams; no effects in fetuses	See note 4 under the table	Rabbits: abortion due to bleeding. **No developmental or teratogenic effects** in animal studies. Classification with H360D based on read-across from warfarin
NOAEL maternal (mg/kg bw/day)	Rabbit: 0.01	Rat: 0.035 Rabbit: 0.0125	N.d.	A. rat: 0.001 B. rabbit: 0.002	C. rabbit: <0.002 D. rabbit: 0.008 Rat: 0.035	Rabbit: 13-day exposure (gestation days 8-20) E. NOEL/NOAEL: 0.005	Rat NOAEL: ≥0.05 Rabbit: 0.005	Rabbit: 0.002 Rat: 0.02

						22-day exposure (gestation days 7-28) F. LOAEL: 0.001 Rat: NOEL/NOAEL: 0.03		
NOAEL developmental (mg/kg bw/day)	Rabbit: 0.025	Rat: Embryotoxicity and/or foetotoxicity: 0.14 Teratogenicity: 0.14 Rabbit: Embryotoxicity and/or foetotoxicity: 0.025 Teratogenicity: 0.05	N.d. Lowest relevant developmental adverse dose levels NOAEL (Rat): 0.04 LOAEL (Human): 0.04 (based on effects seen at 2.5 mg/day).	A. rabbit: ≥0.005 B. rabbit: 0.004	C. rabbit: 0.004 D. rabbit: ≥ 0.008 rat: ≥ 0.07	Rabbit: 13-day exposure (gestation days 8-20) E. NOEL/NOAEL: 0.015 22-day exposure (gestation days 7-28) F. NOEL/NOAEL: 0.01 Rat: NOEL/NOAEL: 0.09	Embryofoetal toxicity (rat) – NOAEL: ≥ 0.05 Embryofoetal toxicity (rabbit) – LOAEL: > 0.01	Rabbit: > 0.004

N.d. Not determined

Note 1. Rabbit: Clinical of toxicity and necropsy pathology demonstrated that mortality was due to internal haemorrhage caused by the anticoagulant properties of the substance. Treatment-related clinical observations were limited to does causing mortality prior to death. There were no treatment-related clinical signs of toxicity at lower doses. At scheduled necropsy, there were no treatment-related findings in surviving pregnant animals. **No developmental effects** were noted at any tested evaluated dose. 100 % mortality was observed at 75 µg/kg bw/day and at 25 µg/kg bw/day, a high mortality (13 of 16) was also observed but no significant effect were detected in the foetus of the surviving does.

Note 2. **Haemorrhagic syndrome in foetuses, structural malformations of the hind limbs, internal hydrocephalus, metabolic damage of foetus livers** (rat, repeated dose of 0.04–8 mg/kg bw); **maxillonasal hypoplasia, calcium deposits in cartilage of the nasal septum and epiphyseal cartilage of vertebrae and long bones** (rat, 100 mg/kg bw subcutaneous injection). Exposure during the first trimester is associated with **FWS** (Fetal warfarin syndrome) and exposure throughout pregnancy or during the second and third trimester is associated with adverse effects on **CNS development** (human, 2.5 to 20 mg/day).

Note 3. A. Rabbit (maternal toxicity): deaths with internal haemorrhages. **No developmental effects**. Rat (maternal toxicity): internal haemorrhages. **No developmental effects**. B. Rabbit (maternal toxicity): increased prothrombin time. **No developmental effects**. Rat **no** significant maternal toxicity or **developmental effect**.

Note 4. Difethialone **did not cause any observed teratogenic effects** in experimental animal studies. Rat: In the absence of effects on dams or foetuses and with no maternal mortality or signs of toxicity, no critical effects were identified at the doses used in the main study (up to 50 µg/kg bw/day). Maternal death resulting from haemorrhages was evident in a preliminary study (dosed at 50 or 70 µg/kg bw/day). Rabbit: No embryofoetal toxicity and **no developmental toxicity indicative of teratogenicity observed**. Maternal toxicity: Haemorrhages, mortality.

2.2 Comparison – Exposure and risk assessment

The exposure assessment of AVK products is safe for users (trained professionals, professionals and non-professionals) with the RMM presented below. Because a risk is expected through indirect exposure, the RMM in place and presented below ensure that products are placed either in bait stations or fixed to a structure where only rats and mice can eat it. In situations where bait boxes cannot be used, such as sewers, the bait is covered so that non-target organisms and infants cannot reach them. When no more bait is eaten and rodent activity stops, the remains of all bait are removed for disposal.

Table 11. Risk Mitigation Measures (RMM) for AVKs as included in BPC opinions and RARs.

	Chlorophacinone	**Coumatetralyl**	**Warfarin**	**Brodifacoum**	**Bromadiolone**	**Difenacoum**	**Difethialone**	**Flocoumafen**
	FGAR	FGAR	FGAR	SGAR	SGAR	SGAR	SGAR	SGAR
	RMM							
Max a.s. concentration	50 mg/kg non-contact formulations 2000 mg/kg in contact formulations	375 mg/kg in non-contact formulations 4000 mg/kg in contact formulations	790 mg/kg	50 mg/kg	50 mg/kg	75 mg/kg	25 mg/kg	50 mg/kg
Contact formulations only used only indoors by trained professionals	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Aversive agent / dye	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes
Only RTU* products	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
tracking powder products	No	No	No	No	No	No	No	No
wear protective gloves / wash hands when removing dead bodies, uneaten bait	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

<table>
<tr><th></th><th>Chlorophacinone</th><th>Coumatetralyl</th><th>Warfarin</th><th>Brodifacoum</th><th>Bromadiolone</th><th>Difenacoum</th><th>Difethialone</th><th>Flocoumafen</th></tr>
<tr><td>Labelling of bait stations</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Method of disposal of dead bodies on label</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Recommendation on frequency for revisiting treated area</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td></td><td colspan="8">RMM for products used by general public</td></tr>
<tr><td>Use only in Tamper-resistant bait stations</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>maximum quantity of bait</td><td colspan="3"><table><tr><th>target species</th><th>bait type</th><th>maximum quantity of bait per pack (g)</th></tr><tr><td rowspan="2">mice only</td><td>grain, pellet or paste</td><td>250</td></tr><tr><td>wax block</td><td>500</td></tr><tr><td rowspan="2">rats only or mice and rats</td><td>grain, pellet or paste</td><td>750</td></tr><tr><td>wax block</td><td>1,500</td></tr></table></td><td colspan="5"><table><tr><th>target species</th><th>bait type</th><th>maximum quantity of bait per pack (g)</th></tr><tr><td rowspan="2">mice only</td><td>grain, pellet or paste</td><td>50</td></tr><tr><td>wax block</td><td>100</td></tr><tr><td rowspan="2">rats only or mice and rats</td><td>grain, pellet or paste</td><td>150</td></tr><tr><td>wax block</td><td>300</td></tr></table></td></tr>
<tr><td>for rats: use indoors and around buildings</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>For mice: use indoors</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Loose bait formulations (grains, pellets) in sachets or similar</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Use in permanent or pulse baiting</td><td>No</td><td>Yes</td><td>No</td><td>No</td><td>No</td><td>No</td><td>No</td><td>No</td></tr>
<tr><td></td><td colspan="8">RMM for professionals</td></tr>
<tr><td>Use in sewage, open areas, waste dumps</td><td>No</td><td>No</td><td>No</td><td>No</td><td>No</td><td>No</td><td>No</td><td>No</td></tr>
</table>

	Chlorophacinone	Coumatetralyl	Warfarin	Brodifacoum	Bromadiolone	Difenacoum	Difethialone	Flocoumafen
Use in permanent or pulse baiting	No	No	No	No	No	No	No	No
Use only in tamper-resistant bait stations	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	RMM for trained professionals							
use in sewage, open area, waste dumps	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
use in covered/ protected bait points only if it is as safe as tamper-resistant bait station	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Use in permanent or pulse baiting	No	No	No	No	No pulse baiting/ Permanent baiting allowed in case of high re-invasion potential	No pulse baiting/ Permanent baiting allowed in case of high re-invasion potential	No permanent baiting/ Pulse baiting allowed	No permanent baiting/ Pulse baiting allowed

*: ready to use.

2.3 EU Poison Centre data

2.3.1 Background

ECHA launched a consultation of EU Poison Centres using the EU Survey tool from February 2022 to April 2022 to collect information on anticoagulant rodenticides primary and secondary poisoning data and reports on accidental poisoning.

A total of 79 contact points were invited to contribute to the EU Survey and 19 contributions were received from the following 16 MSs: PT, IT, HR, FR, SE, IE, FI, NL, DE, NO, EE, ES, HU, BE, MT, LT.

The anticoagulant rodenticides in scope of the EU Survey are depicted in Table 12.

Table 12. Active substances in the scope of this request

Active substance	EC No.	CAS No.
Brodifacoum	259-980-5	56073-10-0
Bromadiolone	249-205-9	28772-56-7
Bromadiolone | Difenacoum	-	-
Chlorophacinone	223-003-0	3691-35-8
Coumatetralyl	227-424-0	5836-29-3
Difenacoum	259-978-4	56073-07-5
Difethialone	600-594-7	104653-34-1
Flocoumafen	421-960-0	90035-08-8
Warfarin	201-377-6	81-81-2

2.3.2 Approach for the analysis

ECHA's full analysis of the data received from the EU Poison Centres, and the detailed individual inputs received from the Poison Centres, can be found in Annex 2: EU Poison Centre data_ECHA Analysis. A summary of the main conclusions from the analysis of this data is provided below.

In summary, several Member States answered that they are collecting primary and secondary poisoning data and/or preparing reports (e.g. annual reports) on accidental poisonings involving any of the anticoagulant rodenticides active substances in scope of the request.

The availability of data and reporting formats varied significantly between the EU Poison Centres. For example:

- Some Poison Centres provided data on anticoagulant rodenticides as a group, while others could also provide data on individual substances;
- Some data sets included substances not in scope of the request;
- Some Poison Centres differentiated intentional from unintentional/accidental poisonings, while this differentiation was not available for the data from other Poison Centres;
- Information on potential co-exposures was sometimes available, while this information was missing in other data sets;
- The case numbers (or calls) were sometimes provided per year, while other Poison Centres provided numbers on a period basis (covering multiple years);
- Some Poison Centres explained that they register calls, which are not per se linked to

real poisoning cases;
- The Dutch poison centre clarified that in the Netherlands the Poisons Center is only available for medical professionals and not for the general public;
- The reporting format (e.g. intentional vs. unintentional; mono-intoxication vs. multi-intoxications) was not always detailed/specific enough;
- The reporting schemes and criteria applied to confirm a poisoning case, and/or to assess the severity of the symptoms observed or outcome, were not always provided or sufficiently detailed;
- Limited information was available regarding the dose intake for the reported poisoning cases;
- Most of the Poison Centres informed that the poisoning cases were not confirmed to be due to a specific anticoagulant rodenticide active substance since the substance was not analysed.

These limitations make the analysis and comparison of the poisoning cases between MSs challenging. Caution should therefore be applied when interpreting the data and drawing conclusions.

Whenever possible, ECHA has attempted to organize the data provided by the Poison Centres in a standardized way, in order to facilitate the comparison between MSs and to identify trends (e.g. by reporting the data in standardized tables). Human and animal poison cases were analysed separately.

In order to answer the question (f) from the mandate, ECHA focused its analysis on:
- data on the individual anticoagulant rodenticide substances in scope;
- unintentional/accidental cases;
- mono-intoxication cases with one anticoagulant rodenticide substance (by avoiding multiple-intoxications/co-exposures) when this information is available.

Information on the number of authorized biocidal products (BPs) containing a specific anticoagulant rodenticide substance in a specific Member State (MS) for the concerned period (for which the poisoning cases were reported) was extracted to put the number of poisoning cases in perspective, although acknowledging that this does not give information about sales volumes (or amounts of BPs used).

2.3.3 Human poisonings

- Most of the human poisonings occurred with the active substance being unknown/not identified.
- When information on the substance was available, most of the human poisoning cases related to SGARs. Poisoning cases were rarely reported with FGAR substances.
- Some variations were seen in the anticoagulant rodenticide active substances involved in most of the human poisoning cases per Member State (MS). **Bromadiolone** and **difenacoum** were most often reported, followed by **brodifacoum** and **difethialone**.
- The highest number of poisoning cases is usually correlated to anticoagulant rodenticide substances having the highest number of BPs authorized during the reporting period in that specific MS. It therefore seems that the number of poisoning cases are linked to the availability of BPs containing a specific anticoagulant rodenticide substance on that market.
- The main route of poisoning was via the oral/ingestion route. Occasionally, the dermal and inhalation exposure routes were mentioned. Other routes (e.g. ocular, subcutaneous, intramuscular, nasal) were rarely reported. Based on available data, there were no differences seen in the route of exposure between

anticoagulant rodenticide substances, or between FGARs vs. SGARs.

- Most of the human poisoning cases were reported as unintentional/accidents. Based on the available data, no differences were seen between AVK substances, or between FGARs vs. SGARs.
- Most of the unintentional human poisoning cases occurred in a younger human population/children (age group <5 years). Most of the intentional cases occurred in the adult population (e.g. age groups 40-60 years).
- The most common place of poisoning is at home (for both intentional and unintentional cases). No differentiation could be made between AVK substances, or between FGARs vs. SGARs, regarding the place of poisoning.
- Most of the reporting indicated that the poisoning cases had no symptoms or symptoms of minor severity.
- FR data indicated that FGARs may lead to more symptomatic cases than SGARs. Other Poison Centres reported an opposite trend where SGARs were associated more frequently with cases of "moderate" severity than FGARs. When looking in more details into the type and severity of the reported symptoms, it is difficult to make clear differentiations between anticoagulant rodenticide substances, or between FGARs and SGARs.
- The reported symptoms affected several functional systems, the most common being coagulation disturbances and bleeding. No clear differences were seen between anticoagulant rodenticide substances.
- It should be noted that the severity of the symptoms may depend on the anticoagulant rodenticide active substance but also to the dose for which only limited (or no) information on the dose was available. In addition, different scoring systems of the severity of symptoms could also impact the reporting of the Poison Centres, thereby complicating the comparison and interpretation of the data.

Based on the available data from the Poison Centres, no clear conclusions could be drawn regarding specific anticoagulant rodenticide substances being consistently linked to more (or less) severe poisoning cases in humans, and/or to conclude that some anticoagulant rodenticide substances would have a significantly better safety profile in humans than others.

2.3.4 Animal poisonings

- Most of the animal poisonings occurred with the active substance being unknown/not identified.
- When information on the substance was available, most of the animal poisoning cases reported related to SGARs. A similar trend was observed for human poisoning cases (section 2.3.3).
- Some variations were seen in the anticoagulant rodenticide active substances involved in most of the animal poisoning cases per MS.
  Brodifacoum, **bromadiolone**, **difenacoum** and **difethialone** were mostly reported as being involved in animal poisoning cases.
- In many cases, the highest number of poisoning cases relate to anticoagulant rodenticide substances having the highest number of BPs authorized during the reporting period in that specific MS. A similar trend was observed for human poisoning cases (section 2.3.3).
- Several animal species may be affected by anticoagulant rodenticide poisonings, with most of the poisoning cases being reported in dog (more than 80% of cases) followed by cats (about 5% of cases). No clear differentiation between anticoagulant rodenticide substances could be seen in the animal species impacted.
- The main route of poisoning was via ingestion and most frequent location of poisoning is at home.

- With the exception of Belgium who reported a higher proportion of severe cases, most of the reporting indicated that the poisoning cases had no symptoms or symptoms of minor severity.
- The more severe poisoning cases seem to occur with SGARs compared to FGARs – but SGARs are also the anticoagulant rodenticide substances involved in the highest number of poisoning cases overall (and with the highest number of authorized BPs).
- No clear differentiation can be done between SGARs when looking at the severity and/or management advice provided at the time of the poisonings.
- France reported that the symptoms observed in animals poisoned were similar between species, with 16.5% of cases being recorded as fatal.
- Using Vitamin K1 for several weeks was considered a successful treatment in animal poisoning cases.

In conclusion, based on the available data provided by the Poison Centres, it is not possible to identify an anticoagulant rodenticide substance that would have a significantly better safety profile than another for the safety of domestic animal species.

3 Environment

The Environment (ENV) section is structured as follows:

- Comparison at screening level including:
  - a comparison of the harmonised classification for environmental hazards
  - a comparison of the PBT/vPvB properties

- Comparison with additional criteria:
  - A comparison of exposure and risk assessment with the aim to identify and compare the most relevant exposure pathways and environmental receptors
  - A comparison based on hazard data from the List of Endpoints available in the regulatory assessment reports:
    - Environmental fate and behaviour
    - Environmental effect properties
  - Overview of information from public literature

Data in the regulatory assessments were compiled from Renewal Assessment Report, Assessment Report (first approval), and Competent Authority Report of each substance:

- Chlorophacinone [23], [24], [25]
- Coumatetralyl [9], [22], [26]
- Warfarin [27], [28], [29]
- Brodifacoum [30], [18], [31], [32]
- Bromadiolone [33], [19], [34], [35]
- Difenacoum [36], [20], [37], [38], [39]
- Difethialone [40], [41], [42]
- Flocoumafen [43], [44], [21]

3.1 Comparison – Screening level

3.1.1 Comparison based on harmonised classification

The harmonised classification for environmental hazards of the anticoagulant rodenticides is summarised in Table 13. Information from the RAC opinions and ECHA's dissemination website was used to compile the information ([1], [2], [3], [4], [5], [6], [7], [8]).

Table 13. Summary of harmonised classification for environmental hazards

	Chlorophacinone	Coumatetralyl	Warfarin	Brodifacoum	Bromadiolone	Difenacoum	Difethialone	Flocoumafen
Type	FGAR	FGAR	FGAR	SGAR	SGAR	SGAR	SGAR	SGAR
Acute	Aquatic Acute1 M = 1	none none	none	Aquatic Acute1 M = 10	Aquatic Acute1 M = 1	Aquatic Acute1 M = 10	Aquatic Acute1 M = 100	Aquatic Acute1 M = 10
Chronic	Aquatic Chronic1 M = 1	Aquatic Chronic1 M = 10	Aquatic Chronic 2	Aquatic Chronic1 M = 10	Aquatic Chronic1 M = 1	Aquatic Chronic1 M = 10	Aquatic Chronic1 M = 100	Aquatic Chronic1 M = 10
Category code	H400 H410	H410	H411	H400 H410	H400 H410	H400 H410	H400 H410	H400 H410

FGAR: first generation anticoagulant rodenticide, SGAR: second generation anticoagulant rodenticide
H400 Very toxic to aquatic life, H410 Very toxic to aquatic life with long lasting effects, H411 Toxic to aquatic life with long lasting effects, H412 Harmful to aquatic life with long lasting effects

Classification of hazards to aquatic environment

All the anticoagulant rodenticides warrant a classification due to their environmental hazard properties. The most hazardous anticoagulant rodenticide based on the aquatic classification is difethialone and the least hazardous is warfarin. Regarding the other anticoagulant rodenticides, the ranking is more equivocal.

Overall, at a group level, SGARs in general warrant a more stringent aquatic hazard classification in comparison to FGARs but the difference is not distinct especially between individual SGAR substances.

It is noted that for the analysis of the overall risks, it is important to complete the comparison with terrestrial hazard information which is not reflected in the harmonised classification based on aquatic toxicity information.

3.1.2 Comparison based on PBT/vPvB properties and POP assessment

Conclusions of the PBT/vPvB assessment and POP assessment are reported in Table 14. The information has been compiled from renewal assessment reports of the active substances ([23] [9] [27] [33] [36] [40] [43] [30]) and AR/CAR documents as relevant.

Table 14. Summary of PBT/vPvB assessment and POP assessment conclusions anticoagulant rodenticides.

	Chlorophacinone	**Coumatetralyl**	**Warfarin**	**Brodifacoum**	**Bromadiolone**	**Difenacoum**	**Difethialone**	**Flocoumafen**
Type	FGAR	FGAR	FGAR	SGAR	SGAR	SGAR	SGAR	SGAR
PBT/vPvB								
P/vP	P	Not P	Not P	P	P	P, vP	P, vP	P, vP
B	Not B	Not B	Not B	B	B	B	B, vB	B, vB
T	T	T	T	T	T	T	T	T
Criteria met	2/3	1/3	1/3	3/3	3/3	3/3	3/3	3/3
Overall	Not PBT	Not PBT	Not PBT	PBT	PBT	PBT (**vP**)	PBT, **vPvB**	PBT, **vPvB**
POP								
LRTP	Not fulfilled	Not fulfilled	Not fulfilled	Not fulfilled	Not fulfilled	Not fulfilled	Not fulfilled	Not fulfilled
Overall	Not POP	Not POP	Not POP	Not POP	Not POP	Not POP	Not POP	Not POP

FGAR: first generation anticoagulant rodenticide, SGAR: second generation anticoagulant rodenticide
P / vP: persistent, very persistent, B / vB : bioaccumulative, very bioaccumulative, T_{ENV} / T_{HH}: toxic environment criteria / toxic human health criteria
POP: persistent organic pollutant, LRTP : long-range transport potential

All the anticoagulant rodenticides are concluded to be not POP substances. Therefore, they are regarded as having similar hazard profiles in that aspect.

Overall, at a group level, the SGARs are all concluded as PBT substances, two of them meeting the vPvB criteria as well. In contrast, the FGARs have been concluded as not PBT/vPvB substances. In the group of FGARs, chlorophacinone was concluded not to meet the B criteria based on a low log Kow value and a calculated BCF_{fish} (no experimental data was available). Regarding coumatetralyl, conclusion on P was based on the rapid degradation in soil (DT50 13.1 and 19.4 days at 12 °C) and the conclusion on B on measured bioconcentration factors from a fish study (BCF 3.3 – 20.8). Warfarin, in contrast to other ARs, is regarded as readily biodegradable. The maximum BCF value for warfarin determined in fish was 21.6. It is noted that in general the relevance of fish BCF studies to ARs has been questioned (eg. difenacoum RAR, see also section 3.2.3 of this document).

3.2 Comparison – Additional criteria

3.2.1 Exposure and risk assessment

A consolidated overview of the environmental risk assessments for air, aquatic and terrestrial compartment is presented in Table 15. The aim is to identify and compare the exposure pathways, which can help to focus the comparison to most relevant receptors. In this high-level comparison, no differentiation is made between the product formulations and use categories (e.g. in and around buildings, open areas etc). When a refinement was performed in the exposure assessment (Tier 1, Tier 2), the higher tier conclusion was considered for this general overview. Since the data used in the comparison is extracted from the assessment reports from the initial approval (2007 – 2009) and from renewal (2016), the compared assessments are not based on the latest version of the ESD PT14 (UBA 2018). Consequently, for instance the bank slope scenario, new primary and secondary poisoning calculations or the currently mandatory groundwater assessment are not considered for this ranking of the active substances.

Exposure to atmosphere has been estimated to be negligible or unlikely for all anticoagulant rodenticides. This is mainly due to the low vapour pressure and Henry's law constant. In addition, potential for rapid photo-oxidative degradation has been a waiving argument for the exposure assessment to air. Furthermore, the type of formulation (paste) and use pattern are expected to reduce exposure to atmosphere. Consequently, the properties related to fate in air are not considered further in the comparison of the overall risks of anticoagulant rodenticides.

In the initial or renewal assessment of anticoagulant rodenticides, the exposure to STP micro-organism and to surface water has been assessed quantitatively (application in sewers[6]) except for flocoumafen (sewer scenario not assessed). Unacceptable risks to STP or surface water have not been identified. Also, risks to sediment compartment have in general been assessed to be low. For chlorophacinone and coumatetralyl no quantitative assessment of sediment was performed since it was assumed to be covered by the surface water scenario. For brodifacoum with a log Kow > 5, the risk characterization for the sediment compartment was covered by the PEC/PNEC ratio for aquatic organisms increased by a factor of 10. Regarding bromadiolone, as a worst case

[6] According to the Revised Emission Scenario Document for Product Type 14 (UBA, 2018) in addition to application in sewers, direct emission of waterways may result from the control of rodents at bank slopes of water courses and surroundings of locks and sluices.

estimate a PEC/PNEC > 1 in sediment was determined while in an alternative scenario the ratio was below 1. The differences were considered to reflect the uncertainties related to the assessment. Similarly, for difethialone a sediment PEC/PNEC value > 1 was identified, but due to the related uncertainties it was expected to be an overestimation and it was concluded that sediment dwelling organisms are not likely to be at risk.

It is noted that the current requirements for the assessment of surface water and sediment compartments are described in the latest version of ESD PT14 (2018). Furthermore, according to ENV WG agreement (ENV WG IV 2016), for all anticoagulants, a quantitative groundwater assessment needs to be performed.

Table 15. Overview of the environmental compartments covered in the exposure assessment and the outcome of the risk assessments of anticoagulant rodenticides. See text for further details. Air, aquatic and terrestrial compartment

Active substance	**Compartment**					
	air	**STP**	**surface water**	**sediment**	**soil**	**ground water**
chlorophacinone	0	(+)	(+)	-	(+) / 0	(+)
coumatetralyl	0	(+)	(+)	-	(+)	(+)
warfarin	0	(+)	(+)	(+)	(+)	0
brodifacoum	0	(+)	(+)	-	(+)	(+)
bromadiolone	0	(+)	(+)	**+**	(+)	**+**
difenacoum	0	(+)	(+)	(+)	(+)	(+)
difethialone	0	(+)	(+)	**+**	(+)	0
flocoumafen	0	-	-	-	(+)	0

Not assessed: -
Negligible exposure based on qualitative assessment: 0
Quantitative assessment, below threshold: (+)
Quantitative assessment, above threshold: **+**, see text for further explanation

Soil has been estimated to be the main receiving environmental compartment, but unacceptable risks have not been identified for soil organisms. For warfarin and for its three toxicologically significant metabolites, soil PEC/PNEC values > 1 were determined with a Tier 1 modelling (no degradation considered) for a hot spot contamination. However, in Tier 2 assessment a safe use was concluded. Therefore, the overall conclusion was that warfarin is not expected to result in relevant exposure of soil organisms.

Groundwater assessment has mainly been performed qualitatively based on the high adsorption and the pattern of use. For some anticoagulant rodenticides, a quantitative assessment was nevertheless performed. For bromadiolone, in a worst-case emission estimation, the trigger value for groundwater was slightly exceeded. However, this was based on assessment without a higher tier estimation for a hot spot contamination. Together with risk mitigation measures it was concluded that exposure to groundwater will not be significant.

Overall, the risks to STP, surface water, sediment, soil and groundwater have been considered to be acceptable based on the PEC/PNEC comparison or by conclusion from a qualitative assessment. Therefore, ranking based on the risk assessment for these compartments is not possible. Environmental fate properties in aquatic and terrestrial compartment are further considered in section 3.2.2 to investigate possible further differentiation between FGARs and SGARs and between the individual anticoagulant rodenticide substances.

The exposure via aquatic food chain and terrestrial food chain has not been assessed consistently between the anticoagulant rodenticides (Table 16), which makes the comparison difficult. The highest risk was indicated for brodifacoum both for aquatic and terrestrial food chain, whilst it is more difficult to indicate which would have the lowest risk.

Similar to the surface water and sediment scenarios, it is noted that the current requirements for the assessment of aquatic and terrestrial food chain are described in the latest version of ESD PT14 (2018).

Table 16. Overview of the risk assessments of anticoagulant rodenticides for aquatic food chain (water – fish – bird/mammal) and terrestrial food chain (soil – earthworm – bird/mammal).

Active substance	**Aquatic food chain**		**Terrestrial food chain**	
	bird	mammal	bird	mammal
chloro-phacinone	-	-	-	-
coumatetralyl	-	-	-	-
warfarin	-	-	-	-
brodifacoum	PEC/PNEC >> 1	PEC/PNEC >> 1	PEC/PNEC >> 1	PEC/PNEC >> 1
bromadiolone	0	0	0	0
difenacoum	PEC/PNEC<1	PEC/PNEC<1	PEC/PNEC >1	PEC/PNEC<1
difethialone	PEC/PNEC >1	PEC/PNEC >1	PEC/PNEC<1	PEC/PNEC<1
flocoumafen	-	-	PEC/PNEC<1	PEC/PNEC >> 1

-: not assessed
0: based on qualitative risk assessment no risk identified/limited exposure
Red: PEC/PNEC >> 1, orange PEC/PNEC >1, Green PEC/PNEC<1

The most critical aspect of the risk assessment has been the well-known risks of anticoagulant rodenticides related to primary poisoning (rodenticide bait → bird or mammal) and secondary poisoning (rodenticide bait → rodent → bird or mammal). Based on the PEC/PNEC comparison in the assessment reports, brodifacoum has the highest estimated risk and the lowest is for warfarin (Table 17.)

Table 17. Overview of the risk assessments (PEC/PNEC, rounded values) of anticoagulant rodenticides for primary and secondary poisoning.

Active substance	**Max. content in product (in %)**	**Primary poisoning**		**Secondary poisoning**	
		bird	mammal	bird	mammal
chlorophacinone	0.005	1200… 1700	1800… 37 000*	8… 15	200… 3000*
coumatetralyl	0.0375	600.. 1900	2700… 270 000	0.9… 12	4… 15 000
warfarin	0.079	10… 1200	30… 61 000	7… 150	60… 6400
brodifacoum	0.005	125 000… 1 600 000	180 000… 1 300 000	20 000… 220 000	15 000… 860 000
bromadiolone	0.005	2100… 23 000	4100… 260 000	700… 4300	3200… 590 000
difenacoum	0.0075	17 000… 500 000	600… 170 000	50… 24 000	800… 12 000
difethialone	0.0025	76 000… 380 000	5700… 130 000	11 000… 33 000	7900… 70 000
flocoumafen	0.005	24 000… 99 000	89 000… 300 000	<3300… <10 000	13 000… 97 000

*ETE/ENEL Red: PEC/PNEC >> 1, orange PEC/PNEC >1, Green PEC/PNEC<1

In general, the estimated primary and secondary poisoning risk of FGARs is lower than of SGARs, especially secondary poisoning to birds. This is well in line with general knowledge and available literature data on anticoagulant rodenticides (section 3.2.4). In the group of SGARs, it is more difficult to make ranking between the individual substances (except the highest risk observed for brodifacoum). It should also be noted that despite the differences in the PEC/PNEC values, for all FGARs and SGARs, a high risk of primary and secondary poisoning is demonstrated.

In the case of SGARs, it is necessary to note that interpretation of the PEC/PNEC comparison is problematic due to the identified PBT/vPvB properties. However, the quantitative assessment can point out the area of exposure where most attention is needed. In addition, the comparison shows that all anticoagulant rodenticides pose unacceptable environmental risk and therefore (at the high level) it is not possible to state that one of the substances would have a significantly better profile. Rather in terms of safety to environment the differences are not relevant since all are concluded to have unacceptable environmental risks. The properties related to primary and secondary poisoning are further compared in section 3.2.3.2.

3.2.2 Environmental fate and behaviour

3.2.2.1 Physico-chemical properties

Differences in the environmental fate and behaviour between the FGAR and SGAR substances are reflected by their physico-chemical properties (Table 18). SGARs have lower water solubility (in the range 0.1 to 18.4 mg/L) in comparison to FGARs (in the range 260 to 460 mg/L). Likewise, the SGAR substances have higher log Kow partition coefficients in comparison to FGARs. This indicates that SGARs have higher lipophilicity and bioaccumulation potential than FGARs. Based on the log Kow minimum values and water solubility, there are indications that in the group of SGARs, bromadiolone has the lowest lipophilicity and potential for bioaccumulation. All of the substances have a low vapour pressure, warfarin having the highest (3.47^{-03} Pa) and difenacoum having the lowest (1.90^{-11} Pa). Therefore, not expected to partition to the atmosphere.

Table 18. Summary of selected physico-chemical properties of the first-generation (FGAR) and second-generation anticoagulant rodenticide substances (SGAR)

	Warfarin	**Chlorophacinone**	**Coumatetralyl**	**Brodifacoum**	**Bromadiolone**	**Difenacoum**	**Difethialone**	**Flocoumafen**
Type	FGAR	FGAR	FGAR	SGAR	SGAR	SGAR	SGAR	SGAR
Water solubility, pH 7 (mg/L)	267	344	460	0.24	2.48 – 18.4	1.7	0.39 (pH 5)	0.114
Vapour pressure (Pa)	3.47E-03 (20°C)	4.76E-04 (22.8°C)	1.00E-03 (20°C)	1.00E-06 (20°C)	2.13E-08 (25°C)	1.90E-11 (25°C)	1.33E-05 (22.6°C)	1.00E-03 (20°C)
Log Kow min	0.6 pH 9, 30-35 °C	1.93 no pH control, 23 °C	-0.1 pH 9, 20 °C	4.58 pH 9, 30 °C	2.5 pH 9-10, 20-25 °C	3.35 pH 9, 25 °C	6.29 pH 7.3, ambient temperature	5.11 pH 9, 20 °C
Log Kow max	2.9 pH 4, 30-35 °C	3.08 pH 4, 23 °C	3.4 pH 5, 20 °C	8.5 calculated	≥ 5 pH 4-5, 20-25 °C	7.22 pH 3.8, 25 °C		>6.12 pH 4, 20 °C

3.2.2.2 Degradation in water and in soil

In terms of degradation in the aquatic compartment, the available data from the assessment reports do not allow to make a ranking between the anticoagulant rodenticide substances. All the anticoagulant rodenticides have been determined to be hydrolytically stable. Furthermore, all of the anticoagulant rodenticides, except warfarin, are not readily biodegradable in the screening level studies. Higher tier studies in water or water/sediment systems are not available. Waiving of the data has been based on the considerations that exposure to the water compartment is limited due to the pattern of use and/or the expected partitioning into sludge.

Information on degradation in soil is available for all anticoagulant rodenticide substances in the assessment reports. The determined DT50 values (at 12 °C) range from 4 d to 833 d (Table 19). The FGARs are the ones with the lowest DT50 values in soil used in the P assessment (19.4 d – 128 d), and SGARs have the highest values (162 d – 833 d).

Table 19. Summary of soil DT50 values of the first-generation (FGAR) and second-generation anticoagulant rodenticide substances (SGAR)

Active substance	DT50 in soil (at 12 °C)
chlorophacinone	128 d
coumatetralyl	19.4 d
warfarin	110.5 d
brodifacoum	298 d
bromadiolone	for the parent DT50 = 4- 53 d but read-across from difenacoum applied, in addition bromadiolone ketone metabolite DT50 = 162 d
difenacoum	833 d
difethialone	635 d
flocoumafen	404 d

3.2.2.3 Distribution / mobility, exposure to groundwater

There is a wide variation in the Koc values from moderately mobile to immobile in soil (FAO soil mobility classification[7] based on Koc) among the anticoagulant rodenticide substances (Table 20). However, none of the anticoagulant rodenticides is classified as “mobile” or “highly mobile”. In general, the risk from the use of anticoagulant rodenticides to groundwater contamination has been assumed to be low or the calculated PECgw values are below the trigger value. In addition to the adsorption behaviour, the type of formulation and pattern of use will reduce or mitigate the risk for groundwater contamination.

It is noted that the anticoagulant rodenticides with the highest potential for mobility (warfarin, coumatetralyl) are not P in soil.

Table 20. Summary of adsorption coefficients (organic content normalised) values of anticoagulant rodenticides.

Active substance	Koc	Mobility class*
chlorophacinone	15 600	Hardly mobile
coumatetralyl	177-258	Moderately mobile

[7] https://www.fao.org/3/X2570E/X2570E06.htm

warfarin	127	Moderately mobile
brodifacoum	9155 – 50 000	Hardly mobile
bromadiolone	14 770	Hardly mobile
difenacoum	1 803 018	Immobile
difethialone	100 000 000 – 5 300 000 000	Immobile
flocoumafen	101 684	Immobile

* Highly mobile (Koc < 10), Mobile (Koc 10-100), Moderately mobile (Koc 100 – 1000), Hardly mobile (Koc 10 000 – 100 000), Immobile (Koc > 100 000)

3.2.3 Effect assessment

3.2.3.1 Toxicity to aquatic organisms, bioaccumulation in aquatic species

Toxicity to fish

All assessments of toxicity to fish rely on Rainbow trout (*Oncorhynchus mykiss*; *Salmo gairdneri*), which is a cold-water species (Table 21). Acute toxicity data is available for all substances, with values spanning approximately 3 orders of magnitude, with the majority of the SGAR values ranging from 0.04 to 0.45 mg/L while the FGAR are generally less (acutely) toxic to fish. It is important to keep in mind that the dose response curves are very steep and thus the focus should not be on the exact value but rather on the range. In addition, there are three substances for which more than one fish acute toxicity test is available (Brodifacoum, Bromadiolone and Difenacoum): these data show up to a 5-fold difference between the two independent tests.

Little data is available for chronic exposure to fish, except for Warfarin and Coumatetralyl. Where data is available, these indicate (specifically for Coumatetralyl) much lower toxic concentrations compared to the acute toxicity tests.

There is very little data available on the BCF of the rodenticides for fish, as due to the high acute toxicity, BCF values are difficult to determine experimentally. As a results, most values are based on in silico estimations based on the (high) LogKow (except Flocoumafen and Coumatetralyl). Based on the high logKow values for all substances, all substances are expected to concentrate into fish.

Table 21. Aquatic toxicity values (mg/L) and bioconcentration factors (L/kg ww) of anticoagulant rodenticides[1]

	Warfarin	Chlorophacinone	Coumatetralyl	Brodifacoum	Bromadiolone	Difenacoum	Difethialone	Flocoumafen
Type	FGAR	FGAR	FGAR	SGAR	SGAR	SGAR	SGAR	SGAR
Fish, acute (LC50; 96 h)	65	0.45	53	0.04 (0.042)	2.86 (8)	0.064 (0.33)	0.051	0.07
Fish, chronic (NOEC; 21 d)	2	No data	0.005	No data	No data	No data	No data	No data
Crustacea, acute (EC50, 48h)	>105	0.64	>14	0.25	2 (5.79)	0.52 (0.91)	0.0044	0.18
Crustacea, chronic (NOEC, 21 d)	0.059	No data	0.1	No data	No data	No data	No data	No data
Algae, reproduction (ErC50, 72 h)	>83.2	2.2	18	0.04	1	0.8	>0.18	>18.2
Bioconcentration								
BCFfish	21.6	22.75	2.851 (3.32[3]) (11.4[3])	35645	339 (460) (575)	1100[3] (9010) (35645)	39974	24300[3]
BCFworm	No data	No data	No data	15820	No data	120639 (477729)	23943	1547 (15820)

[1] In cases where more than one value is reported, the lower of the two values is listed as the main value. The second (higher) value is reported in parentheses.
[2] Due to the high acute toxicity, BCF values are difficult to determine experimentally. As a results, most values are based on in silico estimations based on the (high) LogKow.
[3] Measured data

Toxicity to invertebrates

While anticoagulants are unlikely to affect invertebrates in the same way as fish (and other vertebrates) because of fundamental differences in the blood clotting system, a similar pattern is observed for the toxicity to invertebrates (i.e. *Daphnia magna*) compared to fish.

Very little data is available for longer duration exposure to Daphnia. However, the data for coumatetralyl and in particular warfarin indicate large acute:chronic ratios (>1000).

Toxicity to algae

Both FGARs and SGARs are not very toxic to algae, although similar to fish and Daphnia, the SGARs are more toxic than the FGARs.

3.2.3.2 Toxicity to birds and mammals, primary and secondary poisoning, bioaccumulation in terrestrial species

The data on toxicity to birds is limited to a relatively small number of species (mostly quail and mallard duck, supplemented with occasionally captive wild birds (e.g. various species of hawks and owls). Some authors have suggested that predatory and scavenging birds are more sensitive (especially under environmental conditions and stressors) and as well have a higher likelihood of exposure. Several studies on residual levels of anticoagulants in wildlife species have demonstrated exposure of many non-target species (see e.g [45]), including many species that do not normally eat rats.

Based on the data available in the CARs, FGARs are less toxic to birds than SGARs (Table 24). However, as pointed out by Rattner and Harvey 2021 ([46]), the LD50 values derived from the dietary exposure studies can be misleading. Given the mode of action of the substances, they are more toxic when given at lower doses over several days. In contrast, these relatively short-lived substances are fed by gavage during a relatively short time to achieve a threshold dose and therefore strongly underestimate the toxicity under more realistic exposure scenario conditions.

Overall, while the SGARs are more acutely toxic at lower doses, increasing the potential for primary poisoning also in non-target species, the increased tissue half-lives of the SGARs increase the risk for secondary poisoning. In addition, as poisoned rodents might still remain active, they remain available for capture, especially if in a lethargic state due to the AVK exposure. The higher accumulation and persistence potential of SGARs increases the secondary (or even tertiary) poisoning potential to predators ([47], [48]). However, based on the limited toxicity and especially exposure data available, it is not possible to clearly rank the rodenticides in terms of risk.

Table 22. Summary of data on toxicity to birds for the anticoagulant rodenticides.

	Warfarin	Chlorophacinone	Coumatetralyl	Brodifacoum	Bromadiolone	Difenacoum	Difethialone	Flocoumafen
Type	FGAR	FGAR	FGAR	SGAR	SGAR	SGAR	SGAR	SGAR
Acute toxicity (LD50 (mg/kg bw))								
Bobwhite quail	>2000	257 (Bobwhite quail)	>2000 (Japanese quail)		138 (Bobwhite quail)	56 (Bobwhite quail)	0.264 (Bobwhite quail)	
Mallard duck				0.31 (Mallard duck)				24 (Mallard duck)
Dietary toxicity (LC50 (mg/kg food)	>5000 (Mallard duck)	95 (Bobwhite quail)	1733 (Japanese quail)	0.72 mg ai/kg food (Laughing gull)	62 (Bobwhite quail)	18.9 (Mallard duck), 1.4 (Japanese quail)	0.56 (LC50) (Bobwhite quail)	12 (Mallard duck)
Dietary toxicity (secondary poisoning) (NOAEL, mg/kg food)	17.1 (Tawny owls)				0.056 mg/kg bw/d (great horned owl) (7-day LD100)			
Reproductive toxicity, (NOEC, mg/kg food)	20 (Japanese quail)	1 (Japanese quail)	20	0.0038 (read across from Difenacoum)	0.1 (read across from Difenacoum)	0.1 (Japanese quail)	0.01 (read across from Difenacoum)	0.063 (read across from Difenacoum)

3.2.4 Excerpts from literature

A non-systematic literature search was performed with the aim to complement the available information in the regulatory assessment reports. The literature search was focussed on comparing the hazard properties and environmental risks of anticoagulant rodenticide substances.

Abundant information is available in the literature regarding exposure of non-target wildlife to anticoagulant rodenticides. It is demonstrated that the exposure is wide and many of the anticoagulant rodenticide compounds have been detected in nature (e.g. [49] [49] [50], [51], [45], [52], [53], [54], [55], [56], [57], [58], [59]).

The available information in the literature indicates toward higher prevalence of SGARs in comparison to FGARs ([60], [61], [62], [53], [54], [63]). Among the most frequently detected ARs are **bromadiolone** ([49], [60], [64], [62], [53], [54], [63], [56], [57], [65], [66]), **difenacoum** ([49], [53], [54], [56], [57]) and **brodifacoum** ([49], [60], [53], [54], [63], [56], [57], [58]).

On the contrary, FGARs are detected less frequently and/or at lower concentrations ([49], [60], [53], [63]). Coumatetralyl has been detected for instance in studies conducted in Norway ([56]),) Finland ([64], and Germany ([67]).

However, comparison of the extend of wildlife exposure and the associated risks is complicated by the fact that prevalence is not affected only by the intrinsic properties but also by other factors such as the use volumes, formulation type, area of use and pattern of use ([60], [68], [62], [52], [53], [54], [63], [56], [57], [65], [69], [46], [66]). In addition, there are a number of other factors affecting the exposure and the resulting adverse effect such as inter-species sensitivity, feeding habitats and behavioural features, prey composition, diversity of exposure routes, and seasonal/temporal trends in prey abundance and in the use of anticoagulant rodenticides ([61], [45], [62], [52], [53], [70], [49], [66], [71]). Furthermore, factors related to the monitoring design will have an impact on the comparison of the results, e.g. often only selected species and selected anticoagulant rodenticides are analysed and not all FGAR and SGAR compounds are covered in the analysis.

Another aspect which complicates the interpretation of the monitoring data is that it is not possible in all situations to define if the emissions to the environment are due to a use as intended, or by a misuse of the product against wildlife ([72], [73]). Also, some anticoagulant rodenticides are not only used as biocides but in plant protection products as well ([65], [74]).

Nevertheless, as indicated above, the literature data demonstrate that exposure of wildlife species is taking place. Residues have been analysed for instance in predatory mammals such as mink, bobcat, stoats, weasels, red fox, and polecat, and in small mammals like bank vole, field vole and common shrew. Likewise, exposure has been observed in a number of bird species, especially raptors and scavengers but also in passerine birds. In addition to birds and mammals, invertebrates and reptiles have found to contain residues and may act as vectors of anticoagulant rodenticide exposure ([75], [62], [54], [49], [65], [69], [76], [46], [71], [74]). In spite of the known exposure of wildlife animals, the population level impacts are still largely unclear and the translation of laboratory data into wildlife effects has been challenging ([63], [77], [78], [79], [80], [81], [57], [70], [69]). Decline of local populations of non-target small mammals however has been demonstrated in connection to rodenticidal rat control for instance in a study by Brakes and Smith ([48]). Furthermore, evidence of potential population limiting effects were provided in a study of SGAR impacts to a raptor species ([66]).

Besides the well-known exposure of the terrestrial food chain, it has been suggested that exposure via the aquatic food chain may be relevant as well especially in connection to sewer baiting ([67], [51], [62], [55], [82], [71]). More specifically, the sediment compartment and suspended matter have been estimated to be the more likely exposure pathways in comparison to water phase ([55]). Also in the aquatic systems, exposure to SGARs was found to be more relevant in comparison to FGARs ([62]).

Despite the multiple factors contributing to the detection frequency and level of residues of anticoagulant rodenticides in wildlife, the published literature show that persistence and bioaccumulation potential are key drivers behind the enhanced residue levels of SGARs observed in wildlife in comparison to FGARs. For instance, in a study by Regnery et al. 2020 [82], it was shown that wide-spread exposure to a pharmaceutical anticoagulant active substance (phenprocoumon) resulted, compared to brodifacoum, in low concentration in fish due to its low bioaccumulation potential.
Also, when comparing the anticoagulant substances at a group level, the SGARs are shown to be more persistent and have a higher acute toxicity, which will lead to increased primary and secondary poisoning in comparison to FGARs ([60], [51], [62], [52], [53], [54], [63], [78], [80], [65], [73], [71], [74]). In a comparative study, which covered three FGARs and three SGARs, **brodifacoum** and **difethialone** were concluded to pose the highest risk to birds and mammals, based on primary and secondary poisoning effects ([83], [49], [65]). In other studies, it has not been possible to rank SGARs in relation to their ecotoxicity or their environmental risks ([45], [57], [76], [74]). It has also been noted that a higher volume/concentration of FGAR is required to achieve the same effect level when compared to SGAR baits ([64], [77], [74]). In addition, the development of resistance is a known disadvantage in the use of FGARs.

4 Conclusions

4.1 Risks to human health and animal health

Overall, regarding the outcome of the classification and hazard assessment, the classification and hazard profiles of the substances are similar. No differentiation/ranking between the substances is possible. It is also not possible to conclude that FGARs would be overall less toxic than SGARs. It should be emphasized that the differences in the hazard profile (classification and other toxicity information including AEL values) between the anticoagulant rodenticides are rather minor. All substances are classified for Repro 1A/1B, STOT RE 1 and Acute Toxicity.

Regarding the outcome of the exposure assessment and risk characterisation, the risk is similar and no differentiation between the AVKs is possible. No ranking can be suggested as the exposure is safe for the users (trained professionals, professionals and non-professionals) and the risk from indirect exposure is managed with appropriate RMMs put in place for all AVK products.

4.2 Environmental risks

Overall, based on the available data in the regulatory assessment reports and information in the literature, the environmental profile of SGARs is worse in comparison to FGARs. The observed differences in the environmental profile are mainly related to the PBT properties of the anticoagulant rodenticide active substances. It was considered that a definitive ranking of the individual substances is not possible since there are too many uncertainties in the available data for the comparison of the substances such as quality of the input values in the different exposure assessments and completeness of the data packages. The outcome of the risk assessment used in the comparison reflects the uses assessed under first approval and/or renewal, while the exposure assessment of current and future applications should be performed according to the latest exposure scenario document (ESD PT 14).

While at group level, it may be clearer that FGARs are less hazardous than SGARs, it is more difficult to state that one specific anticoagulant rodenticide substance would have a significantly better hazard profile than another with regards to environmental properties. Warfarin however, may be considered having the least hazardous profile in comparison to other anticoagulant rodenticide active substances. Warfarin is practically not detected in biota, it has a better profile with regards to primary poisoning of birds and mammals in comparison to other FGAR/SGAR, and it is the only anticoagulant rodenticide which is readily biodegradable. In addition, warfarin is the only anticoagulant rodenticides with a classification of Aquatic Chronic 2, whilst other FGAR and SGAR warrant Aquatic Chronic 1.

4.3 Overall conclusions

Regarding the overall risk for human health, no ranking is possible between individual substances. Similarly, it is not possible to conclude that FGARs would be overall less toxic than SGARs.

Regarding overall risk for the environment, at group level, it can be concluded that FGARs are less hazardous than SGARs. However, it is more difficult to state that one specific anticoagulant rodenticide substance would have a significantly better[8] (or worse) hazard profile than another with regards to environmental properties.

[8] Significantly better profile for human health, animal health or for the environment: in line with the definition in TGN-CABP, this means that for one of these elements, the observed differences between the compared substances are not marginal but relevant in terms of biological significance for the safety to humans, animals or the environment

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Annexes

Annex 1 – Extracts of pharmacokinetic information from the ARs of the anticoagulant rodenticides (confidential).

Annex 2 - EU Poison Centre data - ECHA Analysis.