The UK Rodenticide Resistance Action Group: Response to ECHA public consultation on cholecalciferol

SUMMARY

Cholecalciferol is a pro-hormone and fulfils the exclusion criteria on the basis of having endocrine disrupting properties as defined in Regulation (EU) No 2017/2100) (although the Commission has explicitly not exempted an intended biocidal mode of action via the endocrine system of vertebrates from the criteria (see point (3) of section B of the Annex to Regulation (EU) No 2017/2100) [see pg. 11, ECHA/BPC/180/2017 – Cholecalciferol]).

It is the view of UK RRAG that approving the active substance cholecalciferol would provide the UK pest control industry with a highly valuable tool for the control of house mice and Norway rats, particularly in areas where the prevalence of anticoagulant resistance is high.

In respect of the Article 5 derogation conditions to the exclusion criteria, and in consideration of the information provided in the body of this document:

> *(a) the risk to humans, animals or the environment from exposure to the active substance in a biocidal product, under realistic worst case conditions of use, is negligible, in particular where the product is used in closed systems or under other conditions which aim at excluding contact with humans and release into the environment;*

This condition is not met.

> *(b) it is shown by evidence that the active substance is essential to prevent or control a serious danger to human health, animal health or the environment;*

Given the widespread nature of resistance to the anticoagulants in rats and mice in the UK (Prescott et al., 2017), cholecalciferol, and biocidal products based on it, would be highly valuable to protect human health and animal health against the serious dangers presented by the severe diseases commonly transmitted by rodent pests. Presently, no other alternatives to the anticoagulants are sufficiently safe and efficacious (ECHA, 2017 a). Therefore the unique characteristics and benefits of products containing cholecalciferol (see ECHA, 2017b) would be welcomed by those involved in the management of rodent pests in the UK.

> *(c) not approving the active substance would have a disproportionate negative impact on society when compared with the risk to human health, animal health or the environment arising from the use of the substance.*

The risks caused to human and animal health by rodents are described by the European Commission as follows: "*Rodents can carry pathogens that are responsible for many zoonoses, which can pose*

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serious dangers for human or animal health" (European Commission, 2017). The diseases commonly carried by rodents are further described by (Battersby, 2015). Therefore, there can be no doubt that rodent pests have significant potential to cause severe negative impacts on society if they are not adequately controlled. Currently, in the UK, the anticoagulants are used almost exclusively as chemical interventions in rodent pest management. Resistance to some anticoagulant active substances is widespread and growing in severity and scope (Prescott et al., 2017). Therefore, an alternative mode of action to the anticoagulants is particularly necessary, such as that offered by cholecalciferol. ECHA provides risk characterisation information (ECHA, 2017b) on cholecalciferol and none of the risks characterised thereby appears to be unacceptable provided available, and already commonly applied, risk mitigation measures are adopted by users. Hence, it is evident that this derogation condition is met, namely that not approving cholecalciferol may have a disproportionate negative impact on society when compared to the risks of biocidal products based on this active substance to human health, animal health and the environment arising from their use.

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1. Current position of cholecalciferol and the requirement for a public consultation

According to the ECHA opinion on cholecalciferol (ECHA 2017b) and the exclusion criteria set in Article 5(1)(d) of Regulation (EU) No 528/2012 on the basis of the criteria defined in Regulation (EU) No 2017/2100, the overall conclusion of the BPC is that cholecalciferol should normally not be approved unless one of the conditions for derogation set out in Article 5(2) of Regulation (EU) No 528/2012 is met, viz.:

> Article 5 - Exclusion criteria
>
> *2. Without prejudice to Article 4(1), active substances referred to in paragraph 1 of this Article may be approved if it is shown that at least one of the following conditions is met:*
>
> > *(a) the risk to humans, animals or the environment from exposure to the active substance in a biocidal product, under realistic worst case conditions of use, is negligible, in particular where the product is used in closed systems or under other conditions which aim at excluding contact with humans and release into the environment;*
> >
> > *(b) it is shown by evidence that the active substance is essential to prevent or control a serious danger to human health, animal health or the environment; or*
> >
> > *(c) not approving the active substance would have a disproportionate negative impact on society when compared with the risk to human health, animal health or the environment arising from the use of the substance.*

This document provides a response from the UK Rodenticide Resistance Action Group (RRAG) to the request by ECHA for consultation on the active substance cholecalciferol in respect of these derogation conditions.

2. Alternative PT 14 biocidal active substances

Biocidal products to be considered as eligible alternatives are any biocidal products authorised in accordance with Article 17 of the BPR for some of the intended uses or biocidal products authorised in accordance with Articles 3 or 4 of Directive 98/8/EC8 (the Biocidal Products Directive, later the Biocidal Products Regulation, 2009/0076 (COD)).

As per 16 November 2016, according to the information available in the R4BP database, there are six active substance types for PT14 with a mode of action different from that of cholecalciferol (Table 1).

Table 1. Approved active substances for PT14 with a different mode of action than cholecalciferol.

Active substance	Mode of action
Anticoagulants	The mode of action of both first and second generation anticoagulants is to block the vitamin K cycle and prevent the activation of the four vitamin K dependent blood clotting factors (Factors II, VII, IX and X). Once endogenous levels of the active form of one of these blood clotting factors is depleted, coagulation is compromised and lethal haemorrhage can occur. The haemorrhage can occur at any location in the body, and as a result, time to death can vary, typically from 3 days to 12 day after consumption of a lethal dose.

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Alpha chloralose	The mode of action of alphachloralose is based on sedation, central nervous system depression, narcosis, inducing death by hypothermia. Alphachloralose is most effective at temperature below 16ºC, against small animals with rapid metabolism (e.g. mice). Increase in temperature may reduce killing efficiency.
Aluminium phosphide releasing phosphine	The active ingredient aluminium phosphide reacts with moisture in soil and air and releases the toxic gas, phosphine. Phosphine induces oxidative stress in mammalian cells and administration of high doses causes methaemoglobinemia in the rodent.
Carbon dioxide	The biocidal action of carbon dioxide is primarily due to it causing respiratory acidosis following oxygen displacement in target animals. CO2 is released in the closed chamber where rodents are trapped. Carbon dioxide levels build up in the blood causing staggering, panting, coma and ultimately death.
Hydrogen cyanide	The substance functions as a respiratory poison, killing pests by damaging their metabolism. It is absorbed mainly through airways, digestive tract, unbroken skin and mucous membranes. The mitochondrial cytochromoxidase enzyme is effectively inhibited by the cyanide ion resulting in fatal failure of cellular respiration.
Powdered corn cob	The substance when consumed by rodents, rapidly causes a state of dehydration. This leads to significant perturbation of normal physiological feedback pathways because dehydration is accompanied not by an increase in water intake but rather by a reduction in it. Dehydration results in hypovolemia (i.e. reduced blood volume), reduced blood pressure, tissue ischemia (oxygen deprivation), and circulatory shock leading to death.

Products based on these active substances have only been authorised for eight anticoagulants (warfarin, chlorophacinone, coumatetralyl, bromadiolone, difenacoum, brodifacoum, flocoumafen and difethialone) and the individual substances alphachloralose (aluminium phosphide releasing phosphine), and carbon dioxide. These, therefore, constitute the only eligible alternatives to be considered and, of these, three have serious drawbacks or other restrictions:

- Alphachloralose is used as a bait formulation that can only be used against house mice
- Carbon dioxide is used as a lethal gas that can only be used against house mice that are contained in a closed chamber
- Aluminium phosphide (releasing phosphine gas) is used as a fumigant that is restricted for use against Norway rats that are located some distance away from human or animal habitation.

Therefore, presently, chemical interventions for general rodent pest management in the UK, particularly against rats, are restricted to the anticoagulants.

3. Rodent Control in the UK and wider EU – the role of anticoagulants

Efficacious rodent control across the EU is largely dependent upon the anticoagulant rodenticide bait formulations that are widely used against Norway rats, house mice and Black rats (Berny et al., 2014).

A disadvantage with the anticoagulant active substances is the potential occurrence of resistance. Current evidence indicates that resistance in both rats and mice to the first generation anticoagulants and two of the second generation anticoagulants (bromadiolone and difenacoum)

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can be of sufficient magnitude to result in treatment failures (i.e. Practical Resistance) (Berny et al., 2014).

In contrast, the minor reductions in the toxicity of the remaining three second generation anticoagulants (brodifacoum, flocoumafen and difethialone), to some strains of resistant rats and mice are insufficient to have a practical impact on treatment outcome (i.e. Technical Resistance). Therefore, presently, there are anticoagulant rodenticides available to all user groups in the UK (though not elsewhere in the EU) that will allow all resistance strains of rats and mice to be adequately controlled (Rodenticide Resistance Action Group 2011, 2012; RRAC, 2016).

However, with anticoagulants there are also concerns about the persistent binding of a small fraction of active ingredient in specific binding sites that are primarily located in the liver (see for example Smith and Shore, 2015); and about the classification of anticoagulant rodenticides with active ingredient content of at least 0.003% as "toxic to reproduction" (European Commission, 2016).

4. Cholecalciferol – Mode of Action

Cholecalciferol, or Vitamin D3, is the naturally occurring form of the D Vitamin that is essential for the healthy development of mammals. It is produced by UV irradiation of 7-dehydroxycholesterol, a sterol present in animal fats including the oily secretions from mammalian skin and from the preen gland of birds (Prescott et al. 1992). Vitamin D is essential for the formation of normal bone, but in overdose promotes intestinal absorption of calcium plus reabsorption of bone materials, which can lead to hypercalcaemia, ostomalacia and metastatic calcification of the blood vessels (Meehan, 1984). The rodenticidal properties of the calciferols result from these symptoms, and are thought to cause death primarily by the calcification of blood vessels, particularly around the heart.

5. Cholecalciferol – Efficacy and Uses in the UK

Information from independent studies in the public domain on the effectiveness of cholecalciferol is rare from sources in Europe because an alternative (and similar) active substance, ergocalciferol vitamin D2, was previously used as a rodenticide. However, to the knowledge of members of RRAG, the two substances do not differ appreciably in their mode of action, efficacy and other characteristics (Buckle and Eason, 2015). Therefore, for the purposes of this consultation response the two substances are considered to be equivalent.

The acute oral LD_{50} of cholecalciferol against Norway rats and house mice is reported to be 30-50mg/kg and that of ergocalciferol is similar (20-60 mg/kg) (Buckle and Eason, 2015).

Early laboratory and field trials of calciferol (presumably ergocalciferol) against rats and mice in the UK were mainly conducted with mixtures of calciferol and an anticoagulant. Therefore, it is difficult to separate the effectiveness of the two active substances in these studies However, Greaves et al. (1974) concluded from laboratory testing that the minimum concentration likely to give good results in the field was 0.1%, either alone or in mixture with warfarin. These authors suggested that care would be required in field applications because feeding on baits is limited to little more than two days before illness curtails feeding.

Mixtures of 0.1% calciferol and 0.025% warfarin were successful (97-100% estimated mortality) in the field against house mouse provided a highly palatable bait base (whole canary seed) was used

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(Rowe et al., 1974). Trials using pinhead oatmeal as the bait base were less successful (29-92% mortality).

Calciferol alone and the same mixture of 0.1% calciferol and 0.025% warfarin were used in field trials against Norway rats in an oatmeal bait by Rennison (1974). It was concluded that calciferol is an effective poison against Norway rats, either alone or mixed with warfarin, but that in some environments there was a case for employing pre-baiting to ensure that rats feed freely from the beginning of treatment.

Bait shyness was studied in laboratory tests against Norway rats, and mortality was reported between 5 and 8 days after initial presentation of cholecalciferol rodenticide bait; with a marked reduction in food consumption between 24 and 48 hours after initial exposure, and evidence of bait shyness in animals that recovered from sub lethal dosing (Prescott et al., 1992).

Three field trials against Norway rats of 0.1% ergocalciferol in whole wheat bait were conducted by Brunton et al. (1993) in the area of the UK that we now know to contain rats having the L120Q resistance mutation. A seven-day pre-treatment bait census also served as a pre-bait. Estimates of mortality of 43, 49 and 80% mortality respectively were made using census baiting. Radio-tracking confirmed the activity of surviving rats in very close proximity to bait stations.

In a fully monitored field trial against an extensive population of Norway rats, 48.5kg of 0.1% ergocalciferol bait was consumed over the course of the trial, with 74% of bait consumed over the first two days of the treatment, thus providing supporting evidence of the impact of calciferol bait on food consumption. (Quy et al., 1995). With a three week period of pre-baiting, the calciferol treatment achieved an estimated 69% reduction in the rat population. In addition, there was mortality of numerous small passerine primary non-target species. This was most likely the result of a prolonged pre-baiting period, and the use of a particulate bait formulation that was similar to that used in the pre-baiting period.

Prior to the removal of ergocalciferol from the UK market in 2006, products based on this active substance, mainly in mixture with an anticoagulant, were used for the control of house mice and were generally considered to be highly effective and useful against anticoagulant-resistant rodents. When used against house mice, pre-baiting was not recommended. However, when used against Norway rats (see above) pre-baiting was normally advocated.

The nature of the finished formulation is of great importance in the efficacy of rodenticide active substances. The members of the RRAG have no available information on the nature of the formulations that may be employed with the use of cholecalciferol in the UK. The Commission provides only the following information on efficacy and use: "*Sufficient efficacy data were provided for Rattus norvegicus and house mouse (Mus musculus). Insufficient data were provided for Rattus rattus. Effectiveness was shown for two representative products containing 0.075% cholecalciferol*."

6. Cholecalciferol – Risks to human health and the environment

The members of the RRAG have limited experience in the field of human health and environmental risk assessment and therefore rely on information provided by ECHA (2017b). Environmental risks are assessed in the following table.

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Table 2. Summary table: environmental risk scenarios. From ECHA (2017b).

Scenario	**Description of scenario including environmental compartments**	**Conclusion**
Soil organisms	Exposure (PEC) of soil organisms (consumers, producers, decomposers) compared with PNECsoil	Acceptable
Acute primary poisoning, birds	Bird eats bait	Acceptable
Acute primary poisoning, mammals	Mammal eats bait	Not acceptable
Acute secondary poisoning, birds	Bird eats poisoned rodent	Acceptable
Acute secondary poisoning, mammals	Mammal eats poisoned rodent	Not acceptable
Long-term primary poisoning: birds	Diet consisting largely of rodent baits or poisoned rodents	Not acceptable
Long-term primary poisoning: mammals	Diet consisting largely of rodent baits or poisoned rodents	Not acceptable
Long-term secondary poisoning via poisoned rodents – barn owl	Diet consisting largely of poisoned rodents	Not acceptable
Long-term secondary poisoning via poisoned rodents – weasel	Diet consisting largely of poisoned rodents	Not acceptable
Secondary poisoning via earthworms – birds	Bird eats earthworms which live in contaminated soil	Acceptable

The environmental risks listed above deemed not acceptable are those commonly found with rodenticides which, by their very nature, must be potent toxins of mammals and other closely allied taxonomic groups. These risks are generally managed by a wide range of risk mitigation measures already well-known and widely applied by rodent pest control practitioners, such as the use of tamper-resistant bait boxes, inclusion of a human taste deterrent, careful choice of the positions of bait stations, limited duration of periods of poisoned baiting, checking for and the removal of poisoned rodents and regular checks of bait station for signs of the presence of non-target organisms (Buckle and Prescott, 2017). Long-term risks of secondary poisoning cannot be so managed however.

The human health risks of cholecalciferol were summarised by ECHA (2017b) as follows:" *The intended use of the products leads to acceptable risks for human health as long as relevant risk mitigation measures are followed*." Therefore, once again, commonly applied risk mitigation measures will be appropriate.

Risk assessment is a challenging subject and outside the scope of the RRAG. Comparative risk assessment between two active substances, or groups of active substances, is even more complex and no attempt is made here to compare relative risks, for example, of cholecalciferol and the anticoagulants.

7. Conclusions

The consensus view of RRAG, based on the information presented in this paper, is as follows:

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1. Cholecalciferol rodenticides provide a valuable alternative mode of action to that of the anticoagulants that can be used as an important tool for anticoagulant resistance management.
2. According to ECHA (2017b), cholecalciferol is not carcinogenic, mutagenic, toxic for reproduction, persistent or bio-accumulative. (Although insufficient data are apparently available to make definitive assessments on some of these toxicological characteristics.) However, cholecalciferol is a pro-hormone and fulfils the exclusion criteria on the basis of having endocrine disrupting properties as defined in Regulation (EU) No 2017/2100) although the Commission has explicitly not exempted an intended biocidal mode of action via the endocrine system of vertebrates from the criteria (see point (3) of section B of the Annex to Regulation (EU) No 2017/2100) [see pg 11, ECHA/BPC/180/2017 – Cholecalciferol].
3. According to the published research on calciferols (though note that much of this research was done on ergocalciferol and with formulations no longer available), the combination of neophobia and the stop-feed effect may make it difficult to achieve complete control against Norway rats, particularly for larger infestations.
4. Because of neophobia, products based on cholecalciferol may be less likely to be fully efficacious against Norway rats than against house mice.
5. There is some evidence that non-target species are at risk, particularly where prolonged pre-baiting is deployed, and where the bait formulation is palatable to the non-target species, although these risks may be managed sufficiently using commonly-applied risk mitigation measures so that use will not engender unacceptable risks.
6. In the light of the above, cholecalciferol should not be considered as a substitute for AVKs, but rather as a valuable alternative method of rodent control that can be employed as a useful resistance management tool.

UK Rodenticide Resistance Action Group

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The UK Rodenticide Resistance Action Committee

The UK Rodenticide Resistance Action Group (RRAG) is a voluntary body comprising invited members. General information on the UK Resistance Action Groups may be found here: https://cereals.ahdb.org.uk/crop-management/stewardship/resistance-action-groups.aspx. RRAG members possess expertise in matters relating to the resistance of rodents to rodenticides that are the most commonly-used chemical interventions for rodent pest management. Members offer advice and guidance to UK practitioners about ways to prevent the spread of rodenticide resistance and, where it is established, about managing resistant infestations. This advice is provided independent of any affiliation to an organisation or commercial entity. More information on RRAG and the advice it provides is found here: https://bpca.org.uk/about/partners/rrag.

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[1] No claim in made that this reference list is exhaustive on this subject. It is restricted mainly to research published in peer-review journals and conducted by independent scientists in UK academic and governmental institutions.

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