Exponent is an international consultancy with offices located in
UK, Germany, Switzerland, USA and China (including Hong Kong SAR).

CENTRE FOR CHEMICAL REGULATION AND FOOD SAFETY (EUROPE)
The Lenz, Hornbeam Park,
Harrogate. HG2 8RE UK
T: (+44) 1423 853200
F: (+44) 1423 810431
E: biocides@exponent.com

CHOLECALCIFEROL (VITAMIN D_3)
PUBLIC CONSULTATION IN ACCORDANCE WITH ARTICLE 5(2) OF THE BIOCIDAL PRODUCTS REGULATION (528/2012)

APPLICANT COMMENTS

QAID: 2303384.UK0 - 5409

APPLICANT: BASF/ENVU CHOLECALCIFEROL TASK FORCE

BASF Agro B.V.
Arnhem (NL) - Freienbach Branch
Huobstrasse 3
8808 Pfäffikon SZ
Switzerland

2022 Environmental Science FR S.A.S.
Lyon Vaise Business Center,
3 Place Giovanni DaVerrazzano
Lyon 69009, France

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1. Background

The active substance cholecalciferol (EC 200-673-2, CAS 67-97-0) was previously evaluated by the Swedish Competent Authority and approved under the BPR as a rodenticide (PT 14). Cholecalciferol received approval according to Commission Implementing Regulation EU/2019/637 on 23rd April 2019[1]. The date of inclusion was 1st July 2019 and the expiry date is 30th June 2024. The application for renewal of the active substance was submitted to the Swedish CA in December 2022. No other product types are approved or supported. Annex VI of the CLP regulation was recently revised (EU/2018/1480).

The initial approval of cholecalciferol concluded[2]:

i. it fulfils the exclusion criteria in Article 5(1)(d) of Regulation (EU) No 528/2012 on the basis of having endocrine disrupting properties as defined in Regulation (EU) No 2017/2100 ; and
ii. there is a concern with respect to the occurrence of primary and secondary poisoning, even when applying restrictive risk management measures, cholecalciferol fulfils criterion (e) of Article 10 of Regulation (EU) No 528/2012.

The first approval was made on the basis of a derogation under Article 5(2)(c)[3] and the applicant considers that the same derogation is appropriate for the first renewal.

The active substance cholecalciferol fulfils the exclusion criteria in Article 5(1)(d) of Regulation (EU) No 528/2012 on the basis of having endocrine disrupting properties as defined in Regulation (EU) No 2017/2100. Furthermore, as there is a concern with respect to the occurrence of primary and secondary poisoning, even when applying restrictive risk management measures, cholecalciferol fulfils criterion (e) of Article 10 of Regulation (EU) No 528/2012.

[1] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2019.109.01.0013.01.ENG
[2] Biocidal Products Committee Opinion on the application for approval of the active substance: Cholecalciferol, Product type: 14, ECHA/BPC/180/2017
[3] 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.

2. Introduction

This position paper reviews the available information to clearly demonstrate that cholecalciferol, which is an important alternative to existing rodent control solutions, meets the conditions for derogation according to Article 5(2) points b and c.

Article 5(2) states:

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;
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

3. Biocidal Products Committee Opinions

The Biocidal Products Committee (BPC) on a request according to Article 75(1)(g) of Regulation (EU) No 528/2012 on Questions relating to the comparative assessment of anticoagulant rodenticides ECHA/BPC/386/2023 was recently published[4] and is supportive of the renewal of cholecalciferol. The opinion considered:

a) Is the chemical diversity of the active substances in authorised rodenticides in the EU adequate to minimise the occurrence of resistance in the target harmful organisms?

b) For the different intended uses specified in the applications for renewal, are alternative authorised biocidal products or non-chemical means of control and prevention methods available?

c) Are these non-chemical alternatives sufficiently effective? In particular, ECHA should conclude based on the information collected via a targeted consultation whether there is sufficient scientific evidence from field trials to prove that rodent traps are effective to control rodent populations in accordance with the criteria established in agreed
d) Do the alternative authorised biocidal products or non-chemical alternatives present no other significant economic or practical disadvantages?

e) Do the alternative authorised biocidal products or non-chemical alternatives present a significantly lower overall risk for human health, animal health and the environment?

f) ECHA should also examine whether some anticoagulant active substances contained in rodenticides would have a lower overall risk for human health, animal health and the environment than others. The following information should be used to address this question:

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

The answers to these questions (a-e) are relevant not only to anticoagulant rodenticides, but also to cholecalciferol-containing rodenticides. The following table summarises the conclusions of ECHA/BPC/386/2023.

[4] https://echa.europa.eu/documents/10162/2166576/art_75_1_g_anticoagulant_rodenticides_final_bpc_opinion_en.zip

Summary of ECHA/BPC/386/2023 in relation to Cholecalciferol

<table>
<tr><th colspan="2">Question</th><th colspan="2">Conclusion</th></tr>
<tr><td>a</td><td>Chemical diversity</td><td colspan="2">The Opinion showed that the minimum requirement of three different alternatives is reached for use #4, use #7 (only for the mice; not for the brown rat and the black or roof rat) and use #11. For the remaining uses this evaluation shows an inadequate chemical diversity to minimize the occurrence of resistance in the target harmful organisms.</td></tr>
<tr><td>b</td><td>Identifying eligible chemical alternatives</td><td colspan="2">Eligible chemical alternatives are alphachloralose, carbon dioxide and cholecalciferol for use #4, #7 (only house mice) and #11 as only for these uses the criterion of three different and independent “active substances/mode of action” combinations is met.</td></tr>
<tr><td>c</td><td>Are non-chemical alternatives sufficiently effective</td><td colspan="2">The opinion concluded that only for mouse control inside buildings non-chemical (trapping) control methods were effective.</td></tr>
<tr><td rowspan="2">d</td><td rowspan="2">Economic or practical disadvantages of eligible chemical alternatives</td><td>Disadvantages</td><td>Advantages</td></tr>
<tr><td>Products containing cholecalciferol can only be used by professional and trained professional users. However, this is not considered a disadvantage of these products when comparing them with other products used in anticoagulant rodenticides uses #4 (professional users) and #7 (trained professional users).

There is no antidote which is for example mentioned for observed cases of accidental poisoning of pets.

It is concluded that cholecalciferol poses no significant economic or practical disadvantages for uses #4, #7 and #11.</td><td>Rodents have no known resistance to cholecalciferol; resistance to cholecalciferol is also highly unlikely to develop in the future.

Fast acting: rodents that have consumed a lethal dose of the biocidal product will stop feeding within 1-2 days after ingestion and will die within 2-5 days after uptake of a lethal dose (including those strains resistant to anticoagulants). This seems to have the consequent advantage of less bait needed and lower number of inspection visits needed.

No restrictions on use were identified in relation to temperature.</td></tr>
<tr><td>e</td><td>Risk considerations of eligible chemical alternatives</td><td colspan="2">Overall, cholecalciferol has a more favourable toxicological profile and is considered of significantly lower toxicological hazard compared to the anticoagulant rodenticides. Cholecalciferol could have a better hazard profile in comparison with SGARs, and similar or better profile compared to FGARs.</td></tr>
</table>

4. APPLICABILITY FOR DEROGATION ACCORDING TO ARTICLE 5(2)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

Rodenticide resistance and the need for cholecalciferol as an alternative

Because chemical control of rodents relies almost exclusively on the use of ARs (also known as anticoagulant rodenticides), many distinct resistant strains of Norway rat (*Rattus norvegicus*) and house mouse (*Mus musculus*) have been characterised[5]. Resistant strains have been identified in most Western European countries. Resistance to this chemical class is likely to increase further if only these compounds are available for use against rodents. Chemical alternatives to ARsare limited. No new active substance has been developed since the late 1980s for the control of rodent infestations.

There are two main reasons, which substantiate the authorisation of cholecalciferol-based baits: Spreading resistance to anticoagulant rodenticides, and the much-reduced environmental hazards of cholecalciferol compared to the most potent second generation anticoagulant rodenticides (SGARs). These compounds tend to build long lasting residues, in particular in the liver, exceeding half-life times of six months. In consequence, they pose a considerable hazard of secondary poisoning.

At high doses cholecalciferol (Vitamin D_3) acts as a rodenticide by causing mobilisation of calcium from the bone matrix to plasma and death from hypercalcemia and therefore its mode of action is different to that of use of anticoagulant rodenticides (ARs). An important driver behind the development and support of cholecalciferol as a rodenticidal active substance under the BPR, was the need to make available innovative rodenticide products that offer an effective alternative to existing ARs.

The systematic use of anticoagulant rodenticides of the group of hydroxy-coumarins has resulted in the selection of resistant rats and mice against the chemical class. Cholecalciferol has no known resistance, acts as a resistance breaker due to its mode of action being different to that of AVKs and is not a PBT compound. Therefore, its approval is necessary to ensure the effective control of rodent infestations, safeguarding human and animal health, particularly in regions where the use of SGARs is restricted. Coupled with the wealth of evidence available on anticoagulant resistance and the known requirement of chemical control of rodents (with adequate chemical diversity) it is clearly demonstrated here the need for cholecalciferol as a rodenticide.

BPC Opinion ECHA/BPC/386/2023 'Questions regarding the comparative assessment of anticoagulant rodenticides (June 2023).' Trapping can be effective for small infestations but is time-consuming and rodents can become trap-shy. Ultrasound, repellents and attractants are of limited utility, because rodents readily become habituated. Some interesting areas of research, including pheromones and fertility control (likely to be classified as reprotoxic), are under investigation, but are unlikely to become commercially available in the near future. As stated in the Commission Report 'Risk Mitigation Measures for Anticoagulant Rodenticides as Biocidal Products' (October 2014), "*Resistance in rodent populations should be managed by ensuring that only effective ARs* [anticoagulant rodenticides] *are used to control population rodents*."

Cholecalciferol has a different mode of action than AVKs and is therefore a very powerful tool for resistance management; indeed, resistance to cholecalciferol has not been observed in non-EU countries where cholecalciferol has been on the market for several decades. Resistance is also not expected because any species developing a mutation to endogenous vitamin D_3 would experience a sharp decrease of vitamin D_3 levels and its active metabolites (25-OH-calciferol and 1, 25–$(OH)_2$-calciferol) which, in turn, would be not viable, as vitamin D_3 is essential. Cholecalciferol is therefore an important tool in integrated pest management (IPM) and in resistance management, acting as a resistance breaker.

The current status in Europe of resistant strains of Norway rats and house mice to AVKs is clearly illustrated by the current 'live' RRAC Resistance data maps – the current status in UK, Germany, France and Denmark (1-4) is presented in Appendix 1.

[5] McGee, C. F., McGilloway, D. A. & Buckle, A. P. Anticoagulant rodenticides and resistance development in rodent pest species - a comprehensive review. J Stored Prod Res 88, (2020).

Resistance in Norway Rats

There have been more than fifty years of continuous research into anticoagulant resistance in the UK, both in Norway rats and house mice. The UK is home to more anticoagulant resistance mutations in Norway rats than any other country world-wide, with five having practical impacts (5). Changes in DNA sequences of the *VKORC1* gene (single nucleotide polymorphism or SNPs) have the potential to confer anticoagulant resistance on individuals that possess them. For example, L128Q in Norway rats, indicates that at location 128 of the VKORC1 protein, the wildtype amino acid, leucine (abbreviated as L) has been replaced by the amino acid glutamine (abbreviated as Q). Nine genetic mutations in regions of the genome known to be important for the action of anticoagulants have been identified in UK Norway rats. Three (L120Q, Y139C, Y139F) confer resistance to the first-generations anticoagulants (FGARs) and at least one of the SGARs.

The research by Prescott *et al*. (5) shows the great extent of L120Q resistance in Norway rats, the most severe form of resistance in this species, across the whole of central southern England. The ubiquity of Y139F resistance among rats in Kent and East Sussex is also apparent. Of further concern are isolated records of these mutations, far from their core areas, suggesting either transportation of resistant rodents or the development of new foci. The scarcity of wild-type (i.e., fully susceptible) Norway rats, particularly in central-southern and south-east England, suggests that it is reasonable to assume that almost any rodent infestation in those areas will contain rats carrying one or other of the severe L120Q or Y139F mutations.

For Norway rats elsewhere in Europe, there is an indication that in France a similar number of mutations is present (6). A total of nine different anticoagulant resistance mutations (single nucleotide polymorphisms, SNPs, or haplotypes) are found among Norway rats in France (7). From a survey conducted in 2010 (6), among the 268 Norway rat tissue samples collected from across France, 37.3% possessed one or more aberrations of the genetic material in areas associated with anticoagulant resistance. Samples were received from a total of 37 French Départements and known resistant SNPs were found in 23 (62.2%) of Départements for which samples were obtained (7).

In Germany, only one or two resistance mutations have been identified to date (8), however there is a concentration of resistant Norway rats in North-West Germany (2).

In Denmark, in the first three decades after resistance was first found in 1962, resistance was reported in 48 municipalities. By 2008, resistance to bromadiolone and difenacoum was evident in 92 municipalities. Since 2014 genetic resistance testing has been conducted on 118 rats sampled from sites with possible control problems and also from areas where resistance was not expected. In total 57 sampling locations were tested for presence of the Y139C mutation. In 33 of these locations, Y139C resistant rats were identified (9).

In addition to these well characterised resistance mutations, it has recently been demonstrated in Norway rats that resistance can also be caused by increased metabolism of anticoagulant rodenticides(10). Here, a strain of Norway rat notorious for extreme resistance, known as the Berkshire strain (which even exhibit technical resistance to the very potent SGAR, brodifacoum[6], was examined to determine the mechanisms supporting this resistance. The authors showed that Berkshire rats display an accelerated detoxification of difenacoum through elevated cytochrome P 450 (CYP450) oxidative metabolism. This is a crucial development in the understanding of resistance, which goes beyond the genetic selection of resistant strains with *vkorc1* mutations. With this new information, resistance strategies should now also consider the development of metabolic resistance, further stressing the need for alternatives to the AVKs and the importance of cholecalciferol for the alternation of active substances when controlling infestations.

Resistance in the house mouse

The house mouse (*Mus musculus*) is known to possess a degree of natural tolerance to anticoagulant rodenticides and as a result, anticoagulants are generally less effective against house mice than they are against Norway rats. True resistance to anticoagulants, conferred by genetic mutation, has been known among house mice in the UK since the 1960s. Resistance is now widespread (5). Both mostly distributed mutations found in house mice (L128S, Y139C) confer resistance to FGARs and to at least one SGAR (bromadiolone).

[6] Gill, J. E., G. M. Kerins, et al. (1992). Inheritance of low grade brodifacoum resistance in the Norway rat. Journal of Wildlife Management 56(4): 809-816.

In house mice elsewhere in Europe, both L128S and Y139C mutations have also been recorded, particularly in Germany and France, and there is a third VKORC1 sequence variant (A12T, A26S, A48T and A61L) that is also associated with a substantial loss of efficacy against anticoagulants (8). This strain evolved from the adaptive introgression of *vkorc1* genome from *Mus spretus* into the genome of *Mus musculus* probably in South Spain, where both species are endemic. This strongly resistant strain was first described in Germany[7] and was confirmed in other countries recently. In 2011 in Germany, a study of the distribution of resistance in house mice was conducted using DNA sequencing for the detection of anticoagulant resistant mutations (11). It revealed that resistant house mice are very widespread and frequent in Germany. More than 90% of the mice examined carried genetic resistance mutations and resistance was found at 29 of the 30 locations sampled (7). More recently, hybrid resistant strains of mice developed, and a strongly reduced susceptibility of the VKOR enzyme to second generation SGARs was confirmed in-vitro[8]. These strains, such as hybridizations of *spretus-vkorc1* and L128S and Y139C haplotypes, have been detected recently in France, Spain, and Germany (see resistance maps at www.rrac.info).

Cholecalciferol has a different mode of action than AVKs and is therefore a very powerful tool for resistance management; indeed resistance to cholecalciferol has not been observed in non-EU countries where cholecalciferol has been on the market for several decades. Resistance is also not expected because any species developing a mutation to endogenous vitamin D_3 would experience a sharp decrease of vitamin D_3 levels which, in turn, would be not viable, as vitamin D_3 is essential. Cholecalciferol is therefore an important tool in integrated pest management (IPM) and in resistance management, acting as a resistance breaker.

Consequences of rodent populations not adequately controlled

Unchecked, a single rat can produce more than 14,000 pups and descendants in a single year, assuming fertility at 9 weeks and giving birth to 11-pup litters every 11 weeks (12).

Unchecked, a single mouse can produce around 65376 pups and descendants in a single year, assuming fertility at 40-45 days (13) and giving birth to 12 litters per year, each containing an average of 6 pups.

Resistance leads to larger populations, which leads to increased exposure to rodents, with consequential negative health impacts, property and infra-structure damage and food spoilage, all with economic consequences (see section 4 socio-economic analysis and Appendix 1).

Conclusion

The problem of increasing occurrence of anticoagulant rodenticide resistant Norway rats and house mice in Europe has been clearly demonstrated. Thus increased exposure to rodents can be expected, with consequential negative health impacts, property and infra-structure damage and food spoilage, all with economic consequences. Additionally, further spread of resistance would result in an extended use of high potent PBT SGARs.

[7] Song, Y. *et al.* Adaptive introgression of anticoagulant rodent poison resistance by hybridization between old world mice. *Current Biology* **21**, (2011).

[8] Goulois, J., Lambert, V., Legros, L., Benoit, E. & Lattard, V. Adaptative evolution of the Vkorc1 gene in Mus musculus domesticus is influenced by the selective pressure of anticoagulant rodenticides. Ecol Evol 7, (2017).

5. APPLICABILITY FOR DEROGATION ACCORDING TO ARTICLE 5(2)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

Cholecalciferol is the only current effective non-AVK alternative to existing rodent control solutions: The Commission approval decision for cholecalciferol[9] and recent BPC opinion on comparative assessment both acknowledge a role for cholecalciferol. Whereas clauses 10-13 of EU/2019/637 state

(10) Rodents can carry pathogens that are responsible for many zoonoses, which can pose serious dangers for human or animal health. Anticoagulant active substances, which are the main active substances used in rodenticides for now, also meet the exclusion criteria laid down in Article 5(1) of Regulation (EU) No 528/2012 as they are classified as toxic for reproduction category 1B and most of them are persistent, bio-accumulative and toxic (PBT) or very persistent and very bio-accumulative (vPvB) substances. Other alternative active substances currently approved for product-type 14 and not subject to exclusion, namely carbon dioxide, alphachloralose, aluminium phosphide, hydrogen cyanide and powdered corn cob, have constraints inherent in their nature and restricted conditions of use. Non-chemical control or prevention methods for rodents, such as mechanical, electrical or glue traps, may not be sufficiently efficient and may raise further questions as to whether they are humane and whether they cause unnecessary suffering to rodents.

(11) The approval of cholecalciferol would bring an additional active substance on the market and would be useful to manage the increasing development of resistance of rodents to anticoagulant active substances, as cholecalciferol acts in a completely different way compared to the anticoagulants. The availability of cholecalciferol may also reduce the use of anticoagulant active substances and in particular of the most potent second-generation thereof. Thus, cholecalciferol can play a role in the future to ensure satisfactory control of rodent populations within an integrated pest management approach, in support of the above-mentioned alternatives not subject to the exclusion criteria, and possibly reducing the recourse to anticoagulant active substances in rodenticides.

(12) Furthermore, insufficient rodent control may cause not only significant negative impacts on human or animal health or the environment, but also affect the public's perception of its safety with regard to exposure to rodents or the security of a number of economic activities that could be vulnerable to rodents, entailing economic and social consequences. Despite its endocrine disrupting properties, cholecalciferol may be considered to have overall better toxicological and ecotoxicological profiles compared to anticoagulant active substances as it is neither classified as toxic for reproduction category 1B, nor a PBT or vPvB. Cholecalciferol is Vitamin D3, which — at the right dose — is an essential element for human life, and is expected to present lower risks to humans compared to anticoagulant active substances when used as a rodenticide. The risks to human health, animal health or the environment arising from use of products containing cholecalciferol can be mitigated if certain specifications and conditions are respected. As already explained, cholecalciferol can play a role in the future to contribute to a satisfactory control of rodent populations within an integrated pest management approach, in support of the above-mentioned alternatives not subject to the exclusion criteria, and possibly reducing the recourse to anticoagulant rodenticides which present higher overall concerns. In this context, not approving that active substance would deprive users of a tool for rodent control which could bring added value and which is at least as suitable as many other alternative substances used. Therefore, the non-approval of cholecalciferol as an active substance would have a disproportionate negative impact on society in comparison to the risks arising from the use of the substance. The condition set out in Article 5(2)(c) is thus satisfied.

(13) It is therefore appropriate to approve cholecalciferol for use in biocidal products of product-type 14, subject to compliance with certain specifications and conditions.

This conclusion is still considered to be valid.

A major infestation would have serious consequences for the public health situation; rodents are responsible for causing, spreading or exacerbating more than 35 diseases to humans and animals, including leptospirosis, asthma, salmonellosis, hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome. Economic consequences include costs of treatment and costs for lost work of patients and caregivers. The consequences of rodent fire-damage, damage to infrastructure (such as transport, power services, water and sewerage), property value and spoilage of food would also be significant (See Appendix 2).

Users require a high level of control that has historically been provided by AVKs, however with the recent re-classification of AVKs to reprotoxic, cholecalciferol provides a true alternative offering products with no CMR

[9] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R0637

classification, which would be a real benefit for end users, particularly for the general public, if approved, who will only have deconcentrated AVK products at their disposal.

It is clear that rodent damage has a significant impact on local businesses and the economy overall (see Appendix 2).

Innovation:
According to the 'Summary of the workshop on the RMM report held in Brussels on 26/02/2015' (CA-Nov15-Doc.5.4), regulators and industry agree that innovation is needed, both in developing new active substances and non-chemical alternatives. Industry has explained that there are new developments, but it is difficult to find new compounds and risk assessment often fails because of their toxicity.

At high doses cholecalciferol acts as a rodenticide by causing mobilisation of calcium from the bone matrix to plasma and death from hypercalcemia and therefore its mode of action is different to that of AVKs. An important driver behind the development and support of cholecalciferol as a rodenticidal active substance under the BPR, was the need to make available innovative rodenticide products that offer an effective alternative to existing AVKs.

Favourable profile compared to AVKs:
Cholecalciferol presents a good human health profile: as concluded in the cholecalciferol BPC Opinion, the intended rodenticide use of products containing cholecalciferol is not expected to present a risk to humans and unlike AVK rodenticides, cholecalciferol is not classified as reprotoxic. Cholecalciferol presents a better environmental profile when compared to the SGARs as it is not a PBT and has a lower primary and secondary (birds) poisoning toxicity. Indeed, the accumulation of cholecalciferol residues in dead / poisoned rodents is not expected, and the likelihood of the transfer of cholecalciferol residues from dead / poisoned rodents to predatory birds / mammals is low (14).

Furthermore at doses used for rodenticidal purposes, cholecalciferol induces an anti-feeding effect (loss of appetite) which is typically observed in rodents 3 days after the onset of treatment. This effect, which is also relevant to other mammals, is an important consideration with regards to primary and secondary poisoning. For these reasons, primary and secondary poisoning exposure to non-target organisms is expected to be limited in reality and can be acceptably managed with the use of stringent RMMs as proposed by the BPC.

Monitoring data supports safe use of Cholecalciferol:
In the 'Summary of the workshop on the RMM report held in Brussels on 26/02/2015' (CA-Nov15-Doc.5.4) it was agreed by all parties that non-target poisoning is an important issue and should be monitored. The MSs supported monitoring and it was suggested that monitoring of non-target poisoning is the responsibility of the industry. It was stated that "*In the long term, information from monitoring will also better inform regulatory decisions (e.g. at active substance renewal) in terms of the efficiency of the applied RMMs or the need for new ones*."

As stated in the Commission Report 'Risk Mitigation Measures for Anticoagulant Rodenticides as Biocidal Products' (October 2014), "*Non-target poisoning monitoring should be reinforced. Human exposure cases can be dealt with by poison control centres. Domestic animal exposure may also be monitored using poison control centres or dedicated veterinary structures. Wildlife exposure monitoring should be considered. Dedicated wildlife pesticide poisoning surveillance systems exist in some MSs*." Therefore it was widely agreed that incident monitoring was a useful tool to inform regulatory decision-making. In their submission to the public consultation in September 2017, the Applicants provided specific monitoring data on cholecalciferol from the USA and New Zealand, where it has been used safely for many years. Cholecalciferol is not known to be frequently associated with poisoning incidents from either primary or secondary exposure to non-target animals. Poisoning incidents relating to humans are also limited. These incident monitoring data supports the fact that the applied risk management measures are effective. This should be taken into account in the forthcoming consideration of cholecalciferol.

Risk to humans – comparison with other sources:
It should be taken into account that vitamin D_3 is an essential compound for human health and exposure from use as a rodenticide is well below exposure from other sources, including endogenous synthesis and off-the-

shelf vitamin supplements available to consumers without restriction. Indeed there is an EFSA set Adequate Daily Intake (15 µg) with intake encouraged via national programmes.

Humans are exposed to vitamin D_3 through a myriad of sources (see Table 3 below). The major source is endogenous synthesis from exposure of the skin to sunlight (15). Vitamin D_3 is also consumed via a wide range of foods, either naturally or through fortification. Supplement pills and medical prescriptions are another important source, with medicinal guidelines highly recommending supplementation. EFSA have set the 'Tolerable Upper Intake Level' (UL) to 100 µg/day for adults (16), but many off-the-shelf supplements contain qualities of vitamin D_3 far greater than the UL.

Conversely, exposure from rodenticidal use is minimal. Risk assessments have been performed on representative products (containing 0.075% cholecalciferol) and the worst-case level of systemic exposure a general public user (not using any gloves) is predicted to be 0.786 µg/person/day (14), which is 318 – 795 times lower than from sun exposure and 64 times lower than dietary exposure at the UL for adults.

Table 3: Examples of cholecalciferol exposure to humans.

Exposure	Route of exposure	Systemic dose
Sun exposure (15)	Endogenous synthesis	250 to 625 µg/day
Dietary exposure (16): 100 µg/day UL	Oral*	 50 µg/day
Medicinal doses: 1.25 mg every week (17) 2 mg every 2 or 3 months (18) 5 mg every 6 months (18)	Oral*	 625 mg/week 1000 µg/2-3 months 2500 µg/6 months
Rodenticidal exposure (14)	Dermal	0.786 µg/day

*50% oral absorption

Anthropogenic and endogenous environmental loadings:
Given that cholecalciferol is synthesised by animals and plants and is ubiquitous in the environment, environmental loadings from its proposed use as a rodenticide with effective risk management measures should not give any cause for concern. Although theoretical calculations of environmental risk to non-target mammals and birds imply cause for concern, the modelled scenario is based on worst case assumptions and therefore derives very conservative values which are unrealistic for an endogenous substance that has also a long history of safe use in fortified foodstuffs and animal feed, as a dietary supplement and in human medicinal products. By comparison to poisoning incident data, it has been demonstrated that the theoretical risk assessment does not reflect reality at all. In addition, the theoretical worst-case calculations should be viewed in the context of other anthropogenic and endogenous loadings.

Theoretical worst-case calculated loadings of vitamin D_3/ha from use as a rodenticide (up to 82.5 g/ha) are comparable to the calculated higher loadings occurring in cultivated tomato crops (up to 72.6 g/ha) (19). The environmental loading of vitamin D_3 in areas where applied as a rodenticide will not be of any greater magnitude than naturally-occurring levels in certain agricultural crops.

Socio-economic analysis: See Appendix 2

There are multiple categories of exposures to rodents that can result in socio-economic impacts. These include exposure to rodents directly (such as rat bite fever), exposure to pathogens transmitted by rodents and exposure to allergens (such as asthma). These exposures can be associated with acute and chronic diseases such as Leptospirosis, Hantavirus Pulmonary Syndrome (HPS), and Hemorrhagic Fever with Renal Syndrome (HFRS), Meningeoencephalitis and Salmonellosis. Exposures can also be associated with significant food spoilage and with property and infrastructure damage such as fires, and damage to sewers, railways, air and rail transport.

For illustrative purposes Appendix 2 also contains a potential economic impact assessment associated with a worst case scenario where an infestation of rodents cannot be controlled by anticoagulant rodenticides or any other means. This is an illustration on a small scale only; costs are indicative and based on the assumptions presented. The scenario is based on the vicinity of Reading (a large town with an urban population of around 318,000) in the UK, which currently has the highest percentage resistance of Norway Rats to AVKs, where up to 50% of rats carry resistance markers, according to Rodenticide Resistance Action Committee Resistance Maps. Based on (i) a conservative assumption where the rodent population has increased by a factor of 10 and (ii) the modelled factors (treatment of leptospirosis and salmonellosis; reduction in value of domestic dwellings where there is evidence of rodent infestation; rodent-related damage to public infrastructure; fire damage; and food spoilage), an indicative total cost of 2084 million euro (£1603 m) over a year has been estimated.

This assessment is an illustration only, however demonstrates the impact that a rodent population could have if not adequately controlled. Extrapolating this scenario across other regions of Europe where AVK-resistant strains of Norway rats and house mice are prevalent leads to the conclusion that resultant costs could be thousands of millions. Given the increasing occurrence of anticoagulant rodenticide resistant Norway rats and house mice in Europe the use of alternative solutions such as cholecalciferol for professional and domestic rodent control is vital.

Conclusion

Cholecalciferol is considered as having ED properties due to the fact it is a pro-hormone, and the risks assessed in its draft Assessment Report (human, animal, environment) are directly linked to its endocrine mode of action. Risks to human health are not expected (with safe use demonstrated) and risk to animals and the environment are limited due to the proposed RMMs, which is supported by incident data from countries outside of the EU.

There are a lack of other viable alternatives to the AVKs, which are becoming increasingly restricted due to their human health and environmental profile. Furthermore, they share a common mode of action, with increasing resistance developing due to their sustained use. As shown in the socio-economic analysis, rodent infestations bring significant costs to society, and if unchecked, can result in thousands of millions of Euros in damages.

Therefore, weighing against any risk to human health, animal health or the environment, cholecalciferol should be approved as a PT 14 active substance to ensure:

- the continued safeguarding of human and animal health against rodent-borne diseases;
- upholding food security – protecting food stocks from consumption and soiling; and
- preventing damage to property and infrastructure, with all the associated costs to the economy.

Thus, not approving the cholecalciferol would have a disproportionate negative impact on society and it can be concluded the Article 5(2)c derogation criterion is clearly met.

6. Conclusions

From all of the evidence presented, cholecalciferol meets **two** Article 5(2) derogation criteria:

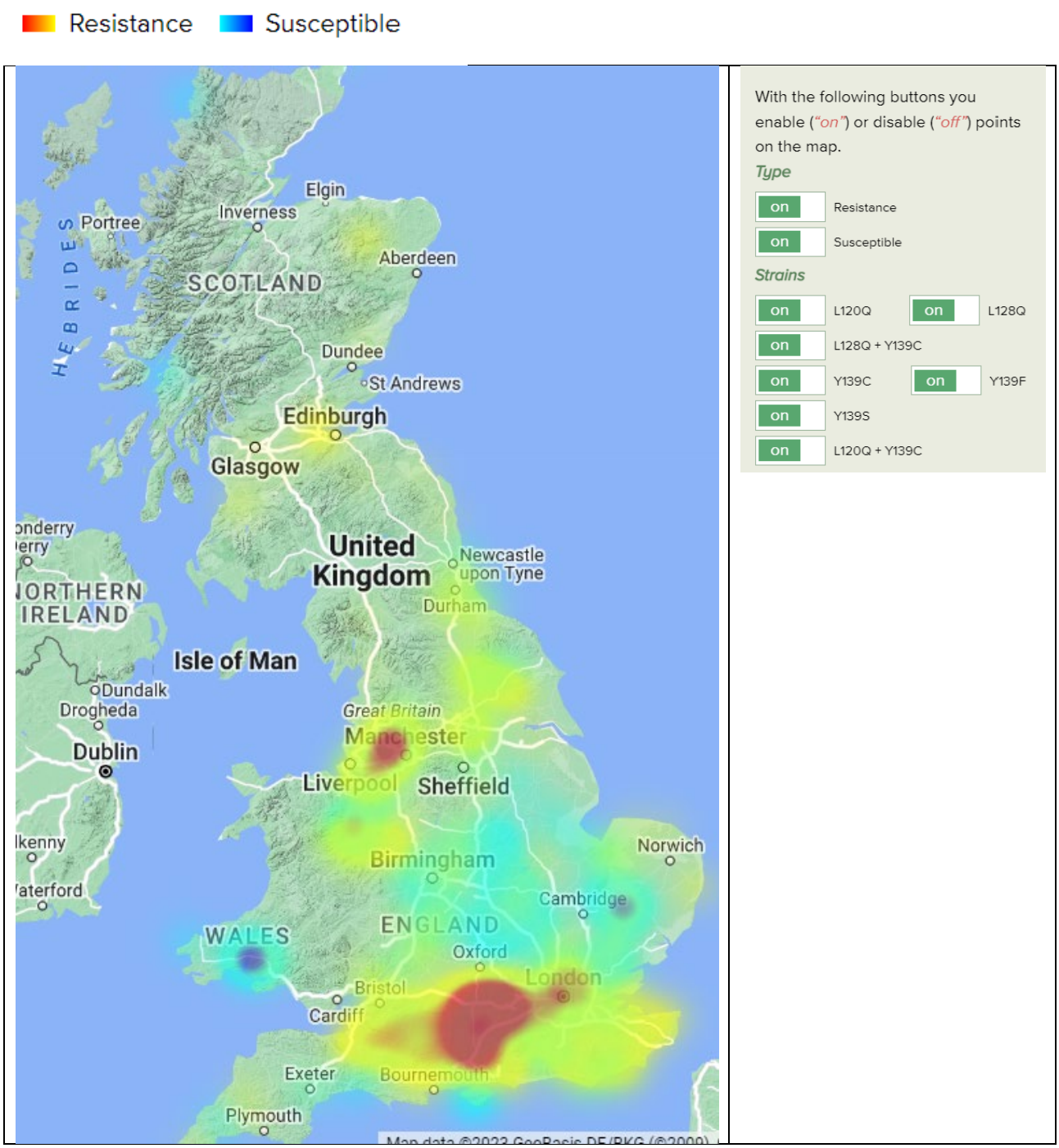
> **(b)** it is shown by evidence that the active substance is essential to prevent or control a serious danger to human health, animal health or the environment;
>
> **(c)** not approving the active substance would have a disproportionate negative impact on society when compared with the risk to human health, animal health or the environment arising from the use of the substance

Therefore, cholecalciferol should be approved for use in the EU to ensure that public health, animal health, food security and urban & rural infrastructure continues to be protected from disease and damage caused by rodent infestations.

APPENDIX 1 Rodenticide Resistance Action Committee Resistance Maps – Accessed 03rd Nov. 2023

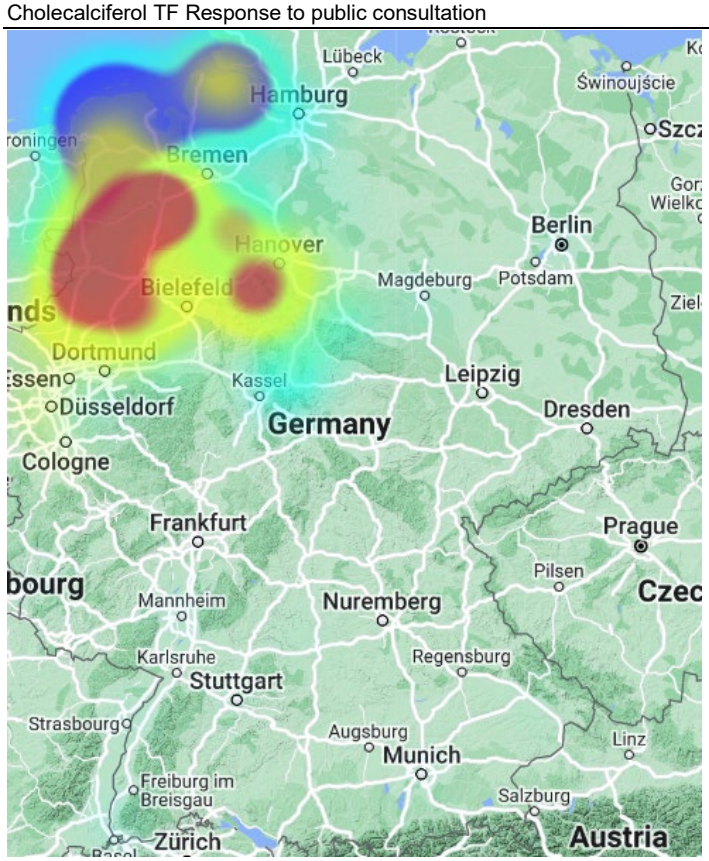
1A. United Kingdom – Norway rat 03rd Nov. 2023

http://guide.rrac.info/resistance-maps/united-kingdom/ (1)



1B. Germany – Norway rat 03rd Nov. 2023

http://guide.rrac.info/resistance-maps/germany/ (2)



Resistance Susceptible

Options

Click on the map to zoom in and center a specific area. Click an drag to change the viewport. Use the zoom buttons to zoom in and out. With the following buttons you enable (*"on"*) or disable (*"off"*) points on the map.

Type

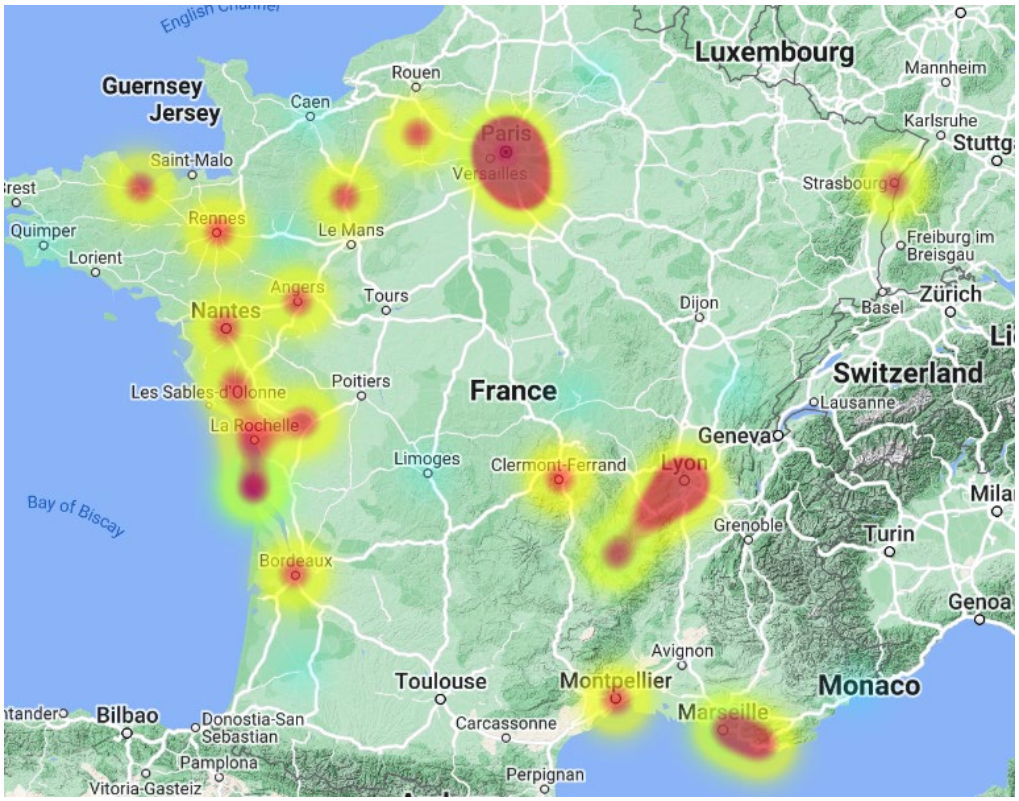
on Resistance on Susceptible

Strain

on Y139C

1C. France – Norway rat 03rd Nov. 2023

http://guide.rrac.info/resistance-maps/france/ (3)



Resistance Susceptible

Options

Click on the map to zoom in and center a specific area. Click an drag to change the viewport. Use the zoom buttons to zoom in and out. With the following buttons you enable (*"on"*) or disable (*"off"*) points on the map.

Type

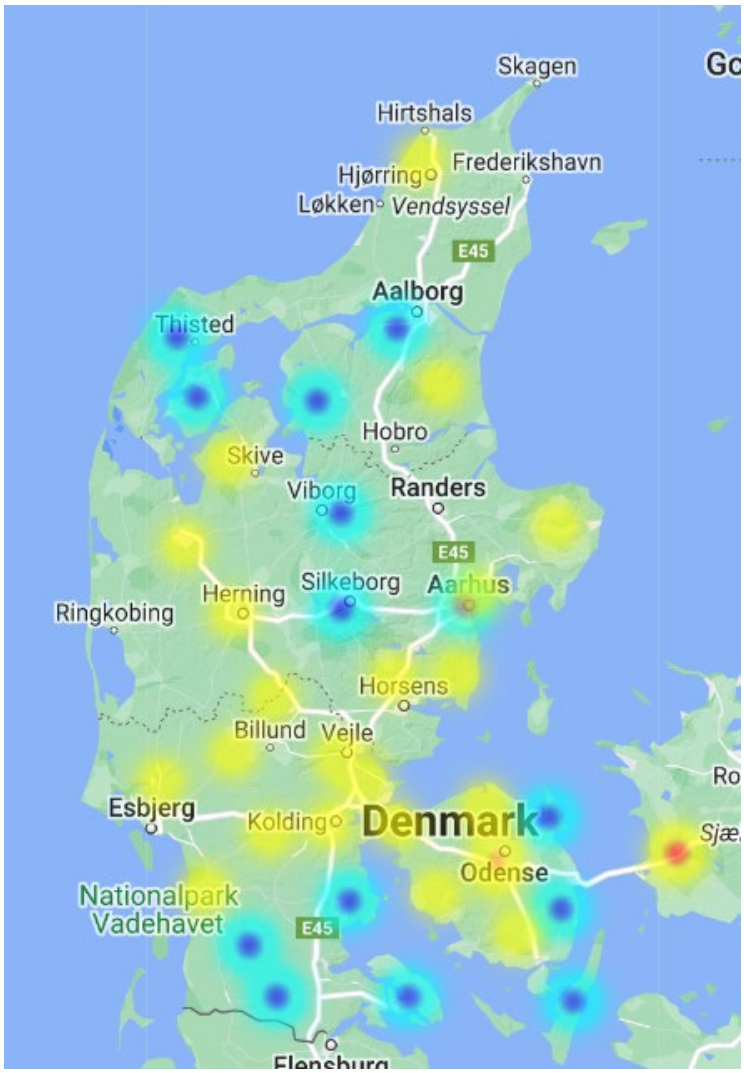
on Resistance on Susceptible

Strain

on L120Q on L128Q on Y139C on Y139F

Denmark – Norway rat 03rd Nov. 2023

http://guide.rrac.info/resistance-maps/denmark/ (4)



Resistance Susceptible

Options

Click on the map to zoom in and center a specific area. Click an drag to change the viewport. Use the zoom buttons to zoom in and out. With the following buttons you enable (*"on"*) or disable (*"off"*) points on the map.

Type

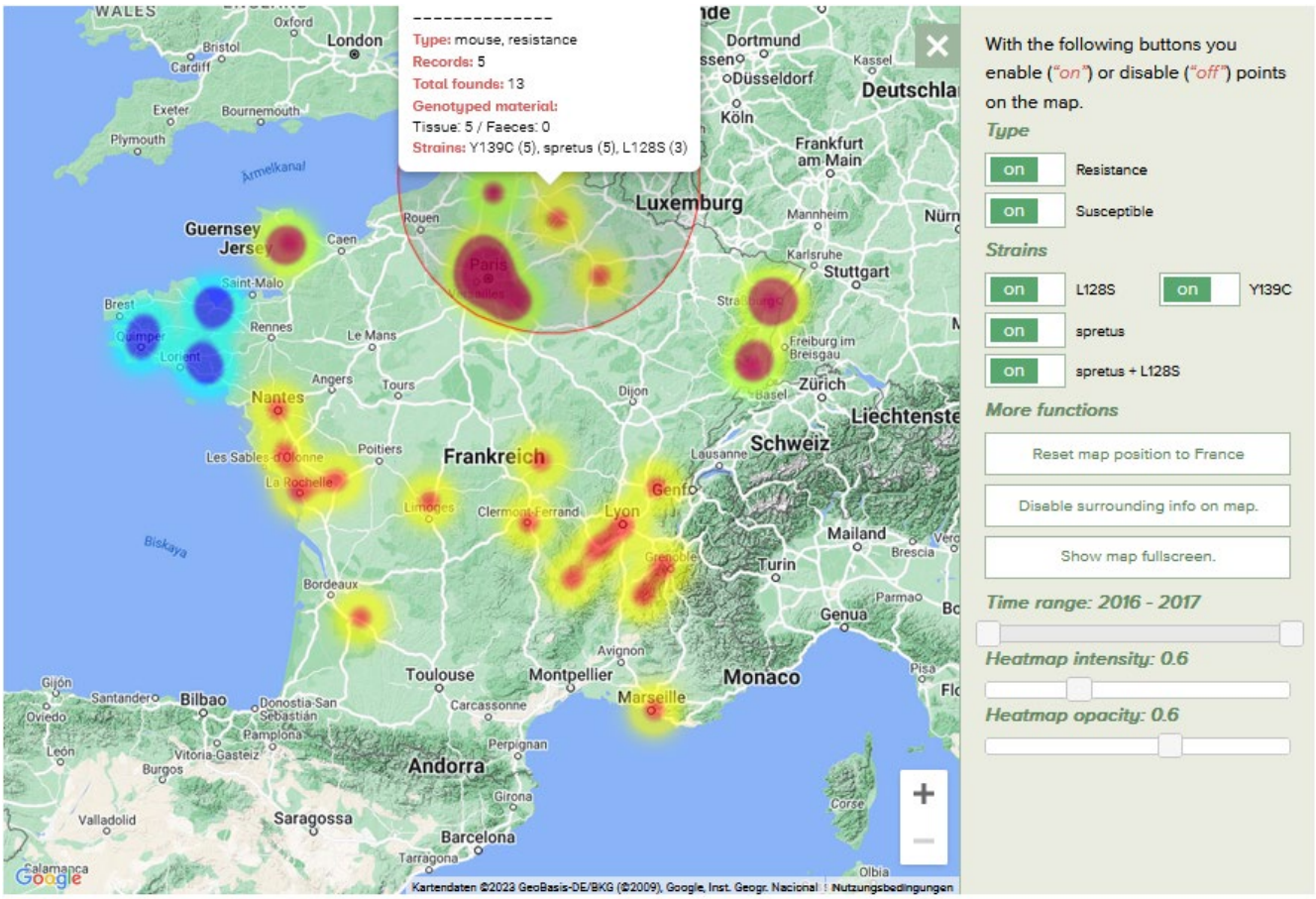
on Resistance on Susceptible

Strain

on Y139C

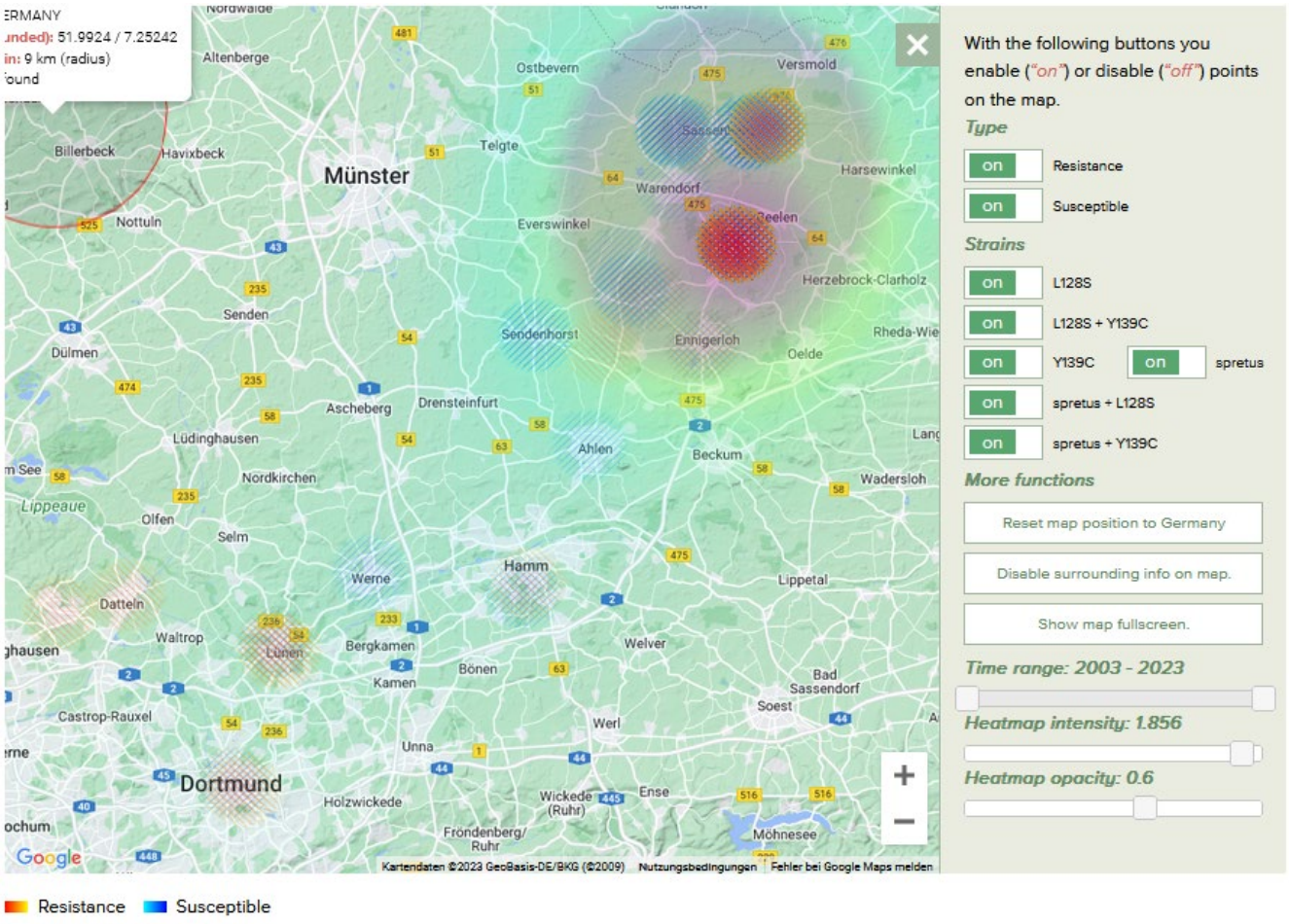
France – house mouse, 03rd Nov. 2023

https://guide.rrac.info/resistance-maps/house-mouse/europe/france.html



Germany, North-West – house mouse, 03rd Nov. 2023

https://guide.rrac.info/resistance-maps/house-mouse/europe/germany.html



APPENDIX 2 SOCIO-ECONOMIC IMPACT ANALYSIS[10]

The costs presented in this appendix were originally submitted for the public consultation launched for the first approval of cholecalciferol in 2018. The socioeconomic costs are based on those published for the UK. No corresponding publicly available information was available for EU member states. Although the UK is no longer part of the EU, these historic costs serve as an indication and guide to the likely costs for the EU member states.

There are multiple categories of exposures to rodents that can result in socio-economic impacts. They include exposure to rodents directly, exposure to pathogens transmitted by rodents, and exposure to allergens. These exposures can be associated with acute and chronic disease as well as property and infrastructure damage and food spoilage.

DISEASE

Bites and scratches: Direct exposure can be associated with trap- and bait-setting activities or accidental contact. These contacts can lead to bites or scratches. Treatment for rodent bites is often limited to antibiotics after initial presentation, although infection or rat bite fever, attributed to *Spirillum minus* or *Streptobaccilus monoliformis*, can occur (20, 21). Costs and consequences associated with bites that are not diagnosed and treated adequately can be substantial should infection or rat bite fever present. The NHS recommends that victims of animal bites seek medical advice, with treatment with a GP or a walk-in centre, with severe bites potentially requiring emergency care (22). Rat bite fever is not reportable in the UK; case reports exist but the number of cases annually is unknown. The outpatient attendance price for a general outpatient visit is £190 (€214) and represents the likely lowest cost associated with a rat bite; an analysis of health care claims coded with ICD-10 A25 (*Spirillum minus, Streptobaccilus monoliformis* and rat bite fever unspecified) could identify cases and treatment burden associated with rat bite fever.

Leptospirosis: Leptospirosis is acquired through contact with urine of infected animals, of which rodents (notably the Norway rat) are by far the most important reservoir. The incidence of leptospirosis has been increasing worldwide. In England and Wales, there were 82 leptospirosis cases reported in 2017 (23). There are data, although limited, on the treatment costs associated with leptospirosis. Among countries that reported hospitalisation rates for patients to the European Centre for Disease Prevention and Control in 2014, 93% of patients with leptospirosis were hospitalised (24). Other studies worldwide suggest hospital stays of 4-6 days. The 2018-19 tariff lists a price for a hospital bed day (standard infectious diseases without interventions, with CC score 0-1) at £419 (€472), with costs for the most severe infections (complex infectious diseases with multiple interventions) at £12,055 (€13,590). With a median of 6 days and this average cost per day, leptospirosis hospital care would exceed £2,514 (€2,834) per hospitalisation at the minimum, with costs higher for more severe patients or those with complications or comorbidities. Further, hospital cost estimates exclude lost work for patients and caregivers as well as transportation and outpatient follow-up, all of which would increase the total cost of illness. An analysis of health care claims coded with ICD-10 A27 (Leptospirosis) could identify the treatment burden associated with rat bite fever.

Hantavirus Pulmonary Syndrome (HPS), and Hemorrhagic Fever with Renal Syndrome (HFRS),which can cause hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome, is believed to be increasing in Europe for many reasons (25). Newer strains may be more virulent than the circulating strains (26). A total of 2,889 cases, including 4 in the UK, were reported to the European Centre for Disease Prevention and Control in 2015, although not all countries contributing have mandatory reporting (27). Many cases are associated with mice and rats, although many are associated with other wild rodents. Treatment can vary substantially based on the strain; morbidity and mortality vary (28). The Sin Nombre virus, found in the United States, has demonstrated mortality approximately 40% but Puumala and Dobrava are associated with mortality less than 1% and up to 20%, respectively (29, 30).

[10]Please note that costs are as presented in the original references and have not been updated to current. Current conversion rates to euros have been used. Costs are for indicative purposes.

Without an early diagnosis or with other causative agents, hantavirus pulmonary syndrome typically requires respiratory support, with severe cases requiring intensive care and intubation or blood oxygenation. A typical hospital stay was 7 days, as reported in Canada (31). Most HPS patients have fatigue, exercise intolerance, and small airways obstruction for several months following recovery (32); some have extended recovery periods (33). HFRS treatment is also primary supportive, with fluid therapy essential; dialysis may be required. Renal function is generally resolved in less than six months, although some patients have residual renal disease (33). A Swedish study found that a majority of patients presenting to their GP with nephropathia epidemica (NE) caused by a Puumala hantavirus could be treated as outpatients (34). NE is a mild form of HFRS. Among patients who presented later, more extensive treatments were needed. Thus costs for hantavirus treatment can range from outpatient presentation and follow up with systemic antibiotics to inpatient hospitalisation of a week or more with long-term support required.

No studies have quantified the indirect costs associated with HPS or HFRS in Europe, but it is likely to be substantial, particularly for the patients with protracted recovery periods and for viruses with high mortality.

Asthma: We considered the potential for an increase in asthma-related injuries due to the possibility of increased exposures in households to allergens from rodents. The preeminent work on allergen exposure and asthma in inner cities was conducted in the United States, as part of the National Cooperative Inner City Asthma Study (NCICAS). Children who were both sensitised and exposed had an annual rate of health care utilisation (hospital admissions, outpatient care, emergency care) substantially higher than other children (35) (36). Asthma prevalence in England increases as socioeconomic status, as measured by deprivation, decreases (37). Unlike the US, it is not remarkably higher in inner cities, with speculation that tree-lined streets compensate for urban exposures such as pollution and other allergens (38). In the US, increased rodent exposure is associated with higher prevalence and severity of asthma, particularly among children and the elderly. Initially, sensitisation to the allergen develops; with continued exposure symptoms can present (39).

Meningitis, encephalitis, and meningeoencephalitis: House mice are the usual host of lymphocytic choriomeningitis virus (LCMV), which causes meningitis, encephalitis, or meningeoencephalitis. Human exposure can be associated with direct contact with rodents or their secretions in the context of a home infestation (40), but is often transmitted through contact with pets. It is recommended to take precautions in the purchase and care of pet rodents (41). There is limited information on treatment patterns and costs of LMCV. While treatment is supportive, the range of symptoms can require various resources (42).

Salmonellosis: Salmonellosis is generally associated with consumption of contaminated food, although in some regions, direct contact with animals or human-to-human contact are also methods of transmission (43). More than two thousand strains of *Salmonella* exist; symptoms can vary based on whether the infection is typhoidal or not. In 2015, there were 8558 laboratory reports of *Salmonella* in England and Wales, although it is estimated that there are 4.7 unconfirmed cases in the community for each laboratory-confirmed case (44). While investigations may identify the food that contained the *Salmonella*, whether rodents are the source of transmission is not frequently reported. However, rodent control is routinely part of multi-model *Salmonella* control efforts that have successfully reduced outbreaks (45) and rodent control is acknowledged to be essential to control salmonellosis on the farm (46). Thus some portion of food-borne salmonellosis can reasonably be attributed to rodents.

Property Damage

Value of property: Regulations about disclosure and the thoroughness of inspection can vary by locality. However, potential real estate purchasers in the UK may ask for reduction in price of an average of 9%, if there is evidence of rodent infestation (47).

Construction: Costs associated with rodents include careful construction to minimise rodent entry paths, continued attention to possible routes of entry, and energy loss associated with entries made or increased in size by rodents (48). There is no consensus on incremental costs required to design and construct rodent-proof buildings compared to similar structures, nor is there a general estimate available for the cost of rodent-proofing an existing home from any public or readily available resources. A single study from the US National Park Service reported a cost of $600 (£430 / €487) per structure for initial efforts to minimise entries to existing park structures, although it is unclear whether the cost includes labour as well as materials and in what year the costs are presented (49). It is likely that park-owned structures are often less complex and less aesthetically-demanding than residences or businesses, thus the cost for rodent-proofing is likely higher in the community.

Fires: There is substantial evidence that a non-trivial proportion of fires are associated with animals. Some of these are likely caused by pets rather than animal infestations. There is limited information on the proportion of fires that are rodent-caused. The US National Fire Protection Association points out that some fires listed as "animal-caused" may be attributed to pets and that animal-caused fires could be coded without mentioning animal (i.e., electrical issue caused by chewed wires) (50, 51). Various estimates suggest that up to 25% of fires of "unknown cause" may be attributable to rodents (52), or that a total of 7% of fires are caused by rats (53); an older estimate suggests rodents cause 5-25% of fires in the US (54). UK data suggest that 10% of fires are of unknown cause, and approximately another 15% are due to "faulty appliances and leads" (GOV.UK), both of which may include some animal-caused fires. While uncertainty as to the exact proportion of fires attributed to rodents exists, it seems unlikely to be less than 5%.

Individual fires that are attributed to rodents appear in many news articles, including several in the UK (53, 55-58). In 2008, the average consequential and response cost per fire in England was estimated to be £3,186 (€3,592). There were 170,519 fires in England attended to by Fire and Rescue services from October 2017-September 2017 (59). If 5% of these fires were rodent-related, that would equate to more than 8500 fires. A report summarising total costs of fire found that the costs of direct property loss, loss of business, death or injury and administration of insurance claims in 1993 and 1999 summed to at least twice as much as Fire and Rescue costs (60). If the proportion of total fire costs attributable to Fire and Rescue are steady, one could assume £3,186 (€3,592) for Fire and Rescue means additional £6,372 (€7,184) per fire for those categories, totalling £9,558 (€10,776) per fire before inflating to the current fiscal year.

Airline delays: The impact of rodents on transportation has also been documented. Besides rodent control in and around airports to maintain facilities, there are many reports of take-off delays associated with rodents on planes worldwide (61-71).

Railway impacts: Rats have also been found to affect railways, both in terms of damage and related delays as well as substantial costs for control. Overall, the total annual costs to the rail system and passengers in England and Wales are estimated to range from £1.66 to 5.76 million (€1.87 to 6.49 million) (72). A survey and follow-up communication reported by Battersby identified reports of rail incidents (that is, delays attributed to rodent damage), with costs to the railway, including treatment costs as well as a penalty mandated by the Rail Regulator, exceeding £122,500 (€138,105) (believed to be expressed in £1999) (72). Data are limited, but signalling system failures and power failures have also been attributed to rats (72).

Public works: Rats have also been shown to have substantial effects on infrastructure. Battersby summarised reports on flooding caused by rats and gas and electrical damage but data are sparse (72). There are data on rodent control efforts in England and Wales, suggesting that more than £450,000 (€507,330) are spent annually (expressed in 1988/89 £), excluding costs associated with damage. Damage was estimated to be between £2.24 and 5.98 million (€2.53 to 6.74 million) annually (72)

Although sewer baiting appears to be limited, it is estimated that up to 40% of the almost 1 million infestations in England and Wales may be associated with underground drainage; thus the rate of drain and sewer repair may be related to infestations.

FOOD SPOILAGE

Crop damage: Food producers can encounter rodent impacts at multiple points in the production process: rodents can eat and contaminate product and livestock feed, infect livestock, and damage structures. Estimates vary by region and type of product, but it is estimated that rodents destroy approximately one-fifth of the world's food supply overall (73). Several studies have examined costs associated with damage to crops (74-76). In some regions, rodent damage has raised concern about food shortages (77). Estimates about crop damage range from 1-25%, depending on the region (78) and type of crop (75). Greaves (1988) (79) estimated that around 94% of farms in Hampshire (England) were rat infested in 1979 – 1980; this was one of the worst damaged areas in the country, with damage in other areas varying from 21 to 44%. Losses from damage to stored grain and animal feed were estimated to be worth £10-20 million (€11.2-22.4 million) a year.

Rodents can consume and contaminate food destined for livestock and other animals, as well as humans. Each rat on a farm will eat, spoil or damage approximately $25 (£17.9 / €20.2) worth of grain per year (80). A colony of 100 rats will consume over 1 tonne of feed in 1 year. A rat can contaminate 10 times the amount of feed it eats with its droppings, urine and hair. A rat produces 25,000 droppings per year, a mouse 17,000. The United States Department of Agriculture estimates that the equivalent of more than $2 billion in feed is destroyed by rodents each year (81).

Infestations in restaurants, shops, and warehouses are not well-documented. A recent survey in New York City found that business owners reported pest control to be their primary cost following an infestation, with merchandise, structure repairs, and poison traps the next largest expenses, respectively (82). Damage and costs to businesses exceed those mentioned in the previous study; loss of reputation as well as fines and lawsuits are also relevant (83); damage to staff morale was also cited as an effect of business infestation (84). These concerns vary by the type of industry, size of the company and whether it is public-facing or not; for example, firms with food as a core business reported being more proactive with pest control compared to firms for which food is not a core business component (84). In a survey of 212 firms in the UK, 92% reported having at least one pest infestation over the previous 5 years (84), though the report did not differentiate between rodents and other types of pests.

The total cost of rodent damage, exclusive of health impacts, in the UK has been estimated to be between £61.9 and £209 million (if presented in £2003, 2017 values are £92.2 to £311.4 million / €103.9 to 351 million) (72), although Battersby points out that there is "a surprising lack of data on rats and damage."

'FUTURISTIC' SCENARIO

We have illustrated below a potential economic impact associated with the non-approval of cholecalciferol in a worst case scenario where an infestation of rodents cannot be controlled by anticoagulant rodenticides or any other means. This is an illustration on a small scale only. Costs are indicative and based only on assumptions described below. There are a number of other factors for which insufficient quantitative information is available, such as asthma, which have therefore not been included in this model, and thus can be considered as a conservative estimate.
Currently the highest area of resistance of Norway Rats to AVKs in the UK is in the south of England in the vicinity of Reading, where 50% of rats carry resistance markers (at least one of the nine mutations described on page 4 (1-4).

Reading is a large town with an urban population of around 318,000 (mid-2016, most recent estimate). It is an important commercial centre in southern England. Reading has over 100 parks and playgrounds, including 5 miles of riverside paths. It has one main hospital and four other hospitals. Main water and sewerage services are provided by one utility company and the local electricity and gas distribution networks are run by a further two utility companies. Many major companies have their headquarters in Reading and it is a major retail centre. Reading has some important heritage sites: six Grade I listed buildings, 22 Grade II* and 853 Grade II buildings (nationally protected historic buildings). All sites, facilities and companies could potentially be impacted by a significant increase in rodent population.

According to population models (12) if unchecked a rodent population can increase by a factor of thousands over a single year. Obviously the greater incidence of AVK resistance in a population, the faster the population can grow if not controlled with effective alternative rodent control solutions. However, as a reasonable approach the following have been assumed:

- For the purposes of this scenario we are conservatively assuming a factor of 10 growth in rat population (compared to the current situation), with a concurrent increase in the number of premises affected, as although effective treatment with AVKs would be limited there would likely be attempts to control rodents by other methods rather than leaving the populations completely unchecked.
- For the purposes of this scenario we are assuming a factor of 5 increase leptospirosis cases, which is considered plausible (given an assumption of a 10-fold increase in rodent population growth) based on the information given in this document above.
- For the purposes of this scenario, we are assuming 5% of fires are caused by rodents (see the above section on property damages – fires).

Infrastructure/area affected	Assumptions	Potential cost (£) per annum	Information and relevant data
HEALTH			
Treatment of leptospirosis	Cases are likely to correspond with areas of high resistance to AVKs and therefore likely to be in the south of England. Area of highest resistance (currently *ca* 50%) is in the vicinity of Reading. Therefore it is assumed, as a worst case, that the current cases were in the Reading area. Anticipated increase of leptospirosis cases 5 fold. Anticipated number of leptospirosis cases 400. Cost of leptospirosis 'treatment' per case £1500.	£0.6 million	In England and Wales, there were 82 leptospirosis cases reported in 2017. With a median of 6 days and £222 average cost per day, leptospirosis hospital care would exceed £1330 per hospitalisation, not including costs for lost work of patients and caregivers as well as transportation and outpatient follow-up, therefore £1500 per hospitalisation is assumed.
PROPERTY			
Reduction in value of domestic dwelling where evidence of rodent infestation	A 9% decrease in property price equates to an average of £38,319 per dwelling. 30% of dwellings in Reading impacted (3% of dwellings in UK in 2012; 10-fold increase). 41,478 dwellings impacted.	£1589 million	The average price for property in Reading is currently £425,769 in February 2018 (85) According to the last UK census (2011) the average household size in the UK was 2.3 people per household. Applying this to the urban population of Reading, this equates to 138,261 domestic dwellings. 3% of dwellings in the UK with rats present account for *ca* 1.5 million rats (86)
Fire damage	Per head of population (England = 55,268,067) the number of fires attended annually equates to 0.31% and therefore on a *pro-rata* basis 986 fires in Reading could currently be expected on an annual basis. Conservatively assume 5% of fires are rodent related. 49 rodent-related fires could currently be expected on an annual basis in Reading. 10 fold-increase: 490 rodent-related fires per year. Average cost per fire (including fire service, direct property loss, loss of business, death or injury and administration of insurance claims) is £25,000.	£12.25 million	According to information from the Fire and Rescue incident statistics bulletin 8 Feb 2018, 7% of fires are caused by rats (59). Fire and Rescue services attended 170,519 fires in England in the year ending September 2017 in England. The average cost per fire in buildings has been estimated (87), as £21,500 (domestic), £44,300 (public sector) and £63,600 (commercial) (Weiner, 2001). The data also suggests that the cost of direct property loss, loss of business loss, death or injury and claims administration historically of insurance claims in 1993 and 1999 summed to at least twice the amount attributed to the fire service costs (60). Of the 25% building fires, 17% were in domestic dwellings.

Infrastructure/area affected	Assumptions	Potential cost (£) per annum	Information and relevant data
Public works	Per head of population (UK 65,648,100) the cost of rodent-related damage annually is around £2-6 million and therefore on a *pro-rata* basis the cost is £9600 - £28,800 in urban Reading (urban Reading population is 0.48% of UK population). 10-fold increase in rodent-related damage from 10-fold increase in rodent population	£96,000 - £0.288 million	Rodent-related damage to public infrastructure has been estimated to be between £2.24 and 5.98 million annually in the UK (72).
FOOD			
FOOD SPOILAGE	Per head of population (UK 65,648,100) the cost of rodent-related damage annually is around £15 million and therefore on a *pro-rata* basis the cost is £72,000 in urban Reading (urban Reading population is 0.48% of UK population). 10-fold increase in rodent-related damage from 10-fold increase in rodent population	£0.72 million	Losses from damage to stored grain and animal feed were estimated to be worth £10-20 million a year in 1979-80 in the UK (79)
TOTAL MODELLED COST FOR FACTORS ASSESSED ABOVE		**£1603 million (€2084 million)**	

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