"Available in Supermarkets, banned for Consumer Rodent Control"

The regulatory paradox of considering vitamin D_3 as an Endocrine Disruptor (under the BPR)

Summary

Cholecalciferol (vitamin D_3) is one of the main forms of vitamin D, continuously produced in the skin from pre-cholesterol through UV light synthesis and, therefore, naturally present in the human body. It is essential for vertebrates, critical for bone formation and maintenance. It plays an important role for infants and elderly people, supporting infantile development or preventing/overcoming health conditions in advanced age. As any other natural hormone, vitamin D_3 has endocrine properties as it plays a key role in the regulation of blood and tissue calcium levels

Outside of the human system, vitamin D_3 is naturally present in certain *foods* such as fatty fish, egg yolk and milk available in supermarkets, and is widely used as a food additive in a large variety of consumer products as supplement intakes for vitamin D_3. Moreover, it is recommended by doctors in the form of pills available in any pharmacy, and is specially used during pregnancy as well as by the general population in countries / regions with fewer hours of sun exposure to supplement lower body production of vitamin D_3.

In addition to these uses, a recent innovation in the biocidal industry has enabled vitamin D_3 (also known as cholecalciferol) to be effectively used as a **biocidal active substance** for the PT 14 category, the control of rodents. This has been the first innovation in the rodenticides sector in decades, especially since the classification of anticoagulant rodenticides as Reprotoxic Cat 1A or B, and is highly welcomed by authorities as a potential alternative of the latter given its high efficacy properties and better toxicological and environmental profiles. The substance is currently being evaluated under the Biocidal Product Regulation (BPR).

However, despite the positive effects and widespread use of vitamin D_3 in the food chain and medicines, and **considering the ongoing adoption of criteria for defining endocrine disrupting substances** under the BPR, the substance could be considered as an endocrine disruptor, and its use as a rodenticide for the consumer market in Europe would accordingly be banned. In other words, unless addressed by authorities, Europe will ban vitamin D_3 "to protect consumers" from an endocrine disrupting substance, while that same substance will continue to be freely available (even at higher rates of exposure) across the food chain, in supplementation products, including vitamin pills, and prescribed medicines.

Vitamin D_3: critical component of a healthy lifestyle

It is generally recognized[1] that the **Vitamin D Deficiency (VDD)** pandemic affects almost 50% of the population worldwide, which is on the increase and affecting all age groups, including in Europe. VDD affects the human system in different ways:

- Rickets
- Depression/mood
- Back/muscular pain
- Bone health
- Increased sensitivity to viruses and bacteria (e.g. flu)

[1] See for instance "Vitamin D: The "sunshine" vitamin", Rathish Nair and Arun Maseeh, J Pharmacol Pharmacother. 2012 Apr-Jun; 3(2): 118–126.

- There is increasing information about the possible role of vitamin $D_3$3 in cancer prevention in humans.

Accordingly, the **human system requires** additional vitamin intake, which is measured in International Units (IU) (with 1 IU corresponding to 0.025 micrograms, µg), with **adequate intake (AIs)**set by EFSA[2] at **600 IU (or 15 µg)/day** for adults and a **'Tolerable Upper Intake Levels'** (ULs) set at **4000 IU or 100 µg/day** for adults (including pregnant and lactating women) and for adolescents (11-17 years). These additional intakes are currently supplied, at different concentrations and exposure through multiple sources.

There are several major sources of vitamin D_3:

- ***The first major source of intake is sun exposure***. Cholecalciferol is synthesized in the skin by the reaction of 7-dehydrocholesterol with UVB radiation, present in sunlight with an UV index of three or more. The vitamin is synthesized from the exposure of the skin to sunlight typically between 1000 h and 1500 h in the spring, summer, and fall. For instance, the body can generate from 10,000 IU (250 µg) to 25,000 IU (625 µg) of vitamin D_3 in just a little under the time for human skin to begin to burn[3].

- ***The second major source is consumer food***. Even though few foods contain sufficient amounts of vitamin D_3 to compensate for a lack of sun, the substance is present in the most common products found in groceries stores either in natural form or in supplement form:

    - With regards to a natural presence, the *best sources* are fatty fish (like tuna, mackerel, and salmon) and fish livers. *Smaller amounts* are to be found in milk, cheese, egg yolks and beef liver. For instance, an average portion of 200 grams of tuna contains approximately 250 IU (6.25 µg) of vitamin, a cup of milk – 100 IU (2.5 µg).[4]
    - With regards to supplemented forms of vitamin D_3, hundreds of daily products found in supermarket are fortified with vitamin D, such as, for instance, many dairy products, orange juice, soymilk, and cereals. Half a cup of a fortified orange juice for instance gives 50 IU (1.25 µg).[5]

- ***A third major source is medicinal supplements,*** available, depending on the country, either in pharmacies or off-the-shelf in supermarkets and health food shops. For instance, in the UK vitamin D_3 can be obtained both off-the-shelf or prescribed by a physician when a deficiency is diagnosed. The importance of national fortification programs has been recently reaffirmed[6] as incidences of melanoma linked the excessive exposure to sunlight have increased over the recent decades. Due to an inadequate consumption of vitamin D_3 via food, medicinal guidelines highly recommend supplementation of vitamin D at tolerable UL levels. Vitamin pills are also available in the market that go beyond the tolerable UL level, for example a single pill of an off-the-counter Solaray Food Supplement Super Strength Vitamin D_3 contains 10 000 IU (250 µg)[7]. In France,

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[2] Dietary reference values for Vitamin D, EFSA, 29 Jun 2016, http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2016.4547/epdf, retrieved on 24 Oct 2017

[3] "How do I get the vitamin D my body needs?", https://www.vitamindcouncil.org/about-vitamin-d/how-do-i-get-the-vitamin-d-my-body-needs/, retrieved on 5 Oct 2017

[4] "Food Sources of Vitamin D", Dietitians of Canada, 23 Nov 2016, https://www.dietitians.ca/Your-Health/Nutrition-A-Z/Vitamins/Food-Sources-of-Vitamin-D.aspx, retrieved on 5 Oct 2017

[5] Ibid

[6] "Vitamin D Intake: A Global Perspective of Current Status", Mona S. Calvo, Susan J. Whiting, and Curtis N. Barton, Symposium: Vitamin D Insufficiency: A Significant Risk Factor in Chronic Diseases and Potential Disease-Specific Biomarkers of Vitamin D Sufficiency

[7] https://labdoor.com/review/carlson-labs-vitamin-d3, retrieved on 5 Oct 2017

the famous ZymaD for young children or old adults every 6 months contains up to 200 000 IU (5 mg) in 2 mL – a concentration which is in fact close to the amount of vitamin D_3 found in a rodenticidal bait.

Overall, all of these sources of exposure to vitamin D_3 are largely available to any consumer and EU citizen, as scientific studies demonstrate safety and efficacy of vitamin D_3 supplementation,[8] and even in 2016 one EU Member State explored plans to propose a mandatory fortification program at EU level[9]. In other words, the widespread presence of vitamin D_3 in our society and the medical recommendations for the intake of this substance to fortify and supplement lower naturally produced levels of vitamin D_3 point to a riskless substance despite its endocrine properties, inherent to any hormone.

The benefit of using vitamin D_3 as a biocidal product

Rodents have been found to be more susceptible to excessive doses of vitamin D_3 than other species, a situation which has led to the development of an innovative type of **rodenticide** based on cholecalciferol, acting through an oversaturation of calcium in the target animals. Following this innovation, vitamin D_3 is currently being evaluated under the BPR (Regulation 528/2012), for its approval as an active substance under PT 14.

For the intended use in a biocidal product, **concentrations** of vitamin D_3 will be at a maximum of 15 mg in each bait unit. Bait units will be wrapped in sachets and label instructions will recommend the use of gloves. Therefore, the only expected exposure to vitamin D_3 is through dermal contact and, knowing that the dermal penetration of vitamin D_3 accounts for only 0.22% of the applied dose, the internal systemic dose is expected to be low. It is not expected that there will be accidental ingestion, particularly by infants, as the bait contains a human taste deterrent and units will be placed in stations located in inaccessible places. Therefore, it is important to put into context the exposure of vitamin D_3 through its use as a rodenticide compared to exposure through other uses, such as vitamin supplementation.

To assess human exposure from rodenticidal use, risk assessments were performed on representative products containing 0.075% w/w (0.75 g/kg) cholecalciferol[11]. According to the evaluating Competent Authority's calculations (Sweden), the **worst-case** levels of systemic exposure for professional and non-professional users were predicted to be up to **4.14 µg/person/day and 5.48 µg/person/day**, respectively. This is well **within the tolerable upper intake level set by EFSA** (4000 IU or **100 µg/person/day**) **and lower than oral exposure from readily available vitamin supplements** (e.g. a pill containing 1000 IU / 25 µg, would result in 12.5 µg/person/day, based on 50% oral absorption) **or 45-fold to 90-fold lower than endogenous production of vitamin D_3 after a whole-body sun exposure** (250-625 µg/person/day).

While under the *interim criteria* for the identification of Endocrine Disruptors in the BPR (C2R2) vitamin D_3 would not be considered an ED (last year ECHA´s Risk Assessment Committee determined that no CMR classification is applicable to vitamin D_3), under the ***definitive criteria*** currently proposed by the European Commission (though voted down by the European Parliament on 4 Oct 2017) vitamin D_3, due to its hormonal mode of action, will by definition **very likely meet such criteria**.

The regulatory consequences of this under the BPR are clear: an automatic ban of the substance. **While professional uses could still be approved via the so-called derogations under socio-economic considerations, its use by EU consumers will**

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8 "Vitamin D Intake: A Global Perspective of Current Status", Mona S. Calvo, Susan J. Whiting, and Curtis N. Barton, Symposium: Vitamin D Insufficiency: A Significant Risk Factor in Chronic Diseases and Potential Disease-Specific Biomarkers of Vitamin D Sufficiency

9 Draft Competent Authority Report (CAR), Cholecalciferol (PT 14), KemI. May 2017

be totally forbidden. In other words, rodenticide biocidal products containing vitamin D_3 will not be available in shelfs in any general or specialized shop for consumers.

Banning vitamin D_3 for biocide consumer market while allowing it in our supermarket?

Cholecalciferol is facing a **complex regulatory paradox**. On one hand, regulators recognize the substances' beneficial effects on the human health and encourage its additional intake as part of national supplementation programmes, and in parallel allowing the use of the substance freely in the food chain for human and animal intake.

In contrast, the same substance, when used as a rodenticide and with lower estimated exposure than ingestion of vitamin D_3 through fortified food or supplement pills, will be banned for consumers on grounds of human health protection.

It will be hard for EU citizens to understand that a substance that is supposedly harmful for them as it has been identified as an Endocrine Disruptor according to the BPR, is then freely allowed, without restrictions in food and medicines. In other words, the question will arise on why are we banning a substance from the consumer market of biocides to protect citizens, while are allowing the same substance in our supermarkets?

In order to avoid this absurd situation, it seems logical and in line with Better Regulation principles to find a regulatory solution under the BPR for vitamin D_3 or other substance with endocrine properties whose primary uses are in food/feed supplementation or medicine and with agreed upper tolerable limits, should not be identified as endocrine disruptors for regulatory purposes.

The annex contains an overview of relative human exposure from the use of vitamin D_3 as rodenticide and the dietary and endogenous exposure from the myriad of sources outlined in the paper.

ANNEX – COMPARATIVE ANALYSIS VITAMIN D_3 EXPOSURE SOURCES

As shown in the table, the worst-case human exposure resulting from a systemic exposure for professional and non-professional users applying a rodenticidal paste bait of cholecalciferol containing 0,075% w/w (0,75 g/kg) is estimated at 5.48 µg/day and is significantly lower than exposure from other possible uses and notably is 10-fold lower than the ULs defined by EFSA and 90-fold lower than an endogenous production of vitamin D_3 after a whole-body sun exposure.

Exposure	**Route of exposure**	**Systemic dose** ***(oral absorption of 50% as proposed in the draft CAR)***
Sun exposure	Endogenous synthesis	250 to 625 µg/day
Dietary exposure - EFSA ULs	 Oral	 100 µg/day
Rodenticidal exposure	Dermal	5.48 µg/day