WORLD IODINE ASSOCIATION

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Position paper on Endocrine Disruptors and Active Substances

The case of iodine

Introduction

Iodine and iodate are vital for nutrition and human health, playing a crucial role in thyroid hormone synthesis and the functioning of the thyroid gland. Moreover, both iodine and iodate are utilised in various forms for **different purposes, ranging from addressing iodine deficiency disorders to serving as potent disinfectants and biocides**.

Iodine is an essential trace element that naturally occurs in the human body and that is crucial for the synthesis of thyroid hormones, which are responsible for regulating the body's metabolism and promoting proper growth and development, particularly in infants and young children. It is widely used to **support the human hormonal system** and **constitutes an essential dietary trace element for ensuring population health**. More specifically, as recognised by the European Food Safety Agency's (EFSA) favourable opinion on health claims related to iodine, it **contributes to normal cognitive and neurological function** (ID 273), **normal energy-yielding metabolism** (ID 402) as well as **normal thyroid function and production of thyroid hormones** (ID 1237)[1]. This is further underlined by EFSA's scientific advice on nutrition and health claims[2] from 19 April 2022, which stresses the **importance of iodine in the development of neurological and cognitive functions, normal thyroid function, as well as the prevention of iodine deficiency disorders**. Moreover, povidone-iodine (PVP-I) is commonly used in the healthcare sector, due to the its broad-spectrum antimicrobial properties and its high effectiveness against bacteria, fungi, and viruses, including SARS-CoV-2 (COVID-19).[3]

Iodate, on the other hand, occurs when iodine bonds with oxygen and is the most common form of iodine in nature. When iodate is ingested, it is reduced to iodide in the gastrointestinal tract before being transported to the **thyroid gland where it is converted into iodine**, **which is then used to produce thyroid hormones**[4]. Due to its crucial role in ensuring population health, the World Health Organisation (WHO) recommends the fortification of food with iodate.[5] Moreover, iodate is **added to food (i.e. salt) as per Regulation (EC) 1333/2008 on food additives, as a way to fight iodine deficiency disorders**. It is further **prescribed to pregnant and breast-feeding women** as food supplement **to secure proper iodine intake for both the mother as well as the foetus** and contribute to the latter's cognitive and physical development.

Policy background

In the European Union (EU), biocides are regulated by the EU Biocidal Products Regulation (BPR) which governs the approval, placing on the market, and use of products containing biocidal active substances. In February 2020, building on COM(2018) 743 concerning a comprehensive EU framework on endocrine disruptors, the European Commission (EC) triggered the early review of the approval of biocidal active substances. Subsequently, on 17 May 2021, the European Chemicals Agency (ECHA) received the mandate on the review of the approval of biocidal substances, which assigned the Swedish Chemicals Agency (KEMI) as a rapporteur to develop and deliver ECHA's opinion to the EC. In September 2022, KEMI's working group on the environment and human health identified iodine and povidone-iodine (PVP-I) as endocrine disruptors, given their potentially adverse effect on thyroid function - an assessment that was later confirmed by ECHA and the EC.

Endocrine effect versus endocrine disruptor

The classification of iodine and PVP-I as an endocrine disruptor represents a drastic shift compared to a previous 2013 assessment report[6] commissioned by ECHA, which clearly distinguishes between an active substance having an endocrine *effect* or being an endocrine *disruptor*.

Specifically, the report states that:

- "…both iodine deficiency as well as excess iodine can impair thyroid homeostasis/thyroid hormone levels. This is to be considered as an endocrine effect. However, it would not be justified to conclude from this that iodine should be considered to be an endocrine disruptor." (p.32)

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[1] EFSA (2010). Scientific opinion of the EFSA Panel on Dietetic Products, Nutrition and Allergies on the substantiation of health claims related to iodine.
[2] EFSA (2022). Scientific advice related to nutrient profiling for the development of harmonised mandatory front-of-pack nutrition labelling and the setting of nutrient profiles for restricting nutrition and health claims on foods.
[3] Anderson et. al (2020). Povidone-Iodine Demonstrates Rapid In Vitro Virucidal Activity Against SARS-CoV-2.
[4] Institute of Medicine, Food and Nutrition Board (2001). Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.
[5] World Health Organisation (2014). Guideline: fortification of food-grade salt with iodine for the prevention and control of iodine deficiency disorders.
[6] European Chemicals Agency (2013). Regulation (EU) n°528/2012 concerning the making available on the market and use of biocidal products. Assessment Report.

- "Consequently, the concept of endocrine disruption is not meaningful for essential elements such as iodine since it neglects that they are needed for maintaining hormone homeostasis." (p.33)

The 2022 opinion[7], on the other hand, utilises a different methodology which no longer accounts for this critical distinction. Moreover, the methodology did not assess the actual risks posed by using iodine in biocides, but only evaluated the substances' inherent properties without accounting for the dosage, exposure, and application. Whereas **endocrine effects encompass intended action on the hormonal system to correct a certain malfunction or deficiency, endocrine disruptors interfere with the proper functioning of the endocrine system**. Clearly distinguishing between endocrine effect and endocrine disruption based on the **specific dosage, exposure, and application of iodine is crucial**, as it avoids extreme simplifications and misconceptions about iodine.

It is crucial to note that any current authorisation of iodine-based biocidal products already considers an upper limit of iodine intake which accounts for endocrine properties and represents a conservative basis for the risk assessment. **Classifying iodine as an endocrine disruptor therefore provides no additional safety, but rather fuels misperceptions by end users of iodine-based biocides such as patients, healthcare professionals, farmers, and livestock owners**.

Implications

Considering that the EC endorses ECHA's assessment of iodine being considered as an endocrine disruptor, it no longer qualifies for Union Authorisation, in line with Article 5(1) of the BPR. After discussions between EU Member States and ECHA, the European Commission has opted for a compromise approach whereby **existing Union Authorisation will remain valid until August 2025 before having to be renewed on a case-by-case basis at national level. All requests for the authorisation of new biocidal products have to be individually assessed** by the competent authorities at national level.

The revocation of the Union Authorisation will have **severe consequences for users of iodine-based biocides (e.g. patients, healthcare professionals, farmers, and livestock owners), as well as for producers, processors, retailers**, as the products' **placing on the market would only be possible if authorised by the competent national authorities on a case-by-case basis**. As iodine-based biocides play a crucial role in surface disinfection, pre-operative skin preparation, or impregnated dressings, the revocation of the Union Authorisation could **affect existing infection control practices and adversely affect patient safety**. In addition, it could negatively affect the population's iodine status, as iodine-based biocides used in the livestock sector (e.g. teat dips) play a crucial role in the fortification of milk.[8]

Finally, the decision to consider iodine as an endocrine disruptor poses the risk of **setting precedence for other sectors**, **potentially affecting the placing on the market of, and public perception of, iodine-containing products such as x-ray contrast media, cosmetics, colorants, or dyes**. The same applies to fortified food, feed, or crops, posing a risk of negatively impacting public perception about the benefits of iodine in food fortification. This is particularly concerning, given the high prevalence of iodine deficiency and implications on public health across Europe, as stressed by the Krakow Declaration on iodine[9]. Lastly, the early review of the BPR is **closely monitored outside of the EU**, for instance in the United States and Asia Pacific Region, risking a similar classification of iodine and the **same implications for healthcare professionals, the patient community, as well as the biocides value chain, in these regions**.

Derogation criteria

Article 5(2) of the BPR lists several derogation criteria that allow for the authorisation of substances that have been labelled as an endocrine disruptor. Specifically, the BPR states that the authorization of a substance with endocrine-disrupting properties may be justified if:

1. **"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."**

Human health

Any authorisation of iodine-based biocidal products already accounts for a conservative upper limit intake as part of the risk assessment. This risk assessment is specifically intended to avoid any negative effects on human health and, given that iodine-based biocides been used for decades without any reports of adverse effects to human health, appears to be highly effective.

[7] European Chemicals Agency (2022). Opinion on a request according to Article 15(2) on the review of approval of the active substance iodine and polyvinylpyrrolidone iodine.
[8] French et. al (2016). Iodide Residues in Milk Vary between Iodine-Based Teat Disinfectants.
[9] EUthyroid consortium (2018). The Krakow Declaration on Iodine.

Moreover, ECHA's very own 2013 risk assessment of iodine[10] clearly states that:

- "Iodine is not harmful via oral exposure." (p.17)
- "Because of the low absorption through skin, acute dermal toxicity in man is very unlikely and cases of death due to single application or exposure via dermal route are virtually unknown." (p.17)
- "…iodine is not regarded as a skin sensitizer." (p.18)
- "Several expert groups which have evaluated the available data base have concluded that iodine is not considered to be a mutagen in vivo." (p.19)
- With respect to carcinogenetic properties, "No clear dose-response relationship is evident." (p.19)

The same applies to ECHA's 2018 risk assessment of betadine solution[11], stating that:

- "No physico-chemical hazard was identified..." (p.4)
- "If the professional users follow the instructions about the safe application of the product it is unlikely that the intended uses cause any unacceptable acute or chronic risk to professional users or to the patients." (p.4)

Animal health

Primary applications of iodine-based biocides in this context are composed of disinfection of animals' teats or udders, as well as an antiseptic agent for a wide range of wounds. Povidone-iodine is often the first choice for the treatment of wounds due to its broad antimicrobial spectrum, lack of resistance, efficacy against biofilms, good tolerability, and its effect on excessive inflammation.[12] **As such, iodine-based biocides do not pose a risk to animals but are, in fact, critical to safeguarding their health.**

Moreover, ECHA's 2018 risk assessment of iodine teat dip products[13] states that "the biocidal product family has no immediate or delayed unacceptable effects itself, or as a result of its residues, on the health of humans, including that of vulnerable groups, or animals, directly or through drinking water, food, feed, air, or through other indirect effects." (p.13)

Environment

With respect to environmental risks poses by iodine-based biocides, ECHA's 2018 risk assessment of betadine solution, states that "…the intended uses of the product do not pose unacceptable risk to the environment." (p.4). Moreover, ECHA's 2018 risk assessment of iodine teat dip products clearly states that "the biocidal product family has no unacceptable effects itself, or as a result of its residues, on the environment..." (p.13)

In light of the presented evidence, iodine-based biocides pose a negligible risk to humans, animals, and the environment.

2. "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."

Human health

Iodine-based biocides are widely used in the healthcare sector, due to iodine's broad-spectrum antimicrobial properties and its high effectiveness against bacteria, fungi, and viruses.[14]

PVP-I formulations in particular are crucial in a healthcare setting for limiting the impact and spread of infectious diseases with potent antiviral, antibacterial, and antifungal effects. In addition, PVP-I has been shown to be highly effective against SARS-CoV-2 (COVID-19), both with respect to reducing the viral load in patients[15], as well as protecting healthcare professionals.[16]

Moreover, the broad antimicrobial spectrum of PVP-I, its efficacy against biofilms, good tolerability and its effect on excessive inflammation position it extraordinarily well for wound healing.[17] Due to its rapid, potent, broad-spectrum antimicrobial properties, and favorable risk/benefit profile, PVP-I is expected to remain a highly effective treatment for acute and chronic wounds in the foreseeable future.[18]

[10] ECHA (2013). Assessment Report – Iodine (including PVP-iodine).
[11] ECHA (2018). Risk assessment of a biocidal product for national authorization applications – Betadine solution/Betadine oldat.
[12] Bigliardi et. al (2017). Povidone iodine in wound healing: A review of current concepts and practices.
[13] ECHA (2018). Opinion on the Union authorisation of Iodine Teat Dip Products BPF based on Iodine.
[14] Eggers (2019). Infectious Disease Management and Control with Povidone Iodine.
[15] Anderson et. al (2020). Povidone-Iodine Demonstrates Rapid In Vitro Virucidal Activity Against SARS-CoV-2.
[16] Concepcion et. al (2021). Use of Povidone-Iodine to reduce transmission of SARS-CoV2 virus; Chopra et. al (2021). Can povidone iodine gargle/mouthrinse inactivate SARS-CoV-2 and decrease the risk of nosocomial and community transmission during the COVID-19 pandemic? An evidence-based update.
[17] Bigliardi et. al (2017). Povidone iodine in wound healing: A review of current concepts and practices.
[18] Ibid.

Animal health

Iodine-based teat dips are widely used by the livestock industry to prevent mastitis, an inflammation of the mammary gland in the udder, typically caused by bacterial infection. Iodine-based teat dips are used after milking to kill bacteria on the teat's surface, preventing the bacteria from entering the teat canal and causing mastitis. By preventing mastitis and other infections, iodine-based teat dips contribute animal health, as well as the safety and quality of the milk supply. In addition, they increase the iodine content of milk, thereby contributing to the population's iodine status.

Moreover, the same antimicrobial and wound healing properties mentioned in the context of human health also apply to animals and iodine-based biocides remain widely utilized for the treatment of animal wounds, both by veterinarians, as well as the livestock sector.

In conclusion, iodine-based biocides are essential to controlling serious dangers to both human and animal health by limiting the impact and spread of infectious diseases, as well as its excellent properties for wound healing.

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."

As previously highlighted, iodine-based biocides play a crucial role for healthcare professionals and patients by limiting the impact and spread of infectious diseases, including COVID-19, as well as being highly effective in the treatment of acute and chronic wounds.

Moreover, iodine-based biocides are a staple product in the livestock sector and are widely used to prevent infectious diseases such as mastitis in cows, thereby enhancing the safety and quality of the milk supply, as well as supporting the population's iodine intake via the fortification of milk.

Considering the essential role of iodine-based biocides in both human and animal health, its safety, as well as the fact that it does not pose unacceptable risks to human health, animal health, as well as the environment, not approving iodine as an active substance would indeed have a disproportionate negative impact on society.

Call to action

Based on Article 5(2) of the BPR and the related scientific findings presented above, WIA calls on the competent national authorities to support **the authorisation of iodine-based biocides at Member State level**, taking into account the presented scientific evidence, in order to **avoid a disproportionate negative effect on patients, healthcare professionals, farmers, livestock owners, as well as on producers, processors, and retailers.**

About WIA

WIA is an international non-profit organization advocating in favour of the essential role of iodine in nutrition and health with a focus on the sustainable prevention of iodine deficiency disorders in Europe and beyond. Moreover, WIA represents the interests of the iodine value chain towards end users in relevant industry and government bodies.

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