Biocidal Products Committee (BPC)

Opinion on a request according to Article 15(2) on the review of approval of the active substance iodine and polyvinylpyrrolidone iodine

ECHA/BPC/357/2022

Adopted

27 September 2022

Opinion of the Biocidal Products Committee

on the review of approval of the active substance iodine and polyvinylpyrrolidone iodine

In accordance with Article 15(2) of Regulation (EU) No 528/2012 of the European Parliament and of the Council 22 May 2012 concerning the making available on the market and use of biocidal products, the Biocidal Products Committee (BPC) has adopted this opinion on the review of approval of the active substance iodine and polyvinylpyrrolidone iodine.

This document presents the opinion adopted by the BPC, having regard to the conclusions of the rapporteur.

Process for the adoption of the opinion

A request by the Commission was received by ECHA on 17 May 2021**.** The BPC appointed the rapporteur at its meeting of 5-7 and 12-14 October 2021. In order to review the ED assessment, the Agency organised consultations via the BPC (BPC-44) and its Working Groups (WG II 2022, 10 June 2022).

Adoption of the opinion

Rapporteur: Sweden

The BPC opinion was adopted on 27 September 2022.

The BPC opinion was adopted by consensus.

The opinion is published on the ECHA webpage at: https://echa.europa.eu/bpc-opinions-on-article-15-2.

Further details of the opinion and background

1. Request for the opinion and background

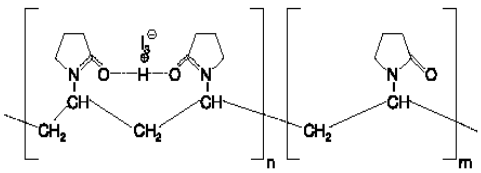
Iodine and polyvinylpyrrolidone iodine (PVP-iodine) have been identified as possible endocrine disruptors in the screening study performed during the impact assessment accompanying the proposal that led to Commission Delegated Regulation (EU) 2017/2100. The information collected for this screening study provides significant indications that these active substances may have endocrine-disrupting (ED) properties and therefore may no longer satisfy the conditions laid down in Article 4(1) of the BPR. In accordance with Article 15(1) of the BPR, and in light of the significant indications that the active substances iodine and PVP-iodine may have ED properties, the Commission started the review of their approval.

On 17 May 2021, the Commission submitted to ECHA a mandate pursuant to Article 15(2) of the BPR. The mandate requested ECHA to provide opinions on whether the active substances iodine and PVP-iodine are considered to have ED properties with respect to humans and/or non-target organisms according to the scientific criteria for determining ED properties specified in the Commission Delegated Regulation (EU) No 2017/2100 and in accordance with the ECHA and EFSA Guidance for identification of endocrine disruptors.

2. Summary of the evaluation

2.1. Presentation of the active substance

In 2014, iodine and PVP-iodine were approved as biocidal active substances in product types 1, 3, 4, and 22. Sweden was the Rapporteur Member State (RMS). The conclusions of the risk assessment are laid down in the assessment report (AR), 2013. The current approval expires on 31 August 2025.

Common name	**Iodine**	**PVP-iodine**
CAS no.	7553-56-2	25655-41-8
EC no.	231-442-4	607-771-8
IUPAC name	Iodine	Polyvinylpyrrolidone iodine
CA name	Iodine	2-Pyrrolidinone, 1-ethenyl-, homopolymer, compd. with iodine
Molecular formula	I_2	$(C_6H_9NO)_x * n\ I_2$
Structural formula	I-I	 m/n = ca. 18

2.2. Information sources

The following information sources, as indicated in the mandate, were considered by the rapporteur:

(a) The information available from the biocidal assessment report(s) available on the active substances and the data submitted in the original applications for approval.

(b) The data underlying the conclusions in the screening study performed during the impact assessment accompanying the proposal that led to Commission Delegated Regulation (EU) 2017/2100.

(c) The information submitted by applicants to the Commission within the scope of the review of the approval of the substances.

(d) The information submitted by applicants within the scope of this Commission request.

(e) Further information available to ECHA that is relevant to assess the ED criteria.

Under the point (e) above, the rapporteur considered in particular the information available for iodine in the REACH registration dossier, recent published review articles and the evaluation of iodine by authoritative bodies such as WHO and EFSA.

In PVP-iodine, PVP is a carrier of iodine and there is no chemical bond between these. PVP is a water-soluble polymer that is biologically inert and non-toxic with good tolerance (Kurakula and Rao, 2020). Therefore, the assessment of ED properties of iodine is applicable also to PVP-iodine.

In May 2020, within the scope of the review of the approval, the applicant submitted their assessment of ED properties of iodine (and PVP-iodine, which was basically similar to that of iodine). The applicant considered the data available in the biocidal assessment report and also performed a literature search. The applicant assessment of iodine and the comments of the rapporteur on it is available as an Annex to this opinion.

With respect to non-target organisms, the applicant's literature search did not retrieve any relevant information on endocrine disrupting mechanisms or effects related to the EAS modalities, nor do the REACH registration dossier or the biocidal assessment report[1] contain any relevant information in that respect. ECHA is not aware of any published information on effects related to the EAS modalities from iodine, PVP-iodine or any other iodine containing compound in non-mammalian species. Published scientific research with respect to effects of iodine on the thyroid and resulting effects is available and was considered in the assessment of endocrine disruption in non-target organisms.

2.3. Summary of information

Iodine is an essential nutrient for mammals, required as a mandatory structural and functional element of thyroid hormones – thyroxine or tetraiodothyronine (T4) and triiodothyronine (T3). Through these hormones, iodine has an important role in energy-yielding metabolism and on the expression of genes that impact many physiological functions, including embryogenesis and growth, and the development of neurological and cognitive functions (EFSA, 2014).

The relationship between iodine intake and thyroid disorders is U-shaped and both iodine deficiency and excess intakes may lead to thyroid dysfunction (Farebrother et al., 2019). Robust human data is available on the adverse health effects due to both deficiency and excess of iodine.

"The clinical effects of iodine deficiency, referred to as iodine deficiency disorders, are the result of insufficient intakes leading to insufficient thyroid function. Iodine deficiency disorders are seen at all stages of development and are particularly of concern in pregnancy and infancy. Chronic iodine deficiency may lead to compensatory thyroid hypertrophy with an enlargement of the thyroid gland denoted as goitre." (EFSA, 2014)

[1] Available at https://echa.europa.eu/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/1319/PT03, last accessed in March 2022.

"The adverse effects associated with high levels of iodine intake are linked to disruption of thyroid hormone metabolism and the thyroid–pituitary axis, and the compensatory mechanisms that protect this metabolism from low or high levels of iodine intake. **Previous exposures to iodine and the complex effects of pre-existing thyroid conditions also influence the effects of subsequent exposure** [emphasis added]. Members of the general population who are vulnerable to iodine toxicity include pregnant and lactating women, and neonates." (WHO, 2020).

Thyroid gland is the primary target organ for systemic effects of repeated exposure of excess iodine through ingestion. The thyroid disorders lead to secondary effects on the endocrine system (pituitary and adrenal glands) and many other organs (including skin, cardiovascular system, pulmonary system, kidneys, GI tract, liver, blood, neuromuscular system, skeleton and reproductive systems) (WHO, 2020).

Excess iodine leads to the following thyroid disorders (Farebrother et al., 2019[2]):

- **Increased thyroidal volume and goitre**

  "Goiter, an enlargement of the thyroid, is caused by thyrocyte hyperplasia following overstimulation by TSH[3], typical in regions affected by iodine deficiency. Yet, with iodine excess, goiter can occur due to failure to escape from the Wolff–Chaikoff effect[4], or due to persistent stimulation by thyroid-stimulating antibodies that keep the NIS[5] activated and/or propagate lymphocytic infiltration causing an increase in thyroid size."

- **Hypothyroidism**

  "In subjects with an underlying thyroid disorder, acute excessive iodine intakes may lead to temporary overt or subclinical hypothyroidism that resolves when iodine intakes decrease [Markou et al., 2001]. Vulnerable individuals may have an increased risk of failing to adapt to the acute Wolff–Chaikoff effect." "The prevalence of subclinical and overt hypothyroidism is generally higher in areas of optimum or chronic excessive iodine intake than in settings of mild-to-moderate iodine deficiency (Katagiri et al., 2017, Weng et al., 2017, Laurberg et al., 1991)."

- **Thyroid autoimmunity**

  "Excessive iodine consumption has been widely described as a risk factor for the development of thyroid autoimmunity (Laurberg et al., 2010, Flores-Rebollar et al., 2015, Luo et al., 2014, Prete et al., 2015, Ferrari et al., 2017)."

- **Postpartum thyroiditis**

  "Postpartum thyroiditis is a thyroid dysfunction characterized by lymphocytic infiltration of the thyroid gland within the first year postpartum in women who were euthyroid before pregnancy (Bari et al., 2017, Stagnaro-Green, 2012), or a new occurrence of thyroid autoimmunity (excluding Graves' disease (GD)) postpartum."

[2] The original articles from this review paper are not evaluated by the rapporteur but are included in citations and the reference list.
[3] TSH: Thyroid Stimulating Hormone.
[4] Wolff–Chaikoff effect: In 1948, Wolff and Chaikoff demonstrated that organification of iodide in the rat thyroid was blocked when plasma concentrations were raised to a critical level, and that once iodide levels dropped an "escape" from this block occurred.
[5] NIS: Sodium-iodide symporter; a plasma membrane glycoprotein responsible for active transport of iodide in the thyroid gland and in the extrathyroidal tissues (for e.g., in the lactating mammary gland).

- **Iodine-induced hyperthyroidism**

  "Iodine-induced hyperthyroidism, also known as the Jod–Basedow effect, is most frequently observed following iodine supplementation or fortification in areas of very low iodine intake, where the risk of nodular goitre is increased (Laurberg et al., 2010)."

- **Grave's disease**

  "Though nodular goiter is one of the major causes of hyperthyroidism in iodine-deficient or previously endemic areas, GD is the most common cause of hyperthyroidism in iodine-sufficient regions, affecting 0.5% of the population, particularly younger adults (Brent 2008, Girgis et al., 2011, De Leo et al., 2016)."

- **Increased risk of thyroid cancer**

  "A comprehensive review on thyroid cancer [Zimmermann and Galetti, 2015] concluded that iodine excess may be a weak promoter; a recent meta-analysis of 16 studies reported an OR of 1.4 (95% CI: 1.1–1.9) between exposure to excessive iodine intakes and risk of papillary thyroid carcinoma, a tendency that was more pronounced when considering only studies conducted in high iodine intake regions (OR 2.2; 95% CI: 1.4–3.5) (Lee et al., 2017)."

Exact mechanisms of thyroid disorders due to excess of iodine are not known. However, there is data in the literature proposing several endocrine modes of action for thyroid toxicity. For e.g.,

- Iodide excess inhibits the iodination of thyroglobulin in the thyroid gland and inhibits the release of T4 and T3 from the gland (Pisarev and Gärtner, 2000, as cited in ATSDR, 2004).

- In a recent study, excess iodine was shown to increase serum thyrotropin-releasing hormone (TRH) levels and increased the type 2 deiodinase activity in hypothalamus of rats (Sun et al., 2021; abstract).

- Initial response to excess iodine in rats is suggested to be involving inhibition of the NIS once the level of organified iodine in the thyrocyte reaches a critical level (Calil-Silveira et al., 2016, as cited in Farebrother et al., 2019).

- In rats, high intracellular iodide concentrations lead to the formation of iodopeptides that inhibit TPO[6] activity and prevent organification (Leung and Braverman, 2014, as cited in Farebrother et al., 2019).

Given the physiological needs of iodine as an essential dietary element for mammals, authoritative bodies worldwide have established dietary adequate intake levels and upper intake levels for iodine in human populations. In Europe, the adequate intake levels for iodine range from 70 µg/day (for infants) to 200 µg/day (for pregnant & lactating women) (EFSA, 2014); the upper intake levels for iodine range from 200 µg/day (for infants and children 1-3 years) to 600 µg/day (for adults and pregnant & lactating women) (SCF, 2002). The upper intake level of 600 µg/day was derived from LOAELs of 1700 – 1800 µg/day (by applying an assessment factor of 3) that were based on mild increase in TSH observed in three small subchronic iodine exposure studies[7] in euthyroid adults (Farebrother et al., 2019).

[6] Thyroid peroxidase enzyme
[7] Chow et al., 1991, Gardner et al., 1988 and Paul et al., 1988.

In the biocidal assessment report for (PVP-)iodine, the dietary upper intake level of 600 µg/day was used for adults and 250 µg/day for a 6-year-old child as a reference value for risk assessment.

Although there is robust human data on excess iodine leading to thyroid disorders, there is currently inadequate data to establish a linear and temporal dose-response relationship between iodine intake and altered thyroid function in humans (WHO, 2018).

Data is also lacking to conclude on EAS-modalities for (PVP-)iodine. The studies required for EAS-related activity (OECD 441 and OECD 456; OECD 229/230) or EAS-mediated adversity (OECD 416, ver. 2001 or OECD 443; OECD 240/OPPTS 850.1500) to be considered as sufficiently investigated according to the ECHA/EFSA ED Guidance are lacking.

In water, iodine will be transformed to several chemical species, mainly iodide, iodate and in presence of organic matter to organic iodine compounds (Assessment report (AR); 2013). In guidelines for toxicity tests with amphibians it is stated that sufficient iodide should be made available to the larvae to support normal metamorphosis. Thus, an optimal concentration range likely exists. It is also stated that, currently, there are no empirically derived guidelines for minimal iodide concentrations. However, iodide availability may affect the responsiveness of the thyroid system to thyroid active agents and is known to modulate the basal activity of the thyroid gland (OECD TG 231, 2009, and OECD TG 241, 2015).

Relevant information on potential endocrine effects of iodine in other organisms than humans or mammals is scarce. It appears to be limited to investigations on amphibian metamorphosis, done already 100 years ago. Then, scientists established that iodine, iodide and various iodine-containing compounds affect the metamorphosis in amphibia if administered either to the surrounding water or via diet (among others: Swingle, 1919a, 1919b; Spaul, 1924; Abderhalden and Hartmann, 1928). Thereafter, it appears that very few attempts were made to further investigate the effects of iodine compounds on non-mammalian species. Only recently, the 100-year-old findings were confirmed by Krishnapriya et al. (2014) and Olker et al. (2018). The results obtained by Krishnapriya et al. confirm that exposure to iodine via diet leads to adverse outcome. The accelerated metamorphosis observed, showing a clear dose-related response, is a specific T-mediated endocrine effect. Advanced development is only known to occur through effects which are thyroid hormone related, as stated in the OECD Guideline for The Amphibian Metamorphosis Assay (OECD 231; 2009). The results by Olker et al. support the understanding that mechanisms in amphibians and mammals are similar, and that amphibia efficiently take up iodide from the aquatic medium.

The applicant's assessment of endocrine-disrupting properties of iodine and the rapporteur's comments on it are found as annex to this opinion.

3. Overall conclusion

According to the Commission Delegated Regulation (EU) No 2017/2100, a substance is identified as having endocrine-disrupting properties with respect to humans if it meets the following three criteria

(a) it shows an adverse effect in an intact organism or its progeny;

(b) it has an endocrine mode of action, i.e., it alters the function(s) of the endocrine system; and

(c) the adverse effect is a consequence of the endocrine mode of action.

Iodine, in excess of physiological needs, meets all the above three criteria – it shows adverse effects (thyroid disorders) in humans; it has an endocrine mode of action (disruption of

thyroid hormones metabolism and hypothalamic-pituitary-thyroid axis); and the adverse effects are a consequence of the endocrine mode of action. Therefore, the biocidal active substances, iodine and PVP-iodine, are identified as having endocrine-disrupting properties with respect to humans.

According to the Commission Delegated Regulation (EU) No 2017/2100, a substance is identified as having endocrine-disrupting properties with respect to non-target organisms, if it meets the criteria for humans, unless there is evidence demonstrating that the adverse effects identified are not relevant at the (sub)population level for non-target organisms. Since iodine and PVP-iodine meet the criteria for endocrine disruption with respect to humans, it can be concluded that the substances are endocrine disruptors also in non-target organisms. Evidence demonstrating that the adverse effects identified are not relevant at the (sub)population level has not been provided. Furthermore, it is highly plausible that external administration of iodine to amphibia via water or diet interferes with endocrine mechanisms related to the thyroid and in excess of physiological needs subsequently leads to adverse effects in intact organisms, namely accelerated metamorphosis. Overall, there is sufficient evidence to demonstrate population relevant effects as a consequence of excess of iodine and these are a consequence of an endocrine mode of action. Thus, iodine and PVP-iodine meet the ED criteria for non-target organisms for the T modality.

This further supports the conclusions that the criteria for endocrine disruption in non-target species are met.

Due to lack of relevant data, no conclusion is possible on the EAS-modalities for the active substance iodine and PVP-iodine. However, since these substances are identified as having endocrine-disrupting properties due to adverse effects on T-modality, no further studies are justified to conclude on the EAS-modalities. However, as a note outside the scope of the current mandate, some members of the BPC-WG (combined Human Health and Environment Working Group WG-II 2022) recommended that a risk assessment approach should be considered during the decision-making on these active substances because iodine is an essential dietary element. In such case, further information may be needed also on the EAS-modalities.

The table below presents the assessment of exclusion and substitution criteria as a result of the identified endocrine disrupting properties.

Property		**Conclusions**	
Endocrine disrupting properties	Section A of Regulation (EU) 2017/2100: ED properties with respect to humans	Yes	Iodine and PVP-iodine fulfil Article 5(1)(d) and 10(1)(e) of Regulation (EU) No 528/2012.
	Section B of Regulation (EU) 2017/2100: ED properties with respect to non-target organisms	Yes	
	Article 57(f) and 59(1) of REACH	No	
	Intended mode of action that consists of controlling target organisms via their endocrine system(s)	No	

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Annex – Applicant assessment of endocrine-disrupting properties of iodine and the comments of the rapporteur on it.

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