# Biocidal Products Committee (BPC)

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

ECHA/BPC/431/2024

Adopted

29 May 2024

# Opinion of the Biocidal Products Committee

**on the review of approval of the active substance zineb**

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 zineb.

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

## Process for the adoption of opinions

A request by Commission was received by the Agency 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-51) and its Working Groups (WG-I-2024).

## Adoption of the opinion

**Rapporteur: Ireland**

The BPC opinion was reached on 29 May 2024.

The BPC opinion was adopted by consensus. The opinion is published on the ECHA website.

# Further details of the opinion and background

## 1. Request for the opinion and background

Zineb has 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 this active substance 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 substance zineb 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 substance zineb is 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 information supporting the request for the opinion

### 2.1 Presentation of the active substance

In 2016 zineb was approved as biocidal active substances in product type 21[1]. Ireland was the Rapporteur Member State (RMS). The conclusions of the risk assessment are laid down in the assessment report (AR). The current approval expires on 31 December 2025.

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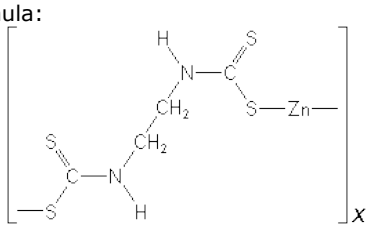
|---|---|
| Common name | zineb |
| CAS No. | 12122-67-7 |
| EC No. | 235-180-1 |
| IUPAC Name | Zinc ethylenebis(dithiocarbamate) (polymeric) |
| CA name | zineb |
| Molecular formula | (C4H6N2S4Zn)x |
| Structural formula | Molecular formula: $(C_4H_6N_2S_4Zn)x$<br>Structural Formula:<br>  |

[1] Commission Implementing Regulation (EU) No 92/2014 (EU) No 92/2014. Available at: http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32014R0092

## 2.2. Information sources

The Commission announced its intention to carry out an early review of the approval of the biocidal active substances iodine, PVP iodine and zineb on February 18th, 2020.

Arysta Lifescience Benelux SPRL acting for UPL Europe Ltd considered as "the Review Program participant", as referred in the Article 95 list of ECHA did not respond to this announcement.

Agria SA, an alternative supplier for zineb as an Active Substance under the Biocidal Products regulation (BPR) did respond. However, article 15 is silent as regards alternative suppliers but it was concluded comments of Agria could indeed be seen a third-party comments.

Neither Arysta Lifescience Benelux SPRL nor Agria SA submitted an ED assessment for zineb, so in mid 2022 it was concluded that Ireland should carry out the assessment with the data that was available at that time. The written Procedure assessing the Endocrine disrupting potential of zineb on human health and non-target organisms was completed late 2023.

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 and third parties to the Commission within the scope of the review of the approval of the substances.

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

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

## 2.3. Summary of information

**Information evaluated for the assessment of zineb's potential for Endocrine Disruption.**

The original evaluation of zineb for its effects on human health and non-target organisms was based on the assessment of toxicity data generated using zineb as the test substance as required by the BPR. However, the evaluation relied on read-across to data derived from studies on Mancozeb and studies on the shared metabolite ethylene thiourea (ETU).

The read-across approach was re-examined in the zineb endocrine disruption assessment using ECHA's Read-Across Assessment Framework (2017). In the context of the framework, the simplest case of the analogue approach was considered which relied essentially on the structural similarity between the source (mancozeb) and target substances (zineb) and on the read-across hypothesis ((bio)transformation of mancozeb to common metabolite (ETU).

Zineb and mancozeb are ethylenebisdithiocarbamate (EBDC) salts containing the metals zinc and/or manganese.

In zineb the only metal ions present are $Zn^{2+}$, whereas mancozeb contains both $Mn^{2+}$ and $Zn^{2+}$ in the ratio 10:1. It is generally recognised that the effects of EBDC compounds are

entirely due to the presence (as an impurity) or the formation via transformation processes, of ethylene thiourea (ETU).

Additionally, it has been demonstrated through the public domain data/studies that ADME profile of zineb is comparable with that of mancozeb. Absorption was rapid for both substances, the degradation products of zineb and mancozeb, both members of the EBDC group, are the same with the principal metabolite in mammalian metabolism studies being ethylene thiourea (ETU) and the biological target of the common compound ETU is the same for both mancozeb and zineb (Thyroid gland).

Therefore, the read across from Mancozeb was considered acceptable with high confidence and without reservation. It was thus considered that the predictions of the endocrine disrupting potential of zineb was sufficiently covered by the data generated for mancozeb.

**Effects on the Thyroid gland**

The striking toxicological feature common to all ethylene bisthiocarbamates (EBDCs) is their effect on the thyroid gland.

ETU belongs to a class of compounds that inhibits synthesis of thyroid hormone and induces release of high levels of TSH by the pituitary. A clear mode of action (MoA) has been identified for ETU;

1) Changes in thyroid hormones levels: ETU inhibits the peroxidase activity of TPO within the thyroid thus preventing the oxidation of iodide and hence the formation of the thyroid hormone precursors (MIT and DIT) on thyroglobulin. The net result of this direct mode of action is that production of the thyroid hormones T4 (thyroxine) and T3 (triiodothyronine) is inhibited. This results in disturbance of the hypothalamus-pituitary-thyroid axis (HPT) as the hormonal feedback control mechanisms attempt to adjust thyroid hormone concentrations to normal endogenous levels. The low levels of thyroid hormones are sensed by the hypothalamus and pituitary and may result in increased release of TRH (thyrotropin releasing hormone) and TSH (thyroid stimulating hormone) respectively. TSH acts on thyroid follicular cells to stimulate the production of new thyroid hormones.

2) Thyroid Histopathology and Increased Thyroid weights: The low levels of thyroid hormones (T3 and T4) are sensed by the hypothalamus and pituitary (disturbance of the hypothalamus-pituitary-thyroid axis (HPT)), the hormonal feedback control mechanisms attempt to adjust thyroid hormone concentrations to normal endogenous levels by stimulating TSH production, evident by increased TSH serum concentrations. Increased levels of TSH act on thyroid follicular cells to stimulate the production of new thyroid hormones, acting to return thyroid hormone concentrations to normal endogenous levels. The increased concentrations and excessive stimulating action of TSH on thyroid follicular cells leads to thyroid follicular cell hypertrophy, changes in cell shape and loss of colloid from the thyroid follicle. This generally results in increased thyroid weight. Under conditions of prolonged exposure, thyroid follicular cell hyperplasia occurs, leading to tumours of the thyroid gland (adenomas and carcinomas).

In the human health ED assessment limited data for zineb was available: two non-acute studies, a 28-day rat study and a 90-day rat study, were in the database. The database for mancozeb was more extensive with 16 sub-chronic and chronic studies available in several species including rats, mice and dogs. The database for the shared metabolite ETU was also extensive with 17 sub-chronic and chronic studies in a number of species evaluated.

There is overwhelming evidence from the *in vivo* level 4 & 5 studies conducted with mancozeb and ETU in rats, mice, dogs and monkeys that support the hypothesis that the production of

thyroid hormones T4 (thyroxine) and T3 (triiodothyronine) are inhibited, resulting in disturbance of the HTP axis and an increase in TSH release, respectively. This results in excessive stimulation of thyroid follicular cells, resulting in hyperplasia and tumours during prolonged exposure.

The weight of evidence indicates that zineb (through read-across from mancozeb) and its metabolite ETU, interact with the thyroid hormonal systems. Thus, it can be concluded that zineb is an endocrine (thyroid) disruptor of relevance to humans according to the ED scientific criteria in Regulation (EC) (EU) No 2017/2100[2] and in accordance with the ECHA and EFSA Guidance for identification of endocrine disruptors[3].

Specific ED studies in zineb for non-target organisms were not available. However, studies for birds and fish were available for mancozeb and ETU. Additionally, four larval amphibian metamorphosis assays (AMA) studies with ETU have been identified as relevant for the assessment of endocrine disruption potential of zineb with respect to non-mammalian vertebrates. In all the studies with amphibians, changes in thyroid histopathology, when investigated, were observed. Those changes were considered consistent with the adverse effects observed in mammals.

**Similar dithiocarbamate substances**

**EU Commission concluded after EFSA processes**

- Mancozeb meets the criteria to be identified as having endocrine disrupting properties for humans and for non-target organisms- according to the T (thyroid) modality.
- Maneb was also regarded as having endocrine disrupting properties for humans and for non-target organisms- according to the T (thyroid) modality.
- In 2023 Metiram (another dithiocarbamate) was also regarded as having endocrine disrupting properties for humans and for non-target organisms- according to the T (thyroid) modality.

## 2.4 Overall conclusions

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.

Using a weight of evidence approach, the link between the adverse effect(s) and the endocrine mode of action was established based on biological plausibility, which was determined in the light of current scientific knowledge and under consideration of internationally agreed guidelines.

There is overwhelming evidence from the *in vivo* level 4 & 5 studies conducted with mancozeb and ETU in rats, mice, dogs and monkeys that support the hypothesis that the production of thyroid hormones T4 (thyroxine) and T3 (triiodothyronine) are inhibited, resulting in

[2] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R2100
[3] https://efsa.onlinelibrary.wiley.com/doi/pdfdirect/10.2903/j.efsa.2018.5311

disturbance of the HTP axis and an increase in TSH release, respectively. This results in excessive stimulation of thyroid follicular cells, resulting in hyperplasia and tumours during prolonged exposure.

Zineb meets all the above three criteria – it shows adverse effects (thyroid disorders) in humans; it has an endocrine mode of action (disruption of hormones metabolism and hypothalamic-pituitary-thyroid axis); and the adverse effects are a consequence of the endocrine mode of action. Therefore, the biocidal active substance zineb is identified as having endocrine-disrupting properties with respect to humans.

Regarding EAS modalities for humans no level 3 studies are available for zineb, mancozeb or ETU.

The weight of evidence indicates that zineb (read-across from mancozeb) and it's metabolite ETU, do not interact with the oestrogenic or androgenic hormonal systems. The mancozeb *in vitro* data are supported by a very large database of repeated dose and reproductive studies on mancozeb and ETU in rats, mice and dogs, also indicating that oestrogen and androgen hormonal systems are unaffected. The evidence from the experimental animal studies indicates mancozeb and ETU produce few or no effects on male or female reproductive organs or an effect on fertility.

Additionally, epidemiology studies have investigated possible associations between mancozeb exposure and adverse outcomes associated with modulation of the oestrogen and/or androgen hormonal systems. All findings are therefore supportive of mancozeb and ETU not affecting the oestrogen or androgen hormonal systems in mammalian species, including humans. Overall, it can be concluded that zineb (through read across from mancozeb) is not an endocrine disruptor in relation to the EAS modalities and that these modalities have been sufficiently investigated.

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 zineb meets 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 zineb to amphibia via water or diet interferes with endocrine mechanisms related to the thyroid and subsequently leads to adverse effects in intact organisms, namely perturbations in metamorphosis. Studies with ETU support this finding.

Overall, there is sufficient evidence to demonstrate population relevant effects as a consequence of exposure to zineb and that these are a consequence of an endocrine mode of action.

Thus, zineb meets 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. As this substance is identified as having endocrine-disrupting properties due to adverse effects on T-modality, no further studies are justified to conclude on the EAS-modalities in non-target organisms.

| **Property** | | **Conclusions** | |
|---|---|---|---|
| | Section A of Regulation (EU) 2017/2100: ED properties with respect to humans | Yes | Zineb fulfils 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 | |

## Reference list

Ireland, 2013 Assessment Report (AR) on the biocidal active substance zineb prepared by the rapporteur Member State Ireland. Regulation (EU) 92/2014. Available Online: www.echa.europa.eu

United Kingdom, 2019. Revised Renewal Assessment Report (RAR) on the active substance mancozeb prepared by the rapporteur Member State the United Kingdom in the framework of Commission Implementing Regulation(EU) No 844/2012, March 2019. Available Online: www.efsa.europa.eu

Italy, 2017. Renewal Assessment Report (RAR) on the active substance metiram prepared by the rapporteur Member State Italy, in the framework of Commission Implementing Regulation (EU) No 844/2012, November2017. Available online at: www.efsa.europa.eu

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