HEAL comments – SVHC identification proposal for Resorcinol

The Health and Environment Alliance (HEAL) thanks France for the proposal to identify resorcinol as a substance of very high concern (SVHC) under REACH article 57(f). We fully support this proposal and our detailed comments can be found below.

Resorcinol is a high-volume substance (registered at 1,000-10,000 tons/annum), which is used in a myriad of applications, including among others, cosmetics, hygiene products, pharmaceuticals, flame retardants, and industrial applications such as the manufacture of rubber products, adhesives, resins. Therefore, we consider that workers' and public exposure to resorcinol is high.

1) EDC properties and equivalent level of concern

Existing concerns relating to the substance endocrine disrupting properties for humans are well-known; and for this reason resorcinol has already been listed on both the SIN list and the TEDX list of potential endocrine disruptors for several years.

A 2012 analysis by the Danish Technical University[1] already concluded that Resorcinol was meeting the then proposed Danish criteria for endocrine disruption (category 1 – recognised EDC, based on vivo and in vitro data supporting: 1) adverse in vivo effects where an ED mode of action is highly plausible, and 2) an ED mode of action in vivo that is clearly linked to adverse in vivo effects (by e.g. read-across)). Highlights in the findings included the following: "*According to human case reports, resorcinol exerts anti-thyroid functions. Data are old, but quite clear: long-term administration of resorcinol to permeable (damaged) skin can cause myxoedema (reduced thyroid function) [...] In vitro, resorcinol has been shown to be a very potent inhibitor of the enzyme thyroid peroxide and to inhibit uptake of radioactive iodide, which are both effects that in vivo could lead to decreased thyroid hormone levels.*"

It is also relevant to note that resorcinol is part of a list of substances used in cosmetic products, for which the European Commission recently issued a call for data (May 2019), based on the very concerns of potential endocrine disrupting properties.[2]

We consider that the dossier supporting the proposed SVHC identification provides clear data to demonstrate that the substance meets the criteria of article 57(f) because of its endocrine disrupting properties for human health causing equivalent level of concern.

- Endocrine disrupting activity

Resorcinol acts on the endocrine system by inhibiting thyroperoxidase (TPO), a key step in thyroid hormone synthesis. In that regard, it is relevant to highlight that a recent scientific consensus

[1] Hass, U., Christiansen, S., Petersen, M. A., Boberg, J., Andersson, A-M., Skakkebæk, N. E., ... Bjerregaard, P.(2012). Evaluation of 22 SIN List 2.0 substances according to the Danish proposal on criteria for endocrine disrupters. DTU Food. https://backend.orbit.dtu.dk/ws/portalfiles/portal/51554411/SINreportandAnnex.pdf

[2] European Commission, DG Grow, Call for data on ingredients with potential endocrine-disrupting properties used in cosmetic products, May 2019, https://ec.europa.eu/growth/content/call-data-ingredients-potential-endocrine-disrupting-properties-used-cosmetic-products_en

statement included the alteration of hormone synthesis in its proposal for ten key characteristics of endocrine disrupting chemicals[3].

In vitro data shows that resorcinol *"is a potent TPO inhibitor compared to PTU and MMI in cells from porcine, rat or human origin"* (supporting dossier, p75). Both PTU (propylthiouracil) and MMI (methimazole or thiamazole) are used to treat hyperthyroidism. This strength of endocrine activity when compared with known endocrine-active agents, and the consistency of mechanism across species, provide very strong evidence for resorcinol's endocrine action.

- Mechanistic data

The impacts of TPO inhibition on thyroid function have been long studied and are clearly established. As detailed in the dossier, *"inhibition of TPO activity is widely accepted to directly impact TH synthesis and this is supported by more than three decades of research in humans and animals"* (supporting dossier, p75). Moreover, *"These key event relationships are considered established with a high level of evidence"* (supporting dossier, p.75).

Mechanistic data on TPO inhibition and thyroid function allows us to predict and explain biologically plausible effects of substances such as resorcinol. In the case of PTU and MMI, these effects may be therapeutic. However, in the case of unintended exposure to resorcinol, unintended changes in thyroid function must be seen as adverse. These effects are seen in vivo, for example through significant changes in thyroid hormone levels after resorcinol exposure in pups (supporting dossier, p.75).

The complexity of thyroid regulation sometimes might make these data hard to interpret (supporting dossier, p. 76). In practice, however, any unintentional modulation of thyroid function must be seen as adverse and potentially dangerous.

- Relevance to humans

There is incomplete but suggestive evidence that these same pathways lead to similar adverse effects in humans than in animals. Epidemiological data is limited to case studies described in detail in the supporting dossier, but it shows a high degree of consistency with the toxicological data and mechanisms. Considering the wide use of and exposure to resorcinol, it deserves to be fully considered.

It is also important to note that the limited epidemiological data should not be used as an argument against the clearly established mechanism of action. The human case study data alone is not definitive, but it provides one more piece of support that the well-established endocrine mechanism of action is relevant to humans.

As clarified in the ECHA/EFSA guidance on the EDC criteria for pesticides and biocides, *"when assembling and assessing the line of evidence, any available epidemiological studies should be considered as supportive evidence for the evaluation of whether an ED is likely to have adverse effects for humans. However, they cannot be used to override or dismiss evidence of adversity found in laboratory studies, nor can they replace laboratory studies."*[4]

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[3] La Merrill, M.A., Vandenberg, L.N., Smith, M.T. et al. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. Nat Rev Endocrinol 16, 45–57 (2020). https://doi.org/10.1038/s41574-019-0273-8

[4] ECHA-EFSA, "Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009", 7 June 2018, https://doi.org/10.2903/j.efsa.2018.5311

When it comes to the relevance of the animal data used for humans, we know that the thyroid systems are highly conserved across vertebrate species and there is no supporting evidence that animal data is not relevant; all the contrary. In this regard, we recall some of the highlights of a workshop organised by the European Commission on thyroid disruption in 2017: *"Observations of thyroid disruption in rodent laboratory studies can be useful for the identification of thyroid disrupting properties in other wildlife mammalian species. Considering the preservation of the thyroid system across taxa, such data would also raise concerns for e.g. birds, fish or amphibians, although species-species extrapolations will not be straight-forward due to differences in exposure routes (e.g. dermal in amphibians versus oral in rodents) and other factors (e.g. the presence of the placenta in mammals). Conversely, data from non-mammalian test species can be used to inform on the mode of action of putative thyroid disrupting chemicals in mammals. This is strongly supported by the observation that most amphibian thyroid disruptors have elicited positive responses also in rodent tests."*[5]

The evidence for resorcinol's endocrine action via TPO inhibition is extremely strong. Although the scientific understanding of the mechanistic action of the thyroid system for humans remains to be perfected, the understanding acquired across numerous species leads us to assign the observed adverse effects a very high level of biological plausibility[6].

2) <u>ELOC assessment</u>

Resorcinol disrupts thyroid hormone synthesis through a key mode of action. This mechanism is well understood and has a very high biological plausibility. Case studies accompanying the dossier provide strong (although not definitive) evidence that the adverse effects seen in animals are relevant in humans (and on the contrary no evidence suggests that the effects seen in animals are not relevant in humans).

It is a fact that the thyroid hormone plays an extremely important role in the prenatal brain development of the child. Endogenous concentrations of TH are extremely low, and very tightly regulated (8–30 pg/ml). Given the sensitivity and complexity of the thyroid system, any unintended effect must therefore be seen as adverse. On the other hand, because existing test methods are mostly lacking sensitivity when it comes to thyroid disruption, it has been clarified that changes in TH are relevant for risk assessment when looking for potential neurodevelopmental effects[7].

Also the recently agreed ECHA-EFSA guidance on the EDC criteria for pesticides and biocides[8] brings useful clarifications in relation to interpreting thyroid-related data from experimental animals:

> *1) Substances inducing histopathological changes (i.e. follicular cell hypertrophy and/or hyperplasia and/or neoplasia) in the thyroid, with or without changes in the circulating levels*

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[5] Kortenkamp, A., Martin, O., Baynes, A., Silva, E., Petersen, M. A., & Hass, U. (2017). Supporting the organization of a workshop on thyroid disruption – final report. European Commission. https://doi.org/10.2779/921523

[6] R. Thomas Zoeller, Shirlee W. Tan & Rochelle W. Tyl (2007) General Background on the Hypothalamic-Pituitary-Thyroid (HPT) Axis, Critical Reviews in Toxicology, 37:1-2, 11-53, DOI: 10.1080/10408440601123446

[7] Kortenkamp, A., Martin, O., Baynes, A., Silva, E., Petersen, M. A., & Hass, U. (2017). Supporting the organization of a workshop on thyroid disruption – final report. European Commission. https://doi.org/10.2779/921523

[8] ECHA-EFSA, "Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009", 7 June 2018, https://doi.org/10.2903/j.efsa.2018.5311, p. 102

> *of THs, would pose a hazard for human thyroid hormone insufficiency in adults as well as pre- and post-natal neurological development of offspring.*
>
> *2) Substances that alter the circulating levels of T3 and/or T4 without histopathological findings would still present a potential concern for neurodevelopment.*
>
> *3) In the absence of substance-specific data which provide proof of the contrary, humans and rodents are considered to be equally sensitive to thyroid-disruption (including cases where liver enzyme induction is responsible for increased TH clearance).*

Disruption of TH is known to have very significant and clearly adverse developmental impacts, including:

- Goitre: As rightly highlighted in the dossier, *"these observations are in line with the physio pathological pattern of effects observed in experimental animals exposed to resorcinol and indicate that a moderate inhibition of TPO can result in goitre in the long-term in humans."* (supporting dossier, p. 77)

- Neurological impacts: In vivo data provides strong evidence of neurodevelopmental impacts of resorcinol, consistent with the known mechanisms (supporting dossier p.78, and Figure 5 on that page). Again the supporting dossier rightly points out that perinatal modulation of thyroid hormone *"could trigger long-term modifications in the neural structures underlying locomotor activity, thereby resulting in changed activity during adulthood (Zoeller & Rovet, 2004)"* (supporting dossier, p.78). Similarly, it clarifies that *"the importance of even modest changes in TH during pregnancy has emerged and strengthened recently. The results of a comprehensive review by the US EPA (2019) lend support to the concept that maternal FT4, especially in the hypothyroxinemic range, is critical to proper neurodevelopment of the offspring. Across different age ranges and neurodevelopmental indices, the impact of altered FT4 is seen even with small incremental changes in FT4".* (supporting dossier, p. 10)

- Hypothyroidism: This condition has very significant adverse effects, and *"has clinical implications related to nearly all major organs"* (supporting dossier, table 30, p.87). Again, the dossier rightly points out that: *"It is therefore a serious condition and the capacity for resorcinol to induce or contribute to existing hypothyroidism raises significant concern"* (supporting dossier, p. 88). Neurological effects of thyroid disruption are developmental, and thus not reversible.

Irreversibility of the effects and difficult derivation of a safe concentration

It has been suggested that resorcinol may not reach the level of equivalent concern because of the reversibility of some thyroid system effects, particularly hypothyroidism. However, the dossier submitter has rightly argued that, while hypothyroidism can be treated, it is quite likely to take years not only to be diagnosed, but also reversed.

More importantly, in our view, even though hypothyroidism is treatable, *"many patients with a diagnosis of hypothyroidism report a decreased quality of life compared to people without hypothyroidism."* In this sense, these impacts may be considered irreversible or incompletely reversible, and are likely to have lifelong implications.

Finally, it is unclear whether a safe concentration can be derived for the effects of TPO inhibition. Many EDCs have or are suspected to have non-monotonic dose-response (NMDR) curves, making low-dose effects important, yet hard, to identify, and overall making the case for using a non-threshold approach by default to account for uncertainties[9]. There is as yet no strong evidence for NMDR of resorcinol. However, in a study of ethylenethiourea exposure in rats, Maranghi et al (2013)[10] identified altered thyroid function at very low doses, concluding, *"these findings suggest the existence of an inverted U-shape dose–response curve between ETU exposure and these biomarkers of thyroid function with maximal response observed at intermediate dose."* Since ethylenethiourea acts via the same pathway as resorcinol, via the inhibition of TPO, it is very plausible that resorcinol might also have NMDR.

3) Appreciation of the earlier Finnish evaluation

For the purpose of these comments, it is relevant to come back to the earlier evaluation carried out by the Finnish Competent Authority.

Clarifications on the conclusions of the Finnish evaluation

Firstly, it is important to highlight that Finland's earlier analysis agrees with the current French proposal on several of the scientific conclusions, including that *"resorcinol has the potential to cause severe adverse health effects in humans"*[11] (RMOA conclusion, p. 7) and that *"adverse effects on thyroid gland can impair quality of life and are a societal concern"* (RMOA conclusion p.7).

Moreover Finland's evaluation report[12] already highlighted that resorcinol *"is likely an ED substance"* (evaluation report, p.8) that works via a specific mode of action (inhibition of TPO). We also note with interest that the reason why Finland did not ask for more data from the registrant is that they concluded at the time *"that it may not be possible to gain such new information with AMA or LAGDA test that would significantly change or improve the conclusion on thyroid disrupting properties of resorcinol"*. (Evaluation report, p. 8)

In other words, according to the Finnish CA, additional non-mammalian (AMA and LAGDA, amphibian) data would be unlikely to provide data clarifying the issue. This conclusion however overlooks the important fact that the LAGDA test has recently been included in the OECD conceptual framework for apical effects related to the thyroid. Together with other amphibian tests, the LAGDA is increasingly being used in the context of testing for thyroid disruption and is recognised as more sensitive that certain mammalian studies for testing in the context of thyroid disruption.

As highlighted in a recent review about non-mammalian in vivo thyroid testing: *"Although alternative models represented by amphibians, fish and avian species may appear too far removed*

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[9] Danish Centre on endocrine disruptors. Report on Interpretation of knowledge on endocrine disrupting substances (EDs) – what is the risk?. http://www.cend.dk/files/ED_Risk_report-final-2019.pdf

[10] Francesca Maranghi,Simona De Angelis,Roberta Tassinari,Flavia Chiarotti,Stefano Lorenzetti,Gabriele Moracci,Daniele Marcoccia,Enzo Gilardi,Antonio Di Virgilio,Agostino Eusepi,Alberto Mantovani,Antonella Olivieri, Reproductive toxicity and thyroid effects in Sprague Dawley rats exposed to low doses of ethylenethiourea, Food and Chemical Toxicology, September 2013, https://doi.org/10.1016/j.fct.2013.05.048

[11] Tukes - Finnish Safety and Chemicals Agency (2018). Risk Management Option Analysis Conclusion Document. Resorcinol, EC No 203-585-2, CAS No 108-46-3. 8 may 2018 https://echa.europa.eu/documents/10162/af20d0cd-aa45-5cb7-4fe8-9fdf38f3cf15

[12] Tukes - Finnish Safety and Chemicals Agency (2017). Substance Evaluation Conclusion as required by REACH Article 48 and Evaluation Report for Resorcinol, EC No 203-585-2, CAS No 108-46-3. Evaluating Member State(s): Finland. 24 October 2017 https://echa.europa.eu/documents/10162/97172844-3552-65bd-a03e-c75e445c0b62

from mammals to be relevant to human health, molecular components of the HPT axis are highly conserved across vertebrate taxa and TH signalling involves the same circulating hormones (…). Markedly, the peak of THs observed around the perinatal period in mammals is also found during developmental transitions in other vertebrates (…) as demonstrated by amphibian metamorphosis (…), subtle or spectacular post-hatching metamorphosis in teleost fish (…), and hatching in precocial birds."[13] Therefore, the Finnish conclusion and rationale are questionable.

Flawed legal interpretation of the purpose of the SVHC identification

Strangely, Finland argued against the SVHC identification based on the argument that the factors qualifying a substance for SVHC identification is that there should be a specific need to apply the authorisation process (for which SVHC identification is the first step). In other words, Finland concluded that an SVHC identification (hazard identification) is not necessary based on arguments that risks can be controlled without authorisation.

In our view, this is however a flawed legal argument, which shows a misunderstanding of the REACH regulation and the purpose of SVHC listing. The Court of Justice of the EU has already clarified this point.

According to the Court:

- The *"inclusion of a substance in the candidate list of substances are carried out solely on account of the intrinsic properties of a substance and not on account of the use of that substance"*[14].
- In the context of article 57(f), when interpreting the notion of "concern", *"ECHA has a discretion but is not obliged to take into account information other than concerning intrinsic properties"*[15].

Therefore, the hazard assessment step (through the SVHC identification) is fully justified and should not be jeopardized by risk management considerations.

Conclusion

Based on the supporting dossier and all of the above considerations, we consider that resorcinol clearly meets the criteria for SVHC identification according to article 57(f).

[13] S. Coudercq, M. Leemans, J.B. Fini, "Testing for thyroid hormone disruptors, a review of non-mammalian in vivo models", 6 March 2020, https://doi.org/10.1016/j.mce.2020.110779
[14] European Court of Justice, T-185/17 paragraph 75, referring to C-650/15P; and C-324/15P paragraph 25
[15] European Court of Justice, T-185/17 paragraph 79, referring to C-650/15P; and T-636/17 paragraphs 41 and 67