12/06/2020

OPINION OF THE MEMBER STATE COMMITTEE

ON THE IDENTIFICATION OF

RESORCINOL

AS A SUBSTANCE OF VERY HIGH CONCERN

According to Articles 57 and 59 of
Regulation (EC) 1907/2006[1]

Adopted on 12 June 2020

This opinion concerns

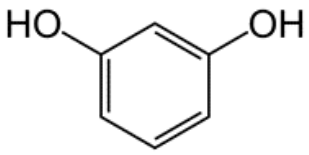
Substance name: Resorcinol

EC number: 203-585-2

CAS number: 108-46-3

Molecular formula: $C_6H_6O_2$

Structural formula:



[1]Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

France presented a proposal in accordance with Article 59(3) and Annex XV of the REACH Regulation (25 February 2020) on identification of *Resorcinol (EC No. 203-585-2)* as a substance of very high concern due to its endocrine disrupting properties for which there is scientific evidence of probable serious effects to human health which give rise to an equivalent level of concern to those of other substances listed in paragraphs (a) to (e) of Article 57 of REACH Regulation.

The Annex XV dossier was circulated to Member States on 3 March 2020 and the Annex XV report was made available to interested parties on the ECHA website on the same day according to Articles 59(3) and 59(4).

Comments were received from both Member States and interested parties on the proposal.

The dossier was referred to the Member State Committee on 18 May 2020 and discussed in the meeting on 10-12 June 2020 of the Member State Committee.

MSC did not reach unanimous agreement on whether the information provided in the SVHC proposal is sufficient to constitute an equivalent level of concern to CMRs and PBTs/vPvBs in accordance with Article 57 (f) of the REACH Regulation.

Three MSC members expressed a minority position, including their grounds, which is made available in a separate document. Pursuant to Articles 59 (9) and 85 (8) of REACH in order for the Commission to draft a proposal on the identification of the substance in accordance with the procedure outlined in Article 133 (3) of the REACH Regulation, the Member State Committee provides this opinion, consisting of the position of the majority of its members, including its grounds. The minority views will be attached. In accordance with Article 59 (9), a final decision on the identification of resorcinol shall be taken in accordance with the procedure referred to in Article 133(3).

Opinion of the Member State Committee in accordance with Article 59(8):

Resorcinol should be identified as a substance meeting the criteria of Article 57 (f) of Regulation (EC) 1907/2006 (REACH) because it is a substance with endocrine disrupting properties for which there is scientific evidence of probable serious effects to human health which give rise to an equivalent level of concern to those of other substances listed in paragraphs (a) to (e) of Article 57 of REACH Regulation.

UNDERLYING ARGUMENTATION
FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN

Resorcinol should be identified as a substance of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) because it is a substance with endocrine disrupting properties for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 REACH.

ED properties of resorcinol relevant for human health

Resorcinol fulfils the definition of an endocrine disruptor relevant for human health on the following basis:

It is well established based on a series of case reports, where high doses of resorcinol were given, that severe hypothyroidism[2] was diagnosed and reversed when exposure to resorcinol was stopped. This leads to the conclusion that exposure to resorcinol can affect the regulation of the thyroid function inducing hypothyroidism in humans. The endocrine disrupting properties of resorcinol have therefore been demonstrated in humans under these specific conditions of exposure.

The medical cases reporting these effects are patients that applied resorcinol to damaged skin for 9 out of 10 cases. However, considering that the skin was reported as intact in one additional case and that skin absorption has been demonstrated *in vitro*, these data are considered relevant in the assessment.

In addition, findings consistent with the MoA (mode of action) of thyroid disruption via TPO (thyroperoxidase) inhibition are also reported in several experimental studies via drinking water. Similar findings reported in studies conducted by subcutaneous, dietary and inhalation routes provide supportive evidence. In particular histopathological changes in the thyroid and changes in the circulating levels of T3 (triiodothyronine) or T4 (thyroxine), are considered as adverse effects.

Inhibition of TPO by resorcinol, a key enzyme in the synthesis of thyroid hormones, is established *in vitro* in several experimental designs.

Altogether, the effects observed in humans and in some experimental studies are fully consistent with the MoA via TPO inhibition. Based on current knowledge, the biological plausibility of a causal link between inhibition of TPO, disruption of thyroid hormone levels and adverse effects linked to low thyroid hormone levels is strong. A recently validated AOP (adverse outcome pathway) described the relationship between inhibition of TPO, decreased T4 and neurodevelopmental alteration due to maternal low T4 concentration as having a high level of evidence for humans (AOP n°42[3]). With the validation of this AOP by the OECD, further experimental data investigating (neuro)development are not necessary to confirm the effects observed in the preliminary two-generation study available in the registration dossier.

Based on a weight of evidence analysis of the available data, there is scientific evidence that resorcinol can have adverse effects on human health through thyroid disruption and fulfils the definition of an endocrine disruptor.

Overall assessment of an equivalent level of concern

[2] Hypothyroidism is characterised by low FT4 and high TSH
[3] https://aopwiki.org/aops/42

Due to the ED properties of resorcinol, it is a substance of equivalent level of concern as specified in article 57 of REACH on the following basis:

- Human cases have been identified under specific conditions and this may raise some questions on their relevance for actual conditions of human exposure. The effects induced by resorcinol in humans and in experimental animals are complementary in the demonstration that they cannot be considered as specific to exceptional conditions of exposure, in particular because some populations and periods of exposure can be associated with specific sensitivity. Besides, the possibility that resorcinol may induce effects in humans under common conditions of exposure can not be excluded on a toxico-kinetic basis.

- Hypothyroidism has clinical implications related to nearly all major organs. It is a serious condition and the capacity for resorcinol to induce or contribute to existing (subclinical[4]) hypothyroidism raises significant concern. Alterations of foetal development, in particular brain development as a consequence of low maternal levels in TH, have been associated with serious adverse health outcomes.

- Although generally considered reversible, hypothyroidism raises concern because of the delay in the onset of symptoms. Effects can be compensated for in the short-term but it may result in severe forms that appear after long-term exposure. In addition, less severe forms are expected to be more difficult to identify because symptoms are generally unspecific. This results in delays in diagnosis and treatment. In contrast, the neurodevelopmental effects expected as a consequence of maternal low concentration of T4 have consequences that are observed later in life, without a direct exposure. They are considered as permanent and irreversible and raise an additional concern. The difficulty posed by latency both in terms of detection of the effect and induction of developmental effects is considered as an additional concern.

- The adverse effects induced or enhanced by resorcinol may lead to a reduced quality of life.

- Thyroid-disrupting chemicals may have a role in the increased incidence of pathologies of the thyroid or conditions associated with thyroid dysfunction, in particular hypothyroidism, thyroid cancer and neurodevelopmental disorders. This raises a societal concern.

- A number of uncertainties to derive a ‘safe concentration’ have emerged considering the resorcinol data as detailed below as well as considering recent developments in the understanding of the consequences of thyroid disruption.

    - The potency of TPO inhibition can be modulated by several factors, in particular iodine levels.

    - Considering the wide range of functions influenced by TH (thyroid hormone), it is also highly challenging to fully characterise these effects and their dose-response in experimental studies. In particular, neurodevelopmental effects are generally considered as the most sensitive. There is some evidence indicating a possible neurodevelopmental effect of resorcinol but that has not been investigated in detail.

    - Lack of information on internal levels of exposure (plasma concentration) in human cases and on incidence of less severe hypothyroidism preclude the estimation of a dose-response relationship in humans.

    - The discrepancy between experimental results depending on the route of administration is not fully understood. In particular, internal exposure and

[4] Subclinical hypothyroidism is characterised by normal FT4 and high TSH

toxicokinetic differences depending on route of exposure and vehicle have not been fully characterised. Comparing the severity of effects between rodents and humans, a higher sensitivity of humans or certain humans cannot be excluded. Depending on the route of administration, some effects have been observed in experimental studies at doses associated with low systemic concentrations of resorcinol in experimental studies. Large uncertainties remain on the level of systemic exposure to resorcinol that induces effects on the thyroid function. Additional uncertainty remains on the level of systemic exposure to resorcinol after different routes of exposure.

- Hypothyroidism is among the most common of endocrine conditions and resorcinol can aggravate existing conditions. Any additional thyroid disturbance by resorcinol may in some instances counteract part of the compensatory mechanisms developed by the thyroid gland, namely increased expression of TPO, and could aggravate an existing condition that is of relatively common prevalence although often undiagnosed. Pregnancy is also a period that is highly sensitive to disruption of TH regulation because of a higher need for TH and physiological changes affecting their toxicokinetics. Besides, 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 (free T4), especially in the hypothyroxinemic range[5], 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. Pregnancy is therefore likely to be a period of sensitivity to the alteration of TH regulation by resorcinol, with consequences for the neurodevelopment of the offspring that can be affected even by small changes. A number of vulnerable populations may therefore be of particular concern. Sensitive populations include those with undiagnosed subclinical hypothyroidism, marginal dietary iodine deficiency, pregnant women, the developing foetus, the newborn, and young infant – all of which may be particularly susceptible to TH disruption induced by resorcinol. Establishing safe levels for these particularly sensitive populations is surrounded with large uncertainties due to the lack of agreed parameters to identify such persons and high symptom variability in relation to the physiological status.

Some of the effects that resorcinol may induce in relation to its thyroid-disrupting potential are serious and are irreversible or may not be detectable without delay. They can impact on the quality of life and raise societal concern of a high and increasing burden. Most importantly, the difficulty to establish a safe level with sufficient certainty raises concern on the capacity to manage safe use of the substance in particular for sensitive populations and with the emergence of the understanding that small changes in maternal T4 can affect brain development of the offspring. Altogether, this gives rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 REACH.

Conclusion

Based on these elements, there is scientific evidence of probable serious effects to human health of resorcinol in relation to its thyroid-disrupting potential, which gives rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 REACH.

[5] Hypothyroxinemia is characterised by low FT4 and normal TSH

Reference:

Support Document to the MSC opinion for *Resorcinol* (Member State Committee, 12 June 2020)