Risk Management Option Analysis Conclusion Document

Substance Name: Resorcinol

EC Number: 203-585-2

CAS Number: 108-46-3

Authority: Finnish Safety and Chemicals Agency

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Foreword

The purpose of Risk Management Option analysis (RMOA) is to help authorities decide whether further regulatory risk management activities are required for a substance and to identify the most appropriate instrument to address a concern.

RMOA is a voluntary step, i.e., it is not part of the processes as defined in the legislation. For authorities, documenting the RMOA allows the sharing of information and promoting early discussion, which helps lead to a common understanding on the action pursued. A Member State or ECHA (at the request of the Commission) can carry out this case-by-case analysis in order to conclude whether a substance is a 'relevant substance of very high concern (SVHC)' in the sense of the SVHC Roadmap to 2020[1].

An RMOA can conclude that regulatory risk management at EU level is required for a substance (e.g. harmonised classification and labelling, Candidate List inclusion, restriction, other EU legislation) or that no regulatory action is required at EU level. Any subsequent regulatory processes under the REACH Regulation include consultation of interested parties and appropriate decision making involving Member State Competent Authorities and the European Commission as defined in REACH.

This Conclusion document provides the outcome of the RMOA carried out by the author authority. In this conclusion document, the authority considers how the available information collected on the substance can be used to conclude whether regulatory risk management activities are required for a substance and which is the most appropriate instrument to address a concern. With this Conclusion document the Commission, the competent authorities of the other Member States and stakeholders are informed of the considerations of the author authority. In case the author authority proposes in this conclusion document further regulatory risk management measures, this shall not be considered initiating those other measures or processes. Since this document only reflects the views of the author authority, it does not preclude Member States or the European Commission from considering or initiating regulatory risk management measures which they deem appropriate.

[1] For more information on the SVHC Roadmap: http://echa.europa.eu/addressing-chemicals-of-concern/substances-of-potential-concern/svhc-roadmap-to-2020-implementation

1. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Harmonised classification

Resorcinol has got harmonised classification for being very toxic to aquatic life, is harmful if swallowed, causes serious eye irritation and causes skin irritation.

REACH registration

The initial registration year was 2010.

Substance evaluation (SEv)

Evaluation year was 2016 and the evaluating member state was Finland. The draft conclusions of the evaluation were discussed in the Endocrine Disruptor Expert Group in 10-11 November 2016.

Information requests were not considered necessary and no decision was drawn up. The SEv conclusion and evaluation report[2] was submitted in October 2017.

Risk management options analysis (RMOA)

To further analyse adequate risk management options, an RMOA was initiated after the substance evaluation.

The draft conclusions of the RMOA was discussed in the Risk Management Expert Meeting (RiME-3/2017) in 4-5 October 2017.

2. CONCLUSION OF RMOA

This conclusion is based on the REACH and CLP data as well as other available relevant information taking into account the SVHC Roadmap to 2020, where appropriate.

Conclusions	**Tick box**
Need for follow-up regulatory action at EU level:	
Harmonised classification and labelling	X
Identification as SVHC (authorisation)	
Restriction under REACH	
Other EU-wide regulatory measures	
Need for action other than EU regulatory action	
No action needed at this time	

[2] SEv Report (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), 24 October 2017.

https://echa.europa.eu/fi/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e1807eaff8

3. NEED FOR FOLLOW-UP REGULATORY ACTION AT EU LEVEL

3.1 Harmonised classification and labelling

Resorcinol has the following harmonised classifications: Acute Tox 4* (minimum classification according to the earlier legislation), Skin Irrit 2, Eye Irrit 2, and Aquatic Acute 1. Although skin sensitising properties of resorcinol seem to be well established, it does not have harmonised classification for this hazard end point. The Registrant(s) have self-classified resorcinol as Skin Sens 1B.

The sensitisation properties of resorcinol were not in the scope of substance evaluation and were not assessed in depth. Based on animal and human data, Skin Sens 1 classification according to CLP criteria seems to be warranted and probably also subcategorization. Based on the sensitising properties, the Registrants have self-classified resorcinol as Skin Sens 1B; H317 (May cause an allergic skin reaction). When Category 1A cannot be excluded, Category 1 should be applied instead of Category 1B as stated in the guidance on the application of the CLP criteria.

SCCS[3] has concluded that resorcinol should be regarded as a strong sensitiser. This is based on LLNA (Local Lymph Node Assay) in mice. According to the guidance on CLP criteria, the EC value 1.4% indicates strong skin sensitisation potency, and classification to sub-category Skin Sens 1A could be possible as EC is ≤ 2%.

Therefore, it was concluded that harmonizing the classification could increase the safety of workers against the risk of resorcinol-induced skin sensitisation. Harmonised classification for skin sensitisation could lead the Scientific Committee on Consumer Safety (SCCS) to re-evaluate the use of resorcinol in cosmetics that seems to be the only consumer use. Although skin sensitisation is not one of the hazard end points which normally are subject to harmonised classification and labelling, harmonisation is possible if justification is provided demonstrating the need for such action at EU level.

The need to harmonise self-classifications for other health hazards could also be considered. In addition, the minimum classification for Acute toxicity could be addressed in CLH proposal.

Resorcinol has a harmonised classification Aquatic Acute Category 1 according to the CLP Regulation (EC) 1272/2008. The substance has also been self-classified as Aquatic Chronic Category 3 based on the available data (adequate chronic toxicity data available with the lowest NOEC of ≥ 0.172 mg/l, biodegradable substance). This classification might be considered rather conservative as the NOEC value of 0.172 mg/l was the highest concentration tested with no observed effects.

However, Aquatic Chronic Category 3 classification cannot be excluded for resorcinol as there are no long-term studies available on the most sensitive species *Daphnia magna*, with test concentration range reaching the classification criteria for Chronic Category 3 (≤ 1 mg/l). If the chronic classification became warranted for resorcinol the label elements would slightly change (hazard statement H410 'Very toxic to aquatic life with long-lasting effects' replacing H400 'Very toxic to aquatic life). GHS pictogram has already been applied based on the harmonised aquatic acute classification.

Harmonisation of long-term aquatic hazard might impact the level of protection in downstream legislations, but this has not been currently analysed.

[3] SCCS (2010). SCCS (Scientific Committee on Consumer Safety), Opinion on Resorcinol, 23 March 2010, SCCS/1270/09. http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_015.pdf

Harmonisation of the skin sensitisation and/or aquatic chronic classification for resorcinol might result in improved risk management measures under downstream legislations. Comparable improvement in RMMs could be achieved by harmonising also classification for other hazards self-classified by the Registrant(s), if classification is warranted according to the CLP criteria.

3.2 Identification as a substance of very high concern, SVHC (first step towards authorisation)

SVHC identification and subsequent authorisation - human health

The intrinsic properties of resorcinol may fulfil the definition of an endocrine disruptor from WHO/IPCS[4] and further elaborated by the European Commission's Endocrine Disrupters Expert Advisory Group[5].

The medical case reports from 1950 to 1977 demonstrate some evidence of a causal association between hypothyroidism and use of resorcinol containing ointments in large quantities to broken skin over long periods. Due to several confounding factors, a definite link between resorcinol and thyroid related effects cannot be confirmed. Older studies in experimental animals using subcutaneous injection of resorcinol in an oily solution and dermally in ointment, reviewed in WHO/IPCS document from 2006[6], can be considered as a supportive evidence for resorcinol effects on thyroid gland. Experimental animal studies and epidemiological studies on occupational exposure in the registration dossier do not indicate clear effects on thyroid gland.

Overall, when the available *in vitro* data on the mode of action (inhibition of thyroid peroxidase, decrease of iodine uptake and iodine organification) is taken into account, the causal association between the exposure to resorcinol and thyroid dysfunction (hypothyroidism) is considered plausible. However, due to the poor quality and reliability of the data, the thyroid effects in these reports and studies are considered to represent a borderline case regarding the fulfilling of the definition for an endocrine disrupter. Therefore, the results must be interpreted with caution.

There is currently no guidance available on how to assess that an adverse health effect represents an equivalent level of concern (ELoC) to a CMR substance, thereby fulfilling criteria for SVHC identification according to article 57(f) of REACH for human health. A discussion paper of ECHA is however available[7] with a specific focus on sensitisers. The criteria identified in this paper to evaluate the ELoC are considered relevant for the present case. To conclude on whether resorcinol, possibly fulfilling the definition of an endocrine disruptor, also fulfils Article 57(f), the following factors are considered.

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[4] WHO/IPCS (2002). Global Assessment of the State-of-the-Science of Endocrine Disruptors. WHO/IPCS/EDC/02.2. Geneva: World Health Organisation

[5] JRC (2013). Key scientific issues relevant to the identification and characterisation of endocrine disrupting substances - Report of the Endocrine Disrupters Expert Advisory Group. Eds: S. Munn and M. Goumenou. European Commission, Joint Research Centre. http://ihcp.jrc.ec.europa.eu/

[6] WHO/IPCS (2006). CICAD - Concise International Chemical Assessment Document for Resorcinol 71. International Programme for Chemical Safety, Geneva.

[7] ECHA (2012). Identification of substances as SVHCs due to equivalent level of concern to CMRs (Article 57(f)) – sensitisers as an example. Available at: https://echa.europa.eu/documents/10162/13657/svhc_art_57f_sensitisers_en.pdf/a50728cc-6514-486c-9108-193a88b4bc9e

- Health effects:
  - Type of possible health effects
  - Irreversibility of health effects
  - Delay of health effects
- Other factors:
  - Quality of life affected
  - Societal concern
  - Is derivation of a 'safe concentration' possible?

The observed effects on thyroid gland (i.e. myxoedema and goitre) in the medical case reports (adult patients) indicate that resorcinol has the potential to cause severe adverse health effects in humans. The medical case reports suggest that the observed effects were not permanent and irreversible because in most of the cases effects relieved/disappeared after cessation the use of ointment. There seems to be a delay between the exposure and manifestation of severe thyroid gland effects because individuals had been exposed to resorcinol for a long period (months/years) before the effects were noticed. Indeed, adverse effects on thyroid gland can impair quality of life and are a societal concern. Based on the presently available information, it is not possible to derive a reliable dose-response relationship for the thyroid effects seen.

It should be noted that resorcinol is only used in the industrial sites and exposure of consumers to resorcinol in articles has been excluded. Furthermore, thyroid effects in the medical case reports have been seen only in unrealistic exposure conditions after using resorcinol containing ointments as a medicine in large quantities over long periods (months or years) to ulcerated skin where direct vascular exposure may have occurred. It has been estimated that the exposure levels in these studies were very high (greater than 2 grams resorcinol per day). Based on available toxicokinetic information, dermal absorption of resorcinol through healthy/intact skin seems to be very low (< 1 %). Moreover, animal studies suggest that the efficient and rapid metabolism (probably by first pass metabolism in the liver) and excretion of resorcinol, in most cases, prevents resorcinol from reaching systemic concentrations which are toxic for the thyroid gland.

To be in line with the Judgment of the court[8] related to the interpretation of Art 57(f) and ELoC estimation (paragraph 36), the necessity of the authorisation process to control the risk from the use of resorcinol was assessed during the RMOA.

As a result, SVHC identification based on thyroid disrupting properties seen in humans and subsequent inclusion in the Annex XIV (authorisation) was not considered a necessary risk management action for resorcinol, because

a) thyroid effects have been observed only in unrealistic exposure conditions in the reported medical cases, and therefore it is unlikely that the effects occur under the normal conditions of use of resorcinol,

b) recommended RMMs, described in the registration dossier, seem to adequately control worker exposure to resorcinol used at industrial sites,

c) based on the information provided in the registration dossier, exposure of consumers to resorcinol in articles can be excluded,

d) risks of resorcinol are also managed under the OSH legislation and

e) the human risk assessment and risk management of consumer uses of resorcinol in cosmetic products are in the scope of the Cosmetic Regulation.

Overall, when taking account of all the available information, the current evidence was not considered to indicate that resorcinol would be a substance of very high concern because of its thyroid disrupting properties, causing probable serious effects to human

[8] Court of Justice of the European Union (2017). Judgment of the court (First Chamber), 15 March 2017. Case C-323/15 P.

health, which give rise to an equivalent level of concern to those of other substances listed in paragraphs (a) to (e) of Article 57.

In conclusion, SVHC identification and subsequent inclusion in the Annex XIV (authorisation) is currently not seen a necessary risk management action for resorcinol to protect human health.

However, a future need for follow-up action (e.g. SVHC identification) cannot be excluded if new information on risks in humans becomes available.

SVHC identification and subsequent authorisation - environment

In the course of substance evaluation resorcinol could be identified as a potential ED substance for thyroid in the environment, due to its thyroid disrupting potency, i.e. thyroid peroxidase inhibition, on fish embryos.

No apical endpoints straight related to thyroid disruption have been measured in the environmental assays. In fish early life stage toxicity tests embryotoxic effects were seen in rather high concentrations (LOEC ≥ 100 mg/L). No effects were seen in *Daphnia* reproduction in the highest tested concentration (0.172 mg/L). However, these results cannot be considered as diagnostic for thyroid effects.

Resorcinol has shown not to be accumulative in the environment (not P(ersistent), not B(ioaccumulable)), has low sorption potential to organic matter and is well-soluble in water, and hence no constant elevation of concentrations of resorcinol in the environment would be expected. Resorcinol is also a natural plant phenol and therefore potentially present in the environmental compartments.

Considering all the available information on resorcinol it was concluded that the applicability of SVHC identification of resorcinol on the grounds of environmental ED criteria and the following authorisation process, to manage risks of resorcinol, should be examined by taking all the available information into account. To evaluate the equivalent level of concern (ELoC), the environmental fate properties of resorcinol were considered relevant, in addition to the intrinsic hazardous properties (potential ED mode of action). This approach has been approved in the Judgement of the court[8].

The current evidence on the intrinsic hazard properties and other environmental properties of resorcinol were not considered sufficient to conclude that the thyroid effects would give rise to an equivalent level of concern in the environment as compared to those of other substances listed in paragraphs (a) to (e) of Article 57.

In conclusion, SVHC identification and subsequent authorisation were not seen necessary to control the risks to the environment, arising from the use of resorcinol.

3.3 Restriction under REACH

The evaluation of the available information on resorcinol did not indicate such unacceptable risks to human health or the environment arising from the manufacture, placing on the market and use of a substance that the risks would need to be addressed on a community wide basis. Therefore, it was concluded that restriction process seems to be inappropriate for resorcinol.

4. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS IF NECESSARY

Follow-up action	Date for follow-up	Actor
CLH proposal	2020/21	FI