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

Dated: 24 October 2017

Template Version 2.1
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Evaluating Member State Competent Authority

Finnish Safety and Chemicals Agency (Tukes)
P.O. Box 66 (Opastinsilta 12 B)
FI-00521 Helsinki,
Finland
Tel: +358 29 5052 000
Fax:
Email: Reach_Evaluation@tukes.fi

Year of evaluation in CoRAP: 2016

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the Registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Resorcinol was originally selected for substance evaluation to clarify concerns about:

Potential endocrine disruptor (ED)

and

Wide dispersive use

Consumer use

High (aggregated) tonnage

During the evaluation, no other concerns was identified.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Resorcinol has a harmonized classification (Acute Tox. 4, Skin Irrit. 2, Eye Irrit. 2, Aquatic Acute 1) in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation).

Risk Management Option (RMO) analysis of resorcinol is ongoing.

The European Food and Safety Authority (EFSA) Panel on Food Additives and Nutrient Sources added to Food (ANS) has delivered a scientific opinion on the safety of resorcinol when used as an antioxidant in crustaceans (EFSA, 2010). The conservative estimates of acute consumption of shrimps (the only category for which experimental data were reported) indicate that dietary exposure to resorcinol for adults and for children would exceed the ADI (Acceptable Daily Intake) when the residual concentration of resorcinol in whole raw shrimps is above 35 mg/kg. The Panel notes that this value is only applicable if other uses of resorcinol are excluded.

The Scientific Committee on Consumer Products has expressed its opinion (SCCP, 2008) on the use of resorcinol as an ingredient in oxidative hair dye formulations. In its opinion SCCP concludes: Resorcinol is a strong sensitiser. The Scientific Committee on Consumer Safety is of the opinion (SCCS, 2010) that the use of resorcinol as an ingredient in oxidative hair dye formulations with a maximum on-head concentration of 1.25% will not pose a risk to the health of the consumer, apart from its sensitising potential. Studies on genotoxicity/mutagenicity in finished hair dye formulations should be undertaken following the relevant SCCNFP/SCCP opinions and in accordance with its Notes of Guidance.

The Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work aim at protecting workers from the risk related to exposure to chemicals at the workplace. Pursuant to Directive 98/24/EC, the EU Indicative Occupational Exposure Limit (IOEL) has been given for resorcinol in Commission directive 2006/15/EC. The EU IOEL for exposure to airborne resorcinol is 10 ppm or 45 mg/m³ (an 8-hr TWA IOELV). A skin notation is also assigned for resorcinol.

Resorcinol has ATC classification (ATC D10AX02, the Anatomical Therapeutic Chemical classification), a unique code assigned to a medicine according to the organ or system it works on and how it works. The classification system is maintained by the World Health Organization (WHO). The current status of resorcinol as human medicine is not known and it is not in the scope of this evaluation.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State (evaluating MS) to the following conclusions, as summarised in the **Table 1** below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	**Tick box**
Need for follow-up regulatory action at EU level	X
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	

The evaluating Member State will prepare a separate risk management option analysis (RMOA) in which the appropriate option will be clarified.

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

Environment

ED (endocrine disrupting) mechanism(s) of resorcinol have been identified in several screening studies and evaluations. In this substance evaluation, it was concluded that resorcinol is likely an ED substance for the thyroid with a TPO (thyroid peroxidase) inhibitor mode of action. However, the apical endpoints have not been studied to prove population level adversity in the environment.

In the review of the exposure assessment it was noted that resorcinol showed little risk to the environment based on ecotoxicological information (PNECs) and environmental concentrations (PECs) (all RCR values < 1, except for one unidentified use). A PNEC value for environmental endocrine disrupting effects could not be derived for resorcinol as the available fish embryo assay indicates thyroid disrupting effect on mechanistic level, and no recording of thyroid mediated apical endpoints are included in the test. Moreover, there is no general consensus whether a threshold can be determined for ED effects or not, so that a PNEC could be derived.

The evaluating MSCA concluded 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 (see 7.10.2) and hence no new data was requested. The currently available environmental mechanistic data, supported by modelling, *in vitro* and mammalian/human data, refers to potential thyroid disrupting activity of resorcinol.

Considering the possibility of SVHC identification of resorcinol as an endocrine disruptor in accordance with Article 57(f), the eMSCA concluded that it would be appropriate to evaluate whether resorcinol gives rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57, taking into account all available

information on resorcinol, including the environmental fate and monitoring studies. To clarify the need for SVHC identification or other risk management measures a risk management option analysis (RMOA) is initiated.

Human health

The medical case reports demonstrate some evidence of a causal association between hypothyroidism and use of resorcinol containing ointments in large quantities to broken skin over long periods. Because of 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, can be considered as a supportive evidence for resorcinol 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 considered, the causal association between the exposure to resorcinol and thyroid dysfunction (hypothyroidism) is plausible. It is not possible to derive dose-response relationship for the thyroid effects seen based on the available information.

Overall, the evaluating MSCA considers that the relevance of the findings in the medical case reports for evaluation of a health risk by resorcinol exposure for workers in industrial settings is limited because the dermal absorption of resorcinol seems to be low (< 1 %) when applied on healthy/intact skin. The evaluating MSCA notes that based on the current harmonized classification resorcinol has skin irritating properties, which may damage the skin surface and enhance penetration. In addition, resorcinol is a potential skin sensitiser according to self-classifications and the opinion of the Scientific Committee on Consumer Products. Therefore, it is important that appropriate RMMs are in place to adequately control skin exposure to resorcinol.

The evaluating MSCA concluded not to request further information from the Registrant(s).

However, based on the available information the evaluating MSCA decided to prepare a risk management option analysis (RMOA) to consider whether further risk management measures would be needed. In this analyses it will be considered if ED mode of action of resorcinol rises equivalent level of concern to CMR/PBT substances (1907/2006 art 57 f).

4.1.1. Harmonised Classification and Labelling

The need for a CLH proposal to update the current harmonised classification will be evaluated during the RMO analysis.

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

The need for SVHC identification of resorcinol will be evaluated during the RMO analysis.

4.1.3. Restriction

The need for a proposal for restriction for resorcinol will be evaluated during the RMO analysis.

4.1.4. Other EU-wide regulatory risk management measures

The need for other EU-wide risk management measures for resorcinol will be evaluated during the RMO analysis.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Not applicable.

5.2. Other actions

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Indication of a tentative plan is not a formal commitment by the evaluating Member State.

Table 2

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
RMO analysis	Starting in June 2017	Member State Finland

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Resorcinol was selected for substance evaluation to clarify suspected risks about:

- Potential endocrine disruptor (ED)

and

- Wide dispersive use
- Consumer use
- High (aggregated) tonnage

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Endocrine disruption	Evaluation completed. No further information is requested. Respective outcome of evaluation is discussed in more detail in the sections below.

7.2. Procedure

Resorcinol has been evaluated previously in the European Union under other legislations. These uses (food, cosmetics, medical use) are not in the scope of this evaluation:

The EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) has delivered a scientific opinion on the safety of resorcinol when used as an antioxidant in crustaceans (EFSA, 2010). The conservative estimates of acute consumption of shrimps (the only category for which experimental data were reported) indicate that dietary exposure to resorcinol for adults and for children would exceed the ADI when the residual concentration of resorcinol in whole raw shrimps is above 35 mg/kg. The Panel notes that this value is only applicable if other uses of resorcinol are excluded.

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works on and how it works. The classification system is maintained by the World Health Organization (WHO). The current status of resorcinol as human medicine is not known and it is not in the scope of this evaluation.

Additionally, the Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work aim at protecting workers from the risk related to exposure to chemicals at the workplace. Pursuant to Directive 98/24/EC, the EU Indicative Occupational Exposure Limit (IOEL) has been given for resorcinol in Commission directive 2006/15/EC. The EU IOEL for exposure to airborne resorcinol is 10 ppm or 45 mg/m³ (an 8-hr TWA IOELV). A skin notation is also assigned for resorcinol.

Substance evaluation

Resorcinol was initially screened to be included in the Community Rolling Action Plan (CoRAP) for substance evaluation under REACH regulation due to concern related to potential endocrine disrupting effects along with wide dispersive use including consumer use and high aggregated tonnage. The justification document was dated in 20 March 2013.

The substance evaluation under REACH regulation started in March 2016.

The evaluation of resorcinol is based on
- the registration dossier
- full study reports provided by the Registrant(s)
- open literature sources

In the course of the evaluation the evaluating MSCA (eMSCA) has communicated with the Registrant(s) and received the requested full study reports and some additional information. The registration dossier and chemical safety report is expected to be updated based on this additional information in near future.

Substance was discussed in The Endocrine Disruptor Expert Group 10-11 November 2016. Different options how to progress in substance evaluation (SEv) were discussed, but no consensus or clear advise was reached in the group.

Substance will be under discussion on the Risk Management Expert group 4-5 October 2017.

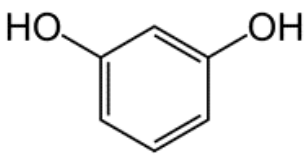
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	1,3 benzenediol (resorcinol)
EC number:	203-585-2
CAS number:	108-46-3
Index number in Annex VI of the CLP Regulation:	604-010-00-1
Molecular formula:	$C_6H_6O_2$
Molecular weight range:	110.1
Synonyms:	1,3-dihydroxybenzene

Type of substance x Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES of RESORCINOL	
Property	**Value**
Physical state at 20°C and 101.3 kPa	solid
Vapour pressure	0.065 Pa @ 25 °C
Water solubility	717 g/L @ 25 °C and pH 7
Partition coefficient n-octanol/water (Log Kow)	0.8 @ 20 °C
Flammability	N/A
Explosive properties	N/A
Oxidising properties	N/A
Granulometry	N/A
Stability in organic solvents and identity of relevant degradation products	N/A
Dissociation constant	Yes (100%)

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☐ 1000- 10,000 t	☒ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

This substance is used in the following areas: formulation of mixtures and/or re-packaging. This substance is used for the manufacture of: rubber products, chemicals, plastic products, cosmetics and personal care products and wood and wood products.

Resorcinol is not manufactured in the EU.

Table 7 Uses of resorcinol listed in the public dissemination site.

USES	Use(s)
Uses as intermediate	Manufacture of UV Stabilisers Manufacture of Flame Retardants Manufacture of Agricultural Chemicals Manufacture of Industrial Dyes
Formulation	Use in manufacture of rubber compounds – tires Use in manufacture of rubber compounds - other rubber compounds Dipping - Use in manufacture of rubber compounds Manufacture of PRF Resins Use of Phenol Resorcinol Formaldehyde resin as a wood adhesive Hair dye formulation Manufacture of other resins Manufacture of cosmetic product Use in coatings Processing of resins Formulation and (re) packing of preparations
Uses at industrial sites	Use in manufacturing rubber compounds – tires Use in manufacture of rubber compounds - other rubber products Dipping - Use in manufacture of rubber compounds Manufacture of PRF Resins Manufacture of RF resins Use of Phenol Resorcinol Formaldehyde resin as a wood adhesive Use in coatings Use in other adhesives and sealants Processing of Resins Manufacture of other resins
Uses by professional workers	
Consumer Uses	Use of Hair Dyes End use of cosmetic products
Article service life	
Uses advised against	Skin Peels

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Resorcinol has a harmonised classification according to CLP Regulation (EC) 1272/2008 (**Table 8**).

Table 8

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
604-010-00-1	resorcinol 1,3-benzenediol	203-585-2	108-46-3	Acute Tox. 4* Skin Irrit. 2 Eye Irrit. 2 Aquatic Acute 1	H302 H315 H319 H400		

7.6.2. Self-classification

In the registration(s):

The classification follows the harmonised classification in Annex VI of Regulation (EC) 1272/2008. Additionally, the Registrant(s) have given a self-classification for resorcinol to the following hazard categories in the dossier:

Eye Damage 1	H318
Skin Sens. 1B	H317
STOT SE 1	H370
STOT SE 2	H371
Aquatic Chronic 3	H412

A specific concentration limit (>= 25.0%) is also given for the category 'Aquatic Acute 1' in the dossier.

Altogether the following hazard classes are notified among the aggregated self-classifications in the C&L Inventory:

Acute Tox. 3	H301
Acute Tox. 4	H312
Skin Sens. 1B	H317
Skin Sens. 1	H317
Skin Sens. 1A	H317
Eye Dam. 1	H318
STOT SE 1	H370
STOT SE 2	H371

STOT RE 1	H372
Aquatic Chronic 3	H412
Flam. Sol. 2	H228

7.7. Environmental fate properties

7.7.1. Degradation

Biodegradation

The Registrant(s) concluded that the substance is not persistent under aerobic nor under anaerobic conditions based on several ready and inherent biodegradability tests. Ready biodegradation following OECD TG 301C was 66.7% after 14 days and inherent degradation following OECD TG 302B was 97% in 4 days. Several supporting studies (Klimisch 2, reliable with restrictions) confirmed aerobic biodegradation.

Resorcinol is likely to be biodegraded under anaerobic conditions although there are some inconsistencies in the experimental results, obviously depending on the origin of the used inoculum. The rate of anaerobic dedradation has ranged from 0 to 98 % in different studies as also referred in Hahn et al. 2006.

Considering the available information, the eMSCA can support the conclusion on ready biological degradability of resorcinol.

Abiotic degradation

The Registrant(s) also state that the substance does not undergo hydrolysis as it contains no functional groups susceptible to hydrolysis under environmentally relevant pH and temperature conditions. This conclusion is supported by the eMSCA.

In addition, resorcinol in air is not expected to undergo direct photolysis, but may undergo indirect photolysis through hydroxyl radical oxidation, with calculated half-life of 38.16 min in air.

Transformation

Hahn et al. (2006) refer to studies showing that resorcinol in aqueous medium can be metabolized by bacteria and fungi via hydroxy hydroquinone (1,2,4- trihydroxy benzene) and maleyl acetate to β-ketoadipate and via hydroxy hydroquinone and acetyl pyruvate to formic, acetic and pyruvic acids. Another potential pathway is via pyrogallol. Anaerobic degradation of resorcinol is catalysed by resorcinol reductase and hydratase. The products are 1,3-dioxocyclohexane, which is immediately hydrolysed to 5-oxohexanoate, and 5-oxohex-2-enecarboxylate. Further degradation probably proceeds via β-oxidation.

7.7.2. Environmental distribution

The Registrant(s) concluded that low soil sorption is expected with resorcinol as the measured adsorption coefficient Koc value is 10.36 at 20 °C. An estimated Koc of 50.27 L/kg (USEPA 2010) is in line with the experimental value. Considering the available information, the eMSCA can support the conclusion of potentially low soil sorption.

Based on the calculated value of Henry's Law constant H (0.000010012 Pa m^3/mol) the volatility of resorcinol from water is expected to be low (<0.00000001 atm m^3/mol or <0.001 Pa m^3/mol at 25 °C). However, the calculated values are considered of limited

reliability for water miscible compounds such as resorcinol, as this calculation is meant for substances with low water solubility.

The Registrant(s) have used the EQC Level III Fugacity model (USEPA 2006) to evaluate the fate, transport and distribution of resorcinol between environmental matrices. Loading rate of 1000 kg/h for each media (air, soil, and water) was applied.

The following percent distribution was calculated (presented in the dossier), according to which resorcinol will be distributed mainly into soil and water compartments when loading to all compartments was applied:

air	0.00222 %
water	36.1 %
soil	63.8 %
sediment	0.07 %

The input parameters used in calculation were:

melting point	110 °C
boiling point	277 °C
water solubility	717 g/L
vapour pressure	0.000489 mmHg (0.0652 Pa)
Log Kow	0.80

According to another model calculation with Mackay Level I (distribution of a substance in a closed environment where no degradation occurs), the following distribution of resorcinol in different environmental compartments was predicted (Hahn et al. 2006). Here resorcinol will be distributed mostly to the water compartment:

air	<0.01 %
water	99.9 %
sediment	0.05 %
soil	0.05 %
biota	<0.01 %

The input parameters used in calculation were:

Chemical parameters:

molecular mass	110.11 g/mol
temperature	25 °C
melting point	110 °C
water solubility	717 g/l
vapour pressure	0.065 Pa
log Kow	0.80

Environmental parameters:

air, 6×10^{-9} m^3	1.19 kg/m^3
water, 7×10^{-6} m^3	1000 kg/m^3
sediment, 2.1×10^{-4} m^3	1500 kg/m^3
soil, 4.5×10^{-4} m^3	1500 kg/m^3
suspended particles, 35 m^3	1500 kg/m^3
biota, 7 m^3	1000 kg/m^3

Environmental monitoring

The Nordic countries have systematically been screening the environment for potential hazardous substances. One of the screening programs (Nordic Council of Ministers 2007) focused on resorcinol and bronopol primarily due to their toxicity and volume. Several samples were collected from different environmental compartments (municipal and industrial sewage treatment plants (STPs), STP sludges, landfill leachates, surface waters, sediments and biota from Denmark, Faroe Islands, Finland, Iceland, Norway and Sweden.

Resorcinol was detected from municipal STP in concentration range from 0.075 µg/L to 3.5 µg/L in influent waters and between 0.007 µg/L and 0.24 µg/L in effluent waters. Concentrations in pulp and paper mill effluents ranged from 0.008 µg/L and 0.071 µg/L. Resorcinol occurred also in 15 out of the 19 analysed municipal STP sludge samples (from 9 ng/g dw to 220 ng/g dw) and in 2 of the 5 industrial STP sludge samples (from 24 ng/g to 48 ng/g).

Additionally, resorcinol was found in surface water at several locations in concentrations ranging from 0.008 µg/L to 0.35 µg/L. Resorcinol occurred in sediment samples outside two point sources (3 - 17 ng/g dw) and at one lake (3.2 ng/g dw).

Resorcinol was not detected in leachate waters nor in air samples and biota (concentrations below detection limits).

An estimated $PNEC_{water}$ value of 1.72 µg/L (safety factor 100; PNEC, predicted no effect concentration; based on one trophic level) for resorcinol was given in the report. For risk assessment indicative MEC/PNEC ratios (measured concentrations vs. predicted no effect concentrations) were calculated for STP effluents, landfill leachates and surface waters. All ratios were well below 1 (0.0004 - 0.2), except for one surface water sample (ratio 1.4, when using a PNEC value based on an Environmental Quality Standard, EQS, derived from an atypical Daphnia study with exceptionally long 96 h exposure time, which may result in death by starvation), meaning no negative effects of the substance are expected regarding ecotoxicity.

Moreover, the Registrant(s) have conducted targeted monitoring studies for different industrial uses of resorcinol (tyre manufacturing, phenolic resin production, plants using wood adhesives, phosphate ester flame retardant production). The estimated environmental concentrations were at the same level as in the Nordic monitoring study described above. The unpublished results are presented and discussed in the Confidential annex.

Natural sources of resorcinol

The resorcinol moiety has been found in a wide variety of natural products, as summarized followingly in the report produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals (Hahn et al 2006). In particular, the plant phenolic substances, of which resorcinol ring-containing constituents are a part, are ubiquitous in nature and are well documented. Resorcinol itself has been found in the broad bean (*Vicia faba*), detected as a flavour-forming compound in the honey mushroom (*Armillaria mellea*) and found in exudates of seedlings of the yellow pond lily (*Nuphar lutea*).

Resorcinol has also been found in extracts of tobacco leaves and is a component of tobacco smoke. In terms of resorcinol derivatives, resorcinol ethers are components of fragrance agents, and there is considerable literature on long-chain alk(en)yl resorcinols in plants and bacteria.

Resorcinol is one of the main natural polyphenols in argan oil, extracted from fruit kernels of argan trees for culinary oil and cosmetic purposes (Charrouf et al 2007).

According to Hahn et al (2006) resorcinol is also a monomeric by-product of the reduction, oxidation, and microbial degradation of humic substances. Humic substances are present in coals, shales, and possibly other carbonaceous sedimentary rocks. This occurrence may explain the detection of resorcinol in wastewater effluents of coal conversion processes due to thermal breakdown found resorcinol in some samples as a decomposition product of corn residues in soil.

7.7.3. Bioaccumulation

The Registrant(s) concluded that the substance is not bioaccumulative based on the calculated values of BCF (3.16; 2.4) (USEPA 2006). Considering the available information, the eMSCA can support this conclusion.

Additional data from the terrestrial compartment and metabolism data from animals and humans are available, which support the conclusion that resorcinol is not bioaccumulative and that it is rapidly eliminated through metabolic pathways (see section 7.9.1 Toxicokinetics).

7.8. Environmental hazard assessment

Only limited amount of data has been located on the potential endocrine effects of resorcinol on wildlife. The general environmental toxicity information summarized in the following sections has been considered as background and reference material in the assessment of potential endocrine mediated effects. The information has been mostly obtained from the registration dossier and the chemical safety report and has been taken as accurate (IUCLID dossier). Individual source documents have not been evaluated except for studies considered relevant for the assessment of potential ED effects and for studies for which a full study report has been submitted by the Registrant(s).

7.8.1. Aquatic compartment (including sediment)

Fish

Several short-term toxicity studies on fish are available for resorcinol (**Table 9**). Lethal concentration for free-swimming fish varies from 26.8 to over 100 mg/L. The result of the short-term key study was based on measured concentrations and all other studies on nominal concentrations. The short-term tests include static, semi-static and flow-through exposure9

A short-term early life stage test with zebrafish eleutheroembryos indicating both systemic toxicity and thyroid disrupting effects was available for resorcinol. This method is included int the OECD scoping document on assays for the identification of modulators of thyroid hormone signalling and ranked as having a strong biological plausibility (OECD 2014).

The early life stage test with zebrafish eleutheroembryos showed mortality in a rather high concentration: 72 h-LC50 550 mg/L (Thienpont et al. 2011). However, the exposure of zebrafish eleutheroembryos to the maximum tolerated concentration of resorcinol (200 mg/L) resulted in a significantly decreased concentration of interfollicular T4 hormone content (IT4C) when compared to the control ($p<0.05$). Based on these results, resorcinol was considered a thyroid gland function disruptor (TGFD) by the authors. In a further experiment examining the concentration-response of this effect an EC50 of 82 µM (9.02 mg/L) was reported, based on decreased IT4C (see 7.10.1 for further details). A NOEC value 10 µM (1.1 mg/L) was obtained from experimental data by performing one-way ANOVA analysis (Thienpont et al. 2011 Supporting Information).

Furthermore, long-term fish early life stage studies were available for resorcinol (Van Leeuwen 1990). The test method based on FELS draft guideline at the time (OECD TG 210). The TG is now included in the draft update of the OECD guidance document on standardised test guidelines for evaluating chemicals for endocrine disruption (OECD 2017) on Level 4 as a method with 'Endpoints potentially sensitive, but not diagnostic of, EATS, juvenile hormone, ecdysone or retinoid modalities' with justification that 'Some thyroid-active chemicals may interfere with embryonic development and metamorphosis'.

In the available studies Van Leeuwen et al. (1990) studied teratogenicity in fish early life stages carried out with zebra fish (*Brachydanio rerio*) and rainbow trout (*Salmo gairdneri*). Newly fertilised eggs of each species were exposed to 10 chemicals used in the rubber industry, including resorcinol, for periods of 7 and 60 days, respectively, in the concentration range of 1 to 1000 mg/L. The endpoints were total embryotoxicity (teratogenicity) and mortality.

Resorcinol induced teratogenic effects both in zebra fish and rainbow trout (**Table 9**). For zebra fish the 7 day EC50 of total embryotoxicity (lethality and malformations) was 54.8 mg/L, 7 day LC50 was 262 mg/L, 7 day LOEC (mortality) was 320 mg/L, and 7 day LOEC (total embryotoxicity) was 100 mg/L (nominal concentrations). In the 60-day study with rainbow trout the EC50 of total embryotoxicity (lethality and malformations) was 260 mg/L, 60 day LOEC (mortality) was 320 mg/L, 60 day LOEC (total embryotoxicity) was 320 mg/L, 60 day LOEC (length) was 100 mg/L, and 60 day LOEC (weight) was 32 mg/L. However, there is no information of the mechanism of action for these teratogenic effects.

Table 9

AQUATIC TOXICITY - FISH					
Test	**Method**	**EC/LC50 (h)**	**Species**	**Reliability**	
Short-term, fish	EPA-660/3/75-009 (flow-through)	26.8-29.5 mg/L (96 h) (measured conc.)	*Pimephales promelas*	Kl. 2 (key study)	unpublished study report, 1981 [1]
	Follows guidelines (static)	34.7 mg/L (96 h) (nominal conc.)	*Leuciscus idus*	Kl. 2	unpublished study report 1981 [1]
	Other (flow-through)	100 mg/L (96 h) (nominal conc.)	*Pimephales promelas*	Kl. 2	DeGraeve et al. 1980a [2]
	Other (flow-through)	>100 mg/L (96 h) (nominal conc.)	*Oncorhynchus mykiss*	Kl. 2	DeGraeve et al. 1980b [2]
	OECD 236 FET, draft guideline [1] (semi-static)	5003 µmol/l (72 h) (=550 mg/L) (mortality)	*Danio rerio, embryo*	Kl. 2	Thienpont et al. 2011
		82 µmol/l (72 h) (=9.02 mg/L) (thyroid disrupting effect)	*Danio rerio, embryo*	Kl. 2	Thienpont et al. 2011
Long-term, fish	OECD draft guideline Early life stage test guideline	260 mg/L (60 d) (embryotoxicity)	*Oncorhynchus mykiss*	Kl. 2	Van Leeuwen et al. 1990
	OECD draft guideline Early life stage test guideline	54.8 mg/L (7 d) (embryotoxicity) (nominal conc.)	*Danio rerio*	Kl. 2	Van Leeuwen et al. 1990

[1] Ref. IUCLID dossier [2] Ref. Hahn et al. 2006

Aquatic invertebrates

Short-term toxicity (EC50 values) ranged from 1 mg/L to over 100 mg/L in studies with aquatic invertebrates (**Table 10**), *Daphnia magna* being the most sensitive species.

Only one long-term experiment was available for aquatic invertebrates, following the OECD GD 211 (**Table 10**). Nominal test item concentrations were: 25, 50, 100, 200 and 400 µg/L, but the mean measured concentrations during the test were 11, 35, 53, 111 and 172 µg/L, indicating instability of the test substance. The authors concluded that the decrease in the test substance concentration was due to biological degradation or uptake by the organisms.

The data generated during the 21-day reproduction test demonstrated that concentrations up to 172 µg/L (highest measured) had no adverse effects on survival, growth or reproduction of *Daphnia magna*. Induction of male neonates to indicate specifically hormone related activity was not recorded in the test. The highest measured concentration with no effects has been set as NOEC in the dossier and used in PNEC derivatisation.

Table 10

AQUATIC TOXICITY - INVERTEBRATES					
Test	**Method**	**EC50 (h)**	**Species**	**Reliability**	
Short-term, invertebrates	OECD 202	1 mg/L (48 h) (measured conc.)	*Daphnia magna*	Kl. 1	unpublished study report 2010 [1]
	Other	>100 mg/L (48 h) (nominal conc.)	*Daphnia pulicaria*	Kl. 2	DeGraeve et al. 1980 [1]
	Other (2-4 d old animals)	1.28 mg/L (48 h) (nominal conc.)	*Daphnia magna*	Kl. 2	Herbes et al. 1977 [1]
	EPA	32.7 mg/L (96 h) (measured conc.)	*Palaeomonetes pugio*	Kl. 2	Curtis et al 1979 [2]
Long-term, invertebrates	OECD 211	≥172 µg/L (21 d) (measured conc.)	*Daphnia magna*	Kl. 1	unpublished study report 2004 [1]

[1] Ref. IUCLID dossier

[2] Ref. Hahn et al. 2006

Algae and aquatic plants

In algae test the 72 hr E_bC50 and E_rC50 values (biomass and growth rate) were both greater than the highest mean measured dose tested (>97 mg/L) (**Table 11**). The mean measured NOEC for growth inhibition based on the biomass endpoint was 47 mg/L and 97 mg/L for the growth rate endpoint.

Table 11

AQUATIC TOXICITY - ALGAE					
Test	**Method**	**EC/LC50 (h)**	**Species**	**Reliability**	
Toxicity, algae	OECD 201	>97 mg/L (72 h) (measured conc.)	*Pseudokirchneriella subcapitata*	Kl. 1	unpublished study report 2006 [1]

[1] Ref. IUCLID dossier

Sediment organisms

Not available.

Other aquatic organisms

Resorcinol has also been tested in a multispecies test system with simultaneous exposure of seven species from five phyla (juveniles of water flea, flatworm, snail, minnow, side swimmer, pill bug and segmented worm) (Ewell et al. 1986). The 96-h LC50 values were derived for each species. Water flea *Daphnia magna* was found to be the most susceptible of the tested organisms, with LC50 96 h value of 0.25 mg/L. However, the exposure time of 96 h without feeding (feeding not indicated in the report) is very long for Daphnia juveniles, exceeding also the standard exposure time of 48 h (OECD 202), which probably resulted in deaths due to starvation.

Summary of aquatic toxicity

Based on the available results from laboratory tests with fish, invertebrates, plants, and a multispecies test system, resorcinol is considered to show low short-term toxicity to most aquatic organisms. The most sensitive species appears to be water flea (*Daphnia magna*) with EC50 48 h value of 1 mg/L, which has resulted in harmonized hazard classification 'Aquatic Acute 1' (H400).

In a Daphnia reproduction test no adverse effects on survival, growth, or reproduction were observed at the highest concentration tested (measured value 172 µg/l). The LOEC was estimated to be >0.172 mg/L. Because a LOEC could not be determined, the actual 21-day NOEC value for *Daphnia magna* is probably higher than 0.172 mg/L stated in the study. This NOEC value was applied for self-classification of resorcinol to hazard category 'Aquatic Chronic 3'.

In chronic aquatic toxicity studies with fish early life stages, low toxicity was shown as well. In the early life stage semi static test with rainbow trout (*Oncorhynchus mykiss*), a 60-day EC50 of 260 mg/L (in respect to total embryotoxicity: lethality and malformation) was obtained. An embryolarval test with zebra fish (*Danio rerio*) for embryotoxicity gave a 7-day EC50 value of 54.8 mg/L.

Based on a 3-day zebrafish embryo test, resorcinol was considered a thyroid gland function disruptor (TGFD), with an EC50 value of 82 µM (9.02 mg/L) for decreased intrafollicular T4 hormone content (IT4C) when compared to the control ($p<0.05$). The NOEC value for this endpoint was 10 µM (1.1 mg/L) (Thienpont et al. 2011, Supporting Information).

7.8.2. Terrestrial compartment

A long-term toxicity test with earthworm showed toxicity only at very high concentration level (**Table 12**).

Table 12

TERRESTRIAL TOXICITY - INVERTEBRATES					
Test	**Method**	**EC/LC50 (h)**	**Species**	**Reliability**	
Toxicity, earthworm	Other	LOEC 10000 mg/kg soil dw (growth)	*Eisenia foetida*	Kl. 2	Hartenstein 1982 [1]

[1] Ref. IUCLID dossier

7.8.3. Microbiological activity in sewage treatment systems

Resorcinol showed toxicity to microorganisms of activated sludge in biological wastewater treatment system at the same concentration level as in many of the aquatic toxicity studies (**Table 13**).

Table 13

MICROBIOLOGICAL ACTIVITY					
Test	**Method**	**EC/LC50 (h)**	**Species**	**Reliability**	
Toxicity, microorganisms	OECD 209	79 mg/L (3 h)	Activated sludge	Kl. 1	unpublished study report, 2010 [1]

[1] Ref. IUCLID dossier

7.8.4. PNEC derivation and other hazard conclusions

The Registrant(s) have derived PNEC values for the hazard assessment conclusion for the environment (see following **Table 14**). Experimental values from aquatic invertebrate test, sewage treatment microorganism test and terrestrial test with earthworm have been applied with appropriate assessment factors for calculation of PNECs. For the derivation of PNEC for fresh and marine water, the lowest NOEC value from *Daphnia magna* reproduction test has been used, which represents also the highest exposure concentration tested. It is noted that the actual NOEC may be even higher which would result also in a higher PNEC, and therefore, the PNECwater used in the registration dossier may be considered conservative.

No experimental data for sediment toxicity was available and thus the equilibrium partitioning method (EPM) was applied according to the ECHA Guidance on information requirements and chemical safety assessment, Chapter R.10. There are two slightly different PNECsediment values for fresh and marine sediment available in the registration dossier, and the reason for this was unclear. No calculations were presented. However, this had no effect on the conclusion of risk characterization.

A PNEC value for environmental endocrine disrupting effects could not be derived for resorcinol as the available fish embryo assay indicates thyroid disrupting effect on mechanistic level, but no recording of thyroid mediated apical endpoints is included in the test. Moreover, no general consensus has been reached whether a threshold can be determined for ED effects or not, so that a PNEC could be derived. The issue on

thresholds of ED substances is discussed e.g. in the report from the EU Commission (European Commission 2016).

Even so the assay could be regarded as a chronic toxicity method, as the Daphnia reproduction assay used for derivation of PNEC aqua. In comparison to the NOEC from the Daphnia reproduction test (0.172 mg/L) the NOEC from the zebrafish test was higher (1.1 mg/L).

Table 14

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks/Justification**
Freshwater	PNEC aqua (freshwater): 0.0172 mg/L	Assessment factor: 10 Extrapolation method: assessment factor The PNECaquatic was calculated according to ECHA Guidance on information requirements and chemical safety assessment Chapter R.10, Sections R10.3.1.2 dated May 2008
Marine water	PNEC aqua (marine water): 0.00172 mg/L	Assessment factor: 100 Extrapolation method: assessment factor The PNECsaltwater was calculated according to ECHA Guidance on information requirements and chemical safety assessment Chapter R.10, Sections R10.3.2.3 dated May 2008
Intermittent releases to water		Covered by the PNEC aqua calculation
Sediments (freshwater)	PNEC sediment (freshwater): 0.0797 mg/kg sediment dw PNEC sediment (freshwater): 0.109 mg/kg sediment dw	Extrapolation method: statistical extrapolation The PNECsediment was calculated according to ECHA Guidance on information requirements and chemical safety assessment Chapter R.10, Sections R10.5.2 dated May 2008. Conversion: 0.0797 mg/kg dw = 0.0173 mg/kg ww. Conversion: 0.109 mg/kg dw = 0.0237 mg/kg ww.
Sediments (marine water)	PNEC sediment (marine water): 0.00797 mg/kg sediment dw PNEC sediment (marine water): 0.0109 mg/kg sediment dw	Extrapolation method: statistical extrapolation The PNECmarine sediment was calculated according to ECHA Guidance on information requirements and chemical safety assessment Chapter R.10, Sections R10.5.3 dated May 2008.

		Conversion 0.00797 mg/kg dw = 0.00173 mg/kg ww. Conversion 0.0109 mg/kg dw = 0.00237 mg/kg ww.
Sewage treatment plant	PNEC STP: 0.79 mg/L	Assessment factor: 100 Extrapolation method: assessment factor The PNECstp was calculated according to ECHA Guidance on information requirements and chemical safety assessment Chapter R.10, Sections R10.4.2 dated May 2008.
Soil	PNEC soil: 10 mg/kg soil dw	Assessment factor: 1000 Extrapolation method: assessment factor The PNECsoil was calculated according to ECHA Guidance on information requirements and chemical safety assessment Chapter R.10, Sections R10.6 dated May 2008. Although long term data are available for earthworms, in the absence of a full set of terrestrial species data, the study has been treated as a short-term study and PNEC derived from the EC50 value rather than the NOEC.
Air	No hazard identified	
Secondary poisoning	No potential for bioaccumulation	The BCF for resorcinol is 3.16, limited to no bioaccumulation is expected.

7.8.5. Conclusions for classification and labelling

Resorcinol has a harmonised classification related to environmental hazards (Aquatic Acute 1), obviously based on the classification criteria for short-term toxicity to crustacean, 48 h EC50 ≤1 mg/l, which is fulfilled with resorcinol (the 48 h EC50 to *Daphnia magna* is 1 mg/L).

The Registrant(s) have self-classified resorcinol to hazard category Aquatic Chronic 3, H412). The classification criteria for this category concern chronic toxicity (chronic NOEC or ECx ≤ 1 mg/L to fish or crustacean or algae/plants for substances that are readily biodegradable). The self-classification is based on the available Daphnia reproduction test (OECD TG 211) where the highest tested concentration was 0.172 mg/L, but which did not induce any effects. Therefore the actual NOEC is ≥ 0.172 mg/L, and the self-classification Aquatic Chronic 3 may be conservative. The lowest available NOEC value 1.1 mg/L for ED effect in zebrafish eleutheroembryos indicates lower sensitivity and would not alone result in the Aquatic Chronic 3 classification.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Toxicokinetic studies in rats and rabbits suggest that orally-administered resorcinol is rapidly absorbed, metabolized and excreted in the urine primarily as monoglucuronide conjugate (unpublished report, 2004a, EFSA 2010, Garton et al. 1949, Kim and Matthews 1987, Merker *et al.* 1982, unpublished report, 2005). Minor metabolites included a monosulphate conjugate, a mixed sulphate-glucuronide conjugate, and a diglucuronide conjugate. In rats (Kim and Matthews 1987) most of the orally-administered [14C]-resorcinol was excreted via urine (90.8 – 92.8%) with a minimal amount excreted via the feces (1.5 – 2.1%) within 24 hrs. In rats (Merker *et al.* 1982) after single subcutaneous dosing [14C]-resorcinol the [14C] activity in plasma decreased rapidly (ca. 90 % clearance within the first 2 hours). The elimination was biphasic, with half-lives of 18–21 min and 8.6–10.5 h. Within 24 h, 98% of the applied dose was excreted via urine and 1% via faeces, mainly as glucuronide conjugate (84%). The available data do not show accumulation in any organ or tissue, including the thyroid gland, when 14C-resorcinol was administered either subcutaneously or orally to rats. The eMCSA agrees with the Registrant(s) that available studies give no indication of bioaccumulation.

In a *in vitro* dermal absorption study using human skin (unpublished report, 2005), dermal absorption of resorcinol was evaluated from a representative hair dye formulation (oxidative and non-oxidative test preparations) that contained [14C]-resorcinol (**Table 15**). The absorbed dose was 0.32 % (oxidative preparation) and 0.82 % at 24 hours (non-oxidative preparation) of the applied dose.

In a human volunteer study (Yeung et al. 1983) to measure absorption and metabolic disposition, 2% resorcinol (800 mg resorcinol/day, a maximal exaggerated use level) was applied topically in a hydro-alcoholic vehicle over an application area of 2600 cm^2 twice a day, six days a week for four weeks to three male volunteers with one control volunteer (**Table 15**). The test substance penetrated the skin at a rate of 0.37 µg/cm2/hour. After two weeks of application, an average of 1.64% of the dose was being excreted in 24-hr urine specimens as the glucuronide or as the sulphate conjugate. There was no resorcinol or its conjugates in blood drawn at week 1, 2, 3, and 4.

In *in vitro* permeability studies using human skin treated with 10% w/v resorcinol, there was a long lag time (80 min) (Roberts et al. 1977). A steady state permeability coefficient (Kp) of 0.00024 cm/h was calculated.

In conclusion, the Registrant(s) identified a 2% absorption rate being conservative absorption rate for risk assessment purposes, while recent studies suggest the dermal absorption to be < 1% (0.82%). The Registrant(s) concluded that when applied to intact skin dermal absorption is low in humans but utilises the same urinary excretion pathway and forms common metabolites as via the oral route.

The eMSCA agrees with the Registrant(s) that the available studies suggest the dermal absorption to be low when applied to intact skin. The physico-chemical properties of resorcinol indicate high hydrophilicity that does not either suggest high dermal penetration cross the stratum corneum in intact skin (i.e. water solubility 717 g/L, Log Kow 0.8 and MW 110.11). The eMSCA notes that resorcinol has skin irritating and skin sensitising properties which may damage the skin surface and enhance penetration.

Table 15 Overview of dermal absorption studies.

DERMAL ABSORPTION			
Study	**Remarks**	**Results**	**Reference**
Dermal absorption study *in vitro* human split-thickness skin membranes Exposure regime: 0.5 hours then wash, samples taken at 24 hrs post-exposure. Doses/conc.: Actual Resorcinol concentration in formulation (% w/w): 2.55 (Oxidative); 2.52 (Non-Oxidative). Actual Resorcinol concentration in Test Preparation (% w/w): 1.26 (Oxidative); 1.27 (Non-Oxidative). Actual application rate of Test Preparation (mg/m3): 21.08 (Oxidative); 20.07 (Non-Oxidative). OECD Guideline 428 (Skin Absorption: *In Vitro* Method) (; OECD Environmental Health and Safety Publications Series on Testing and Assessment No. 28. Guidance Document for the Conduct of Skin Absorption Studies (2004); Basic Criteria for the *In Vitro* Assessment of Percutaneous Absorption of Cosmetic Ingredients)	Reliability: 1 (reliable without restriction) Key study Test material (IUPAC name): Benzene-1,3-diol	Absorption Study – Oxidative Test Preparation The total recovery, dislodgeable dose, unabsorbed dose, absorbed dose and dermal delivery were 252.02, 248.92, 250.97, 0.84 and 1.04 µg equiv./cm2, respectively. Absorption Study – Non-Oxidative Test Preparation The total recovery, dislodgeable dose, unabsorbed dose, absorbed dose and dermal delivery were 249.57, 242.65, 246.62, 2.10 and 2.95 µg equiv./cm2, respectively. Percutaneous absorption rate: 0.32 % at 24 hours (oxidative), 0.82 % at 24 hours (non-oxidative)	unpublished study report 2005[1]
Dermal absorption study Human skin ex-vivo Other	Reliability: 4 (not assignable) supporting study Test material (IUPAC name): Benzene-1,3-diol	Percutaneous absorption rate: 10 %	Roberts et al. 1977

DERMAL ABSORPTION			
Study	**Remarks**	**Results**	**Reference**
Four healthy males with intact skin (aged 18 +). Three were in the treatment group and one untreated control. 4-week dermal application (to the face, shoulders, upper chest and upper back) 20 ml of 2 % resorcinol in hydroalcoholic vehicle. Twice daily 6 days/week 150 microg/cm2 of body surface. Daily dose 12 mg/kg/bw. Only the vehicle was applied to the control subject. This study was used to investigate: (1) blood and urinary levels of resorcinol after maximal exaggerated subchronic topical administration to human subjects (intact skin); (2) possible changes in thyroid function and blood chemistries; and (3) skin penetration rates of resorcinol under these exaggerated usage conditions. Blood samples were drawn at day 0, and at weeks 1, 2, 3, and 4 after the initiation of treatment. These samples were assayed for free resorcinol and/or its conjugates or metabolites; blood chemistries (SMAC 24) and thyroid functions (T3, T4, T7 and TSH) were also measured. 24-hour urine specimens were collected from each subject two and four weeks after initiation of treatment. All plasma and urine samples were frozen until analysed. Under the new analytical methods, the minimum detectable level of resorcinol was 0.1 µg/ml. Other	Reliability: 2 (reliable with restrictions) supporting study Test material (IUPAC name): Benzene-1,3-diol	No detectable levels of free resorcinol or its conjugates were found in blood at weeks 1, 2, 3 and 4. In 24-hour urine samples collected after 14 days of continuous treatment, a maximum of 0.47 to 2.87% (an average of 1.64%, up to 23 mg resorcinol) of the applied daily dose was excreted and detected as the glucuronide and sulphate conjugates. No significant changes were observed in any of the thyroid functions measured (T3, T4, T7 and TSH) in the three treated subjects. Reported to be within normal ranges. Dermal absorption: The adsorption and metabolic disposition of 2% resorcinol applied topically in a hydroalcoholic vehicle was determined in three human subjects. The test substance penetrated the skin at a rate of 0.37 µg/cm2/hour.	Yeung et al. 1983

[1] Ref. IUCLID dossier

7.9.2. Acute toxicity and Corrosion/Irritation

Acute toxicity and corrosion/irritation properties of resorcinol were not evaluated by the eMSCA.

7.9.3. Sensitisation

The sensitisation properties of resorcinol were not evaluated by the eMSCA.

7.9.4. Repeated dose toxicity

Table 16 Overview of repeated dose toxicity studies via oral route in the registration dossier of resorcinol.

REPEATED DOSE TOXICITY ORAL ROUTE			
Study	**Remarks**	**Results**	**Reference**
Sprague-Dawley rat, male/female (10 animals/sex/dose and 6 control and high dose animals/sex for recovery group and 6 animals/dose /sex for toxicokinetics) Subchronic Administration: oral, gavage 0, 40, 80, 250 mg/kg bw Vehicle: purified water Exposure: 13 weeks (5 days/week) following 4 weeks' recovery period OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents)	Key study Reliability: 1 (reliable without restriction) Experimental result Test material: (IUPAC name): Benzene-1,3-diol Purity: 98.8%	NOAEL: 80 mg/kg bw/day (nominal) for both males and females. At 250 mg/kg bw/day: intermittent convulsive movements and excessive salivation in both sexes from between weeks 6 and 8 until the end of the dosing period. Reduced body weight gain in females at weeks 4 to 8. Decreased absolute and relative thyroid weights in both sexes (absolute weights statistically significantly in females). No histological findings. Statistically significantly increased absolute thyroid weights in recovery group females.	unpublished study report (2004a) [1]
Fischer 344 rat, male/female (5 animals/sex/dose) Subacute Administration: oral, gavage 0, 27.5, 55, 110, 225, 450 mg/kg bw Vehicle: deionized water Exposure: 17 days (once daily for 5 days a week 12 doses dispensed over 17 days) Range finding study	Supporting study Reliability: 2 (reliable with restrictions) Experimental result Test material (IUPAC name): Benzene-1,3-diol Purity: >99%	NOAEL: 27.5 mg/kg bw/day (nominal) in females based on hyperexcitability at doses ≥ 55 mg/kg bw and tachypnea at 110. Decreased absolute and relative thymus weights at 450 mg/kg bw. NOAEL: 110 mg/kg bw/day in males based on hyperexcitability and tachypnea at 225 mg/kg bw and 450 mg/kg bw.	National Toxicology Program (NTP) (1991) National Toxicology Program (NTP) (1992)
Fischer 344 rat, male/female (10 animals/sex/dose)	Supporting study Reliability: 1 (reliable without restriction)	NOAEL: 32 mg/kg bw/day (nominal) females based on increased absolute and relative liver weights at 65	National Toxicology Program (NTP) (1991)

REPEATED DOSE TOXICITY ORAL ROUTE			
Study	**Remarks**	**Results**	**Reference**
Subchronic Administration: oral, gavage 0, 32, 65, 130, 260, 520 mg/kg/bw Vehicle: deionised water Exposure: 13 weeks (once a day 5 days a week) Equivalent or similar to OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents)	experimental result Test material (IUPAC name): Benzene-1,3-diol Purity: >99%	mg/kg/bw and higher doses. Tremors and complete mortality at 520 mg/kg bw. NOAEL: 65 mg/kg bw/day (nominal) in males based on increased absolute liver weights at 130 and 260 mg/kg/bw. Tremors and high mortality were observed at 520 mg/kg bw. Significantly increased absolute and relative adrenal weights in all surviving dosed male groups without dose-response.	National Toxicology Program (NTP) (1992)
Fischer 344 rat, male/female (60 animals/sex/dose) Chronic (oral: gavage) 0, 112, 225 mg/kg bw (males) 0, 50, 100, 150 mg/kg bw (females) Vehicle: deionised water Exposure: 104 weeks (Daily: 5 days/week) Interim sacrifice (15 animals/sex/dose) at 15 months equivalent or similar to OECD Guideline 453 (Combined Chronic Toxicity / Carcinogenicity Studies)	1 (reliable without restriction) supporting study experimental result Test material (IUPAC name): Benzene-1,3-diol Purity: >99%	NOAEL: 50 mg/kg bw/day (nominal) in females. Based on ataxia, prostration, salivation and tremors at 100 mg/kg bw. Decreased body weight and increased mortality were seen at 150 mg/kg/bw. LOAEL: 112 mg/kg bw/day (nominal) in males based on ataxia, prostration, salivation and tremors at all doses. Body weight decrease and increased mortality were seen at 225 mg/kg/bw. No significant increases in the incidences of neoplasms or nonneoplastic lesions.	National Toxicology Program (NTP) (1991) National Toxicology Program (NTP) (1992)

REPEATED DOSE TOXICITY ORAL ROUTE			
Study	**Remarks**	**Results**	**Reference**
B6C3F1 mouse male/female (5 animals/sex/dose) Subacute Administration: oral, gavage 0, 37.5, 75, 150, 300, 600 mg/kg/bw Vehicle: deionized water Exposure: 17 days (once a day 5 days a week, 12 doses over 17 days) Range finding study	Supporting study Reliability: 2 (reliable with restrictions) Experimental result Test material (IUPAC name): Benzene-1,3-diol Purity: >99%	NOAEL: 75 mg/kg bw/day (nominal) in males. Based on prostration and tremors at 150 mg/kg bw. There was 20% mortality at 300 mg/kg bw and 80% mortality at 600 mg/kg bw. NOAEL: 150 mg/kg bw/day (nominal) in females. Based on prostration and tremors at 300 mg/kg bw. Complete mortality at 600 mg/kg bw.	National Toxicology Program (NTP) (1991) National Toxicology Program (NTP) (1992)
B6C3F1 mouse male/female (10 animals/sex/dose) Subchronic Administration: oral, gavage 0, 28, 56, 112, 225, 420 mg/kg/bw Vehicle: deionized water Exposure: 13 weeks (once a day, 5 days a week) Equivalent or similar to OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents)	Supporting study Reliability: 1 (reliable without restriction) Experimental result Test material (IUPAC name): Benzene-1,3-diol Purity: >99%	NOAEL: 225 mg/kg bw/day (nominal) for both sexes based on dyspnea, prostration and tremors and mortality occurring at the highest dose of 420 mg/kg bw. Significantly decreased absolute and relative adrenal weights in all dosed male groups without clear dose-response.	National Toxicology Program (NTP) (1991) National Toxicology Program (NTP) (1992)
B6C3F1 mouse male/female (60 animals/sex/dose) Chronic (oral: gavage) 0, 112, 225 mg/kg bw Vehicle: deionized water Exposure: 104 weeks (Daily; 5 days/week) Equivalent or similar to OECD Guideline 453 (Combined Chronic	Reliability: 1 (reliable without restriction) supporting study experimental result Test material (IUPAC name): Benzene-1,3-diol Purity: >99%	no NOAEL identified LOAEL: 112 mg/kg bw/day (nominal) in both sexes based on ataxia, recumbency and tremors. In females, decreased body weight at 225 mg/kg bw. No significant increases in the incidences of neoplasms or nonneoplastic lesions.	National Toxicology Program (NTP) (1991) National Toxicology Program (NTP) (1992)

REPEATED DOSE TOXICITY ORAL ROUTE			
Study	**Remarks**	**Results**	**Reference**
Toxicity / Carcinogenicity Studies)			

[1] Ref. IUCLID Dossier

The registration dossier of resorcinol includes four repeated dose toxicity studies via oral route in rats and three studies via oral route in mice. The eMSCA considers these studies to be adequate and reliable. The studies mainly revealed signs of neurotoxicity considered as acute responses and changes in organ weights. There were no remarkable treatment related findings that would indicate potential ED properties of resorcinol. The main ED related findings of these studies are summarized as follows.

In a subchronic rat study absolute (statistically significantly) and relative thyroid weights were decreased in high dose (250 mg/kg bw) females after 13 weeks' exposure to resorcinol (unpublished report, 2004a). In high dose males, thyroid weights were slightly but not statistically significantly decreased. However, there were no histopathological findings in thyroids of either sex and thus the significance of these findings remains unclear. In the same study following four-week treatment free period absolute thyroid weights were statistically significantly increased in high dose recovery group females. No histopathology was conducted on animals of recovery groups. Moreover, histopathological examination of this study revealed 2 incidents of degenerated seminiferous tubules in high dose males (principal animals) compared to zero incidence in control group (incidences 0/10 and 2/10 in control and high dose, respectively). There were no differences in testes weights between the resorcinol treated and control animals. No differences in the incidences of degenerated seminiferous tubules between resorcinol treated and control animals were observed in other studies evaluated for this report. Taken also into account that this lesion is relatively common in control animals and that only two cases were observed, the eMSCA considers this to be incidental finding.

In a subchronic rat study adrenal weights were significantly increased in all resorcinol dosed males (NTP 1992), whereas in a subchronic mice study significantly decreased adrenal weights were observed in all dosed males (NTP 1992). However, there was no clear dose-response in adrenal weights in either study and adrenal weights of the controls in the rat study were low. Moreover, due to lack of histological findings and inconsistency between species the toxicological significance of these findings remained obscure. The NTP commissioned a review panel to investigate the CNS effects observed in each of the NTP studies along with the changes in adrenal weights in the 13-week study (NTP, 1992). It was determined by the NTP panel that the CNS effects occurred shortly after dosing and subsided within approximately one hour of dosing. This timing also coincided with the rapid clearance of the test substance. In addition, these effects were exaggerated by day 5 of the weekly dosing cycle but a dose response relationship was not determined. As a result, the NTP review panel concluded these effects to be considered an acute response even though they were observed within the repeated dose studies.

In a chronic rat study (NTP 1991 and 1992) the incidences of mammary gland fibroadenomas in females occurred with a negative trend and incidences in each of the female groups that received resorcinol were significantly lower than controls (25/50, 14/50, 12/50, 9/50). However, the incidences in all groups were within the historical control range for F344/N females of NTP database (16%-53%). In the same study resorcinol treated females had higher total number of nonneoplastic bone lesions than controls. Only one bone lesion (femur osteopetrosis) was reported in control group whereas totally 8 lesions at 50 mg/kg, 4 lesions at 100 mg/kg and 3 lesions at 150 mg/kg were reported. Lower incidences of bone lesions at the two highest doses could be explained by higher mortality in these groups (34, 33, 27 and 24 survived animals at final sacrifice in control, 50 mg/kg, 100 mg/kg and 150 mg/kg, respectively). However,

at week 91 survival of high dose group was still as high as 66% (33/50) and 50 animals of each group including the decedents were examined microscopically for bone lesions. The bone lesions observed in resorcinol treated groups included cranium heperostosis, femur hyperostosis, femur ostepetrosis, femur fibrous osteodystrophy, maxilla hyperostosis, and turbinate hyperostosis. The more general term, increased bone, defined as excessive growth of normal bone can be used to cover all these lesions.

There is a concern for possible thyroid effects of resorcinol (see section 7.10.1). The skeleton is known to be a target tissue of thyroidal hormones e.g. the bone remodeling cycle is regulated by thyroid hormones (e.g. Williams 2013). Therefore, the observed higher number of bone lesions could be related to resorcinol treatment. However, the data does not reveal a clear dose-response and this effect has not been reported in other studies. Moreover, increased amount of bone is occasionally seen as back ground lesion in aged F344 rats, particularly in females, but rarely observed as treatment-related effect (National Toxicology Program, Non-neoplastic Lesion Atlas). Thus, it is not possible to conclude that the slightly increased total number of non-neoplastic bone lesions observed in female rats after two years' resorcinol treatment in this study would be related to resorcinol treatment.

Table 17 Overview of repeated dose toxicity studies via inhalation route in the registration dossier of resorcinol.

REPEATED DOSE TOXICITY INHALATION ROUTE			
Study	**Remarks**	**Results**	**Reference**
HLA-SD Rat male/female (5 animals/sex/dose) Subacute (inhalation) 220 ppm (1000 mg/m^3) Exposure 14 days (8 hours/day) A range finding study conducted prior to main study	Reliability determined by the Registrant(s): 2 (reliable with restrictions) No full study report was available for the eMSCA	Only gross examinations, no histopathology was conducted in this study. At 220 ppm one male rat had slight hemorrhagic spotting on the lungs while the remaining tissues appeared normal. 200 ppm was found appropriate.	unpublished study report, (1977) [1]
HLA-SD Rat male/female (25 animals/sex exposed to resorcinol, 10 controls/sex) Subchronic (inhalation) 220 ppm (1000 mg/m^3) Exposure 90 days (8 hours/day)	Reliability: 3 (not reliable) Not acceptable	The exposure was terminated at 64 days due to excess mortality (possibly caused by an infection). One half of the survivors were sacrificed one week later. After two weeks the exposure was continued for rest of the animals until the total of 90 exposures were completed. 39% (15/38 animals) of resorcinol treated animals (males and females pooled) had thyroid hyperplasia. There were no differences in thyroid weights. No thyroid hyperplasia was observed in controls. Changes in organ weights	unpublished study report (1977) [1]

REPEATED DOSE TOXICITY INHALATION ROUTE			
Study	**Remarks**	**Results**	**Reference**
		(liver, kidney, adrenals, spleen). There were no pulmonary changes attributable to treatment. The study gives an indication of systemic effects after uptake via inhalation.	

[1] Ref. IUCLID dossier

In agreement with the Registrant(s) the eMSCA considers the subchronic repeated dose toxicity study by inhalation route available in the registration dossier not acceptable. The study does not meet the requirements of current guidelines. Moreover, due to high mortality (20% in males and 28% in females) the exposure was temporarily terminated at 64 days. The high mortality was possibly caused by an infection which was demonstrable upon histopathological examination in the heart, lungs and liver in 5/12 of animals that died prematurely. One half of the survivors were sacrificed one week later. After two weeks, the exposure was continued for rest of the animals until the total of 90 exposures were completed. Since no significant differences in lesions of animals sacrificed after 64 and 90 resorcinol exposures were noted, these groups (as well as males and females) were pooled for reporting of the lesions.

In this study 39% of resorcinol treated animals (15/38) had thyroid hyperplasia but there were no differences in thyroid weights. According to the study report the hyperplasia was characterized by a great increase in the number of acini. These were small, lined by columnar epithelium enclosing a very small lumen. The acini contained little or no colloid. None of the control rats had this lesion. There were no pulmonary changes attributable to treatment. Although several alveolar giant cells and macrophage clusters were observed in a few resorcinol exposed animals, similar findings were also present in control animals. Significant differences between resorcinol treated and controls groups were observed in liver, kidney and spleen weights in males and in kidney, adrenal and spleen weights of females. Some differences were also observed in blood chemistry and haematological parameters but no valid conclusions can be drawn based on them.

The eMSCA concludes that despite its significant deficiencies, this study gives an indication of systemic effects after uptake of resorcinol via inhalation. However, due to serious flaws of the study including poor reporting, the eMSCA considers the observed thyroid effects as unreliable and thus no conclusions can be based on them. Instead the Registrant(s) has derived long-term systemic DNEL for inhalation route based on an oral study (unpublished study report, 2004). The eMSCA notes that the available inhalation study indicates systemic effects of resorcinol including effects on thyroid.

However, pure resorcinol is used as flakes having low dustiness and the vapour pressure of resorcinol is relatively low (0.065 Pa) indicating a low potential of inhalation exposure. In addition, during the substance evaluation the eMSCA was informed by the Lead Registrant that the uses in spray applications (PROC 7, industrial spraying) will be removed from all exposure scenarios. Overall, this information seems to indicate a low likelihood for exposure via inhalation route. Therefore, the eMSCA decided not to request further inhalation testing.

Repeated dose toxicity: dermal

The Registrant(s) has waived the data on repeated dose toxicity via dermal route. The eMSCA concludes that resorcinol has low acute toxicity via dermal route and when applied to intact skin dermal absorption is low in humans but utilises the same urinary excretion pathway and forms common metabolites as via the oral route. Thus, taken also into account that under normal working conditions appropriate personal protective equipment is recommended by the registrant, waiving of the data via dermal route is justified.

Repeated dose toxicity studies not included in the registration dossier

A number of studies in open litterature report effects of resorcinol on thyroid hormone system in rats (reviewed in WHO/IPCS 2006). The effects observed include decreased uptake of radioactive iodine, decreases in T3 and T4, increased thyroid weight and altered thyroid histopathology. The divergence between these studies and the studies included in the registration dossier reporting negative results is most likely due to different administration routes and forms (Doniach and Logothetopoulos, 1953 and Lynch 2002). In these studies dosing was performed in a way that allowed for a slow and continuous release of resorcinol to the systemic circulation (e.g. sc. injections in oily solution) whereas in negative studies resorcinol dissolved in water was administered via gavage. Thus, since free resorcinol is extremely efficiently metabolized (probably by first pass metabolism in the liver) and effectively removed from the body via the urine, the rapid metabolism in most cases seems to prevent resorcinol from reaching concentrations which are toxic for the thyroid gland.

7.9.5. Mutagenicity

Mutagenicity of resorcinol was not evaluated by eMSCA.

7.9.6. Carcinogenicity

Carcinogenic effects of resorcinol were not evaluated by eMSCA. The chronic toxicity/carcinogenicity studies included in the dossier are reviewed in the section 7.9.4 (repeated dose toxicity). Only the effects related to reproductive toxicity or ED properties were evaluated.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Effects on fertility

Table 18 Overview of experimental studies on fertility provided in the registration dossier.

REPRODUCTIVE TOXICITY STUDIES			
Study	**Remarks**	**Results**	**Reference**
rat (Crl: CD(SD)) male/female 14/sex/group Dose range-finding reproductive toxicity study Including examination of developmental neurotoxicity in pups and thyroid/pituitary hormone analysis (i.e. T3, T4 and TSH) for F0 and F1 animals. oral: drinking water 0, 10, 40, 120, 360 mg/l In males: 0, 0.8, 3.9, 13.1 and 36.9 mg/kg/day prior to breeding; 0, 0.6, 2.8, 10.5, 31.4 mg/kg/day after breeding In females: 0, 0.8, 5.1, 15.6 and 46.6 mg/kg/day prior to breeding; 0, 1.3, 5.1, 14.6, 44.0 mg/kg/day after during gestation; 0. 2.9, 11.8, 34.1, 100.5 mg/kg/day during lactation In F1 pups (PND21-28): 0, 5.0, 18.5, 58.7, 174.4 mg/kg/day mg/kg/day Vehicle: deionized water Exposure: Administration to F0 animals 28 days prior to mating and continued during mating throughout gestation and lactation until euthanasia. Administration to F1 pups at weaning on PND 21 and continued through euthanasia on PND 28. Non-guideline, GLP study	Reliability: 2 (reliable with restrictions) Supporting study Test material (IUPAC name): Benzene-1,3-diol Purity: 100 %	NOAEL (P): 360 mg/L drinking water (male/female) NOAEL (F1): 360 mg/L drinking water (male/female) concentrations exceeding 360 mg/L were recommended for the two-generation reproductive toxicity study in rats	unpublished study report, (2003)[1]
rat (Crl: CD(SD)) male/female 30/sex/group Two-generation reproductive toxicity study Including thyroid/pituitary hormone analysis (i.e. T3, T4 and TSH) and morphometric analysis of thyroid colloid content.	Reliability: 1 (reliable without restriction) Key study Test material (IUPAC name): Benzene-1,3-diol Purity: ≥ 99.9 %	NOAEL (P): 3000 mg/L drinking water (male/female) NOAEL (F1): 3000 mg/L drinking water (male/female) NOEL (P): 1000 mg/L drinking water (male/female) based	unpublished study report, (2005)[1] Welsch et al. 2008

REPRODUCTIVE TOXICITY STUDIES			
Study	**Remarks**	**Results**	**Reference**
oral: drinking water 0, 120, 360, 1000 and 3000 mg/l In F0 and F1 animals: 0, 11, 31, 86 and 233 mg/kg/day for males over the entire generation; 0, 16, 48, 126 and 304 mg/kg/day for females during premating and gestation; and 0, 28, 85, 225 and 660 mg/kg/day for females during lactation In offspring: 0, 11, 33, 93 and 245 mg/kg/day in males; and 0, 16, 41, 126 and 295 mg/kg/day in females. Vehicle: deionized water Exposure: 70 days prior to mating and throughout mating, gestation and lactation (continuous) According to OECD Guideline 416 (Two-Generation Reproduction Toxicity Study, 2001) (; Other: EPA OPPTS 870.3800) GLP study		on reduction in water consumption	

[1] Ref. IUCLID dossier

The registration dossier includes dose range-finding reproductive toxicity study in rats and two-generation reproductive toxicity study in rats. The eMSCA considers these studies to be adequate and reliable. The main findings from the studies can be summarized as follows:

A drinking water dose range-finding reproductive toxicity study of resorcinol in rats (2003, unpublished report)

The dose-range finding study was conducted to select exposure levels for a two-generation reproductive toxicity study and to provide preliminary screening data to examine the potential of the resorcinol to induce neurotoxicity in weanlings following in utero and postnatal exposure.

In the study, resorcinol (purity 100 %) was administered in drinking water at concentrations of 0, 10, 40, 120 and 360 mg/l to Sprague Dawley rats (14/sex/group) for 28 days prior to mating and continued during mating throughout gestation and lactation until euthanasia (actual doses in **Table 18**). Administration of resorcinol to F1 pups selected for exposure (one pup/sex/litter) began at weaning on PND 21 and F1 pups received resorcinol through euthanasia on PND 28. The F1 pups selected for behavioural testing did not receive direct exposure to resorcinol following weaning on PND 21. Behavioural evaluations (three F1 pups/sex/litter) included functional observation battery (FOB, PND 21), locomotor activity (PND 21 and 61), acoustic startle response (PND 20 and 60) and Biel maze swimming trials (PND 22 and 62).

Hormone analyses for thyroid-stimulating hormone (TSH), total thyroxine (T4) and total triiodothyronine (T3) were conducted at the interim necropsy on F0 males (7 /group), at the scheduled necropsy on all F0 parental animals (7 males/group, 14 females/group), on PND 28 for F1 pups selected, and on PND 4 for all culled F1 pups (pooled without regard to sex). Thyroid glands from all surviving F0 parental animals were examined microscopically.

Brain measurements (wet brain size: length and width) were conducted on all F1 pups exposed to resorcinol or selected for behavioural testing. A qualitative histopathological analysis of the brain (forebrain, midbrain, hindbrain) was conducted for the aforementioned animals in the control and 360 mg/L groups.

Results

No test article related effects were observed on F0 reproductive performance or on F0 and F1 body weights. Food consumption, food efficiency and water consumption were not adversely affected by the test article administration at all dose levels for all F0 parental animals and F1 pups.

Mean TSH levels were increased (no statistical significance) 14.2, 38.7, 30.1 and 42.4 % for F0 males in the 10 40, 12 and 360 mg/L groups compared to the control group at the interim necropsy, respectively. The slight elevations were not sustained in the F0 males examined at the scheduled necropsy. Total T3 and T4 levels in all male groups were comparable to the control group at both the interim and final necropsies. In the F0 females, a slight increase (26.8 %, statistically significant) in total T3 levels, but not in T4 or TSH occurred the scheduled necropsy in the 360 mg/L group. A slight (20.7 %, no statistical significance) increase in total T3 was noted for the pooled F1 litter values evaluated on PND 4 from the 360 mg/L group. Increases in T3 were considered by the author a result of biological variation. The author concluded that no resorcinol-related changes in the mean concentrations of T3, T4 or TSH were noted in the F0 and F1 (PND 4 and PND 28) animals.

No macroscopic findings or changes in mean organ weights were seen in the F0 parental animals or F1 pups at all dose levels. Minimal microscopic changes were observed in the thyroid glands at 360 mg/L F0 generation adults at the interim and scheduled necropsies (follicular hyperplasia; more pronounced in the females and males at the interim sacrifice). At the interim necropsies the incidences (graded as minimal) in males was 3/7 and 6/7 in the control and 360 mg/L groups. At the scheduled necropsies the incidences (graded as minimal) in males was 3/7 and 5/7 in the control and 360 mg/L (minimal or mild) groups. In females, the incidences (minimal or mild) was 7/14 in the 360 mg/L group compared to 3/13 in the control group at the scheduled necropsies. These changes were not statistically significant. The author concluded that no corresponding macroscopic findings or effects on thyroid weights or hormones (T3, T4 and TSH) were noted.

Other histopathological findings in the thyroid gland observed in females at the scheduled necropsy, including follicular dilation (increased size of the follicles) and increased/ decreased amount of follicular colloid, were observed at similar incidences to those in the control group.

There were no qualitative microscopic changes in the brain (forebrain, midbrain or hindbrain) and locomotor activity was also unaffected on PND21. However, when locomotor activity was evaluated as these same animals approached sexual maturity (PND 61), generally statistically significant and dose-related increases in cumulative total (33.9%-41.0%) and/or ambulatory (37.2%-53.4%) counts were noted for F1 males in the 40, 120 and 360 mg/L groups (n=12-14 animals/group). Cumulative total and ambulatory counts for locomotor activity were also increased in F1 females but these changes were not statistically significant or dose-related (similar magnitude across the dose levels). No changes in the habituation pattern were noted in males or females at PND 61. The increases in locomotor activity were not considered conclusive evidence for a change in CNS function because no correlating histopathological changes in the brain were detected in F1 pups and no indications of developmental delay or other changes in CNS function were detected in functional observational battery (FOB) evaluations (PND 21), acoustic startle response (PND 20 and 60) or Biel maze swimming trials (PND 22 and 62).

The author concluded that no detectable potential of resorcinol-related developmental neurotoxicity was seen. Based on the results of this study, concentrations exceeding 360 mg/L were recommended for the definitive two-generation reproductive toxicity study.

A drinking water two-generation reproductive toxicity study of resorcinol in rats (unpublished study report, 2005, Welsch et al. 2008)

In a two generation reproductive toxicity study (OECD TG 416, 2001), resorcinol (purity 100 %) was administered in drinking water at concentrations of 0, 120, 360, 1000 and 3000 mg/L to Sprague Dawley rats (30/sex/group) for at least 70 days prior to mating, then during the mating period and finally during gestation, lactation and weaning (actual doses in **Table 18**). The first (F1) generation received resorcinol during growth into adulthood, mating, gestation, lactation and until weaning of the second generation. The dosing period covers all sensitive periods in reproduction (fertility and development). F0 animals were approximately 6 weeks' age at the initiation of test article administration.

The reproductive parameters evaluated covered gonadal function, estrous cyclicity, mating behaviour, conception, gestation, parturition, lactation and weaning of the F0 and F1 generations and F1 and F2 neonatal survival, growth and development. In addition, thyroid/pituitary hormone analysis (i.e. T3, T4 and TSH) and bioanalysis to determine plasma resorcinol concentration were conducted as part of a study design. In bioanalysis blood samples were collected and analysed from 15 randomly selected F1 parental animals/sex/group during the week prior to necropsy.

The general appearance and behaviour were observed twice daily and particular attention was paid to any symptoms indicative of effects on nervous system function.

For total T3, T4 and TSH analysis, the blood samples were collected via the vena cava from 15 randomly selected F0 and F1 parental animals/sex/group at the scheduled necropsies following weaning of the pups. Blood for hormone analysis were collected from all F1 and F2 culled pups from 15 randomly selected litters on PND 4 (samples were pooled without regard to sex) and from one pup/sex from 15 randomly selected litters on PND 21.

The organs including thyroid gland were weighed from all F0 and F1 parental animals at the scheduled necropsies. For microscopic examination, selected tissues including the thyroid gland from all F0 and F1 parental animals in the control and high concentration level (3000 mg/l) groups and all animals found dead or euthanised in extremis, were examined. The thyroids of all F0 animals in the 1000 mg/l group were also examined. In addition, the stereomicroscopy was done on 15 randomly selected F0 parent animals per sex in the control and 3000 mg/l groups and 15 randomly selected F0 parent males in the 1000 mg/l.

Results

In the bioanalysis, low plasma resorcinol levels could be detected in some animals in the 3000 mg/L group. The results indicated that resorcinol was rapidly absorbed and eliminated.

Decreased mean cumulative body weight gains were noted in the 3000 mg/L group F0 animals during the pre-mating period (females) or the entire generation (males). Mean body weights were decreased by up to 6.3% in the F0 females from study day 56 through 70. Mean body weights in the 3000 mg/L group F0 females were also decreased during the first week of gestation (up to 5.5%), throughout lactation (up to 8.4%) and after the lactation period ended (6.3%). Mean body weights and body weight gains were unaffected in the 120, 360 and 1000 mg/L group F0 males and females. Mean body weights in F1 males were decreased by up to 7.1% during the entire generation. Mean

body weights were also reduced in the 3000 mg/L group F1 females during lactation (up to 6.1%) and after the lactation period ended (up to 7.0%). Mean body weights and body weight gains were unaffected in the 120, 360 and 1000 mg/L group F1 males and females.

Decreased mean water consumption was noted for the 3000 mg/L group F0 and F1 parental animals during the pre-mating period (females) or the entire generation (males) and for the F1 pups gang-housed by litter from PND 21-28. Decreases in water consumption were indicated to be due to the poor palatability of the water containing the two highest concentrations of resorcinol. These were not considered an adverse change due to the lack of associated effects on food intake and food utilization.

There were no F0 or F1 parental resorcinol-related deaths or clinical findings during the weekly detailed physical examinations. There were no signs and symptoms of any central nervous system related toxicity. Reproductive performance (estrous cycles, mating and fertility indices, number of days between pairing and coitus, and gestation length) and parturition in the F0 and F1 animals were unaffected by resorcinol. Spermatogenic endpoints (mean testicular and epididymal sperm numbers and sperm production rate, motility, progressive motility and morphology) in the F0 and F1 males were unaffected. No effects were observed on the mean days of acquisition of balanopreputial separation and vaginal patency in the F1 pups. No effects were observed on F1 and F2 pup survival or the general physical condition of the pups during the pre-weaning period.

Mean TSH concentration was slightly increased (3.2, 21.5, 26.9 and 35 %, not statistically significant) in a concentration-related manner for F0 males (15 rats/group) in the 120, 360, 1000 and 3000 mg/L groups compared to the control group at the scheduled necropsy. A similar increase was not noted in the females (15 rats/group). Increases were in only one sex without concomitant decreases in T3 or T4 (mean T3 concentration was increased in the 3000 mg/L group males when compared to the control group). The author did not consider the higher TSH values in the F0 males to be resorcinol-related in the absence of effects on T3 or T4, organ weights or adverse macroscopic or microscopic findings.

In F1 males there were a statistically significant increase (5.5, 50, 14.3 and 56 %) in the low and high dose group for TSH levels in the 360 and 3000 mg/L groups (15 rats/group) at PND 21. However, the differences were not observed in a concentration-related manner. A similar increase was not noted in the females (15 rats /group).

There appears to be a slight dose-related increase (not statistically significant) in T3 levels in the F0 males, which is consistent with an apparent slight increase in serum T3 levels in the F1 males. However, a similar increase was not evident in either the F0 or F1 females.
In F2 females (15 rats/group) there were a statistically significant decrease (22 %) from the control group for T4 in the 1000 mg/L group at PND 21. However, T4 levels were unaffected at 3000 mg/L. A similar decrease was not noted in the males (15 rats /group).

Mean thyroid gland weights (absolute and relative to final body weight and brain weights) were increased (not statistically significant) in the 3000 mg/L group F0 males compared to the control group. However, the increases were due to a single male, which corresponded to macroscopic and microscopic findings (enlarged thyroid and bilateral benign follicular cell adenomas, respectively) that were not observed for other F0 animals. The author concluded that the single incidence of follicular cell adenomas in a 3000 mg/L group F0 male rat in this study was a spontaneous occurrence.

In histopathology of the thyroid glands decreased colloid was observed in the 3000 mg/L F0 males and females group. Decreased colloid, characterized by small follicles with little or no colloid present within the follicular lumen, was diagnosed in the thyroid glands when the change was diffuse and bilateral. The incidences (graded as minimal) in F0

males were 2/30, 2/30, and 7/30 in the control, 1000 and 3000 mg/L groups. In females, the incidence of this change was 3/30, 6/30, and 4/30 in these same treatment groups. A relationship to resorcinol concentration was only noted in the F0 males.

Decreased colloid was observed in the F1 males with incidences of 6/30 and 4/30 in the control and 3000 mg/L group, respectively, and 3/30 and 4/30 in the control and 3000 mg/L group females, respectively. None of the differences in the F0 and F1 group were statistically significant.

In addition to conventional histopathology of the thyroid gland, a quantitative stereomicroscopic analysis (morphometric) of thyroid colloid content was conducted. The mean percent of colloid was statistically significantly decreased by 11 % compared to the control group in the 3000 mg/l F0 male group. In contrast, mean colloid in the 3000 mg/L group F0 females was reduced by only 3.55% compared to the controls, and was not statistically significant. The author concluded that the reduced colloid content was resorcinol-related finding but not to be an adverse effect. This was justified by a lack of functional effects associated with the decreased colloid; serum T3, T4 and TSH were not statistically significantly different from controls, and there were no alterations in functional reproductive outcome. Furthermore, there were no alterations in mean absolute and/or relative thyroid gland weights in any treatment group of either sex.

Overall, the author concluded that no resorcinol-related macroscopic findings, organ weight (absolute, relative to final body weight and relative to brain weight) or adverse microscopic effects were observed in the F0/F1 parental animals. No effects were observed on F1 and F2 pup survival, macroscopic findings or effects on organ weights. No statistically significant resorcinol-related changes in the mean concentrations of thyroid/pituitary hormones were noted in the F0 or F1 parental animals or in the F1 or F2 pups selected for analysis.

The NOAEL was considered to be 3000 mg/L for parental systemic and offspring toxicity (ca. 233 mg/kg/day (males), 304 mg/kg/day (females (premating and gestation)), and 660 mg/kg/day (females (lactation)) while the NOEL is 1000 mg resorcinol/L for decreases in water consumption (ca. 86 mg/kg/day (males), 126 mg/kg/day (females (premating and gestation)) and 225 mg/kg/day (females (lactation)). The NOAEL for reproductive toxicity (fertility and development) is 3000 mg/L which corresponds to 245 mg/kg bw (males) and 295 mg/kg bw (females) in the F1 generation.

Discussion on reproductive toxicity studies

No indications of reproductive toxicity were seen in the dose range-finding study (unpublished study report, 2003) or in the two-generation reproductive toxicity study in rats (unpublished study report, 2005, Welsch *et al.* 2008).

No consistent changes in circulating thyroid/pituitary hormone values (i.e. serum total T3, T4 and TSH) or in thyroid histopathology were seen in the two-generation reproductive toxicity study. Most of the changes in hormone values were seen in male rats only without statistical significance. Some of the changes were statistically significant but without dose-related pattern. Decreased colloid content in the follicular lumen (graded as minimal) occurred with slightly increased incidence in 3000 mg/L group F0 males but without statistical significance. Follicular cell height was not examined. In the morphometric analysis, the mean percent of colloid was statistically significantly decreased (11 %) compared to the control group in the 3000 mg/l F0 male group. However, the magnitude of the decrease is low, serum T3, T4 and TSH were not statistically significantly different from controls and no other alterations in histology, effects on thyroid gland or pituitary weights were reported.

The eMSCA considers that the toxicological significance of changes in thyroid/pituitary hormone levels (i.e. serum T3, T4 and TSH) should be interpreted in conjunction with

histopathological changes in thyroid gland, weights of thyroid/pituitary glands and overall toxicity. The changes in the hormone levels represent a measurement at a single point in time and can be transient and affected by several factors, whereas thyroid weight and histopathology are endpoints that may represent cumulative effects. The decreased colloid content in the follicular lumen could be interpreted as an indication of increased biological activity (increased endocytosis of colloid into the follicular cells), compensatory reaction, of the thyroid gland rather than clear adverse effect. Not studied in the aforementioned studies, but the change in the colloid amount may be reversible depending on the level of biological activity. These slight non-consistent changes in circulating T3, T4 and TSH hormone values and in follicular colloid content seen in the two-generation reproductive toxicity study (without any other histopathological alterations, effects on thyroid/pituitary weights or reproductive toxicity) are not considered toxicologically significant by the eMSCA.

Endpoints for neurotoxicity (i.e. brain weight and width, brain histology, functional observation battery (FOB), locomotor activity, acoustic startle response and Biel maze swimming trials) was investigated in a dose range-finding study (unpublished study report, 2003), where dose-related effects on locomotor activity (in cumulative total and ambulatory counts) was observed in sexually mature F1 males at PND 61 (young adult). Locomotor activity was also increased in F1 females but the change was not statistically significant or dose-related. The eMSCA considers that increased motor activity at PND 61 may be an indication of latent alteration in motor activity. However, the eMSCA considers that resorcinol, based on the results from limited developmental neurotoxicity measurements in the dose range-finding study is probably not a developmental neurotoxicant because significant effects was seen only in males, other behavioral endpoints were not affected, no indications of developmental delay were reported and no concurrent correlating changes in brain histopathology, weight or width were reported.

Overall, the eMSCA conclude that no clear adverse effects were seen on the hypothalamus-pituitary-thyroid axis (HPT axis).

In addition, the eMSCA considers that extrapolation of effects on follicular colloid content and thyroid hormone levels from rodents to human is not straightforward, due to suggested species differences in thyroid hormone homeostasis i.e. healthy adult humans have lower thyroid hormone turnover rates (due to binding to thyroxine-binding globulin), the rat follicles contain much less colloid than primate follicles and humans have larger reserves of iodinated thyroglobulin, allowing them to compensate for reduced hormone synthesis in the thyroid (Lewandowski et al. 2004, Fisher et al. 2012, EFSA 2015).

Developmental toxicity

The registration dossier includes four oral developmental toxicity studies. Two studies with resorcinol have been carried out in rats and one study in rabbits. In another oral study in rabbits, exposure to resorcinol bis-diphenylphosphate (RPD) was used to evaluate developmental toxicity potential of resorcinol. This is based on read-across from RPD for which resorcinol is known to be one of the major urinary metabolites. Overview of these studies is presented in **Table 19**. In addition, the Registrant(s) provided the eMSCA with an additional oral rat developmental toxicity study which has not been included in the registration dossier. The eMSCA considers these studies to be adequate and reliable.

Table 19 Overview of experimental studies on developmental toxicity provided in the registration dossier.

DEVELOPMENTAL TOXICITY			
Study	**Remarks**	**Results**	**Reference**
Rat (Sprague-Dawley) Female (24 rats/dose) 0, 40, 80 and 250 mg/kg bw/day Vehicle: purified water Constant dose volume: 5 ml/kg Oral: gavage Exposure: 6 – 19 days of gestation (daily) OECD Guideline 414: Prenatal Developmental Toxicity Study GLP study	Reliability: 1 (reliable without restrictions) Key study Test material: Benzene-1,3-diol (IUPAC name), Resorcinol (common name) Purity: >95%	NOAEL (maternal toxicity): 80 mg/kg bw/day NOAEL (teratogenicity): 250 mg/kg bw/day	unpublished study report, (2004d)[1]
Rabbit (New Zealand White) Mated females (18 – 26 rabbits/dose 0, 25, 50 and 100 mg/kg bw/day Positive control: vitamin A Vehicle: water Oral: gavage Exposure: 6 – 18 days of gestation (once a day) Equivalent or similar to OECD Guideline 414 (1981): Prenatal Developmental Toxicity Study Non-GLP study	Reliability: 2 (reliable with restrictions) Key study Test material: Resorcinol (common name) Study conducted before the newest version of OECD Guideline 414 (2001)	NOAEL (maternal toxicity): 50 mg/kg bw/day Maternal bodyweight gain reduces statistically significantly compared to controls at the highest dose level NOAEL (developmental toxicity): 100 mg/kg bw/day No effects on foetal development were observed	unpublished study report, (1982a)[1]

DEVELOPMENTAL TOXICITY			
Study	**Remarks**	**Results**	**Reference**
Rat (Sprague-Dawley) Female (10 – 13/dose) 0, 125, 250 and 500 mg/kg bw/day Vehicle: propylene glycol Oral: gavage Exposure: 6 – 15 days of gestation (daily) Method: other (not OECD guideline study)	Reliability: 2 (reliable with restrictions) Supporting study Test material: Benzene-1,3-diol (IUPAC name), Resorcinol (common name)	NOAEL (teratogenicity): 500 mg/kg bw/day	DiNardo et al. 1985[1]
Rabbit (New Zealand White) Female (27 rabbits/dose) 0, 50, 200 and 1000 mg/kg bw/day (actual ingested) Vehicle: corn oil Oral: gavage Exposure: 6 – 28 days of gestation (single dose daily) EPA OPPTS 870.3700: Prenatal Developmental Toxicity Study	Reliability: 1 (reliable without restrictions) Weight of evidence Read-across from supporting substance (structural analogue or surrogate) Test material: tetraphenyl m-phenylene bis(phosphate) (EC name)	NOAEL (maternal toxicity): 1000 mg/kg bw/day NOAEL (developmental toxicity): 1000 mg/kg bw/day Based on test material: No adverse effects	Ryan et al. 2000[1]

[1]Ref. IUCLID dossier

Oral developmental toxicity study of resorcinol in rats (unpublished study report, 2004d)

Prenatal developmental toxicity (OECD 414) study was carried to evaluate toxicity of resorcinol on pregnant female rats and potential toxic effects of resorcinol on fetal development. In this study, pregnant female Sprague-Dawley rats were exposed to resorcinol (purity >95%) in purified water via oral route (gavage) daily on days 6 – 16 of gestation (11 consecutive days). The dose levels were 40, 80 and 250 mg/kg bw/day and each dose group had 24 rats. Similarly, the control group of rats received purified water over the same period of time. In all treatments, constant dose volume of 5 ml/kg was used and volume was adjusted according to the most recently recorded body weight. On day 20 of gestation, the female rats were sacrificed and macroscopically examined. The number of corpora lutea, implantations and live foetuses were recorded. The weight and sex distribution of foetuses were determined. The foetuses were externally examined and half of them were subjected to soft tissue examination and the other half to skeletal examination.

No maternal mortality occurred during the study and no clinical observations were considered to be consequence of resorcinol treatment. At the highest dose level (250 mg/kg bw/day), the maternal net bodyweight change was 19% lower than in control group (statistical significant effect, $p < 0.05$). No other resorcinol treatment related

effects on maternal bodyweight, bodyweight gain or food consumption were observed. At maternal necropsy, only occasional observations were recorded at two lowest dose levels. These were not considered to be related to resorcinol treatment. Based on the reduction of maternal net bodyweight change, NOAEL of 80 mg/kg bw/day for maternal toxicity was derived.

Litter data showed that the mean numbers of implantations and live foetuses were comparable with controls as was also pre- and post-implantation losses at all studied resorcinol doses. In all resorcinol treated groups, the mean number of corpora lutea, implantation sites, live foetuses and resorptions were similar as in the control group. In the highest dose group (250 mg/kg bw/day), weights of male and female foetuses were significantly higher than in control group. This was considered to be due to low weights of foetuses in control group rather than an effect caused by the resorcinol treatment. This conclusion was based on the fact that in control group foetal weights were outside the range of the last version of historical control data (3.8 g – 4.5 g) and within the range of the control group values during the period where this study was conducted (3.6 g – 3.9 g). This was further evaluated. It was considered that the probability to mask an effect in foetal body weights resulting from the low control group value is very low. This was based on the homogeneity of individual foetal body weights, the absence of dose-related trend in foetal body weights or the good general ossification of the skeletons. The percentage of male foetuses was similar to controls for all groups.

Foetal evaluation showed that no external, soft tissue or skeletal malformations were considered to be related to resorcinol treatment as the observed malformations were only occasional in nature without any dose-response and statistical significance, and were also observed in the control group. Also, only occasional external variations were observed. Similarly, mostly occasional soft tissue variations were observed without dose-response and statistical significance. Statistically significantly higher incidence of dilated ureter was observed at the dose level of 80 mg/kg bw/day compared to control ($p < 0.05$), i.e. in 0 fetuses in the control group vs. 7 fetuses (in 6 litters) in the mid dose group. No dose-response on this soft tissue variation was observed. In the lowest dose group (40 mg/kg bw/day) and the highest dose group (250 mg/kg bw/day), the foetal incidence of dilated ureter was 4 (in 3 litters) and 3 (in 3 litters), respectively.

In this study, total incidence of skeletal variations was very common (**Table 20**). At the two lowest dose levels, the incidence of foetuses with incompletely ossified interparietal increased significantly (40 mg/kg bw/day: $p < 0.05$ and 80 mg/kg bw/day: $p < 0.01$) when compared to control. Statistically significant ($p<0.05$) increase in the incidence of incompletely ossified parietals was observed at dose level of 80 mg/kg bw/day. These observations were considered not to be due to the resorcinol treatment because these effects were not observed at the highest dose (250 mg/kg bw/day). In the highest resorcinol dose group, the incidence of foetuses with incompletely ossified 5th sternebra increased significantly ($p<0.01$). The incidence of incomplete ossification of 5th sternebra was very high also in the control group. This variation was observed in 118 foetuses of 170 foetuses studied in the control group. In the highest dose group, this skeletal variation was observed in 144 foetuses of 176 foetuses studied. Incomplete ossification of 5th sternebra was observed in all 24 litters both in control group and all resorcinol dose groups. Interestingly, the highest fetal and litter incidence of unossified 5th sternebra was observed in the control group. The effect was not, however, statistically significant except if percentual amount of affected foetuses/litter in control group was compared to that in the highest dose group (**Table 20**). As the thoraco-lumbar region is known to be particularly labile in the rat, and the absence of other variations or malformations, the effect on 5th sternebra was not considered to be consequence of resorcinol treatment. Based on these observations and justifications, NOAEL of 250 mg/kg bw/day for developmental toxicity was derived.

Table 20 Total foetal incidence of skeletal variations and statistically significant skeletal effects observed in Sprague-Dawley rats (unpublished study report, 2004d).

FETAL SKELETAL VARIATIONS				
	Resorcinol dose (mg/kg bw/day)			
	0	40	80	250
Litters evaluated (number)	24	23	24	24
Fetuses evaluated (number)	170	164	164	176
Incomplete ossification of INTERPARIETAL				
Fetal incidence (number)	6	**18***	**21****	2
(%)	3.5	11.0	12.8	1.1
Litter incidence (number)	4	7	8	2
(%)	16.7	30.4	33.3	8.3
Affected fetuses/litter (Mean% ± SD)	3.5±8.8	11.3±21.2	12.4±23.2	1.2±4.0
Incomplete ossification of PARIETAL				
Fetal incidence (number)	1	3	**8***	0
(%)	0.6	1.8	4.9	0.0
Litter incidence (number)	1	3	5	0
(%)	4.2	13.0	20.8	0.0
Affected fetuses/litter (Mean% ± SD)	0.5±2.6	1.9±5.0	**4.8•**±10.9	0.0
Incomplete ossification of 5th STERNEBRA				
Fetal incidence (number)	118	126	128	**144***
(%)	69.4	76.8	78.0	81.8
Litter incidence (number)	24	23	24	24
(%)	100	100	100	100
Affected fetuses/litter (Mean% ± SD)	69.1±24.8	76.6±19.9	78.5±19.2	81.9±19.6

FETAL SKELETAL VARIATIONS				
	Resorcinol dose (mg/kg bw/day)			
	0	40	80	250
Unossified 5th STERNEBRA				
Fetal incidence (number)	42	27	24	17
(%)	24.7	16.5	14.6	9.7
Litter incidence (number)	18	16	16	11
(%)	75.0	69.6	66.7	45.8
Affected fetuses/litter (Mean% ± SD)	24.1±23.2	17.1±16.0	14.1±15.3	**9.6**•±13.8
Total fetal skeletal variations				
Fetal incidence (number)	163	159	158	169
(%)	95.9	97.0	96.3	96.0
Litter incidence (number)	24	23	24	24
(%)	100.0	100.0	100.0	100.0
Affected fetuses/litter (Mean% ± SD)	95.3±13.3	96.9±12.1	96.3±6.6	95.9±9.9

*) $p < 0.05$ and **) $p < 0.01$ (Fishers exact test)
•) $p < 0.05$ (ANOVA + Dunett-test)

Teratological assessment of five oxidative hair dyes in the rat (DiNardo et al. 1985)

In a study by DiNardo et al. (1985), teratogenic potential of five hair dye substances, including resorcinol, was evaluated in Sprague-Dawley rats. Pregnant female rats (10 – 13 rats/dose) were exposed to resorcinol (125, 250 and 500 mg/kg) by oral route (gavage at volume 10 ml/kg) on days 6 to 15 of gestation (10 consecutive days). Control group of rats received propylene glycol (10 ml/kg), which was used as solvent to dissolve resorcinol.

Resorcinol did not affect the maternal bodyweight gain statistically significantly, although at the highest dose level (500 mg/kg) reduction in bodyweight gain was observed. No significant differences were observed in the incidence of foetuses with gross, visceral or skeletal anomalies or any of the other parameters investigated (e.g. mean number of corpora lutea, total implantations, viable foetuses, mean fetal body weight gain). Based on these results, NOAEL of 500 mg/kg bw/day for maternal and developmental toxicity was derived. In this study, Vitamin A was used as a positive control and it was administered as a single dose (100 000 IU/rat) on day 9 of gestation. Vitamin A significantly increased the number of abnormal fetuses.

Oral developmental toxicity study of resorcinol bis-diphenylphosphate in rabbits (Ryan et al. 2000)

The Registrant(s) has also included a developmental toxicity study (Ryan et al. 2000) in which pregnant female New Zealand White rabbits were exposed to resorcinol bis-diphenylphosphate (RPD) to evaluate developmental potential of resorcinol. This is based

on read-across from RPD for which resorcinol is known to be one of the major urinary metabolites. This study has been carried out according to EPA OPPTS 870.3700 (Prenatal Developmental Toxicity Study) guideline and under GLP. Pregnant female rabbits (27 rabbits/dose) were administered daily RPD in corn oil at doses of 50, 200 or 1000 mg/kg bw/day by oral route (gavage) on days 6 to 28 of gestation (23 consecutive days) at constant dosing volume (1.5 ml/kg bw). Control rabbits were similarly treated with corn oil. Dams were killed on day 29 of gestation.

No maternal mortality related to the treatment was observed. Furthermore, RPD did not affected clinical observations, maternal bodyweight and bodyweight gain. No significant differences in liver, kidney, spleen and gravid uterus weights were observed, and there were also no gross pathological abnormalities in any of the treated dams. Occasional and isolated significant increases in bodyweight gain and food consumption were observed in the highest dose group. These were, however, not considered biologically relevant. Thus, NOAEL of 1000 mg/kg bw/day for maternal toxicity was derived.

RPD did not significantly affected the number of corpora lutea, pre-implantation loss, total implants, live implants or resorptions at any dose level studied. There were also no significant differences in sex ratios and mean foetal bodyweight. At the highest dose level (1000 mg/kg bw/day), the number of dead foetuses was highest. This was associated with deaths in a single litter. Therefore, it was regarded as a cluster effect in that litter. Incidence of foetal anomalies was reported to be similar to or below published historical control values (the Middle Atlantic Reproductive and Teratology Association and the Midwest Teratology Association). There were no significant differences in the number of malformed foetuses. Total number of foetuses with malformations (gross external, visceral, cephalic or skeletal) in control and RPD-treated groups were as follows 1/217 (control), 3/215 (50 mg/kg bw/d), 3/215 (200 mg/kg bw/d) and 3/219 (1000 mg/kg bw/d). Skeletal observations were mostly common variations. These were regarded to be unrelated to RPD-treatment because their incidence was within the range of normal occurrence. As no effects related to developmental toxicity were observed, NOAEL of 1000 mg/kg bw/day for developmental toxicity was derived.

Oral developmental toxicity study of resorcinol in rabbits (unpublished study report, 1982a)

In a developmental toxicity study (unpublished study report, 1982a), pregnant female New Zealand White rabbits were administered resorcinol in water at dose levels of 25, 50 and 100 mg/kg bw/d by oral route (gavage) daily on days 6 – 18 of gestation (13 consecutive days). Resorcinol groups had 20 – 26 animals/dose. Control rabbits (22 animals) were similarly treated with water. In addition, a positive control group (18 animals) received Vitamin A in rape oil (6 mg/kg). Study was similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study) with some deviations. The number of pregnant females/dose group was lower than recommended in the guideline; i.e. 13 – 15 pregnant rabbits was used per dose. The exposure period covered days 6 – 18 of gestation (13 consecutive days). According to the present OECD 414 guideline each test and control group should contain a sufficient number of females to result in approximately 20 female animals with implantation sites at necropsy. Groups with fewer than 16 animals with implantation sites may be inappropriate. OECD 414 guideline is not intended to examine solely the period of organogenesis (days 6-18 in the rabbit) but also effects from preimplantation, when appropriate, through the entire period of gestation to the day before caesarean section. In this study, the animals were maintained until day 28 of gestation and killed on that day.

Maternal mortality occurred in the control group (3 animals) and in all resorcinol groups (1 – 4 animals/dose). The maternal mortality was mainly considered to be attributable to pulmonary disorders and also deaths caused by intubation errors. Deaths were considered not to be related to resorcinol exposure. Among the surviving females, there were no changes in clinical condition attributable to resorcinol treatment. No macroscopic changes were observed in maternal necropsy.

At the highest dose level (100 mg/kg bw/d), maternal bodyweight gain was slightly reduced during the dosing period. Resorcinol did not affect pregnancy incidence and the number of implantations. The number of corpora lutea was comparable in all groups. Although post-implantation loss was slightly higher in the two lowest resorcinol groups (25 and 50 mg/kg bw/d) than in the control group, total number of intra-uterine deaths was within historical control ranges. Thus, these were considered not to be a consequence of resorcinol treatment. Based on the reduction of maternal bodyweight gain at the highest resorcinol dose, NOAEL of 50 mg/kg bw/d was derived for maternal toxicity.

Resorcinol did not affect the mean number of foetuses per doe and the sex distribution of foetuses which were both comparable to controls. Litter and foetal weights were comparable for all dose groups. There were no foetuses with external, visceral or skeletal malformations in the control group or in any of the resorcinol groups. In these groups, visceral variations were not observed in any of foetuses. Fetal skeletal variations were observed in all resorcinol groups, but the incidence was comparable to effects seen in the control group and without no clear dose response (**Table 21**). Positive control (Vitamin A) affected slightly foetal weight and had slight teratogenic effects. Because no resorcinol treatment related developmental effects were observed, NOAEL of 100 mg/kg bw/d was derived for developmental toxicity.

Lack of clear effects on maternal animals (only bodyweight gain was reduced in the top dose group) and reduced number of foetuses examined may have affected the sensitivity of the study.

Table 21 Foetal skeletal variations in New Zealand White rabbits (unpublished study report, 1982a).

FETAL SKELETAL VARIATIONS				
	Resorcinol dose (mg/kg bw/day)			
	0	25	50	100
Fetuses examined (number)	35	35	34	51
Number of foetuses with skeletal variations	28	30	30	43
% of foetuses examined	80.0	85.7	88.2	84.3
Litter incidence (number)	11	11	12	14
Skeletal variations (number of foetuses)				
• Sternebra incompletely ossified	13	16	13	15
• Sternebra not ossified	9	6	10	9
• Sternebra asymmetrically ossified	1	1	1	1
• Single extra rib	3	3	5	3
• Extra pair ribs	14	15	14	27
• Single extra rib without connection to the vertebral column	5	3	3	5
• Extra pair ribs without connection to the vertebral column	1	0	1	0

Oral developmental toxicity study of resorcinol in rats (unpublished study report, 1982b)

In addition to studies included in the registration dossier, the Registrant(s) provided a full study report on developmental toxicity study in rats (unpublished study report, 1982b). In this study, female Sprague Dawley rats were treated with resorcinol orally by gavage at dose levels of 40, 80 or 250 mg/kg daily from day 6 to day 15 of gestation (treatment in 10 consecutive days). Each treated group had 23 sexually mature female rats. Similarly, a control group and a positive control group (both with 23 female rats) received distilled water and 15 mg/kg of Vitamin A daily over the same period of time, respectively. After the treatment period (6 – 15 days of gestation), animals were maintained without any treatment until day 19 of gestation when they were killed.

There were no mortalities among rats at any dose level of resorcinol. One control rat died on day 13 of gestation most likely due to perforation of the oesophagus by the dosing cannula. In addition, one control rat was killed on day 7 of gestation due to accidental injuries to the hindfeet. There were no changes in behaviour or clinical condition attributable to resorcinol treatment. Resorcinol at dose levels of 40 and 80 mg/kg did not affect maternal bodyweight gain. At the highest dose level (250 mg/kg), maternal bodyweight gain was slightly, but not statistically significantly, reduced compared to control animals during the dosing period; i.e. 46.4 ± 8.0 g (control) vs. 42.0 ± 17.9 g (250 mg/kg group). This finding was due to the fact that three animals (3 of 23) in the highest dose group showed no bodyweight gain during days 6 to 15 of gestation. This lowers the mean value of bodyweight gain in that group but at the same time increases clearly the standard deviation. No changes were observed at necropsy in rats treated with resorcinol.

Total number of pregnancies were comparable between groups. Resorcinol treatment did not affect the mean number of corpora lutea and implantations per dam. Resorcinol did not affect pre-implantation loss. Post-implantation loss was slightly higher in resorcinol groups compared to control group. This was not considered to be a resorcinol-induced effect as differences from the controls were not statistically significant and also group incidences were not dose-related; i.e. 2.9%, 4.1%, 7.2% and 3.8% post-implantations loss in control, 40 mg/kg, 80 mg/kg and 250 mg/kg groups, respectively. Resorcinol did not affect the mean number of foetuses per dam as the number was comparable in all groups. Also, the sex distribution, mean litter weight and mean foetal weight in the resorcinol-treated groups were comparable to control group. Occasional external foetal malformations were observed at two highest dose levels of resorcinol; i.e. one umbilical hernia (80 mg/kg) and one conjoined twins (250 mg/kg). These can be regarded as incidental. In the control group, also one external malformation was observed (short tail). Foetal visceral or skeletal malformations were neither observed in the control group nor in the resorcinol-treated groups. In the positive control group (Vitamin A), 18% of foetuses examined (in 9 litters) had external malformations and 18.8% of foetuses examined (in 9 litters) had visceral malformations. No foetal skeletal malformations were observed in the positive control group.

The incidence of foetal skeletal variations was higher in resorcinol-treated groups compared to control (see **Table 22**). In control group, 2% of foetuses examined (in two litters) showed skeletal variations whereas these were observed in 7.7% (in five litters), 8.5% (in six litters) and 10.6% (in eight litters) of foetuses examined in resorcinol-treated groups of 40, 80 and 250 mg/kg, respectively. In the full study report provided, it is stated that incidence of foetal skeletal variations was higher in resorcinol-treated groups than in the control group, but comparable with other control groups. Therefore, the occurrence of these skeletal variations was considered to be incidental and not related to resorcinol treatment. The reference to "other control groups" in the full study report is not fully clear to the eMSCA but it most likely refers to the historical control data (not available for the eMSCA). Skeletal variations appear to be very common in rats as can be also seen in unpublished study report (2004d). Variations are regarded as changes which occur regularly also in control group and which are not of functional

significance. In this study, only skeletal variations were observed in the absence of any skeletal malformations.

Table 22 Foetal skeletal variations in Sprague-Dawley rats (unpublished study report, 1982b).

FETAL SKELETAL VARIATIONS				
	Resorcinol dose (mg/kg bw/day)			
	0	40	80	250
Fetuses examined (number)	98[a]	91[b]	117	142
Number of foetuses with skeletal variations	2	7	10	15
% of foetuses examined	2.0	7.7	8.5	10.6
Litter incidence (number)	2	5	6	8
Skeletal variations (number of foetuses)				
• Parietals incompletely ossified	2	5	4	7
• Interparietal incompletely ossified	0	1	2	5
• Occipital incompletely ossified	0	1	2	0
• Parietals not ossified	0	0	0	0
• Interparietals not ossified	0	0	0	0
• Occipital not ossified	0	0	0	0
• Splitting of ossification centres	0	1	1	3
• Single extra rib	0	0	2	4
• Extra pair of ribs	0	0	0	2
• Wavy ribs	0	0	0	0

[a] one foetues was excluded by mistake

[b] six foetuses were excluded by mistake

Discussion on developmental toxicity studies

The eMSCA considers that the findings observed in the evaluated developmental toxicity studies with resorcinol and in the developmental toxicity study with RPD do not raise concern of resorcinol-induced developmental effects. This conclusion is also drawn in each individual study. Resorcinol has been shown to be TPO inhibitor in *in vitro* studies (See section 7.10.1). This raises a concern of possible thyroid effects by resorcinol. Skeleton is known to be target of thyroidal hormones. Developing skeleton is sensitive to thyroid hormones and normal functioning of thyroid is needed for normal skeletal development (Williams, 2013). In the evaluated developmental toxicity studies, some observed foetal skeletal variations were statistically significantly higher at some resorcinol dose levels than in foetuses in the control group. However, there is no direct indication that the observed skeletal variations were due to disorder in thyroid functioning. Moreover, it seems likely that observed increases in some skeletal variations are not due to resorcinol treatment as no clear dose-response was observed and there was no statistically significant difference in the number of litters in which these variations

were observed. No skeletal malformations were observed at all or the observed skeletal malformations were only occasional in nature and thus not related to resorcinol treatment.

7.9.8 Human information

Table 23 Overview of medical case studies.

HUMAN CASE STUDIES		
Background	**Findings**	**Reference**
Two females (68 and 59 years old) Both patients were overweight and suffering from medical complications such as diabetes. Long-term (over 5 years) dermal application of resorcinol-based ointment (7 g or 4 g ointment per day) to broken skin for varicose leg ulcers.	Two patients presented a level of goitre. The association of resorcinol use with goitre was mainly based on the return to normal thyroid function in both cases following cessation of the treatment. The authors hypothesised that there was a disturbance in the organification of iodine and it is possible that resorcinol would only induce thyroid disturbances in cases where there is an underlying thyroiditis.	Berthezene et al. 1973 (In French)
One female (39-year-old) Since the age of 20 had been suffering from bilateral phlebitis, varicose veins of both legs complicated by chronic oedema and ulcerations. Long-term dermal application of ointment containing 2 % resorcinol to broken skin for leg ulcers for about one year.	During the course of treatment, a hyperplastic parenchymatous goitre (hyperplasia of thyroid) with discrete hypothyroid symptoms was described. Upon cessation of the treatment the goitre reduced in volume, this also coincided with liothyroxine treatment.	Guinet et al. 1967(In French)
Three females (60, 59 and 50 years old) One patient was complicated with cardiac insufficiency. Long-term (years) dermal application of ointments containing resorcinol (up to 12 %) to broken skin for varicose leg ulcers.	The clinical evidence of a goiotrenic effect and myxoedema in all three patients. Clinical signs of enlarged thyroid glands, hypoactivity and a low serum-bound iodine level were reported. Hyperplasia of the thyroid glands were seen in histopathology. Hyperplasia was seen with small and large follicles depleted or empty of colloid (case 1 and 2). In case 3 the majority of the follicles contained colloid, mostly peripheral vacuolation was seen. The colloid accumulation suggested a phase of recovery. When ointment applications were stopped, the thyroid took up iodine 131 avidly and myxoedematous features disappeared with a return to normal levels of the serum protein-bound iodine. Re-application of ointment immediately reduced the thyroid ability to concentrate iodine 131 and lowered serum protein bound iodine levels to levels found in myxoedema.	Bull & Fraser et al. 1950

HUMAN CASE STUDIES		
Background	**Findings**	**Reference**
One male (54-year old) Dermal application of ointments containing resorcinol (4-12 %) to broken skin for varicose leg ulcers once a day for several months.	The patient showed clinical symptoms of goitre (enlarged thyroid) and myxoedematous faces. Protein-bound iodine was low. Withdrawal of ointment resulted in increased uptake of iodine 131. Re-application of ointment resulted in diminished thyroid uptake and increased urinary excretion. The goitre was smaller but palpable.	Hobson et al. 1951
One male (70-year old) The patient had renal failure secondary to diabetic glomerulosclerosis with other complications. The patient was in chronic hemodialysis and was taking several medications. The patient had dry and coarse skin containing multiple senile keratosis. Reported to be intact skin. Dermal (over ca. 3 months) application of Lanacane ointment for puritis containing 2 % resorcinol (up to 7.5 g ointment per day).	The patient had hypothyroidism following dermal application of ointment. The patient had low free thyroxine index with high TSH and equivocal enlargement of the thyroid gland in palpation. After stopping the use of ointment and commencing treatment with levothyroxine (synthetic form of T4), free thyroxine and TSH circulating levels were within normal limits within 2 weeks. The thyroid gland was normal size.	Katin et al. 1977
One female (59-year old) Long-term dermal application (13 years) of an ointment containing 12.5 % resorcinol (12.5 % glycerin in a soft paraffin base) for chronic leg ulcers (ca. 500g/week).	One myxoedematous patient with a moderate goitre. Symptoms relieved by treatment with thyroid tablets. 2.1 % of the applied dose was found in urine as glucuronide and monosulphate metabolites. Free resorcinol was not detected. The patient died as a result of thrombosis, gangrene of the small intestine and mural thrombus in the aorta. An enlarged thyroid gland was confirmed at autopsy.	Thomas and Gisburn 1961
Four healthy males with intact skin (aged 18 +). Three were in the treatment group and one untreated control. 4-week dermal application (to the face, shoulders, upper chest and upper back). 20 ml of 2 % resorcinol in hydroalcoholic vehicle. Twice daily 6 days/week 150 microg/cm2 of body surface. Daily dose 12 mg/kg/bw. Only the vehicle was applied to the control subject.	No detectable levels of free resorcinol or its conjugates were found in blood at weeks 1, 2, 3 and 4. In 24-hour urine samples collected after 14 days of continuous treatment, a maximum of 0.47 to 2.87% (an average of 1.64%, up to 23 mg resorcinol) of the applied daily dose was excreted and detected as the glucuronide and sulphate conjugates. No significant changes were observed in any of the thyroid functions measured (T3, T4, T7 and TSH) in the three treated subjects. Reported to be within normal ranges.	Yeung et al. 1983

HUMAN CASE STUDIES		
Background	**Findings**	**Reference**
This study was used to investigate: (1) blood and urinary levels of resorcinol after maximal exaggerated subchronic topical administration to human subjects (intact skin); (2) possible changes in thyroid function and blood chemistries; and (3) skin penetration rates of resorcinol under these exaggerated usage conditions. Blood samples were drawn at day 0, and at weeks 1, 2, 3, and 4 after the initiation of treatment. These samples were assayed for free resorcinol and/or its conjugates or metabolites; blood chemistries (SMAC 24) and thyroid functions (T3, T4, T7 and TSH) were also measured. 24-hour urine specimens were collected from each subject two and four weeks after initiation of treatment. All plasma and urine samples were frozen until analyzed. Under the new analytical methods, the minimum detectable level of resorcinol was 0.1 µg/ml.	Dermal absorption: The absorption and metabolic disposition of 2% resorcinol applied topically in a hydroalcoholic vehicle was determined in three human subjects. The test substance penetrated the skin at a rate of 0.37 µg/cm2/hour.	

There was a total of six medical case reports from 1950 to 1977 describing reversible hypothyroidism (including myxoedema and goitre) in patients using topically large amounts of ointments containing resorcinol (**Table 23**). No other medical case reports were found by the eMSCA. In most of cases the patient had been using ointments containing resorcinol up to 12 % in large quantities applied to large areas of ulcerated skin (damaged skin) over long periods (months or years). Indications of thyroid dysfunction were demonstrated by changes in biological markers such as T3, T4, TSH and effects on iodine uptake into the thyroid gland as well as clinical evidence of goitre (enlarged thyroid gland) and myxoedema (swelling of face/arms/legs). Hyperplasia of the thyroid glands were seen in histopathology. The potential for causal relationship was provided by the resolution of goitre, myxoedema and other symptoms upon discontinuance of the use of the ointment. Cessation of the treatment caused the clinical findings of hypothyroidism to relieve/disappear. Re-application of ointment reduced again rapidly the thyroid uptake of iodine and lowered serum protein bound iodine to levels noted before cessation of the use of ointment (Bull & Fraser 1950, Hobson et al. 1951).

It has been suggested that observed thyroid dysfunction were caused by prolonged high rates of absorption of resorcinol in the systemic circulation from ointment through impaired skin barrier. Systemic exposure to resorcinol is suspected as a consequence of the application conditions but no measurements of resorcinol in blood were performed. It has been estimated that effect levels in the medical case studies were greater than 34 mg/kg resorcinol per day (Lynch et al. 2002). It has been suggested that when applied on healthy skin, percutaneous absorption is limited and rapid metabolism precludes resorcinol from reaching thyroid gland toxic concentrations. In a clinical study by Yeung

et al. 1983 investigating dermal uptake in healthy males having intact skin no significant changes were observed in any of the thyroid functions measured. No detectable levels of free resorcinol or its conjugates were found in blood.

The eMSCA note that the medical case reports are old and mainly poorly reported. Several sources of uncertainty were identified such as a very small sample size (a total of nine individuals), history of the individuals not known (e.g. underlying thyroid dysfunction), most of the patients were reported to have other clinical issues (e.g. symptoms, diseases and other medical treatments), a lack contemporary controls and lack of data to demonstrate the level of exposure to resorcinol (i.e. blood measures). In addition, there is a lack of information on other ingredients in the ointments and how the formulation affect on the bioavailability and toxicity of resorcinol. The eMSCA considers that the case reports demonstrate some evidence of a causal association between hypothyroidism and use of resorcinol containing ointments in large quantities to broken skin over long periods. Because of 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, can be considered as a supportive evidence for resorcinol effects on thyroid gland. Overall, when the available *in vitro* data on mode of action (inhibition of thyroid peroxidase, decrease of iodine uptake and iodine organification; see section 7.10.1) is taken into account, the causal association between the exposure to resorcinol and thyroid dysfunction (hypothyroidism) is considered to be plausible. It is not possible to derive dose-response relationship for thyroid effects seen based on the available information.

Overall, the eMSCA considers that the relevance of findings in the medical case reports for evaluation of a health risk by resorcinol exposure for workers in industrial settings is limited because the dermal absorption of resorcinol seems to be low (< 1 %) when applied on healthy/intact skin. For more detailed information on dermal absorption see section 7.9.1 (Toxicokinetics). The eMSCA notes that resorcinol has skin irritating and skin sensitising properties which may damage the skin surface and enhance penetration. Therefore, it is important that appropriate RMMs are in place to adequately control skin exposure to resorcinol.

The eMSCA recognises that in the CSR and IUCLID Section 11 gloves are recommended as a personal protective equipment in all exposure scenarios. Furthermore, in dusty areas it is recommended to wear protective apparel, including necessary head, hand and footwear protection. Therefore, the risk management measures to prevent dermal exposure to resorcinol seem to be currently in place to adequately control worker exposure. However, there is a concern whether workers are properly informed to use the right type of gloves. **The eMSCA recommends to include exposure scenario specific recommendations for protective gloves in the CSR (for more detailed information see section 7.12.1.1).**

7.9.8. Hazard assessment of physico-chemical properties

Not evaluated.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

Table 24

CRITICAL DNELS/DMELS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Workers- hazard via inhalation route	Systemic effects	unpublished study report, (2004)	NOAEC 140 mg/m³	5,6 mg/m³	key oral study (unpublished study report, 2004) was used for DNEL derivation, with route-to-route extrapolation
Workers – hazard via dermal route	Systemic effects	unpublished study report, (2004)	NOAEL 4000 mg/kg bw/day	40 mg/kg bw/day	key oral study (unpublished study report, 2004) was used for DNEL derivation, with route-to-route extrapolation

In the registration dossier, there are two repeated-dose inhalation studies in rats available (for more detailed information see section 7.9.4). The dossier includes a 14-day inhalation dose range-finding study and a 90-day inhalation study by unpublished study report, (1977). The dose-range finding study was considered reliable with restrictions by the Registrant(s) (Klimisch 2) and the 90-day inhalation study was considered invalid by the Registrant(s). Both studies have deficiencies and do not meet the requirements of current test guidelines. Therefore, the Registrant(s) has derived DNEL for repeated exposure via inhalation based on an oral study (unpublished study report, 2004).

The CSR contain information on irritancy and skin sensitisation properties showing that registered substance is a skin and eye irritant and skin sensitizer. Resorcinol has a harmonized classification as Skin Irrit. 2 and Eye Irrit. 2. In addition, resorcinol is self-classified as Eye Damage 1 and Skin Sens. 1B by the concerned registrants. The eMSCA agrees with the Registrant(s) conclusion in the CSR that based on irritation effects observed on the skin and eyes of experimental animals it is likely that respiratory irritation will also be observed. Skin irritant, skin sensitizing and eye irritant properties are often considered as an indication for local effects, also for local effects in airways tissues. According to current Lead Registrant's CSR there might be exposure of workers via inhalation route during several activities and thus there is a concern that the registered substance may cause local respiratory effects and inhalation DNEL for local effects would be necessary.

However, based on the available information in the CSR, pure resorcinol is used as flakes having low dustiness and the vapour pressure of resorcinol is relatively low (0.065 Pa) indicating a low potential of inhalation exposure. In addition, during the substance evaluation the eMSCA was informed by the Lead Registrant that the uses in spray applications (PROC 7, industrial spraying) will be removed from all exposure scenarios.

Overall, this information seems to indicate a low likelihood for exposure via inhalation route. In the CSR and IUCLID Section 11 use of appropriate respiratory protection and sufficient general/local exhaust ventilation are recommended by the Lead Registrant to control inhalation exposures where needed.

The eMSCA recommends that the Registrant(s):

- **update the registration dossier, taking into account the information that the uses in spray applications (PROC 7, industrial spraying) will be removed from all exposure scenarios.**
- **make a reassessment of the appropriateness of the relevant risk management measures (RMM) to ensure that the RMMs currently in place adequately control worker exposure to resorcinol.**

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

Resorcinol has a harmonised classification (Acute Tox. 4, Skin Irrit. 2, Eye Irrit. 2, Aquatic Acute 1) and some additional self-classifications (see section 7.6). Evaluating MSCA is in the opinion that harmonized classification and self classifiacations are appropriate. In the risk management option analyses it will be considered if further harmonisation for the self-classified endpoints is needed.

7.10. Assessment of endocrine disrupting (ED) properties

Resorcinol was added to the community rolling action plan (CoRAP) for substance evaluation as a potential endocrine disruptor and due to its wide dispersive use, consumer use and high (aggregated) tonnage. Both human health relevant and wildlife relevant endocrine disruption were evaluated.

Resorcinol has also been listed as a potential endocrine disrupting substance in several inventories and screenings (see examples below).

i. European Commission (2000):

Annex 1: Candidate list of 553 substances (categorized in Group I, II or III).

Nr	*CASNR*	*Name*	*Group*
60	*108-46-3*	*Resorcinol (chemno 560)*	*I*

Selection criteria for Group I (60 substances):

- *Highly persistent and/or HPV*
- *At least one study showing endocrine disruption in an intact organism (Category 1)*
- *High concern in terms of human and wildlife exposure*

An in-depth scientific evaluation of 12 substances, including resorcinol, from the priority list of actions has also been conducted (Johnson and Harvey 2002). *In vitro* EAST profiles could be determined based on the positive responses that were found for at least one of the fifteen endpoints considered. In the evaluation, resorcinol could be identified as a weak anti-androgen and as a moderate TPO-inhibitor.

ii. WHO/UNEP (2012):

Table 3.1. Endocrine disrupting chemicals (EDCs) can be grouped in multiple ways. In this table known or potential EDCs are grouped into 11 categories with examples of individual EDCs. Bolded chemicals were selected since they are regarded to be of specific interest as EDCs, and are described in more detail in the text.

Classification	*Specific Examples of EDCs*
...	
Less persistent and less bioaccumulative chemicals	
Non-halogenated Phenolic Chemicals (Non-HPCs) (section 3.1.1.5)	*Bisphenol A, Bisphenol F, Bisphenol S, Nonylphenol, Octylphenol, Resorcinol*
...	

iii. IPCP (The International Panel on Chemical Pollution) (2016):

Table 5. List of recommended chemicals and groups of chemicals for inclusion in the subsequent overview reports – identified EDCs, basis for recommendation and their presence on the other lists.

Chemical Name	*CAS Number*	*Basis Lists for Recommen-dation*	*Regulation Lists*	*Evaluation Lists*	*Industry Action Lists*	*Other Lists*
Resorcinol	*108-46-3*	*SIN, Danish Criteria*	*EU REACH Registered*	*EU CoRAP*		*EU Impact Assessment, EU Priority List Category 1, Our Stolen Future, ScoreCard, TEDX, Trade Union Priority*

iv. Hass et al. (2012):

Evaluation of 22 SIN List 2.0 substances according to the Danish proposal on criteria for endocrine disrupters:

An overview of the separate evaluations based on epidemiological data, in vitro data plus animal experimental data, and ecotoxicity data as well as the overall evaluations is shown in table 4. Among the 22 substances, 15 are evaluated as ED in category 1 and 6 as suspected ED in category 2a.

Table 4 Overview of the preliminary evaluations based on epidemiological data, in vitro data plus animal data, and ecotoxicity data and the overall evaluation.

Chemical	*Tox (in vitro and in vivo toxicity studies related to human health)*	*Hum (human data)*	*Eco (ecotoxicological and environmental data)*	*Overall*
…				
Resorcinol	*Cat. 2a*	*Cat. 1*	*Cat. 2b*	*Cat. 1*
…				

Category 1 - Endocrine disruptor
Category 2a - Suspected ED
Category 2b - Substances with indications of ED properties

7.10.1. Endocrine disruption – *in vitro* activity

Effects on thyroid peroxidase and iodide uptake

There are various mechanisms by which chemicals can disrupt thyroid function. These include the inhibition of thyroid hormone synthesis by inhibiting thyroid peroxidase (TPO) or iodide uptake to thyroid. Others include interference with thyroid receptors, and thyroid hormone transport and metabolism. Resorcinol has been shown to inhibit TPO in *in vitro* TPO activity assays (**Table 25**) utilizing isolated and purified TPO enzymes (Cooksey et al. 1985, Lindsay et al. 1992, Divi and Doerge 1994), and also thyroid microsomes (Paul et al. 2014). As TPO is needed for synthesis of thyroid hormones (Montaga et al. 2016), its inhibition can be regarded as a plausible mode of action for ED. *In vitro* activity assays give information on the inhibitory potential of resorcinol on TPO, but information on toxicokinetic properties (ADME) is important to assess to what extent resorcinol is able to enter the thyroid gland in *in vivo* exposure situation. To inhibit TPO *in vivo*, resorcinol must be able to enter the thyroid gland at the levels needed for TPO inhibition since this enzyme is located at the apical membrane of follicular thyroid cells (Motonaga et al. 2016).

Resorcinol has also been shown to inhibit iodide (^{125}I) uptake and its incorporation into thyroid hormones in porcine thyroid slices (Cooksey et al. 1985, Lindsay et al. 1992). On the contrary, it has been shown that resorcinol (5 – 10 µM) increased ^{125}I uptake in the presence of TSH (100 µU/ml) in rat thyroid FRTL cells. Without TSH resorcinol did not affect the uptake of ^{125}I. This study was not available to the eMSCA, but the results of this study are described in the report by Johnson and Harvey (2002). Ghisari and Bonefeld-Jorgensen (2009) assessed thyroid hormone disrupting potential of resorcinol (1×10^{-10} – 5×10^{-5} M) by T-screen, i.e. effect on the thyroid hormone –dependent proliferation of rat pituitary GH3 cells. Resorcinol increased the proliferation statistically significantly at the highest concentration tested and also potentiated T3-induced cell proliferation. This indicates a thyroid hormone-like activity for resorcinol in this *in vitro* assay.

Table 25 Resorcinol-induced thyroid peroxidase inhibition *in vitro.*

***in vitro* TPO activity assay**	**Source of TPO**	**Results**	**Reference**
TPO activity assay	Purified porcine TPO	TPO inhibition by resorcinol	Cooksey et al. 1985
TPO-catalyzed iodination (^{125}I) of bovine serum albumin	Purified porcine TPO	TPO inhibition by resorcinol ID50 value [a] of 0.27 µM	Lindsay et al. 1992

in vitro TPO activity assay	Source of TPO	Results	Reference
		for resorcinol determined	
TPO-catalyzed iodination of tyrosine to yield monoiodotyrosine	Isolated TPO (species not mentioned)	TPO inhibition by resorcinol and resorcinol derivatives Irreversible, hydrogen peroxide-dependent loss of activity	Divi and Doerge 1994
Amplex UltraRed TPO inhibition assay	Rat thyroid microsomes	TPO inhibition by resorcinol IC_{50} value [a] (predicted) of 253 µM determined for resorcinol	Paul et al. 2014

a) concentration which produces 50% inhibition of TPO

Effects on estrogen, androgen and aryl hydrocarbon receptors

Only few *in vitro* studies are available on the effects of resorcinol on estrogen (ER), androgen (AR) or aryl hydrocarbon (AhR) receptors.

Resorcinol (1×10^{-10} – 5×10^{-5} M) did not have any estrogenic or anti-estrogenic effects in an ER transactivation assay in human MVLN cells (Ghisari and Bonefeld-Jorgensen 2009). MVLN cells are derived from human breast cancer cell line carrying estrogen response element-luciferase reporter vector. An earlier study utilizing a mammalian cell-based luciferase reporter gene assay or a yeast two-hybrid assay has also shown that resorcinol (0.001 – 10 µM) did not cause any estrogenic or anti-estrogenic effects. This study was not available to the eMSCA, but the results of the study are described in the report by Johnson and Harvey (2002).

Resorcinol (1×10^{-10} – 1×10^{-4} M) did not have any agonistic effect on AR in a AR transactivation assay in CHO-K1 cells transiently co-transfected with MMTV-LUC reporter vector (Krüger et al. 2008). By using this same assay, Krüger et al. (2008) showed that resorcinol antagonizes R1881 (a synthetic AR agonist) induced activation of AR. Although the effect was not significant, it suggests a weak anti-androgenic effect of resorcinol.

Resorcinol had no agonistic effect alone on aryl hydrocarbon receptor (AhR), but it dose-dependently enhanced TCDD-induced AhR activity in AhR-CALUX assay (Krüger et al. 2008). In this assay, mouse hepatoma Hepa1.12cR cells stably transfected with PAH/HAH-inducible luciferase expression vector were used.

7.10.2. Endocrine disruption – Environment

One screening level study on fish embryos, straightly related to the potential endocrine effects of resorcinol on wildlife has been located. In addition, two embryotoxicity studies with fish embryos and one reproduction study with invertebrates (Daphnia) are available to assess potential chronic effects of resorcinol in the environment (see chapter 7.8.1 for more information).

The potential effects of resorcinol on thyroid gland function in the environment have been studied in a screening level test with fish embryos. The method is included in the scoping document aiming at bringing forward relevant *in vitro* and *ex vivo* thyroid assays to provide recommendations for their development/use (OECD 2014). In a short-term screening test zebrafish eleutheroembryos (48 hours post-fertilization) were exposed for three days to freshly prepared test solutions of 25 substances, including resorcinol, under semistatic conditions (Thienpont et al. 2011). The study was regarded as reliable with restrictions (Kl. 2) by the Registrant(s), which is supported by the eMSCA.

In the first set of the experiments embryos (a minimum of 18 per compound and concentration) were exposed to the maximum tolerated concentrations (MTC, defined as the maximum concentration at which lethality does not exceed levels in vehicle-treated siblings) of the test substances. For resorcinol, the MTC was calculated to be 200 mg/L. Additional concentrations below MTC were tested when any systemic toxicity had been detected. The iodide content of the embryo water used in the study (0.005 µM) was in the low range of the levels commonly found in freshwater systems (0.004 - 0.158 µM). All concentrations were reported as nominal concentrations.

Thyroid gland functionality was evaluated as a decrease in the intrafollicular T4 content (IT4C) by using the so called TIQDT method (T4 immunofluorescence quantitative disruption test). Only compounds positive in TIQDT at concentrations below systemic toxicity were considered thyroid gland function disruptors (TGFD).

The concentration of intrafollicular T4 hormone content (IT4C) in embryos exposed to resorcinol was significantly decreased in comparison to controls ($p < 0.05$) and therefore resorcinol was regarded as TGFD and TPO (thyroid peroxidase) inhibitor on zebrafish eleuthoembryos.

In the second set of the experiments 5 to 8 test substance concentrations were tested for concentration-response curves to obtain EC10 and EC50 values to describe thyroid disrupting potency and the thyroid disrupting index (TDI, LC50/EC50), which was used as a descriptor of thyroid disrupting hazard.

An EC50 value of 82 ± 37 µM (ca. 9.02 mg/L) for thyroid disrupting potency of resorcinol and an EC10 value of 2 ± 4 µM (ca. 0.22 mg/L), respectively, were reported. Systemic toxicity, expressed as LC50, was 5003 ± 100 µM (ca. 550 mg/L) for resorcinol, resulting in a thyroid disrupting index (TDI; LC50/EC50) of 61.

The measured endpoint, concentration of intrafollicular T4-content, was shown to be sensitive in reflecting a direct effect on thyroid gland function, i.e. TPO inhibition, but the method was found to be not sensitive to indirect or secondary thyroid disrupting mechanisms. Zebrafish eleuthoembryos showed also a high degree of concordance with mammalian data, where data was available, in relation to direct effect on thyroid gland function.

The other available aquatic toxicity test results (Daphnia reproduction, fish embryo/early life stage toxicity) are not specific for endocrine disrupting effects, but the fish early life stage toxicity is considered "potentially sensitive to, but not diagnostic of, EATS modalities" (i.e. those operating via estrogen/ androgen/ thyroid/ steroidogenesis modalities) as some thyroid active chemicals may interfere with embryonic development and metamorphosis (OECD 2012).

The 21-d reproduction test with Daphnia did not show any adverse effects in the highest measured test concentration (172 µg/L) of resorcinol (IUCLID dossier). Fish embryo toxicity was observed in much higher concentrations than the thyroid peroxidase inhibiting effect in zebrafish eleutheroembryos: 60-d EC50 was 260 mg/L with *Oncorhynchus mykiss* and 7-d EC50 with *Danio rerio* was 54.8 mg/L (Van Leeuwen et al. 1990). In addition, no 72-h algae toxicity was discovered in the highest measured test concentration of 97 mg/L (IUCLID dossier).

Discussion of environmental ED effects

In conclusion, the eMSCA considers that the mode of action of being a potential thyroid peroxidase (TPO) inhibitor seems probable for resorcinol based on the available *in vitro* and *in vivo* information.

The environmental *in vivo* information is based on the non-guideline zebrafish eleutheroembryo thyroid assay, which is one of the 18 methods in a scoping study on new assays for the identification of modulators of thyroid hormone signalling (OECD 2014). In the study it was concluded that this assay has strong potential for identifying water soluble chemicals that directly affect thyroid function. Based on strong conservation of mechanism, the assay has the potential to be relevant to vertebrates in general if species differences in metabolism are taken into account. Therefore, the eMSCA considers the available information on the thyroid active MoA relevant (Thienpont et al. 2011), although no apical endpoints are included in the assay.

An information requirement in a SEv decision should provide added value for the conclusion on initial concern(s). In this case the added value could be the proof of adverse apical effects resulting from thyroid disrupting activity. The OECD Test Guidelines include two methods with amphibians (AMA test, OECD TG 231 and LAGDA test, OECD TG 241) sensitive to thyroid effects, where metamorphosis is the sensitive developmental phase for substances that interfere with the normal function of hypothalamic-pituitary-thyroid (HPT) axis.

In both amphibian tests the specific thyroid function endpoints related to interaction with the HPT axis are thyroid histopathology (larval sub-sample) and time to metamorphosis/ develomental phases. Developmental delay may not, by itself, be considered a reliable diagnostic indicator of anti-thyroidal activity, as stated in the guidance, but the anti-thyroidal diagnostic criteria include thyroid gland hypertrophy/atrophy, follicular cell hypertrophy, follicular cell hyperplasia, and as additional qualitative criteria: follicular lumen area, colloid quality and follicular cell height/shape.

Several other endpoints in these tests are rather indicators of generalised toxicity like impacts on morphometrics and growth (length, weight) or mortality and abnormalities. In addition, the LAGDA test includes juvenile endpoints controlled primarily by EAS-hormones (such as genetic/phenotypic sex ratios, histopathology of gonads, reproductive ducts, and plasma vitellogenin) that are likely to respond to interference with the hypothalamic–pituitary–gonadal (HPG) axis.

Thus the diagnostic indicators for thyroid disrupting activity of the AMA and LAGDA test are focused on mechanistic rather than apical effects. Yet substances interacting with the thyroid hormone synthesis might trigger adverse effects also on the HPG axis as well as effects on the 'generalised toxicity' indicator, growth.

The eMSCA considers that it may not be possible to gain such new infromation with AMA or LAGDA test that would significantly change or improve the conclusion on thyroid disrupting properties of resorcinol, due to the lack of apical endpoints in the test methods that would indicate clear (population level) adversity mediated by the HPT axis. The currently available environmental mechanistic data, supported by modelling, *in vitro* and mammalian/human data, refers to potential thyroid disrupting activity of resorcinol.

Hence the eMSCA decided not to request new animal tests in the course of substance evaluation. A request for an amphibian test would probably have verified the thyroid disrupting activity of resorcinol, but taking into account the principle of using animal tests as the last resort, the eMSCA came to the conclusion that the added value might not be significant enough.

Regarding all available information on resorcinol, including environmental fate and monitoring studies, the eMSCA considers that a way forward would be to assess whether resorcinol would or would not fulfil the conditions for SVHC identification stated in article 57(f) of REACH Regulation as being an endocrine disruptor that gives rise to an equivalent level of concern (ELoC) to those substances listed in points (a) to (e) of Article 57. For this purpose a risk management option analysis (RMOA) is initiated.

7.10.3. Endocrine disruption - Human health

Predicted profile

QSAR modelling of endocrine and molecular endpoints based on Danish (Q)SAR database (DTU Food 2016). The predicted results showed thyroid receptor binding activity in relatively high concentrations (315 - 17613 mg/L) (**Table 26**), but no other endocrine activity.

The principles of the modelling have been described in the User Manual. When possible, the endpoints have been modelled in the three software systems: Leadscope, CASE Ultra and SciQSAR. The structure set has been predicted in the different systems and an overall battery prediction is made. With the battery approach it is in many cases possible to reduce "noise" from the individual model estimates and thereby improve accuracy and/or broaden the applicability domain. Detailed information of the applied DTU QSAR models are documented in QMRFs (QSAR Model Reporting Format) and available online (http://qsardb.jrc.it/qmrf/).

Table 26 QSAR modelling of resorcinol for endocrine and molecular endpoints based on Danish (Q)SAR database.

ENDOCRINE AND MOLECULAR ENDPOINTS					
	Exp	**Battery**	**CASE Ultra**	**Leadscope**	**SciQSAR**
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		NEG_IN	NEG_IN	NEG_OUT	NEG_IN
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		NEG_IN	NEG_IN	NEG_OUT	NEG_IN
Estrogen Receptor α Activation (Human *in vitro*)		NEG_OUT	POS_OUT	NEG_OUT	NEG_IN
Androgen Receptor Antagonism (Human *in vitro*)	NEG	NEG_IN	NEG_IN	NEG_IN	NEG_IN
Thyroid Receptor α Binding (Human *in vitro*) (mg/L)			17612.73	306.6456	36.63758
domain		OUT	**IN**	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*) (mg/L)		1059.075	3563.092	22.25598	314.7942
domain		**IN**	**IN**	OUT	**IN**
Pregnane X Receptor (PXR) Binding (human *in vitro*)	NA	NEG_IN	NEG_IN	NEG_OUT	NEG_IN

Abbreviations:
INC: inconclusive. A definite call within the defined applicability domain could not be made.
NEG: negative
POS: positive
IN: inside applicability domain
OUT: outside applicability domain
Exp: Experimental values, from EpiSuite experimental databases or DK DTU QSAR models training sets.
NA: Not applicable, because training set data cannot be released for commercial models.

Repeated dose toxicity

The registration dossier of resorcinol includes four repeated dose toxicity studies via oral route in rats and three studies via oral route in mice. The oral studies mainly revealed signs of neurotoxicity considered as acute responses and changes in organ weights. The eMSCA concludes that there were no remarkable treatment related findings that would indicate potential ED properties of resorcinol in these studies. A number of studies in open literature report effects of resorcinol on thyroid hormone system in rats. In these studies dosing was performed in a way that allowed for a slow and continuous release of resorcinol to the systemic circulation (e.g. sc injections in oily solution) wehereas in negative studies included in the registration dossier resorcinol was dissolved in water and administrated by gavage. Thus it seems that since free resorcinol is extremely efficiently metabolized and effectively removed from the body via the urine, the rapid metabolism in most cases prevents resorcinol from reaching concentrations which are toxic for the thyroid gland.

The registration dossier does not include adequate repeated dose toxicity study via inhalation route (the available study is invalid) and dermal route (data waived, see section 7.9.4).

Toxicity to reproduction (effects on fertility and developmental toxicity)

No indications of reproductive toxicity were seen in the dose range-finding reproductive toxicity study (unpublished study report, 2003) or in the two-generation reproductive toxicity study in rats (unpublished study report, 2005, Welsch et al. 2008). No consistent and toxicologically significant changes in circulating thyroid/pituitary hormone values (i.e. serum T3, T4 and TSH), thyroid/pituitary weights or in thyroid histopathology were seen in the two-generation reproductive toxicity study. The eMSCA considers that resorcinol, based on the results from limited developmental neurotoxicity measurements in the dose range-finding study, is probably not a developmental neurotoxicant. Overall, the eMSCA concludes that no clear adverse effects were seen on the hypothalamus-pituitary-thyroid axis (HPT–axis) in these studies.

The registration dossier includes four oral developmental toxicity studies of which two were carried out in rats and two in rabbits. In addition, the Registrant(s) provided the eMSCA with an additional oral rat developmental toxicity study which has not been included in the registration dossier. The eMSCA considers that the findings observed in these studies with resorcinol and RPD do not raise concern of resorcinol-induced developmental effects by ED or other mechanism(s).

Human data

There was a total of six medical case reports from 1950 to 1977 describing reversible hypothyroidism (including myxoedema and goitre) in patients using topically large amounts of ointments containing resorcinol. In most of cases the patient had been using ointments containing resorcinol up to 12 % in large quantities applied to large areas of ulcerated skin (damaged skin) over long periods (months or years). Indications of thyroid dysfunction were demonstrated by changes in biological markers such as T3, T4, TSH and effects on iodine uptake into the thyroid gland as well as clinical evidence of goitre (enlarged thyroid gland) and myxoedema (swelling of face/arms/legs). Hyperplasia of the thyroid glands were seen in histopathology. The potential for causal relationship was provided by the resolution of goitre, myxoedema and other symptoms upon discontinuance of the use of the ointment. Cessation of the treatment caused the clinical findings of hypothyroidism to relieve/disappear. Re-application of ointment reduced again rapidly the thyroid uptake of iodine and lowered serum protein bound iodine to levels noted before cessation of the use of ointment (Bull & Fraser 1950, Hobson et al. 1951).

It has been suggested that observed thyroid dysfunction were caused by prolonged high rates of absorption of resorcinol in the systemic circulation from ointment through impaired skin barrier. Systemic exposure to resorcinol is suspected as a consequence of the application conditions but no measurements of resorcinol in blood were performed. It has been estimated that effect levels in the medical case studies were greater than 34 mg/kg resorcinol per day (Lynch et al. 2002). It has been suggested that when applied on healthy skin, percutaneous absorption is limited and rapid metabolism precludes resorcinol from reaching thyroid gland toxic concentrations.

The eMSCA notes that the medical case reports are old and mainly poorly reported. Several sources of uncertainty were identified such as a very small sample size (a total of nine individuals), history of the individuals not known (e.g. underlying thyroid dysfunction), most of the patients were reported to have other clinical issues (e.g. symptoms, diseases and other medical treatments), a lack contemporary controls and lack of data to demonstrate the level of exposure to resorcinol (i.e. blood measures). In addition, there is a lack of information on other ingredients in the ointments and how the

formulation affect on the bioavailability and toxicity of resorcinol. The eMSCA considers that the case reports 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. When the available *in vitro* data on the mode of action (inhibition of thyroid peroxidase, decrease of iodine uptake and iodine organification; see section 7.10.1) is taken into account, the causal association between the exposure to resorcinol and thyroid dysfunction (hypothyroidism) is considered to be plausible. However, it is not possible to derive dose-response relationship for thyroid effects seen based on the available information.

Overall, the eMSCA considers that the relevance of findings in the medical case reports for evaluation of a health risk by resorcinol exposure for workers in industrial settings is limited because the dermal absorption of resorcinol seems to be low (< 1 %) when applied on healthy/intact skin. For more detailed information on dermal absorption see section 7.9.1 (Toxicokinetics). The eMSCA notes that resorcinol has skin irritating and skin sensitising properties which may damage the skin surface and enhance penetration. Therefore, it is important that the appropriate RMMs are in place to adequately control skin exposure to resorcinol.

7.10.4. Conclusion on endocrine disrupting properties (combined/separate)

Environment

ED mechanism(s) of resorcinol have been identified in several screening studies and evaluations. In this substance evaluation, it was concluded that resorcinol is likely an ED substance for the thyroid with a TPO inhibitor mode of action. However, the apical endpoints have not been studied to prove population level adversity in the environment.

In the review of the exposure assessment it was noted that resorcinol showed little risk to the environment based on ecotoxicological information (PNECs) and environmental concentrations (PECs) (all RCR values < 1, except for one unidentified use). A PNEC value for environmental endocrine distupting effects could not be derived for resorcinol as the available fish embryo assay indicates thyroid disrupting effect on mechanistic level, and no recording of thyroid mediated apical endpoints are included in the test. Moreover, there is no general consensus whether a threshold can be determined for ED effects or not, so that a PNEC could be derived.

The evaluating MSCA concluded that it may not be possible to gain such new infromation with AMA or LAGDA test that would significantly change or improve the conclusion on thyroid disrupting properties of resorcinol (see 7.10.2) and hence no new data was requested. The currently available environmental mechanistic data, supported by modelling, *in vitro* and mammalian/human data, refers to potential thyroid disrupting activity of resorcinol.

Considering the possibility of SVHC identification of resorcinol as an endocrine disruptor in accordance with Article 57(f), the eMSCA concluded that it would be appropriate to evaluate whether resorcinol gives rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57, taking into account all available information on resorcinol, including the environmental fate and monitoring studies. To clarify the need for SVHC identification or other risk management measures a risk management option analysis (RMOA) is initiated.

Human health

The medical case reports demonstrate some evidence of a causal association between hypothyroidism and use of resorcinol containing ointments in large quantities to broken skin over long periods. Because of 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, can be considered as a supportive evidence for resorcinol 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 to be plausible. It is not possible to derive dose-response relationship for thyroid effects seen based on the available information.

Overall, the evaluating MSCA considers that the relevance of the findings in the medical case reports for evaluation of a health risk by resorcinol exposure for workers in industrial settings is limited because the dermal absorption of resorcinol seems to be low (< 1 %) when applied on healthy/intact skin. The evaluating MSCA notes that based on the current harmonized classification resorcinol has skin irritating properties, which may damage the skin surface and enhance penetration. In addition, resorcinol is a potential skin sensitiser according to self-classifications and the opinion of the Scientific Committee on Consumer Products. Therefore, it is important that appropriate RMMs are in place to adequately control skin exposure to resorcinol.

The evaluating MSCA decided not to request further information. Instead it was concluded that a RMOA of resorcinol as a follow-up of substance evaluation would be appropriate.

7.11. PBT and vPvB assessment

Degradation, bioaccumulation and toxicity of resorcinol has been discussed in detail in chapters 7.7 and 7.8 and is summarised here to conclude the PBT/vPvB assessment.

Persistence (P)

Ready biodegradation following OECD TG 301C was 66.7% after 14 days and inherent degradation following OECD TG 302B was 97% in 4 days. Several supporting studies confirmed aerobic biodegradation.

Resorcinol is likely to be biodegraded under anaerobic conditions although there are some inconsistencies in the experimental results. The rate of anaerobic degradation has ranged from 0 to 98 % in different studies.

Considering the available information, resorcinol is considered not P/vP (readily degradable >60%).

Bioaccumulation (B)

Resorcinol is not bioaccumulative based on the calculated values of bioconcentration factor BCF (3.16; 2.4).

Additional data from the terrestrial compartment and metabolism data from animals and humans support a rapid elimination of the test substance.

Considering the available information, resorcinol is considered not B/vB (BCF < 2000).

Toxicity (T)

Based on available data the most sensitive species in both acute and chronic aquatic toxicity tests is the aquatic invertebrate, *Daphnia magna*. The lowest NOEC available is from the 21-day study in which the highest dose tested serves as the NOEC, 0.172 mg/L. The lowest short-term toxicity value was the 48 h EC50, 1 mg/L, for Daphnia.

Considering the available information, resorcinol is considered not T (short-term EC50 > 0.1 mg/L; long-term NOEC > 0.01 mg/L).

Overall conclusion

Based on the assessment summarised above resorcinol is not considered a PBT / vPvB substance. This conclusion is in concordance with the Registrant(s) conclusion.

7.12. Exposure assessment

7.12.1. Human health

Worker

Table 27 Overview of occupational exposure

OCCUPATINAL EXPOSURE		
Background	**Findings**	**Reference**
In 1978, medical examinations, chest X-rays and pulmonary function, haematology and clinical chemistry have been performed with 281 of 329 persons actively employed.	About 60 % were under 40 years of age and about 50% had worked at this plant for at least 10 years. Data concerning the different job categories were not provided. The prevalence of medical findings possibly consistent with subclinical hypothyroidism (low T4 and/or high TSH) was 5/280 (1.8 %) and the prevalence of possible goiter was 2/280 (0.7 %). One person showed a palpable thyroid with normal T4 and TSH values.	unpublished study report, (1978)
In 1980, medical examinations (see above) and thyroid assessments were performed with 247 of 387 presumably active plant workers (214 men and 33 women).	About 60 % were under 40 years of age and 153 of these subjects were tested for total T4 and TSH. 5/153 (3.3 %) showed signs of clinical/subclinical hypothyroidism, but in 3 of these 5 cases other reasons such as treatment with radioiodine were given as cause for the thyroid abnormalities (observed findings	unpublished study report, (1981)
A research project entitled 'Occupational exposure to some endocrine disrupting phthalates and phenols in Finland' was conducted by the Finnish Institute of Occupational Health (FIOH) in 2014–2016.	Three workers were occupationally exposed to resorcinol in the tyre manufacturing company. In this case also, exposure was below biomonitoring equivalents estimated on the basis of health-based limit values (DNEL, ADI, OEL). The workers in phenolic resin manufacturing and glued wood manufacturing were not occupationally exposed - the urinary resorcinol concentrations remained at the level of the occupationally non-exposed population.	FIOH (2016)

In 1978, medical examinations, chest X-rays and pulmonary function, haematology and clinical chemistry were performed with 281 of 329 persons actively employed at a resorcinol manufacturing plant having occupational exposures to resorcinol, benzene, by-products of benzene sulfonation, and formaldehyde. About 60 % were under 40 years of age and about 50 % had worked at this plant for at least 10 years. The jobs of these workers at the time of medical examination entailed no or minimal exposure to resorcinol (dry fusion operator, dry fusion material handler, process engineer, storekeeper,

labourer, and utility operator). The prevalence of medical findings possibly consistent with subclinical hypothyroidism (low T4 and/or high TSH) was 5/280 (1.8 %) and the prevalence of possible goiter was 2/280 (0.7 %). One person showed a palpable thyroid with normal T4 and TSH values (unpublished study report 1978, Ref. IUCLID dossier). The investigators concluded that the thyroid evaluations "did not reflect any resorcinol hazards from the work environment".

In 1980, medical examinations (see above) and thyroid assessments were performed with 247 of 387 presumably active plant workers (214 men and 33 women). About 60 % were under 40 years of age and 153 of these subjects were tested for total T4 and TSH. 5/153 (3.3 %) showed signs of clinical / subclinical hypothyroidism, but in 3 of these 5 cases other reasons such as treatment with radioiodine were given as cause for the thyroid abnormalities (observed findings, unpublished study report 1981, Ref. IUCLID dossier). The report did not provide any evidence that resorcinol exposure was responsible for the thyroid effects in the remaining two workers. Three workers were occupationally exposed to resorcinol in the tyre manufacturing company. In this case also, exposure was below biomonitoring equivalents estimated on the basis of health-based limit values (DNEL, ADI, OEL). This means that health risks related to exposure are low. The workers in phenolic resin manufacturing and glued wood manufacturing were not occupationally exposed - the urinary resorcinol concentrations remained at the level of the occupationally non-exposed population. The urinary resorcinol concentrations of the occupationally non-exposed women were clearly higher than the respective concentrations of men. The reason for this difference remains unclear.

Documentation for the recommended personal protective equipment, i.e. gloves

The eMSCA notes that in the Lead Registrant's CSR and IUCLID Section 11 gloves are recommended as a personal protective equipment in all exposure scenarios. However, there is a concern whether workers are properly informed to use the right type of gloves, since no clear exposure scenario specific recommendations for gloves are given in the CSR. Gloves are recommended as follows: "Gloves (APF 5), generally accepted occupational hygiene standards are maintained". To ensure the safe use of a substance, Annex I Section 5.1.1. requires a description of the risk management measures to reduce or avoid direct and indirect exposure of humans. Generally, gloves that can prevent exposure to the skin for a pre-determined duration shall be specified. Typically, this information, as a minimum, must specify the glove material and, depending on the exposure scenarios, may also need to include the breakthrough time and thickness of the glove material. Therefore, the Registrant(s) are recommended to provide in the CSR a description of the gloves to be used when handling the pure substance. The information provided by the Registrant(s) should be sufficiently detailed to allow suppliers to fulfil their obligations specified under Annex II for the compilation of the safety data sheets. **The eMSCA recommends to include exposure scenario specific recommendations for protective gloves in the CSR.**

7.12.2. Environment

The initial concerns for performing a substance evaluation of resorcinol were the endocrine disruptor potential, wide dispersive use, consumer use and high (aggregated) tonnage (tonnage band > 10 000 t/a). Chemical safety reports with exposure scenarios were available during the evaluation and the environment exposure assessment was reviewed by the eMSCA. Environment exposure was modelled by the Registrant(s) using the EUSES v2.1. Also, monitoring data which is presented in the confidential annex was available during the evaluation.

All identified uses reported in the chemical safety reports were covered in the exposure scenarios. Based on the review it seems that regarding these indicated uses significant releases of resorcinol to the environment are not expected. This is supported by the

available monitoring data, the Nordic screening program and the monitoring surveys provided in the registration dossier. In the monitoring surveys, most of the calculated values ($PEClocal_{freshwater}$ range 0.28 – 7.03, one value 11.81 µg/L) based on measured resorcinol concentrations in effluents were in the lower level than the modelled ones ($PEClocal_{freshwater}$ range 0.002 – 16 µg/L). Safe use of resorcinol was demonstrated in all except one exposure scenario. This use, "formulation of resins", was not among the identified uses and it is unclear whether it is still active as the concerned chemical safety report has not been updated during the evaluation period. In case the use is still active, the Registrant is requested to revise chemical safety assessment and the concerned exposure scenario. It is also noted that different types of release factors have been assigned in the registration dossier (OECD 2004 ESD, EU TGD, EUSES model output, SpERC COLIPA, and SpERC CEPE/FEICA). However, the applicability of these factors was not assessed further during this substance evaluation period.

Resorcinol has a low bioaccumulation potential with low log Kow (0.8) and BCF of 2.16. Further to this, under environmentally relevant conditions it undergoes rapid biodegradation. Data on short-term and long-term toxicity to the aquatic environment was available for resorcinol and *Daphnia magna* was considered as the most sensitive species by the eMSCA. Resorcinol has harmonized classification Aquatic Acute 1 according to CLP. It is not considered to be a PBT or vP/vB substance but in the substance evaluation it was concluded to have endocrine disrupting potential. However, taking into account the fate properties of resorcinol and the low exposure values modelled with EUSES, supported by the monitoring data, no significant concern for the environment is currently identified.

7.13. Risk characterisation

Based on the review of the exposure assessment undertaken by the eMSCA it seems that there is no risk (RCRs <1) for workers. **The eMSCA recommends to include exposure scenario specific recommendations for protective gloves in the CSR.**

Based on the review of the exposure assessment undertaken by the eMSCA it seems that there is no risk (RCRs <1) for the environment except in one scenario where potential risk to the freshwater and marine sediment was identified with RCR of 1. The use in this scenario was not identified, and it is unclear whether it is still active. The RCRs do not cover potential endocrine distrupting effects to the environment.

Although the eMSCA is currently not able to complete the evaluation whether resorcinol constitutes a risk to the environment for this scenario, the Substance evaluation decision is not considered to be the best available option to request the further information. In order to clarify the remaining concern the **Registrant is recommended to revise the Chemical safety report and the concerned scenario including risk management measures accordingly to clarify this concern.**

Table 28 The exposure scenarios with RCR values of 1

Scenario	RCR
ES 22: Use at industrial site – Formulation of resins Sediment (freshwater) Sediment (marine)	 1 1

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7.15. Abbreviations

ADME	Absorption, Distribution, Metabolism, Excretion
AhR	Aryl hydrocarbon receptor
AR	Androgen receptor
BCF	Bioconcentration Factor
CoRAP	Community Rolling Action Plan
CSR	Chemical Safety Report
DNEL	Derived No Effect Level
EAS	Estrogen / Androgen / Steroidogenic
EATS	Estrogen / Androgen / Thyroid / Steroidogenic
EC50	Effective Concentration 50 percent
EDC	Endocrine Disrupting Chemical

ELoC	Equivalent Level of Concern
eMSCA	Evaluating MSCA
EPM	Equilibrium Partitioning Method
EQS	Environmental Quality Standard
ER	Estrogen receptor
GLP	Good Laboratory Practice
HPG axis	Hypothalamus-Pituitary-Gonadal axis
HPT axis	Hypothalamus-Pituitary-Thyroid axis
HPV	High Production Volume
IOEL	Indicative Occupational Exposure Limit
LC50	Lethal Concentration 50 percent
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Effective Concentration
MTC	Maximum Tolerated Concentration
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational Exposure Limit
PBT	Persistent, Bioaccumulative, Toxic
PEC	Predicted Environmental Concentration
PND	Postnatal Day
PNEC	Predicted No Effect Concentration
PROC	Process Category
QSAR	Quantitative Structure-Activity Relationship
RMOA	Risk Management Option Analysis
SCCP	Scientific Committee on Consumer Products
SCCS	Scientific Committee on Consumer Safety
SEv	Substance Evaluation
STP	Sewage treatment plants

SVHC	Substance of Very High Concern
T3	Triiodothyronine
T4	Thyroxine
TDI	Tolerable Daily Intake
TSH	Thyroid-Stimulating Hormone
WHO	World Health Organization
vPvB	Very Persistent, Very Bioaccumulative

Annex with confidential information is removed from this public version of the report.