Committee for Risk Assessment

RAC

Annex 1
Background document
to the Opinion proposing harmonised classification and labelling at EU level of

resorcinol; 1,3-benzenediol

EC Number: 203-585-2
CAS Number: 108-46-3

CLH-O-0000007036-78-01/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

16 September 2021

CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

International Chemical Identification:

resorcinol; 1,3-benzenediol

EC Number: 203-585-2

CAS Number: 108-46-3

Index Number: 604-010-00-1

Contact details for dossier submitter: **Finnish Competent Authority
Finnish Safety and Chemicals
Agency (Tukes)
Finland**

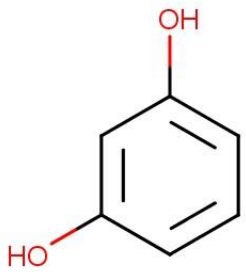
Version number: 2.0 **Date: 06.11.2020**

CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	1,3-benzenediol; 1,3-dihydroxybenzene; m-dihydroxybenzene; m-hydroquinone; 3-hydroxyphenol; m-phenylenediol
Other names (usual name, trade name, abbreviation)	resorcinol
ISO common name (if available and appropriate)	resorcinol
EC number (if available and appropriate)	203-585-6
EC name (if available and appropriate)	resorcinol
CAS number (if available)	108-46-3
Other identity code (if available)	
Molecular formula	$C_6H_6O_2$
Structural formula	
SMILES notation (if available)	C1=CC(=CC(=C1)O)O
Molecular weight or molecular weight range	110.1 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not applicable (the structure of the substance does not demonstrate stereo-isomerism)
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not applicable (the substance is not an UVCB)
Degree of purity (%) (if relevant for the entry in Annex VI)	98.8-100 % (w/w)

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
resorcinol; 1,3-benzenediol CAS 108-46-3 EC 203-585-6	-	Acute Tox. 4* Skin Irrit. 2 Eye Irrit. 2 Aquatic Acute 1	Acute Tox. 4* Skin Irrit. 2 Eye Irrit. 2 Aquatic Acute 1

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
Hydroquinone; 1,4-dihydroxybenzene hydroquinone quinol CAS 123-31-9 EC 204-617-8	-	Acute Tox. 4* Eye Dam. 1 Skin Sens. 1 Muta. 2 Carc. 2 Aquatic Acute 1		There is no impurity of >0.1% including hydroquinone in the registered substance

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

No additives relevant for classification.

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors, ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	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	GHS07 GHS09 Wng	H302 H315 H319 H400	-	*	-
Dossier submitters proposal	604-010-00-1	resorcinol; 1,3-benzenediol	203-585-2	108-46-3	**Modify** Acute Tox. 4 **Add** Skin Sens. 1A STOT SE 1 **Retain** Aquatic Acute 1	**Modify** H302 **Add** H317 H370 (nervous system) **Retain** H400	GHS07 GHS09 Wng	**Modify** H302 **Add** H317 H370 **Retain** H400	-	Remove * Add Oral: ATE = 500 mg/kg bw Add M = 1	-
Resulting Annex VI entry if agreed by RAC and COM	604-010-00-1	resorcinol; 1,3-benzenediol	203-585-2	108-46-3	Acute Tox. 4 STOT SE 1 Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1A Aquatic Acute 1	H302 H370 (nervous system) H315 H319 H317 H400	GHS07 GHS09 Wng	H302 H370 H315 H319 H317 H400	-	Oral: ATE = 500 mg/kg bw M = 1	-

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not applicable	No
Flammable gases (including chemically unstable gases)	Hazard class not applicable	No
Oxidising gases	Hazard class not applicable	No
Gases under pressure	Hazard class not applicable	No
Flammable liquids	Hazard class not applicable	No
Flammable solids	Hazard class not applicable	No
Self-reactive substances	Hazard class not assessed in this dossier	No
Pyrophoric liquids	Hazard class not applicable	No
Pyrophoric solids	Hazard class not assessed in this dossier	No
Self-heating substances	Hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	Hazard class not assessed in this dossier	No
Oxidising liquids	Hazard class not applicable	No
Oxidising solids	Hazard class not applicable	No
Organic peroxides	Hazard class not assessed in this dossier	No
Corrosive to metals	Hazard class not applicable	No
Acute toxicity via oral route	Harmonised classification proposed	Yes
Acute toxicity via dermal route	Data conclusive but not sufficient for classification	Yes
Acute toxicity via inhalation route	Data inconclusive	Yes
Skin corrosion/irritation	Hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	Hazard class not assessed in this dossier	No
Respiratory sensitisation	Hazard class not assessed in this dossier	No
Skin sensitisation	Harmonised classification proposed	Yes
Germ cell mutagenicity	Hazard class not assessed in this dossier	No
Carcinogenicity	Hazard class not assessed in this dossier	No
Reproductive toxicity	Hazard class not assessed in this dossier	No
Specific target organ toxicity-single exposure	Harmonised classification proposed	Yes
Specific target organ toxicity-repeated exposure	Hazard class not assessed in this dossier	No
Aspiration hazard	Hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	Harmonised classification proposed	Yes
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Resorcinol has been included in Annex I of Dangerous Substances Directive (67/548/EEC) on 19 December 1994 (21. ATP) and translated to harmonised CLP classification in Annex VI, Regulation (EC) No 1272/2008.

RAC general comment

Resorcinol is a chemical used in various industrial and consumer products, such as rubber products, wood adhesives, flame retardants, dyes, anti-acne ointments, and hair colours.

Toxicokinetic studies suggest rapid absorption of orally administered resorcinol. The main metabolite is a monoglucuronide conjugate. After oral or subcutaneous administration in rats, the most of the substance was excreted via urine within 24 hours. Dermal absorption in human skin is low (between 0.32 and 5 % of the applied dose) and depends on concentration, vehicle and metabolic activity. Higher absorption rates (up to 74 %) were observed in frozen, thus not metabolically active, human skin explants using low doses (< 100 µg/cm^2) with phosphate buffered saline (PBS) as vehicle.

The substance had a harmonised classification under the Dangerous Substances Directive (DSD) which was transposed to a harmonised classification under the CLP Regulation. A minimum classification was applied to the acute oral toxicity endpoint and for aquatic toxicity no M-factor at that time was introduced. Thus, the current Annex VI entry for resorcinol is Acute Tox 4* H302, Skin Irrit. 2 H315, Eye Irrit. 2 H319, and Aquatic Acute 1 H400. The dossier submitter (DS) proposed to remove the minimum classification for acute oral toxicity, and to add Skin Sens. 1A H317 and STOT SE 1 H370 (nervous system) classifications. Acute Aquatic 1 classification is proposed to be retained, and an M-factor of 1 added. Other hazard classes were not assessed in the dossier and were not open for discussion at the consultation phase.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

[B.] Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

Change in existing entry due to changes in the criteria (Acute oral toxicity)
Change in existing entry due to changes in the criteria (Hazardous to the aquatic enviroment)
Disagreement by DS with current self-classification (Skin sensitisation)

Further detail on need of action at Community level

Resorcinol had a harmonised classification under the Dangerous Substances Directive (67/548/EEC). This was translated to a harmonised CLP classification in Annex VI, Regulation (EC) No 1272/2008 (CLP Regulation), and a minimum classification (according Annex VI) was applied to acute oral toxicity (marked as Acute Tox. 4*). The acute toxicity studies in animals reveal acute neurotoxicity as the pivotal toxic effect of resorcinol. Signs of acute neurotoxicity have also been described in case reports of human accidental poisonings with resorcinol. Harmonised classification of resorcinol as STOT SE 1 (nervous system) along with the removing

of the minimum classification of acute toxicity are therefore justified to ensure adequate risk management measures of the substance.

Finland carried out substance evaluation on this substance in 2016, as well as the subsequent RMOA under the REACH regulation (EC) No 1272/2008. As justified in section 10.7 below, the dossier submitter (DS) considers that for resorcinol classification as Skin Sens. 1A is warranted while the existing self-classification entries in the C&L Inventory only indicate classification as Skin Sens. 1, i.e. without sub-categorisation. Harmonised classification as Skin Sens. 1A would ensure an adequate perception of the skin sensitisation hazard associated with resorcinol, inter alia by lowering the concentration limit for the classification of mixtures containing resorcinol from 1% (Skin Sens. 1) to 0.1% (Skin Sens. 1A).

5 IDENTIFIED USES

Resorcinol is used by consumers, by professional workers (widespread uses), in formulation or re-packing and at industrial sites. Resorcinol has various uses; for example in the manufacture of rubber products and in wood adhesives, flame retardants, UV stabilizers, and dyes. It is also used in personal care products such as hair colorants, anti-acne preparations, and peels.

6 DATA SOURCES

The data for resorcinol were obtained from the REACH registration dossier, last modified on 23-May-2020 (https://echa.europa.eu/fi/registration-dossier/-/registered-dossier/13740/1), as well as from open literature sources.

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Solid	PubChem Compound Summary on Resorcinol (CID 5054)	Observed
Melting/freezing point	110°C	INRS (2000), Kirk-Othmer (1981)	Handbook data/published data
Boiling point	277.5°C (550.65 K) at 1013 hPa	Yaws 1994 (Handbook of Thermodynamic and Physical Properties of Chemical Compounds, McGraw Hill)	Handbook data/published data
Relative density	1.278 at 20°C	Lide 2008 (CRC Handbook of Chemistry and Physics, 89th edition, McKenzie Books)	Handbook data/published data
Vapour pressure	0.065 Pa at 25°C	Yaws (1994a), [extrapolated] EPI Suite v3.12 (2006), Yaws (1997), SRC Physprop database (cited in)	Handbook data/published data
Surface tension	72 mN/m at 20°C and 1000 mg/l	Anonymous (2009)	Measured OECD TG 115/EU Method A.5 As the result is greater than 60 mN/m, the test substance was not considered to be surface active.
Water solubility	717 g/l at 25°C	Yalkowsky and Dannenfelser (1992), US EPA (2000), EPIsuite v 3.12 (October 2006), SRC Physprop database (cited in)	Handbook data/published data
Partition coefficient n-octanol/water	Log Kow 0.8 at 20°C	Camilleri et al. (1985), Fijota (1964), Hansch et al. (1981), Hansch (1995), Leo (1978)	Handbook data/published data
Flash point	161.5°C at 101.3 kPa	Anonymous (2012)	Measured Pensky-Martens closed cup method
Flammability	Not flammable	Fire Protection Guide on Hazardous Materials (NFPA 1986)	Handbook data/published data
Explosive properties	Not explosive	Anonymous (1995)	-

Property	Value	Reference	Comment (e.g. measured or estimated)
Self-ignition temperature	605-608 °C	Hawley 1981 (The Condensed Chemical Dictionary, 10th ed.), Kirk-Othmer 1981 (Encyclopedia of Chemical Technology, 3rd ed.), Sax 1989 (Dangerous Properties of Industrial Materials, 7th ed.)	Handbook data/published data; data on pressure was not specified
Oxidising properties	No oxidising properties	Anonymous (2009)	Does contain oxygen atoms, however, they are are chemically bonded to carbon and hydrogen.
Granulometry	Not applicable	ECHA Guidance Document, R.7.a: Endpoint Specific Guidance, Section 1.14.4	The substance is supplied as a flake which is a non-granular form, so no granulometry needs to be conducted.
Stability in organic solvents and identity of relevant degradation products	No information available	-	Study scientifically not necessary/other information available
Dissociation constant	9.81 at 25°C	Schulz (1987)	Handbook data/published data
Viscosity	31 at 150°C 38 at 140°C (unit not given)	Inspec Chemical Corporation (1998)	Handbook data/published data

8 EVALUATION OF PHYSICAL HAZARDS

Not assessed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 8: Summary table of toxicokinetic studies

Method	Remarks	Results	Reference
In vivo 90-day oral toxicity study OECD TG 408 GLP Key study Reliability: 1 Test material: Resorcinol (AO11), batch no. 706030517, purity: >95%	Sprague-Dawley rat, males and females 10 animals/sex/dose Doses: 0, 40, 80 and 250 mg/kg bw/day Administration by gavage Vehicle: purified water Six animals of each sex in groups 2, 3 and 4 were used for toxicokinetic investigations; blood samples were taken from the animals on day 1 and in week 13 at 0.5, 1, 2, 4, 8 and 24 hours post-dosing. Each animal was sampled on three occasions.	For all treated groups, plasma levels of resorcinol generally increased quickly from 0.5 hours to reach a first C_{max} at 0.5-2 hours. In some cases, a second C_{max} was seen at 8/24 hours. The exposure on day 1, as measured by the C_{max} and by AUC_{0-t}, showed no clear increase with the dose level. The mean concentration remained stable over the 24 hour-period at 40 and 80 mg/kg/day, which may suggest enterohepatic recycling of resorcinol. The differences in blood levels at day 1 and week 13 suggest that adaptation to the substance had occurred.	Anonymous (2004a)
In vivo toxicokinetic study Non-guideline GLP: not specified Supporting study Reliability: 2 Test material: [14C]-Resorcinol, non-radioactive (purity: >99%)	Fischer 344 rat, males and females 3 animals/sex/dose Doses: 112 and 225 mg/kg Administration by gavage and via i.v. injection Vehicle: corn oil (gavage), saline (i.v. injection) For the disposition study, the animals were sacrificed either 4, 8, 12, 16, 20 or 24 hours after administration of 112 or 225 mg/kg of resorcinol. For the repeated exposure study, the animals were administered resorcinol 225 mg/kg for five consecutive days.	Resorcinol was readily absorbed from the gastrointestinal tract and rapidly metabolized and excreted. In both sexes, >90% of the substance was excreted in urine within 24 hours after oral administration of 112 mg/kg, indicating little potential for bioaccumulation. Less than 3% (1.5-2.1%) was excreted in faeces within 24 hours. At least 50% of the total dose underwent enterohepatic circulation. The major metabolite (ca. 65%) was a monoglucuronide conjugate. Minor metabolites included a monosulphate conjugate, a mixed sulfate-glucuronide conjugate, and a diglucuronide conjugate. In females, a greater proportion was excreted as sulfate conjugate, while males excreted a higher proportion of a diconjugate (both sulfate and glucuronide groups).	Kim and Matthews (1987)
In vivo toxicokinetic study Non-guideline GLP: not specified Supporting study Reliability: 2 Test material: [U-14C]-Resorcinol (purity: not specified)	Male Sprague-Dawley rat 25 animals per dose Doses: 10, 50 and 100 mg/kg Administration: single s.c. dosing Vehicle: water Two or three animals were sacrificed at 1, 3, 6 and 24 hours after administration for the collection of samples. For multiple-dose studies, rats were treated daily with unlabeled resorcinol at a total dose of 100 mg/kg, given s.c. in two divided doses of 50 mg/kg, each given 6 hours apart.	The 14C activity was rapidly distributed in major tissues without indication of bioaccumulation. Resorcinol was rapidly eliminated from the plasma (90% in urine within two hours of dosing). The elimination was biphasic, with half-lives of 18-21 minutes and 8.6-10.5 hours. Within 24 hours after dosing with 10 mg/kg bw, 95% of the applied dose was excreted via urine and 1% via faeces, mainly as glucuronide conjugate (84%).	Merker et al. (1982)

Method	Remarks	Results	Reference
	After 14 and 30 days of treatment, groups of rats were injected with a single 50 mg/kg dose of resorcinol containing trace amounts of 14C-resorcinol. Then, three rats were sacrificed 1, 3, 6 and 24 hours after injection and samples were collected.		
In vivo toxicokinetic study Non-guideline Non-GLP Supporting study Reliability: 2 Test material: Resorcinol (purity: not specified)	Chinchilla rabbit, sex not specified 6 animals per dose Doses: 0.1 and 0.2 g/kg resorcinol dissolved in water Administration orally by gavage Objective: to study metabolites of resorcinol from urine	13.5% of resorcinol was conjugated as ethereal sulphate, and 52% as glucuronide for a total of 65.5%, with a ratio of 3 to 9 (glucuronide to ethereal sulphite). A total of 11.4% was recovered from the urine in a free state. Free resorcinol comprised 11%. The substance did not oxidize further.	Garton and Williams (1949)
In vivo toxicokinetic study OECD TG 416 (Two-generation study) GLP Reliability: 1 Test material: Resorcinol (purity: not specified)	Crl:CD SD rat, males and females 30 per sex per group Doses: 0, 120, 360, 1000 and 3000 mg/l Administration: in drinking water (controls received purified water) Limited bioanalysis was conducted for selected F1 parental animals. Blood samples for determination of plasma resorcinol concentration were collected from 15 randomly selected F1 parental animals/sex/group via the retro-orbital sinus (under isoflurane anesthesia) during the week prior to necropsy, which is at the end of maximum course of treatment on consecutive exposure days (143 - 155).	Although resorcinol is known to be readily absorbed and eliminated, blood resorcinol levels could be detected in 3/20 animals in the 3000 mg/l group at 116 to 612 ng/ml. Remaining concentrations were below the limit of detection or the lower limit of quantification for the assay (100 ng/mL). Metabolites were not identified in this study.	Anonymous (2005a)
Toxicokinetic study in human volunteers Supporting study Reliability: 2 Test material: Resorcinol 2% in a hydroalcoholic vehicle (purity: not specified)	Resorcinol was applied topically to three volunteers for two weeks, and the percutaneous absorption and metabolic disposition of the substance were investigated.	After 2 weeks of treatment, an average of 1.64% (range of 0.47-2.87%) of the administered dose was excreted in 24-h urines. No resorcinol could be detected in any of the blood samples collected after 1, 2, 3 and 4 weeks of drug application. There is no bioaccumulation potential based on study results. Metabolites were not identified in this study.	Yeung et al. (1981)
In vitro dermal absorption study OECD TG 428 Key study Reliability: 1 Test material: [U-14C]-Resorcinol (purity: not specified)	Exposure regime: 0.5 hours then wash, samples taken at 24 hours post-exposure. Doses: actual resorcinol concentration in formulation (% w/w): 2.55 (oxidative), 2.52 (non-oxidative) Actual resorcinol concentration in	<u>Absorption study – oxidative test preparation:</u> 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./cm^2, respectively.	Anonymous (2005b)

Method	Remarks	Results	Reference
Human split-thickness skin membranes	test preparation (% w/w): 1.26 (oxidative), 1.27 (non-oxidative) Actual application rate of test preparation (mg/m^3): 21.08 (oxidative), 20.07 (non-oxidative)	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)	
Dermal absorption study Human skin ex-vivo Supporting study Reliability: 4 Test material: Resorcinol (10% w/v) (purity: not specified)	No additional details available	Percutaneous absorption rate: 10% Lag time: 80 minutes K_p (steady state permeability coefficient): 0.00024 cm/h	Roberts et al. (1977)
Dermal absorption study in human volunteers Non-guideline GLP: not specified Supporting study Reliability: 2 Test material: Resorcinol (2% in hydroalcoholic vehicle) (purity: not specified) The study was used to investigate (1) blood and urinary levels of resorcinol after maximal exaggerated subchronic topical administration; (2) possible changes in thyroid function and blood chemistries; and (3) skin penetration rates of resorcinol under these exaggerated usage conditions.	Four healthy adult males with intact skin (three in treatment group, one as untreated control) Exposure regime: dermal application twice daily, six days per week to the face, shoulders, upper chest and upper back for 28 days. Doses: 12 mg/kg/bw (20 ml) of resorcinol was applied over an area of 2600 cm^2 Sample collection: blood samples were drawn at day 0 and at weeks 1, 2, 3 and 4 after initiation of treatment. These samples were assayed for free resorcinol and/or its conjugates or metabolites; blood chemistries and thyroid functions (T3, T4, T7 and TSH) were also measured. 24-hour urine specimens were collected from each subject 2 and 4 weeks after initiation of treatment. All plasma and urine samples were frozen until analysed.	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 detectable levels of free resorcinol or its conjugates were found in blood at weeks 1, 2, 3 and 4. 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: 2% resorcinol penetrated the skin in treated subjects at a rate of 0.37 µg/cm^2/hour.	Yeung et al. (1983)

<table>
<tr><th>Method</th><th>Remarks</th><th>Results</th><th>Reference</th></tr>
<tr><td>Distribution and metabolism in pig and human abdominal skin (4 donors)

Non-guideline

Test material: [U-14C]-Resorcinol (purity: 98%), 55 mCi/mmol</td><td><u>Pig ear skin</u> (female Pietrain breed):
Dose: 2.4 nmol/cm^2
Dosing volume: 10 µL/cm^2
Tissues were incubated for a total of 48 hours.
Mass balance (% of applied dose at end of incubation): 92.7 ± 5.92

<u>Human abdominal skin:</u>
Dose: 8.7 nmol/cm^2
Dosing volume: 10 µL/cm^2
Tissues were incubated for a total of 24 hours.
Mass balance (% of applied dose at end of incubation): 94.2 ± 3.5</td><td><table><tr><td></td><td colspan="2">Applied dose (%)</td></tr><tr><td></td><td>Pig</td><td>Human</td></tr><tr><td>Parent compound + metabolites</td><td>50.9 ± 1.2</td><td>46.7 ± 0.7</td></tr><tr><td>Parent compound</td><td>1.8 ± 0.8</td><td>4.8 ± 0.7</td></tr><tr><td>Total metabolites</td><td>49.1 ± 0.8</td><td>41.9 ± 0.6</td></tr><tr><td>Resorcinol glucuronide</td><td>48.6 ± 0.8</td><td>33.7 ± 0.6*</td></tr><tr><td>Resorcinol sulphate</td><td>0.5 ± 0.03</td><td>8.2 ± 0.1*</td></tr></table>*statistical difference between pig and human skin (P < 0.05)</td><td>Géniès et al. (2019)</td></tr>
<tr><td>Dermal metabolism using EpiSkin™ S9 and human skin explants

Non-guideline

Test material: unlabelled resorcinol (EpiSkin™), [U-14C]-Resorcinol (human skin explants)
(purity not specified)</td><td><u>EpiSkin™ S9:</u>
Concentration: 5 µM
Incubation for 2-4 hours (short-term)

<u>Human abdominal skin:</u>
Concentration: 55 mCi/mmol
Dose: 10 µL/cm^2
Incubation for 2 hours (short-term) and 18 and 24 hours (long-term)

Vehicle (in both experiments): 0.1 M phosphate buffered saline (PBS)</td><td><u>EpiSkin™ S9:</u>

Short term: metabolite resorcinol glucuronide (1% of the parent compound metabolized)

<u>Human abdominal skin:</u>

Short-term: no detected metabolites (0% of the parent compound metabolized)

Long-term: metabolites resorcinol sulphate and glucuronide (23-90% of the parent compound metabolized)

The metabolite production followed Michaelis-Menten kinetics, reaching a plateau (saturation) between 500 and 2000 nmol/disc.</td><td>Géniès et al. (2020)</td></tr>
<tr><td>Dermal metabolism using EpiSkin™ S9 and primary human hepatocytes

Non-guideline

Test material: resorcinol (purity not specified)</td><td>Human hepatic S9 fractions (a pool of 200 donors) were incubated with 5 µM resorcinol for 2 hours.

Primary human hepatocytes (a pool of 5 donors) were incubated with 1 µM resorcinol for 180 minutes.</td><td>Half-life with human hepatic S9 fractions: 55 minutes (± 8.5)

Half-life with primary human hepatocytes: 22 minutes

A glucuronide metabolite was formed.</td><td>Eilstein et al. (2020)</td></tr>
<tr><td>In vitro skin absorption
OECD TG 428
GLP: not specified

Test material: [U-14C]-Resorcinol (purity: 98%)</td><td>Human abdominal skin
Dose: 97.86 µg/cm^2 (± 1.79)
Dosing volume: 10 µL/cm^2
Vehicle: 0.01 M phosphate buffered saline (PBS)
Mass balance (% of applied dose): 96.5 ± 2.5</td><td>Dermal delivery (total amount in epidermis, dermis and receptor fluid, stratum corneum strips not included): 74.18% (± 8.79%) of the applied amount

Dermal flux: 5.86 µg/h

Since the assay was conducted using frozen skin, metabolite formation via metabolizing enzymes was not expected.</td><td>Hewitt et al. (2020)</td></tr>
</table>

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Toxicokinetic studies in rats and rabbits suggest that orally administered resorcinol is rapidly absorbed, metabolized and excreted in urine primarily as monoglucuronide conjugate (Anonymous 2004a and 2005a; Garton and Williams 1949; Kim and Matthews 1987; Merker et al. 1982). Minor metabolites include a monosulphate conjugate, a mixed sulphate-glucuronide conjugate, and a diglucuronide conjugate.

In rats, 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 hours (Kim and Matthews 1987). After a single subcutaneous dosing of [14C]-resorcinol, the [14C]-activity in plasma decreased rapidly (ca. 90% clearance within the first two hours) in rats (Merker et al. 1982). The elimination was biphasic, with half-lives of 18-21 minutes and 8.6-10.5 hours. Within 24 hours, 95% 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.

No clear conclusion on dermal absorption rate of resorcinol can be made based on the available data. A low dermal absorption rate (up to 3% after 24 hours) has been reported in a human volunteer study (Yeung et al. 1981) and in several in vitro studies on human skin (0.1-5% after 24 hours) using hydroalcoholic vehicle or hair-dye formulations (e.g. Anonymous et al. 2005b). In an in vitro study using human skin, dermal absorption of the substance was evaluated from a hair dye formulation that contained [14C]-resorcinol (Anonymous 2005b). The absorbed dose was 0.32% (oxidative preparation) and 0.82% (non-oxidative preparation) at 24 hours of the applied dose. In a human volunteer study to measure absorption and metabolic disposition, 2% resorcinol was applied topically over an area of 2600 cm^2 twice a day, six days a week for four weeks (Yeung et al. 1983). The substance penetrated the skin at a rate of 0.37 µg/cm^2/hour. After two weeks of application, an average of 1.64% of the dose was being excreted in 24-hour urine specimens as the glucuronide or as the sulphate conjugate. However, a series of recent in vitro studiesreport a much higher absorption of low concentrations of resorcinol in PBS (50 to 70% after 24 hours; Géniès et al. 2019 and 2020, Hewitt et al. 2020). The differences between the results could be explained by the choice of vehicle and/or concentration of the test substance.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Table 9: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance (including purity), vehicle	Dose levels, duration of exposure	Signs of toxicity	Value LD_{50}	Reference
OECD TG 401 (1981) GLP Reliability: 2 Study forms part of a comparison of the OECD TG 401 and fixed dosing method	Sprague-Dawley rat, males and females Total 30 animals (number per dose level not specified)	Resorcinol Purity: not specified Vehicle: not specified	Dose levels not specified Administration by gavage	9 animals were found dead (dose level not indicated) Clinical signs: ptosis, posture, respiratory effects, lethargy, abnormal gait, tremors, convulsions and salivation. No necropsy findings	Males: 425-723 mg/kg bw (533 mg/kg bw) Females: 397-650 mg/kg bw (489 mg/kg bw)	van den Heuvel et al. (1990) **Key study**

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance (including purity), vehicle**	**Dose levels, duration of exposure**	**Signs of toxicity**	**Value LD_{50}**	**Reference**
Fixed dose method (similar to OECD TG 420 (1992)) GLP: not specified* Reliability: 2 Study forms part of a comparison of the TG 401 and fixed dosing method 26 fixed dose studies for resorcinol were conducted by 26 laboratories	Sprague-Dawley rat (21 laboratories), Wistar rat (9), Fischer 344 rat (1) Total 370 rats (average 14.23 per study) 5 animals per sex per dose	Resorcinol Purity: not specified Vehicle: not specified	5, 50, 500 and 2000 mg/kg Administration by gavage Observation for 14 days	146 animals were found dead (average 5.62 per test; dose level not indicated) (stated in general terms, not associated with any given chemical) Clinical signs (no. of laboratories reporting): ptosis (2), posture (5), respiratory effects (10), diarrhoea and diuresis (1), lethargy (10), ataxia (2), abnormal gait (3), tremors (13), convulsions (9), prostrate coma (4), salivation (5), lacrimation (4), exopthalmus (1). Necropsy findings: liver, kidney, stomach and intestine discoloured. Oedema of glandular gastric mucosa. Rapid heart beat.	Not specified in the publication but the results indicated the same classification category for acute toxicity as the OECD TG 401 test carried out in this comparison.	van den Heuvel et al. (1990) **Key study**
OECD TG 420 (2001) GLP Reliability: 2	Sprague-Dawley rat, female Preliminary study: 1 animal per dose level Main study: 4 animals	Resorcinol (purity: 98.8%) Vehicle: purified water Dose volume applied: 10 ml/kg	Preliminary study (sighting study): 200, 500 and 2000 mg/kg Main study: 200 mg/kg Administration by gavage Observation for 14 days	<u>Preliminary study:</u> At 200 mg/kg, piloerection and dyspnea were observed within 2 hours of treatment. At 500 mg/kg, mortality occurred within 20 minutes of treatment. At 2000 mg/kg, mortality occurred within 15 minutes and tonic-clonic convulsions were observed prior to death. <u>Main study:</u> No mortality Clinical signs: Hypoactivity or piloerection, dyspnea and tremors were observed in all animals on day 1; recovery was complete on day 2. No effects on body weight were observed. No necropsy findings	No (LD_0 = ca. 200 mg/kg)	Anonymous (2004b)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance (including purity), vehicle	Dose levels, duration of exposure	Signs of toxicity	Value LD_{50}	Reference
Acute oral toxicity Conducted in accordance with U.S. Federal Hazardous Substances Labeling Act (FHSLA, 1961) Non-GLP Reliability: 2	Albino rat (strain not specified), male, non-fasted 5 animals per dose level	Resorcinol (flaked and industrial grade) Vehicle: water The concentration of the material in water was adjusted for the various dose levels so that no less than 1.0 ml of the mixture was administered to any rat at the lowest level and no more than 10 ml at the highest level.	398, 795, 1580 and 3160 mg/kg Administration by gavage Observation for 14 days	Mortality: 398 mg/kg 0/10 rats 795 mg/kg 1/5 rats (3 h after administration) 1580 mg/kg 5/5 rats (3 h after administration) 3160 mg/kg 5/5 rats (2 h after administration) All of the rats which died during the observation period revealed hyperemia and distention of stomach and intestines upon necropsy. The majority of the rats which survived the observation period showed body weight gains within significant limits of those of control rats. None of the rats sacrificed following the holding period exhibited any gross lesions upon pathological examination.	Somewhere between 795 mg/kg bw and 1580 mg/kg bw	Anonymous (1962), Flickinger (1976), NIOSH (1992)

***Plausibly carried out according to GLP, but this cannot be verified.**

Table 10: Summary table of human data on acute oral toxicity

Type of data/report	Test substance (including purity)	Relevant information about the study (as applicable)	Observations	Reference
Case report Accidental human oral exposure	Resorcinol (purity not specified)	A 27-year-old woman at 30 weeks of pregnancy was to be given glucose (50 g) during a glucose challenge test but was given 50 g resorcinol in error.	Within minutes following ingestion, the patient described sore throat, tachycardia, shortness of breath and shivering. 20 minutes later she was transferred to ED due to unconsciousness and respiratory failure that required mechanical ventilation along with tonic-clonic seizures and hypothermia. Laboratory findings: leucocytosis, high bilirubin levels, increase in liver enzyme activity, severe metabolic acidosis and green-coloured urine. The fetus was considered dead at 24 h after urgent caesarean delivery. Mother's prognosis was well with supportive management.	Duran et al. (2004)

Type of data/report	Test substance (including purity)	Relevant information about the study (as applicable)	Observations	Reference
Case report Accidental human oral exposure	Resorcinol (purity not specified)	A 46-year-old woman was to be given glucose (75 g) during a glucose challenge test but was given 75 g resorcinol in error.	Two hours after ingestion, the patient was transferred to ED because of unconsciousness, convulsions and coma. After resuscitation, hypotension, pulmonary edema and oliguria occurred. Metabolic acidosis was not corrected in spite of treatment. The patient died of cardiopulmonary arrest approximately 6 hours after hospital admission. Autopsy findings: diffuse pulmonary edema, renal congestion, eosinophilic substance in renal cortical tubular lumina, and hyperemia in all organs. 10% methemoglobin was estimated in the blood by CO-oximetry.	Bulut et al. (2006)

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

Animal data on acute oral toxicity

In 1990, the OECD performed a comparison between oral toxicity studies following the OECD TG 401 and fixed dose method (van den Heuvel et al. 1990). It appears plausible that the studies conducted under the patronage of the OECD were conducted according to GLP. However, the publication does not reveal whether this is the case, and the full study reports are not available.

One laboratory conducted the classic LD_{50} study following OECD TG 401 (1981) to ensure that information on both sexes would be available for comparison with the fixed dose test results. For resorcinol, 26 laboratories conducted fixed dose testing for comparison purposes. The classic LD_{50} study used 30 Sprague-Dawley rats, whereas the fixed dose testing used different rat strains, 370 rats in total. The used vehicle is not specified, but it was identical in all laboratories. The doses used in the classic LD_{50} were 5, 50, 500 and 2000 mg/kg, but they are not specified more closely. Each of the 26 laboratories testing resorcinol following the fixed dose method was to administer at least one of the following doses: 5, 50, 500 or 2000 mg/kg bw by gavage. 5 animals per sex were used for each dose level tested. In the classic LD_{50} study the LD_{50} was 439- 642 mg/kg bw in males, 397-650 mg/kg bw in females, and 510 mg/kg as combined (male/female). A definitive LD_{50} was not determined for rats with the fixed dose method but the results indicated the same classification category for acute toxicity as the LD_{50} study. Common clinical signs included ptosis, respiratory effects, lethargy, abnormal gait, tremors, convulsions and salivation. Autopsy findings in the fixed dose tests showed discoloration of the liver, kidney, stomach and intestine, odema of the glandular gastric mucosa and rapid heartbeat.

Acute oral toxicity was also investigated in a fixed dose study (Anonymous 2004b). The study was conducted mainly according to OECD TG 420 (2001). However, one dose differed slightly from those specified in the test guideline and 200 mg/kg was chosen instead of 300 mg/kg. The dose was chosen according to information available on the test item, but as a consequence the results are inconclusive to determine the hazard category between categories 3 and 4.

In the study rats were administered resorcinol by gavage at single doses of 200, 500 or 2000 mg/kg bw in a preliminary test. Piloerection and dyspnea were observed in the animal given 200 mg/kg within two hours following the treatment. At 500 mg/kg, death occurred within 20 minutes following the treatment.

At the 2000 mg/kg dose level, death occurred within 15 minutes following the treatment and tonic-clonic convulsions were observed prior to death. According to the results of the preliminary test, resorcinol was administered at the dose level of 200 mg/kg bw to group of four female rats. Hypoactivity or piloerection, dyspnea, and tremors were observed in all animals on day 1 with complete recovery on day 2. No mortality, treatment-related effects on bodyweight or gross abnormalities were observed. The dose of 200 mg/kg bw was identified as the maximum non-lethal dose of resorcinol in these experimental conditions.

In an acute oral toxicity study conducted in accordance with U.S. FHSLA, groups of five male albino rats were administered 398, 795, 1580 or 3160 mg/kg bw of flaked or industrial grade resorcinol by gavage (Anonymous 1962, Flickinger 1976 and NIOSH 1992). In older studies, two commercial products have been available for resorcinol: flaked and industrial. However, this distinction is no longer made. The LD_{50} was between 795 mg/kg bw and 1580 mg/kg bw. Hyperemia and distention of stomach and intestines were observed in the animals that died during the observation period. There were no effects on body weight gain and no findings at necropsy in surviving animals.

Human data on acute oral toxicity

There are two case reports presenting accidental human oral exposure to resorcinol (Duran et al. 2004 and Bulut et al. 2006). In both cases, a woman was given resorcinol (50 g and 75 g, respectively) instead of glucose in error. The major clinical and laboratory findings in both patients were unconsciousness, respiratory failure requiring mechanical ventilation, generalized tonic-clonic seizures, leukocytosis and severe metabolic acidosis. The first patient was pregnant, and the fetus was considered dead 24 hours after urgent caesarean delivery. Mother´s prognosis was well with supportive treatment. The second patient died of cardiopulmonary arrest approximately eight hours after the ingestion.

10.1.2 Comparison with the CLP criteria

Resorcinol currently has a harmonised classification as Acute Tox. 4*; H302 for the oral route.

Classification for acute oral toxicity under the CLP Regulation is required for substances with an acute oral LD_{50} value of $\leq$ 2000 mg/kg bw. Category 4 is assigned for substances with an LD_{50} value of > 300 and $\leq$ 2000 mg/kg bw and Category 3 for substances with an LD_{50} value of > 50 and $\leq$ 300 mg/kg according to the table 3.1.1 of Annex I to the CLP Regulation. In the available fixed dose method study (Anonymous 2004b), the LD_{50} value is between 200 mg/kg bw and 500 mg/kg bw. Based on the study findings it is not possible to determine between Category 3 and 4. In the acute oral toxicity study (van den Heuvel et al., 1990), the LD_{50} values of resorcinol in rats were approximately 533 mg/kg bw for males and 489 mg/kg bw for females. According to the results of this study, females are more sensitive to resorcinol, and the classification should therefore be based on the LD_{50} for females.

The proposed oral ATE value for resorcinol is the converted acute toxicity point estimate according to the Table 3.1.2 of Annex I to the CLP Regulation. For Category 4 (oral) classification the converted acute toxicity point estimate is 500 mg/kg bw for classification of mixtures.

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Based on the available data, there is sufficient evidence to remove the asterisk from the classification, since the relevant LD_{50} value is in the range of > 300 and $\leq$ 2000 mg/kg bw based on the CLP classification criteria. **Acute Tox. Category 4** is therefore proposed for resorcinol, with the corresponding hazard statement **H302: Harmful if swallowed**, with an oral ATE value of 500 mg/kg bw for the classification of mixtures containing resorcinol.

10.2 Acute toxicity - dermal route

Table 11: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance (including purity), vehicle	Dose levels, duration of exposure	Signs of toxicity	Value LD_{50}	Reference
Acute dermal toxicity Conducted in accordance with U.S. Federal Hazardous Substances Labeling Act (FHSLA, 1961) Non-GLP Reliability: 2	Rabbit (strain not specified), male, weighing between 2.3-3.0 kg 4 animals per dose Control animals (amount not specified)	Resorcinol (flaked and industrial grade) Purity: not specified Vehicle: physiological saline Area covered: approximately 10% of the body surface Exposure: 24 hours occlusive dermal application	1000, 2000, 3980 and 7950 mg/kg Observation for 14 days	Mortality (flaked and industrial grade, respectively): 1000 mg/kg: 0/4; 0/4 2000 mg/kg: 1/4; 0/4 3980 mg/kg: 2/4; 4/4 (1 day after dosing) 7950 mg/kg: 4/4; 4/4 (1 day after dosing) Clinical signs: significantly reduced body weight gains in survivors compared to controls. Necrosis of the skin at 3980 mg/kg and above (flaked grade) and at 2000 mg/kg and above (industrial grade). Animals exposed to 1000 mg/kg showed slight hyperkeratosis following signs of moderate to severe irritation (flaked grade). There were no signs of irritation with the same dose of industrial grade. No necropsy findings	3360 mg/kg bw (flaked grade), 2830 mg/kg bw (industrial grade)	Anonymous (1962) **Key study**
Acute dermal toxicity Non-guideline Non-GLP Reliability: 4	Albino rabbit (strain not specified) 5 animals per sex per dose	Resorcinol (purity: not specified) Vehicle: water	2150, 3160, 4640 and 6810 mg/kg Observation for 14 days	Mortality: 2150 mg/kg: 0/5 animals 3160 mg/kg: 2/5 animals 4640 mg/kg: 3/5 animals 6810 mg/kg: 5/5 animals Clinical signs: salivation, tremors and convulsions prior to death. Onset of symptoms occurred within 12 h at all doses. Time of recovery was dose-dependent. Dermal irritation signs were very slight erythema and extreme dryness (dose levels not specified). No necropsy findings in survivors; hemorrhage of the gastrointestinal tract was observed in animals that died.	3830 mg/kg bw (with 95% CL 2940-5000 mg/kg)	Anonymous (1970)

Table 12: Summary table of human data on acute dermal toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Case report	Resorcinol	Three females (aged 50, 59 and 60) had a history of long-term (years) application of ointments containing resorcinol (up to 12%) to broken skin to treat varicose leg ulcers.	There was clinical evidence of a goitrogenic 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 (in two patients). In the third patient the majority of the follicles contained colloid, and mostly peripheral vacuolation was seen. The colloid accumulation suggested a phase of recovery. When the 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 and Fraser (1950)
Case report	Resorcinol	A 39-year old female had a history of long-term (about 1 year) application of ointment containing 2% resorcinol to broken skin to treat leg ulcers. She had suffered from bilateral phlebitis complicated by chronic oedema and ulcerations since the age of 20.	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, which also coincided with liothyroxine treatment.	Guinet (1967)
Case report	Resorcinol	Two females (aged 59 and 68) had a history of long-term (over 5 years) application of resorcinol-based ointment to broken skin to treat varicose leg ulcers. The daily amount of ointment used was 4 or 7 grams. Both patients were overweight and suffering from medical complications, e.g. diabetes.	Both patients presented with 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)
Case report	Resorcinol	A 70-year-old male had a history of application of Lanacane® ointment containing 2% resorcinol to treat pruritus. The used amount was up to 7.5 g per day, and he had used the ointment for over three months. He had dry and coarse skin containing multiple senile keratosis (the skin was reported to be intact). He also had renal failure secondary to diabetic glomerulosclerosis with other complications. The patient was in chronic hemodialysis and was taking several medications.	The patient had hypothyroidism following the dermal application of ointment. The patient had low free thyroxine index with high TSH and equivocal enlargement of the thyroid gland upon palpation. After cessation of the use of ointment and commencing treatment with levothyroxine (synthetic form of T4), free thyroxine and TSH circulating levels were within normal limits within two weeks. The thyroid gland was normal in size.	Katin et al. (1977)

10.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

In a dermal study conducted in accordance with FHSLA, groups of four male albino rabbits were administered 1000, 2000, 3980 and 7950 mg/kg bw of flaked and industrial grade resorcinol. The test substance was applied to abraded and intact trunk skin via gauze for 24 hours and covered with an impervious plastic film (Anonymous 1962). With flaked grade resorcinol in rats administered 1000, 2000, 3980 and 7950 mg/kg bw the following number of deaths were observed: 0, 1, 2 and 4, respectively. With industrial grade resorcinol in rats administered 1000, 2000, 3980 and 7950 mg/kg 0, 0, 4 and 4 deaths were observed, respectively. The LD_{50} was determined to be 3360 mg/kg for flaked grade and 2830 mg/kg for industrial grade resorcinol. Flaked grade resorcinol produced necrosis of the skin in all rabbits exposed to 3980 mg/kg and above, while industrial grade resorcinol produced necrosis in three of the rabbits exposed to 2000 mg/kg. The rabbits exposed to 1000 mg/kg flaked grade resorcinol showed only slight hyperkeratosis following signs of moderate to severe irritation after 24 hours´ contact. However, the same dose of industrial grade resorcinol showed no signs of irritation seven days following contact. Body weight gains were reduced in surviving animals. There were no findings at necropsy. The study report does not specify any clinical signs of toxicity either at lethal or non-lethal doses.

In another dermal study resorcinol was applied as a paste to the skin to groups of five albino rabbits (strain not specified) at 2150, 3160, 4640 and 6810 mg/kg bw. The animals were observed for mortality and clinical signs of toxicity for 14 days. The LD_{50} was 3830 mg/kg (exposure time not stated) (Anonymous 1970). Clinical signs occurred within 12 hours of administration and included salivation, tremors, and convulsions prior to death. Time of recovery was dose-dependent with no symptoms being present after 1 day at 2150 mg/kg, while animals in the 3160 and 4640 mg/kg groups had recovery times of 3 and 4 days, respectively. Very slight erythema and extreme dryness was noted. Necropsy on the surviving animals showed no significant findings, whereas animals that died showed hemorrhage of the gastrointestinal tract.

In humans, goitre (hyperplasia of thyroid), hypothyroidism and myxoedema have been reported after dermal application of resorcinol to open or abraded skin (Berthezene et al., 1973; Bull and Fraser, 1950; Guinet, 1967; Katin et al., 1977). In all these case reports, the patient(s) had applied an ointment containing 2-12% resorcinol to the skin for several months or even years, to treat varicose leg ulcers. Cessation of the treatment resulted in increased uptake of iodine and reduced volume of the thyroid in all cases.

The available toxicokinetic data indicate that dermal absorption of resorcinol through healthy/intact skin is low, < 1% (0.82%), but the new in vitro studies suggest a much higher dermal absorption rate (see section 9).

10.2.2 Comparison with the CLP criteria

Classification for acute dermal toxicity under the CLP Regulation is required for substances with an acute dermal LD_{50} value of ≤ 2000 mg/kg bw. Category 4 is assigned for substances with an LD_{50} value of > 1000 and ≤ 2000 mg/kg bw according to the Table 3.1.1 of Annex I to the CLP Regulation.

Based on the results of the two available in vivo acute dermal toxicity studies, the LD_{50} values (2830 mg/kg bw - 3830 mg/kg bw) are above the lowest classification category criteria according to the CLP Regulation.

10.2.3 Conclusion on classification and labelling for acute dermal toxicity

No classification and labelling for acute dermal toxicity according to the CLP classification criteria is proposed for resorcinol based on available data.

10.3 Acute toxicity - inhalation route

Table 13: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance (including purity), form and particle size (MMAD)	Dose levels, duration of exposure	Signs of toxicity	Value LC_{50}	Reference
Acute inhalation toxicity Non-guideline Non-GLP Reliability: 3 Not acceptable	Harlan-Wistar rat, female 6 animals per dose	Resorcinol (purity not specified) dissolved in distilled water, aerosol Particle size: 1 µm or smaller	1h exposure: 2.13 mg/l (473 ppm), 7.80 mg/l (1732 ppm) 8h exposure: 2.00 mg/l (444 ppm), 2.48 mg/l (551 ppm), 2.80 mg/l (622 ppm) At the doses 2.48 mg/l and 7.80 mg/l, the solution turned milky and some precipitation was noted. It is likely that flow concentrations were less than the concentration indicated. Observation for 14 days	No mortality Clinical signs: not specified All animals had normal 14-day body weight gains No necropsy findings	LC_{50} could not be determined	Flickinger (1976)

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

In the only available acute inhalation toxicity study (non-guideline), groups of six female Harlan-Wistar rats were exposed for one or eight hours to resorcinol at concentrations of 2.13 and 7.80 mg/l or 2.00, 2.48 and 2.80 mg/l, respectively (Flickinger, 1976). Aerosols were generated after dissolving resorcinol in water. No lethality occurred and the animals were sacrificed 14 days post-exposure. At concentrations of 2.48 and 7.80 mg/l, the solution turned milky and some precipitate was noted. Therefore, it is likely that flow concentrations were less than the concentration indicated and the actual concentrations is not reported. All animals had normal weight gains, and no lesions attributable to inhalation of the aerosol were observed at gross necropsy.

10.3.2 Comparison with the CLP criteria

Classification for acute inhalation toxicity under the CLP Regulation is required for substances with an acute inhalation LC_{50} value of ≤ 5 mg/l for dust and mists (CLP Regulation, Annex I, Table 3.1.1.). The available acute inhalation study on resorcinol is not considered acceptable due to several shortcomings (e.g. purity of the substance is not given, and the actual concentrations are likely lower than indicated). Therefore, the data is considered inconclusive for acute inhalation toxicity classification.

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Data is inconclusive for acute inhalation toxicity classification according to the CLP Regulation (EC) No. 1272/2008.

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Oral

The DS summarised two human case reports and four oral toxicity studies in rats.

In both human cases, patients received resorcinol in lieu of glucose during a glucose challenge test. One adult female, who came to treatment with signs of intoxication approximately two hours after ingestion of 75 g of resorcinol and subsequently died of cardiopulmonary arrest six hours later. The other adult female, who was pregnant and was treated already half an hour after ingestion of 50 g of resorcinol, survived but lost her child 24 hours after an emergency caesarean section. Clinical signs in both cases included unconsciousness, respiratory failure, convulsions, tonic-clonic seizures, and severe metabolic acidosis. In the woman who died, methaemoglobinaemia and hyperaemia in all organs were observed at autopsy.

The available animal data comprised one OECD TG 401 (1981) acute oral toxicity study which was comparable to studies using the fixed dose method similar to OECD TG 420 (1992) performed according to good laboratory practice (GLP) in 26 laboratories, one OECD TG 420 (2001) GLP compliant study, and one non-GLP acute oral toxicity study performed according to the U.S. Federal Hazardous Substances Labeling Act (FHSLA, 1961) in 1962.

In the oldest study, the LD_{50} was between 795 mg/kg bw and 1580 mg/kg bw. For the OECD TG 401 study, which the DS deemed the key study, the available publication states that mean LD_{50} values are 533 mg/kg bw for males and 489 mg/kg bw for females. The publication does not specify vehicle, purity, dose levels or number of animals used per dose level. In the fixed dose studies used for comparison, a total of 370 rats were dosed by gavage with 5 to 2000 mg/kg bw (5 rats/sex/dose, vehicle and purity of the test substance not specified). No LD_{50} values were stated in the publication but according to the DS results suggest the same dose range as for the OECD TG 401 study.

The newest study (2004) used one Sprague-Dawley rat each in a preliminary study with a dosing of 200, 500, and 2000 mg/kg bw of resorcinol (98.8 %) in purified water. The test substance was administered by gavage. Animals of the two higher dose groups died within 20 or 15 minutes after dosing, respectively. At 200 mg/kg bw piloerection and dyspnea were observed. The main study used four animals and the lowest dose from the preliminary study. No mortalities occurred and no LD_{50} could be derived.

Based on the mean LD_{50} of 489 mg/kg bw for female rats in the OECD TG 401 study, the DS proposed to remove the minimum classification leading to an **Acute Tox. 4, H302** classification. For ATE value, the category 4 converted acute toxicity point estimate of 500 mg/kg bw was proposed.

Dermal

The DS summarized two old (1962 and 1970) non-GLP acute dermal toxicity studies in rabbits. In both studies, LD_{50} values were above the cut-off for category 4 (2000 mg/kg bw).

The DS also listed several human case reports that all described cases of adverse reactions to repeated use of resorcinol containing ointments on broken skin resulting in goitre (hyperplasia of the thyroid). No clear conclusion on acute dermal toxicity of resorcinol in humans could be drawn from these reports.

No classification for acute dermal toxicity was proposed by the DS.

Inhalation

There is only one old (1976) non-guideline, non-GLP acute inhalation toxicity study in female Harlan-Wistar rats available. Resorcinol of unspecified purity was dissolved in distilled water and administered as aerosol in different concentrations. In some concentrations the solution turned milky and precipitation was noted. The achieved concentrations were therefore not clear. No LC_{50} could be determined in this study after an 1-hour- or 8-hour exposure up to a nominal concentration of 1732 ppm (7.8 mg/L). Clinical signs were not reported.

The DS concluded that no classification for acute inhalation toxicity was possible due to inconclusive data.

Comments received during consultation

Two member state competent authorities (MSCA) commented, both supported the proposed acute toxicity classification. However, one MSCA requested clarification why the proposed ATE for oral toxicity was not based on the LD_{50} for female rats (489 mg/kg bw). The DS responded that this value could be used but that they proposed the value of 500 mg/kg bw due to deficiencies in the study used to derive the LD_{50}.

Assessment and comparison with the classification criteria

Oral

Acute oral toxicity was assessed in several studies. The most recent test guideline and GLP-compliant study failed to establish an LD_{50} due to a low dose (200 mg/kg bw) in the main study. In the preliminary dose range finding study, animals died at a dose of 500 or 2000 mg/kg bw resorcinol. At 200 mg/kg bw piloerection and dyspnea were observed within 2 hours after treatment. 200 mg/kg bw dose was also chosen for the main study and none of the four treated animals died. Clinical signs comprised hypoactivity, piloerection, dyspnea and tremors, which all resolved by day 2 after treatment. No conclusions can be drawn from this study regarding acute toxicity classification.

In the oldest reported study from 1962, resorcinol of unspecified purity (reported as flaked grade and industrial grade) was administered via gavage to ten (low dose) or five male albino rats per dose at doses of 398, 795, 1580, and 3160 mg/kg bw. All animals died in the two highest dose groups, 3 and 2 hours after exposure, respectively. At 795 mg/kg bw one animal died 3 hours after exposure. At necropsy, all animals that died showed hyperaemia and distention of the stomach and intestines. The LD_{50} was between 795 mg/kg bw and 1580 mg/kg bw and therefore within the ATE boundaries for category 4 (300 to 2000 mg/kg bw).

In the key study, as noted by the DS, as performed according to OECD TG 401 (1981), neither dose levels, vehicle or purity of the test substance were specified. The LD_{50} values

were between 425 and 723 mg/kg bw for males (mean 533 mg/kg bw) and between 397 and 650 mg/kg bw for females (mean 489 mg/kg bw). These results support assignment to category 4. For comparison, 26 laboratories performed an acute toxicity study according to the fixed dose method. No details on the test substance and number of animals that died at each dose level were given, and no LD_{50} values were reported. According to the DS, the results support assignment to category 4.

Two human case reports were also summarised. In both cases, women received resorcinol by accident. Upon review of the publications, RAC estimated the doses. The dose of 769 mg/kg bw was not lethal. However, the patient's baby died within 24 hours after emergency caesarean section. The dose of 833 mg/kg bw proved to be lethal in the other case. Both doses are in the range of observed lethal doses in the animal studies.

In conclusion, RAC supports the DS proposal to remove the minimum classification and to classify resorcinol as **Acute Tox. 4, H302**. As for **ATE**, RAC considers the converted acute toxicity point estimate of **500 mg/kg** bw appropriate given the reporting gaps in the study that derived an LD_{50} of 489 mg/kg bw for female rats.

Dermal

The LD_{50} values in the two available non-GLP, non-guideline studies were 3360 mg/kg bw for the flaked grade resorcinol, 2830 mg/kg bw for industrial grade resorcinol, and 3830 mg/kg bw for resorcinol without grade specification. Although the determination of the LD_{50} of 3360 mg/kg bw is not clear to RAC because 2 out of 4 animals died at 3980 mg/kg bw in this study, all of the LD_{50} values are above the cut-off for classification.

The human case reports summarised by the DS all describe symptoms observed after repeated application of resorcinol containing ointment. They are therefore not suitable to draw conclusions on acute dermal toxicity in humans. On the contrary, these reports could have been used in an assessment on STOT RE, but this endpoint was not evaluated in the dossier.

RAC concurs with the DS that **no classification** for acute dermal toxicity is warranted.

Inhalation

Since no reliable study on toxicity via inhalation is available (deficiencies in reporting and realisation and no LC_{50} established), RAC concurs with the DS that **no classification** is possible due to inconclusive data.

10.4 Skin corrosion/irritation

Resorcinol has a harmonised classification and labelling as Skin Irrit. 2, H315; Causes skin irritation. The hazard class is not assessed in this dossier.

10.5 Serious eye damage/eye irritation

Resorcinol has a harmonised classification and labelling as Eye Irrit. 2, H319; Causes serious eye irritation. The hazard class is not assessed in this dossier.

10.6 Respiratory sensitisation

Not assessed in this dossier.

10.7 Skin sensitisation

Table 14: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, purity, vehicle, positive control	Dose levels, duration of exposure	Results	Reference
LLNA 1. OECD TG 429 (2010) GLP Reliability: 1	CBA/J female mice 4 per treatment group and control groups (n=56)	Resorcinol (purity: 98.8%) Vehicle: dimethylformamide (DMF) Positive control: 25% (v/v) hexyl cinnamic aldehyde in DMF	0.1, 0.5, 1, 5 and 25% Induction on days 1, 2 and 3 Necropsy on day 6	Sensitising The SI values at 0.1, 0.5, 1, 5 and 25% were 1.58, 2.87, 1.97, 3.51 and 5.74 respectively. EC3 value = 1.4% Clinical signs: hypoactivity, piloerection and dyspnea were observed on day 3 in 1/4 animals in the 5% group and in 2/4 animals in the 25% group. No cutaneous reactions and no noteworthy increase in ear thickness were observed.	Anonymous (2005c) **Key study**
LLNA 2 A. OECD TG 429 (2010) GLP Reliability: 2 (no full study report, data from secondary literature)	CBA/Ca female mice 4 per treatment group and control groups	Resorcinol (99,9%) Vehicle: acetone:olive oil (4:1 v/v) Positive control: hexyl cinnamic aldehyde (HCA)	1, 5, 10, 25 and 50% (w/v) Induction on days 1, 2 and 3 Necropsy on day 6	Sensitising The SI values at 0, 1, 5, 10, 25 and 50% were 1.0, 0.7, 2.2, 5.2, 8.4 and 10.4, respectively. EC3 value = 6.3%	Basketter et al. (2007)
LLNA 2 B. OECD TG 429 (2010) Non-GLP Reliability: 3 Data from secondary literature	CBA/Ca female mice 4 per treatment group and control groups	Resorcinol (99.9%) Vehicle: DMF Positive control is lacking	5, 10 and 25% (w/v) Induction on days 1, 2 and 3 Necropsy on day 6	Not sensitising The SI values at 0, 5, 10 and 25% were 1.0, 2.2, 2.2 and 2.7, respectively. Lack of positive control may have impacted the test method sensitivity.	Basketter et al. (2007)
LLNA 2 C. OECD TG 429 (2010)	CBA/Ca female mice 4 per	Resorcinol (99.9%) Vehicle:	0.1, 0.25, 0.5, 1.0 and 2.5% (w/v)	Not sensitising The SI values at 0, 0.1, 0.25, 0.5, 1.0 and 2.5%	Basketter et al. (2007)

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, purity, vehicle, positive control**	**Dose levels, duration of exposure**	**Results**	**Reference**
Non-GLP Reliability: 3 Data from secondary literature	treatment group and control groups	acetone:olive oil (4:1 v/v) Positive control is lacking	Induction on days 1, 2 and 3 Necropsy on day 6	were 1.0, 0.4, 0.2, 0.5, 0.8 and 1.0, respectively. Deficiencies in the vehicle control values have impacted the overall study results. Disintegrations per minute (d.p.m.)/node values obtained with the test material are lower than that obtained with the vehicle control, resulting in SI values of <1 in all cases. Further scrutiny of these data show that the AOO vehicle control values should be higher.	
GPMT OECD TG 406 GLP Reliability: 1	Pirbright-Hartley white guinea pigs 10 in the treatment group, 5 in the control group and 20 in an accompanying group (vehicle only)	Resorcinol (99.9%) Vehicle: 0.9% sodium chloride	2% for intradermal induction exposure and 25% for topical induction and challenge exposure	Sensitising After the topical induction, very slight to clearly circumscribed erythema was observed in 3 and 2 animals at 24 and 48 h, respectively. After the challenge exposure, very slight to clearly circumscribed erythema was observed on 7 animals at 24 h and on 5 animals at 48 h. Minor swelling was also observed in 1 animal at 24 h. No clinical signs	Anonymous (1989)

Table 15: Summary table of human data on skin sensitisation (sorted by year of publication)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Patch test data	Resorcinol (concentration and vehicle not specified)	1694 dermatitis patients Limited information available	Positive reaction to resorcinol in 0.7-0.8% of the patients. In further case histories of 34 dermatitis patients, resorcinol was established as the cause after epicutaneous testing.	Baer et al. (1955)
Patch test data	Resorcinol (1% and 2% solutions in 95% alcohol)	Eight persons with dermatitis had been shown to have been exposed to resorcinol in creams and medicines. Limited information available	All reacted positively to resorcinol	Keil (1962)
Patch test data	Resorcinol (5% in aqueous solution)	Presentation of 24 contact allergens that produced a positive patch test reaction in 3% or more of the patient population of the New York University Skin and Cancer Unit in 1968-1970.	Positive reaction to resorcinol in 7.9% of 340 patients	Baer et al. (1973)
Patch test data	Resorcinol (0.5% in pet.)	Limited information available	Positive reaction to resorcinol in 7 of 359 (1.9%) patients	Storck & Baumann (1975)
Patch test data	Resorcinol (2% in pet.)	330 patients with eczematous lesions were tested with 27 topical substances at a Belgian dermatological clinic during three years	Positive reaction to resorcinol in 4.5% of 330 patients	Blondeel et al. (1978)
Patch test data	Resorcinol (0.5% in pet.)	1385 patients were tested with the standard epicutaneous series and a new series of allergens at the University Dermatology Clinic in Vienna in 1972-1976.	Positive reactions to resorcinol (sorted by year): 1972: 2/131 (1.5%), 1973: 1/205 (0.5%), 1974: 1/252 (0.4%), 1975: 1/408 (0.2%), 1976: 1/389 (0.3%)	Jarisch & Sandor (1978)
Case report	Resorcinol (5% in pet.)	A 66-year-old male had developed an erythematous, papulovesicular eruption after application of Castellani paint (containing resorcinol) to the skin.	Positive patch test (+++) to both Castellani´s paint and resorcinol after 48 hours	Marks & West (1978)
Patch test data	Resorcinol (2% in pet.)	192 patients with stasis dermatitis or chronic leg ulcer were tested with an epicutaneous test series in 1976-1978	Positive reaction to resorcinol in 2 of 74 (2.7%) patients	Fräki et al. (1979)
Case report	Resorcinol (2% in pet.)	A 30-year-old female with chronic psoriasis developed an erythematous vesicular reaction on all treated areas within 48h of application of a skin cream containing 2% resorcinol. She had been treated with the same cream approximately 4 years earlier.	Positive reaction to resorcinol and negative reactions to all other cream ingredients	Waddell & Finn (1981)

Epidemiological study in tyre makers	Resorcinol (concentration and vehicle not specified)	42 workers at a motorcycle tyre plant with hand dermatitis (red pigmentation in all subjects, slight sensation of burning and slight itch in half of the subjects).	The start test carried out on the first group of 10 subjects showed a resolution of the pathology after one week and the re-appearance after starting to work in the section once more. The modification of the compound with the use of resorcinol already mixed in the polymers resulted in a reduced incidence of the phenomenon Skin test to resorcinol was negative in all subjects	Abbate et al. (1989
Case report	Resorcinol (2% in pet.)	A 26-year-old female hairdresser developed intense itching of the scalp, erythema and edema after dyeing her hair for 4 years with the same dye. After going back to work, she developed intense itching of the hands when in contact with certain hair dyes, and erythematous papules on the dorsa of the hands after 1 week.	Positive patch test to resorcinol: ++ (day 2), +++ (day 4).	Vilaplana et al. (1991)
Patch test data	Resorcinol (2% in pet.)	302 hairdressers with dermatitis were tested with hairdressers´ series and other allergens by the members of GIRDCA in 9 Italian dermatological centers in 1985-1990.	Positive reaction to resorcinol in 4 of 302 (1.3%) patients	Guerra et al. (1992a)
Patch test data	Resorcinol (2% in pet.)	261 hairdressers´ clients with contact dermatitis were tested with the hairdressers´ screening series in 1985-1990.	Positive reaction to resorcinol in 1 out of 261 (0.4%) patients	Guerra et al. (1992b)
Case report	Resorcinol (2% in pet.)	Three female patients (aged 18, 21 and 24) had been using a 2% resorcinol cream for inflammatory acne and developed itchy, eczematous facial lesions at contact sites. All had been applying the cream for 1-2 days before the onset of symptoms.	Each patient had a positive patch test to resorcinol (++) and to the used commercial cream (++) after 48 and 72 hours	Serrano et al. (1992)
Patch test data	Resorcinol (2% in pet.)	A patch test was carried out both in hairdressers and their clients with the hairdressers´ series and PPD in nine European centres (majority of patients seen in 1988-1991)	Positive reaction to resorcinol in 2 of 354 (0.6%) hairdressers and in 1 of 104 (1.0%) hairdressers´ clients	Frosch et al. (1993)
Patch test data	Resorcinol (5% in pet.)	839 patients were tested with a standard test series and a series of plastic and glue allergens at the University Dermatologic Clinic in Helsinki in 1985-1992	Positive reaction to resorcinol in 4 of 839 (0.5%) patients	Tarvainen (1995)

Patch test data	Resorcinol (2% in pet.)	Eight patients (five females, three males) aged 9-44 years used an ointment containing salisylic acid, resorcinol and petrolatum to treat plantar warts. All had used the ointment earlier. 1-3 days after the onset of treatment, they developed a marked eczematous, sometimes bullous reaction at the contact site. Patients 1-4 also developed generalized urticaria with angioedema, and patient 4 had a severe generalized urticaria with fever and symmetrical arthralgia. Pompholyx of palms and soles appeared in patient 5. Patients 6-8 developed a generalized papulovesicular eczema with pompholyx.	Positive reaction to resorcinol in all patients (+++ in 4 of 8 patients and ++ in 4 of 8 patients) at both 48 and 96 hours. Patient 7 also had a positive reaction to 0.01% resorcinol dilution. All patients reacted negatively to salisylic acid (2% in pet.).	Barbaud et al. (1996)
Patch test data	Resorcinol (1% in pet.)	Patient data over the last 2-6 years were obtained from databases in 9 dermatology centres in the UK (no further information provided)	Resorcinol had been tested in 7 testing centres, with a total of 501 conducted tests. Of these, 2 cases (0.4%) were relevant positive reactions (with current/past exposure to the substance).	Katugambola et al. (2005)
Patch test data	Resorcinol (1% in pet.)	210 patients (hairdressers or their clients) suspected of having contact dermatitis from hairdressing chemicals were tested with the hairdresser standard series and a supplemental hairdresser series at the Mayo Clinic in three US states in 2000-2008.	209 patients were tested with resorcinol (allergen in the supplemental series), and 1.9% had a positive allergic reaction (4 of 209 patients). There were no irritant reactions to resorcinol. Of these positive reactions, 50% were considered as relevant allergic reactions (reaction to the product containing the allergen, or verified presence of the allergen in the product plus verified use of the product) and 50% as reactions of questionable relevance (current exposure to products likely containing the allergen) according to the authors.	Wang et al. (2011)
Patch test data	Resorcinol (concentration and vehicle not specified)	399 hairdressers with contact dermatitis registered in the database of Danish Contact Dermatitis Group had been tested with the European baseline series and hairdressing series in 2002-2011. Each hairdresser was matched with 5 eczema patients (controls).	Positive reaction to resorcinol in 1 of 283 patients tested (0.4%).	Schwensen et al. (2013)

Patch test data	Resorcinol (1% in pet.)	2939 eczema patients attending 12 dermatology clinics during a 6-month period (in 2007-2008) were patch tested with an extended series of hair dye ingredients	Positive reaction to resorcinol in 3 of 2939 (0.1%) patients; in 16 patients (0.5%) the reaction was doubtful.	Søsted et al. (2013)
Patch test data	Resorcinol (1% in pet.)	1187 subjects were patch tested with resorcinol at the University Hospital in Leuven (BE) in 1990-2015. The substance was tested either as part of the hairdressing series, or when it had been used topically, or to check for cross-reactivity.	Positive reaction to resorcinol in 5 of 1187 subjects (0.4%). Doubtful or irritant reactions were not observed. Recording of reactions to resorcinol: Patient 1: - (day 2), + (day 4) Patient 2: ++ (day 2, not read on day 4) Patient 3: + (day 2), ++ (day 4) Patient 4: ++ (day 2), +++ (day 4) Patient 5: ++ (day 4)	Darcis & Goossens (2016)

Table 16: Summary table of other studies relevant for skin sensitisation

No other data is available.

10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

The potential of the resorcinol to cause skin sensitisation has been investigated in four Local Lymph Node Assays (LLNAs) and one Guinea Pig Maximisation Test (GPMT).

LLNAs

The LLNA study 1. was conducted according to the principles of GLP and was mainly performed according to OECD test guideline 429 (2010) (Anonymous 2005c). Yet, there were some minor deviations. The animals were housed individually, although mice should be group housed, and the temperature of the experimental animal room was sometimes outside of the target ranges (22 ± 3ºC). The animals were also placed under light isoflurane anesthesia during the administration. However, these deviations do not most likely affect the validity of the study.

To determine the highest non-irritant test concentration, a pre-test was performed. Four mice were treated by topical application to the external surface of each ear with test item concentrations of 5%, 10%, 25% and 50% once daily each on three consecutive days. Measurement of the ear thickness was performed each day before treatment and 24 hours after the last application. Since the test item was non-irritant in the pre-test, the highest concentration retained for the main test was the maximal achievable concentration (50%).

In the first main test, five concentrations of the test substance (2,5%, 5%, 10%, 25% and 50%) in DMF were selected and topically applied to female mice (4 mice/group). On days 1, 2 and 3, test substance or control preparations was applied to the dorsal surface of both ears. In order to avoid licking and to ensure an optimized application of the test materials, the animals were placed under light isoflurane anesthesia during the administration. A vehicle control group and a positive control group (25% (v/v) HCA in DMF) were maintained under the same environmental conditions and treated in the same manner as the test animals.

On day 6, the cell proliferation in the local lymph nodes was measured by incorporation of tritiated methyl thymidine and the obtained values were used to calculate proliferation indices. No mortality or any signs of systemic toxicity were observed during the first main test. Positive lymphoproliferative responses were observed at all tested concentrations. In the absence of local irritation, these positive responses seem to be due to skin sensitisation reactions. However, no clear dose-related increase was seen in the stimulation index (SI) (Table 16, first main test).

In the second main test, five treated groups of four animals were administered resorcinol at concentrations of 0.1, 0.5, 1, 5 and 25%. The test was otherwise conducted as the first main test. Clinical signs in the second main test included hypoactivity, piloerection and dyspnea on day 3 in 1 of 4 animals in the 5% group and 2 of 4 animals in the 25% group. There was no effect on body weight, and no cutaneous reactions or noteworthy increases in ear thickness were observed at any tested concentrations. A dose-related increase in the stimulation index, except at the concentration of 1 %, was noted and the threshold positive value of 3 was exceeded at the concentrations ≥ 5 % (Table 16, second main test). The EC3 value for resorcinol calculated on the basis of the results obtained in the second main test was 1.4%. The value at the concentration of 1% was excluded and not used for the calculation of EC3.

Table 17: Skin sensitisation potential of resorcinol in the first and second main tests (LLNA study 1., Anonymous 2005c)

First main test	**no/group**	**SI**	**SI > 3**	**Second main test**	**no/group**	**SI**	**SI > 3**
Vehicle	4	1.0	No	Vehicle	4	1.0	No
2.5 % resorcinol	4	3.83	Yes	0.1 % resorcinol	4	1.58	No
5 % resorcinol	4	4.14	Yes	0.5 % resorcinol	4	2.87	No
10 % resorcinol	4	3.97	Yes	1 % resorcinol	4	1.97	No
25 % resorcinol	4	3.51	Yes	5 % resorcinol	4	3.51	Yes
50 % resorcinol	4	3.30	Yes	25 % resorcinol	4	5.74	Yes
Positive (concurrent) control	4	7.48	Yes	Positive (concurrent) control	4	6.79	Yes

Three other mouse LLNAs (2 A, 2 B and 2 C) are reported in Basketter et al (2007). In the studies 2 B. and 2 C., animals were tested in 4 per group at the concentrations of 5, 10, 25% w/v (2 B.) and 0.1, 0.25, 0.5, 1.0, 2.5% w/v (2 C.) resorcinol. The authors question the findings of these studies as methods have since evolved. Positive controls are also lacking in both studies. Within the same article, a newly conducted study 2 A. following OECD TG 429 is reported: groups of four CBA/Ca female mice were treated topically to concentrations of 0, 1, 5, 10, 25 and 50% (w/v) resorcinol. The vehicle in this study was a 4:1 ratio of acetone:olive oil. No discrepancies were noted with the negative and positive controls. A very clear dose-response was obtained. Stimulation indices (SI) of 0.7, 2.2, 5.2, 8.4 and 10.4 were determined with the test item at concentrations of 1 %, 5 %, 10 %, 25 % and 50 % in acetone:olive oil (4:1). The maximum SI value was 10.4 with an EC3 value of 6.3%.

GPMT

The GPMT was conducted according to the principles of GLP and mainly performed according to the OECD test guideline 406 (1992). Ten Pirbright White guinea pigs (treatment group 10 animals, control group 5 animals and accompanying group 20 animals) were induced with intradermal injections of 2% resorcinol followed by occlusive, epicutaneous application of 25% resorcinol (Anonymous, 1989). Challenge exposure was performed using 25% resorcinol in an occlusive epicutaneous application. There were no clinical signs. After the first challenge exposure, very slight to clearly circumscribed erythema was observed on the skin of two or three animals in the exposure group at 24 and 48 hours (Table 18). The skin of the control animals was clear of signs of irritation. After the second challenge exposure, very slight to clearly circumscribed erythema was observed in 7/10 animals at 24 hours and in 5/10 animals at 48 hours (Table 18). Very slight edema (Score 1) was also observed in one animal at 24 hours after bandage removal. 7/10 animals in the exposure group presented a positive reaction after the challenge exposure, and the relative frequency of the positively reacting animals is over the limit value of 30%.

Table 18: Summary table of the skin reactions (GPMT study, Anonymous 1989)

Topical induction and challenge exposure	Erythema Score 1	Erythema Score 2
Topical induction (24 h.)	2/10	1/10
Topical induction (48 h.)	2/10	-
Second challenge exposure (24 h.)	5/10	2/10
Second challenge exposure (48 h.)	4/10	1/10

Human data on skin sensitisation

Resorcinol has elicited positive skin reactions in a number of patch tests carried out on patients with dermatitis (Table 14). Blondeel et al. (1978) examined 330 dermatological patients, and positive responses could be observed in 4.5% of them. In 42 workers from a tyre factory exhibiting hand dermatitis, an epicutaneous test with resorcinol performed in accordance with ICDRG proved negative (Abbate et al., 1989). When patch tested with resorcinol (2% in petrolatum), 1.3% of 302 hairdressers suffering from contact dermatitis gave a positive reaction (Guerra et al., 1992). In a study by Frosch et al. (1993), 0.6% of 354 hairdressers and 1% of 104 hairdressers´ clients reacted positively to 2% resorcinol in petrolatum. Positive skin reactions to resorcinol (concentration not specified) were also observed in 0.1% of 2939 eczema patients (Søsted et al. 2013). There are also a few case reports describing dermal sensitisation caused by resorcinol.

10.7.2 Comparison with the CLP criteria

Substances are classified as Category 1 skin sensitisers where data are not sufficient for sub-categorisation, if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons, or if there are positive results from an appropriate animal test (Annex I, Table 3.4.2 of the CLP Regulation).

Substances are classified as Sub-category 1A skin sensitisers where there is evidence of a high frequency of occurrence in humans and/or a high potency in animals. Such evidence includes:

Human evidence: diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure.

GPMT: ≥30% responding at ≤0.1% intradermal induction dose or ≥60% responding at >0.1% to ≤1% intradermal induction dose.

LLNA: EC3 value ≤2%.

Substances are classified as Sub-category 1B skin sensitisers where there is evidence of a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals. Such evidence includes:

> Human evidence: diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure.
>
> GPMT: ≥30% to <60% responding at >0.1% to ≤1% intradermal induction dose or ≥30% responding at >1% intradermal induction dose.
>
> LLNA: EC3 value >2%.

In the key LLNA resorcinol showed an EC3 value of 1.4%. According to the Guidance on the Application of the CLP Criteria (ECHA 2017b, Table 3.4.4), the result indicates a strong skin sensitisation potency and suggests Category 1A as the EC3 value is ≤ 2%. The EC3 was calculated to be 6.3% in the study 2 A. of the three reported LLNAs by Basketter et al. (2007), which would allow classification in Category 1B.

In the GPMT, 70% of the animals responded at 2% intradermal induction dose, suggesting moderate skin sensitisation potency and Category 1B. However, the incidence of sensitised guinea pigs is so high that the possibility of the substance being a Category 1A sensitiser cannot be excluded, especially when concentration(s) under 2% were not tested in the study.

Human data

The Guidance on the Application of the CLP Criteria outlines how high or low frequency of occurrence of skin sensitisation shall be assessed (ECHA 2017b, Section 3.4.2.2.3.1., Table 3.2):

Human diagnostic patch test data	**High frequency**	**Low/moderate frequency**	**Resorcinol**
General population studies	≥ 0.2 %	< 0.2 %	No studies
Dermatitis patients (unselected, consecutive)	≥ 1.0 %	**< 1.0 %**	Positive reaction to resorcinol: 2 of 501 (0.4 %) patients (Katugambola et al. 2005) 6 of 1385 (0.4 %) patients (Jarisch & Sandor 1978) 4 of 839 (0,5 %) patients (Tarvainen 1995) 13 of 1694 (0.75 %) patients (Baer et al. 1955) 7 of 359 (1.9 %) patients (Storck & Baumann 1975) 15 of 330 (4.5%) patients (Blondeel et al. 1978) 27 of 340 (7.9 %) patients (Baer et al. 1973) (median **0.75 %**)
Selected dermatitis patients (aimed testing, usually special test series)	≥ 2.0 %	**< 2.0 %**	Positive reaction to resorcinol: 3 of 2939 (0.1%) patients (Søsted et al. 2013) 1 of 261 (0.4 %) patients (Guerra et al. 1992b) 5 of 1187 (0.4 %) patients (Darcis & Goossens 2016) 1 of 104 (1.0%) patients (Frosch et al. 1993) 2 of 209 (1.9 %) patients (Wang et al. 2011) 2 of 74 (2.7 %) patients (Fräki et al. 1979) 8 of 8 (100%) patients (Keil 1962) 8 of 8 (100%) patients (Barbaud et al. 1996) (median **1.45 %**)

Workplace studies: 1: all or randomly selected workers 2: selected workers with known exposure or dermatitis	≥ 0.4 % ≥ 1.0 %	< 0.4 % **< 1.0 %**	1: No studies 2: Positive reaction to resorcinol: 1 of 283 (0,4 %) hairdressers with dermatitis (Schwensen et al. 2013) 2 of 354 (0.6%) hairdressers (Frosch et al. 1993) 4 of 302 (1,3 %) hairdressers with dermatitis (Guerra et al. 1992a) (median **0.6%**)
Number of published cases	**≥ 100 cases**	< 100 cases	117 patch-test positive cases

A total of 22 clinical studies have been identified for resorcinol, which is usually tested either separately or as part of the hairdressing series. Its established test concentration is 1% in petrolatum, yet in the available studies the concentration varies between 0.5% and 5%. The studies comprise a total of 117 patients who tested positive to the substance, which exceeds the limit for high frequency. There is no sufficient information regarding the extent of exposure. The available human data altogether indicate a low to moderate frequency of occurrence of skin sensitisation for resorcinol.

To conclude, the overall weight of evidence from human and animal data indicates that resorcinol is a skin sensitiser. Evidence from animal studies is usually more reliable than evidence from human exposure, and negative human data should not normally be used to negate positive results from animal studies (ECHA 2017). Resorcinol shows a high potency in mice based on the results of the key LLNA and can therefore be presumed to have the potential to produce significant sensitisation in humans. The results meet the criteria for subcategorization, and Category 1A is justified. There is no scientific information showing that the hazard is evident below the generic concentration limit for classification, and no specific concentration limit is therefore proposed.

10.7.3 Conclusion on classification and labelling for skin sensitisation

Based on the available data, the proposed classification and labelling for skin sensitisation is **Category 1A**. The corresponding hazard statement is **H317: May cause an allergic skin reaction**.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Animal Data

The DS presented data from one OECD TG 429 and GLP-compliant Local Lymph Node Assay (LLNA), data from three LLNAs compiled in a publication, and one OECD TG 406 and GLP-compliant Guinea Pig Maximisation Test (GPMT).

The first LLNA that used dimethylformamide (DMF) as a vehicle and 25 % hexyl cinnamic aldehyde (HCA) as a positive control. This was deemed the key study by the DS. Two tests were run in this study. In the first test, all tested (non-irritating) concentrations (2.5 to 50 %) gave positive results with stimulation index (SI) values > 3. Since no dose-response was observed, a second test was performed with concentrations 0.1, 0.5, 1, 5 and 25 %

(producing SI values 1.58, 2.87, 1.97, 3.51 and 5.74, respectively). As the SI value measured at 1 % departed from the otherwise observed dose-response, it was excluded from the calculation of the EC3. This yielded an EC3 value of 1.4 %.

Basketter et al. (2007) reported results from three different LLNAs, the latest of which was compliant with GLP and OECD TG 429. In the two older datasets no positive controls were used and both tests were negative. The oldest data was considered unreliable by the authors since vehicle controls gave higher SI values than treated samples. The second test yielded SI values of 1.0, 2.2, 2.2, 2.7 at 0, 5, 10, and 25 % resorcinol in DMF, respectively. Since no positive control was included, reliability of these results was deemed questionable. The most recent LLNA was performed with 1, 5, 10, 25, and 50 % resorcinol in acetone: olive oil (4:1). There was a clear dose response and an EC3 value of 6.3 % was calculated.

In the GPMT, 7 out of 10 animals showed very slight to clearly circumscribed erythema at the 24-h-observation after topical challenge with 25 % resorcinol in 0.9 % sodium chloride (intradermal induction: 2 %). At the second reading at 48 h after challenge, 5 animals showed erythema.

Human Data

The DS presented data from 17 patch test series in dermatitis patients, one epidemiological worker study in a tyre factory, and several case reports. The number of published cases exceeded 100, but frequencies in unselected and selected dermatitis patients as well as workers (including hairdressers) were low with median values of 0.75, 1.45, and 0.6 %, respectively. Highest frequencies were generally observed in older patch test series from the 1960s and 70s.

Based on the results from the key LLNA, the DS proposed classification of resorcinol as Skin Sens. 1A, H317. Since there is no scientific information showing concern for a potential high sensitising potency of resorcinol, no specific concentration limit (SCL) was proposed.

Comments received during consultation

Two MSCAs and one industry association (IND) submitted comments in the consultation. Both MSCAs supported the proposed classification. One of them pointed out, that systemic toxicity was observed in the key LLNA concentrations from 5 % onwards but as these effects occurred above the EC3, the classification proposal was accepted.

Industry noted in their comment that the Scientific Committee on Consumer Safety (SCCS October 2020) and others have re-evaluated the first LLNA study (Anon. 2005) since the initial submission of the REACH registration dossier and used the previously excluded SI value (1.97) from 1 % test concentration as point of departure for EC3 value calculation. By linear extrapolation the corrected EC3 value was 3.67. Industry queried the interpretation of human data provided by the DS, noting that negative results from 42 workers at a tyre factory were not included in the overall number of workplace cases, thus skewing the median positive rate. Moreover, positive data from sensitised hairdressers may have been compromised by positive responses to other substances usually present in hair dye formulations and therefore, these should have been excluded from the number of reported cases.

The DS in their response insisted that using the 0.5 % test concentration SI value as point of departure in calculating the EC3 was justified. They noted deficiencies in the reporting

of the tyre factory data as to the concentration of resorcinol used in the patch test. Including these 42 workers into the overall workplace cases would alter the median positive rate from 0.6 to 0.5 %. The DS clarified that reports of positive reactions to hair dye formulations were excluded from the evaluation, and that the patch tests included in the evaluation use defined substances, not formulations. The DS concluded that category 1A was warranted based on human and animal data applying a weight of evidence approach. Severe reactions to low resorcinol concentrations were observed in some cases and based on the reliable LLNA data with an EC3 value of 1.4 %.

Assessment and comparison with the classification criteria

Animal Data

According to the guidance, criteria for category 1A are:

- for LLNA test results; EC3 value ≤ 2%,
- for GPMT test results; ≥ 30 % tested animals are responding at ≤ 0,1 % intradermal induction dose or ≥ 60 % responding at > 0,1 % to ≤ 1 % intradermal induction dose.

and criteria for category 1B are:

- for LLNA test results; EC3 value > 2 %,
- for GMPT test results; ≥ 30 % to < 60 % responding animals at > 0,1 % to ≤ 1 % intradermal induction dose or ≥ 30 % responding at > 1 % intradermal induction dose.

The LLNA (Anon. 2005), which the DS considered the key study, yielded an EC3 value of 1.4 % or 3.67 %, depending on which data point was used as point of departure for the calculation. For the second LLNA performed in the Basketter working group (2007), an EC3 value of 6.3 % was calculated. RAC notes that the newest experiments of this publication were performed according to OECD TG 429 and GLP standards and that Basketter made a significant contribution to the validation of the LLNA-method and has solid experience in conducting this assay. The results reported by this working group can be considered reliable. The two other LLNAs summarised in the same publication predated the recommendation to include a positive control and results are therefore less reliable. Basketter et al. performed a re-evaluation of the results of the first test that yielded SI values < 1 because of unusually high vehicle SI values. They used historical SI values for this vehicle (acetone-olive oil) from their lab to re-calculate values for treatment groups. When combined with data from the latest LLNA, a clear dose-response was observed over a wide concentration range (0.1 % to 50 %, for graphical analysis see supplemental information). The combined EC3 value was 5.5 % which is similar to the re-calculated EC3 value for the LLNA reported in Anon. 2005.

Depending on the calculation method, there are reliable LLNA data that point to category 1A in one case and category 1B in one case, or category 1B in two cases.

In the GPMT, > 30 % of the tested animals reacted to an intradermal induction concentration of > 1 % pointing to category 1B. However, lower induction concentrations were not tested in this study. Thus, category 1A cannot be excluded and no sub-categorisation is possible based on these results alone.

Human Data

When considering human data, frequencies of sensitisation to the substance in general population, unselected dermatitis patients, selected dermatitis patients, unselected workers, and workers with known exposure have to be considered as well as overall exposure levels. The DS presented a whole series of patch test data from unselected and selected dermatitis patients as well as workers with known exposure to resorcinol (mostly hairdressers). In these populations a low median frequency of occurrence of sensitisation towards resorcinol was generally observed. Resorcinol concentration used in patch tests was mostly 1-2 %. In two series, a 5 % concentration was used yielding a high positive rate of 7.9 % in one of them (Baer et al. 1973), and a 0.5 % concentration in another two series in unselected, consecutive patients with positive rates between 0.2 to 1.9 % (Storck and Baumann 1975; Jarisch and Sandor 1978). Other high positive rates of 4.5 % and 2.7 % were reported in patch test series using 2 % resorcinol in petrolatum (Blondeel et al. 1978; Fräki et al. 1979). Selected patients with known exposure to resorcinol containing ointments/creams all reacted positively to 1 or 2 % resorcinol (8 each, Keil 1962; Barbaud et al. 1996). The highest positive rates were seen in the oldest patch test series. More recent series in selected patients reported positive rates of 1.9 % to 0.1 % using resorcinol concentrations of 1-2 %.

In summary, median frequencies for all tested populations were in the range of a low to moderate frequency according to CLP guidance. These are less than 1 % in unselected, consecutive dermatitis patients (median 0.75 %), less than 2 % in selected patients (median 1.45 %), and less than 1 % in selected workers with known exposure (median 0.6 %).

More than 100 cases were reported which is regarded as high frequency according to CLP guidance. RAC notes that these 117 positive patch test cases were reported over a time span of 54 years (1962 to 2016), amounting to an average of 2 cases per year. For comparison, positive patch tests for cinnamaldehyde which RAC recently proposed to classify as Skin Sens. 1A based *inter alia* based on a high frequency of sensitisation in dermatitis patients, comprised more than 2300 cases in 38 years (~ 60 cases/year).

As to exposure, the DS stated that data is insufficient to draw a conclusion on its extent and no data were presented in the CLH report.

Conclusion on classification

RAC follows the re-calculation of the LLNA data (Anon. 2005) published by the SCCS (see also supplemental information) yielding an EC3 value of 3.67 % that is above the cut-off of 2 % for category 1A classification. Similar values (6.3 % with the newest data alone, and 5.5 % using historical control data to re-calculate SI values for a second dataset) were obtained in a second reliable LLNA dataset (Basketter et al. 2007). The GMPT results fall within the guidance values for category 1B but category 1A cannot be excluded based on concentrations tested.

In contrast to the DS conclusion on the weight of evidence, in RAC's view human as well as most animal data clearly meet criteria for category 1B and thus classification of resorcinol as **Skin Sens. 1B**, **H317** is warranted.

Supplemental information - In depth analyses by RAC

To visualise data provided for the LLNA (Anon. 2005) and the effects of excluding one or the other value, data were plotted and a 4PL (four parameter logistic regression) interpolation was used as the most "natural" regression for such biological data (see Figure 1 below). A better fit to the regression curve is seen with the SI value for 0.5 % resorcinol excluded (R^2 = 0.99) in comparison with the SI value for 1 % resorcinol excluded (R^2 = 0.97).

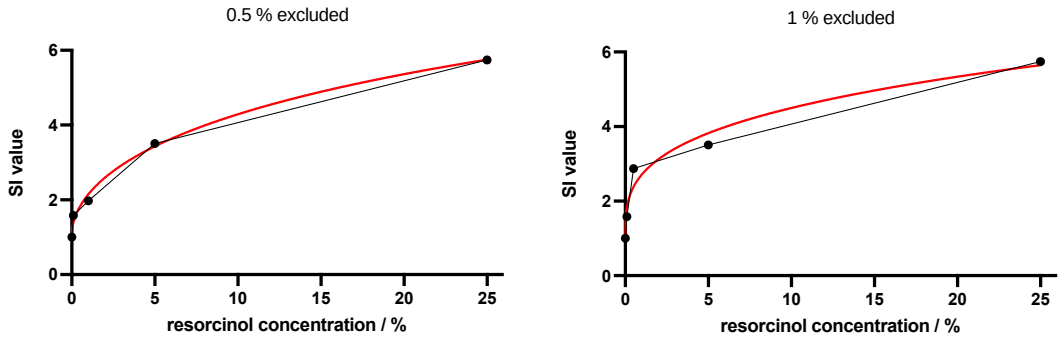


Figure 1: 4PL interpolation of data from Anon 2005 as reported in the CLH dossier excluding SI values for 0.5 % resorcinol (left; R^2 = 0.99) or 1 % resorcinol (right; R^2 = 0.97).

The same analysis was performed with the combined dataset of re-calculated SI values for an older LLNA and new LLNA data reported by Basketter et al. (2007) and depicted in Figure 2.

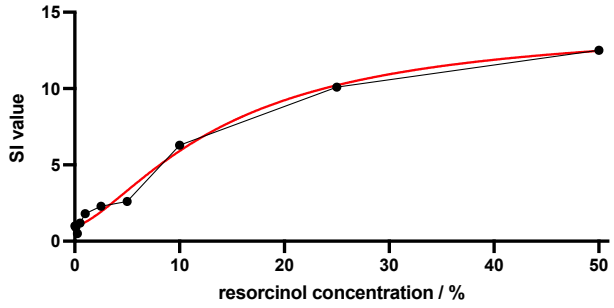


Figure 2: 4PL interpolation of data from Basketter et al. 2007 as reported in the publication (R^2 = 0.99).

The dose-response seen in the combined Basketter data is similar to the one seen in the Anon. 2005 data with the SI value for 0.5 % excluded.

Based on this graphical analysis, RAC concludes that

a) in the Anon. 2005 dataset the outlier value is from the 0.5 % test concentration and 3.67 % is the correct EC3 value for this study, and
b) re-calculation of SI values using historical control data from the performing laboratory and combination of re-calculated values with newly measured values in Basketter et al. 2007 was reasonable and yields a reliable combined EC3 value 5.5 %.

10.8 Germ cell mutagenicity

Not assessed in this dossier.

10.9 Carcinogenicity

Not assessed in this dossier.

10.10 Reproductive toxicity

Not assessed in this dossier.

10.11 Specific target organ toxicity-single exposure

Table 19: Summary table of animal studies on STOT SE

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance (including purity), vehicle	Dose levels, duration of exposure	Signs of toxicity	Value LD_{50}	Reference
OECD TG 401 (1981) GLP: not specified Key study Reliability: 2 Study forms part of a comparison of the OECD TG 401 and fixed dosing method	Sprague-Dawley rat, males and females Total 30 animals (number per dose level not specified)	Resorcinol (purity: not specified) Vehicle: not specified	Dose levels not specified Limit dose 2000 mg/kg bw Administration by gavage	9 animals were found dead (dose level not indicated) Clinical signs: ptosis, posture, respiratory effects, lethargy, abnormal gait, tremors, convulsions and salivation. No necropsy findings	510 mg/kg bw (with 95% CL 439-642 mg/kg) for males and females Males: 533 mg/kg bw Females: 489 mg/kg bw	van den Heuvel et al. (1990)
Fixed dose method (similar to OECD TG 420) GLP: not specified Key study Reliability: 2 Study forms part of a comparison of the OECD TG 401 and fixed dosing method 26 fixed dose studies for resorcinol	Most of the laboratories used Sprague-Dawley rat (21 laboratories). In addition, Wistar rat (9) and Fischer 344 (1) were used. Total 370 rats (average 14.23 per study) 5 animals	Resorcinol (purity: not specified) Vehicle: not specified	5, 50, 500 and 2000 mg/kg Administration by gavage Observation for 14 days	146 animals were found dead (average 5.62 per test; dose level not indicated) (stated in general terms, not associated with any given chemical) Clinical signs (no. of laboratories reporting): ptosis (2), posture (5), respiratory effects (10), diarrhoea and diuresis (1), lethargy (10), ataxia (2), abnormal gait (3), tremors (13), convulsions (9), prostrate coma (4), salivation (5), lacrimation (4), exopthalmus (1). Necropsy findings: liver, kidney, stomach and intestine discoloured. Oedema of glandular gastric	Not specified in the publication but the results indicated the same classification category for acute toxicity as the OECD TG 401 test carried out in this comparison.	van den Heuvel et al. (1990)

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance (including purity), vehicle**	**Dose levels, duration of exposure**	**Signs of toxicity**	**Value LD_{50}**	**Reference**
were conducted by 26 laboratories	per sex per dose			mucosa. Rapid heartbeat.		
Acute oral toxicity Conducted in accordance with U.S. Federal Hazardous Substances Labeling Act (FHSLA, August 12, 1961) GLP: no Supporting study Reliability: 2	Albino rat (strain not specified), male, non-fasted 5 animals per dose level	Resorcinol (flaked and industrial grade) Vehicle: water Purity: not specified The concentration of the material in water was adjusted for the various dose levels so that no less than 1.0 ml of the mixture was administered to any rat at the lowest level and no more than 10 ml at the highest level.	398, 795, 1580 and 3160 mg/kg Administration by gavage Observation for 14 days	Mortality: 398 mg/kg 0/10 rats 795 mg/kg 1/5 rats (3 h after administration) 1580 mg/kg 5/5 rats (3 h after administration) 3160 mg/kg 5/5 rats (2 h after administration) All of the rats which died during the observation period revealed hyperemia and distention of stomach and intestines upon necropsy. The majority of the rats which survived the observation period showed body weight gains within significant limits of those of control rats. None of the rats sacrificed following the holding period exhibited any gross lesions upon pathological examination.	980 mg/kg bw (with 95% CL 740-1290 mg/kg)	Anonymous (1962), Flickinger (1976), NIOSH (1992)
OECD TG 420 (1992) GLP Key study for STOT SE Reliability: 2 (the doses differ from that specified in the TG (5, 50, 300, 2000 mg/kg)	Sprague-Dawley rat, female Preliminary study: 1 animal per dose level Main study: 4 animals	Resorcinol (purity: 98.8%), batch no. 706030517 Vehicle: purified water Dose volume applied: 10 ml/kg	Preliminary study (sighting study): 200, 500 and 2000 mg/kg Main study: 200 mg/kg Administration by gavage Observation for 14 days	<u>Preliminary study:</u> At 200 mg/kg, piloerection and dyspnea were observed within 2 hours of treatment. At 500 mg/kg, mortality occurred within 20 minutes of treatment. At 2000 mg/kg, mortality occurred within 15 minutes and tonic-clonic convulsions were observed prior to death. <u>Main study (200 mg/kg):</u> No mortality Clinical signs: Hypoactivity or piloerection, dyspnea and tremors were observed in all animals on day 1; recovery was complete on day 2. No	Not assigned	Anonymous (2004b)

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance (including purity), vehicle**	**Dose levels, duration of exposure**	**Signs of toxicity**	**Value LD_{50}**	**Reference**
				effects on body weight were observed. No necropsy findings.		

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance (including purity), vehicle**	**Dose levels, duration of exposure**	**Signs of toxicity**	**Value LD_{50}**	**Reference**
Acute dermal toxicity Conducted in accordance with U.S. Federal Hazardous Substances Labeling Act (FHSLA, August 12, 1961) Non-GLP Key study Reliability: 2	Rabbit (strain not specified), male, weighing between 2.3-3.0 kg 4 animals per dose level Control animals (number not specified)	Resorcinol (flaked and industrial grade) (purity: not specified) Vehicle: physiological saline Area covered: approximately 10% of the body surface Exposure: 24 hours occlusive dermal application	1000, 2000, 3980 and 7950 mg/kg Observation for 14 days	Mortality (flaked and industrial grade, respectively): 1000 mg/kg: 0/4; 0/4 2000 mg/kg: 1/4; 0/4 3980 mg/kg: 2/4; 4/4 (1 day after dosing) 7950 mg/kg: 4/4; 4/4 (1 day after dosing) Clinical signs: significant decrease in body weight gain in survivors compared to controls Necrosis of the skin in all animals at 3980 mg/kg and in 3/4 animals at 2000 mg/kg. Animals exposed to 1000 mg/kg showed slight hyperkeratosis following signs of moderate to severe irritation after 24 h contact. No necropsy findings.	3360 mg/kg bw (flaked grade), 2830 mg/kg bw (industrial grade)	Anonymous (1962)
Acute dermal toxicity Non-guideline Non-GLP Supporting study Reliability: 4 Only results reported shortly, no reporting of the methods available	Albino rabbit (strain not specified) 5 animals per sex per dose	Resorcinol (purity: not specified) Vehicle: water	2150, 3160, 4640 and 6810 mg/kg Observation for 14 days	Mortality: 2150 mg/kg: 0/5 animals 3160 mg/kg: 2/5 animals 4640 mg/kg: 3/5 animals 6810 mg/kg: 5/5 animals Clinical signs: salivation, tremors and convulsions prior to death at 3160 – 6810 mg/kg bw). No clinical signs of toxicity were reported at 2150 mg/kg. Onset of symptoms occurred within 12 h at all doses. Time of recovery of surviving animals was dose-dependent (2-3 days. Dermal irritation signs were very slight erythema and extreme dryness (dose levels not specified). No necropsy findings in survivors; hemorrhage of the gastrointestinal tract was observed in animals that died.	3830 mg/kg bw (with 95% CL 2940-5000 mg/kg)	Anonymous (1970)

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance (including purity), form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Signs of toxicity**	**Value LC_{50}**	**Reference**
Acute inhalation toxicity Non-guideline GLP: not specified Key study Reliability: 3	Harlan-Wistar rat, female 6 animals per dose	Resorcinol (purity not specified) dissolved in distilled water, aerosol Particle size: not specified	1h exposure: 2.13 mg/l (473 ppm), 7.80 mg/l (1732 ppm) 8h exposure: 2.00 mg/l (444 ppm), 2.48 mg/l (551 ppm), 2.80 mg/l (622 ppm) At the doses 2.48 mg/l and 7.80 mg/l, the solution turned milky and some precipitation was noted. It is likely that flow concentrations were less than the concentration indicated. Observation for 14 days	No mortality Clinical signs: not specified All animals had normal 14-day body weight gains No necropsy findings	-	Flickinger (1976)
In vivo toxicokinetic study Non-guideline GLP: not specified Supporting study Reliability: 2	Male Sprague-Dawley rat 5 animals /dose (dose selection study) 25 animals /dose (main study)	Test material: [U-14C]-Resorcinol (purity: not specified)	To select the dose levels for the main study rats were injected subcutaneously with doses 55, 88, 140, 220 and 350 mg/kg. The animals were then observed for treatment related signs. Administration: single s.c. dosing Vehicle: water	No clinical signs at 55 and 88 mg/kg bw. At doses ≥ 140 mg/kg bw slight tremors progressing to moderate to marked tonic clonic convulsions occurred within 10 minutes of dosing. All affected animals recovered completely within 1-1.5 hours after dosing (coinciding with the clearance of resorcinol from the blood). Based on these observations 100 mg/kg bw was selected as the maximum dose for the main study.		Merker et al. (1982)

Table 20: Summary table of human data on STOT SE

Type of data/report	Test substance (including purity)	Relevant information about the study (as applicable)	Observations	Reference
Case report Accidental human oral exposure	Resorcinol (purity not specified)	A 27-year-old woman (body weight 65 kg) at 30 weeks of pregnancy was to be given glucose (50 g) during a glucose challenge test but was given 50 g resorcinol in error.	Within minutes following ingestion, the patient described sore throat, tachycardia, shortness of breath and shivering. 20 minutes later she was transferred to ED due to unconsciousness and respiratory failure that required mechanical ventilation along with tonic-clonic seizures and hypothermia. Laboratory findings: leucocytosis, high bilirubin levels, increase in liver enzyme activity, severe metabolic acidosis and green-coloured urine. The fetus was considered dead at 24 h after urgent caesarean delivery. Mother's prognosis was well with supportive management.	Duran et al. (2004)
Case report Accidental human oral exposure	Resorcinol (purity not specified)	A 46-year-old woman (body weight 90 kg) was to be given glucose (75 g) during a glucose challenge test but was given 75 g resorcinol in error.	Two hours after ingestion, the patient was transferred to ED because of unconsciousness, convulsions and coma. After resuscitation, hypotension, pulmonary edema and oliguria occurred. Metabolic acidosis was not corrected in spite of treatment. The patient died of cardiopulmonary arrest approximately 6 hours after hospital admission. Autopsy findings: diffuse pulmonary edema, renal congestion, eosinophilic substance in renal cortical tubular lumina, and hyperemia in all organs. 10% methemoglobin was estimated in the blood by CO-oximetry.	Bulut et al. (2006)
Case reports of use in topical medications	Resorcinol (purity not specified) Repeated dosing in ointment, paste or peeling agent, concentrations up to 50%.		The observed potential symptoms of neurotoxicity included burning sensation, convulsions, dyspnea, dizziness, drowsiness, vertigo, confusion, disorientation, amnesia, tremors and hypothermia. Some patiens suffered also from methaemoglobinemia, haemolytic anaemia, haemoglobinurinia, cyanosis and hypothyroidism. In most cases, the symptoms disappeared within several days after discontinuing resorcinol treatment but some of the cases were fatal.	Reviewed in WHO/IPCS

Table 21: Summary table of other studies relevant for STOT SE

Type of study/data	Test substance	Observations	Reference
OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) GLP 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) Reliability: 1	Resorcinol Purity: 98.8% Administration: oral, by gavage Vehicle: purified water 0, 40, 80, 250 mg/kg bw Exposure: 13 weeks (5 days/week) following 4 weeks' recovery period	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.	Anonymous (2004a)
Range-finding study Fischer 344 rat, male/female (5 animals/sex/dose) Supporting study Reliability: 2	Resorcinol Purity: >99% 0, 27.5, 55, 110, 225, 450 mg/kg bw Administration: oral, by gavage Vehicle: deionized water Exposure: 17 days (once daily for 5 days a week, 12 doses dispensed over 17 days)	NOAEL: 27.5 mg/kg bw/day (nominal) in females based on hyperexcitability at doses ≥ 55 mg/kg bw and tachypnea at doses ≥ 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)
Equivalent or similar to OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) GLP Fischer 344 rat, male/female (10 animals/sex/dose) Reliability: 1	Resorcinol, Purity: >99% Administration: oral, by gavage 0, 32, 65, 130, 260, 520 mg/kg/bw Vehicle: deionised water Exposure: 13 weeks (once a day 5 days a week)	NOAEL: 32 mg/kg bw/day (nominal) females based on increased absolute and relative liver weights at 65 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) (1991) National Toxicology Program (NTP) (1992)

Equivalent or similar to OECD Guideline 453 (Combined Chronic Toxicity/ Carcinogenicity Studies) GLP Fischer 344 rat, male/female (60 animals/sex/dose) Reliability: 1	Resorcinol Purity: >99% Administration: oral, by 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	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 non-neoplastic lesions.	National Toxicology Program (NTP) (1991) National Toxicology Program (NTP) (1992)
Range finding study B6C3F1 mouse male/female (5 animals/sex/dose) Reliability: 2	Resorcinol Purity: >99% Administration: oral, by 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)	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)
Equivalent or similar to OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) GLP B6C3F1 mouse male/female (10 animals/sex/dose) Reliability: 1	Resorcinol Purity: >99% Administration: oral, by gavage 0, 28, 56, 112, 225, 420 mg/kg/bw Vehicle: deionized water Exposure: 13 weeks (once a day, 5 days a week)	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)
Equivalent or similar to OECD Guideline 453 (Combined Chronic Toxicity / Carcinogenicity Studies)	Resorcinol Purity: >99% Administration: oral, by gavage	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.	National Toxicology Program (NTP) (1991) National Toxicology Program (NTP) (1992)

GLP B6C3F1 mouse male/female (60 animals/sex/dose) Reliability: 1	0, 112, 225 mg/kg bw Vehicle: deionized water Exposure: 104 weeks (daily, 5 days/week)	No significant increases in the incidences of neoplasms or non-neoplastic lesions.	

10.11.1 Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure

Specific target organ toxicity after single exposure of resorcinol has been studied in three oral acute toxicity studies (van den Heuvel et al. 1990, Anonymous 1962 and Anonymous 2004b), in two acute toxicity studies via dermal route (Anonymous 1962 and 1970), and in one acute toxicity study via inhalation (Flickinger et al. 1976). Only two of these studies, oral acute toxicity studies by van den Heuvel et al. (1990) and Anonymous 2004b, comply with the OECD test guidelines (TG 401 1981, TG 420 1992).

The Anonymous 2004b study has been conducted in accordance with GLP. It appears plausible that the validation studies conducted under the patronage of the OECD (see below) were also conducted according to GLP. However, the publication by van den Heuvel et al. does not reveal whether this is the case and the full study reports are not available. The dermal and inhalation studies are old, non-GLP studies. It is not possible to assess the reliability of the dermal study (Anonymous 1970) since reporting of the methodology is not available. Two published case reports on accidental human oral exposure to resorcinol are available (Duran et al. 2004, Bulut et al. 2006). In a toxicokinetic study by Merker et al (1982) signs of neurotoxicity were reported after single doses of resorcinol via subcutaneous route. In addition, several OECD test guideline and GLP compliant repeated dose toxicity studies report acute signs of neurotoxicity associated with bolus dosing of resorcinol (Anonymous 2004a, NTP 1991 and 1992). The studies are briefly described below. Further details are given in the sections 10.1.-10.3. of this CLH report and in the REACH registration dossier.

Resorcinol was one of the substances included in a validation study carried out in 1988-1989 for comparison of the newly developed fixed dose procedure with the oral acute toxicity study OECD TG 401 (1981). The validation study was sponsored by the European Commission and the UK Government and was conducted under the patronage of the OECD. One European testing laboratory carried out an acute toxicity study in rats according to OECD TG 401 (1981) with resorcinol, while 26 European testing laboratories studied acute toxicity of resorcinol according to the fixed dose procedure. The fixed dose procedure used has been described in detail in the publication by van den Heuvel et al 1990. Resorcinol was administrated orally by gavage in both studies. In the fixed dose method at least 10 animals (5 females and 5 males) were used for each dose level. The dose level used by each laboratory was one of the four levels associated with classification, 5, 50, 500 and 2000 mg/kg/bw. During a 14-day period animals were observed for signs of toxicity including behavioural and clinical abnormalities, gross lesions, body weight changes, and other toxic effects. The animals were observed at least twice per day during the dosing period and once a day thereafter. All animals were subject to gross necropsy. The publication by van den Heuvel et al. (1990) reports overall results of the validation study for resorcinol including the LD_{50} value (510 mg/kg bw for males and females), EEC hazard classification (Harmful) according to fixed dose procedure tests and the clinical signs reported in these studies. The clinical signs observed with resorcinol in the validation study included ptosis, posture, respiratory effects, diarrhoea and diuresis, lethargy, ataxia, abnormal gait, tremors, convulsions, prostrate coma, salivation, lacrimation and exopthalmus (Table 17). Respiratory effects, ataxia, abnormal gait, tremors and convulsions may be considered clear signs of neurotoxicity. However, the publication by van den Heuvel et al. does not reveal at which dose levels these clinical signs were observed, and therefore it remains unclear whether clinical signs of neurotoxicity were observed at non-lethal doses. The full study reports of the validation study are not available.

In an acute oral toxicity study conducted in accordance with U.S. Federal Hazardous Substances Labeling Act (FHSLA), doses of 398, 795, 1580 and 3160 mg/kg of flaked or industrial grade resorcinol were administered by gavage to groups of 5 non-fasted male albino rats weighing between 200-300 g (Anonymous 1962). The animals were observed for 14 days post exposure period. All fatalities were subjected to necropsy to exclude extraneous causes of death. The survivors were sacrificed and examined for existence of gross lesions. The single dose oral LD_{50}, based upon mortality during the 14-day observation period, was estimated to be 980 mg/kg bw. All the rats that died during the observation period revealed hyperemia and distention of stomach and intestines upon necropsy. There were no effects on body weight gain and no findings at necropsy in surviving animals. None of the rats sacrificed following the holding period exhibited any gross lesions upon pathological examination. The study report and the publications do not specify any clinical signs of toxicity either at lethal or nonlethal doses.

In a fixed dose study conducted according to OECD TG 420 (1992) (with minor deviation, i.e. the doses), female Sprague-Dawley rats were administered resorcinol by gavage at single doses of 200, 500 or 2000 mg/kg bw (1 animal/dose) in a preliminary test and a dose of 200 mg/kg bw (4 animals) in the main test (Anonymous 2004b). The dose of 200 mg/kg bw, instead of 5 and 300 mg/kg bw stated in the guideline, was selected based on the prior information on the substance. The animals were observed frequently during the hours following administration for detection of possible treatment-related clinical signs and mortality.

Thereafter, the animals were observed at least once a day until the end of the 14-day observation period. Animals were checked for bodyweight gain and subjected to necropsy. In the preliminary test piloerection and dyspnea were observed in the animal given 200 mg/kg bw after 2 hours following the administration and these signs were recovered after 4 hours. At 500 mg/kg, death occurred within 20 minutes following the treatment. At 2000 mg/kg, death occurred within 15 minutes following the treatment and tonic-clonic convulsions were observed prior to death. A dose of 200 mg/kg bw was selected for the main test. In the main test with 200 mg/kg bw hypoactivity, dyspnea and tremors were observed in all animals 20 minutes after administration and dyspnea and tremors from 1 to 4 hours after administration. After 6 hours only dyspnea was observed in all animals with complete recovery of the symptoms on day 2. No mortality, treatment-related effects on bodyweight or gross abnormalities were observed. The dose of 200 mg/kg bw was identified as the maximum non-lethal dose of resorcinol in these experimental conditions.

In a dermal study conducted in accordance with FHSLA, groups of 4 male albino rabbits (strain not specified) were administered 1000, 2000, 3980 and 7950 mg/kg bw of flaked and industrial grade resorcinol. The test substance was applied to abraded and intact trunk skin via gauze for 24 hours and covered with an impervious plastic film (Anonymous 1962 and Flickinger 1976). The LD_{50} was determined to be 3360 and 2830 mg/kg bw for flaked and industrial grade resorcinol, respectively. Flaked grade resorcinol produced necrosis of the skin in all rabbits exposed to 3980 mg/kg bw and above; industrial grade resorcinol produced necrosis in three of the rabbits exposed to 2000 mg/kg bw. The rabbits exposed to 1000 mg/kg flaked grade resorcinol showed only slight hyperkeratosis following signs of moderate to severe irritation after 24 hours contact. However, the same dose of industrial grade resorcinol showed no signs of irritation seven days following contact. Body weight gains were reduced in surviving animals. There were no findings at necropsy. The study report does not specify any clinical signs of toxicity either at lethal or non-lethal doses.

In the other dermal study resorcinol was applied as a paste to the skin to groups of five albino rabbits (strain not specified) at 2150, 3160, 4640 and 6810 mg/kg bw (Anonymous 1970). The animals were observed for mortality and clinical signs of toxicity for 14 days. The LD_{50} was 3830 mg/kg bw. Clinical signs occurred within 12 hours of administration at doses 3160, 4640 and 6810 mg/kg bw and included salivation, tremors, and convulsions prior to death. Time of recovery was dose-dependent with 3160 and 4640 mg/kg bw groups having recovery times of 3 and 4 days, respectively. No lethality or clinical signs of toxicity were reported at dose 2150 mg/kg bw. Very slight erythema and extreme dryness was noted. Necropsy on the surviving animals showed no significant findings, while animals that died showed hemorrhage of the gastrointestinal tract.

In an aerosol inhalation study, groups of 6 female Harlan-Wistar rats were exposed for one or eight hours to concentrations of 2130 and 7800 mg/m^3 and 2000, 2480 and 2800 mg/m^3, respectively (Flickinger

1976). Aerosols were generated after dissolving resorcinol in water. Animals were sacrificed 14 days post-exposure. It should be noted that at concentrations of 2480 and 7800 mg/m^3, the solution turned milky and some precipitate was noted. It is likely that the flow concentrations were below the concentration indicated. There was no mortality and all animals had normal weight gains and no lesions attributable to inhalation of the aerosol were seen at gross necropsy. No clinical signs of toxicity were specified in the study report.

To select the dose levels for the in vivo toxicokinetic study (Merker et al. 1982) groups of five rats were injected subcutaneously with doses 55, 88, 140, 220 and 350 mg/kg. The animals were then observed for treatment related signs. There were no clinical signs at 55 and 88 mg/kg bw. At doses ≥ 140 mg/kg bw slight tremors progressing to moderate to marked tonic clonic convulsions occurred within 10 minutes of dosing. All affected animals recovered completely within 1 to 1.5 hours after dosing (coinciding with the clearance of resorcinol from the blood). Based on these observations 100 mg/kg bw was selected as the maximum dose for the main study.

Human data on STOT SE

Resorcinol has been used in human medicine as an antiseptic and in kerolytic topical medications in concentrations 1-2%. Higher concentrations (up to 50%) were used in peeling agents or in pastes for the treatment of leg ulcers during 1920-1970. Several old medical case reports describe toxic effects resulting from the use of resorcinol (up to 50%) containing ointment or paste to ulcerated skin for varying time intervals (reviewed in WHO/IPCS, 2006). Oral uptake in these cases can not be excluded. The observed potential symptoms of neurotoxicity included burning sensation, convulsions, dyspnea, dizziness, drowsiness, vertigo, confusion, disorientation, amnesia, tremors and hypothermia. Some patiens suffered also from methaemoglobinemia, haemolytic anaemia, haemoglobinurinia, cyanosis and hypothyroidism. In most cases the symptoms disappeared within several days after discontinuing resorcinol treatment but some cases were fatal. More recently, Hernández-Pérez (2002) reported mild or transitory dizziness as acute systemic symptoms after application of the peel containing 53% resorcinol.

There are also two more recent case reports presenting accidental human oral exposure to resorcinol (Duran et al., 2004 and Bulut et al., 2006). In both cases, a woman was given resorcinol (50 g and 75 g, respectively) instead of glucose in error. The major clinical and laboratory findings in both patients were unconsciousness, respiratory failure requiring mechanical ventilation, generalized tonic-clonic seizures, leukocytosis and severe metabolic acidosis. The other patient described tachycardia, shortness of breath, shivering and hypothermia. She was pregnant, and the fetus was considered dead 24 hours after delivery. The mother recovered with supportive management. The second patient died of cardiopulmonary arrest approximately eight hours after the ingestion.

Other relevant data

Four repeated dose toxicity studies via oral route in rats and three studies via oral route in mice are available for resorcinol (Anonymous 2004a, NTP 1991 and 1992). These studies consistently report signs of neurotoxicity as the pivotal toxic effect of resorcinol. Although observed in repeated dose studies, the signs of neurotoxicity were considered as acute responses associated with oral bolus dosing of resorcinol (NTP 1991 and 1992).

In a 90-day study according to OECD TG 408 groups of 10 male and female Sprague-Dawley rats received doses of 0, 40, 80 or 250 mg/kg/day resorcinol via gavage orally 5 days/week (Anonymous 2004a). The animals were checked daily for mortality and clinical signs. Detailed clinical observations were carried out weekly, and a Functional Observation Battery (including motor activity) was performed at the end of the treatment period. Detailed observations included (but were not limited to) changes in the skin, fur, eyes, mucous membranes, occurrence of secretions and excretions and autonomic activity (e.g. lachrymation, piloerection, pupil size, unusual respiratory pattern). Changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypes or bizarre behavior were also recorded. In the functional observation battery the following parameters were assessed and graded: "touch escape" or ease of removal from the cage; in the hand: fur appearance, salivation, lachrymation, piloerection, exophthalmia, reactivity to handling, pupil size (presence of myosis or mydriasis); in the standard arena (two-minute recording): grooming, palpebral closure, defecation, and urination counts, tremors, twitches, convulsions, gait, arousal (hypo- and hyper-activity), posture, stereotypic behaviour

and breathing, ataxia and hypotonia. In addition, the following parameters, reflexes and responses were recorded: touch response, forelimb grip strength, pupil reflex, visual stimulus, auditory startle reflex, tail pinch response, righting reflex, landing foot splay, and rectal temperature at the end of observation. The few observed deaths at doses 80 and 250 mg/kg bw were considered not to be treatment-related but probably due to gavage errors. At 250 mg/kg/day, all males and females showed intermittent convulsive movements, starting between weeks 6 and 8 and lasting until the end of the treatment period. The majority of the animals in this group also had excessive salivation during approximately the same period. Two males receiving 250 mg/kg bw resorcinol had loud breathing, one during week 6 and the other between weeks 11 and 13. No clinical observations considered to be treatment-related were noted after the cessation of treatment. There were no effects on body weight or bodyweight gain in males. Female animals receiving 250 mg/kg/day from week 4 to 8 showed reduced bodyweight gain. The group mean landing foot splay was comparable with the controls for all groups of males receiving resorcinol. The females receiving 80 or 250 mg/kg/day had a group mean landing foot splay that was 11% and 13% greater than in the controls. As this observation was not correlated with any other parameter, it was considered to be fortuitous and not clearly treatment-related.

The repeated toxicity studies conducted by National Toxicology Program of the U.S. (NTP 1991 and 1992) with Fischer 344 rats and B6C3F1 mice report clinical signs of neurotoxicity after oral bolus dosing of resorcinol. In a 17-day range finding study in rats hyperexcitability was observed in females dosed at and greater than 55 mg/kg bw along with tachypnea at 110, 225 and 450 mg/kg bw, whereas hyperexcitability and tachypnea were observed at 225 and 450 mg/kg bw in males. These effects appeared within half an hour of dosing and lasted 1 to 2 hours. In a 13-week study (OECD TG 408) all female rats and all but 2 males receiving 520 mg/kg died from compound-related toxicity during first 4 weeks of the study. Tremors were observed at 520 mg/kg bw. In a 104-week study, male Fischer 344 rats were administered 0, 112 and 225 mg/kg and female rats were administered 0, 50, 100 and 150 mg/kg bw resorcinol in water by gavage 5 days/week. The females had ataxia, prostration, salivation and tremors at 100 mg/kg bw and 150 mg/kg bw. Body weight decrease and increased mortality were seen at the highest dose of 150 mg/kg bw. Males had ataxia, prostration, salivation and tremors at all doses (112 and 225 mg/kg bw). Body weight decrease and increased mortality were seen at the highest dose of 225 mg/kg bw.

In a 17-day range finding study using B6C3F1 mice, females had prostration and tremors at 300 mg/kg bw and complete mortality occurred at 600 mg/kg bw. The males had prostration and tremors at 150 mg/kg bw with 80% mortality at 600 mg/kg bw and 20% mortality at 300 mg/kg bw. In a 13-week study study both males and females had dyspnea, prostration, tremors and mortality occurring at 420 mg/kg bw. In a 104-week study male and female B6C3F1 mice were administered 0, 112, 225 mg/kg bw resorcinol in water by gavage 5 days/week. Both males and females had ataxia, recumbency and tremors at both dose levels (112 and 225 mg/kg bw). In females a decrease in body weight occurred at 225 mg/kg bw.

The NTP commissioned a review panel to investigate the CNS effects observed in each of the NTP studies (NTP, 1992). The panel determined 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. The data indicated a very sharp dose response for lethality both in rats and mice. While no deaths occurred in rats administered doses up to 450 mg/kg bw during 17-day study, nearly all rats given 520 mg/kg died during the first 14 days of the 13-week study. A similar pattern of mortality occurred in mice. The deaths appeared to be result of acute toxic reaction. However, the few deaths during the later part of the 13-week studies suggest for a possibility of a cumulative toxic effect associated with continued exposure.

Respiratory tract irritation

There are no case reports or other data on respiratory tract irritation of resorcinol in humans. No signs of respiratory tract irritation were reported in acute inhalation studies in rats (Flickinger 1976). However, it is unclear whether the clinical signs of toxicity were adequately recorded in these studies.

Resorcinol has a harmonised classification for skin and eye irritation (Skin Irrit. 2, Eye Irrit. 2). In a throat spray test, groups of guinea-pigs and rats (sex and strain not specified) received three daily throat

sprayings with 1% resorcinol in water over 2 weeks. The animals were then examined weekly for 10 additional weeks. During the application, the throats of the animals showed signs of irritation, which was reversible after termination of the exposure. There was no gross evidence for respiratory damage, and the histopathological examination of the lungs revealed no adverse effects when compared with controls (water spray) (Flickinger, 1976).

10.11.2 Comparison with the CLP criteria

Classification as either STOT SE 1 or 2 is applicable to substances that have produced non-lethal toxicity in humans, or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant non-lethal toxicity in humans following a single exposure. The guidance value ranges to be used for weight of evidence for oral exposure are ≤ 300 mg/kg bw and 2000 ≥ C > 300 mg/kg bw for categories 1 and 2, respectively.

Classification as STOT SE 3 is reserved for transient target organ effects and is limited to substances that have narcotic effects or cause respiratory tract irritation.

According to the Guidance on the Application of the CLP criteria, "specific target organ toxicity (single exposure) is defined as specific, non-lethal target organ toxicity arising from a single exposure to a substance or mixture" (ECHA 2017). This refers to all significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed. "STOT SE should be considered where there is clear evidence of toxicity to a specific organ especially when it is observed in the absence of lethality. […] Care must be taken not to classify for STOT SE for effects which are not yet lethal at a certain dose, but would lead to lethality within the numeric classification criteria. In other words, if lethality would occur at relevant doses then a classification for acute toxicity would take precedence and STOT SE would not be assigned."

Clear signs of neurotoxicity (CNS) were reported in rats in response to single resorcinol dose ≥ 200 mg/kg bw by oral route. These signs included for example dyspnea, hypoactivity, tremors, ataxia and convulsions. Signs of neurotoxicity, such as tachycardia, shortness of breath, hypothermia, generalized tonic-clonic seizures and convulsions have also been reported in human cases after accidential single oral exposure to resorcinol (doses approximately 700-800 mg/kg bw, Duran et al. 2004, Bulut et al. 2006). These cases were severe and even fatal. In the key animal study, hypoactivity, dyspnea and tremors were observed in all animals (females) at 200 mg/kg bw while there was no lethality at this dose level (Anonymous 2004b). For comparison, the acute oral LD_{50} values for resorcinol in rat are 533 mg/kg and 489 mg/kg bw for males and females, respectively. Signs of neurotoxicity including tremors and convulsions were also observed in one acute dermal toxicity study in rabbits, but these symptoms were only reported at lethal doses (3160, 4640 and 6810 mg/kg bw). The acute dermal LD_{50} in this study was 3830 mg/kg bw (Anonymous 1962). Clinical signs of toxicity are not specified in the acute inhalation studies available for resorcinol. Subcutaneous injection of resorcinol at doses 140, 220 and 350 mg/kg bw in rats resulted slight tremors progressing to moderate to marked tonic clonic convulsions within 10 minutes (Merker et al. 1982). All animals recovered completely within 1-1.5 hours after dosing. Although subcutaneous route has limited relevance for classification purposes, these results confirm the observed effects in oral acute toxicity studies at non-lethal doses.

Repeated dose toxicity studies with resorcinol report signs of neurotoxicity after oral bolus dosing in rat and mice (Anonymous 2004a, NTP 1991 and 1992). The clinical signs of neurotoxicity such as tremors, tachypnea, ataxia, prostration and intermittent convulsive movements were observed at doses approximately 100 mg/kg bw and above in both species. Hyperexitability was reported in female rats at a dose as low as 55 mg/kg bw (NTP 1991 and 1992). The signs of neurotoxicity were also observed at dose levels where no treatment-related lethality occurred (250 mg/kg bw in Anonymous 2004a, approximately 55-150 mg/kg bw in the NTP studies). In the NTP studies the signs of neurotoxicity were reported to occur shortly after dosing and to subside within approximately one hour. Thus, they were considered acute responses although observed in repeated dose studies. In addition, several medical case reports describe CNS disturbances such as dizziness, drowsiness, vertigo, confusion, disorientation, amnesia, tremors, burning sensation and hypothermia in humans in response to use of resorcinol (up to 50%) containing ointment, paste or peel to skin for varying time intervals (reviewed in WHO/IPCS, 2006).

In some human cases the CNS effects were described as acute systemic symptoms to resorcinol use (Hernández-Pérez 2002). In most cases, the symptoms reversed after discontinuing resorcinol treatment but some of the cases were fatal.

Gatgounis and Walton (1962) have reported that resorcinol and its isomers catechol and hydroquinone administred to dogs and rabbits can act on the brainstem medulla and the spinal cord to produce symphatetic nervous system stimulation. The specific mode of action is not known. The reported signs of acute CNS toxicity in response to resorcinol exposure (e.g. breathing disturbances, tachycardia, tremors, convulsions, ataxia, hypoactivity, hypothermia, dizziness) in experimental animals and in humans could be coused by symphatetic nervous system stimulation. Similar signs of CNS disturbances to resorcinol have also been reported in response to hydroquinone and catechol exposure (Topping et al. 2007, Angel and Rogers, 1972).

Classification for STOT SE based on neurotoxic effects should be considered for resorcinol.

The signs of neurotoxicity in response to single oral exposure were also observed at doses were no lethality occurred (200 mg/kg bw in the key study, Anonymous 2004b). The non-lethal dose levels where signs of neurotoxicity occurred (approximately 55-250 mg/kg bw) are at least approximately half of the oral LD_{50} for the substance and lie within the different numeric classification criteria range than the oral LD_{50} values, i.e. 489 mg/kg bw, 533 mg/kg and 980 mg/kg bw (Acute Tox. 4). The neurotoxic signs at non-lethal doses primarily occurred below the guidance value for STOT SE Category 1 (300 mg/kg bw). Thus, classification for STOT SE 1 for nervous system is proposed.

Signs of neurotoxicity were observed in response to acute oral and dermal exposure but not after inhalation exposure. However, due to low quality of the inhalation studies, it remains unclear whether clinical signs were adequately observed, and the doses used may have been lower than stated in the study reports. Therefore, it is considered that effects due to inhalation exposure cannot be excluded and the route of exposure is not proposed to be specified with classification.

Resorcinol is a skin and eye irritant acknowledged by harmonised classification (Skin Irrit. 2, Eye Irrit. 2) suggesting for effects in the respiratory tract. No signs of respiratory tract irritation were reported in the available acute inhalation studies. In a throat spray test on guinea pigs and rats reversible irritation in throats of animals was observed (Flickinger 1976). However, in the absence of human data on respiratory tract irritation this data alone is not considered sufficient for classification.

The observed neurotoxicity, though transient in nature, does not fulfil the criteria for narcotic effects. Therefore classification for STOT SE 3 is not warranted.

10.11.3 Conclusion on classification and labelling for STOT SE

Based on signs of neurotoxicity observed consistently at both lethal and non-lethal doses, classification for **STOT SE 1; H370** (nervous system) is proposed.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

Animal Data

The DS summarised clinical signs observed in the acute toxicity studies (four oral, two dermal, and one inhalation studies) and in a non-guideline, non-GLP toxicokinetic study with exposure via subcutaneous injection in male rats. Furthermore, they provided data from several repeated dose toxicity studies in rats and mice within the U.S. National

Toxicology Program (NTP 1992), and from one GLP-compliant OECD TG 408 study in rats (Anon. 2004a).

Clear signs of neurotoxicity (dyspnea, hypoactivity, ataxia, tremors, and convulsions) were seen in rats after single exposure to resorcinol at non-lethal doses 200 mg/kg bw and above. Tremors and convulsions were also observed in rabbits after a single dermal exposure but at doses associated with lethality. In rats, at doses of 140 mg/kg bw and above via subcutaneous injection, slight tremors progressing to tonic-clonic convulsions occurred within ten minutes of dosing. Although this route of exposure is less relevant, these results underpin the neurotoxic properties of resorcinol. Clinical signs were not specified in the acute inhalation toxicity study available.

In repeated dose toxicity studies in rats and mice, neurotoxic effects (tremors, tachypnea, prostration, ataxia, and intermittent convulsive movements) were observed after bolus doses 100 mg/kg bw and above. At these doses no treatment-related lethality occurred. The effects were observed shortly after dosing and subsided within one hour.

Human Data

Human data included the two case reports already described in the acute toxicity section, and WHO reviewed case reports of patients repeatedly using ointments and peeling agents with resorcinol concentrations of up to 50 %. Symptoms in humans comprised green-coloured urine, sore throat, burning sensation, tachycardia, hypotension, shortness of breath, respiratory failure, pulmonary oedema, dyspnea, shivering and tremors, dizziness, drowsiness, vertigo, confusion, disorientation, amnesia, unconsciousness, coma, tonic-clonic seizures, convulsions, and hypothermia.

Laboratory examinations showed increase in liver enzyme activity, severe metabolic acidosis, oliguria, haemoglobinuria, methaemoglobinaemia, leucocytosis, high bilirubin levels, haemolytic anaemia, cyanosis and hypothyroidism.

Some of these intoxications were fatal.

Respiratory tract irritation and narcotic effects

Although resorcinol has a harmonised classification as skin and eye irritant, no signs of respiratory tract irritation were observed in the acute inhalation toxicity study and no human data are available that would show respiratory tract irritation in humans. A throat spray test in guinea pigs and rats (Flickinger 1976) showed transient irritation in the throats of the animals, but this was not considered sufficient for classification.

The DS concluded that the observed neurotoxic effects do not fulfil criteria for narcotic effects.

Conclusion on classification

Neurotoxicity was observed in several animal studies at doses relevant for classification in category 1 (< 300 mg/kg). Human data affirm neurotoxic effects of the substance.

The DS proposed classification as **STOT SE 1, H370 (nervous system)**.

Since the quality of inhalation toxicity study is poor, neurotoxic effects cannot be ruled out after inhalation exposure. Therefore, no specification of the route of exposure was proposed.

Comments received during consultation

Two MSCAs commented on this endpoint. Both supported the proposed classification.

Assessment and comparison with the classification criteria

Animal data

The DS summarised several studies in rats, mice, rabbits, and guinea pigs with oral, inhalation, dermal, and subcutaneous routes of exposure. Where reported, clinical signs after single exposure (or occurring in repeated dose toxicity studies but shortly after dosing and resolving within hours) at non-lethal doses relevant for classification were the following:

- piloerection and dyspnea in a preliminary study by gavage in rats at 200 mg/kg bw (Anon 2004b),
- hypoactivity, dyspnea, and tremors in rats at 200 mg/kg bw in the main OECD TG 420 study resolving after 2 days (Anon 2004b),
- slight tremors progressing to moderate to marked tonic clonic convulsions in rats after subcutaneous injection occurring within 10 minutes and resolving within 1 to 1.5 hours after dosing in a toxicokinetic study,
- hyperexcitability and tachypnea at oral doses from 55 mg/kg bw in female rats and at doses from 225 mg/kg bw in male rats appearing within 30 minutes and resolving within 2 hours after dosing in a 17-d range finding study (NTP 1991, 1992),
- ataxia, prostration, salivation, and tremors at oral doses of 100 mg/kg bw in female rats and at 112 mg/kg bw in male rats in a 104-week study (NTP),
- prostration and tremors at oral doses of 300 mg/kg bw in female mice and at 150 mg/kg bw in male mice in a 17-d range finding study (NTP),
- ataxia, recumbency, and tremors in mice at oral doses from 112 mg/kg bw in a 104-week study (NTP),
- for ptosis, posture, respiratory effects, diarrhoea and diuresis, lethargy, ataxia, abnormal gait, tremors, convulsions, prostrate coma, salivation, lacrimation and exophthalmus in rats after oral exposure in the validation study for the fixed dose method (similar to OECD TG 420) performed in 26 laboratories no dose levels were reported,
- irritation of the throat was observed in rats and guinea pigs in a throat spray test with 1 % resorcinol in water with three daily sprayings over two weeks without histopathological correspondence.

A panel reviewed the central nervous system symptoms reported in the NTP studies and concluded they were acute responses occurring shortly after dosing and resolving within two hours, in a time frame corresponding with the rapid clearance of the test substance.

Human Data

Human data are already described in detail in the acute oral toxicity section. Overall symptoms observed in humans after accidental ingestion of resorcinol match clinical signs seen in the animal studies. No data on respiratory tract irritation in humans are available.

Conclusion on classification

Neurotoxic effects in laboratory animals were consistently seen at doses below the cut-off 300 mg/kg bw for category 1 in oral toxicity studies in rats and mice.

Such effects were also reported in studies with dermal exposure but at doses also inducing mortality. Clinical signs were not specified in the acute inhalation toxicity study report. RAC concurs with the DS that it cannot be excluded with certainty that exposure to resorcinol via these routes will not lead to neurotoxic effects. Therefore, RAC concurs not to specify the route of exposure in the classification.

Clinical signs in animals and symptoms in humans that did not lead to death were transient in nature, but they included tonic clonic convulsions, tremors, and severe respiratory symptoms which go beyond effects considered for a STOT SE 3 - narcotic effects classification.

In conclusion, RAC concurs with the DS that data from experimental animals and humans warrant classification of resorcinol as **STOT SE 1, H370 (nervous system)** without specification of the route of exposure.

10.12 Specific target organ toxicity-repeated exposure

Not assessed in this dossier.

10.13 Aspiration hazard

Not assessed in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

11.1 Rapid degradability of organic substances

Summary of relevant studies from the registration dossier of resorcinol on degradation are reported briefly below. Only relevant, reliable and valid studies for the proposed classification of resorcinol have been included from the REACH registration dossier. Reliability of the studies are provided based on the Klimisch scores in the registration dossier.

Table 22: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
OECD TG 301 C (Modified MITI test (I)). GLP compliance not specified.	Aerobic degradation: 66.7 % (BOD) after 14 days. 100 % (TOC removal) after 14 days.	2 (reliable with restrictions). Key study. Initial test concentration 100 mg/L. Activated sludge, non-adapted (concentration 30 ppm).	Kitano (1978)
OECD TG 302 B (Inherent biodegradability: Zahn-Wellens Test).	Biodegradation in water, inherent biodegradability: 97 % after 4 days.	2 (reliable with restrictions). Supporting study.	Wellens (1990)

Method	Results	Remarks	Reference
No GLP compliance.		The inoculum was taken from the biological wastewater treatment plant.	
EU Method C.5 (Degradation: Biochemical Oxygen Demand), 84/449/EEC, C.8. No GLP compliance.	Aerobic degradation: 90 % (COD) within 5 days. COD: 57.5 mg O2/g test mat. BOD5 / COD: ca. 1.74	2 (reliable with restrictions). Supporting study. Initial test concentration 200 mg/L. Activated sludge taken from a sewage plant.	Pitter (1976)
Non guideline study similar to OECD TG 302 B. No GLP compliance	Aerobic degradation: 95 – 98 % (O2 consumption) within 1-2 days.	2 (reliable with restrictions). Supporting study.	Tabak (1964)
Non guideline study similar to OECD TG 302 B. GLP compliance not specified.	Aerobic degradation: > 90 % in 2 – 5 days.	2 (reliable with restrictions). Supporting study. Initial test concentration 250 ppm	Singer (1979)
Inherent biodegradation test; Modified German Detergentien test No GLP compliance	Aerobic degradation: 60 % (DOC) after 5 days (500 mg/L test conc.) 100 % (DOC) after 5 days (138 mg/L test conc.)	2 (reliable with restrictions). Supporting study. Initial test concentration 138 and 500 mg/L	Gubser (1969)

11.1.1 Ready biodegradability

In a modified MITI test (following OECD TG 301C) fulfilling the 10 day window criterion results indicate 66.7 % (BOD) biodegradation after day 14 in 25 °C and pH 7 for resorcinol and 100 % TOC removal after 14 days (Kitano 1978). Biodegradation was 10 % on day 1 and 60% on day 5. Initial test substance concentration of 100 mg/L was used. Total Organic carbon was measured using UV-Vis at 100% and HPLC at 100% by direct measurement. Oxygen concentration was automatically measured.

Based on the results of the study, resorcinol can be considered as readily biodegradable under aerobic conditions. In the registration dossier it is referred that data on Kitano 1978 study are provided from Japan government website. Only limited information is available, however study is considered valid and reliable for classification purposes by evaluated MS.

Other biodegradability studies in registration dossier can be considered as inherent biodegradability tests and are summarised in section 11.1.4.2.

11.1.2 BOD_5/COD

BOD5/COD was determined for resorcinol with the value of ca. 1.74 in the registration dossier demonstrating the rapid degradation of resorcinol (Pitter 1976).

11.1.3 Hydrolysis

Resorcinol has no functional groups susceptible to hydrolysis under environmentally relevant pH and temperature conditions (Harris, 1990). Hydrolysis is not expected to occur. The study has been evaluated as reliability 2 (reliable with restrictions) in the REACH registration dossier.

11.1.4 Other convincing scientific evidence

11.1.4.1 Field investigations and monitoring data (if relevant for C&L)

11.1.4.2 Inherent and enhanced ready biodegradability tests

Following OECD TG 302B, 97% degradation was observed after 4 days (Wellens 1990) for resorcinol. Elimination rates of > 90 % were observed after 2 to 5 days in studies similar to OECD TG 302B (Pitter 1976, Tabak et al. 1964 and Singer et al. 1979). Test substance concentrations of 138 and 500 mg/L of resorcinol resulted in rates of 60 – 100 % degradation (DOC) after 5 days (Gubser, 1969). Based on the results of the inherent biodegradation studies, resorcinol can be considered as inherently biodegradable.

11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies)

11.1.4.4 Photochemical degradation

Photodegradation in air

Resorcinol in air is not expected to undergo direct photolysis, but may undergo indirect photolysis through hydroxyl radical oxidation. Resorcinol does not absorb sunlight at wavelengths above 296 nm to a significant extent (Perbet et al. 1979). Indirect photolysis via hydroxyl radical oxidation was calculated via EPIWIN v3.12 which contains AOPWIN v 1.91 in the registration dossier. Results indicate the overall OH rate constant to be 200.28 E-12 cm3/molecule-sec and a half-life of 0.053 days (38.16 minutes) for a 12-hour day with a hydroxyl radical concentration of 1.5 $x10^6$ OH - radicals/cm3.

Photodegradation in water

The light absorbance and photolytic properties of resorcinol were found to be highly dependent on solution pH and can be adequately described with a three-species distribution model. For the UV-H2O2 process, the individual contribution to the decomposition of pollutants by direct photolysis and indirect hydroxyl radical destruction was differentiated by studying the linear addition of UV light absorbance of various reactant species. The contribution to the decomposition of resorcinol by hydroxyl radical destruction was more than 95 % in acidic and neutral solutions for treatment with the UV-H2O2 process (Shen et al. 2003).

11.2 Environmental transformation of metals or inorganic metals compounds

11.2.1 Summary of data/information on environmental transformation

11.3 Environmental fate and other relevant information

11.4 Bioaccumulation

11.4.1 Estimated bioaccumulation

11.4.2 Measured partition coefficient and bioaccumulation test data

The measured partition octanol/water coefficient (Log Kow) of 0.8 at 20 °C was determined for resorcinol (REACH registration dossier). The log Kow of resorcinol does not reach the cut-off value of log Kow ≥ 4 relevant for the classification. Thus, resorcinol has a low potential for bioaccumulation.

11.5 Acute aquatic hazard

Summary of relevant studies from the REACH registration dossier of resorcinol on acute aquatic toxicity are reported briefly below. Only relevant, reliable and valid studies under CLP for the proposed classification of resorcinol have been included from the registration dossier. Reliability of the studies are provided based on the Klimisch scores in the registration dossier.

Table 23: Summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results	Remarks	Reference
Fish					
Methods for Acute Toxicity Tests (EPA-660/3/75-009) GLP compliance not specified 96 h flow-through test	*Pimephales promelas*	Resorcinol No information on purity of the test material	96h LC50: 26.8 – 29.5 (mean measured)	2 (reliable with restrictions) Key study	Anonymous (1981a)
Fish short term toxicity study (test guideline not specified) GLP compliance not specified 96h static test	*Leuciscus idus*	Resorcinol (99% purity)	96h LC50: 34.7 mg/L (nominal)	2 (reliable with restrictions) Supporting study	Anonymous (1981b)
In house method, similar to OECD TG 203 GLP compliance not specified 96h semi-static test	*Gambusia affinis*	Resorcinol (analytical grade)	96h LC 50: 181 mg/L (nominal) 72h LC50: 184 mg/L	2 (reliable with restrictions) Supporting study Rate of oxygen uptake was significantly	Anonymous (2000)

				decreased at higher concentrations.	
Methods for Acute Toxicity Tests (EPA-660/3/75-009) No GLP compliance 96h static test	*Pimephales promelas*	Resorcinol (industrial grade)	96h LC50: 49.5 mg/L (measured concentration)	2 (reliable with restrictions) Supporting study	Anonymous (1979)
Method not described in the registration dossier GLP compliance not specified 96h flow-through test	*Pimephales promelas*	Resorcinol No information on purity of the test material	96h LC50: 100 mg/L (nominal)	2 (reliable with restrictions) Supporting study	Anonymous (1980)
Method not described in the registration dossier GLP compliance not specified 96h flow-through test	*Oncorhynchus mykiss*	Resorcinol No information on purity of the test material	96h LC50: >100 mg/L (nominal)	2 (reliable with restrictions) Supporting study	Anonymous (1980)
Aquatic invertebrates					
OECD TG 202 GLP compliant 48h semi-static	*Daphnia magna*	Resorcinol (99,75%)	48h LC50: 1.0 mg/L (geom. mean measured) 48h LC50: 1.3 mg/L (nominal)	1 (reliable without restriction) Key study	Harlan (2010)
Non-guideline study GLP compliance not specified 48h flow-through test	*Daphnia pulicaria*	Resorcinol No information on purity of the test material multi-test substance study	48h LC50: > 100 mg/L (nominal)	2 (reliable with restrictions) Supporting study	DeGraeve (1980)
Non-guideline study GLP compliance not specified 48h static test	*Daphnia magna*	Resorcinol No information on purity of the test material	48h LC50: 1.28 mg/L (nominal)	2 (reliable with restrictions) Supporting study	Herbes & Beauchamp (1977)
Methods for Acute Toxicity Tests (EPA 660/3-75-009) No GLP compliance	Daggerblade grass shrimp *(Palaemonetes pugio)*	Resorcinol No information on purity of the test material	96h LC50 (mortality): 42.2 mg/L (nominal) and 32.7 mg/L (direct photometric measument of	2 (reliable with restrictions) Supporting study Saltwater media	Curtis (1979)

96h static test			phenol concentration)		
Algae					
OECD TG 201 GLP compliant 72h static test	*Pseudokirchneriella subcapitata*	Resorcinol No information on purity of the test material	72h EC50 (growth rate): >97 mg/L (measured) 72h EC50 (biomass): >97 mg/L	1 (reliable without restriction) Key study Limit test	Springborn (2006)
Non-guideline study GLP compliance not specified 72h static test (saltwater)	Diatom *(Nitzchia Closterium)*	Resorcinol No information on purity of the test material	89% inhibition compared to control based on growth rate (55.05 mg/L nominal)	2 (reliable with restrictions) Supporting study	Florence & Stauber (1986)

11.5.1 Acute (short-term) toxicity to fish

Six acute aquatic toxicity studies are available for fish following protocols similar to OECD test guideline 203. These are consired valid and reliable for the classification purposes.

The 96 h LC50 values of resorcinol in fathead minnows (*Pimephales promelas*) ranged from 26.8 mg/L (mean measured) to 100 mg/L (nominal) under flow through conditions and under static conditions the 96 h LC50 was 49.5 mg/L. In a flow through test, two individual tests were conducted in which groups of 10 fish were exposed per test concentration (Anonymous, 1981a). In test 1, 10 fish per test group were exposed to mean measured concentrations of 0, 16.2, 25.8, 34, 39.6 and 46.4 mg/L and in test 2 to concentrations of 0, 12.8, 22.8, 32, 40 and 49.8 mg/L. The 96h LC50 value of 29.5 mg/L (mean measured) and 26.8 mg/L (mean measured) were observed for tests 1 and 2, respectively. These results are consistent with those reported for the pure form of resorcinol (99%). In a study conducted using Resorcin DS technical grade (99% resorcinol), 10 fish per test concentration were exposed to 0, 10, 25, 31.5, 40, 63 and 100 mg/L (nominal) (Anonymous, 1981b). In the 31.5 to 100 mg/L groups 5 fish died up to 95 hours after addition of the test substance, with the following symptoms: surface swimming, uncoordinated swimming movements, drifting in a lateral position, hyper-reflexivity and reduced frequency of gill action. The fish in the 25 and 10 mg/L groups did not differ in their behaviour from those in the control groups. The fish in the 100 mg/L group presented punctuate red flecks on the body surface. Dissection showed no macroscopically visible changes in all test groups. The resulting 96 h LC50 was 34.7 mg/L (nominal).

In a 96-hour study an LC50 value of 34.7 mg/L was observed for *Leuciscus idus* (Anonymous, 1981b).

11.5.2 Acute (short-term) toxicity to aquatic invertebrates

Several acute toxicity tests are available for aquatic invertebrates. These are considered valid and reliable for the classification purposes.

In an initial 48 hour semi-static study conducted according the OECD TG 202 (with test concentrations of 1.0, 1.8, 3.2, 5.6, 10, 18, 32 and 56 mg/L) immobilization of daphnids were observed in all test concentrations (Harlan, 2010). The results from the initial experiment differed from range-finding test (no immobilization at 1.0 mg/L), therefore, a second definitive test was performed. In a definitive test following test concentrations were assigned 0.10, 0.18, 0.32, 0.56, 1.0, 1.8, 3.2, 5.6 and 10 mg/L resulting the 48 hour LC50 value of 1.3 mg/L (based on nominal but analytically verified test concentrations ranging from 92 % to 104 % of initial test concentrations) (Table 24). In the test 10 daphnids were places in each test and control vessel and maintained in a temperature at 20 °C with a photoperiod of 16 hours light and 8 hours darkness. Some of the test temperatures were measured to be slightly in excess of the

20 ± 1 C° given in the study plan. This was considered not to affect the results of the test as no adverse effects of exposure were observed in the control daphnids throughout the duration of the test and that the test temperatures were within the test guideline. The oxygen concentration in some of the test vessels was observed to have an air saturation value (ASV) in excess of 100 %. This was considered to be due to the presence of microscopic air bubbles in the media super-saturating the diluent and was considered not to have had an impact on the outcome or integrity of the test as no adverse effects were observed. The study is considered valid and reliable by the evaluating MS.

Table 24. Cumulative immobilisation data in the definitive test (Harlan 2010).

Nominal Concentration (mg/l)	Cumulative Immobilised *Daphnia* (Initial Population: 10 Per Replicate)							
	24 Hours				48 Hours			
	R_1	R_2	Total	%	R_1	R_2	Total	%
Control	0	0	0	0	0	0	0	0
0.10	0	0	0	0	0	0	0	0
0.18	0	0	0	0	0	0	0	0
0.32	0	0	0	0	0	0	0	0
0.56	0	0	0	0	1	2	3	15
1.0	1	1	2	10	7	3	10	50
1.8	3	4	7	35	10	10	20	100
3.2	4	6	10	50	10	10	20	100
5.6	5	6	11	55	9	10	19	95
10	5	7	12	60	9	10	19	95

Test concentrations were verified at 0 (fresh media), 24 (old and fresh media) and 48 hours (old media) and ranged from 92 to 104 % of the nominal value in a definitive study, so it was considered justifiable to calculate the LC50 values in terms of the nominal test concentrations only (Harlan, 2010). In the registration dossier also a LC50 value of 1.0 mg/L (95% confidence limit of 0.041 – 27 mg/L) based on the geometric mean measured concentrations has been calculated from this study.

A 48 hour flow through multi-test substance study was conducted in *Daphnia pulicaria* with resorcinol being one of the test substances (DeGraeve et al., 1980). In this study 10 animals were added to each test tank unless due to limited animals only 5 were added. Results indicated the 48 hour LC50 was > 100 mg/L (nominal).

In a 48 hour static study, concentrations of resorcinol were calculated from compositions of the stock solutions (Herbes & Beauchamp, 1977). The 48 hour LC50 value of 1.28 mg/L (nominal) was observed for *Daphnia magna*. The actual LC50 may be lower than the nominal LC50 as there is lack of indication of analytical monitoring.

In a EPA-660/3-75-009 (1975) guideline study with the salt water species *Palaemonetes pugio* (Daggerblade grass shrimp) the 96h LC50 value of 42.2 mg/L (nominal) and 32.7 mg/L (measured; direct photometric measurement of phenol concentration) were observed for resorcinol (Curtis (1979).

In conclusion, aquatic invertebrates are the most sensitive trophic level for resorcinol for aquatic acute toxicity. The lowest acute toxicity value in the registration dossier (48h LC50) for *Daphnia magna* was 1.0 mg/L based on the geometric mean measured concentration (Harlan 2010).

11.5.3 Acute (short-term) toxicity to algae or other aquatic plants

In an OECD TG 201 study, algae (*Pseudokirchneriella subcapitata*) were exposed for 72 hours to mean measured concentrations of 3.0, 5.8, 12, 24, 47 and 97 mg/L of resorcinol (Springborn, 2006). The 72 h

EbC50 and ErC50 values (biomass and growth rate) were both greater than the highest mean measured concentration tested (>97 mg/L).

Florence & Stauber (1986) study was designed to assess the impact of copper complexes to the marine diatom *Nitzschia closterium*. Several substances were tested, including resorcinol, to determine impact on photosynthesis and growth rate. Resorcinol when applied to nominal concentration of 55.05 mg/L yielded a 72 h growth rate of 89% compared to control.

These acute toxicity studies with algae are considered valid and reliable for classification purposes.

11.5.4 Acute (short-term) toxicity to other aquatic organisms

11.6 Long-term aquatic hazard

Table 25: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Results[1]	Remarks	Reference
Fish					
Similarities with OECD TG 210 (early draft) GLP compliance not specified 60d semi-static test	*Oncorhynchus mykiss*	Resorcinol (≥ 99% purity)	60d LOEC: 320 mg/L (mortality, total embryotoxicity)) 60d LOEC: 100 mg/L (length) 60d LOEC: 32 mg/L (weight) Based on nominal concentrations	2 (reliable with restrictions) Key study	Anonymous (1990)
OECD TG 212 GLP compliance not specified 7d semi-static test	*Danio rerio*	Resorcinol (≥ 99% purity)	7d LOEC (mortality): 320 mg/L 7d LOEC (total embryotoxicity): 100 mg/L Based on nominal concentrations	2 (reliable with restrictions) Supporting study	Anonymous (1990)
Aquatic invertebrates					
OECD TG 211 GLP compliant 21d flow-though test	*Daphnia magna*	Resorcinol (USP Grade Flake) 99.96 % purity	21 d NOEC (reproduction): ≥ 0.172 mg/L (mean measured) No adverse effects observed at the highest test concentration	1 (reliable without restriction) Key study	Springborn (2004)
Algae					
OECD TG 201 GLP compliant 72h static test	*Pseudokirchneriella subcapitata*	Resorcinol No information on purity of the test material	72h NOEC (biomass): 47 mg/L (measured) 72h NOEC (growth rate): 97 mg/L (measured)	1 (reliable without restriction) Key study Limit test	Springborn (2006)

11.6.1 Chronic toxicity to fish

Following draft OECD Early life stage guidelines an embryolarval test with rainbow trout (*Oncorhynchus mykiss*) were initiated with freshly fertilized eggs. About 3 hours after fertilization, 100 eggs were transferred to 15-liter all-glass aquaria containing 10 L of test solution made up in reconstituted water with a hardness of 50 mg/L (as CaC03), a pH of 7.7 ± 0.2, and an oxygen concentration of 10.8 ± 0.2. The test media were renewed three times a week. No analytical monitoring was performed. Results for *Oncorhynchus mykiss* indicate a 60 day LOEC (mortality) value of 320 mg/L, a 60 day LOEC (total embryotoxicity) value of 320 mg/L, 60 day LOEC (length) value of 100 mg/L and 60 day LOEC (weight) value of 32 mg/L for resorcinol (Anonymous, 1990). The actual toxicity values may have been lower as no analytical monitoring was performed in the study. Resorcinol is susceptible to biodegradation during the aquatic long-term tests (Harlan 2010). Only LOEC (lowest observed effect concentration) values are presented for this study.

In the same study (Anonymous, 1990), 60 day results with rainbow trout were compared to 7 day test results of zebrafish (*Danio rerio*) performed according to the OECD TG 212. The results for zebrafish indicated 7 day LOEC (mortality) value of 320 mg/L (nominal) and 7 day LOEC (total embryotoxicity) value of 100 mg/L (nominal) for resorcinol. The EC50 value for total embryotoxicity was 54.8 mg/L. Test solutions renewed three times a week, however, the toxicity values may have been lower as they represent only nominal test concentrations.

11.6.2 Chronic toxicity to aquatic invertebrates

One long-term toxicity study according to OECD TG 211 is available for resorcinol (Springborn 2004).

In a 21-day flow-through study, *Daphnia magna* were exposed to mean measured concentrations of 11, 35, 53, 111 and 172 µg/L of resorcinol (nominal test concentrations were 25, 50, 100, 200 and 400 µg/L). Test concentrations were based on static-renewal range-finding study with nominal concentrations of 0.95, 3.1, 9.8, 30 and 100 µg/L. Test temperature ranged from 19 to 21 °C and pH from 8.0 to 8.2 during the main test. The 21-day mean measured EC50 value was > 172 µg/L and the NOEC value was ≥ 172 µg/L (mean measured, highest concentration tested). The test is considered reliable and valid by the evaluated MS. At termination of the test, survival of 95, 95, 95, 95 and 100% was observed among daphnids exposed to the 11, 35, 53, 111 and 172 µg/L treatment levels. No adverse effects were observed at the end of the study for the reproduction, mortality, total body length or dry weight endpoints. Thus, the actual NOEC values for *Daphnia magna* are anticipated to be higher than the observed NOEC value of 172 µg/L, which only represents the highest test concentration. The decrease in the test substance concentration was believed to be due to biological degradation or uptake by the organisms (Springborn 2004). In a separate experiment by Springborn 2004, microbes that were present throughout the diluter system in pipes and filters as well as test vessels developed quickly an affinity for resorcinol resulting degradation rates that could not be fully compensated under flow-through conditions.

11.6.3 Chronic toxicity to algae or other aquatic plants

In an OECD TG 201 study, algae (*Pseudokirchneriella subcapitata*) were exposed for 72 hours to mean measured concentrations of 3.0, 5.8, 12, 24, 47 and 97 mg/L of resorcinol (Springborn, 2006). The mean measured NOEC value for growth inhibition (biomass) endpoint was 47 mg/L and 97 mg/L for the growth rate endpoint.

11.6.4 Chronic toxicity to other aquatic organisms

NA

11.7 Comparison with the CLP criteria

11.7.1 Acute aquatic hazard

Acute aquatic toxicity data for resorcinol are available for fish, aquatic invertebrates and algae. Aquatic invertebrates are the most sensitive taxonomic group and *Daphnia magna* can be considered as the most sensitive aquatic invertebrate species tested. Based on the key study (Harlan 2010) the lowest 48h LC50 value for *Daphnia magna* was 1.0 mg/L (based on mean measured concentrations).

For acute aquatic hazards, based on acute aquatic LC50 value being in the range 0.1 mg/l < L(E)C50 ≤ 1 mg/l, resorcinol should be classified as Aquatic Acute 1 (H400) with an M-factor of 1. Thus, the M-factor of 1 should be added to previous harmonised classification of Aquatic Acute 1 (H400) for resorcinol.

11.7.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

In a modified MITI test (following OECD TG 301C) fulfilling the 10 day window criterion results indicate 66.7 % (BOD) biodegradation after day 14 and 100 % TOC removal after 14 days (Kitano 1978). Other biodegradability studies in registration dossier can be considered as inherent biodegradability tests and are summarised in section 11.1.4.2.

Consequently, resorcinol is considered to be **rapidly degradable** because:

- it was demonstrated that resorcinol is readily biodegradable > 60 % (BOD) (Kitano 1978).
- the BOD5/COD ratio was determined with the value of ca. 1.74 (Pitter 1976) supporting the conclusion.

Furthermore, resorcinol has **a low potential to bioaccumulate** (log Kow = 0.8 at 20 °C).

Long-term aquatic toxicity data for resorcinol are available for fish, aquatic invertebrates and algae. No adverse effects are observed for the resorcinol below the criteria set out in CLP in Table 4.1.0(b)(ii) for rapidly degradable substance. The lowest NOEC value of ≥ 0.172 mg/L (mean measured) for *Daphnia magna* was determined for resorcinol (Springborn 2004). However, as no adverse effects were observed at the highest test concentration (0.172 mg/L), the long-term aquatic toxicity is expected to be higher for *Daphnia magna* (the most sensitive species based on acute endpoints). It is noted that no chronic toxicity data is available for the most sensitive fish species based on acute testing (*Pimephales promelas*), however, still no chronic classification is derived either from CLP Table 4.1.0(b)(iii) as resorcinol is both rapidly degradable and non-bioaccumulative.

Thus, for long-term aquatic hazards, based on the all available information, no long-term aquatic hazard classification according to Regulation EC 1272/2008 is warranted for resorcinol.

11.8 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

Conclusions on classification and labelling for environmental hazards of resorcinol:

Hazard Class and Category code(s)	M factor	Hazard Statement
Aquatic Acute Category 1, H400	1	Very toxic to aquatic life

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

For the environmental hazard, the DS provided studies from the REACH registration dossier. The DS proposed to keep the classification as Aquatic Acute 1 (H400), adding an M-factor of 1 based on the results in the relevant ecotoxicological studies on *Daphnia magna*, as described below. From the available information, no classification for chronic aquatic hazards was warranted.

Degradation

Hydrolysis is not expected to occur since resorcinol has no functional groups susceptible to hydrolysis under environmentally relevant pH and temperature conditions (Harris, 1990).

A study related to the effect of pH on the decomposition of hydrophenols in aqueous solutions by ultraviolet direct photolysis and the ultraviolet hydrogen peroxide process (Shen *et al*., 2003) indicated that the light absorbance and photolytic properties of resorcinol are highly dependent on pH and can be adequately described with a three-species distribution model. For the UV-H_2O_2 process, the individual contribution to the decomposition of pollutants by direct photolysis and indirect hydroxyl radical destruction was differentiated by studying the linear addition of UV light absorbance of various reactant species. The contribution to the decomposition of resorcinol by hydroxyl radical destruction was more than 95 % in acidic and neutral solutions for treatment with the UV-H_2O_2 process.

Several biodegradation studies are available from the registration dossier. The ready biodegradability was investigated by a modified MITI test (following OECD TG 301C). Resorcinol was added to non-adapted activated sludge at a concentration of 100 mg/L. The degree of biodegradation was 66.7 % (BOD) after 14 days at 25 °C and pH 7 and 100 % TOC removal after 14 days (Kitano, 1978). Based on the results of the study, resorcinol can be considered as readily biodegradable under aerobic conditions. Only limited information is available for this study, but the DS considered it valid and reliable for classification purposes.

BOD5/COD was determined for resorcinol with the value of ca. 1.74 demonstrating the rapid degradation of resorcinol (Pitter, 1976).

No simulation studies are available.

Based on the result of ready biodegradability study supported by the BOD5/COD value, the DS considered resorcinol to be rapidly degradable.

Bioaccumulation

A study on the bioaccumulation behaviour of the substance is not available. Based on a measured log K_{ow} of 0.8 at 20 °C (REACH registration dossier) being below the CLP criterion of 4, the DS considered resorcinol to have a low potential for bioaccumulation.

Aquatic toxicity

Acute and chronic aquatic toxicity studies are available for three trophic levels.

Acute Aquatic Toxicity

The table below shows a summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results	Remarks	Reference
Fish					
Methods for Acute Toxicity Tests (EPA-660/3/75-009) GLP compliance not specified 96 h flow-through test	*Pimephales promelas*	resorcinol No information on purity of the test material	96h LC_{50}: 26.8 – 29.5 mg/L (mean measured)	2 (reliable with restrictions) Key study	Anonymous (1981a)
Fish short term toxicity study (test guideline not specified) GLP compliance not specified	*Leuciscus idus*	resorcinol (99% purity)	96h LC_{50}: 34.7 mg/L (nominal)	2 (reliable with restrictions) Supporting study	Anonymous (1981b)
In house method, similar to OECD TG 203 GLP compliance not specified 96h semi-static test	*Gambusia affinis*	resorcinol (analytical grade)	96h LC_{50}: 181 mg/L (nominal) 72h LC_{50}: 184 mg/L	2 (reliable with restrictions) Supporting study Rate of oxygen uptake was significantly decreased at higher concentrations.	Anonymous (2000)
Methods for Acute Toxicity Tests (EPA-660/3/75-009) No GLP compliance	*Pimephales promelas*	resorcinol (industrial grade)	96h LC_{50}: 49.5 mg/L (measured concentration)	2 (reliable with restrictions) Supporting study	Anonymous (1979)
Method not described in the registration dossier GLP compliance not specified 96h flow-through test	*Pimephales promelas*	resorcinol No information on purity of the test material	96h LC_{50}: 100 mg/L (nominal)	2 (reliable with restrictions) Supporting study	Anonymous (1980)
Method not described in the registration dossier GLP compliance not specified 96h flow-through test	*Oncorhynchus mykiss*	resorcinol No information on purity of the test material	96h LC_{50}: >100 mg/L (nominal)	2 (reliable with restrictions) Supporting study	Anonymous (1980)
Aquatic invertebrates					
OECD TG 202 GLP compliant 48h semi-static	*Daphnia magna*	resorcinol (99,75%)	48h LC_{50}: 1.0 mg/L (geom. mean measured) 48h LC_{50}: 1.3 mg/L (nominal)	1 (reliable without restriction) Key study	Harlan (2010)

Non-guideline study GLP compliance not specified 48h flow-through test	*Daphnia pulicaria*	resorcinol No information on purity of the test material multi-test substance study	48h LC_{50}: > 100 mg/L (nominal)	2 (reliable with restrictions) Supporting study	DeGraeve (1980)
Non-guideline study GLP compliance not specified 48h static test	*Daphnia magna*	resorcinol No information on purity of the test material	48h LC_{50}: 1.28 mg/L (nominal)	2 (reliable with restrictions) Supporting study	Herbes & Beauchamp (1977)
Methods for Acute Toxicity Tests (EPA 660/3-75-009) No GLP compliance 96h static test	Daggerblade grass shrimp *(Palaemonetes pugio)*	resorcinol No information on purity of the test material	96h LC_{50} (mortality): 42.2 mg/L (nominal) and 32.7 mg/L (direct photometric measurement of phenol concentration)	2 (reliable with restrictions) Supporting study Saltwater media	Curtis (1979)
Algae					
OECD TG 201 GLP compliant 72h static test	*Pseudokirchneriella subcapitata*	resorcinol No information on purity of the test material	72h EC_{50} (growth rate): > 97 mg/L (measured) 72h EC50 (biomass): > 97 mg/L	1 (reliable without restriction) Key study Limit test	Springborn (2006)
Non-guideline study GLP compliance not specified 72h static test (saltwater)	Diatom *(Nitzchia Closterium)*	resorcinol No information on purity of the test material	89 % inhibition compared to control based on growth rate (55.05 mg/L nominal)	2 (reliable with restrictions) Supporting study	Florence & Stauber (1986)

For **fish**, 1 key study and 5 supporting studies are available, all based on non-OECD protocols, but which are claimed similar to OECD TG 203. The DS considered them valid and reliable for the classification purposes.

The lowest value was obtained in a test following EPA-660/3/75-009 on fathead minnows (*Pimephales promelas*) under flow through conditions (96h LC_{50} = 26.8 mg/L, mean measured).

Four studies were provided for **aquatic invertebrates**, all of them were considered valid and reliable by the DS. The key study was a 48h semi-static study with *Daphnia magna*, conducted according the OECD TG 202 and GLP compliant (Harlan, 2010). The nominal test concentrations were 0.10, 0.18, 0.32, 0.56, 1.0, 1.8, 3.2, 5.6 and 10 mg/L. A 48h LC_{50}

value of 1.3 mg/L was calculated based on nominal concentrations as analytically verified test concentrations ranged from 92 % to 104 % of initial test concentrations. An LC_{50} value of 1.0 mg/L (95 % confidence limit of 0.041 – 27 mg/L) based on the geometric mean measured concentrations was calculated.

For **algae** two studies were provided: an OECD TG 201 study, for *Pseudokirchneriella subcapitata* (Springborn, 2006) and a study on the marine diatom *Nitzschia closterium* (Florence & Stauber, 1986*).* The key study is Springborn (2006) during which algae were exposed for 72 hours to mean measured concentrations of 3.0, 5.8, 12, 24, 47 and 97 mg/L of resorcinol (nominal test concentrations = 3.1, 6.3, 13. 25. 50 and 100 mg/L from Registration Dossier). The 72h E_bC_{50} and E_rC_{50} values (biomass and growth rate) were both greater than the highest mean measured concentration tested (> 97 mg/L).

These acute toxicity studies with algae are considered valid and reliable for classification purposes.

Chronic Aquatic Toxicity

The table below shows a summary of relevant information on chronic aquatic toxicity.

Method	Species	Test material	Results	Remarks	Reference
Fish					
Similarities with OECD TG 210 (early draft) GLP compliance not specified 60d semi-static test	*Oncorhynchus mykiss*	resorcinol (≥99% purity)	60d LOEC: 320 mg/L (mortality, total embryotoxicity) 60d LOEC: 100 mg/L (length) 32 mg/L (weight) Based on nominal concentrations	2 (reliable with restrictions) Key study	Anonymous (1990) *
OECD TG 212 GLP compliance not specified 7d semi-static test	*Danio rerio*	resorcinol (≥ 99% purity)	7d LOEC (mortality): 320 mg/L 7d LOEC (total embryotoxicity): 100 mg/L Based on nominal concentrations	2 (reliable with restrictions) Supporting study	Anonymous (1990) *
Aquatic invertebrates					
OECD TG 211 GLP compliant 21d flow-through test	*Daphnia magna*	resorcinol (USP Grade Flake) 99.96 % purity	21 d NOEC (reproduction): > 0.172 mg/L (mean measured, highest test concentration) No adverse effects observed at the highest test concentration	1 (reliable without restriction) Key study	Springborn (2004)

Algae					
OECD TG 201 GLP compliant 72h static test	*Pseudokirchneriella subcapitata*	resorcinol No information on purity of the test material	72h NOEC (biomass): 47 mg/L (measured) 72h NOEC (growth rate): 97 mg/L (highest mean measured dose tested)	1 (reliable without restriction) Key study Limit test	Springborn (2006)

*The Registration dossier provided Van Leeuven *et al*. (1990) as Reference

For **fish**, the DS reported two results (for *Oncorhynchus mykiss* and *Danio rerio*) claimed valid and reliable with restrictions (K2). The lowest value is a 60-day LOEC (weight) value of 32 mg/L for *Oncorhynchus mykiss* indicated as key study (Anonymous, 1990).

It is noted that the actual toxicity values may have been lower as no analytical monitoring was performed in the study and Resorcinol is demonstrated to be susceptible to biodegradation during the aquatic long-term tests for *Daphnia magna* (Springborn, 2004).

For **aquatic invertebrates,** a 21-day flow-through study according to OECD TG 211 and GLP compliant was performed with *Daphnia magna*. The daphnids were exposed to mean measured concentrations of 11, 35, 53, 111 and 172 µg/L of resorcinol (nominal test concentrations were 25, 50, 100, 200 and 400 µg/L). No adverse effects were observed at the end of the study for the reproduction, mortality, total body length or dry weight endpoints and the DS considered the NOEC value as ≥ 172 µg/L (mean measured), that corresponds to the highest concentration tested.

For **algae,** the DS reported the outcomes of the OECD TG 201 study on *Pseudokirchneriella subcapitata* (Springborn, 2006) exposed for 72 hours (mean measured concentrations of 3.0, 5.8, 12, 24, 47 and 97 mg/L of resorcinol (nominal test concentrations = 3.1, 6.3, 13. 25. 50 and 100 mg/L according to Registration dossier). The mean measured NOEC value for growth inhibition (biomass) endpoint was 47 mg/L and 97 mg/L (highest mean measured dose tested) for the growth rate endpoint.

Comments received during consultation

Three Member States and a National Authority commented on the environmental classification proposals.

The National Authority asked for additional information about the key biodegradation study (Kitano, 1978) since limited data are available and the DS considers it to be Klimisch 2. However, the National Authority recognised that the wider fate data in the CLH report appear to support the substance being considered as rapidly degradable; moreover, they asked if there are useful QSAR predictions to support this weight of evidence position.

The DS agreed that the study had shortcomings due to limited documentation, but no further information was found in the existing databases. However, it can be concluded that resorcinol is rapidly degradable based on the Kitano (1978) study together with the supporting information in the classification proposal. In addition, the DS provided Biowin V4.10 model predictions supporting the conclusion that resorcinol is rapidly degradable.

The Member States supported the DS proposal of Aquatic Acute 1 with an M-factor of 1. However, one of them suggested adding the chronic classification as Aquatic Chronic 3

(H412) according to criteria set in table 4.1.0 (b) (ii) and an observed 21d NOEC for *Daphnia magna* of ≥ 172 µg/L. Although the NOEC value could have been higher than the highest concentration tested, as the Member State considered chronic toxicity values likely to be below the 48h EC_{50} for *Daphnia magna* (same species) of 1.0 mg/L, the Member State hypothesized that the NOEC value could be between 0.172 and 1.0 mg/L, triggering to a chronic classification as Aquatic Chronic 3.

The DS responded that the long-term aquatic hazard classification was not warranted in the range of 0.172 – 1.0 mg/L, considering that no information is available for the aquatic chronic toxicity for *Daphnia magna* in the range of 0.172 – 1.0 mg/L and resorcinol being rapidly degradable and non-bioaccumulative.

Assessment and comparison with the classification criteria

RAC noted that the DS provided relevant acute and chronic aquatic toxicity studies for three trophic levels. RAC agrees with the DS that invertebrate is the most sensitive trophic level.

Degradation

RAC agrees with the DS proposal to consider resorcinol as rapidly degradable. The substance can be considered readily biodegradable, even if the information about the study is limited regarding the test design and validity. BOD5/COD value of 1.74 (greater than 0.5) supports the conclusion that resorcinol is rapidly degradable.

Bioaccumulation

No BCF data is available for resorcinol but based on experimental data, resorcinol has a measured log K_{ow} of 0.8. Therefore, RAC agrees with the DS's proposal to consider that the bioaccumulation potential of resorcinol is low.

Aquatic toxicity

For the fish trophic level, RAC noted some critical issues that do not allow clear conclusions on the reliability. Indeed, the studies are not carried out according to standard test guidelines, although they are claimed similar to OECD TG. No information is provided on the validity criteria for the OECD protocols, as, for instance, demonstrating that the concentrations of the test substance in solution have been satisfactorily maintained within $\pm$ 20% of the mean measured values, in particular for the chronic tests for which only nominal concentrations are provided.

However, despite the above shortcomings, RAC agrees that fish is not the most sensitive trophic level for the aquatic toxicity.

Regarding the proposal of a commenting Member State to classify resorcinol as Aquatic Chronic 3, RAC agrees with the DS's response confirming that the long-term aquatic hazard classification is not warranted, considered that: a) no adverse effect was observed up to the highest test concentration of 0.172 mg/L for the most sensitive organism *Daphnia magna*; b) no information is available for aquatic chronic toxicity in the range 0.172 – 1.0 mg/L for *Daphnia magna,* and c) resorcinol is rapidly degradable and non-bioaccumulative. Furthermore, RAC notes that for all the tested organisms no chronic adverse effects are

observed below the criteria of 1 mg/L set out in CLP Table 4.1.0(b)(ii) for rapidly degradable substances.

However, RAC considers that the classification might be revised in case new data becomes available demonstrating long-term effects.

Comparison with the criteria

For acute aquatic toxicity, relevant information is provided for fish, aquatic invertebrates, and algae, indicating that invertebrates are the most sensitive trophic level. Based on the key study on *Daphnia magna* (Harlan, 2010) the lowest 48h LC_{50} value for was 1.0 mg/L (mean measured).

Therefore, RAC agrees that, based on the 48h EC_{50} value being in the range 0.1 mg/l < $L(E)C_{50}$ ≤ 1 mg/l, for resorcinol, hazard classification as Aquatic Acute 1 (H400) with an M-factor of 1 is warranted.

For chronic aquatic toxicity, relevant information is provided for fish, aquatic invertebrates, and algae, all indicating no classification for chronic hazards.

No adverse effects are observed for resorcinol for any of the tested organisms below the criteria of 1 mg/L set out in CLP Table 4.1.0(b)(ii) for rapidly degradable substances. For the most sensitive species (also under acute testing, invertebrate: *Daphnia magna*) no adverse effects were observed at the highest test concentration (NOEC > 0.172 mg/L).

In conclusion, RAC agrees that based on the available information, no long-term aquatic hazard classification is warranted for resorcinol.

Conclusion

RAC agrees with the DS that resorcinol warrants classification as **Aquatic Acute 1, M = 1.**

12 EVALUATION OF ADDITIONAL HAZARDS

Not assessed in this dossier.

13 ADDITIONAL LABELLING

Not applicable.

14 REFERENCES

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SCCS (2021) *Opinion on Resorcinol.* SCCS/1619/20 (final opinion, adopted March 2021)

15 ANNEXES

None