EUROPEAN COMMISSION

Health & Consumer Protection
Directorate-General

Scientific Committee on Consumer Products

SCCP

OPINION ON

Resorcinol

COLIPA n° A11

Scientific Committees
on consumer products
on emerging and newly identified health risks
on health and environmental risks

The SCCP adopted this opinion at its 15th plenary of 15 April 2008

About the Scientific Committees
Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Evaluation Agency (EMEA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCP
Questions concerning the safety of consumer products (non-food products intended for the consumer).
In particular, the Committee addresses questions related to the safety and allergenic properties of cosmetic products and ingredients with respect to their impact on consumer health, toys, textiles, clothing, personal care products, domestic products such as detergents and consumer services such as tattooing.

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Opinion to be cited as: SCCP (Scientific Committee on Consumer Products), Opinion on resorcinol, 15 April 2008

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1. BACKGROUND

Submission I for resorcinol with the chemical name 1.3-dihydroxybenzene was submitted in August 1980 by COLIPA [1, 2].

Submission II for this substance was submitted in June 1985 by COLIPA[2].

Submission III for this substance was submitted in March 1987 by COLIPA[2].

The Scientific Committee on Cosmetology (SCC) has expressed its opinion at the meeting on 10-11 October 1988 with the conclusion:

"*The SCC does not consider the use of resorcinol in the hair dyes to be linked to any particular toxic risk for consumers. National Toxicology Program's result might confirm the absence of any type of toxic risk in the use of resorcinol*".

Submission IV for this substance was submitted in December 1993 by COLIPA.

SCC has at the 54th plenary meeting of 10 December 1993 confirmed its conclusion: "The SCC does not consider the use of resorcinol in hair dyes to be linked to any particular toxic risk for consumers".

The substance is currently regulated by the Cosmetics Directive (76/768/EC), Annex III, Part 1 under entry 22 on the List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down.

Submission V of Resorcinol was submitted by COLIPA in July 2005. According to this submission resorcinol is used in oxidative hair colouring products at a maximum concentration of 2.5%, which after mixing in a 1:1 ratio with hydrogen peroxide just prior to use, corresponds to a concentration of 1.25% upon application.

Submission V presents updated scientific data on the above mentioned substance in line with the second step of the strategy for the evaluation of hair dyes (http://europa.eu.int/comm/enterprise/cosmetics/doc/hairdyestrategyinternet.pdf) within the framework of the Cosmetics Directive 76/768/EEC.

2. TERMS OF REFERENCE

1. *Does the Scientific Committee on Consumer Products (SCCP) consider resorcinol safe for use as an oxidative hair dye with a concentration on the head of maximum 1.25% taken into account the scientific data provided?*

2. *Does the SCCP recommend any restrictions with regard to the use of resorcinol in oxidative hair dye formulations?*

[1] COLIPA - European Cosmetics Toiletry and Perfumery Association
[2] According to records of COLIPA

3. OPINION

3.1. Chemical and Physical Specifications

3.1.1. Chemical identity

3.1.1.1. Primary name and/or INCI name

Resorcinol (INCI)

3.1.1.2. Chemical names

1,3-Dihydroxybenzene
1,3-Benzenediol
m-Dihydroxybenzene
m-Hydroquinone
3-Hydroxyphenol
m-Phenylenediol
Resorcin

3.1.1.3. Trade names and abbreviations

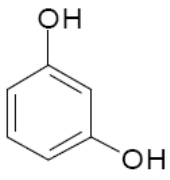
Colorex RES-CG
Covastyle RCN
Jarocol RL
Rodol RS
Rodol RS TECH
Rodol RS TECH SP
Rodol RS USP-C
Rodol RS USP-F
Unichem RSC

COLIPA n° A11

3.1.1.4. CAS / EINECS number

CAS: 108-46-3
EINECS: 203-585-2

3.1.1.5. Structural formula



3.1.1.6. Empirical formula

Formula: $C_6H_6O_2$

3.1.2. Physical form

Light pink flakes

3.1.3. Molecular weight

Molecular weight: 110.11

3.1.4. Purity, composition and substance codes

Description	Batch			
	706030517	**03346009**	**IN-79-7087**	**706010501**
Identification/ characterisation	MS, IR, NMR, UV, HPLC, Elemental analysis	IR, UV, HPLC	IR, NMR UV, HPLC	NMR, UV, GC-FID
Titre[1] (g/100 g)	98.8	> 98.4	> 99	
HPLC content (% peak area)	> 99.5	> 99.5	> 99*	100% (GC peak area)
Impurities[2] (g/100 g)	see 3.1.5	< 0.5	< 0.5	see 3.1.5
Water content (µg/g)	< 50			
Loss on drying (g/100g)	< 0.1			

[1] Bromination in an acetic acid medium, potassium iodide addition and titration of the liberated iodine with sodium thiosulfate.
[2] Informed total impurity
* *102% relative to the USP standard*

3.1.5. Impurities / accompanying contaminants

Batch n° 706030517
Hydroquinone <0.01% (w/w)
Pyrocatechol <0.01% (w/w)
Orcinol <0.01% (w/w)
Phenol <0.01% (w/w)
Ag, Al, As, Ba, Bi, Cd, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pb, Pd, Pt, Sb, Se, Sn, Ti, V, Zn: each < 1 mg/kg
Hg: < 0.1 mg/kg

Solvent residues: Less than 100 µg/g of solvents such as methanol, ethanol, isopropanol, n-propanol, acetone, ethyl-acetate, cyclohexane, methylethyl ketone and monochlorobenzene

Possible impurities (g/100 g) in USP resorcinol 706010501 Lot No. 02-77RP-1 (described in 2-generation drinking water study), reanalysis by capillary GC

Phenol	0.002
o-Cresol	< 0.001
2,6-xylenol	< 0.001
m-Cresol	< 0.001
3,5-xylenol	< 0.001
Catechol	< 0.005
Mercaptophenol	< 0.02
Methylresorcinol	< 0.001
Unknowns (No.)	0.035 (3)
2,2'-Biphenyldiol	< 0.001
Unknowns (No.)	0.001(3)
2,5-Biphenyldiol	< 0.001
Unknowns (No.)	< 0.005
3,4-Biphenyldiol	< 0.005
Unknowns (No.)	< 0.005
3,3'-Biphenyldiol	< 0.005
3,4'-Biphenyldiol	< 0.005
4,4'-Biphenyldiol	< 0.01
Unknowns (No.)	< 0.01
THD isomer	< 0.01
Unknowns (No.)	< 0.01
2,4,3'-THD	< 0.01

3.1.6. Solubility

Water: 678 ± 21 g/L at 20 °C (according to EEC Method A6)
Ethanol: ≥ 20 g/100 ml at 22 °C after 24h
DMSO: ≥ 20 g/100 ml at 22 °C after 24h

3.1.7. Partition coefficient (Log P_{ow})

Log Po/w: 0.04 at 24°C and pH 7.2 (Experimental value according EEC Method A8 – HPLC)

3.1.8. Additional physical and chemical specifications

Melting point:	108-111 °C
Boiling point:	276-280 °C
Flash point:	/
Vapour pressure:	0.03 Pa at 25 °C
Density:	/
Viscosity:	/
pKa:	/
Refractive index:	/
pH:	/
UV_Vis spectrum:	absorption maxima at 275.8 nm and at 281.6 nm

3.1.9. Stability

Resorcinol was stable in the dosage forms at 0.1 and 200 mg/mL in purified water over a 6-hour period at room temperature and over a 9-day period at +4°C, protected from light and under inert gas atmosphere; at 0.1 and 250 mg/mL in DMSO and at 0.1, 10 and 500 mg/mL in DMF over a 4-hour period at room temperature, protected from light and under inert gas atmosphere: deviation from the original concentration were in the range of -5 to +3%.

Ref.: 11

Batch 706010501
Solutions of 300 ng resorcinol/mL and 1000 ng resorcinol/mL in a HPLC mobile phase (water/acetonitrile, 85/15) stored at room temperature were shown to be stable up to 7 days:

300 ng /mL, storage time 7 days, concentration 104% of the original concentration,
1000 ng/mL, storage time 3 days, concentration 90.2% of the original concentration

The solutions of 5000 ng resorcinol/mL in a HPLC mobile phase (water/acetonitrile, 85/15) stored at room temperature were less stable up to 7 days: concentration 88.4-89.8% of the original concentration

1000 ng resorcinol/mL and 5000 ng resorcinol/mL plasma were stable at room temperature up to 4 hours: concentrations 90.9- 93.7% of the original concentration

Decay of resorcinol in 1000 ng resorcinol/mL plasma and 5000 ng resorcinol/mL plasma, stored frozen (-20°C), was 10% in 29 days, 20% in 61 days and 50% in 191 days.

The water solutions of resorcinol (120 -3000 mg/L), used in the 2 generation drinking water study, were stable up to 24 days: concentration 95.3 - 100 % after storage at room temperature for 15 days, and 87.5-96.1% after storage at room temperature for 24 days.

The water solutions of resorcinol, used in the 2 generation drinking water study, were shown to be homogeneous after storage for 1, 8 and 15 days in a refrigerator (range 95.7-102% of the original concentration)

Ref.: 12

General Comments to physico-chemical characterisation

- The stability of resorcinol in the marketed products is not described.

3.2. Function and uses

Resorcinol is used in oxidative hair colouring products at a maximum concentration of 2.5%, which after mixing in a 1:1 ratio with hydrogen peroxide just prior to use, corresponds to a concentration of 1.25% upon application.

3.3. Toxicological Evaluation

3.3.1. Acute toxicity

3.3.1.1. Acute oral toxicity

Guideline:	OECD 420 (fixed dose method)
Species/strain:	Rats, Sprague-Dawley Rj:SD (IOPS Han)
Group size:	5 females
Test substance:	Resorcinol
Batch:	706030517
Purity:	98.8%
Dose:	200 mg/kg bw
Route:	Oral by gavage
Exposure:	single oral dosing
GLP:	in compliance
Date:	18 February – 23 March 2004

A sighting test was performed in three female rats at doses of 200, 500 and 2000 mg/kg bw to determine the dose level for the principal study. Based on the results of the preliminary study, the main study was performed in a group of 4 female rats at the dose of 200 mg/kg bw.
Animals were observed at least once daily for mortality/morbidity and daily for clinical signs over a period of 14 days following a single administration of the test substance. Body weights were recorded on day 1 prior to treatment, and on days 7 and 14 thereafter. All study animals were subjected to a macroscopic examination as soon as possible after death.

Results
In the sighting experiment, the animal treated at 2000 mg/kg bw died within 15 minutes of treatment; tonic-clonic convulsions were observed prior to death. At 500 mg/kg bw, death occurred within 20 minutes of treatment. Piloerection and dyspnoea were observed within two hours of treatment at 200 mg/kg bw.
In the main experiment, no mortality occurred at 200 mg/kg bw. Hypoactivity, dyspnoea and tremors were observed in all animals on day 1. Recovery was complete on day 2. No effect on body weight gain and no gross abnormalities were observed.

Conclusion
The maximal non-lethal dose of resorcinol was 200 mg/kg bw.

Ref.: 1

3.3.1.2. Acute dermal toxicity

No data submitted

3.3.1.3. Acute inhalation toxicity

No data submitted

3.3.2 Irritation and corrosivity

3.3.2.1. Skin irritation

Guideline:	OECD 404
Species:	New Zealand White rabbits
Group:	3 male
Substance:	resorcinol
Batch:	706030517
Purity:	98.8%
Dose:	0.5 mL of a 2.5% solution
Vehicle:	water
GLP:	in compliance
Date:	17 - 22 February 2004

The cutaneous irritation potential of resorcinol at a concentration of 2.5% in water was assessed. A single dose of 0.5 mL of resorcinol was placed on a dry gauze pad and then applied to a clipped area on the posterior right flank (4 hours), the anterior right flank (1 hour) and the left flank (3 minutes) of one animal. The gauze pads were held in place under a semi-occlusive dressing and a restraining bandage. Untreated skin served as a control.
Because the dosage form was not irritant in the first animal, it was applied for 4 hours to the two additional animals.
The skin was examined at 1, 24, 48 and 72 hours after removal of the dressing, and then daily until day 4 in the absence of persistent irritation reactions.

Results
No cutaneous reactions were observed in any of the animals tested.

Conclusion
A 2.5% aqueous solution of resorcinol was not irritant when applied to rabbit skin.

Ref.: 2

3.3.2.2. Mucous membrane irritation

Guideline:	OECD 405
Species:	New Zealand White rabbits
Group:	3 males
Substance:	resorcinol
Batch:	706030517
Purity:	98.8%
Dose:	0.1 mL of 2.5% solution
Vehicle:	water
GLP:	in compliance
Date:	24 – 29 February 2004

The ocular irritation potential of resorcinol at a concentration of 2.5% in purified water was assessed. Because the possibility of irritant effects was suspected, the test substance was first administered to a single animal. As it was not irritant, it was evaluated in two additional animals.
A single dose of 0.1 mL of a preparation of resorcinol was placed into the conjunctival sac of the left eye of the animals. The upper and lower lids were held closed for about 1 second to avoid any loss of the test substance. The eyes were not rinsed after administration of the test substance. The untreated right eye of each animal served as a control. Evaluations of the conjunctiva, cornea and iris were made 1 hour after compound administration, and at 24, 48 and 72 hours thereafter.

Results
Grade 1 conjunctival redness was observed in 2/3 animals on day 1 or day 2. No other ocular lesions were observed during the study.

Conclusion
A 2.5% aqueous solution of resorcinol caused mild conjunctival irritation to the rabbit eye.
Ref.: 3

3.3.3. Skin sensitisation

Local Lymph Node Assay (LLNA)

Guideline:	OECD 429
Species:	CBA/J mice
Group:	two independent experiments were performed in 7 groups of 4 mice; fifty-six (56) female
Substance:	resorcinol
Batch:	706030517
Purity:	98.8%
Dose:	experiment 1: 2.5%, 5%, 10%, 25% and 50% Experiment 2: 0.1%, 0.5%, 1%, 5% and 25%
Vehicle:	dimethylformamide
Control:	25% (v/v) α-hexylcinnamaldehyde in DMF
GLP:	in compliance
Date:	17 February – 14 June 2004

The sensitisation potential of resorcinol in dimethylformamide (DMF) was assessed. A preliminary test was performed in four (4) female mice to determine the irritant potential of the test compound. The maximum practicable, non-irritant concentration was found to be 50%.
For the principal study, two independent experiments were performed in 7 groups of 4 mice. The dose volume of 25 µl was applied to the dorsal surface of both ears once daily for 3 days. In the first experiment, concentrations of 2.5%, 5%, 10%, 25% and 50% resorcinol were tested. Vehicle control animals received DMF, while positive control animals received 25% (v/v) α-hexylcinnamaldehyde in DMF. A second experiment was performed at the concentrations of 0.1%, 0.5%, 1%, 5% and 25% resorcinol to more precisely determine the EC_3 value.

On days 1, 2, 3 and 6 of each experiment, the thickness of the left ear was measured and any irritation reactions recorded to assess any possible irritant effect of the test item. Ear thickness was not measured in the positive control group.
On day 6 of each experiment, all animals were administered 250 µl of 0.9% NaCl containing 20 µCi of tritiated thymidine (^{3}H-TdR). After approximately 5 hours, they were killed and the auricular lymph nodes excised. The nodes from each group were pooled, a suspension

of auricular lymph node cells prepared, and proliferation of these cells measured using β-scintillation counting. The results were used to calculate the Stimulation Index (SI) for proliferation. The EC3 value (the theoretical concentration resulting in an SI value of 3) was subsequently determined.

Results
Lymphoproliferative responses observed in negative control groups fell within historical ranges, while significant lymphoproliferation was observed with α-hexylcinnamaldehyde at 25%, thus validating the sensitivity of the test system and procedure used.
No mortality and no clinical signs were observed in the first experiment. In the second experiment, hypoactivity, piloerection and dyspnoea were observed on day 3 in 1/4 and 2/4 animals of the treated groups given 1% and 5%, respectively. No cutaneous reactions and no increase in ear thickness were observed at any tested concentrations.

Dose	SI
Resorcinol 2.5%	3.83
Resorcinol 5.0%	4.14
Resorcinol 10%	3.97
Resorcinol 25%	3.51
Resorcinol 50%	3.30
α-hexylcinnamaldehyde 25% (v/v)	7.48

In the first experiment, positive lymphoproliferative responses (SI>3) were noted at all tested concentrations, but no clear dose-response relationship was observed.

Dose	SI
Resorcinol 0.1%	1.58
Resorcinol 0.5%	2.87
Resorcinol 1%	1.97
Resorcinol 5%	3.51
Resorcinol 25%	5.74
α-hexylcinnamaldehyde 25% (v/v)	6.97

In the second experiment, a dose-related increase in SI was observed (except at the concentration of 1%) and the threshold positive value of 3 was exceeded at concentrations ≥ 5%. The EC3 value for this experiment was 1.4%.

Conclusion
Resorcinol induced contact sensitisation in this study. The EC3 value indicated that it should be considered as a strong sensitiser.

Ref.: 4

3.3.4. Dermal / percutaneous absorption

Guideline:	OECD 428
Tissue:	Human dermatomed skin, female breast, abdomen; 350-400µm in thickness
Group size:	8 donors
Diffusion cells:	flow-through diffusion (7/10 chambers analysed in oxidative conditions, and 12/12 chambers analysed in non-oxidative conditions)
Skin integrity:	permeability coefficient for tritiated water (< $2.5.10^{-3}$ cm/h for all selected membranes)
Test substance:	resorcinol

Batch:	706030517
Purity:	98.8%
Radiolabel	[U-^{14}C]-resorcinol
Radiolabel batch	SEL/1398
Radiolabel purity	> 99%
Test item:	oxidative conditions: typical hair colouring formulation at 2.50% (w/w) associated with p-phenylenediamine (PPD) at 2.45% (w/w) before mixing with hydrogen peroxide (1:1, w/w) to give a final concentration of 1.25% (w/w) Non-oxidative conditions: same formulation devoid of primary intermediate at 2.50% (w/w) before mixing with water (1:1, w/w) to give a final concentration of 1.25% (w/w).
Doses:	20 mg/cm² of oxidative and non-oxidative test preparations.
Receptor fluid:	calcium- and magnesium-free PBS Buffer
Solubility receptor fluid:	>100 g/L in water
Stability:	/
Method of Analysis:	liquid scintillation counting
GLP:	in compliance
Date:	25 August – 9 October 2004

Human skin samples (4 breast and 4 abdomen) were obtained from eight female donors subjected to plastic surgery. They were kept frozen at *ca* -20°C until use.
Skin samples were dermatomed (350-400 µm in thickness) and mounted in flow-through diffusion cells with calcium- and magnesium-free PBS Buffer as the receptor fluid. Their integrity was verified by measuring the permeability coefficient for tritiated water ($< 2.5.10^{-3}$ cm/h for all selected membranes) prior to application of the hair dye formulations. The skin was maintained at *ca* 32°C.

Resorcinol was tested under both oxidative and non-oxidative conditions.
Under oxidative conditions, it was incorporated into a typical hair colouring formulation at 2.50% (w/w) associated with p-phenylenediamine (PPD) at 2.45% (w/w) before mixing with hydrogen peroxide (1:1, w/w) to give a final concentration of 1.25% (w/w).
Under non-oxidative conditions, it was incorporated into the same formulation devoid of primary intermediate at 2.50% (w/w) before mixing with water (1:1, w/w) to give a final concentration of 1.25% (w/w).

Twenty (20) mg/cm² of oxidative and non-oxidative test preparations were applied to the skin surface for 30 minutes. After this time period, the remaining formulation on the skin surface was removed using a standardized washing procedure.
Twenty-four hours after application, the percutaneous absorption of resorcinol was estimated by measuring its concentration in the following compartments using liquid scintillation counting: dislodgeable dose, *stratum corneum* (isolated by tape strippings), skin (living epidermis + dermis) and receptor fluid.

Results
Seven out of ten (7/10, oxidative conditions) and twelve samples (12/12, non-oxidative conditions) yielded data that could be analysed for the oxidative and the non-oxidative conditions, respectively. Three chambers used in the oxidative experiments were rejected because low mass balance (>10%).
The dermal delivery (sum of the amounts measured in the living epidermis, dermis and receptor fluid) was 1.04 ± 0.51 µg/cm² (range 0.37 to 2.0 µg/cm²); 0.40 ± 0.18 % (range 0.15 to 0.74%) under oxidative conditions. Chamber 6, one of the chambers rejected because of poor mass balance, had a dermal delivery of 4.10 µg/cm².
The dermal delivery (sum of the amounts measured in the living epidermis, dermis and receptor fluid) was 2.95 ± 2.22 µg/cm² (range 0.96 to 8.67 µg/cm²); 1.16 ± 0.88% (range 0.36 to 3.42%) non-oxidative conditions.

Conclusion
The dermal absorption (sum of the amounts measured in the living epidermis, dermis and receptor fluid) of resorcinol incorporated at 1.25% (final concentration) in a typical oxidative hair dye formulation containing 1.25% resorcinol (final) was determined to be 1.04 ± 0.51 µg/cm² of the applied dose with an A_{max} of 2.0 µg/cm².

Ref.: 13

Comment
As too few chambers were used, an A_{max} of 2.0 µg/cm² may be used for calculating the MOS of resorcinol under oxidative conditions.

3.3.5. Repeated dose toxicity

3.3.5.1. Repeated Dose (28 days) oral / dermal / inhalation toxicity

No data submitted

3.3.5.2. Sub-chronic (90 days) oral / dermal / inhalation toxicity

Guideline:	OECD 408
Species/strain:	rat, Sprague-Dawley, Crl CD® (SD) IGS BR
Group size:	20/group (10 males and 10 females), 12 (6 males and 6 females) in satellite group
Test substance:	Resorcinol
Batch:	706030517
Purity:	98.8%
Dose:	0, 40, 80, 250 mg/kg bw
Route:	oral
Exposure:	once a day by oral gavage for at least 13 weeks (93 days)
GLP:	in compliance
Date:	15 April – 24 August 2004

Four groups of 10 male and 10 female Sprague-Dawley rats received the test item, (A011, batch No 70603051), daily by gavage at 0, 40, 80 or 250 mg/kg bw/day for at least 13 weeks. Vehicle was degassed purified water. At 0 and 250 mg/kg bw/day (groups 1 and 4), six animals of each sex were treated for 13 weeks and then kept for a 4-week treatment-free period. Six animals of each sex in groups 2, 3 and 4 were used for toxicokinetic investigations.
During the treatment period, animals were observed at least twice daily for mortality/morbidity and daily for clinical signs. Body weight was checked once a week. Detailed clinical observations were performed on each animal, in a standard arena, once before the beginning of the treatment period and then once a week until the end of the study. Any found dead animal was submitted to a macroscopic *post-mortem* examination.

Results
At 250 mg/kg bw/day, all males and females (including satellites) showed intermittent convulsive movements, starting between weeks 6 and 8 and lasting until the end of the treatment period. Also excessive salivation (majority of animals) and loud breathing (2 males) was reported in the 250 mg/kg bw/day group. Mortality was mentioned in the 80 mg/kg bw/day (2 males) and the 250 mg/kg bw/day dosage group (1 female). According to the study report, observed deaths at these dose levels were not treatment-related but may be caused by lung lesions due to incidental gavage errors. With the exception of the two males which had convulsions and died, no clinical observations were recorded at 80 mg/kg bw/day. No treatment-related effects on body weight, food consumption, blood and urine parameters, organ weights and necropsy findings were noted. The female group receiving 250 mg/kg bw/day gained slightly less weight (86% of the weight gained by the controls)

from week 4 to week 8. Examination of the animals during the Functional Observation Battery did not reveal any treatment-related effect.
Under the experimental conditions of the study, the NOEL was reported to be 80 mg/kg bw/day.

Ref.: 5

Comments
In the study described above, absolute and relative thyroid gland weight was slightly decreased (respectively -19% and -13%) in the 250 mg/kg bw/day group. According to the study authors, these effects were considered of no toxicological importance (no dose-response relationship and without relevant histopathological abnormalities). However, since also in the reproductive study effects on the thyroid were observed, these effects might be of relevance. For more discussion on the goitrogenic effects of resorcinol see section 3.3.14.

3.3.5.3. Chronic (> 12 months) toxicity

No data submitted

3.3.6. Mutagenicity / Genotoxicity

3.3.6.1 Mutagenicity / Genotoxicity *in vitro*

Bacterial reverse mutation assay

Guideline:	Not indicated
Species/strain:	TA 98, TA 100, TA 1535, TA 1537, TA102
Replicates:	Three replicates in two independent experiments
Test substance:	Resorcinol
Solvent:	Degassed purified water
Batch:	706030517
Purity:	> 95%
Concentrations:	Experiment 1: 1.6, 8, 40, 200, 1000, 5000 μg/plate Experiment 2: 51.2, 128, 320, 800, 2000 and 5000 μg/plate and TA 102 was also tested at: 3.28, 8.19, 20.48 μg/plate
Treatment:	Standard plate incorporation assay and experiment 2 with metabolic activation was done with the pre-incubation assay. Both experiments were conducted with and without Aroclor 1254 induced rat liver S9-mix.
GLP:	In compliance
Date:	24 March – 23 April 2004

Resorcinol was assayed for mutation in five histidine-requiring strains of *Salmonella typhimurium*, both in the absence and in the presence of metabolic activation.

An initial toxicity range-finder experiment was carried out in strain TA100 in the absence and presence of metabolic activation, using concentrations of resorcinol at 1.6, 8, 40, 200, 1000 and 5000 μg/plate, plus. Evidence of toxicity was observed at the highest dose level in the absence and presence of S9-mix, expressed as a marked decrease in revertant numbers. Negative (solvent) and positive controls were included according to OECD guidelines.

Results
In experiment 1, no toxicity was observed. In experiment 1, a statistically significant increase in revertants was observed at a single dose level for strains TA1537 (at 200 μg/plate) and TA102 (at 8 μg/plate) in the absence of S9-mix. These increases showed no evidence of a dose response, and were not reproducible in Experiment 2. No statistically

significant, dose-related increases in revertant numbers were observed in any other strain in the absence or presence of metabolic activation.
In experiment 2, evidence of toxicity in the form of a marked decrease in revertant numbers and/or a thinning of the background lawn was observed at the highest test dose for strains TA98 and TA1535 in the absence of S9-mix and strains TA98 and TA102 in the presence of S9-mix. There were no indications of any increase in revertant numbers in any tester strains or any concentrations tested.

Conclusion
Under the test conditions used, resorcinol did not induce gene mutations in bacteria.

Ref.: 6

In vitro Gene Mutation Assay (mouse lymphoma assay, $tk^{+/-}$ locus)

Guideline:	OECD 476
Species/strain:	Mouse lymphoma cell line L5178Y (*tk* locus)
Replicates:	Duplicates in two independent experiments
Test substance:	Resorcinol
Solvent:	DMSO
Batch:	706030517
Purity:	99.5% (Area% without response factor, UV detection)
Concentrations:	First experiment without S9-mix and second experiment with and without S9-mix: 5, 6, 7, 8, 9 and 10 mM First experiment with S9-mix: 0.313, 0.625, 1.25, 2.5, 5 and 10 mM
Treatment	3 h treatment with and without Aroclor induced S9-mix.
GLP:	In compliance
Date:	9 June – 16 August 2004

The test substance was examined for its mutagenic activity in the L5178Y $tk^{-/-}$ mouse lymphoma test in the absence and presence of metabolic activation. A preliminary toxicity test was conducted. Following the 3-hour treatment without S9-mix, a moderate to marked toxicity was noted at dose-levels ≥ 1 mM (50-75% decrease in adjusted relative suspension growth (Adj. RSG). Following the 3-hour treatment with S9 mix, a moderate to marked toxicity was observed at dose-levels ≥ 0.2 mM (51-77% decrease in Adj. RSG).

Results
The highest concentration tested, 10 mM (corresponding to 1100 µg/mL) showed no precipitation in the culture medium. Without metabolic activation, in both experiments, a moderate to marked toxicity was noted at all dose-levels as shown by 54-76% decrease in Adj. RSG. Significant increases in the mutation frequency (up to 4.8-fold the vehicle control value) were observed following the 3-hour treatment in both experiments. In the first experiment, the increase was clearly concentration related. In both experiments, there was an increase in large and in small colonies. In the second experiment, the increase was mainly in small colonies, indicating mutagenic as well as clastogenic potential.

With metabolic activation, a slight to marked toxicity was observed at dose-levels ≥ 5 mM, as shown by 30-78% decrease in Adj. RSG. In the first experiment, a clear concentration related increase in mutation frequency was observed. The increase was relatively weak and at the highest concentration (10 mM) a 1.9 fold increase was achieved compared to the control. This increase could not be reproduced in the second experiment, which did not indicate any increase in mutation frequency at the tested concentrations and is therefore not considered biological relevant.

Conclusion
Under the test conditions used Resorcinol is considered genotoxic (mutagenic and or clastogenic) in the absence of metabolic activation.

Ref.: 7

***In vitro* micronucleus test**

Guideline:	Draft OECD 487	
Species/strain:	Human peripheral blood lymphocytes from two female donors	
Replicates:	Duplicates in two independent experiments	
Test substance:	Resorcinol	
Solvent:	Purified water	
Batch:	706030517	
Purity:	>99.5% (Area% without response factor)	
Concentrations:	Experiment 1:	with S9-mix: 360.4, 563.2 and 704 μg/ml
	Experiment 1:	without S9-mix: 60.47, 75.59 and 94.49 μg/ml
	Experiment 2:	with S9-mix: 704, 880 and 1100 μg/ml
	Experiment 2:	without S9-mix: 94.49, 184.5 and 704 μg/ml
Treatment:	Experiment 1:	24 h mitogen stimulation followed by 20 h treatment + 28h recovery period (-S9-mix) 24 h mitogen stimulation followed by 3 h treatment + 45 h recovery period (+S9-mix)
	Experiment 2:	48 h mitogen stimulation followed by 20 h treatment + 28 h recovery period (-S9-mix) 24 h mitogen stimulation followed by 3 h treatment + 45 h recovery period (+S9-mix)
	Both experiments with and without Aroclor induced rat liver S9-mix	
GLP:	in compliance	
Date:	7 June – 20 July 2004	

To calculate the replication index (RI), 500 cells per replicate (1000 cells per dose) were examined for proportions of mononucleate, binucleate and multinucleate cells. 1000 binucleate cells from each culture (2000 cells per dose) were analysed for the occurrence of micronuclei. A broad concentration range (from 31 to 1100 μg/ml), separated by narrow intervals was evaluated for the test item to define as closely as possible the test concentration at which the replication index (RI) was reduced by approximately 60% This test concentration was used as the highest concentration to be evaluated. Two lower test concentrations were selected to cover a range of low (none) to maximum (60%) cytotoxicity.

Results
Experiment 1 with metabolic activation resulted in cytotoxicity between 23 to 55%. The frequency of micronucleated binucleate (MNBN) cells were significantly higher compared to the control at all three concentration tested in a dose dependent manner. Without metabolic activation cytotoxicity was between 0 to 60%. The frequency of MNBN cells was elevated and at the two highest concentrations a significant increase was observed.

Experiment two with metabolic activation resulted in cytotoxicity between 24 to 57%. There were no indications of an increase in frequencies of MNBN cells compared to the control. Without metabolic activation cytotoxicity was between 23 to 55%. The frequency of micronucleated binucleate (MNBN) cells were significantly higher compared to the control at all three concentration tested in a dose dependent manner.

Conclusion
Resorcinol induced micronuclei in cultured human peripheral blood lymphocytes following 20+28 hour treatment in the absence of metabolic activation, where treatment commenced either 24 or 48 hours following mitogen stimulation. Increased frequencies of micronucleated cells were also observed following 3+45 hour treatment in the presence of metabolic activation where treatment commenced 24 hours post mitogen stimulation. No

such increases in micronucleated cells were observed following 3+45 hour treatment in the presence of S9-mix where treatment commenced 48 hours post mitogen stimulation at concentrations up to its limit of cytotoxicity. Based on these results, Resorcinol is evaluated as clastogenic in the absence of metabolic activation and the results were equivocal in the presence of metabolic activation in this *in vitro* assay, since the positive result in the first experiment could not be reproduced in the second experiment.

Ref.: 8

3.3.6.2 Mutagenicity/Genotoxicity *in vivo*

Mammalian Erythrocyte micronucleus test

Guideline:	OECD 474
Species/strain:	Crl:CD (SD)BR rats
Group size:	5 male and 5 female in each group
Test substance:	Resorcinol
Lot no:	706030517
Purity:	>99.5% (Area % without response factor, UV detection
Dose level:	125, 250 and 500 mg/kg bw
Route:	Oral gavage (only once)
Vehicle:	Water
Sacrifice times:	24 h and 48 h (highest dose only)
GLP:	In compliance
Date:	28 October 2004 – 25 May 2005

Dose selection was based on findings in the dose range finding study for toxicity covering a range of 100 to 750 mg/kg bw administered to three males and three females and observed for up to two days for toxic signs and mortality. Based on the results of this study, the maximum tolerated dose was estimated to be 500 mg/kg bw. At least 2000 PCEs per animal were analysed for the frequency of micronuclei. In addition, the ratio between polychromatic and total erythrocytes in at least the first 500 total erythrocytes per animal was analysed.

Results
The test article caused mortality in one female and signs of clinical toxicity in the treated animals at 500 mg/kg bw, including tremors, rapid respiration, salivation, and squinted eyes. There were no indications of increases in micronucleated PCEs at any concentrations tested in either males or females at 24 h and 48 h harvest time-points. There was a significant decrease in the PCE:NCE ratios in females at 500 mg/kg bw at the 48 h harvest time-point indicating cytotoxicity and that the test article had reached the bone marrow.

Conclusion
It is concluded that under the test conditions reported in this study, Resorcinol did not induce clastogenic activity determined by this *in vivo* assay.

Ref.: 9

3.3.7. Carcinogenicity

A 2-year carcinogenicity study was conducted by administering resorcinol (> 99% pure) in water by gavage to groups of F3344/N rats and B6C3F1 mice of each sex. Under the conditions of the study, there was no evidence of carcinogenic activity of resorcinol in male F344/N rats given 112 or 225 mg/kg bw/day or female F344/N rats given 50, 100, or 150 mg/kg bw/day. There was no evidence of carcinogenic activity of resorcinol in male or female B6C3F1 mice given 112 or 225 mg/kg bw/day.

Groups of 60 male rats and male and female mice were administered 0, 112, or 225 mg/kg bw resorcinol in deionized water by gavage, five days per week for up to 104 weeks. Groups

of 60 female rats were initially administered the same doses as male rats, but by week 22 of the study 16 of the high-dose females had died. Consequently, the female rat study was restarted using doses of 0, 50, 100, or 150 mg/kg bw.
After 15 months of exposure, interim evaluations were performed on 10 animals from each group. No chemical-related changes in clinical pathology parameters or incidence of neoplasms or non-neoplastic lesions were found during the 15-month interim evaluations.

Body weights and survival: mean body weights of high-dose male rats were 10% to 15% lower than those of the controls from week 87 to study termination. Mean body weights of high-dose female rats were 11% to 14% lower than those of controls from week 95 to study termination. Mean body weights of other dosed rat groups were similar to those of controls. Survival of high-dose male and female rats was significantly lower than controls. Decreased survival in high-dose
groups was attributed to chemical-related toxicity.

Mean body weights of high-dose female mice were 10% to 15% lower than those of controls from week 85 to study termination, whereas those of the remaining dosed mouse groups were similar to those of the controls. Survival of dosed mice was similar to that of controls. Clinical signs suggestive of a chemical-related effect on the central nervous system, including ataxia, recumbency, and tremors, were observed in rats and mice.

Neoplasms and Non-neoplastic: there were no treatment-related increased incidences of neoplasms or non-neoplastic lesions in rats or mice administered resorcinol for 2 years.

Mammary gland fibroadenomas occurred at significantly reduced incidences in all exposed groups of female rats (25/50, 14/50, 12/50, 9/50). The incidence of subcutaneous fibroma or sarcoma in high-dose male mice was significantly lower than for the controls (8/50, 6/50, 1/50).

Conclusions on carcinogenicity
Under the conditions of the study, there was no evidence of carcinogenic activity of resorcinol in male F344/N rats given 112 or 225 mg/kg bw or female F344/N rats given 50, 100, or 150 mg/kg bw. There was no evidence of carcinogenic activity of resorcinol in male or female B6C3F1 mice given 112 or 225 mg/kg bw.

Ref.: 10

3.3.8. Reproductive toxicity

3.3.8.1. Two generation reproduction toxicity

Guideline:	OECD 416
Species/strain:	rat, Crl:CD®(SD) (prior to 01/01/2005 this strain was named Crl:CD®(SD)IGS BR
Group size:	30/sex group, 4 groups
Test substance:	Resorcinol
Batch:	Lot no. 706010501
Purity:	99.8%
Dose:	0, 120, 360, 1000 and 3000 mg/L for the F0 and F1 generations.
Vehicle:	deionized water
Route:	oral
Exposure:	on a continuous basis in the drinking water for at least 70 consecutive days
GLP:	in compliance
Date:	16 December 2003 – 24 September 2004

Five groups of male and female Crl:CD®(SD) rats (30/sex/group) were administered the test article Resorcinol (batch no 706010501) on a continuous basis in the drinking water for

at least 70 consecutive days prior to mating. Exposure levels were 0, 120, 360, 1000 and 3000 mg/L for the F0 and F1 generations. Vehicle was deionized water. All animals were observed twice daily for appearance and behaviour. Clinical observations, body weights and water and food consumption were recorded at regular intervals for males throughout the study and for females prior to mating and during gestation and lactation.

Results
No F0 or F1 parental test article-related deaths or clinical findings were reported. Mean body weights and body weight gains were affected in the 3000 mg/L treatment group F_0 and F_1 animals. The mean water consumption was decreased with ~10% in the 1000 mg/L (F_0 animals only) and with ~20% in the 3000 mg/L treatment group (F_0 and F_1 animals) due to the poor palatability of high concentration of water containing Resorcinol. Decreases in water consumption were not associated with effects on food intake and food utilization.
Reproductive performance (oestrous cycles, mating and fertility indices, number of days between pairing and coitus, and gestation length) and parturition in the F0 and F1 animals were unaffected by the test article. Spermatogenic endpoints (mean testicular and epididymal sperm numbers and sperm production rate, motility, progressive motility and morphology) in the F0 and F1 males were unaffected by the test article. No test article-related effects were observed on F1 and F2 pup survival or the general physical condition of the pups during the pre-weaning period. No test article-related macroscopic findings, organ weight or adverse microscopic target-organ effects were observed in the F0 or F1 parental animals. In addition, no test article-related macroscopic findings or effects on organ weights were noted in the F1 or F2 pups at the scheduled necropsies; no test article-related macroscopic findings were noted for found dead F1 or F2 pups.
No statistically significant test article-related changes in the mean concentrations of T3, T4 or TSH were noted in the F0 or F1 parental animals or in the F1 or F2 pups selected for analysis (PND 4 or PND 21). The higher (but non-significant) TSH values noted at all dose levels in the F0 males at the scheduled necropsy were not considered test article-related in the absence of effects on T3 or T4, organ weights or adverse macroscopic or microscopic findings. Test article-related decreased colloid within the thyroid glands of the 3000 mg/L F0 males was not considered adverse due to the lack of associated functional effects.

Conclusions
Based on the results of this study, the NOAEL was considered to be 3000 mg Resorcinol/L, which corresponds to ~233 mg/kg bw/day for males over the entire generation, 304 mg/kg bw/day for females during premating and gestation and 660 mg/kg bw/day for females during lactation.

Ref.: 12

Comments
As the mean water consumption was significantly decreased with ~10% in the 1000 mg/L (F_0 animals only) and with ~20% in the 3000 mg/L treatment group (F_0 and F_1 animals), SCCP considers 0.8 * 3000 = 2400 mg Resorcinol/L as the NOAEL. This corresponds to ~186 mg/kg bw/day for males over the entire generation, ~243 mg/kg bw/day for females during premating and gestation and ~528 mg/kg bw/day for females during lactation.

3.3.8.2. Teratogenicity

Guideline:	OECD Guideline 414
Species/strain:	rat, Sprague-Dawley Crl CD® (SD) IGS BR
Group size:	24 females/group; 4 groups
Test substance:	Resorcinol
Batch:	706030517
Purity:	98.8%
Dose:	40, 80 or 250 mg/kg bw/day, control group received vehicle (purified water)
Route:	oral

Exposure: once daily via gavage from GD 6-19
GLP: in compliance
Date: 1 – 25 June 2004

Four groups of Sprague-Dawley Crl CD® (SD) IGS BR rats (24 females/group) were administered with the test item, Resorcinol, by gavage once daily from day 6 to day 19 of gestation at the dose-level of 0, 40, 80 or 250 mg/kg bw/day. The females were sacrificed on day 20 of gestation and subjected to a macroscopic examination.
The numbers of corpora lutea, implantations and live foetuses were recorded. The foetuses were removed from the uterus, weighed, sexed and externally examined. Half of the foetuses underwent soft tissue examination while the remaining foetuses received a skeletal examination.

Results
At 250 mg/kg bw/day the net body weight change was significantly reduced. No other maternal effects were observed. All group mean numbers of implantations and live foetuses and the extent of pre- and post-implantation losses were comparable with the controls.
There were no effects of treatment on foetal body weight. In the litters, no external, soft tissue or skeletal malformations or variations were considered to be treatment-related. There was a significantly increase in the incidence of foetuses with an incompletely ossified interparietal at 40 and 80 mg/kg bw/day, when compared to controls ($p < 0.05$ and $p < 0.01$, respectively). The incidence of incompletely ossified parietals was also significantly greater at 80 mg/kg bw/day, when compared to controls ($p<0.05$). In the absence of any effects at 250 mg/kg bw/day these observations were not considered to be treatment-related.

Conclusion
The maternal NOAEL of Resorcinol administered by gavage to pregnant female rats was 80 mg/kg bw/day and the developmental NOAEL was 250 mg/kg bw/day.

Ref.: 11

3.3.9. Toxicokinetics

No data submitted

3.3.10. Photo-induced toxicity

No data submitted

3.3.11. Human data

In publicly available literature[3], resorcinol has also been described to exert effects on the thyroid due to interruption of the synthesis of thyroid hormones.

3.3.12. Special investigations

No data submitted

3.3.13. Safety evaluation (including calculation of the MoS)

CALCULATION OF THE MARGIN OF SAFETY

Not applicable

[3] Lynch B.S et al. Toxicology Review and Risk Assessment of Resorcinol: Thyroid Effects (2002). Reg. Tox. Pharm 36, 198-210

3.3.14. Discussion

Physico-chemical properties
Resorcinol is used in oxidative hair colouring products at a maximum concentration of 2.5%, which after mixing in a 1:1 ratio with hydrogen peroxide just prior to use, corresponds to a concentration of 1.25% upon application. The stability of resorcinol in the marketed products is not reported.

General toxicity
Relevance of anti-thyroid effects of Resorcinol

Animal data
In the review on resorcinol published by the Health Council of the Netherlands (Committee on Updating of Occupational Exposure Limits), several animal studies are described in which effects on the thyroid were investigated:

1. Acute toxicity studies
A single subcutaneous injection of 154 mg/kg bw Resorcinol in rats produced myxoedema and goitre whereas a similar injection of 50 mg/kg bw failed to produce any such disturbance in rat thyroid. In contrast, a temporary reduction of iodine uptake in the thyroid was noted in rats subcutaneously exposed to 5 mg/kg bw (ACGIH, 1998; Lundberg, 1992).

2. Repeated dose toxicity studies
Oral exposure to 5 mg/kg bw/day for 12 weeks resulted in an early stage of goitre in rats (Seffner et al, 1995). In another study (Cooksey et al, 1985) a similar exposure to 5 mg bw/day for 30 days had resulted in significant enlargement of the thyroid gland and decreased T_3 and T_4 levels in Wistar rats. In contrast, multiple (2/day) subcutaneous daily doses of 100 mg/kg bw for 14 or 30 days to male Sprague-Dawley rats did not result in adverse changes in thyroid function indicated by serum T_3 and T_4 (Merker et al, 1982). Also, in subacute, subchronic, and chronic oral studies performed in rats by the NTP no detectable effects on thyroid function were found (NOAEL 27.5, 32 and 50 mg/kg bw/day, respectively).

Based on these data, the thyroid was considered to be a target organ for (sub-chronic) exposure to resorcinol. However, the Health Council of the Netherlands (Committee on Updating of Occupational Exposure Limits) attached more importance to the NTP studies than to the studies of Seffner et al. and Cooksey et al. and questioned the relevance of the thyroid effects found by these authors because in each case only one concentration was used and thyroidal effects were not substantiated with measurements of thyroid function (Seffner study).
In contrast, a problem with the NTP study is that oral gavage may not optimally reveal goitrogenic effects as oral gavage is associated with an initially high C_{max} and a rapid clearance from the blood.

In conclusion, evidence of anti-thyroid activity of resorcinol in animals is only demonstrated when administered continuously (diet, sc injection with oil-based vehicle) or sub-dermally at higher doses. Additionally, its was stated that 'effects of resorcinol on the thyroid, particularly in rats, must be interpreted with caution as there are species-specific differences […] that complicate interpretation of goitrogenesis in these species' and '…it has been suggested that high doses of substances that cause hormonally induced changes of the thyroid in rodents, have little relevance to humans'

Human data

In a review paper by Lynch et al (2002)[4] case reports of thyroid dysfunction after exposure to Resorcinol have been described. Recurrent exposure over a prolonged period to high doses (greater than 30 mg/kg bw/day) may induce reversible hypothyroidism (after cessation of Resorcinol exposure symptoms of hypothyroidism rapidly disappeared). Also in De Groot et al (1994)[5] case reports of reversible hypothyroidism have been described in patients with persistent skin ulcers. These patients are treated with Resorcinol-containing ointments containing high doses (~12.5-40%) of Resorcinol for several week or months.
Epidemiological studies indicate that exposure via inhalation and dermal contact with concentrations of Resorcinol found in occupational settings is not sufficient to cause thyroid abnormalities. The few cases of hypothyroidism reported in cross-sectional studies of exposed workers may simply reflect the background occurrence of this disorder. The prevalence of hypothyroidism in exposed workers does not appear to be unusual when compared with general population values. The hypothesis of a link between Resorcinol in drinking water and the occurrence of goitre and hypothyroidism is speculative and has not been evaluated adequately.

Conclusion
Based on the human data as reviewed by Lynch et al (2002), thyroid effects may occur as a result of dermal exposure to ulcerized skin at resorcinol dose levels greater than 30 mg/kg bw/day. From these data, a thyroid effect threshold value of 10 mg/kg bw/day for dermal exposure was established based on the application of a threefold safety factor. However, high dose exposure has been rare in the past and has occurred mainly in patients as a result of the treatment of ulcers with large amounts of Resorcinol for a long period of time. Based on Lynch et al (2002), there is no evidence that intermittent or low-dose exposure to Resorcinol causes hypothyroidism or any other adverse health effects.

Summary of general toxicity studies
Based on acute oral toxicity study, resorcinol was found to be non-lethal at 200 mg/kg bw.
Based on the results of a 90-day sub-chronic oral toxicity study, the NOEL following oral gavage administration of resorcinol was 80 mg/kg bw/day.
Based on data from a two-generation toxicity study the NOAEL for parental systemic and reproductive toxicity, as well as neonatal toxicity was 2400 mg resorcinol/L, which corresponds to ~186 mg/kg bw/day for males over the entire generation, ~243 mg/kg bw/day for females during premating and gestation and ~528 mg/kg bw/day for females during lactation.
Based on the results of a prenatal developmental toxicity study the maternal NOEL of resorcinol administered by gavage to pregnant female rats was 80 mg/kg bw/day and the developmental NOEL was 250 mg/kg bw/day.
In the chronic/carcinogenicity study in rats, clinical signs were observed in the mid-and high dose females (112 and 150 mg/kg bw/day) and in both male groups (112 and 225 mg/kg bw/day). No effects were seen in females receiving 50 mg/kg bw/day. Since the dosing was performed by gavage and the clinical signs lasted 30-60 minutes after dosing, these signs might be the result of the high (local) dose. Therefore, 50 mg/kg bw/day will not be used as the NOAEL for the calculation of the MOS.

For the calculation of the MOS, the NOAEL of 80 mg/kg bw/day in the rat developmental toxicity study can be used. The threshold for the thyroid effects of 10 mg/kg bw/day in humans would, therefore, be adequately covered in the MOS.

Irritation / sensitisation
A 2.5% aqueous solution of resorcinol was not irritant when applied to rabbit skin. A 2.5% concentration of resorcinol caused mild conjunctival irritation to the rabbit eye.

[4] Lynch B.S, Delzell E.S., Bechtel D.H. Toxicology Review and Risk Assessment of Resorcinol: Thyroid Effects (2002). Reg. Tox. Pharm 36, 198-210
[5] De Groot, A.C., Weyland, J.W., Nater, J.P., Unwanted effects of cosmetics and drugs used in dermatology, (1994), 3rd ed., Elsevier, Amsterdam

Resorcinol induced contact sensitisation in this study. The EC3 value indicated that it should be considered as a strong sensitiser.

Dermal absorption
As too few chambers were used, the A_{max} of 2.0 µg/cm² may be used for calculating the Margin of Safety of resorcinol under oxidative conditions.

Mutagenicity / genotoxicity
Resorcinol was investigated in valid genotoxicity tests for the three types of genotoxic endpoints: gene mutation, structural and numerical chromosome aberration. Resorcinol did not induce gene mutations in bacteria. Resorcinol was genotoxic (mutagenic and or clastogenic) in the absence of metabolic activation in the mouse lymphoma assay and a potent clastogen in human peripheral blood lymphocytes. The clastogenic effects observed in the *in vitro* assays could not be confirmed in one *in vivo* assay. However, the mutagenic potential of resorcinol observed *in vitro* was not excluded in an *in vivo* study.
Therefore, an *in vivo* comet assay on stomach, liver and bladder cells should be performed.

Carcinogenicity
Under the conditions of the study, there was no evidence of carcinogenic activity of resorcinol in male F344/N rats given 112 or 225 mg/kg bw/day or female F344/N rats given 50, 100, or 150 mg/kg bw/day. There was no evidence of carcinogenic activity of resorcinol in male or female B6C3F1 mice given 112 or 225 mg/kg bw/day.

4. CONCLUSION

The SCCP is of the opinion that the information submitted is insufficient to allow a final risk assessment to be carried out.

Before any further consideration, an in vivo Comet assay on stomach, liver and bladder cells should be performed as the mutagenic potential of resorcinol in vitro was not excluded in an in vivo study.

Studies on genotoxicity/mutagenicity in finished hair dye formulations should be undertaken following the relevant SCCNFP/SCCP opinions and in accordance with its Notes of Guidance.

5. MINORITY OPINION

Not applicable

6. REFERENCES

The references in italics (15-32) were not submitted by the applicant as full reports in the present dossier, since the studies reported therein were not considered to be adequate.

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2. G. Sire. Resorcinol (A011): Acute Dermal Irritation in Rabbits. CIT Study No. 26939 TAL, 2004
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