EUROPEAN COMMISSION

Directorate-General for Health & Consumers

Scientific Committee on Consumer Safety

SCCS

OPINION ON

4-Chlororesorcinol

COLIPA n° A12

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

The SCCS adopted this opinion at its 6th plenary meeting
of 23 March 2010

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 Safety (SCCS), 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).

SCCS

The Committee shall provide opinions on questions concerning all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example: cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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This opinion has been subject to a commenting period of four weeks after its initial publication. All comments received during this time have been considered by the SCCS and discussed in the subsequent plenary meeting. Where appropriate, the text of the relevant sections of the opinion has been modified or explanations have been added. In the cases where the SCCS after consideration and discussion of the comments, has decided to maintain its initial views, the opinion (or the section concerned) has remained unchanged.

Keywords: SCCS, scientific opinion, hair dye, A12, 4-chlororesorcinol, CAS 95-88-5, EC 202-462-0, directive 76/768/EEC

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on 4-chlororesorcinol, 23 March 2010

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1. BACKGROUND

Submission I on 4-Chlororesorcinol was submitted by COLIPA[1] in August 1981[2]. The Scientific Committee on Cosmetology (SCC) in its meeting on 10-11 October 1988 categorised the substance to class B and asked for more data on:

- *A study on skin penetration*
- *Information on the (90-day) oral study in rats to establish the NEL on the thyroid*
- *The results of the aberration test on mammalian cells*
- *The results from an ongoing long-term carcinogenicity study from NTP USA*

Submission II was made in January 1988. The SCC gave its opinion in December 1993 with the same classification B as above and again a reference to the on-going long term study by NTP and it calculated a MOS of 220.

Submission III, made by COLIPA in June 2005, 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 of Consumer Safety (SCCS) consider 4-chlororesorcinol safe for use in oxidative hair dye formulations with a maximal on-head concentration of 2.5% taken into account the data provided?*

2. *Does the SCCS recommend any restrictions with regard to the use of 4-chlororesorcinol 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

4-Chlororesorcinol (INCI name)

3.1.1.2. Chemical names

1,3-Benzenediol, 4-chloro- (9CI)	4-Chloro-1,3-benzenediol
1-Chloro-2,4-dihydroxybenzene	4-Chlororesorcinol
2,4-Dihydroxychlorobenzene	Resorcinol, 4-chloro
4-Chlorobenzene-1,3-diol	p-Chlororesorcinol

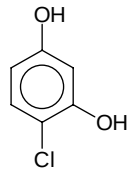
3.1.1.3. Trade names and abbreviations

C.I. 76510
COLIPA A12

3.1.1.4. CAS / EC number

CAS: 95-88-5
EC: 202-462-0

3.1.1.5. Structural formula



3.1.1.6. Empirical formula

Formula: $C_6H_5O_2Cl$

3.1.2. Physical form

Beige-brown powder

3.1.3. Molecular weight

Molecular weight: 144.56 g/mol

3.1.4. Purity, composition and substance codes

Batch 4 CRB 921 (= SAT 030386, SAT 030626, SAT 040291)

Identification by NMR and IR spectroscopy
Purity by NMR assay: 100.1 weight%
Purity by HPLC assay: 98.1 area%
Solvent content (water): < 1.0 weight%

Impurities
Resorcinol 0.80 weight%
4,6-Dichlororesorcinol 0.62 weight%
Sulphated ash < 0.1 weight%

Declaration of the purity of other batches

Specification of 'Currently' used material

Purity by NMR assay:	> 97.0 weight%	
Purity by HPLC assay:	> 97.5 area%	(irrespective of salts and other non-detectable impurities)
Solvent content (water):	< 1.0 weight%	
Sulphated ash:	< 0.2 weight%	

Impurities

Resorcinol	< 1.0 weight%
4,6-Dichlororesorcinol	< 1.0 weight%
Heavy metal content	Pb < 20 ppm; Sb, Ni < 10 ppm; As, Cd < 5 ppm; Hg < 1 ppm

The applicant declared that *'The batch of COLIPA A12 used in the acute oral toxicity test is not fully analytically described. However, due to the reported chemical synthesis pathway and the fact that the given melting point of 105-108 °C is identical to that of the currently tested batch (4CRB921) the specification can be considered to be quite similar*'.

3.1.5. Impurities / accompanying contaminants

See point 3.1.4. Purity, composition and substance codes

3.1.6. Solubility

Water:	> 100 g/l	at room temperature
Ethanol:	> 100 g/l	at room temperature
DMSO:	> 100 g/l	at room temperature

Comment
The water solubility is not determined by the EC method A6.

3.1.7. Partition coefficient (Log P_{ow})

Log P_{ow}: 0.965 determined by EU A.8 method

Ref.: 16

3.1.8. Additional physical and chemical specifications

Melting point:	105 – 108 °C
Boiling point:	147°C at 18 mm Hg
Flash point:	/
Vapour pressure:	/
Density:	/
Viscosity:	/
pKa:	/
Refractive index:	/
UV_Vis spectrum (200-340 nm)	λmax 280 nm

3.1.9. Homogeneity and Stability

Oral developmental toxicity:
5, 10 and 20 mg/mL solutions in bi-destilled water were homogenous (variation: -6 to +11%), and these solutions were stable (variation <2%), at least for 7 days.

Ref.: 14

Oral 90 day toxicity
3.5, 7.0 and 21 mg/mL solutions in bi-destilled water were homogenous (variation: -2 to +2%), and these solutions were stable (variation <2%), at least for 7 days.

Ref.: 12

4-chlororesorcinol in DMSO solutions (50 mg/ml) was shown to be stable (variation <2%) during the 48 h study period.

Ref.: 17

General Comments to physico-chemical characterisation

- The solubility of 4-chlororesorcinol was not determined by the EC method A6.
- The stability of 4-chlororesorcinol in a typical hair dye formulation was not reported.

3.2. Function and uses

4-Chlororesorcinol is used as a coupler in oxidative hair dye formulations. It reacts with primary intermediates to form the final dye-stuff. The coupling-reaction can be accelerated by addition of an oxidizing agent (e.g. hydrogen peroxide), but can also be achieved by air oxidation.

The final concentration of 4-chlororesorcinol on head can be up to 2.5%.

3.3. Toxicological Evaluation

3.3.1. Acute toxicity

3.3.1.1. Acute oral toxicity

Guideline: /
Species/strain: rat, CFY strain
Group size: 50 (5 males and 5 females per dose group)
Test substance: 4-chlororesorcinol, 10 % solution in aqueous sodium sulphite (0.05%)
Batch: /
Purity: /
Dose levels: 0, 160, 250, 400 and 640 mg/kg bw
Dosage volume: 1.6 to 6.4 ml/kg bw
Administration: oral, gavage
GLP statement: /
Study period: August – September 1975

Rats of the CFY strain, in the weight range of 95 to 122 g were starved overnight before treatment. 4-Chlororesorcinol was prepared as a 10% solution in aqueous sodium sulphite and administered by gavage at a range of dosage volumes of 1.6 to 6.4 ml/kg bw. Rats treated with the vehicle alone (6.4 ml/kg bw) served as controls. During the observation period of 14 days, a record was kept of mortalities and signs of toxicity. All rats that died were examined macroscopically to identify the target organs and surviving animals were similarly examined to detect possible damage. From the mortality data the LD_{50} and its 95% confidence limits were calculated.

Results
The results of preliminary range finding tests indicated that the median lethal oral dose (LD_{50}) was in the region of 250 to 640 mg/kg bw. Dosing was then extended to larger groups of rats (five males and five females) in order to set the median lethal dose more precisely. Signs of reaction to treatment observed shortly after dosing, included lethargy, piloerection and decreased respiratory rate. These signs were accompanied by fine body tremors in rats treated at 160, 250 and 400 mg/kg, by ataxia in female rats at 160 and 400 mg/kg and all rats at 640 mg/kg, and by loss of righting reflex and coarse body tremors in rats at 640 mg/kg. Death occurred from within one to two hours of treatment. Autopsy revealed slight haemorrhage of the lungs, darkening of the liver, kidneys and spleen, and injection of mesenteric blood vessels. Recovery of survivors, as judged by external appearance and behaviour was complete within two days of treatment. This observation was substantiated by normal body weight gains compared with controls and normal autopsy findings. The acute median lethal oral dose (LD_{50}) and its 95% confidence limits to rats of 4-chlororesorcinol were calculated to 369 (314-433) mg/kg.

Ref.: 3

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 (2002)
Species/strain:	Albino rabbit, New Zealand White, (SPF-Quality)
Group size:	3 males
Test substance:	A12 / SAT 030626
Batch:	4 CRB 921
Purity:	98.1%
Vehicle:	water (Milli-U)
Dose level:	0.5 g, moistened with 60 ml Milli-U water
GLP:	in compliance
Study period:	4 – 25 November 2003

Three rabbits were exposed to 0.5 grams of A12, applied onto clipped skin for 4 hours using a semi-occlusive dressing. Observations were made 1, 24, 48 and 72 hours, and 7 and 14 days after exposure

Results
No evidence of full thickness destruction of the skin or scar tissue was observed during the observation period, indicating that no corrosion of the skin had occurred by dermal application of A12 to the intact rabbit skin. Brown staining of the treated skin by the test substance was observed on all animals during the observation period, which did not hamper the scoring of the skin reaction.
Four hours exposure to 0.5 g of A12 resulted in very slight, well defined or moderate to severe erythema and slight or moderate oedema in the treated skin-areas of the three rabbits. The skin irritation had resolved within 14 days after exposure in one animal, but remained present up to termination in the other animals.

Conclusion
4-Chlororesorcinol is irritating to the skin.

Ref.: 4

3.3.2.2. Mucous membrane irritation

Guideline:	OECD 405 (2002)
Species/strain:	Albino rabbit, New Zealand White, (SPF-Quality)
Group size:	1 male
Test substance:	A12 / SAT 030626
Batch:	4 CRB 921
Purity:	98.1%
Vehicle:	/
Dose level:	56.1 mg neat test substance
GLP:	in compliance
Study period:	10 – 11 November 2003

Method
A single sample of 56.1 mg of A 012 (a volume of approximately 0.1 ml) was instilled into an eye of one rabbit. Observations were made 1 and 24 hours after instillation.

Results
The corneal injury consisted of opacity (maximum grade 4) and epithelial damage (100% of the corneal area). The irritation of the conjunctivae consisted of redness (also of the outside of the eyelids), chemosis and discharge. In addition, grey-white discolouration (a sign of necrosis) of the eyelids and nictitating membrane was noted during the observation period. Due to the corneal damage, iridial irritation could not be assessed.
Based on the severity of the eye lesions, the animal was sacrificed for ethical reasons after the 24 hours observation. The other animals assigned to the study were not treated.

Conclusion
4-Chlororesorcinol is corrosive to the eyes.

Ref.: 5

3.3.3. Skin sensitisation

Local Lymph Node Assay (LLNA)

Guideline:	OECD 429 (2002)
Species/strain:	mouse, CBA strain, inbred, SPF-Quality (nulliparous and non-pregnant)
Group size:	35 females (7 groups of 5 animals)
Test substance:	A12 / SAT 030626
Batch:	4 CRB 921
Purity:	98.1%
Vehicle:	acetone:olive oil (4:1 v/v)
Concentration:	2.5, 5, 10, 25 and 50% in acetone:olive oil (4:1 v/v)
Positive control:	α-hexylcinnamaldehyde, tech. 85% (March 2004)
Vehicle pos. control:	acetone:olive oil (4:1 v/v)
GLP:	in compliance
Study period:	29 December 2003 – 15 March 2004

Method
In the main study, three groups of five experimental animals were epidermally exposed to a 5%, 25% and 50% concentration respectively on three consecutive days. Five vehicle control animals were similarly treated, but with vehicle alone (acetone:olive oil (4:1 v/v). Three days after the last exposure, all animals were injected with ^{3}H-methyl thymidine and after five hours the draining (auricular) lymph nodes were excised.
After precipitating the DNA of the lymph node cells, radioactivity measurements were done. Based on the results, additional groups were treated at 2.5 and 10%. Five vehicle control animals were similarly treated, but with vehicle alone.

Results
Four animals treated at 50% were found dead on day 3. Macroscopic post mortem examination revealed no abnormalities. No further mortality occurred and no symptoms of systemic toxicity were observed in the surviving animals of the main study.
The sizes of the nodes of the 2.5 and 5% groups were considered to be normal. Enlarged nodes were found in the 10, 25 and 50% groups. One very large node was found in one control animal. No other macroscopic abnormalities of the nodes were noted.
Mean DPM/animal values for the experimental groups treated with test substance concentrations 5 and 25 % were 232 and 2473 respectively. The DPM Value for the only surviving animal treated at 50% was 2402. The mean DPM/animal value for the vehicle control group was 151.
In order to achieve more information regarding the SI=3 value, additional groups of animals were treated. Mean DPM/animal values for the experimental groups treated with test substance concentrations 2.5 and 10% were 145 and 1351 respectively. The mean DPM/animal value for the vehicle control group was 134.
The SI values calculated for the substance concentrations 2.5, 5, 10 and 25% were 1 .l, 1.5, 10.1, 16.4 respectively. An EC3 value of 5.8% was calculated.

Concentration	Stimulation Index
Test item	
2.5%	1.1
5%	1.5
10%	10.1
25%	16.4
50%	#

Vehicle	1.0
α-hexylcinnamaldehyde	
5%	1.2
10%	2.7
25%	16.8

animals found dead

Ref.: 6

Comment
According to the grading scheme used by the SCCS (SCCP/0919/05), 4-chlororesorcinol should be considered as a moderate skin sensitiser (EC3-value >2).

3.3.4. Dermal / percutaneous absorption

Guideline:	OECD 428 (draft, 2003)
Tissue:	dermatomed pig skin, 380 µm thickness
Group size:	8 membranes from 2 donors
Diffusion cells:	glass diffusion cell, 0.79 cm²
Skin integrity:	electrical resistance > 15 kΩ
Test substance:	A12 / SAT 030626 [Ring-^{14}C(U)]-4-chlororesorcinol; 56.2 mCi/mmol, 0.389 mCi/mg
Batch:	4 CRB 921 3501-095 (radio-labelled)
Purity:	98.1% 99.78% (radio-labelled)
Test item:	2.5% (w/w) A12 in a standard cream formulation with and without hydrogen peroxide and in an aqueous solution
Doses:	10 mg/cm²
Receptor fluid:	physiological saline
Solubility receptor fluid:	/
Stability:	/
Method of Analysis:	Liquid scintillation counting
GLP:	in compliance
Study period:	13 - 23 January 2004

Method
The penetration of A12 has been measured *in vitro* through dermatomed pig skin from a standard cream formulation (with and without hydrogen peroxide) and from a solution in water. The aqueous solution and formulated material all containing 2.5% w/w of A12 were applied to the dermatomed membranes at a rate of 10mg/cm² and left unoccluded. The applications were rinsed off after a 0.5h contact period, with the penetration of A12 through the membrane being assessed throughout the entire 48h exposure period. At the end of the exposure period, the distribution of A12 in the test system was assessed, which included a tape stripping technique to determine its distribution in the skin.
Samples collected during this study were analysed by liquid scintillation counting (LSC).

Results
The dermal penetration of A12 from the cream formulation with and without hydrogen peroxide was low and the vast majority of the dose was recovered in the wash at 0.5h. Most of the penetration occurred during the first 4 hours giving a penetration rate of 0.110 µg/cm²/h, (with hydrogen peroxide) and 0.108 µg/cm²/h (without hydrogen peroxide), after which a small amount of A12 penetrated. After the 0.5h exposure period, the amount which had penetrated was 0.062 µg/cm² (~0.024%) (with hydrogen peroxide) and 0.022 µg/cm² (~0.008%) (without hydrogen peroxide) and after 48h, the amount penetrated was 1.17 µg/cm² (~0.448%) (with hydrogen peroxide) and 1.69 µg/cm² (~0.651%) (without hydrogen peroxide). A small proportion of the dose was found adsorbed to the *stratum corneum* (0.855%) (with hydrogen peroxide) and (0.533%) (without hydrogen peroxide).

The dose in the remaining epidermis/dermis was 0.855% (with hydrogen peroxide and 0.533% (without hydrogen peroxide).
The overall quantity found to be bioavailable (absorbed and penetrated) within 48 hours under the given study conditions was calculated to be 1.50 ± 0.84% (3.91 ± 2.20 μg/cm² (with hydrogen peroxide) and 1.95 ± 1.14% (5.05 ± 2.97μg/cm² (without hydrogen peroxide), respectively. The total recovery of radioactivity was 103% (with hydrogen peroxide) and 107% (without hydrogen peroxide).
For the aqueous solution of A12, penetration occurred during the whole 48 hour test period giving a penetration rate of 2.03μg/cm²/h during the first 4 hours (for comparison with the cream formulations) and the penetration rate between the 4 and 48h time period was 0.623μg/cm²/h.
At 48h the amount penetrated was 35.8 μg/cm² (~14.2%). A small proportion of the dose was found adsorbed to the *stratum corneum* and absorbed in the remaining epidermis/dermis. The overall quantity found to be bioavailable (absorbed and penetrated) within 48 hours under the given study conditions was calculated to be 20.8% (~52.6μg/cm²) of the topically applied amount.

These data demonstrate that the systemic availability, after dermal exposure to A12 from formulations would be low especially under normal use conditions in combination with a hydrogen peroxide developer and would be significantly less than that available from a solution of A12 in water.

Cream formulation with H_2O_2

	Amount recovered (μgeq/cm²)									
Cell number	**1**	**2**	**3**	**6**	**17**	**18**	**19**	**20**	**mean**	**SD**
Skin number	**215**	**215**	**215**	**215**	**216**	**216**	**216**	**216**		
Donor chamber	0.096	0.205	0.222	0.219	0.229	0.167	0.089	0.294	0.190	0.070
Wash at 0.5h	268	242	260	271	261	260	239	268	259	11.9
Wash at 48h	1.78	1.61	1.10	2.48	3.51	1.28	0.896	1.82	1.81	0.845
Stratum corneum	0.583	2.89	3.98	1.44	5.10	1.22	0.847	1.73	2.22	1.61
Epidermis/dermis	0.063	0.121	1.382	3.00	3.23	3.69	3.69	6.72	2.74	2.20
Penetrated	0.645	1.55	1.14	2.72	1.08	0.691	0.736	0.763	1.17	0.698
Bioavailable	0.708	1.671	2.522	5.72	4.31	4.381	4.426	7.483	3.91	2.20
Bioavailable (%)	0.272	0.642	0.971	2.20	1.655	1.686	1.703	2.873	1.50	0.84
Total (%)	104	95.6	103	108	105	103	94.3	107	103	5.06

Cream formulation without H_2O_2

	Amount recovered (μgeq/cm²)									
Cell number	**9**	**11**	**13**	**14**	**21**	**22**	**23**	**24**	**mean**	**SD**
Skin number	**215**	**215**	**215**	**215**	**216**	**216**	**216**	**216**		
Donor chamber	0.278	0.183	0.151	2.610	0.392	0.336	0.200	0.722	0.609	0.829
Wash at 0.5h	274	266	292	263	255	279	262	255	268	12.7
Wash at 48h	8.30	1.20	1.05	2.08	1.85	1.61	1.22	4.08	2.67	2.47
Stratum corneum	0.607	0.670	1.22	0.783	3.75	1.84	0.661	1.50	1.38	1.06
Epidermis/dermis	1.26	0.818	0.575	3.18	5.67	1.49	5.38	8.53	3.36	2.88
Penetrated	1.52	0.825	2.79	1.44	2.01	2.04	0.728	2.14	1.69	0.698
Bioavailable	2.78	1.643	3.365	4.62	7.68	3.53	6.108	10.67	5.05	2.97
Bioavailable (%)	1.073	0.635	1.302	1.785	2.966	1.365	2.361	4.115	1.95	1.14
Total (%)	110	104	115	105	104	111	104	105	107	4.11

A12 in water

	Amount recovered (μgeq/cm²)									
Cell number	**16**	**74**	**75**	**76**	**25**	**26**	**27**	**28**	**mean**	**SD**
Skin number	**215**	**215**	**215**	**215**	**216**	**216**	**216**	**216**		
Donor chamber	71.0	4.35	10.5	3.37	7.94	4.86	9.97	3.58	14.4	23.0
Wash at 0.5h	74	162	181	146	181	190	177	164	159	37.1
Wash at 48h	43.1	20.8	16.0	13.1	29.5	34.8	28.3	28.1	26.7	9.86

	Amount recovered (µgeq/cm²)									
Cell number	**16**	**74**	**75**	**76**	**25**	**26**	**27**	**28**	**mean**	**SD**
Skin number	**215**	**215**	**215**	**215**	**216**	**216**	**216**	**216**		
Stratum corneum	11.4	16.8	8.29	7.47	6.12	7.51	23.6	22.3	12.9	7.03
Epidermis/dermis	24.5	5.90	9.37	12.5	34.6	20.6	16.5	10.4	16.8	9.44
Penetrated	25.3	54.4	34.5	51.8	13.2	29.9	30.2	47.1	35.8	14.2
Bioavailable	49.8	60.3	43.87	64.3	47.8	50.5	46.7	57.5	52.6	7.2
Bioavailable (%)	19.68	23.83	17.3	25.43	18.91	19.93	18.42	22.7	20.8	2.9
Total (%)	98.6	104	103	92.6	108	114	113	109	105	7.1

Ref.: 15

Comments
The dose of the test formulation (10 mg/cm²) was lower than the recommended dose (20 mg/cm²).
The experiment shows high variability with a high relative standard deviation (RSD) of about 56% and 59% for the bioavailability of formulations with and without H_2O_2, respectively. A12 in water showed a smaller RSD of about 14%.
In water, absorption is about ten times higher compared with formulation. Consequently, absorption/MoS will depend largely on the vehicle used.

Because of the too low dose, the high variability in the experiments and the observed vehicle dependency of absorption, the mean + 2SD will be used for calculation of MoS. Accordingly, in the presence of hydrogen peroxide the dermal absorption was 8.31 µg/cm² (3.91 + 2 x 2.20 µg/cm²), in the absence of hydrogen peroxide 10.99 µg/cm² (5.05 + 2 x 2.97 µg/cm²).

3.3.5. Repeated dose toxicity

3.3.5.1. Repeated Dose (28 days) oral toxicity

Guideline:	OECD 407 (1995)
Species/strain:	rat, HanBrl:WIST(SPF)
Group size:	40 (4 groups of 5 males and 5 females)
Test substance:	4-Chlororesorcinol (SAT 040291)
Batch:	4 CRB 921
Purity:	98.1%
Vehicle:	bi-destilled water
Dose levels:	0, 30, 150, 300 mg/kg bw
Dose volume:	10 ml/kg bw
Route:	oral gavage
Administration:	daily for 28 days
GLP:	not mentioned
Study period:	15 July – 19 August 2004

In this 28-Day Oral Range-Finding Toxicity Study in the Wistar Rat, 4-Chlororesorcinol was administered by daily gavage to SPF-bred Wistar rats of both sexes at dose levels of 30, 150, and 300 mg/kg bw/d for a period of 28 days. A control group was treated similarly with the vehicle (H_2O bidest.) only. A total of 40 rats was used in this study. The groups comprised 5 animals per sex which were sacrificed after 28 days of treatment. Clinical signs, food consumption and body weights were recorded periodically during acclimatization and the treatment period. At the end of the treatment period, all animals were killed, necropsied and examined post mortem. Histological examinations were restricted to kidneys but were performed on all animals. Blood samples were taken from all animals for analysis of their T_3 / T_4 hormone levels.

Results

No deaths occurred during this study. During the first few treatment days, sedation, tremor, recumbency, and ruffled fur were observed in all high dose animals. Additional signs including convulsions, abnormal gait, muscle twitchings, and breathing rales were noted during weeks 3 and 4. The overall mean food intake over the entire treatment period did not show relevant differences between controls and treated groups. The body weight development in male and female groups was not affected by treatment. Neither absolute nor relative mean organ weights were influenced by treatment. The macroscopic lesions observed and possibly related to treatment consisted of bilateral pelvic dilation of 1 female animal of the 150 mg/kg group and 1 male animal of the 300 mg/kg group. They could be correlated to pelvic dilation and unilateral hydronephrosis. A slight increase in incidence/severity of hyaline droplets in males of the 150 mg/kg group (4/1.0 in the control group versus 5/1.4 in the 150 mg/kg group) was observed. There were two cases of slight degree unilateral hydronephrosis (one case in the 300 mg/kg group, male and the 150 mg/kg group, female each) that went along with contralateral pelvic dilation.

T_3 / T_4 hormone level determination in blood plasma revealed no relevant differences between controls and groups treated with the test item.

Ref.: 11

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

Guideline:	OECD 408 (1998)
Species/strain:	rat, HanBrl:WIST(SPF)
Group size:	100 (50 males and 50 females, plus 2/2 reserve animals) Groups 1 to 4: 10 males and 10 females (allocation A) Groups 1 and 4: 5 males and 5 females (allocation B)
Test substance:	4-Chlororesorcinol (SAT 040291)
Batch:	4 CRB 921
Purity:	98.1%
Vehicle:	bi-distilled water
Dose levels:	0, 35, 70, 210 mg/kg bw
Dose volume:	10 ml/kg bw
Route:	oral, gavage
Administration:	daily for 91 days
GLP statement:	in compliance
Study period:	7 September 2004 – 7 February 2005

Twenty rats (10 per sex) of the Wistar strain were used per dose and control group. Additional 10 rats (5 per sex) in both the control and high dose group were assessed for recovery, four weeks after the last administration. The test procedure followed the OECD guideline and was conducted in compliance with the principles of GLP. Aliquots of 10 ml/kg bw of 4-Chlororesorcinol were administered in a single dose by gavage. The test substance was given as an aqueous solution for 91 consecutive days in daily doses of 35, 70 and 210 mg/kg bw based on the results of a dose range finding study. The control animals received the vehicle alone (distilled water). During the study the mortality, signs of intoxication, body weight and food consumption were recorded. Clinic ophthalmic examination was performed during acclimatization, at treatment end and recovery end using an ophthalmoscope. The animals of the recovery groups were additionally examined during the 4-week treatment-free period. At the end of the study, functional observational battery, locomotor activity and grip strength were investigated. Blood samples were withdrawn for haematology and blood chemistry analysis. Urine samples were collected for urinalysis. All animals were killed, necropsied and examined post mortem. Histological examinations were performed on organs and tissues from all control and high dose animals, in animals which died spontaneously and in all gross lesions.

Results

Four female rats of the high dose group (210 mg/kg bw/day) died. The death of one male rat was attributed to a misapplication and was considered to be unrelated to the treatment with the test item. The treatment induced spasm/tremor, hunched posture, abnormal gait, and salivation in high dose males and females, initially with sporadic occurrence but then generally progressing in incidence in both sexes. The findings observed following the daily administrations (approximately 10 to 60 minutes post dosing) were followed by rapid recovery. Due to the short and transient occurrence of the toxic signs observed in high dose animals (incl. spasm/tremor, hunched posture, abnormal gait, and salivation) after daily administrations, these findings could not be confirmed on the detailed weekly assessments.
Food and water intake as well as body weight development were not affected. Ophthalmoscopic investigations revealed no evidence of eye toxicity. Reduced forelimb grip strength was recorded in high dose males. A depressed red blood cell count was observed in high dose females at treatment end. At this high dose also effects on reticulocyte count and/or maturity index were observed. An effect on lipid metabolism parameters was observed in high dose males only.
Effects on the electrolyte parameters Na^+, K^+, Cl^- (males and females, affecting all dose levels) and PO_4^- were of a minimal extent and completely regressed during recovery. A yellow-brown discoloration and cloudy appearance of the urine found in some high dose males disappeared after cessation of the daily treatment.
At treatment end, no changes to absolute or relative mean organ weights and no test item-related gross lesions were observed. Minimal changes of liver-to-body weight and thymus-to-body weight in males at 210 mg/kg bw/d were associated with a minimally depressed body weight and the findings were considered incidental. Macroscopic and microscopic examination of the deaths did not reveal an underlying cause. The histopathological investigations revealed no changes to the organ or tissue morphology, which could be related to the treatment with the test item.

Conclusion
Because of changes in the electrolyte parameters Na^+, K^+, Cl^- (both sexes, all doses) and PO_4^-, a NOEL could not be established. Due to mortality, clinical signs and haematotoxicity at 210 mg/kg bw/d the NOAEL in rats after daily oral treatment in rats is determined to be 70 mg/kg bw/day.

Ref.: 12

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:	OECD 471 (1997)
Species/strain:	*Salmonella typhimurium* TA 98, TA 100, TA 102, TA 1535 and TA 1537
Replicates:	triplicate in two independent experiments, both in absence and presence of S9-mix
Test substance:	A12 / SAT 030386
Batch:	4 CRB 921
Purity:	98.1%
Solvent:	DMSO
Concentrations:	33, 100, 333, 1000, 2500 and 5000 µg/plate (experiment I and II)
Treatment:	plate incorporation (exp. I); preincubation method (exp. II)
Control:	without S9-mix: sodium azide, 4-nitro-o-phenylenediamine, methyl methane sulfonate

	with S9-mix:	2-aminoanthracene
GLP:	in compliance	
Study period:	21 August – 10 September 2003	

A12 was tested in the *Salmonella*/microsome assay in five tester strains according to the OECD guideline. In a preliminary toxicity test (plate incorporation test) the test substance was tested in TA 98 and TA 100. Eight concentrations from 3 - 5000 µg/plate were tested in triplicate.
The pre-experiment is reported as part of the main experiment. Appropriate negative and positive controls were included.

Results
Relevant toxic effects, evident as a reduction in the number of revertants, occurred in some of the strains at the maximum concentration with and without metabolic activation.
The plates incubated with the test item showed normal background growth up to 5000 µg/plate with and without S9-mix in all strains used in experiment I. In experiment II, reduced background growth was observed at 5000 µg/plate without metabolic activation in strains TA 1535, TA 1537, TA, 98, and TA 102 and with metabolic activation in strains TA 1535 and TA 102. In strain TA 100 reduced background growth was observed at 2500 and 5000 µg/plate in the presence of metabolic activation.
No substantial increase in revertant colony numbers of any of the five tester strains was observed following treatment with A12 at any dose level, neither in the presence nor absence of metabolic activation (S9-mix). There was also no tendency of concentration related increase in revertant colonies.

Conclusion
In conclusion, it can be stated that the test item did not induce gene mutations in bacteria under the experimental conditions reported

Ref.: 7

In vitro Mammalian Cell Gene Mutation Test

Guideline:	OECD 476 (1997)	
Species/strain:	L5178Y $tk^{+/-}$ mouse lymphoma cells	
Replicates:	two parallel cultures in two independent experiments	
Test substance:	A12 / SAT 030386	
Batch:	4 CRB 921	
Purity:	98.1%	
Vehicle:	deionised water	
Concentrations:	Experiment I:	46.9, 93.8, 187.5, 375, and 562.5 µg/ml without S9-mix 5.9, 11.7, 23.4, 35.1 and 46.9 µg/ml with S9-mix
	Experiment II:	47.5, 95, 190, 285 and 380 µg/ml without S9-mix
Treatment	Experiment I:	4h treatment without and with S9-mix
	Experiment II:	24h treatment without S9-mix
Control:	methylmethane sulfonate (without S9-mix) cyclophosphamide (with S9-mix)	
GLP:	in compliance	
Study period:	23 November 2004 – 29 March 2005	

A12 was tested for the ability to induce gene mutations and/or chromosomal aberrations in the mouse lymphoma assay. The assay was performed as two independent experiments, using two parallel cultures each. The highest concentration (1500 µg/mL) applied in the concentration range finding experiment was equal to a molar concentration of about 10 mM. In the main experiments 5 concentrations were tested both without and with Phenobarbital/β-Naphthoflavone induced rat liver S9-mix. The dose range of the main

experiments was limited by toxicity of the test item. Appropriate positive and negative controls were included in the experiment.

Results
In the pre-toxicity tests following 4 h treatment toxic effects were observed at 750 µg/mL and above without metabolic activation and starting at 23.4 µg/mL with metabolic activation. After 24 hours of treatment, toxic effects occurred at 375 µg/mL and above. No precipitation was noted up to the maximum concentrations tested.
No relevant and reproducible increase of the mutant frequency was observed in both main experiments. The threshold of twice the mutant frequency of the corresponding solvent control was slightly exceeded at the maximum concentration in the first culture of the first experiment with metabolic activation. However, toxicity was severe at this concentration with a relative total growth of 9.9%. Since the absolute value of the mutant frequency was rather low and remained well within the historical range of negative and solvent controls and no comparable effect was detected in the parallel culture under identical conditions this minor increase was judged as biologically irrelevant.

Conclusion
In conclusion it can be stated that under the experimental conditions reported the test item did not induce mutations in the mouse lymphoma thymidine kinase locus assay using the cell line L5178Y in the absence and presence of metabolic activation.

Ref.: 8

Comment
The increase in one culture in the first experiment with S9-mix was dose related and due to an increase in small colonies only, indicating a clastogenic activity. However, the highest induced mutant frequency was 90 x 10^{-6} (at a highly toxic concentration) and therefore below the internationally recommended increase (126 x 10^{-6}) for a positive response. In addition this effect was not seen in the second culture.

In vitro Mammalian Chromosome Aberration Test

Guideline:	OECD 473 (1997)
Species/strain:	Chinese hamster V79 cells
Replicates:	two parallel cultures
Test item:	A12 / SAT 030386
Batch:	4 CRB 921
Purity:	98.1%
Vehicle:	deionised water
Concentrations:	without S9-mix: 200, 300 and 400 µg/ml with S9-mix: 2.5, 5 and10 µg/ml
Performance:	4h exposure, 14h recovery, 18h preparation interval
Positive controls:	ethylmethane sulfonate (- S9-mix), cyclophosphamide (+ S9-mix)
GLP:	in compliance
Study period:	27 August – 23 September 2003

The test item A12, dissolved in deionised water, was assessed for its potential to induce structural chromosome aberrations in Chinese hamster V79 cells. One experiment was performed with parallel cultures for each experimental point. Per culture 100 metaphase plates were scored for structural chromosome aberrations. The selected concentrations in the main experiment were in the range of 50 to 600 µg/ml in the absence of S9-mix; three of six concentrations were evaluated. In the presence of S9-mix the tested concentrations were ranging from 2.5 to 80 µg/ml, three of six concentrations were evaluated. The concentrations in the main experiment were based on a preliminary cytotoxicity test.

Results

In the absence and the presence of S9-mix, statistically significant and biologically relevant increases in the number of cells carrying structural chromosomal aberrations were observed both with and without S9-mix after treatment with the test item. A more than 10 fold increase compared to negative controls was observed, and less than half of the aberrations were exchanges.
No relevant increase in the frequencies of polyploid metaphases was found after treatment with the test item as compared to the frequencies of the controls. Also in the absence of S9-mix slightly increased rates of endomitotic rnetaphases were observed.

Conclusion
In conclusion, it can be stated that under the experimental conditions reported, the test item induced structural chromosome aberrations in mammalian cells *in vitro*, and A12 is considered to be a potent in vitro clastogen both in the absence and the presence of S9-mix.

Ref.: 9

Comment
Since more than half of the structural chromosomal aberrations were chromatid or chromosome breaks, it can be assumed that such changes, but not the remaining exchanges, can be detected in a micronucleus assay.

3.3.6.2 Mutagenicity/Genotoxicity *in vivo*

In vivo Mammalian Erythrocytes Micronucleus Test

Guideline:	OECD 474 (1997)
Species/strain:	mouse, NMRI
Group size:	6 males and six females per dose group
Test substance:	A12 / SAT 030386
Batch:	4 CRB 921
Purity:	98.1%
Vehicle:	deionised water
Dose level:	25, 50 and 100 mg/kg bw (24h preparation interval) 100 mg/kg bw (48h preparation interval)
Dosing volume:	10 ml/kg bw
Route:	intraperitoneal, single standard volume
Control:	cyclophosphamide
GLP:	in compliance
Study period:	26 July – 9 December 2004

The dose selection in the main study was based on two pre experiments with 2 males and 2 females per dose group. In the first experiment the animals received 100 mg/kg bw 4-chlororesorcinol and in the second experiment 150 mg/kg bw. At the highest dose all animals had to be euthanized after 10 minutes due to severe toxicity. Therefore 100 mg/kg was selected as the highest dose in the main experiment. In order to quantify the concentration of the test item in blood, 3 additional males per sampling interval were treated with 100 mg test item/kg bw intraperitoneally. Twenty and 40 minutes as well as 1 and 4 hours after the treatment the animals were sacrificed and their blood was collected and analysed in a separate experiment.

Results
The mean number of polychromatic erythrocytes was slightly decreased after treatment with the test item as compared to the mean value of PCEs of the vehicle control, indicating that A12 had some cytotoxic properties in the bone marrow. In addition the analysis of the blood samples of the males treated with 100 mg test item /kg bw showed, that the test item could be quantified in the blood of the treated animals 20 (53, 53 and 36 µg/mL) and

40 minutes (9.0, 8.1 and 10.1 µg/mL) after the treatment, but not at later time points, showing bioavailability of the test item.
In comparison to the corresponding vehicle controls there was no statistically significant or biologically relevant enhancement in the frequency of the detected micronuclei at any preparation interval and dose level after administration of the test item. The mean values of micronuclei observed after treatment with A 12 were below or near to the value of the vehicle control group.

Conclusion
Based on these data it can be concluded that A12 was not clastogenic and/or aneugenic under the experimental conditions reported.

Ref.: 10

3.3.7. Carcinogenicity

It should be noted that the long-term carcinogenicity study under the USA National Toxicity Programme mentioned in the opinions of 10 October 1988 and of 10 December 1993 (cited in the background of this opinion) has apparently not been performed.

3.3.8. Reproductive toxicity

3.3.8.1. Two generation reproduction toxicity

No data submitted

3.3.8.2. Teratogenicity

Dose-range finding prenatal development toxicity study

Guideline:	OECD 414 (2001)
Species/strain:	rat, HanBrl:WIST(SPF)
Group size:	20 mated females, 5 per group
Test substance:	4-Chlororesorcinol (SAT 040291)
Batch:	4 CRB 921
Purity:	98.1%
Vehicle:	ultra-pure water
Dose levels:	0, 75, 150, 300 mg/kg bw
Dose volume:	10 ml/kg bw
Route:	oral, gavage
Administration:	daily from day 6 through day 20 *post coitum*
GLP statement:	in compliance
Study period:	August 2004

The purpose of this study was to assess the effects of 4-chlororesorcinol on embryonic and foetal development when administered orally by gavage once daily to mated female rats from day 6 through to day 20 post coitum. Each group consisted of 5 mated female rats. 4-Chlororesorcinol was administered once daily at dose levels of 75, 150 and 300 mg/kg bw/d. Control animals were dosed with the vehicle alone (ultra-pure water). All surviving females were sacrificed on day 21 post coitum and the foetuses were removed by Caesarean section.

Results
At the highest dose 300 mg/kg bw/day, one female died on day 7 post coitum and two females died on day 20 post coitum. All other females survived until termination of the study. At this dose

clonic spasms were noted for all females after administration of the test item on most days of the treatment period. On many days, the spasms were accompanied by ventral recumbency. Food consumption was significantly reduced between days 6 - 15 post coitum. At 150 mg/kg bw/day, clonic spasms or tremor were noted for all females after administration of the test item on most days of the treatment period. At 75 mg/kg bw/day, slight tremor was noted for all females after administration of the test item on some days of the treatment period. Only a tendency towards reduced food consumption was noted for the first and the last two recording intervals. At 300 and 150 mg/kg bw/day, mean body weight gain during the treatment period was statistically significantly reduced.

The relevant reproduction data (incidence of post-implantation loss and number of foetuses per dam) were similar in all groups and gave no indication of test item-related effects. None of the foetal parameters under investigation in this study (sex ratios, foetal weights, external examination) gave an indication of test item-related effects. Based on these data 0, 50, 100 and 200 mg/kg/day are considered suitable for a subsequent main study on prenatal development in the Han Wistar rat.

Ref.: 13

Prenatal development toxicity study

Guideline:	OECD 414 (2001)
Species/strain:	rat, HanBrl:WIST(SPF)
Group size:	88 mated females, 22 per group
Test substance:	4-Chlororesorcinol (SAT 040291)
Batch:	4 CRB 921
Purity:	98.1%
Vehicle:	ultra-pure water
Dose levels:	0, 50, 100, 200 mg/kg bw
Dose volume:	10 ml/kg bw
Route:	oral, gavage
Administration:	daily from day 6 through day 20 *post coitum*
GLP statement:	in compliance
Study period:	25 August - 24 September 2004

The purpose of this study was to assess the effects of 4-chlororesorcinol on embryonic and foetal development when administered orally by gavage once daily to mated female rats from day 6 through to day 20 post coitum. Each group consisted of 22 mated female rats and the test substance was administered at dose levels of 50, 100 and 200 mg/kg bw/d. Control animals were dosed with the vehicle alone (ultra-pure water). All females were sacrificed on day 21 post coitum and the foetuses were removed by Caesarean section. Examination of dams and foetuses was performed in accordance with international recommendations.

Results
All animals survived until scheduled Caesarean section. Following administration of 200 mg/kg of the test item clonic spasms or tremor were noted for all females on all treatment days. In the 100 mg/kg group, following administration of the test item tremor was noted for all females during the first six to eleven treatment days. These clinical signs were considered to be test item related. Mean food consumption was similar in all groups. No test item-related effects on body weight gain were noted. Also body weight gain corrected for gravid uterus weights did not give an indication of test item-related effects.

The pregnancy rate was 100% and the mean numbers of Corpora lutea and implantation sites were similar in all groups. Post-implantation losses and the mean number of foetuses per dam were unaffected by treatment with the test item at all dose levels. A slightly higher incidence of post-implantation loss was noted in the 50 and 100 mg/kg groups (8.5 and

8.6% of implantation sites) when compared to the vehicle control (4.3%). In the absence of a dose-relationship these higher incidences were considered to be incidental. This opinion is supported by the fact that these values were well within the range of historical control data.

No test item-related macroscopic findings were noted at necropsy. In the 50 mg/kg group, absence of the right kidney and a (compensatory) enlarged left kidney was noted for one female. Mean foetal body weights and foetal sex ratios were similar in all groups and gave no indication of a test item related effect. No abnormalities were noted during external examination of foetuses. During visceral examination of fixed foetuses no test item related abnormal findings were noted. Skeletal examination gave no indication for test item-related effects.

Conclusion
With respect to the clinical signs noticed in the mid and high dose group, the NOAEL was considered to be 50 mg/kg bw/d for maternal toxicity. For foetotoxicity, the NOAEL was set at 200 mg/kg bw/d.

Ref.: 14

3.3.9. Toxicokinetics

No data submitted

3.3.10. Photo-induced toxicity

3.3.10.1. Phototoxicity / photoirritation and photosensitisation

No data submitted

3.3.10.2. Phototoxicity / photomutagenicity / photoclastogenicity

No data submitted

3.3.11. Human data

No data submitted

3.3.12. Special investigations

No data submitted

3.3.13. Safety evaluation (including calculation of the MoS)

CALCULATION OF THE MARGIN OF SAFETY

4-Chlororesorcinol
(with H_2O_2)

Absorption through the skin	**A (µg/cm²)**	**=**	**8.31 µg/cm²**
Skin Area surface	**SAS (cm²)**	**=**	**580 cm²**
Dermal absorption per treatment	**SAS x A x 0.001**	**=**	**4.82 mg**
Typical body weight of human		**=**	**60 kg**
Systemic exposure dose (SED)	**SAS x A x 0.001/60**	**=**	**0.080 mg/kg**
No observed adverse effect level (maternal toxicity, oral, rat)	**NOAEL**	**=**	**50 mg/kg/d**
Margin of Safety	**NOAEL / SED**	**=**	**625**

(without H_2O_2)

Absorption through the skin	**A (µg/cm²)**	**=**	**10.99 µg/cm²**
Skin Area surface	**SAS (cm²)**	**=**	**580 cm²**
Dermal absorption per treatment	**SAS x A x 0.001**	**=**	**6.37 mg**
Typical body weight of human		**=**	**60 kg**
Systemic exposure dose (SED)	**SAS x A x 0.001/60**	**=**	**0.106 mg/kg**
No observed adverse effect level (maternal toxicity, oral, rat)	**NOAEL**	**=**	**50 mg/kg/d**
Margin of Safety	**NOAEL / SED**	**=**	**472**

3.3.14. Discussion

Physico-chemical properties
4-Chlororesorcinol is used as a coupler in oxidative hair dye formulations. It reacts with primary intermediates to form the final dye-stuff. It is used at a maximum on head concentration of 2.5%.
The solubility of 4-chlororesorcinol was not determined by the EC method A6. The stability of 4-chlororesorcinol in a typical hair dye formulation was not reported.

Toxicity
The acute median lethal oral dose (LD_{50}) and its 95% confidence limits to rats of 4-chlororesorcinol were calculated to 369 (314-433) mg/kg.
In a subchronic toxicity study, due to clinical signs and haematotoxicity at 210 mg/kg bw/d, the No Observed Adverse Effect Level (NOAEL) in rats after daily oral treatment was determined to be 70 mg/kg bw/day.
In the prenatal developmental toxicity study, with respect to the clinical signs noticed in the mid and high dose group, the NOAEL was considered to be 50 mg/kg bw/d for maternal toxicity. For foetotoxicity, the NOAEL was set at 200 mg/kg bw/d. No two generation study was submitted.

Skin/eye irritation and sensitisation

Neat 4-chlororesorcinol is irritating to the skin and corrosive to the eyes.
According to the grading scheme used by the SCCS (SCCP/0919/05), 4-chlororesorcinol should be considered as a moderate skin sensitiser (EC3-value >2).

Percutaneous absorption
The dose of the test formulation was lower (10 mg/cm^2) than the recommended dose of 20 mg/cm². In water, the absorption was about ten times higher compared with the formulations. Consequently, the absorption/Margin of Safety will depend largely on the formulation used. Because of the too low dose, the high variability in the experiments and the observed vehicle dependency of absorption, the mean + 2SD will be used for calculation of MoS. Accordingly, in the presence of hydrogen peroxide the dermal absorption was 8.31 μg/cm² (3.91 + 2 x 2.20 μg/cm²), in the absence of hydrogen peroxide 10.99 μg/cm² (5.05 + 2 x 2.97 μg/cm²).

Mutagenicity/genotoxicity
A12 was tested for genotoxic potential for the three genotoxicity endpoints: gene mutation, structural and numerical chromosomal aberrations. The test substance did not induce gene mutations in bacteria and in mammalian cells at the *tk* locus. It was a strong clastogen, inducing mainly chromosome and chromatid breaks in Chinese hamster V79 lung cells. However, this clastogenic effect could not be confirmed in an *in vivo* micronucleus assay. Therefore, it is concluded that A12 is not an *in vivo* mutagen.

Carcinogenicity
No data submitted

4. CONCLUSION

Based on the information provided, the SCCS is of the opinion that the use of 4-chlororesorcinol itself as an oxidative hair dye substance at a maximum on-head concentration of 2.5% does not pose a risk to the health of the consumer, apart from its moderate skin sensitising potential.

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

5. MINORITY OPINION

Not applicable

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