



Scientific Committee on Consumer Products

SCCP

**MEMORANDUM ON
HAIR DYE SUBSTANCES AND THEIR SKIN SENSITISING
PROPERTIES**

Adopted by the SCCP during the 10th plenary of 19 December 2006

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SCCP

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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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1. BACKGROUND

In view of particular safety concerns expressed in relation to the use of some hair dyes, the Commission agreed in April 2003 together with Member States and the stakeholders, on an overall detailed strategy to regulate hair dye substances within the framework of the Cosmetics Directive (4, 7).

Industry has submitted dossiers on 117 different hair dye substances used in hair dye products. Because of missing dossiers the Commission has recently banned 22, and is in process of acting on others. The potential risk of cancers, genotoxicity or mutagenicity caused by use of certain hair dye substances has raised much concern. The fact that a number of hair dye substances are well-known skin sensitisers has, however, not drawn much attention, until now.

p-Phenylenediamine and related compounds have, for more than 100 years, been used in permanent hair dyes, and more than two thirds of hair dyes currently used contain p-phenylenediamine. p-Phenylenediamine is a well-known and potent skin sensitiser. Scientific reporting and clinical diagnosis in patients with dermatitis from hair dyes have focused on p-phenylenediamine as the main skin sensitiser. p-Phenylenediamine 1% in petrolatum is used in the European standard series for diagnostic patch testing in patients with eczematous skin conditions. Knowledge among dermatologists about the use of other hair dye substances, and access to these for patch testing, are limited. Testing with p-phenylenediamine alone may fail to detect contact allergy to relevant hair dye substances (3, 17).

Several studies in Europe (UK, Germany, Belgium, Portugal) and in Asia (Thailand, Japan, Singapore) show that contact allergy to p-phenylenediamine has increased significantly in the general population and in hairdressers over the last decades. It has been estimated that up to 1.3 million adults in Germany may be sensitive to p-phenylenediamine. (2, 8, 9, 13, 15, 18-20)

In a consumer complaint-based data analysed for persons who reported adverse reactions to hair dyes, 55 cases of severe, acute allergic contact dermatitis were identified. The clinical picture was severe oedema of the face, scalp and ears, clinically often mistaken for angio-oedema. Admissions to hospital and sick leave were reported, which indicate very severe dermatitis (16).

Market surveys in Europe, the US and in Japan, indicate that hair dyeing has become much more prevalent during the last ten years, that it is done at a younger age and that the proportion of men is increasing (9). In Denmark, 75% of women and 18% of men reported that they have used hair dye; the median age at first hair dyeing was 16 years (18).

The objective of this memorandum is to draw the attention of the Commission to the fact that many of currently used hair dye substances are skin sensitisers, and that this property may be of concern for the health of consumers.

2. CLASSIFICATION AND CATEGORISATION OF SKIN SENSITISERS

The animal test methods used in harmonised classification of substances, according to their potential to cause skin sensitisation, are the guinea pig maximisation test (GPMT), the Buehler test, and the local lymph node assay (LLNA) (11, 12). These methods are used in hazard identification and risk assessment for regulatory purpose (Directives on Dangerous Substances 67/548/EEC, Dangerous Preparations 1999/45/EC). As yet, there is not a validated *in vitro* test method accepted for skin sensitisation. Therefore, also for cosmetic

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ingredients the LLNA, the GPMT and the Buhler test are used in accordance with the Cosmetics directive 76/768/EEC and the SCCP Notes of Guidance (14).

According to Directives 67/548/EEC and 1999/45/EC, substances and preparations shall be classified as sensitising and assigned the symbol "Xi", and the risk phrase "R43 May cause sensitisation by skin contact". Positive results from OECD guideline animal tests (11, 12) sufficient to classify a substance with R43 are:

- GPMT: if at least 30% of the animals have a positive response.
- Buehler test: if at least 15% of the animals have a positive response
- LLNA: if at least a 3-fold increase in proliferative counts is induced, compared to vehicle-treated controls (stimulation index $SI \geq 3$).

Further categorisation of substances classified with R43 into three groups according to allergen potency (extreme, strong and moderate) has been proposed (1, 5, 6, 10). Such categorisation is based on EC3 values in the LLNA (Table 1), on intradermal induction concentration in the GPMT (Table 2), and topical induction concentration in the Buehler test (Table 3). When EC3 values are available from more than 1 study, the lowest value should normally be used. Where multiple animal data sets lead to different categorisation of the same substance, the higher potency category should apply (1, 5, 6).

Table 1: Potency categorisation of substances classified with R43, based on the local lymph node assay (LLNA) (1, 6)

Category	EC3 value (%) ^{a)}
Extreme	≤ 0.2
Strong	$> 0.2 - \leq 2$
moderate	> 2

^{a)} EC3 value = the estimated concentration of a chemical necessary to give a 3-fold increase in lymph node cell proliferative activity compared to vehicle-treated controls ($SI \geq 3$).

Table 2: Potency categorisation based on the guinea pig maximisation test (GPMT) (1, 6)

Intradermal concentration employed during induction phase (%) ^{a)}	Incidence of sensitisation (30-<60%)	Incidence of sensitisation ($\geq 60\%$)
≤ 0.1	Strong	Extreme
$> 0.1 - \leq 1$	Moderate	Strong
> 1	Moderate	Moderate

^{a)} According to guideline, intradermal induction concentration must be the highest concentration causing mild to moderate irritation.

Table 3. Potency categorisation based on Buehler test (1, 6)

Concentration employed during induction phase (%) ^{a)}	Incidence of sensitisation (15-<60%)	Incidence of sensitisation ($\geq 60\%$)
≤ 0.2	Strong	Extreme
$> 0.2 - \leq 20$	Moderate	Strong
> 20	Moderate	Moderate

^{a)} According to guideline, the topical induction concentration must be the highest concentration causing mild but not excessive irritation.

3. HAIR DYES AND THEIR SKIN SENSITISING POTENTIAL

The safety of hair dye substances is being assessed by the SCCP, based on documentation submitted by industry, including scientific publications and reports by industry on animal sensitisation tests. The SCCP and the former SCCNFP have, until now, assessed the dossiers of 46 of the 117 hair dye substances of interest to industry regarding their skin sensitising property (Table 4).

In Table 4, the hair dye substances are classified according to the abovementioned classification criteria. Substances fulfilling the criteria for classification with R43, are further categorised as extreme, strong and moderate skin sensitisers (1, 6, 10).

In summary, 27 of the 46 hair dye substances assessed by the SCCP fulfil the EU criteria for classification as skin sensitiser (R43). Further categorisation of skin sensitising potency, shows that 10 of the 27 classifiable hair dye substances are extreme sensitisers, 13 are strong, and 4 are moderate sensitiser.

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Table 4. Hair dye substances assessed by the SCCP and the former SCCNFP concerning their skin sensitising property, based on submissions by industry. Results from studies performed by OECD guideline methods (LLNA, GPMT, Buehler test). Typically, results from one study per method are displayed. The substances fulfilling the criteria for classifications as skin sensitiser (R43) were categorised according to their sensitising potency (1, 6, 10)

COLIPA N°	Substance	Sensitising potency category	LLNA		GPMT		Buehler test		SCCP/SCCNFP opinion (doc. no.)
			EC3 value (%)	category	i.d. ind./incid.	category	t. ind./incid.	category	
A7	p-Phenylenediamine	extreme	0.06	extreme	-	-	-	-	SCCP/0989/06
A9	N-Phenyl-p-phenylenediamine	extreme	0.02	extreme	-	-	-	-	SCCP/0991/06
A33	1,2,4-Trihydroxybenzene	extreme	0.08	extreme	-	-	-	-	SCCP/0962/05
A111	Dihydroxyindole	extreme	0.17	extreme	0.1/0	not classifiable	-	-	SCCP/0952/05
A128	6-Hydroxyindole	extreme	<0.2 b); 0.2	extreme	0.5/40	moderate	5/30	moderate	SCCP/0947/05
A129	Isatin	extreme	<1 b); 2.5	strong; moderate	0.1/100	extreme	25/0 f)	not classifiable	SCCP/0876/05
B7	Basic Brown 17	extreme	n.v.	not classifiable	0.1/70 d.g)	extreme g)	-	-	SCCP/0683/03
B24	4-Nitro-o-phenylenediamine	extreme	≤0.05	extreme	-	-	-	-	SCCP/0980/06
B48	HC Red n° 1	extreme	<2 a)	strong	0.1/100	extreme	-	-	SCCP/0981/06
B54	3-Nitro-p-hydroxyethylaminophenol	extreme	0.07	extreme	-	-	-	-	SCCP/1036/06
A15	m-Aminophenol	strong	0.24	strong	-	-	-	-	SCCP/0978/06
A27	4-Amino-2-hydroxytoluene	strong	0.44	strong	-	-	-	-	SCCP/1001/06
A39	Phenyl methyl pyrazolone	strong	≤1	strong	-	-	-	-	SCCP/1033/06
A50	N,N-bis(2-hydroxyethyl)-p-phenylenediamine sulfate	strong	<0.25 b); 1.04	strong	-	-	-	-	SCCP/0983/06
A74	4-Amino-m-cresol	strong	1.45	strong	-	-	-	-	SCCP/0898/05
A98	Hydroxyethyl-3,4-methylenedioxyaniline HCl	strong	<0.5 b)	strong	-	-	-	-	SCCP/0951/05
A101	2,6-Dimethoxy-3,5-pyridinediamine HCl	strong	1.25	strong	1/15 f)	not classifiable	-	-	SCCP/0908/05
A121	Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine)HCl	strong	-	-	1/90	strong	-	-	SCCP/1051/06
A154	1-Hydroxyethyl-4,5-Diamino Pyrazole Sulfate	strong	-	-	1/100	strong	40/25	moderate	SCCP/0990/06
B66	HC Violet n° 1	strong	0.9	strong	25/0 f)	not classifiable	-	-	SCCP/1025/06
B99	2-Amino-6-chloro-4-nitrophenol	strong	0.68	strong	-	-	-	-	SCCP/0948/05
C117	Hydroxyanthraquinone-aminopropyl Methyl Morpholinium Methosulfate	strong	-	-	0.875/90	strong	26.3/45 8.65/47	moderate	SCCP/0875/05
C146	Lawson	strong	-	-	1/65 f)	strong	-	-	SCCNFP/0798/04
A22	p-Methylaminophenol sulphate	moderate	2.2	moderate	-	-	-	-	SCCP/0963/05
A42	2,4-Diaminophenoxyethanol and its salts	moderate	3.2	moderate	-	-	100/10	not classifiable	SCCP/0979/06
A44	2-Methylresorcinol	moderate	50	moderate	-	-	-	-	SCCP/1002/06
A147	Dihydroxyindoline HBr	moderate	-	-	10/55	moderate	40/0	not classifiable	SCCNFP/0669/03
A25	Hydroxybenzomorpholine	not classifiable	-	-	1/0	not classifiable	-	-	SCCP/0965/05
A31	2-Methyl-5-hydroxyethylaminophenol	not classifiable	n.v.	not classifiable	-	-	-	-	SCCP/0957/05
A84	2-Amino-4-hydroxyethylaminoanisol sulfate	not classifiable	n.v. c)	not classifiable	-	-	-	-	SCCP/0958/05)

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COLIPA N*	Substance	Sensitising potency category	LLNA		GPMT		Buehler test		SCCP/SCCNFP opinion (doc. no.)
			EC3 value (%)	category	i.d. ind./incid.	category	t. ind./incid.	category	
A157	Quinolinium, 4-formyl-1-methyl-, salt with 4-methylbenzenesulfonic acid (1:1)	not classifiable	n.v.	not classifiable	-	-	50/0 h)	not classifiable	SCCP/0923/05
B75	Hydroxyethyl-2-nitro-p-toluidine	not classifiable	n.v.	not classifiable	-	-	-	-	SCCP/0924/05
C29	Acid Yellow 23	not classifiable	-	-	5/0	not classifiable	-	-	SCCNFP/0786/04
C40	Acid Blue 9	not classifiable	n.v.	not classifiable	-	-	-	-	SCCNFP/0787/04
C63	Acid Violet 43	not classifiable	n.v.	not classifiable	-	-	-	-	SCCP/0964/05
C67	Acid Blue 62	not classifiable	n.v.	not classifiable	-	-	-	-	SCCP/0878/05
C169	Lawsonia inermis (Henna)	not classifiable	-	-	-	-	50/0 f)	not classifiable	SCCP/0943/05
C174	Curry Red	not classifiable	n.v.	not classifiable	-	-	-	-	SCCNFP/0791/04
C175	Acid Red 18	not classifiable	n.v.	not classifiable	-	-	-	-	SCCNFP/0792/04
C177	Acid Red 52	not classifiable	-	-	5/0	not classifiable	-	-	SCCNFP/0803/04
C178	Acid Green 25	not classifiable	-	-	5/0 d,f)	not classifiable	-	-	SCCP/0879/05
A16	para-Aminophenol	j) i)	-	-	-	-	-	-	SCCP/0867/05
A80	Hydroxyethyl-p-phenylenediamine Sulfate	i)	-	-	-	-	-	-	SCCP/0666/03
A99	2,6-Dihydroxy-3,4-dimethylpyridine	j)	≤25 a); n.v.	?	-	-	-	-	SCCP/1034/06
B37	HC Blue N°2	j)	≤5 a); n.v.	?	-	-	-	-	SCCP/1035/06
C54	Acid Yellow 3	i)	-	-	-	-	-	-	SCCNFP/0789/04

Sensitisation potency category = based on the highest potency category from the tests with animal guideline methods (LLNA, GPMT, Buehler test)

EC3 value = EC3 values derived from LLNA dose-responses give the amount of chemical sensitiser that is required to elicit a three-fold increase in lymph node cell proliferative activity

i.d. ind./incid = intradermal induction concentration (%)/incidence of sensitisation (%)

t. ind./incid. = topical induction concentration (%)/incidence of sensitisation (%)

- = no data

n.v.=no value, stimulation index (SI) <3

not classifiable = the criteria for classification as R43, based on animal data, not fulfilled

a) = EC3 value was not calculated in the ref.

b) = The lowest test concentration was too high, an EC3 value could not be calculated

c) = The highest test concentration was too low, a stimulation index (SI) of ≥3 might have been achieved with higher concentration

d) = The induction concentration was too low

e) = The challenge concentration was too low

f) = Staining of the skin might have interfered with reading of test reactions

g) = The test was not acceptable

h) = Test vehicle may not be suitable

i) = Guinea pig test performed by non-guideline methods only

j) = Results indicate sensitisation potential

4. CONCLUSION

Contact allergy and allergic contact dermatitis caused by hair dyes is an important and increasing health problem to consumers and society, often causing acute and severe dermatitis on the face, scalp and neck.

Until now, the SCCP and the former SCCNFP opinions on substances, for which the dossiers submitted by industry have been assessed, have largely concerned the general toxicology of the substances, albeit there has been a statement regarding sensitising potential. Of the adopted opinions on 46 hair dye substances, 10 of these substances were categorised as extreme, 13 as strong and 4 as moderate skin sensitisers, all fulfilling the EU criteria for classification as a skin sensitiser (R43).

The SCCP wishes to state that hair dye substances which fulfil the criteria for classification as R43, may not be safe for consumers. This is particularly so for hair dye substances categorised as extreme and strong skin sensitisers.

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