EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Public Health and Risk Assessment
C7 - Risk assessment

SCIENTIFIC COMMITTEE ON CONSUMER PRODUCTS

SCCP

Opinion

On

Personal Use of Hair Dyes and Cancer Risk

Adopted by the SCCP during the 5th plenary meeting
of 20 September 2005

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1. BACKGROUND

The Scientific Committee on Cosmetics and Non Food Products intended for Consumers (SCCNFP) adopted an opinion on "The use of Permanent Hair Dyes and Bladder Cancer Risk" during the 17th plenary meeting of 12 June 2001 (SCCNFP/0484/01), updated on 23 April 2004 by means of the written procedure (SCCNFP/0797/04). In its opinion the SCCNFP stated that the European Commission should take further steps to control the use of hair dye chemicals since the potential risks of using this category of substances give cause for concern.

This opinion was the basis for the Opinion of the SCCNFP adopted during the 22nd plenary meeting of 17 December 2002 on "Assessment Strategies for Hair Dyes" (SCCNFP/0553/02). After discussion within the European Commission and with Member States and stakeholders a step-wise strategy was established to regulate all hair dyes listed as ingredients in cosmetic products.

Recently, the European Commission received publications on the possible link of occupation and bladder cancer, personal hair dye use and bladder cancer, hair-colouring products and non-Hodgkin's Lymphoma as well as hair dye use and adult Acute Leukaemia.

2. TERMS OF REFERENCE

1. *On the basis of currently available information and taken into account the data provided, the SCCP is asked if the data provided in the attached publications change the overall assessment of the use of hair dyes and cancer risk as stated in the opinion SCCNFP/0484/01, updated in the opinion SCCNFP/0797/04?*

2. *On the basis of currently available information and taken into account the data provided, does the SCCP recommend any other requirements for assessing hair dyes than already recommended in its opinion "Assessment Strategies for Hair Dyes" (SCCNFP/0553/02, Opinion of the SCCNFP adopted during the 22nd plenary meeting of 17 December 2002)?*

3. OPINION

Professor Elsebeth Lynge (University of Copenhagen) and Professor Tore Sanner (member of SCCP) were asked to review and assess if personal use of hair dyes represent a cancer hazard. Based on a review of different types of cancer it was decided that the assessment should concentrate on leukaemia and bladder cancer. The results are summarized in section 3.3. Tables.

3.1. Leukaemia

Cohort studies

Grodstein *et al.* (1994) using the Nurses Health Study (cohort study of 99,067 women aged 30-55 years in 1976 followed to 1990), reported no increase in the risk of chronic lymphocytic leukaemia (RR=0.6; 0.3-1.5, 8 cases) or other leukaemia (R=0.8; 0.3-1.9, 8 cases) and the use of permanent hair dyes.

Altekruse *et al.* (1999) reported in a cohort study (CPSII, 547,586 women, enrolled 1982, followed to 1994) some indication for a possible increased risk of death from all leukaemia among women using permanent hair dyes (RR=1.1; 0.9-1.3, 207 cases). The risk increased with duration of use: 1 – 9 years RR=0.9 (0.7-1.2, 69 cases), 10 – 19 years RR=1.2 (0.9-1.5, 78 cases), 20+ years RR=1.3(1.0-1.7, 60 cases), p-value for trend 0.04.

Case control studies

In a hospital-based case-control study (101 matched pairs) of acute non-lymphocytic leukaemia in the Baltimore (USA) area, published only as an abstract, Markowitz *et al.* (1985) found a significant positive association with hair-dye use (OR=3.1). There was, however, no difference between regular use (at least once a year) (OR=2.7) and less frequent use (OR=2.2) [95% confidence intervals and number of cases not presented].

Cantor *et al.* (1988) carried out a population-based case-control study of hair-dye use among 578 men with leukaemia and 1245 population controls in Iowa and Minnesota, USA, in 1980-83. Significantly raised ORs were found for leukaemia (1.8; 1.1-2.7) in association with personal use or other potential exposure to hair tints, any hair colouring product or hair dyes. An elevated risk was also found here for the dysmyelopoietic syndrome (may develop to myeloid leukaemia), RR=2.9 (1.2-7.1).

A population-based case-control study carried out in eastern Nebraska, USA, during 1983-86 investigated use of hair colouring products among a total of 37 male and 19 female cases of chronic lymphocytic leukaemia and 725 male and 707 female residential controls who could be interviewed (Zahm *et al.,* 1992). Use of any hair dye was not associated with chronic lymphocytic leukaemia in either women (1.0; 0.3-2.6, 19 cases) or men (1.0; 0.2-3.8, 37 cases).

Mele *et al.* (1994) using patients from three hospitals in Italy found no statistically significant increased risks for acute myeloid leukaemia, acute lymphocytic leukaemia or chronic myeloid leukaemia. The study involved primarily women and semi-permanent and permanent hair dyes (the two types are not analyzed separately). The authors state that the results were consistent with a modest effect of dark hair dye use: > 10 year use. Acute myeloid leukaemia 1.7 (0.7-4.0, 25 cases), acute lymphocytic leukaemia 1.9 (0.5-7.9, 6 cases), and chronic myeloid leukaemia 1.2 (0.4-3.9 13 cases). No excess risk was found for refractory anaemia with excess of blasts, RAEB or in acute promyelocytic leukaemia (Mele *et al*. 1995).

Elevated risks for the dysmyelopoietic syndrome were also found in two studies from Japan with relative risks among women of 2.50 (0.97-6.41, 29 cases) (Ido *et al*, 1996) and 2.88 (1.38-6.01, 25 cases) (Nagata *et al.* 1999), respectively. In the study by Nagata and co-workers the RR=1.99 (1.17-3.38, 34 cases) for both sexes together. The risk increased with duration of use (10+ years RR=4.10; 1.64-10.23) and total frequency of use (70+ RR=3.08; 1.22-7.75). No increase was found in a small group of men (OR=1.23; 0.53-2.88, 9 cases). It is uncertain whether or not there is an overlap between the cases from the two Japanese studies. Personal communication to the author was not answered.

The risk of chronic lymphatic leukaemia was elevated in two case-control studies. In a study from Yugoslavia it was found that RR 1.97 (1.08-3.59, 11 cases) (Markovic-Denic *et al.* 1995). In a larger study from Spain, no increase in the risk of all lymphomas was found. However, the

risk of chronic lymphocytic leukaemia was increased, RR=2.3 (1.1-4.7, 37 cases). The risk increased with time exposed and with lifetime dose. The risk was only significantly increased among those starting to use hair dyes before 1980 (RR=3.5; 1.5-7.8, 27 cases) and not among those starting after 1980 (RR=1.5; 0.6-3.6, 10 cases). The risk was significantly increased among those using permanent hair dyes (RR=3.4; 1.4-7.8, 35 cases). The numbers using semi-permanent hair dyes were to small to draw any conclusion (RR=1.6; 0.4-6.6, 3 cases). (Benavente *et al*. In press).

Miligi *et al.* (1999) found no increase among hair dye use and leukaemia (0.9; 07-1.3, number of cases not given). The risk was, however, increased among women using dark permanent products (2.0; 1.1-3.8, number of cases not given).

Björk *et al.* (2001) found no relationship between use of hair dyes and chronic myeloid leukaemia (0.35; 0.18-0.68, 25 cases).

Rauscher *et al.* (2004) performed a population-based case-control study of acute leukaemia in 1986–1989 in USA and Canada. There was a modest positive association for ever use of hair dyes (OR= 1.3; 1.0-1.8, 185 cases). The increase was stronger among those only using permanent dye (OR=1.6; 1.1-2.4, 87 cases). The risk increased for long duration (15+ years) of use (OR=1.9; 1.1- 3.6, 39 cases). The greatest odds ratio was for 15 or more years of using hair dyes up to six times per year (OR=2.4; 1.0-5.8, 20 cases). First use before 1970 represented a higher risk (OR=1.7; 1.0-3.0, 45 cases) than first used after 1979 (OR=1.2; 0.51-2.9, 13 cases). When stratified by leukaemia subtype, ever use of permanent hair dyes was associated with an OR of 1.6 (1.1- 2.5) for myelocytic leukaemia, and the trends in risk with duration and frequency were similar to the trends observed for all leukaemia subtypes combined. For lymphoblastic leukaemia, the OR for ever use of permanent dyes was 2.0 (0.9- 4.6). There was a suggestion of a dose response for both duration and frequency, with the OR reaching 4.6 (1.5-14) for 15 or more years of use and the OR reaching 3.8 (1.2-12) for six or more applications per year. The authors conclude that long duration of permanent dye use may have a larger impact on the risk of adult acute leukaemia and other haematopoietic cancers than prior epidemiological data suggest.

Conclusion

Any use of hair dyes

Twelve case-control studies have been evaluated. 5 studies, 1 from Nebraska concerning chronic lymphocytic leukaemia (CLL) with 56 cases (Zahm *et al.* 1992), 3 from Italy on acute myeloid leukaemia (AML) acute promyelocytic leukaemia (APL) and all leukaemia, number of cases were not available Mele *et al.* 1994, 1995 and Miligi *et al.* 1999), and 1 from Sweden with 25 cases on chronic myeloid leukaemia (CML) (Björk *et al.* 2001), where negative.

Seven studies were evaluated as positive. 3 studies were from USA. The first from Baltimore was only published in an abstract (acute non-lymphocytic leukaemia, ANLL) and no confidence interval or numbers of cases were given (Markowitz *et al.* 1985). In the study by Cantor *et al.* (1988) from Iowa and Minnesota the risk was 1.8 (1.1-2.7) (all leukaemia). A recent and large study from USA and Canada (Raucher *et al.* 2004) was only borderline positive (1.3; 1.0-1.8, 185 cases) (acute leukaemia, AL). One study from Spain was positive (2.3; 1.1-4.7) (CLL) (Benavente *et al.* In press) as was 1 study from Yugoslavia (1.97; 1.08-3.59) (CLL) (Markovic-Denic *et al.* 1995) and 2 studies on myelodysplastic syndrome from Japan showed that the risk was increased 2 – 3 times (Ido *et al.* 1996, Nagata *et al.* 1999).

Use of permanent hair dyes
Two cohort studies were evaluated. A small cohort study was negative (16 cases) (CLL and other leukaemia) (Grodstein *et al.* 1994), while a larger study was borderline positive (1.1; 0.9-1.3, 207 cases) (all leukaemia) with a significantly positive trend for year of use (p=0.04) (Altekruse *et al.* 1999).

Four case-control studies were evaluated. One study from Nebraska was negative (0.8; 0.1-4.0) (CLL) (Zahm *et al.* 1992). One study from Italy was equivocal as it was overall negative (1.2; 0.9-1.7) (all leukaemia) while an increased risk was found among those using dark permanent products (2.2; 1.1-3.8) (Miligi *et al.* 1999). Two recent studies, one from USA and Canada (1.6; 1.1-2.4, 87 cases) (AL) (Rauscher *et al.* 2004) and one from Spain (3.4; 1.4-7.8) (CLL) (Benavente *et al.* In press) were positive.

Although the published data are conflicting, especially, when all types of hair dyes is considered, it is concluded that some studies indicate excess risks for acute leukaemia and chronic lymphoid leukaemia for users of hair dyes.

3.2. Bladder cancer

Any use of hair dyes. Nine case-control studies were evaluated. All were negative. No cohort studies were available. It was therefore decided only to discuss on Use of permanent hair dyes.

Cohort studies

A cohort study from 1979 (Hennekens *et al.*) based on Nurses' Health Study was negative (RR=0.62; 0.22-1.58, 5 cases). Henley and Thun (2001) reported a cohort study (CPSII, 547,586 women, enrolled 1982 and followed to 1998). The risk of bladder cancer was not influenced by the use of permanent hair dyes (RR=1.08; 0.84-1.38, 92 cases). Neither was there any risk among non-smokers (RR=0.92; 0.61-1.40, 28 cases. No effect was found in relation to the duration of hair dye use.

Case-control studies

Stavraky *et al.* (1981) found no effect in women in a study involving 12 cases of kidney cancer and 23 cases of bladder cancer (RR=1.1; 0.4-2.8) in a study from Canada.

Gago-Dominguez *et al.* (2001a). A population-based case-control study was conducted in Los Angeles, California, which involved 1,514 incident cases of bladder cancer and an equal number of age-, sex- and ethnicity-matched controls. Information on personal use of hair dyes was obtained from 897 cases and their matched controls. The main results after adjustment for cigarette smoking are presented in Table 1.

Table 1. Odds ratio for bladder cancer in relation to permanent hair dyes.

Study	Numbers	Odds Ratio (95% C.I.)	Comments
Case-Control Bladder Los Angeles	897 cases; Cases/Controls **All hair dye** users 163/162 M+F *Only permanent* M+F; 95/71 F; 82/56 M; 13/15 ***Women used permanent dyes*** Non-smoker Smokers *All women* 15 years or more <12 times/year 31/21 12+ times /year 29/12 ***Hairdresser or barber*** Ever; 20/13 <10 years; 6/10 10+ years; 14/3	 1.0 (0.7-1.4) 1.4(0.9-2.2) 1.8(1.0-3.3) 0.8(0.4-2.0) 2.7(1.2-5.9) 1.4(0.8-2.4) 1.7(0.8-3.6) 3.3(1.3-8.4) 1.5(0.7-3.2) 0.5(0.2-1.6) 5.1(1.3-19.2)	All data adjusted for smoking, except for the lines "Non-smokers" and "Smokers"

Gago-Dominguez *et al.* (2001b) published a letter showing that the hair dye bladder cancers were associated with the N-acetyltransferase 2 (NAT2) phenotype "Slow acetylators".

The above findings have been further explored in a later publication by Gago-Dominguez *et al.* (2003). The authors have previously reported permanent hair dye use to be a significant risk factor for bladder cancer in US women. They have also examined N-acetyltransferase-2 (NAT2) phenotype in relation to the hair dye–bladder cancer relationship, and found that the association is principally confined to NAT2 slow acetylators (Gago-Dominguez *et al*. 2001b). In the present study, the possible modifying effects of a series of potential arylamine-metabolizing genotypes/phenotypes (GSTM1, GSTT1, GSTP1, NAT1, NAT2, CYP1A2) on the permanent hair dye–bladder cancer association among female participants (159 cases, 164 controls) of the Los Angeles Bladder Cancer Study have been further studied.

Among NAT2 slow acetylators, exclusive permanent hair dye use was associated with an OR=2.9 (CI=1.2–7.5, 33/22) for bladder cancer. The corresponding odds ratio in NAT2 rapid acetylators was 1.3 (CI=0.6–2.8, 32/26). Frequency and duration-related dose–response relationships confined to NAT2 slow acetylators were all positive and statistically significant. No such associations were noted among NAT2 rapid acetylators. Among CYP1A2 'slow' individuals, exclusive permanent hair dye use was associated with an OR=2.5 (CI=1.0–6.1,

37/17) for bladder cancer. The corresponding OR in CYP1A2 'rapid' individuals was 1.3 (CI=0.6–2.7). Frequency- and duration related dose–response relationships confined to CYP1A2 'slow' individuals were all positive and statistically significant. No such associations were noted among CYP1A2 'rapid' individuals (all data above was adjusted for smoking). Among lifelong non-smoking women, individuals exhibiting the non-*NAT1*10* genotype showed a statistically significant increase in bladder cancer risk associated with exclusive permanent hair dye use (OR=6.8 (CI=1.7–27.4, 10/11). The comparable OR in individuals with the *NAT1*10* genotype was 1.0 (CI=0.2–4.3, 5/8). Similarly, all frequency- and duration related dose–response relationships confined to individuals possessing the non-*NAT1*10* genotype were positive and statistically significant. On the other hand, individuals of *NAT1*10* genotype exhibited no such associations.

Comment: The above data strengthen the finding of increased risk for bladder cancer among users of permanent hair dyes and implicate arylamines contained in hair dye solution as the putative carcinogenic substances responsible for bladder cancer.

Andrew *et al.* (2004) studied the use of hair dyes and bladder cancer in New Hampshire. Among users of permanent hair dyes the risk of bladder cancer showed a non-significant increase among women (RR=1.5; 0.8-2.7, 32 cases), while no increase was found among a small group of men (RR=0.6; 0.2-1.5, 7 cases). The risk of bladder cancer was increased by a factor of 2.3 (1.1-4.6, 22 cases) among women that had started to use permanent hair dyes before the age of 37. No difference was found between women that had started to use permanent hair dyes before 1975 (1.5; 0.8-2.9, 22 cases) compared with those that started after 1975 (2.0; 0.8-5.4, 10 cases). The risk was increased by a factor of 2.6 (1.1-6.3, 14 cases) among those that started more than 31 years ago. The risk showed a non-significant increase with the total uses over lifetime: 1-35 uses, 1.7 (0.7-3.9, 13 cases); 35-282 uses, 1.3 (0.6-2.8, 12 cases); >282 uses, 3.3 (0.9-13, 7 cases).

No increase was found in an unpublished case-control study from Spain (Kogevinas et al. 2005). Use of any hair dye (OR=0.8, 95%CI 0.5-1.4, 78 cases) or of permanent hair dyes (OR=0.8, 0.5-1.5, 60 cases) was associated with no increased risk. None of the polymorphisms examined modified the hair dye-associated risk, however lagged analysis suggested an increased risk for permanent hair dye use among carriers of the *NAT1*10* allele (OR= 3.6, 1.0-13.0; p-value for interaction= 0.06).

Conclusion

Two cohort studies from USA did not show any effect of permanent hair dye use and bladder cancer. One of the studies involved only 7 cases. The other involved 92 cases. It should be noted that the frequency of use or number of years used is not available.

A case control study from Canada (Stavraky *et al.* 1981) involving 12 cases of kidney cancer and 23 cases of bladder cancer was negative. Two more recent studies from USA are considered positive. The one study (Gago-Dominguez *et al*. 2001) was from Los Angeles involved 82 women using permanent hair dyes showed an increased risk of bladder cancer (RR=1.9; 1.1-3.3) while no increase was found among 13 males (R=0.8; 0.4-2.0). The risk among women increased with increasing use. This study is further supported from studies on implicating arylamines contained in hair dye solution as the putative carcinogenic substances responsible for bladder cancer. It is also supported by a smaller study from New Hampshire (Andrew *et al.* 2004). On

the other hand, a recent unpublished study from Spain (Kogevinas *et al.* 2005) appeared to be negative.

It is concluded that there is an indication of excess risk of bladder cancer for women in USA using permanent hair dyes frequently and for long time.

3.3. Tables

Leukaemia and use of hair dyes

Reference	Location	Controls	Use of any hair dyes	Use of permanent hair dyes
Leukemia				
Cohort				
Grodstein, 1994/ Nurses' Health Study, 1976-90	Chronic lymphocytic	Incident	NR	0.6 (0.3-1.5, 8 cases)
	Other leukaemia		NR	0.8 (0.3-1.9, 8 cases)
Altekruse, 1999/ ACSII, 1982-94	Leukemias	Death	NR	**1.1 (0.9-1.3, 207 cases)**[1]
Case-control				
Markowitz, 1985/ Baltimore, 1980-2	Acute non-lymphocytic	Pop	**All: 3.1 (sign)** Women:2.7(nons) Men: 6.0 (nons)	NR
Cantor, 1988/ Iowa+Minnesota, 1980-3	Leukemias	Pop	**1.8 (1.1-2.7)**	NR
	Acute non-lymphocytic		1.1 (0.5-2.6)	NR
	Dysmyelopoietic syndrome		**2.9 (1.2-7.1)**	
	Chronic lymphocytic		1.4 (0.7-2.6)	
	Chronic myelogenous		2.2 (0.7-6.2)	
	Acute lymphocytic		2.9 (0.4-13.8)	
	Other		**3.3 (1.4-7.6)**	
Zahm, 1992/ Nebraska, 1983-6	Chronic lymphocytic	Pop	1.0 (0.3-2.6, 19 cases) W	0.8 (0.1-4.0) W
			1.0 (0.2-3.8, 37 cases) M	No case
Mele, 1994/ Italy, 1986-9	Acute myeloid	Hosp	1.0 (0.7-1.3) W 1.2 (0.4-4.0) M	NR
	Acute lymphocytic		No case W 1.2 (0.8-1.8) M	
	RAEB		0.8 (0.5-1.4) W 1.0 (0.2-5.1) M	
	Chronic myeloid		1.0 (0.6-1.5) W 2.1 (0.7-6.2) M	
Mele, 1995/ Italy, 1986-9	Acute promyelocytic	Hosp	1.5 (0.6-3.7)	
Markovic-Denic, 1995/ Yugoslavia, 1989	Chronic lymphatic	Hosp	**1.97 (1.08-3.59)**	NR
Ido, 1996/ Japan, 1992-3	Myelodysplastic syndromes MDS	Hosp	**2.50 (0.97-6.41, 29 cases) W**	NR

Reference	Location	Controls	Use of any hair dyes	Use of permanent hair dyes
			1.15 (0.41-3.15) M	NR
Nagata, 1999/ Japan, 1995-6	Myelodysplastic syndromes MDS	Pop	**1.99 (1.17-3.38, 34 cases) M+W**	NR
			2.88 (1.38-6.01, 25 cases) W	NR
Miligi, 1999/ Italy 10 centers, ?	Leukemias	Pop	0.9 (0.7-1.3)	1.2 (0.9-1.7) **2.2 (1.1-3.8) dark products**
Björk, 2001	Chronic myeloid	Pop	0.35 (0.18-0.68, 25 cases)	
Rauscher, 2004/ US+Canada, 1986-9	Acute leukemia	Pop	**1.3 (1.0-1.8, 185 cases)**	**1.6 (1.1-2.4, 87 cases**)
			Freqency ∃6 times/year	1.4 (0.89-2.2, 25 cases)
			Duration ∃15 years	**1.9 (1.1-3.6, 39 cases)**
			Before 1970	**1.7(1.0-3.0, 45 cases)**
	Myelocytic lekemia			**1.6(1.1-2.5)**
	Lymphoblastic leukemia			**2.0(0.9-46)**
Benavente, 2005/Spain 1998-02	Chronic lymphatic	Hosp	**2.3 (1.1-4.7 37 cases)**	**3.4 (1.4-7.8, 35 cases)**
		Use before 1980	**3.5 (1.5-7.8, 27 cases)**	
		Use after 1980	1.5 (0.6-3.6, 10 cases)	

Bladder cancer and use of permanent hair dyes

Reference	Location, year	Controls	Total cases/ controls	Use of any hair dyes	Use of permanent hair dyes
Cohort					
Hennekens, 1979	Nurses' Health Study,1976-?(max 1979)	Incident	Women: 37/120557 cohort	NR	0.62 (0.22-1.58, 5 cases)
Henley, 2001	ACSII, 1982-98	Death	Women:336/547,571 cohort	NR Non-smoking	1.08 (0.84-1.38, 92 cases), as[2] 0.92 (0.61-1.40, 28 cases)
Case-Control					
Stavraky, 1981	Ontario, 1976 (Toronto)	T: Neigh	Women:T: 35/70	NR	1.1 (0.4-2.8, 35 cases[3])
Gago-Domingues, 2001	Los Angeles, 1987-96	Neigh	Women: 203/203	1.3 (0.8-2.2, 124 cases) as	**1.8 (1.0-3.3, 82 cases)** as
			Men: 694/694	0.8 (0.5-1.3, 51 cases) as	0.8 (0.4-2.0, 13 cases) as
Andrew, 2004	New Hampshire, 1994-8	Pop	Women: 98/238	1.1 (0.6-1.9) as	**1.5 (0.8-2.7, 32 cases) as**
			Men: 351/412	0.5 (0.3-0.8) as	0.6 (0.2-1.5, 7 cases) as
Kogevinas, 2005	Spain,	Hosp	Women: 152/166	0.8 (0.5-1.4, 78 cases) as	0.8 (0.5-1.5, 60 cases) as

[1]Positive results or borderline positive when considering the complete study are indicated by **bold**
[2]as = adjusted for smoking
[3] 12 kidney and 23 bladder cancer

3.4. Conclusion

1. SCCP has reviewed and assed if use of hair dyes represent a cancer risk. It was decided that the assessment should concentrate on leukaemia and bladder cancer since no evidence was found linking personal use of hair dyes to a cancer risk at other sites.
   - Although the published data are conflicting, especially, when all types of hair dyes is considered, it is concluded that some studies indicate excess risks for acute leukaemia and chronic lymphoid leukaemia for users of hair dyes.
   - It is concluded that there is an indication of excess risk of bladder cancer for women in USA using permanent hair dyes frequently and for long time.

2. SCCP does not recommend any other requirements for assessing hair dyes than already recommended in its opinion "Assessment Strategies for Hair Dyes" (SCCNFP/0553/02, Opinion of the SCCNFP adopted during the 22nd plenary meeting of 17 December 2002).

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5. ACKNOWLEDGEMENTS

Members of the working group are acknowledged for their valuable contribution to this opinion. The members of the working group are:

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