

THE SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD PRODUCTS
INTENDED FOR CONSUMERS

OPINION

CONCERNING

USE OF PERMANENT HAIR DYES AND BLADDER CANCER

UPDATED 2004

adopted by the SCCNFP on 23 April 2004
by means of the written procedure

1. Terms of Reference

1.1 Context of the question

The adaptation to technical progress of the Annexes to Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products.

The SCCNFP has evaluated the scientific paper on 'Use of permanent hair dyes and bladder cancer risk' by M. Gago-Dominguez et al (Int. J. Cancer : 91, 575-579 (2001)). On the basis of the evaluation SCCNFP recommended that:

- the European Commission provides resources for the urgent review of the information.
- further epidemiological studies are performed to evaluate the possible association between bladder cancer and the use of permanent hair dyes in the EU.
- the European Commission takes further steps to control the use of hair dye chemicals since the potential risks of using this category of substances give cause for concern.

Ref.: 1

1.2 Request to the SCCNFP

The SCCNFP is requested to answer the following question :

* *Does the data provided in the attached publications (Gago-Dominguez et al. 2003, Turesky et al. 2003, Czene et al. 2003) change the overall assessment of the use of permanent hair dyes and bladder cancer risk as stated in the opinion SCCNFP/0484/01?*

* *If yes, what does the SCCNFP recommend on the basis of the new data provided?*

1.3 Statement on the toxicological evaluation

The SCCNFP is the scientific advisory body to the European Commission in matters of consumer protection with respect to cosmetics and non-food products intended for consumers.

The Commission's general policy regarding research on animals supports the development of alternative methods to replace or to reduce animal testing when possible. In this context, the SCCNFP has a specific working group on alternatives to animal testing which, in co-operation with other Commission services such as ECVAM (European Centre for Validation of Alternative Methods), evaluates these methods.

The extent to which these validated methods are applicable to cosmetic products and its ingredients is a matter of the SCCNFP.

SCCNFP opinions include evaluations of experiments using laboratory animals; such tests are conducted in accordance with all legal provisions and preferably under chemical law regulations. Only in cases where no alternative method is available will such tests be evaluated and the

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resulting data accepted, in order to meet the fundamental requirements of the protection of consumer health.

2. Epidemiological Studies of Cancer and Use of Hair Dyes

2.1. Previous evaluations

International Agency for Research on Cancer (IARC)

Evaluation

There is *limited evidence* that occupation as a hairdresser or barber entails exposures that are carcinogenic.

There is *inadequate evidence* that personal use of hair colorants entails exposures that are carcinogenic.

Overall evaluations

Occupation as a hairdresser or barber entails exposures that are *probably carcinogenic* (Group 2A).

Personal use of hair colorants *cannot be evaluated as to its carcinogenicity* (Group 3).

Human carcinogenicity data

There is consistent evidence from five (all from Europe) of the six large cohort studies of an excess risk for cancer of the urinary bladder in male hairdressers and barbers. The increase was significant in three studies, and the overall risk relative to that in the general population amounted to about 1.6. In 12 case-control studies, male hairdressers and barbers had an overall relative risk of about 1.2; smoking was adjusted for in three of these case-control studies, conducted in North America, and these did not show an overall excess risk. The risk for cancer of the urinary bladder was less consistently increased in corresponding studies in women: positive results were obtained in five cohort studies and negative results in three; none was significant. An overall relative risk for lung cancer of about 1.3 was seen among male and female hairdressers in cohort studies. One case-control study from Australia found a significant excess risk for non-Hodgkin's lymphoma among female hairdressers; a non-significant excess of this malignancy was noted in one cohort study from Denmark in men and women and in one case-control study from the USA in men.

One cohort study, from Finland, found a significant excess risk for ovarian cancer; two other studies, in the USA and Japan, found non-significant risks, and a fourth, in Switzerland, showed no effect. Excess risks were seen among male hairdressers for cancers of the buccal cavity and pharynx and prostate in one study from Switzerland; increased risks for cancers at these sites were not reported in another cohort study, from the United Kingdom.

Personal use of hair colorants has been studied in seven case-control studies of cancer of the urinary bladder. Overall, these do not indicate an excess risk; however, one study from Denmark found an association with personal use of brilliantine, although it had methodological limitations. Following a report in 1976 of an excess of breast cancers among hair dye users in New York, USA, six case-control studies and one cohort study examined this subject. None found evidence of a significant excess among hair dye users overall. One case-control study of non-Hodgkin's lymphoma from Iowa and Minnesota showed a significantly increased risk among male users of hair colouring products. A second case-control study, from Nebraska,

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showed an excess risk for this malignancy among female users of hair colorants, but showed no excess among a smaller number of male users. The case-control study from Nebraska also found a significant excess of multiple myeloma among female users of permanent hair dyes, and another study from Iowa reported a nonsignificant excess of this malignancy in male users of hair colorants. One cohort study in the USA showed no excess risk among hair dye users for all lymphomas combined. One case-control study of neuroblastoma and one of Wilms' tumour showed significantly increased risks for the offspring of mothers who had used hair dyes during pregnancy. Single studies have reported significant excess risks for Hutchinson's melanotic freckle, Hodgkin's disease, leukaemia, malignant tumours of the brain and cancers of the salivary gland, cervix and lower female genital tract. Other studies showed no such excesses.

The higher prevalence of smokers reported among male hairdressers and barbers in some studies is consistent with the overall excess of lung cancer but cannot readily explain the magnitude of the increase in risk for cancer of the urinary bladder in the European cohort studies. In particular, studies in Switzerland and Denmark have shown significant excesses of cancer of the urinary bladder unaccompanied by appreciable excesses of lung cancer, which further weigh against smoking as the sole explanation for the overall excess. Specific exposures of hairdressers and barbers have not been evaluated in epidemiological studies.

Ref.: 2

2.2. Studies on the use of hair dyes and risk of bladder cancer

2.2.1. Studies prior to 2001

Cohort studies

Hennekens *et al.* (1979) carried out a cross-sectional postal questionnaire survey in 1976 on 172,413 married female nurses, aged 30-55, in 11 US states whose names appeared in the 1972 register of the American Nurses' Association. Of the 120,557 responders, 38,459 reported some use of permanent hair dyes; of these, 773 had been diagnosed as having a cancer. The risk ratio for the association of cancers at all sites with hair-dye use (at any time) was 1.10 ($p = 0.02$). When 16 cancer sites were examined separately, significant associations with permanent hair-dye use were found for cancer of the cervix uteri (RR, 1.44; $p < 0.001$) and for cancer of the vagina and vulva (RR, 2.58; $p = 0.02$).

In the case of bladder cancer 5 cases were observed while 7.4 cases were expected (RR=0.62)

Ref.: 3

Thun *et al.* (1994) examined prospectively the relationship between the use of permanent hair dyes and selected fatal cancers in 573,369 women. The participants provided information in 1982 on the frequency and duration of hair dye use and the colour of hair dye used. Death rates were measured through 1989. Relative risks (RRs) were computed with subjects who had not used hair dyes serving as the reference group, and 95% confidence intervals (CIs) were calculated on the basis of approximate-variance formulas. Women who had ever used permanent hair dyes showed decreased risk of all fatal cancers combined (RR = 0.93; 95% CI = 0.89-0.98) and of urinary bladder cancers (RR = 0.6; 95% CI = 0.3-1.0).

Ref.: 4

Case-control studies

Jain *et al.* (1977) reported (in a letter) data on hair-dye use among 107 patients with bladder cancer and an equal number of sex- and age-matched controls in Canada. All male controls had benign prostatic hypertrophy, and all female controls had stress incontinence.

The OR for bladder cancer in association with any exposure to hair dyes (based on 19 pairs discordant for use of hair dye) was 1.1 (95% CI, 0.41-3.03). Type of hair dye not stated.

Ref.: 5

Neutel *et al.* (1978) reported (in a letter) data on hair-dye use in a subset of 50 case-control pairs (matched by sex and 10-year age group) re-interviewed after a previous, larger case-control study of bladder cancer in Canada. Use of hair dyes was reported by 18 cases and 19 controls. Frequent use of hair dyes and hairdressing as an occupation, however, were said to show protective effects (the former being significant, $p < 0.01$) against bladder cancer, although the numbers on which these statements were based are not given in the report. Type of hair dye not stated.

Ref.: 6

Howe *et al.* (1980) found that eight male cases (including two of the barbers) and no male control had a history of personal use of hair dyes ($p = 0.004$, one-tailed test); only one of them had used hair dyes for more than six years before diagnosis of bladder cancer. There was no evidence in women of an increased risk for bladder cancer associated with personal use of hair dyes (OR, 0.7; 95% CI, 0.3-1.4 for ever *versus* never use). Type of hair dye not stated.

Ref.: 7

Hartge *et al.* (1982) examined hair dye use among participants in the US National Bladder Cancer Study in a case-control study of bladder cancer involving 2982 incident cases and 5782 controls, of which 615 cases and 1164 controls had dyed their hair. The overall ORs for hair dye users were 1.1 (95% CI 0.9-1.4) among men and 0.9 (0.8-1.1) among women. No trend with frequency or duration of use was seen in people of either sex. Use of black hair dye was associated with elevated ORs in both men and women; the OR was of borderline significance for the two sexes combined (1.4; 95% CI, 1.0-1.9; 68 exposed cases). The study did not differentiate between different types of hair dyes.

Ref.: 8

Ohno *et al.* (1985) conducted a case-control study of 65 female bladder cancer patients in Nagoya, Japan, in the period 1976-78. Hair dye use was associated with an increased RR among those who smoked but not among non-smokers. There was a positive relationship between smoking and hair dye use more than once a month; after adjustment for smoking, no significant effect of hair dyes remained (RR, 1.7; 95% CI, 0.82-3.52; 22 exposed cases). Type of hair dye not stated.

Ref.: 9

A matched case-control study was carried out by Claude *et al.* (1986) of 340 men and 91 women with bladder cancer in Lower Saxony, Germany, in the period 1977-82. It was stated that no association with hair dye use was found, but details were not provided. Type of hair dye not stated.

Ref.: 10

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Nomura *et al.* (1989) carried out a case-control study among 137 Caucasian and 124 Japanese cases of cancer of the lower urinary tract in Hawaii (USA) and two population-based controls for each case, in the period 1977-86. A weak, nonsignificant association with hair dye use was found for both men and women, but there was no positive trend with increasing duration of use. (Men OR, 1.3; 95% CI, 0.6-2.8; 15 cases; Women OR, 1.5; 95% CI, 0.8-2.9; 41 cases). Type of hair dye not stated.

Ref.: 11

Comment: Only two studies were found in relation to permanent hair dyes. Both studies were cohort studies. In the first study, Hennekens *et al.* (1979) only 5 cases of bladder cancer were identified and 7.4 cases were expected. In the second study which involved the American Cancer Society (CPS-II), the number of bladder cancer was not reported. It is reason to believe (ref. 12) that the number was less than 150. Moreover, the study involved only fatal cases which had been asked 7 years prior to the end of the study about their use of permanent hair dyes. It is not possible from the two cohort studies to draw any conclusions with regard to use of permanent hair dyes and risk of bladder cancer.

2.2.2. The GAGO-DOMINGUEZ Study in 2001

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	Odd Ratio (95% C.I)	Comments
Case-control Bladder Los Angeles	897 cases; Cases/Controls All hair dye users, 163/162 <i>Only permanent</i> M+F; 95/71 F; 82/56 Women used permanent dyes Non-smokers Smokers <i>All women</i> 15 years or more <12 times/year 31/21 12+ times/year, 29/12	1.0(0.7-1.4) 1.5(1.0-2.3) 1.9(1.1-3.3) 2.7(1.2-5.9) 1.4(0.8-2.4) 1.7(0.8-3.6) 3.3(1.3-8.4)	All data adjusted for smoking, except for the lines “Non-smokers” and “Smokers”

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Hairdresser or barber			
Ever; 20/13	1.5(0.7-3.2)		
<10 years; 6/10	0.5(0.2-1.6)		
10+ years; 14/3	5.1(1.3-19.2)		

Ref.: 12

SCCNFP has evaluated the paper and made the following conclusions:

- The study is well conducted and important confounding factors (e.g. smoking) were properly addressed.
- The study shows an increased risk of bladder cancer among women who made regular use of permanent hair dyes over many years.
- The risk is positively correlated to the number of years of usage and frequency of application.
- The study confirms the results of earlier occupational health studies in hairdressers and barbers.
- The study is not in contradiction to earlier studies, which did not show a clear correlation.
- The chemical identity of the permanent hair dyes used by the study population is unknown.

Ref.: 1

2.2.3. Studies after 2001

2.2.3.1. Follow-up of the GAGO-DOMINGUEZ Study in 2001

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”.

Ref.: 13

The above finding has 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 (ref. 13). 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.

Ref.: 14

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.

2.2.3.2. Aminobiphenyl derivatives in commercial hair dyes

Turesky *et al.* (2003) sought to determine if 4-aminobiphenyl (4-ABP) a recognized human urinary bladder carcinogen, is present in commercial hair dyes. 4-ABP was isolated from dyes by solvent extraction with hexane, followed by silica gel chromatography, either with or without chemical treatment of the extract with Zinc/HCl, and a final purification with a mixed cation exchange reversed-phase resin. The identity of 4-ABP was confirmed by both HPLC with electrospray ionization tandem mass spectrometry (HPLC-ESI-MS/MS) and gas chromatography with negative ion chemical ionization mass spectrometry (GC-NICI-MS) following chemical derivatization with pentafluoropropionic anhydride (PFPA). The levels of 4-ABP ranged from not detectable (<0.29 parts per billion (ppb)) up to 12.8 ppb. The noncarcinogenic isomer 2-aminobiphenyl (2-ABP) was also found at quantities up to 310 ppb. 4-ABP was detected in eight of the 11 hair dyes and found in black, red, and blonde hair dyes but not in brown hair dyes. 1,4-Phenylenediamine (PPD) is a key constituent for colour development of many permanent hair dyes. Some batches of chemical research grade PPD were contaminated with 4-ABP (up to 500 ppb) and 2-ABP (up to 70 parts per million) and may be a source of ABP contamination in hair dyes. These analytical data demonstrate that 4-ABP is present in some hair dyes. Studies on dermal absorption and bioavailability of 4-ABP from hair dyes are required to determine if this aromatic amine contributes to the increased risk of bladder cancer reported in frequent users of hair dyes. The highest amount reported by the authors in hair dyes was 6.4 ppb

Ref.: 15

Comment : COLIPA note that the industry has not been able to detect 4-ABP in PPD samples used for hair dyes and that the PPD used in hair dyes is synthesized by a route specifically designed to eliminate 4-ABP (letter of 17.10.03 from G.Renner (COLIPA) to A.Carvalho, DG ENTR).

2-ABP is classified by EU as a category 3 carcinogen. 2-ABP hydrochloride has been tested under US NTP (Ref. : 16). The substance was not carcinogenic in male and female rats, it induced hemangiosarcomas in female mice (high dose 7/50, 14%, 3000 ppm; T25=642 mg/kg/d).

Data from an experiment of Schieferstein *et al.* (1985) have been used for quantitative risk characterisation. Male and female (840 each) BALB/cStCrlfC3Hf/Nctr mice were given 0, 7, 14, 28, 55, 110 and 220, and 0, 7, 19, 38, 75, 150 and 300 ppm, respectively, of 4-aminobiphenyl in

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their drinking water. Necropsies on killed animals were performed at 13, 26, 39, 52 and 96 weeks on dose. Dose-related neoplasms were angiosarcomas, bladder urothelial carcinomas and hepatocellular neoplasms. Among male mice with 110 ppm 4-ABP in the drinking water 42% (10/22) developed bladder cancer at 96 week (at 55 ppm, 20% (5/25) developed bladder cancer). No bladder tumours was found among the control mice.

Ref.: 17

Intake of 4-ABP [(110 ppm; 0.11 mg/ml. 5 ml drinking water per day) 0.55 mg. Male mice, default body weight 30 g. (0.55/0.030)] 18 mg/kg/d

T25 [18 mg/kg/d x 25/42] 10.7 mg/kg/d HT25 [10.7 mg/kg/d / (60/0.030)^{0.25}] 1.6 mg/kg/d.

Maximum content of 4-ABP measured in hair dyes (6.4 ng/g x 50 ml) 320 ng.

Dose: It is considered that the permanent hair dye is used once every 30 days. If it is considered that 10% of 4-ABP were absorbed the daily dose would be [320 ng x 0.1/ (60 kg x 30 days)] 0.018 ng/kg/d.

Life time cancer risk [0.018 x 10⁻⁶ mg/kg/d / (1.6 mg/kg/d /0.25) 2.8 x 10⁻⁹

The calculation is described in the reference given.

Ref.: 18

Even if “worst case” calculations are performed the amounts of 4-ABP reported in commercial hair dyes will not represent any risk of urinary bladder cancer in the users [T25 for 2-ABP is about 35 times larger than for 4-ABP, thus even if 2-ABP is included in the risk characterisation it will not influence the conclusion].

2.2.3.3. Cancer risk in hairdressers

Czene *et al.* (2003) carried out a follow-up study of a cohort of 38,866 female and 6,824 male hairdressers from Sweden and analyzed all of their malignancies over a period of 39 years. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for 28 cancer sites were calculated using the economically active population as a reference. During the years 1960–1998 a total of 1,043 cancer cases were recorded in male hairdressers. Excess risks for cancers of the upper aerodigestive tract and lung and colorectal adenocarcinoma were observed. Additionally, male hairdressers working in 1960 had an increased risk for urinary bladder cancer, which was highest in the 1960s with an SIR of 2.56 (95% CI 1.36–4.39) and decreased with the follow-up time. A total of 2,858 cancers were recorded in female hairdressers. An increased risk was observed for cancers of the pancreas, lung and cervix and *in situ* cancer of the skin. The increased risk for *in situ* skin cancer specifically affected the scalp and neck, sites of contact for hair dyes, with an SIR of 2.43 (95% CI 1.14–4.44). The increase in lung cancer, the only site for which cancer was increased in either sex, may depend on confounding from smoking. Bladder cancer was not increased among hairdressers in the recent decades and is therefore not likely to be associated with modern hair dyes.

Ref.: 19

Comment: The authors conclude that their study suggest that occupational exposure to hair dyes is no longer associated with excess risk of urinary bladder cancer in Sweden. The authors point out that the presence of butter yellow (p-dimethylaminoazobenzene) in brilliantine, a past cosmetic product of hairstyling produces bladder tumours in animals. The present study will not change the IARC classification.

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2.3. Effects of concern

The study by Gago-Dominguez *et al.* (2001) (ref.12) reporting an increased risk of urinary bladder cancer among regular users of permanent hair dyes caused concern. The results by Gago-Dominguez has later been strengthened by more recent results indicating by the use of analyses of polymorphism among the participants, that the bladder cancer may be caused by carcinogenic arylamines in the hair dye solutions.

The study by Gago-Dominguez was carried out on persons with a confirmed bladder cancer between 1992 and 1996 and registered at the cancer registry of Los Angeles County, California, USA. The main question is if European women using permanent hair dyes are exposed to the same putative carcinogens as American women.

In the period from 1980, a number of colorants have been banned in EU as well as in individual European countries on the basis of reported carcinogenic effects in animal studies. In USA, prohibition against use of specific colorants in cosmetic preparations is seldom used, while US FDA require that the label should contain information on possible carcinogenic effects. It is the intention that this will limit or eliminate the use. Another difference between the use of hair colorants in USA and EU is that it is more common in USA that the hairdressers mix the colorants themselves. Under such conditions, the control of the dyes used and their purity will be limited.

It has been reported that commercial hair dyes may contain small amounts of the human urinary bladder carcinogen 4-aminobiphenyl. Worst-case quantitative risk characterisation clearly demonstrates that the amount of 4-aminobiphenyl will not represent any cancer risk among women using permanent hair dyes.

Due to the differences outlined above, it is not known whether European women using permanent hair dyes are exposed to the same putative carcinogenic agents as in the study for Los Angeles County. Thus, there is a need to clarify this question.

2.4. Opinion

The data provided in the attached publications (Gago-Dominguez *et al.* 2003, Turesky *et al.* 2003, Czene *et al.* 2003) do not change the overall assessment of the use of permanent hair dyes and bladder cancer risk as stated in the opinion SCCNFP/0484/01 of 12 June 2001.

3. References

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