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REVIEW

Epidemiological evidence on hair dyes and the risk of cancer in humans

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Epidemiological data on occupational exposure and personal use of hair dyes was reviewed with specific focus on bladder cancer and lymphoid neoplasms. At least seven cohort and 11 case–control studies included data on occupational exposure to hair dyes by hairdressers, barbers and beauticians, and their subsequent bladder cancer risk. The relative risk (RR) estimate was 1.4 (183 observed *vs* 129 expected) for cohort studies, and in several case–control studies the RRs were somewhat above unity. These results are compatible with some moderate association between past professional exposure to hair dyes and subsequent bladder cancer risk, but also with errors and biases in observational epidemiological studies, particularly since allowance for smoking was lacking or inadequate in most studies. An open question is whether current occupational exposure to modern hair dyes is still related to some excess bladder cancer risk. Five case–control studies included information on personal use of hair dyes and bladder cancer risk. There was no evidence of any association. Nine cohort and eight case–control studies considering occupational exposure to hair dyes and lymphoid neoplasms were reviewed. In the cohort studies, a total of 100 lymphoid neoplasms was observed compared with 84.4 expected (RR 1.2). The RR estimates were 1.5 for non-Hodgkin's lymphomas (NHL, 17 observed *vs* 11.2 expected) and 1.1 for multiple myeloma (MM, 19 observed cases *vs* 16.8 expected). Interpretation of case–control studies of occupational exposure is seriously hampered by the small number of exposed cases. Five case–control studies considered personal use of hair dyes and the risk of lymphoid neoplasms. Of these, three reported some association, particularly with NHL and MM. However, the RR estimates were only moderately above unity, and inadequate allowance was made for potential confounding factors, including social class and greying hair, which could be correlates of both hair dye use and lymphoid neoplasms. Further, there is little information on the biodistribution and bioavailability of potential carcinogens in hair dyes, particularly their concentrations in lymphoid tissue. These findings, therefore, require further research, particularly since they may be influenced by selective publication of positive findings (publication bias). None of the other neoplasms extensively studied, including breast, skin and lung was related to hair dye use.

Key words: Bladder, hairdressers, hair dyes, lymphoid neoplasms, non-Hodgkin's lymphomas, relative risk.

Introduction

Hair colouring products (hair dyes) are widely used, and it has been estimated that in Europe, North America and Japan over one third of women above the age of 18 and over 10% of men above the age of 40 use some type of hair dye, permanent dyes accounting for about three quarters of global use. This wide spread personal use implies considerable professional exposure by hairdressers and barbers, since there are about two million professional hairdressers, barbers and beauticians in North America and Europe alone (Cosmetics, Toiletry and Fragrance Association, undated).

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Table 1. Components of hair coloring products that have been evaluated in the IARC Monograph series

Compound	Product in which found	Overall evaluation of carcinogenicity to humans	IARC monographs volume no.
2-Amino-4-nitrophenol	Semi-permanent hair dyes	Inadequate evidence	57
2-Amino-5-nitrophenol	Semi-permanent hair dyes	Inadequate evidence	57
4-Amino-2-nitrophenol	Semi-permanent hair dyes	Inadequate evidence	16
CI Disperse Blue 1	Semi-permanent hair dyes	Possible carcinogenic	48
Cobalt salts	Temporary hair dyes	Possibly carcinogenic	52
D & C Red No. 9	Temporary hair dyes	Inadequate evidence	57
2,4-Diaminoanisole	Permanent hair dyes	Possibly carcinogenic	27
2,4-Diaminotoluene	Permanent hair dyes	Possibly carcinogenic	16
2,5-Diaminotoluene	Permanent hair dyes	Inadequate evidence	16
HC Blue No. 1	Semi-permanent hair dyes	Possibly carcinogenic	57
HC Blue No. 2	Semi-permanent hair dyes	Inadequate evidence	57
HC Red No. 3	Semi-permanent hair dyes	Inadequate evidence	57
HC Yellow No. 4	Semi-permanent hair dyes	Inadequate evidence	57
Hydrogen peroxide	Bleaching agents; permanent-wave preparations	Inadequate evidence	36
Hydroquinone	Permanent hair dyes	Inadequate evidence	15
Isopropanol	Permanent hair dyes	Inadequate evidence	15
Lead acetate	Temporary hair dyes	Possibly carcinogenic	23
Nickel salts	Temporary hair dyes	Carcinogenic	49
2-Nitro-*para*-phenylenediamine	Permanent hair dyes; semi-permanent hair dyes	Inadequate evidence	57
Phenacetin	Bleaching agents; permanent-wave preparations	Probably carcinogenic	24
meta-Phenylenediamine	Permanent hair dyes	Inadequate evidence	16
para-Phenylenediamine	Permanent hair dyes	Inadequate evidence	16
Resorcinol	Permanent hair dyes	Inadequate evidence	15
Sodium bisulphite	Permanent hair dyes	Inadequate evidence	54
Sodium sulphite	Permanent hair dyes	Inadequate evidence	54

Hair dyes contain components that are mutagenic *in vitro* (Ames *et al*, 1975), some *arc* carcinogenic in animals, and several have been evaluated by working groups of the International Agency for Research on Cancer of the World Health Organization (IARC/WHO, [redacted]ed in IARC, 1993) for their carcinogenicity to humans. A *summary* tabulation of these components is given in Table 1.

Epidemiological data *on cancer* risk among subjects occupationally exposed to, and long-term personal users of hair dyes have been reported at least since the 1960s, but only during the last two decades has the issue attracted widespread attention in the scientific and lay press. After a summary review of experimental data on cancer in animals, the present overview will consider and discuss epidemiological data in humans with reference Iovarious cancer sites, and with specific focus on two groups of neoplasms whose association with hair dyes has been widely debated in the last few years, *ie* bladder cancer and lymphoid neoplasms.

Evidence of carcinogenicity in experimental animals

In at least three studies which investigated skin applications of permanent (Burnett *et al*, 1975) or semi-permanent (Searle and Jones, 1977; Jacobs et *al*, 1984) hair dye formulations m mice, no *skin* tumour was observed, and no significant difference emerged for lung cancer, lymphomas or any other neoplasm considered. However, the number of animals in each treatment group was small (approximately 20–60), and this precludes any conclusion.

In three studies also comprising 20–60 animals per treatment group, and based on *skin* applications in rats (Kinkel and Holzmann, 1973: Rojanapo *et al*, 1986; Burnett and Goldenthal, 1988), again no skin tumour was observed at the site of application. Likewise, there was no significant difference in body weight or survival time. One study (Rojanapo *er al*, 1986) found an excess of mammary tumours (fibrosarcomas, adenomas and fibroadenomas) in the

treated group, and another (Burnett and Goldenthal, 1988), an elevated incidence of pituitary adenomas in females. No excess risk at any other cancer site was reported.

A small study (based on 10 male and 10 female rats per treatment group), considered subcutaneous injection of *meta*-phenylene diamine every other week for 18 months. There was no excess of mammary lesions (d———'a and adenosis), and two sarcomas and two lymphomas a m e at the site of injection (Rojanapo *et al*, 1986). However, the small absolute numbers of animals again preclude any conclusion.

Thus, evidence of the carcinogenicity of hair dye components in rodents is limited and, from several methodological aspens, it can be criticized: for instance, m most experiments only selected *organs* were examined histologically. Although aromatic amines *act* systemically, tbe urinary bladder and liver often being their targets (hence skin tumours may not be their predominant target), the general absence of skin tumours at the sites of application is worth noting. Some excess *cancer* incidence has b a n reported bur, as a whole, the data are largely inconclusive and offer no clear focus for epidemiological *studies* in humans.

Epidemiological data in humans

Lymphoid neoplasms

At least nine cohort studies reported some data on occupational exposure to hair *dyes* and subsequent risk of lymphoid neoplasms (Alderson, 1980; Kono *et al*, 1983; Teta *et al*, 1984; Gubéran et *al*, 1985; McLaughlin *et al*, 1988; Shibata *et al*, 1989; Skov *et al*, 1990; Pukkala *et 4* 1992; Hrubec *et al*, 1992). Their main results are reported in Table 2. *All studies* were based on very small absolute numbers of cases (1–22 observed); still, most RR *estimates* were close to unity, and all were within the relatively narrow range of 0.4–2.5, with no clear exceptions.

This means that any substantially elevated risk *can* be confidently excluded. When all the data were pooled, a total *of* 100 lymphoid neoplasms was observed *vs* 84.4 expected (summary RR = 12). The corresponding figures were 35 observed *vs* 31.3 expected (RR = 1.1) for leukaemias, one observed *vs* 0.7 expected for Hodgkin's disease, 17 observed *vs* 11.2 *f* expected for non-Hodgkin's lymphomas (RR = 1.5), 24 observed *vs* 20.1 expected for lymphomas unspecified (RR = 1.2), and 19 observed *vs* 16.8 expected for multiple myeloma (RR = 1.1).

Table 2 *Summary* results from selected cohort studies providing information on occupational exposure to hair dyes and lymphoid neoplasms

Authors, year, country	Sex	No. of subjects	Lymphoid neoplasms			Relative risk
			Type[a]	Observed	Expected	
Alderson, 1980 (UK)	M	1,831	LEU	3	2.7	1.1
Kono *et al*, *1983* (Japan)	F	7,736	LEU	6	4.4	1.4
Teta *et al*. 1984 (USA)	F	11,845	LEU	14	11.6	1.2
			MM	3	4.3	0.7
			LYM	22	17.1	1.3
Gubéran *et al*, 1985 (Switzerland)	M + F	1,380	All	4	4.3	0.9
McLaughlin *et al*, 1988 (Sweden)	M	3,067	MM	11	8.5	1.3
Shibata et al, 1989 (Japan)	M + F	8,316	LEU	3	3.8	0.8
			LYM	2	3.0	0.7
Skov *et al*, 1990 (Denmark)	M + F	14.371	NHL	13	8.1	1.6
Pukkala *et al*., 1992 (Finland)	F	3.637	LEU	4	4.2	1.0
			MM	1	2.4	0.4
Hrubec *et al*, 1992 (USA)	M	740	NHL	4	3.1	1.3
			HD	1	0.7	1.4
			MM	4	1.6	2.5
			LEU	5	4.6	1.1
Total	M + F	52,923	LEU	35	31.3	1.1
			HD	1	0.7	1.4
			NHL	17	11.2	1.5
			LYM	24	20.1	1.2
			MM	19	16.8	1.1
Total (all histologies)	M + F	52,923	All	100	84.4	1.2

[a]LEU, leukaemia; MM, multiple myeloma; LYM, lymphomas (unspecified); HD, Hodgkin's disease; NHL, non Hodgkin's lymphomas.

Table 3. Summary results from selected case-control studies of lymphoid neoplasms providing information on occupational exposure to hair dyes

Authors, year country	Sex	Type of cancer[a]	No. of cases	No. of exposed cases	Odds ratio
Giles *et al*, 1984 (Australia)	F	HD	32	2	—
		NHL	116	5	—
		LEU	78	1	—
		MM	59	0	0
Flodin *et al*, 1987 (Sweden)	M+F	MM	131	1	3.3
Boffetta *et al*, 1989 (USA)	M+F	MM	128	0	4
Persson *et al*, 1989 (Canada)	M+F	HD	54	1	27
		NHL	106	I	2.2
Eriksson and Karlsson, 1992 (Sweden)	M+F	MM	256	2	0.7
Pottern *et al*, 1992 (Denmmark)	F	MM	607	I	0.7
Blair *et al*, 1993 (USA)	M	NHL	622	13	2.4
Herrinton *et al*, 1994 (USA)	M	MM	360	I	1.5
	F	MM	321	12	1.3

[a] HD, Hodgkin's disease; NHL, non Hodgkin's lymphomas; MM, multiple myeloma; LEU, leukaemia.
—, no exposed control.

Thus, from a statistical and biological viewpoint, the data on occupational exposure from cohort studies are compatible both with a moderately-increased risk (particularly of non-Hodgkin's lymphomas) and with the absence of association. However, since very little is known about the aetiology of these neoplasms, no plausible suggestion can be made on the priorities for identification or allowance for potential confounding factors.

Data on occupational exposure to hair dyes and the risk of lymphoid neoplasms from case–control studies are given in Table 3. At least eight studies were reviewed (Giles *et al*, 1984; Flodin *et al*, 1987; Boffetta *et al*, 1989; Persson *et al*, 1989; Eriksson and Kalsson, 1992; Pottern *et al*, 1992; Blair et *al*, 1993; Herrington *et al*, 1994). Of these, five (Giles *et al*, 1984; Flodin *et al*, 1987; Persson *et al*, 1989; Blair *et al*, 1993; Herrington *et al*, 1994) showed some increased risk, although most RR estimates were only moderately above unity, and none of them was significant. The remaining three (Boffetta *et of*, 1989; Eriksson and Karlsson, 1992; Pottern *et al*, 1992) found no evidence of association. Only two studies (Persson *et al*, 1989; Blair *er al*, 1993) included data and risk estimates on non-Hodgkin's lymphomas, for a total of 14 exposed cases and a RR of around 2.4.

Case–control studies of occupational exposure to hair dyes and lymphoid neoplasms have at least two major limitations: the extremely small number of exposed cases (only 40), and the fact that none of them was specifically designed to address this *issue*. Thus, no firm conclusions *can* be drawn, although, taken together with cohort studies, the results are compatible with some moderate association between past employment as a hairdresser *or* barber and lymphoid neoplasms as a group, and particularly non-Hodgkin's lymphomas.

These epidemiological findings gain plausibility in the light of the knowledge that exposure to selected chemicals may increase tbe risk of leukaemias (Linet, 1985) and perhaps other lymphoid neoplasms (La Vecchia *et al*, 1989). Our knowledge of the aetiology of these neoplasms in humans is, however, too scanty to allow any more precise inference to be drawn on potential pathogenic links. In any *case*, it must be stressed that any inference is based essentially on exposure to hair dyes (or other potential risk factors) by hairdressers and barbers in the distant past, considering the long duration (latency) of the process of carcinogenesis. Since even the presence of any association is open to discussion, it is not possible to formulate any more precise inference on latency, or any other relevant time factor in the process of lymphoid carcinogenesis.

Additional information on the occupational exposures to hair *dyes* of hairdressers, beauticians or barbers and the risk of lymphoid neoplasms *can* be derived from several descriptive studies on populations. A report for the Office of Population Censuses *and* Surveys (1986), covering occupational exposure in England and Wales in 1979–80 and 1982–83, found non-significantly increased rates for Hodgkin's disease and leukaemias in males, based, however, on five cases or fewer. A larger excess was observed for lung cancer (21 deaths observed *vs* 7.9 expected), again suggesting elevated smoking prevalence in those

Table A *Summary* results from selected cohort studies providing information *on* personal exposure to hair dyes and lymphoid neoplasms

Authors, year, country	Number of women	Lymphoid neoplasms		Relative risk (95% CI)
		Type[a]	Observed	
Hennekens *et al*, 1979 (USA)	120,557	LYM	10	0.6 (0.3–1.1)
Thun *et al*, 1994 (USA)	573,369	NHL	37	1.0 (0.7–1.2)
		HD	6	0.6 (0.2–1.4)
		MM	51	1.1 (0.8–1.5)
		LLEU	16	0.8 (0.4–1.4)
		MLEU	49	0.9 (0.6–1.3)
		LEU	18	1.0 (0.6–1.8)
		All	227	0.9 (0.8–1.1)

[a]LYM, lymphomas; NHL, non-Hodgkin's lymphomas; HD, Hodgkin's disease; MM, multiple myeloma; LLEU, lymphoid leukaemia; MLEU, myeloid and monocytic leukaemia; LEU, leukaemia unspecified.

occupational categories in the past. For females, only breast cancer was in excess (*seven* observed, 1.6 expected). This, however, might be related to differences in reproductive factors or other correlates of breast *cancer* risk (Boyle, 1988) between hairdressers and the general population.

In a Danish study (Clemmesen, 1977, 1981), no excess risk of all cancer sites was observed for males (477 malignant cancers observed *vs* 512.4 expected), whereas data for females were difficult to interpret due to differences in the definition of the occupational categories in the census and *cancer* registration data.

Some excess of multiple myeloma *or* lymphomas was also observed *in* descriptive occupational studies from Los Angeles County (Guidotti *et al*, 1982), Washington State (Milham, 1983) and British Columbia (Gallagher *et al*, 1989), but the figures were generally based *on* small absolute numbers and the results were often inconsistent between the two sexes. Other studies showed no or little evidence of association (Menck *et al*, 1977; Neuberger *et al*, 1991).

Information on personal use of hair dyes and the risk *of* lymphoid neoplasms *can* be obtained from at least two cohort studies (Hennekens *et al*, 1979; Thun *et al*, 1994) and five case–control studies (Smvraky *et al*, 1981; Cantor *et al*, 1988; Zahm *et al*, 1992; Moms Brown *et al*, 1992; Herrinton *et al*, 1994).

Data from cohort studies are summarized in Table 4. Among 120,557 female nurses active in 1972 and recruited in the American Nurses Health Study (Hennekens *et al*, 1979), 10 lymphomas were registered up to 1976 among hair dye users *vs* 15.7 expected, corresponding to a RR *of* 0.6.

The American cancer Society cancer Prevention Study 11 (CSS II) included 573,369 people who were followed-up between 1982 and 1989 (Thun *et al*, 1994). A total of 941 haematopoeitic cancers were observed overall, and 227 among ever users of hair dyes. The overall RR for all lymphoid neoplasms was 0.9 (95% CI 0.8–1.1) and that of non-Hodgkin's lymphomas was 1.0 (95% CI 0.7–1.2), and no excess was observed for any other type of neoplasm. Likewise, there was no indication for the RR to increase with *increasing* duration of exposure, and the only strata of elevated risk were for long term use of black dyes in relation to non-Hodgkin's lymphoma (RR = 4.4, based on three cases), and multiple myeloma (RR = 4.4, based on two cases). Taken as a whole, therefore, these data provide reassuring evidence on the absence of risk of lymphoid cancers in users *of* hair dyes, even for 20 or more years (Thun *et al*, 1994; Colditz, 1994).

The *summary* results of the five case–control studies are given in Table 5. An earlier study from Canada (Stavraky *et al*, 1981), considering 70 cases of all types of lymphoid neoplasms, showed no *evidence* of risk. Some moderate association, however, was apparent in the three subsequent case–control studies, conducted in various areas of the United States (Cantor *et al*, 1988; Zahm *et al*, 1992; Morris Brown *et al*, 1992), although only for non-Hodgkin's lymphomas were meaningful numbers of exposed cases available for analysis.

A population-based study conducted in 1980–83 on males from Iowa and Minnesota (Cantor *et al*, 1988) found an overall RR of 2.0 (95% confidence interval (CI) 1.3–3.0) for non-Hodgkin's lymphomas, and showed some indication of duration–risk relationship. The risk estimates were adjusted for state of residence and age only in two groups.

Another population-based case–control study was conducted between 1983 and 1986 in Nebraska (Zahm

Table 5. Summary results from selected case-control studies of lymphoid neoplasms providing information on personal use of hair dyes

Authors, year, country	Sex	Type of cancer[a]	No. of cases	No. of exposed cases	Odds ratio
Stavraky *et al*, 1981 (Canada)	F	All	*m*	NR	*0.9*
Cantor *et al*, 1988 (USA)	M	LEU	578	43	1.8
		NEIL	622	53	2.0
Zahm *et al*, 1992 (USA)	M	NHL	201	11	0.8
	F	NHL	184	106	1.5 (1.7 permanent, F)
	M	HD	35	3	1.7
	F	HD	35	16	1.7 (3.0 permanent, F)
	M	MM	32	4	1.8
	P	MM	40	*24*	1.8 (2.8 permanent, F)
	M	CLL	37	3	1.0
	F	CLL	*19*	9	1.0 (0.8 permanent, F)
Morris Brown *et al*, 1992 (USA)	M	MM	173	14	1.9
Herrinton *et al*, 1994 (USA)	M	NM	360	17	1.3
	F	MM	319	114	1.1

[a] HD, Hodgkin's disease; NHL, non Hodgkin's lymphomas; MM, multiple myeloma; LEU, leukaemia.
NR, not reported.

et al, 1992), and included 201 men and 184 women with histologically confirmed non-Hodgkin's lymphomas: 11 men and 106 women had ever used hair dyes, the RR estimates being 0.8 and 1.5 (significant), respectively. The RR in women was 1.7 for use of permanent hair dyes. Although this study collected information on several risk factors, these risk estimates were adjusted for age only. When total hair dye use was considered, no relationship was evident with duration (RR 1.2 for the longest duration category, $\geq$ *21* years), age at *first* use, or frequency of use (RR 1.4 for the most frequent category, $\geq$ 52 times per year). Some association with duration was apparent in the subgroup of black, brown/brunette or red dyes only, but this *can* be considered an *a posteriori* subgroup analysis, if not due to selection and confounding bias, *since* greying hair might be a correlate of both hair dye use and lymphomas risk. However, even in this subgroup there was no evidence of a frequency–risk relationship. The same study reported data on 32 male and 40 female cases of multiple myeloma. The RR estimates were 1.8 (not significant) for both sexes and, again, there was no evidence of any relationship with duration, latency or frequency of use. The data were scanty *on* Hodgkin's disease, and there was no evidence of association with leukaemias.

Another study of 173 male cases of multiple myeloma from Iowa (Morris Brown *et al*, 1992) suggested a moderate association (RR = 1.9, 95% CI 1.0–3.1), but provided no details of the type of colour used, and made no allowance for any covariate, except age and vital status. A case-control study based on the Surveillance, Epidemiology, and End Results program found no material association in women (RR=1.1) and only a modest non-significant association in men (RR=1.3).

In a letter discussing the results *on* non-Hodgkin's lymphomas, no association was reported between occupational exposure to hair dyes and lymphoma risk in people with acquired immunodeficiency *syndrome* (AIDS) (Coté *er al*, 1993).

A popularion-based case–control study of multiple myeloma conducted between 1977 and 1981 in four areas participating in the Surveillance, Epidemiology and End-Results Programme (Seattle, Utah, Detroit and Atlanta) included information on occupational and personal exposure *to* hair dyes (Herrinton *et ai*, 1994). Among women employed as hairdressers far 6 months or more, the OR was 1.3, in the absence, however, of any duration–risk relationship (OR for > 5 years exposure = 0.7). *only* one man reported occupational exposure. The ORs for personal use of hair dyes were 1.1 for women and 1.3 for men when all data were considered, and 1.0 and 1.3 when all self-respondents were considered. None of these estimates was significant and tho authors concluded that the study provided little evidence that exposure to hair dyes increases myeloma risk.

The results of epidemiological *studies on* hair dyes should be discussed With reference to our knowledge of the aetiology of lymphomas and myeloma. The beat recognized risk factor for non-Hodgkin's lymphomas is severe immunodepression, since the risk is substantially increased after (kidney) transplantation and in subjects wirh human immunodeficiency virus

(HIV) infection (Kinlen *et al*, 1979; La Vecchia *et al*, 1992; Hartge and Devesa, 1992; Pearce and Bethwaite, 1992). Myeloma is related to ionizing radiation (Cuzick, 1981), but little is known about the role of infections, autoimmune diseases, immunodepression or other potential risk factors (Gramenzi *et al*, 1991).

Certified incidence and mortality for both types of neoplasms have substantially increased over the last few decades, although it is not clear how much of the increase is real and how much is due to improved instruments and criteria for diagnosis and certification (Doll and Peto, 1981; Hartge and Devesa, 1992). A recent analysis and quantification of the role of various risk factors on time trends for non-Hodgkin's lymphoma incidence concluded that about 80% of these trends remain unexplained (Hartge and Devesa, 1992).

In particular, there is no clear evidence of any association between exposure to chemicals and the risk of disease, *even* at the relatively high doses found in the occupational environment. Thus, it is difficult to draw any inference on the roles of the chemical constituents of hair dyes, particularly in the absence of reliable assessments of *exposure* and of allowance for indicators of socio-economic status, which is often a correlate in hair dye use. There is also no information on the doses, biodistribution and bioavailability of potential carcinogens in hair dyes, with particular reference to their concentrations in lymphoid tissues.

In conclusion, therefore, two studies (Cantor *et al*, 1988; Zahm *et al*, 1992) reported a positive, though moderate, association between personal use of hair dyes and non-Hodgkin's lymphomas, and two smaller datasets suggested a link with multiple myeloma (Zahm *et al*, 1992; Morris Brown *et al*, 1992). The analyses, however, can be criticized on epidemiological grounds, particularly because no allowance was made for potential *confounding* factors, and the results lacked a plausible biological interpretation. In addition, epidemiological evidence may be influenced by selective publication of positive results ('publication bias'), since, particularly in the absence of plausible biological hypotheses, there was little rationale for publishing negative studies, *ie* those finding no association.

Since the association was apparently stronger or restricted to subjects using black, brown/brunette or red dyes, it is also at least theoretically conceivable that greying hair may be a correlate both of hair dye use and of the subsequent risk of lymphoid neoplasms.

Thus, suggestions of a positive association between hair dye *use* and the risk of non-Hodgkin's lymphomas and other lymphoid neoplasms may be of interest for future epidemiological studies, but available evidence is inadequate for any public health or regulatory implication.

Bladder cancer

At least seven cohort studies based on 10 different populations provided information on occupational exposure to hair dyes as hairdressers, barbers, beauticians and cosmetologists, and subsequent bladder *cancer* risk (Alderson, 1980; Kono *et al*, 1983; Teta e?*al*, 1984; Gubéran *et al*, 1985; Skov *et* ai, 1990; Hrubec *et al*, 1992; Pukkala *et al*, 1992). The main findings are summarized in Table 6. Four studies were from Europe (*one* was a cooperative study from four Nordic countries), two from the USA and one from Japan, for a total of over 81,000 subjects (63,828 females and 17,247 males). In seven out of 10 studies, some moderate association was reported. A total of 183 *cases* of bladder *cancer* were observed *vs* 129 expected, corresponding to a summary RR of 1.4. The association was apparently, though not significantly, stronger in males (RR = 1.6) than in females (RR = 1.1). Thus, the results of cohort studies are compatible with some moderate association between past professional exposure to hair dyes (or other substances in the working environment) by hairdressers and barbers and subsequent bladder cancer risk.

There is, however, some indication that, at least in the past and in *selected* populations, the prevalence of cigarette smoking, a recognized risk factor for bladder cancer (US Department of Health and Human Services, 1982), was higher in these occupational groups than in the general population, and cohort studies were generally unable to allow for this major confounding factor in the analysis. It is thus possible that at least part of the apparent association is due to confounding by tobacco smoking, as also suggested by the stronger association in males, who were more frequently smokers, than females.

Some indication on *the* smoking issue can be derived from case–control studies, which generally included information *on* smoking, and could therefore allow for this variable in the analysis. The main findings from case–control studies are summarized in Table 7. Out of 11 studies (Wynder *et al*, 1963; Dunham *et al*, 1968; Anthony and Thomas, 1970; Cole *et al*, 1972; Viadana *et al*, 1976; Howe *et al*, 1980; Vineis and Magnani, 1985; Morrison *et al*, 1985; Risch *et al*, 1988; Silverman *et ai*, 1989, 1990), seven showed some assodation between occupational exposure to hair dyes and bladder *cancer* risk. Most estimates, however, were around or only slightly

Table 6. Summary results from selected cohort studies providing information on occupational exposure to hair dyes and bladder cancer

Authors, year, country	Sex	No. of subjects	Bladder cancer		Relative risk
			Observed	Expected	
Alderson, 1980 (UK)	M	1,831	7	5.6	1.3
Kono *et al.* 1983 (Japan)	F	7,736	0	1.0	0
Teta *et al.* 1984 (USA)	F	11,845	14	10.3	1.4
Gubéran *et al.* 1985 (Switzerland)	F	677	2	1.5	1.3
	M	703	11	5.3	2.1
Skov *et al.* 1990 (Norway)	F	4,356	11	7.2	1.5
	M		23	15.1	1.5
Sweden	F	16,942	6	13.5	0.4
	M	6,522	54	36.6	1.5
Finland	F	9,138	3	1.8	1.7
	M	428	0	0.3	0
Denmark	F	9,497	7	4.0	1.8
	M	4,874	41	20.0	2.1
Pukkala *et al.* 1992 (Finland)	Q	3,637	1	2.5	0.4
Hrubec *et al.* 1992 (USA)	M	740	3	4.3	0.7
Total	F	63,828	44	41.8	1.1
	M	17,247	139	87.2	1.6
	F + M	81,075	183	129.0	1.4

Table 7. Summary results from selected case–control studies of bladder cancer providing information on occupational exposure to hair dyes

Authors, year, country	Sex	No. of cases	No. of exposed cases	Odds ratio
Wynder *et al.* 1963 (USA)	M	300	4	—
Dunham *et al.* 1968 (USA)	M	265	4	2.8
Anthony and Thomas, 1970 (UK)	M	812	4	4.1
Cole *et al.* 1972 (USA)	M	356	4	0.6
	F	105	1	1.1
Viadana *et al.* 1976 (USA)	M	NR	5	1.5
Howe *et al.* 1980 (Canada)	M	480	3	—
	F	152	2	—
Vineis and Magnani, 1985 (Italy)	M	512	9	0.9
Morrison *et al.* 1985 (USA)	M	430	7	1.0
(UK)	M	399	2	1.3
(Japan)	M	226	1	1.0
Risch *et al.* 1988 (Canada)	M + F	826	20	0.8
Silverman *et al.* 1989 (USA)	M	2,100	28	1.3
Silverman *et al.* 1990 (USA)	F	652	17	1.4

NR, not reported; —, no exposed control.

above unity, and not statistically significant. Still, the general evidence from case–control studies is in agreement with that from cohort investigations, and is compatible With a moderately increased bladder cancer risk among hairdressers and barbers.

Some excess risk of bladder and other *urinary* sites *cancers* was also observed in descriptive occupational studies From New Zealand (Pearce and Howard. 1986) and Massachusetts (Dubrow and Wegman, 1984). but the figures were based on smaller absolute numbers, and are inconsistent with other studies (Menck *et al.* 1977; Neuberger *et al.* 1991).

It must be stressed that most information from descriptive, cohort and case–control studies concerns exposure in the relatively distant past, when there was less strict control of carcinogenic substances in hair

Table 8. Summary results from case–control studies of bladder cancer providing information on personal use of hair dyes

Authors, year, country	Sex	No. of cases	No. of exposed cases	Odds ratio
Howe *et al.* 1980 (Canada)	F	152	NR	0.7
	M	480	8	—
Hartge *et al*, 1982 (USA)	F	733	443	0.9
	M	2,249	172	1.1
Ohno *et al*, 1985 (Japan)	F	65	42	1.6
Claude *et al*, 1986 (Germany)	F	91	NR	No association
	M	340	NR	
Nomura *a al*, *1989* (USA)	F	66	41	1.5
	M	195	15	1.3

NR, not reported; —, no exposed control.

dyes and of the working conditions and activities of hairdressers. There is therefore a reasonable biological background for the observed association, which could also be compatible with latency and other time-related factors in the process of bladder carcinogenesis (Decarli *et al*, 1985). Thus, a recent IARC working group (IARC/WHO, 1993) stated that 'occupation as hairdresser *or* barber entails exposures that are probably carcinogenic'.

However, the estimated relative risks, as well as the overall pooled estimates, are only moderately above unity, and hence compatible with errors and biases in observational epidemiological studies. A major *open* question, moreover, is whether current exposure to modern hair dyes is still related to some excess risk, or whether the selective elimination *of* carcinogenic compounds (Table 1) over recent years has reduced any such risk to nonmeasurable levels. Only further surveillance and future studies will provide answers.

personal hair dye use in relation to bladder cancer risk was considered by at least one cohort and five case–control studies. The cohort study (Hennekens *et al*, 1979) was the Nurses' Health Study, based on 120,557 female American nurses, active in 1972 and followed-up for incidence of diseases until 1976. Five cases of bladder cancer were registered *vs* 7.4 expected, corresponding to a (nonsignificant) relative risk of 0.6.

The main findings from case–control studies are summarized in Table 8. Five studies were considered (Howe *et al*, 1980; Hartge *et al*, 1982; Ohno *et al*, 1985; Claude *et al*, 1986; Nomura *et al*, 1989), two from the USA and one each from Canada, Germany and Japan. By far the largest study, and hence the most informative one, including over three fourths of the cases and of the exposed subjects, was a multicentre, population-based, case–control investigation conducted by the US National Cancer Institute in 10 US states (Hartge *et al*, 1982). The study was originally focused on artificial sweeteners, but included adequate information on hair dyes, tobacco smoking and other major covariates of interest. There was no evidence of an association between hair dyes and bladder cancer risk, the RR estimates being 0.9 in females (based on 443 exposed cases) and 1.1 in males (based on 172 exposed cases), nor were there any trends in risk with frequency or duration in either sex. The other four studies were much smaller, and thus were less informative, including only a few dozen exposed subjects, but the RR estimates were again close to unity.

Thus, the overall evidence from cohort and case–control studies consistently excludes any appreciable and measurable risk of bladder cancer from personal use of hair dyes.

Other neoplasms

Among other cancer sites, the breast has been most extensively studied, because of the high incidence of the disease in women and the report of a substantially elevated RR of breast cancer from a small study published in the 1970s (Shafer and Shafer, 1976). Of 100 patients from a clinical practice in New York, 87 had been long-term users of hair dyes, as compared with 27% of a comparison group, with a RR estimate elevated over IO-fold.

At least seven case–control studies (Kinlen *ut ai, 1977;* Shore e *al*, 1979; Stavraky *et al*, 1979; Nasca *et al*, 1990, 1992; Wynder and *Goodman*, 1983; Koenig *et al*, 1991) and one cohort study (Hennekens *et al*, 1979) were subsequently published, including a total of over 3,200 breast cancer cases. Some of these were specifically designed to address the hair dye issue. None found evidence of an association, and it is

therefore now established that hair dye use is not a risk factor for human breast cancer.

Same occupational cohort studies (eg Teta *et al*, 1984; Osorio *et al*, 1986; Skov *et al*, 1990; Hrubec et *al*, 1992) reported an excess lung cancer rate in cohorts of subjects occupationally exposed to hair dyes. The results, however, were not consistent across studies and often not even within studies (eg inconsistencies were observed between males and females). Most studies, moreover, were unable to allow for smoking, by far the most important risk factor for lung cancer (Doll and Peto, 1981; US Department of Health and Human Services, 1982), and therefore the most reasonable interpretation of the association observed in a few studies is a somewhat elevated prevalence of smoking among hairdressers and barbers in the past. Likewise, no significant association with lung cancer was observed for personal use in a small study (60 lung *cancer* cases, Stavraky *et al*, 1981).

An excess of laryngeal cancer rates in barbers (Viadana *et al*, 1976) can be interpreted along the same lines, although in *that* study the RR estimate (2.8 based on 10 *cases)* was not materially modified by allowance for smoking.

The results for other neoplasms are scattered. *An* elevated risk of *cancers* of the cervix and of the ovary was reported among hair dye users in a multi-site case–control study conducted in Canada (Stavraky et *al*, 1981). There may have been some confounding by sexual and reproductive factors, which are known correlates of the risk of these neoplasms (Brinton and Fraumeni, 1986; Parazzini *et al*, 1991) and, conceivably, of hair dye use. However, a more carefully designed and conducted case-control study of ovarian *cancer* from Athens, Greece (Tzonou *et al*, 1993) found a significant association, with an RR of 2.2 for frequent hair dye users.

Two studies from Australia (Holman and Armstrong, 1983: Armstrong and Holman, 1985) and Denmark (Osterlind *et al, 1988)* found no association between hair dye use and skin melanoma.

Data are inconsistent for the relationship between hair dye use and brain cancer (Ahlbom *et al*, 1986; Burch *et al*, 1987), as well as for some rarer neoplasms, such as salivary gland cancers (Spitz *et al*, 1990), *and* childhood neoplasms in the offspring (Kramer *et al*, 1987; Bunin *et al*, 1987; Kuijten *et al*, 1990), particularly since some scattered positive findings may be influenced by publication bias.

Thus, there is at present no convincing evidence that occupational or personal exposure to hair dyes is related to the risk of any neoplasms at sites other than the bladder and the lymphoid tissue.

Conclusions and indications for further research

A substantial amount of epidemiological evidence is available on the possible association between hair dyes and several *cancer* sites, permitting a number of well-established conclusions. Occupational exposure ко hair colourants or personal hair dye use is not related *to* breast cancer, nor is it causally related to lung *cancer.* Likewise, there is no convincing evidence linking hair dye use to cancers of the *skin,* brain, female genital tract, stomach and other digestive sites. Further, personal use of hair dyes does not entail any measurable excess bladder cancer risk.

The two remaining open questions are the possible relationships between bladder cancer and (past) occupational *exposure* by hairdressers, barbers and beauticians, and between hair dye exposure and lymphoid neoplasms, with reference to both occupational and personal use.

The association between past occupational *exposure* to hair colourants and bladder *cancer* risk is reasonably consistent on epidemiological data, and plausible on biological grounds (Matanoski and Elliott, 1981). The question arises whether the risk has been eliminated, following selective removal of carcinogens from hair dyes and improvements in working conditions over the last few decades, or whether some excess risk is still identifiable. Thus, further monitoring on more recent cohorts will be an issue of scientific interest and public health relevance.

An association between personal hair dye use and non-Hodgkin's lymphoma and multiple myeloma was recently reported from three case–control studies (Cantor *et al*, 1988; Zahm *et al*, 1992; Morris Brown *et al*, 1992). The relative risk estimates were moderate, generally below a factor of two, and there was no clear evidence of duration or a dose–risk relationship. On epidemiological grounds, therefore, these findings require further study, particularly since they may be influenced by selective publication of positive findings. This publication bias is plausible, considering the absence of any reliable identification and measure of potential carcinogens in hair dyes which could have reached the bone marrow or the lymphoid tissue, and hence of *any* convincing biological link for these epidemiological observations.

These cautious notwithstanding, reports from unpublished investigations and from further case–couuol studies *of* lymphoid neoplasms and hair dye use would be *of* interest, whereas cohort studies are unlikely to provide meaningful information on such rare diseases. These case–control studies, even if designed to investigate several potential risk factors

for lymphoid neoplasms, considering the lack of definite knowledge on their aetiology, *should* nonetheless include a structured and, ideally, an (externally) validated section on the history of hair dye use. They should also include further information on possible confounding factors, and hence adequate allowance should be made in the analysis for the main covariates of potential interest.

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