OCCUPATIONAL EXPOSURES OF HAIRDRESSERS AND BARBERS AND PERSONAL USE OF HAIR COLOURANTS

1. Exposure Data

1.1 Introduction

Throughout history and across cultures, women as well as men have felt the need to change the natural colour of their skin, lips and hair, or to restore the colour of greying hair. For thousands of years, cosmetic dyes have been a part of all human cultures. The use of hair dyes can be traced back at least 4000 years; evidence from royal Egyptian tombs suggests the use of henna for dyeing of hair and fingernails. Henna contains the dye Lawsone (2-hydroxy-1,4-naphthoquinone), which, in its pure form, is also used as a synthetic direct (semi-permanent) hair dye. In the days of the Roman Empire, grey hair was darkened by combing it with lead combs dipped in vinegar. Interestingly, it has recently been shown that this application produces darkening of grey hair by deposition of lead sulfide nanoparticles (diameter of about 5 nm) on the surface of the hair (Walter *et al.*, 2006; Nohynek *et al.*, 2004a). Traditional, lead acetate-based products for darkening grey hair are still found on the international market, although their importance is minor.

Today, millions of consumers use a large variety of cosmetic dyes and pigments to change the appearance of their skin, lips, nails or hair. Hair dyeing has become a common practice in modern industrialised societies; the hair-dye industry has estimated (unpublished data) that between 50 and 80% of women have used hair dyes in the USA, Japan and the European Union. During the last century, synthetic dyes have taken a pivotal role in hair colouration. Their chemistry, use and safety have been reviewed (Corbett 1999, 2000; Corbett *et al.*, 1999; Nohynek *et al.*, 2004a; Zviak & Millequant 2005a,b).

1.2 Composition of modern hair dyes

Modern hair dyes may be classified into the following categories: oxidative (permanent) dyes, direct (temporary or semi-permanent) dyes, and natural dyes.

In the frequently used code system introduced by the European Cosmetic Association (COLIPA), hair-dye ingredients are classified into classes A, B or C: class A includes

ingredients of oxidative hair dyes, class B those of semi-permanent hair dyes, and Class C those of temporary hair dyes (see examples in Tables 1.4, 1.5, 1.6).

1.2.1 *Oxidative (permanent) hair dyes*

(a) Composition

Oxidative (permanent) hair dyes are the most important group and have a market share in the EU or the USA of approximately 80% (Corbett *et al.*, 1999).

Oxidative (permanent) hair dyes consist of two components that are mixed before use and generate the dye within the hair by chemical reactions. Their chemistry and use has recently been reviewed (Corbett *et al.*, 1999; Zviak and Millequant, 2005b). Modern oxidative dyes contain several ingredients with different functions (examples in 507Table 1.1) as follows:

Primary intermediates: arylamines (*para*-phenylenediamine (PPD), *para*-toluenediamine (PTD), substituted *para*-diamines), *para*-aminophenols (*para*-aminophenol, 4-amino-*meta*-cresol), 4,5-diaminopyrazole and pyrimidines. Oxidation of these substances and their chemical coupling with modifier (coupler) molecules result in coloured reaction products.

Couplers or modifiers: these include *meta*-substituted aromatic derivatives (*m*-phenylene-diamines, *meta*-aminophenols, resorcinol), pyridines and naphthols. Couplers determine the final shade by reaction with the oxidized form of primary intermediates, followed by further oxidative coupling reactions.

Oxidants: hydrogen peroxide, urea peroxide, sodium percarbonate, perborate.

Alkalinising agents: ammonia, monoethanolamine or aminomethylpropanol.

(b) Relative concentration of the components

The actual colouring mixture is prepared extemporaneously, before application to the hair, by mixing, generally weight by weight, a solution containing the precursors and the other components of the formula with a solution containing hydrogen peroxide called developer. Each of these two solutions amounts in general to 50 g per use, but it is not uncommon to use 40 g of a colourant formula mixed with 60 g of developer. With non-lightening oxidative colouring the amount of developer may be twice the amount of colourant formula. The final mixture applied to the hair amounts to about 100 g but can vary according to the amount of hair to be treated.

Given that it is diluted by the developer, if the original concentration of a precursor (base or coupler) is X, its concentration in the final mixture coming into contact with the hair, is, at most X/2.

In practice, the initial concentration X used lies between 0.006% and 7%. This range of concentrations corresponds to a spectrum of shades from very pale blond to black. This

Table 1.1. Examples of dye-substance classes used in modern oxidative hair dyes (from Corbett, 1999 and 2000; Hair-dye industry data, 2007)

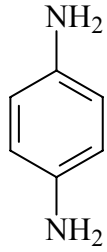
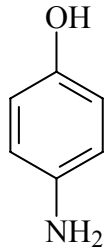
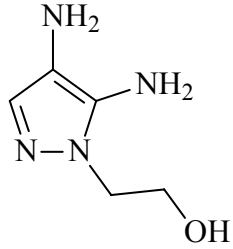
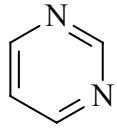
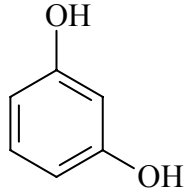
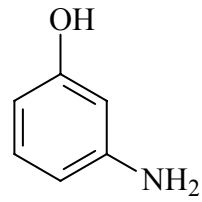
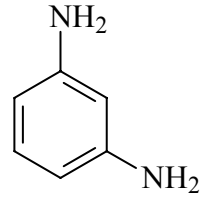
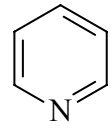
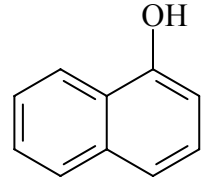
SUBSTANCE CLASS	STRUCTURE	FUNCTION
Para-Phenylenediamine		Primary Intermediate
Para-Aminophenol		Primary Intermediate
4,5-Diaminopyrazole		Primary Intermediate
Pyrimidine		Primary Intermediate
Resorcinol		Oxidative Coupler

Table 1.1 (contd)

SUBSTANCE CLASS	STRUCTURE	FUNCTION
Meta-Aminophenol		Oxidative Coupler
Meta-Phenylenediamine		Oxidative Coupler
Pyridine		Oxidative Coupler
1-Naphthol		Oxidative Coupler

is how the 20–70 shades of an oxidation-dye formulation are built up. It is worth noting that in the market:

- About 50% of shades contain no more than 0.5% precursors or colourants as a whole;
- About 25% of shades contain between 0.5% and 0.75% overall precursors or colourants; and
- About 25% of shades contain more than 0.75% of total precursors or colourants, with even fewer shades with a concentration reaching or exceeding 3.5% before mixing the developer.

The concentrations mentioned above represent the total content of precursors or dyestuffs (sometimes as many as 10) that is necessary to achieve the desired shade. More precisely, oxidation-dye products consist of a mixture of two or three bases, four or five

couplers and sometimes one or two direct colourants (see below) (Zviak & Millequant, 2005b).

The shade/colour achieved on the hair depends on the ingredients and their concentrations. Given the number of ingredients and the different resulting colour tones, a clear correlation of hair-dye shade with the concentration of the primary intermediate and coupler cannot be made. The dye shade, however, permits an estimation of the ingredient concentrations: dark hair dyes tend to contain the highest concentration of ingredients, whereas light (blond) shades tend to contain lower concentrations.

1.2.2 *Direct hair dyes*

Direct hair dyes include semi-permanent (resisting several shampooing processes) or temporary (resisting one or few shampooing processes) hair dyes. Direct hair dyes represent the second category of economically important hair colorants.

Semi-permanent colouring agents contain low-molecular-weight dye molecules, such as nitro-phenylenediamines, nitro-aminophenols, and some azo or anthraquinone dyes. These dyes may be used on their own in semi-permanent hair dyes or in combination with oxidative hair dyes in permanent hair-dye products to improve the tone of the final colour on the hair.

Temporary dyes represent the third class of hair colours. Temporary colouring agents are relatively large molecules and include azo-, triphenylmethane-, indophenol- or indamine-type dyes (Zviak & Millequant, 2005a) that are less resistant to washing and may be rinsed off by a single or a few shampooing processes. Typical formulations of semi-permanent hair dye are presented in Table 1.2.

1.2.3 *Natural hair dyes*

The majority of natural dyes use henna (produced by extraction of the leaves of a North African shrub (*Lawsonia inermis*) or the pure dye ingredient of henna, i.e. Lawsone (2-hydroxy-1,4-naphthoquinone). Henna has a long history of widespread use as a natural hair and body dye; however, a warning was raised against Lawsone by the Scientific Committee on Consumer Products (SCCP) of the European Commission (SCCNFP 2004). In addition, the reported increase in the use of Henna mixed with synthetic dye molecules, such as *para*-phenylenediamine (Black Henna) or other aromatic amines as a direct hair dye or body paint is of concern (Onder, 2003; Arranz Sánchez *et al.*, 2005).

Other natural dyes include extracts of Chamomile, indigo and various woods, barks or flowers (Zviak and Millequant, 2005a).

Natural dyes extracted from plants are of relatively small but growing economic importance.

Table 1.2. Ingredients of typical semi-permanent hair-colouring products

Light blond	*Reddish brown*
Water	Water
Ethoxydiglycol	Butoxyethanol
Polyethyleneglycol-50 tallow amide	Coconut acid diethanolamide
Hydroxyethylcellulose	Hydroxyethylcell ulose
Lauric acid diethanolamide	Lauric acid
Aminomethyl propanol	*N*-Methylaminoethanol
Erythorbic acid	HC Blue No. 2
Fragrance	2-Nitro-5-glyceryl methylaniline
Oleic acid	Fragrance
Triethanolammonium dodecylbenzenesulfonate	Butylparaben
CI Disperse Black 9	Ethylparaben
CI Disperse Blue 3	Methylparaben
CI Disperse Violet 1	Propylparaben
FD&C Yellow No. 6	3-Methylamino-4-nitrophenoxyethanol
HC Blue No. 2	3-Nitro-*para*-hydroxyethylaminophenol
HC Orange No. 1	HC Yellow No. 6
HC Red No. 3	CI Disperse Violet 1
HC Yellow No. 2	2-Amino-3-nitrophenol
HC Yellow No. 4	4-Amino-3-nitrophenol
	CI Disperse Blue 1
Red	*Dark brown*
Water	Water
Ethoxydiglycol	Butoxyethanol
Polyethyleneglycol-50 tallow amide	Polyglyceryl-2 oleyl ether
Hydroxyethylcellulose	Coconut acid diethanolamide
Lauric acid diethanolamide	Hydroxyethylcellulose
Aminomethyl propanol	HC Blue No. 2
Erythorbic acid	Lauric acid
Fragrance	*N*-Methylaminoethanol
Oleic acid	2-Nitro-5-glyceryl methylaniline
Triethanolammonium dodecylbenzenesulfonate	Fragrance
CI Disperse Black 9	HC Violet No. 2
HC Orange No. 1	CI Disperse Blue 1
HC Red No. 1	Butylparaben
HC Red No. 3	Ethylparaben
HC Yellow No. 2	Methylparaben
	Propylparaben
	HC Yellow No. 7
	3-Methylamino-4-nitrophenoxyethanol
	CI Disperse Violet 1
	3-Nitro-*para*-hydroxyethylaminophenol

From Cosmetic, Toiletry, and Fragrance Association (1992)
It should be noted that CI Disperse Blue 3, HC Yellow No. 6, 2-amino-3-nitrophenol, and CI Disperse Blue 1 are now banned by the European Union (*cf* Table 1.9).

1.2.4 *Trends in composition over time*

The invention, history and use of oxidative hair dyes and their ingredients has been reviewed (Corbett, 1999). The components of oxidative hair dyes have considerably changed since their introduction at the end of the 19th century. In the early phase, aromatic amines (primary intermediates, *para*-diamines, *para*-aminophenols) were used on their own in combination with hydrogen peroxide. During the period up the 1920s it was found that primary intermediates (*para*-diamines, *para*-aminophenols) may be combined with coupler molecules (resorcinol, *meta*-diamines, *meta*-aminophenols) to form coloured end products on oxidation. Thus in the early 1930s, the principal primary intermediates and couplers used today were already on the market. From the 1930s up to the 1970s there was little innovation in the components of oxidative and direct hair dyes; in the 1960s most manufacturers used a basic palette of 10–15 typical dye components; substances used in the period between the early 1930s to the 1970s are shown in Table 1.3.

Table 1.3. Some dye components used in typical oxidative and direct hair dyes in the period 1930s–1970s. US data (Corbett, 1999b)

SUBSTANCE	FUNCTION
para-Phenylenediamine	Primary intermediate
2,5-Diaminotoluene	Primary intermediate
N-Phenyl-*para*-phenylenediamine	Primary intermediate
4-Chlororesorcinol	Coupler
2,4-Diaminotoluene	Coupler
2,4-Diaminoanisole	Coupler
ortho-Aminophenol	Primary intermediate
para-Aminophenol	Primary intermediate
2-Amino-4-chlorophenol	Primary intermediate
Hydroquinone	Coupler
meta-Aminophenol	Coupler
Resorcinol	Coupler
Picramic acid	Direct dye
2-Nitro-*para*-phenylenendiamine	Direct dye
4-Amino-2-nitrophenol	Direct dye

In the 1970s and 1980s, major changes took place in the composition of direct and oxidative hair dyes. First, numerous innovative dyes were discovered, and several new direct and oxidative substances were introduced on the market. Second, in 1975, the positive results of mutagenicity tests in *Salmonella typhimurium* (Ames test) initiated a long-lasting controversy about the genotoxic and/or carcinogenic potential of some hair dyes, when Ames *et al.* suggested that nearly 90% of oxidative hair-dye ingredients were mutagenic in *Salmonella typhimurium* and might therefore pose a carcinogenic risk to consumers (Ames *et al.*, 1975).

On the basis of a worldwide survey coordinated by the EU, US and Japanese Cosmetic Associations during late 2007/early 2008, there would currently be 50

ingredients of oxidative, 43 ingredients of semi-permanent, and 88 ingredients of temporary hair dyes on the international market (EU, North- and Latin-America, Asia).

1.3 Production volumes

The major ingredients in oxidative hair dyes and their approximate annual worldwide tonnage of use (2005) are shown in Table 1.4. These data suggest that the bulk of substances used in oxidative hair dyes (total worldwide use at 50 to 250 tonnes) consist of traditional ingredients, such as resorcinol, *para*-phenylenediamine, 2,5-diaminotoluene and 4-amino-2-hydroxytoluene, *para*- and *meta*-aminophenol, 2-methyl-5-hydroxyethyl-aminophenol and 4-amino-*meta*-cresol. A few other ingredients are used at an annual tonnage of 10 to 50 tonnes, whereas most oxidative hair-dye ingredients are used at relatively minor amounts at 5 tonnes or less.

The estimated worldwide annual (2005) use of semi-permanent hair dyes is shown in Table 1.5. These data reveal a tonnage significantly lower than that of oxidative hair dyes and reflect their lesser economic importance. With the exception of two nitro-phenol-type semi-permanent dye ingredients (2-amino-6-chloro-4-nitrophenol and 4-hydroxypropyl-amino-3-nitrophenol), which are used at 5 to 15 tonnes per year, most substances are below 5 tonnes, whereas three substances are below 0.5 tonnes per year.

The estimated worldwide annual (2005) use of temporary hair dyes is shown in Table 1.6. The total annual use of most of these dyes is < 5 tonnes, except for Acid Violet 43 and Acid Red 33, which are used at 5 to 10 tonnes per year.

1.4 Application and formation of hair dyes

1.4.1 *Application of hair dyes*

Oxidative and direct hair dyes are applied to the hair in aqueous solutions or as a gel at a maximal concentration of 2.0 to 3.0% of the primary dye ingredient (dark-shade hair dyes) or < 0.05% (light-shade hair dyes) (see paragraph 1.2.1). After a contact time varying from a few to approximately 30 min permitting the hair-dyeing process to take place, the dye is rinsed off, and the hair is shampooed, rinsed, cut and dried. Detailed modern hair-dyeing techniques were recently reviewed (Zviak & Millequant, 2005a and 2005b).

1.4.2 *Reaction products of hair dyes*

Taking into account the standard volume of 80 mL of commercial hair-dye formulations, human external exposure during hair colouring would be in the range of 40 to 2400 mg. The frequency of hair-dye use varies between once per month (temporary hair dyes) to once per 6–8 weeks (oxidative hair dyes).

Table 1.4. Approximate total (North America, Latin America, EU, rest of the world) annual (2005) worldwide use (metric tonnes) of oxidative hair-dye ingredients. Data were collected by the international hair-dye industry and cover approximately 90% of the world market

INGREDIENT	COLIPA Code	2005 Total Use (tonnes)
2,5-Diaminotoluene	A005	150–200
para-Phenylenediamine	A007	150–200
Resorcinol	A011	200–250
4-Chlororesorcinol	A012	5–10
meta-Aminophenol	A015	50–100
para-Aminophenol	A016	50–100
1-Naphthol	A017	5–10
1,5-Naphthalenediol	A018	1–5
2,7-Naphthalenediol	A018	0.1–0.5
para-Methylaminophenol	A022	10–15
Hydroxybenzomorpholine	A025	0.5–1.0
4-Amino-2-hydroxytoluene	A027	150–200
2-Methyl-5-hydroxyethylaminophenol	A031	50–100
Phenylmethylpyrazolone	A039	10–15
2,4-Diaminophenoxyethanol	A042	20–25
3-Amino-2,4-dichlorophenol	A043	0.1–0.5
2-Methylresorcinol	A044	10–50
N,N-Bis-(2-hydroxyethyl)-*para*-phenylenediamine	A050	5–10
2,4,5,6-Tetraminopyridine	A053	1–5
4-Amino-*meta*-cresol	A074	50–100
6-Amino-*meta*-cresol	A075	1–5
1,3-Bis(2,4-diaminophenoxy)-propane	A079	1–5
Hydroxyethyl-*para*-phenylenediamine	A080	5–10
2-Amino-4-hydroxyethylanisole	A084	10–15
5-Amino-6-*ortho*-cresol	A094	1–5
Hydroxyethyl-3,4-methylenedioxylaniline	A098	1–5
2,6-Dihydroxy-3,4-duimethylpyridine	A099	0.1–0.5
2,6-Dimethoxy-3,5-pyridinediamine	A101	0.1–0.5
Hydroxypropyl-bis-(*N*-hydroxyethyl-*para*-phenylenediamine)	A121	1–5
6-Hydroxyindole	A128	1–5
3-Amino-3-hydroxypyridine	A132	10–15
2,6-Diaminopyridine	A136	0.1–0.5
2,6-Dihydroxyethylaminotoluene	A138	0.1–0.5
2,5,6-Triamino-4-pyrimidinol	A143	1–5
Dihydroxyindoline	A147	1–5
1-Acetoxy-2-methylnaphthalene	A153	1–5
1-Hydroxyethyl-4,5-diaminopyrazole	A154	10–50
2,2'-Methylenebis-4-aminophenol	A155	1–5

Table 1.5. Approximate annual (2005) worldwide use (metric tonnes) of semi-permanent hair-dye ingredients. Data were collected by the major international hair-dye industry and cover approximately 90% of the world market

INGREDIENT	COLIPA Code	2005 Total Use (tonnes)
Acid Yellow 1	B001	1–5
Disperse Red 17	B005	1–5
Basic Brown 17	B007	1–5
4-Nitro-*ortho*-phenylenediamine	B024	1–5
Picramic acid	B028	1–5
HC Red No. 13	B031	1–5
2-Nitro-5-glyceryl methylaniline	B060	1–5
HC Red No. 10 and 11	B071	1–5
2-Hydroxyethyl picramic acid	B072	1–5
4-Amino-2-nitrophenyl-amine-2'-carboxylic acid	B087	0.1–0.5
2-Chloro-6-ethylamino-4-nitrophenol	B089	1–5
2-Amino-6-chloro-4-nitrophenol	B099	10–15
4-Hydroxypropylamino-3-Nitrophenol	B100	5–10
2,6-Diamino-3-((pyridine-3-yl)azo)pyridine	B111	1–5
Basic Violet 2	B115	0.1–0.5
Basic Red 51	B116	0.1–0.5
Basic Yellow 87	B117	1–5
Basic Orange 31	B118	1–5

Table 1.6. Approximate annual (2005) worldwide use (metric tonnes) of major temporary hair-dye ingredients. Data were collected by the international hair-dye industry and cover approximately 90% of the world hair-dye market

INGREDIENT	COLIPA Code	2005 Total Use (tonnes)
Basic Red 76	C008	1–5
Basic Brown 16	C009	1–5
Basic Yellow 57	C010	1–5
Acid Orange 7 sodium salt	C015	1–5
Acid Red 33	CO22	5–10
Acid Yellow 23 trisodium salt	C029	1–5
Acid Yellow 3 mono- and disodium salt	C054	1–5
Basic Blue 99	C059	1–5
Acid Violet 43	CO63	5–10
Curry Red disodium salt	C174	1–5
Acid Red 18 trisodium salt	C175	1–5
Acid Red 52 sodium salt	C177	0.1–0.5
HC Blue 15 phosphate	C182	1–5
Tetrabromophenol blue	C183	1–5

An analytical methodology based essentially on HPLC was developed, which allowed the study of the kinetics of oxidative hair-dye coupling chemistry under conditions reflecting consumer usage, i.e. colour formation over 30 min (SCCNFP 2004, opinion 0941/05; Rastogi *et al.*, 2006). The methodology was applied to 11 different combinations of hair-dye precursors and couplers, and demonstrated that the amount of colour formed increases with time, while the amounts of free precursors and couplers decrease. Only the expected reaction products – based on the chemistry of the oxidative coupling of precursors and couplers – were formed, and no significant additional reactions or unexpected products were detected. Self-coupling products (such as Bandrowski´s base) or transient intermediates were not detected in the hair-dye formulations.

During the dyeing process, the consumer is exposed to the precursor(s), the coupler(s) and the expected reaction product(s). The kinetics of colour formation also revealed that the exposure of the consumer to the reaction product (hair dye) is much less than the exposure to the precursor and coupler over the whole application time. The total concentrations of unreacted precursors and couplers in various experiments were 12–84% of the applied dose. The typical concentration of reaction products in the formulations after 30 min varied from 0.02% to 0.65%. A worst-case scenario for the exposure from hair dyes in the dyeing process was derived from the data: the maximum content of a hair dye formed in the formulation 30 min after application was 0.65%. In a 70-ml (= 70-g) formulation this equals to 455 mg of hair dye formed.

1.5 Personal use of hair colourants

The main route of exposure to hair-dye components during personal use of hair colourants is dermal. Several studies have measured dermal and systemic exposure to hair-dye components, mainly by use of *para*-phenylenediamine (PPD) or [^{14}C]-labelled PPD.

In a study from the USA, seven hair dyes (oxidative and direct) were [^{14}C]-labelled and applied onto volunteers (Wolfram & Maibach, 1985). The extent of scalp penetration was slightly higher for direct dyes but in neither case did it exceed 1% of the applied dose.

In a study on percutaneous absorption of PPD during an actual hair-dyeing procedure, urinary levels of PPD metabolites were monitored during 24 or 48 hours after the dye had been applied (Goetz *et al.*, 1988). The fraction of the applied dose found in the urine 24 hours after application ranged from 0.04% to 0.25%. This study also showed a five- to ten-fold decrease in PPD penetration when the scalp was protected with clay before applying the dye.

In a study from Taiwan, China (Wang & Tsai, 2003), five volunteers dyed their own hair with various dye products containing different concentrations of PPD (2.2–3.2% or 1.1–1.6 g). The PPD excretion in the urine after 48 hours was 0.02–0.45% of the total dose.

Eight volunteers (Hueber-Becker *et al.*, 2004) received an oxidative hair-dye application containing [^{14}C]-PPD. The dye remained on the hair and scalp for 30 min. In the urine samples collected afterwards, 0.50±0.24% of the total applied radioactivity was recovered. The mean systemic dose was calculated to be approximately 0.09±0.04mg [^{14}C]-PPD-equivalents/kg body weight. In an *in-vitro* human skin study, a total of 2.4±1.6% of the applied radioactivity was absorbed (found in epidermis, dermis and receptor fluid), corresponding to an absorption rate of 10.6±6.7 $\mu g_{eq}/cm^2$. In the same eight volunteers, specific PPD metabolites were measured: five different metabolites were found, mainly *N*-mono-acetylated and *N,N′*-diacetylated PPD (Nohynek *et al.*, 2004b).

1.5.1 *Estimation of the internal dose to the user of hair-dye ingredients*

According to its "Notes of Guidance", the Scientific Committee for Consumer Products (SCCP) assesses hair dyes based on data of percutaneous absorption, mainly from in-vitro studies with human or pig skin. In a typical study, 20 mg of a representative hair-dye formulation per cm^2 is applied onto the skin. Following a 30-min contact time, the amount of hair dye in the epidermis (*stratum corneum* excluded), dermis and the receptor fluid after 24 hours is determined and summed-up to provide a worst-case value for the systemic (internal) dose. Taking the commercially important hair dye *para*-phenylenediamine (PPD) as an example, and using a worst-case scenario for a 60-kg adult person, the systemic exposure dose was estimated to be 0.052 mg/kg bw, calculated as follows:

A maximum concentration of 4.0% of PPD is mixed before use with H_2O_2. Thus the usage volume of 100 ml contains at maximum 2.0% PPD. Assuming the highest penetration (0.00447 mg/cm^2) and a typical human body weight (60 kg) and exposed scalp area (700 cm^2), this would give a systemic exposure dose of 0.00447 mg/cm^2 x 700 cm^2/60 kg = 0.052 mg/kg body weight. (source: SCCP's "Notes of Guidance" for the testing of cosmetic ingredients and their safety evaluation, 6th revision, adopted by the SCCP during the 10th plenary meeting of 9 December 2006).

1.6 Occupational exposure as a hairdresser and barber

Occupational exposure studies in hairdressers have mainly focused on airborne exposure. Only few studies have measured dermal and systemic exposure of hairdressers to certain chemicals.

1.6.1 *Airborne exposure in hairdressing salons*

In addition to hair dyes, hairdressers can be exposed to a wide variety of chemicals. Studies to measure the airborne occupational exposure of hairdressers are summarized in Table 1.7. In these studies, ethanol is generally used as a marker for solvent exposure, and *para*-phenylenediamine (PPD) is often used as a marker for dye exposure.

The exposure to organic solvents is generally highest in the hairdressers' breathing zone during the mixing and application of chemicals to the hair. The exposure time is usually short, varying from tens of seconds (hair sprays) to tens of minutes (permanent solutions and dyes) (Leino, 2001), but these tasks may be repeated many times a day. Several studies showed that local exhaust ventilation can significantly reduce airborne exposure (Hollund & Moen, 1998; Leino, 2001), but also indicated that it is seldom used.

The exposure of hairdressers to oxidative hair dyes was measured under controlled conditions. Three separate phases of hair dyeing were monitored: (1) dye preparation/hair dyeing, (2) rinsing/shampooing/conditioning, and (3) cutting/drying/styling, on eighteen hair dressers working for six hours with a dark-shade oxidative hair dye containing 2% of [^{14}C]-*para*-phenylenediamine (PPD). The detected PPD-equivalents in personal air samples (charcoal cartridges) were higher during the hair-dyeing phase than during the other phases, and ranged from < 0.25 μg (detection limit) to 0.88 μg with a mean exposure time of ~30 min (Hueber-Becker *et al.*, 2007).

Table 1.7. Airborne occupational exposure levels in hairdressing salons

Work task Exposure	Concentration in air	Remarks	Reference
Permanenting			
Ammonium thioglycolate	0.5–10 μg/m^3		Leino (2001)
Glyceryl monothioglycolate	0–1.8 μg/m^3		Leino (2001)
Ammonia	1.4–3.5 mg/m^3		Leino (2001)
	0.5–4.4 mg/m^3		Hollund & Moen (1998)
	105 mg/m^3	2 min	Van der Wal *et al.* (1997)
	5–25 mg/m^3		Rajan (1992)
	0.7–7.2 mg/m^3		Hakala *et al.* (1979)
Hydrogen sulfide	0.14–0.7 mg/m^3		Hakala *et al.* (1979)
Organic solvents	45 mg/m^3	Peak	Leino (2001)
Ethanol	2–36 mg/m^3		Almaguer *et al.* (1992)
	2–30 mg/m^3		Rajan (1992)
	0–3 mg/m^3	Breathing zone	Gunter *et al.* (1976)
Isopropanol	0–9 mg/m^3		Rajan (1992)
	0.4–14.8 mg/m^3		Hollund & Moen (1998)
Toluene	0.04–0.11 mg/m^3		Hollund & Moen (1998)
Hydrogen peroxide	0.014–0.14 mg/m^3	Spot measurement	Van der Wal *et al.* (1997)

Table 1.7 (contd)

Work task Exposure	Concentration in air	Remarks	Reference
Dyeing			
p-Phenylenediamine (PPD)	<1.0 µg/m^3	Detection limit	Gagliardi *et al.* (1992)
	<1.0–0.1 µg/m^3	Detection limit	Hollund & Moen (1998)
Diaminotoluene	<1.0–0.1 µg/m^3	Detection limit	Hollund & Moen (1998)
Ammonia	1.4–3.5 mg/m^3		Leino (2001)
	0.4–4.5 mg/m^3		Hollund & Moen (1998)
Hydrogen peroxide	0.007 mg/m^3	Spot measurement	Van der Wal *et al.* (1997)
Organic solvents	25 mg/m^3	Peak	Leino (2001)
Bleaching			
Ammonium persulfate	0–4.7 µg/m^3		Leino (2001)
	30 µg/m^3	Peak	Leino (2001)
Ammonia	1.4–3.5 mg/m^3		Leino (2001)
	0.3–10 mg/m^3		Hollund & Moen (1998)
Hydrogen peroxide	0.014 mg/m^3	Spot measurement	Van der Wal *et al.* (1997)
Hair lacquering			
Organic solvents	45 mg/m^3	Peak	Leino (2001)
Ethanol	150 µl/l		Van der Wal *et al.* (1997)
	0.007–3 mg/m^3		Gunter *et al.* (1976)
Isobutane	373–1935 mg/m^3		Gunter *et al.* (1976)
Butane	30 µl/l	1 min	Van der Wal *et al.* (1997)
Polyvinylpyrrolidone	7–70 µg/m^3		Gunter *et al.* (1976)
Particulates	100 mg/m^3	5 s	Van der Wal *et al.* (1997)
Ambient air in salons			
CO2	400–4500 µl/l		Van der Wal *et al.* (1997)
Volatile organic compounds	0.084–0.465 mg/m^3		Leino (2001)
	0.14–0.66 mg/m^3	8-h TWA C6–C16	Van der Wal *et al.* (1997)

Table 1.7 (contd)

Work task Exposure	Concentration in air	Remarks	Reference
Ethanol	0.1–56.6 mg/m^3	8-h TWA pers. samples	van Muiswinkel *et al.* (1997)
	0.1–43 mg/m^3	8-h TWA ambient air	van Muiswinkel *et al.* (1997)
	4.4–57 mg/m^3	8-h TWA breathing zone	Van der Wal *et al.* (1997)
	2.3–26 mg/m^3	8-h TWA stationary	Van der Wal *et al.* (1997)
	2–59 mg/m^3		Hakala *et al.* (1979)
Ammonia	0.1–1.2 mg/m^3		Hollund & Moen (1998)
	2.6–4.9 mg/m^3	8-h TWA breathing zone	Van der Wal *et al.* (1997)
	0.02–0.44 mg/m^3	8-h TWA winter	Van der Wal *et al.* (1997)
Hydrogen peroxide	0.01–0.069 mg/m^3	8-h TWA	Van der Wal *et al.* (1997)
Total dust	0.066–0.133 mg/m^3		Leino (2001)
	0.28–2.7 mg/m^3	8-h TWA breathing zone	Van der Wal *et al.* (1997)
	0.11–1.01 mg/m^3	8-h TWA stationary	Van der Wal *et al.* (1997)
Particulates	8500–17000 /l	>0.5 µm	Leino (2001)
	160–400 /l	<0.5 µm	Leino (2001)
	0.03–0.39 mg/m^3	8-h TWA stationary	Van der Wal *et al.* (1997)
	0.3–0.6 mg/m^3	8-h personal samples	Palmer *et al.* (1979)

Adapted from Leino (2001)
CO_2, carbon dioxide; TWA, time-weighted average

1.6.2 *Dermal and systemic exposure*

In a study from Sweden (Lind *et al.*, 2005) the dermal exposure of 33 hairdressers was assessed with a hand-rinse method (Lind *et al.*, 2004). Samples were taken in the hairdressing salons during normal working hours: before the hair-dyeing procedure, after the application of the hair dye, and after cutting of the newly dyed hair. The samples were analysed for five different compounds used in common commercial hair-dye products in Sweden: 1,4-phenylenediamine (PPD), toluene-2,5-diaminesulphate (TDS), 3-aminophenol (MAP), resorcinol (RES), and 2-methyl-resorcinol (MRE). The results are shown in Table 1.8. The maximum levels detected after application of hair dyes were: 939 nmol per

Table 1.8. Amounts of hair-dye compounds in hand rinse from professional hair dressers

Compound	Dominant hand		Serving hand	
	Positive samples (*n*)	Amount (nmol per hand) mean (range)	Positive samples (*n*)	Amount (nmol per hand) mean (range)
a. Taken before mixing hair-dye cream with hydrogen peroxide *Total number of samples = 33*				
PPD	3	294 (197–406)	3	263 (201–311)
MAP	19	116 (25–478)	20	100 (21–450)
TDS	7	149 (26–386)	6	192 (55–323)
RES	6	138 (24–433)	5	133 (24–397)
MRE	3	13 (7–20)	1	6
b. Taken after application of hair dye *Total number of samples = 33*				
PPD	4	454 (22–939)	4	426 (36–839)
MAP	22	94 (31–244)	22	73 (23–154)
TDS	12	118 (19–379)	11	142 (13–741)
RES	21	185 (30–513)	21	136 (24–773)
MRE	5	57 (10–187)	3	44 (19–82)
c. Taken after cutting newly dyed hair *Total number of samples = 29*				
PPD	5	178 (33–360)	5	153 (36–324)
MAP	15	49 (26–102)	14	52 (17–116)
TDS	14	71 (11–162)	13	120 (19–365)
RES	20	99 (19–364)	20	158 (22–736)
MRE	3	36 (10–82)	2	62 (14–109)

Adapted from Lind *et al*. (2005)
MAP, 3-aminophenol; MRE, 2-methyl-resorcinol; PPD, 1,4-phenylenediamine; RES, resorcinol; TDS, toluene-2,5-diaminesulphate

hand for PPD, 244 for MAP, 741 for TDS, 773 for RES and 187 for MRE. Positive findings were also reported for samples taken before mixing hair-dye cream with oxidizing cream. This exposure may derive from previous hair-dyeing activities on the same day or from background exposure from contaminated surfaces. Hand exposure was not significantly lower in hairdressers working with gloves compared with hairdressers not using gloves while dyeing hair. It was noted, however, that gloves were often re-used and could be a source of contamination.

In a later study, the penetration of PPD, TDS, and RES through protective gloves during hairdressing was investigated: when properly used, all the tested gloves gave

considerable protection against permeation of the hair-dye components studied (Lind *et al.*, 2007).

A study among 18 hairdressers in controlled conditions using radioactive PPD (2%) in hair dyes measured systemic exposure to PPD (Hueber-Becker *et al.*, 2007). No radioactivity above the limit of detection (< 10 ng PPD_{eq}/ml) was found in blood samples. Several urine samples contained no measurable or quantifiable radioactivity. Using the detected urinary levels and the urine volume, the mean urinary excretion across all hairdressers during the working-day was calculated to be < 25 ± 5.2 μg [^{14}C]-PPD_{eq}.

1.7 Regulations and guidelines

The legislation of cosmetics and the regulation of ingredients in hair-dye formulations in the EU and the USA differ. During the 1980s, several putative carcinogenic hair-dye substances were banned in the EU, but not in the USA. Furthermore, in April 2003 the EU Scientific Committee on Consumer Products (SCCP) started a strategy to ensure the safety of hair-dye products. The SCCP foresees banning of all permanent and non-permanent hair dyes for which industry has not submitted a safety file for the substances involved, and of those on which the SCCP has issued a negative opinion. Table 1.9 gives the list of ingredients that are currently not permitted in hair-dye products in the European Union. A substantial number of those banned substances were of limited commercial interest.

The Japanese regulation of cosmetics is the most restrictive. All cosmetic products are considered equivalent to drugs and are thus subject to premarket approval by the Ministry of Health and Welfare, and may contain only those ingredients included in the Comprehensive Licensing Standards of Cosmetics by Category (CLS); these ingredients must be conform certain defined specifications. Other Asian countries (e.g. Republic of Korea and China) have developed regulatory requirements for hair dyes and their ingredients similar to those in Japan (Corbett *et al.* 1999; Nohynek *et al.* 2004a).

In response to occupational safety concerns, i.e. the risk for developing contact dermatitis, international hair-dye label warnings recommend that hairdressers wear protective gloves during the hair dyeing and rinsing processes (Wilkinson and Shaw, 2005).

Table 1.9. List of 135 hair-dye substances banned by the European Union (updated September 2007)

Ref. No. Annex II to CD	Chemical Name / INCI - Name	CAS No.
363	*ortho*-Phenylenediamine	95-54-5
364	2,4-Diaminotoluene	95-80-7
376	1-Methoxy-2,4-diaminobenzene	615-05-4
377	1-Methoxy-2,5-diaminobenzene	5307-02-8
380	Basic Violet 3	548-62-9
383	2-Amino-4-nitrophenol	99-57-0
384	2-Amino-5-nitrophenol	121-88-0
386	CI 42640	1694-09-3
387	Acid Yellow 36	587-98-4
388	Basic Violet 1	8004-87-3
398	CI 45170, CI 45170:1	81-88-9; 509-34-2
406	4-Ethoxy-2,4-diaminobenzene	5862-77-1
407	1-beta-Hydroxyethyl-2,4-diaminobenzene	14572-93-1
408	Catechol	120-80-9
409	Pyrogallic acid	87-66-1
412	4-Amino-2-nitrophenol	119-34-6
413	1-Methyl-2,6-diaminobenzene	823-40-5
700	Disperse Blue 1	2475-45-8
1188	Basic Green 4	569-64-2
1204	*meta*-Phenylenediamine	108-45-2
1212	6-Methoxy-2,3-pyridinediamine HCl	94166-62-8
1213	2,3-Naphthalenediol	92-44-4
1214	2,4-Diaminodiphenylamine	136-17-4
1215	2,6-Bis(2-hydroxyethoxy)-3,5-pyridinediamine HCl	117907-42-3
1216	2-Methoxymethyl-*p*-aminophenol HCl	29785-47-5 (HCl)
1217	4,5-Diamino-1-methylpyrazole HCl; sulfate	21616-59-1 HCl
1218	4,5-Diamino-1-((4-chlorophenyl)methyl)-1H-pyrazole sulfate	163183-00-4
1219	4-Chloro-2-aminophenol	95-85-2
1220	4-Hydroxyindole	2380-94-1
1221	4-Methoxytoluene-2,5-diamine HCl	56496-88-9
1222	5-Amino-4-fluoro-2-methylphenol sulfate	163183-01-5
1223	*N*,*N*-Diethyl-*meta*-aminophenol	91-68-9
1224	*N*,*N*-Dimethyl-2,6-pyridinediamine HCl	-
1225	*N*-cyclopentyl-*meta*-aminophenol	104903-49-3
1226	*N*-Methoxyethyl-*para*-phenylenediamine HCl	72584-59-9
1227	2,4-Diamino-5-methylphenetol HCl	113715-25-6
1228	1,7-Naphthalenediol	575-38-2
1229	3,4-Diaminobenzoic acid	619-05-6
1230	2-Aminomethyl-*para*-aminophenol HCl	135043-65-1; 79352-72-0
1231	Solvent Red 1	1229-55-6
1232	Acid Orange 24	1320-07-6
1233	Acid Red 73	5413-75-2

Table 1.9 (contd)

Ref. No. Annex II to CD	Chemical Name / INCI - Name	CAS No.
1234	PEG-3,2′,2′-di-*para*-Phenylenediamine	144644-13-3
1235	6-Nitro-*ortho*-toluidine	570-24-1
1236	HC Yellow No 11	73388-54-2
1237	HC Orange No 3	81612-54-6
1238	HC Green No 1	52136-25-1
1239	HC Red No 8 and its salts	97404-14-3; 13556-29-1
1240	Tetrahydro-6-nitroquinoxaline and its salts	158006-54-3; 41959-35-7
1241	Disperse Red 15, except as impurity in Disperse Violet 1	116-85-8
1244	1-Methyl-2,4,5-trihydroxybenzene and its salts	1124-09-0
1245	2,6-Dihydroxy-4-methylpyridine and its salts	4664-16-8
1246	5-Hydroxy-1,4-benzodioxane and its salts	10288-36-5
1247	3,4-Methylenedioxyphenol and its salts	533-31-3
1248	3,4-Methylenedioxyaniline and its salts	14268-66-7
1249	Hydroxypyridinone and its salts	822-89-9
1250	3-Nitro-4-aminophenoxyethanol and its salts	50982-74-6
1251	2-Methoxy-4-nitrophenol (4-Nitroguaiacol) and its salts	3251-56-7
1252	C.I. Acid Black 131 and its salts	12219-01-1
1253	1,3,5-Trihydroxybenzene (Phloroglucinol) and its salts	108-73-6
1254	1,2,4-Benzenetriacetate and its salts	613-03-6
1255	Ethanol, 2,2'-iminobis-, reaction products with epichlorohydrin and 2-nitro-1,4-benzenediamine (HC Blue No. 5) and its salts	68478-64-8; 158571-58-5
1256	N-Methyl-1,4-diaminoanthraquinone, reaction products with epichlorohydrin and monoethanolamine (HC Blue No. 4) and its salts	158571-57-4
1257	4-Aminobenzenesulfonic acid and its salts	121-57-3
1258	3,3'-(Sulfonylbis(2-nitro-4,1-phenylene)imino)bis(6(phenylamino)) benzenesulfonic acid and its salts	
1259	3(or 5)-((4-(Benzylmethylamino)phenyl)azo)-1,2-(or1,4)dimethyl-1H-1,2,4-triazolium and its salts	
1260	2,2'-((3-Chloro-4-((2,6-dichloro-4-nitrophenyl)azo)phenyl)imino)-bisethanol (Disperse Brown 1) and its salts	23355-64-8
1261	Benzothiazolium, 2-[[4-[ethyl(2hydroxyethyl)amino]phenyl]azo]-6-methoxy-3-methyl- and its salts	
1262	2-[(4-Chloro-2-nitrophenyl)azo]-*N*-(2-methoxyphenyl)-3-oxobutanamide (Pigment Yellow 73) and its salts	13515-40-7
1263	2,2'-[(3,3'-Dichloro[1,1'-biphenyl]-4,4'-diyl)bis(azo)]bis[3-oxo-*N*-phenylbutanamide] (Pigment Yellow 12) and its salts	6358-85-6
1264	2,2'-(1,2-Ethenediyl)bis[5-((4ethoxyphenyl)azo]benzenesulfonic acid) and its salts	

Table 1.9 (contd)

Ref. No. Annex II to CD	Chemical Name / INCI - Name	CAS No.
1265	2,3-Dihydro-2,2-dimethyl-6-[(4-(phenylazo)-1naphthalenyl)azo]-1H-pyrimidine (Solvent Black 3) and its salts	4197-25-5
1266	3(or 5)-[[4-[(7-amino-1-hydroxy-3-sulphonato-2-naphthyl)azo]1-naphthyl]azo]salicylic acid and its salts	
1267	2-Naphthalenesulfonic acid, 7-(benzoylamino)-4-hydroxy-3[[4-[(4-sulfophenyl)azo]phenyl]azo]- and its salts	
1268	(μ-((7,7'-Iminobis(4-hydroxy-3-((2-hydroxy-5-(*N*-methylsulphamoyl)phenyl)azo)naphthalene-2-sulphonato))(6-)))dicuprate(2-) and its salts	
1269	3-[(4-(Acetylamino)phenyl)azo]-4-hydroxy-7-[[[[5-hydroxy-6-(phenylazo)-7-sulfo-2-naphthalenyl]amino]carbonyl]amino]-2-naphthalenesulfonic acid and its salts	
1270	2-Naphthalenesulfonic acid, 7,7'-(carbonyldiimino)bis(4hydroxy-3-[[2-sulfo-4-[(4-sulfophenyl)azo]phenyl]azo]-, and its salts	25188-41-4
1271	Ethanaminium, *N*-(4-[bis[4-(diethylamino)phenyl]methylene]-2,5-cyclohexadien-1-ylidene)-*N*-ethyl- and its salts	
1272	3H-Indolium, 2-[[(4-methoxyphenyl)methylhydrazono]methyl]-1,3,3-trimethyl- and its salts	
1273	3H-Indolium, 2-(2-((2,4-dimethoxyphenyl)amino)ethenyl)-1,3,3-trimethyl- and its salts	
1274	Nigrosine spirit soluble (Solvent Black 5)	11099-03-9
1275	Phenoxazin-5-ium, 3,7-bis(diethylamino)-, and its salts	47367-75-9
1276	Benzo[a]phenoxazin-7-ium, 9-(dimethylamino)-, and its salts	
1277	6-Amino-2-(2,4-dimethylphenyl)-1H-benz[de]isoquinoline1,3(2H)-dione (Solvent Yellow 44) and its salts	2478-20-8
1278	1-Amino-4-[[4[(dimethylamino)methyl]phenyl]amino]-anthraquinone and its salts	12217-43-5
1279	Laccaic Acid (CI Natural Red 25) and its salts	60687-93-6
1280	Benzenesulfonic acid, 5-[(2,4-dinitrophenyl)amino]-2-(phenylamino)-, and its salts	15347-52-1
1281	4-[(4-Nitrophenyl)azo]aniline (Disperse Orange 3) and its salts	730-40-5
1282	4-Nitro-*meta*-phenylenediamine and its salts	5131-58-8
1283	1-Amino-4-(methylamino)-9,10-anthracenedione (Disperse Violet 4) and its salts	1220-94-6
1284	*N*-Methyl-3-nitro-*para*-phenylenediamine and its salts	2973-21-9
1285	*N*1-(2-Hydroxyethyl)-4-nitro-*ortho*-phenylenediamine (HC Yellow No. 5) and its salts	56932-44-6
1286	*N*1-(Tris(hydroxymethyl))methyl-4-nitro-1,2-phenylenediamine (HC Yellow No. 3) and its salts	56932-45-7
1287	2-Nitro-*N*-hydroxyethyl-*para*-anisidine and its salts	57524-53-5
1288	*N*,*N'*-Dimethyl-*N*-Hydroxyethyl-3-nitro-*para*-phenylenediamine and its salts	10228-03-2

Table 1.9 (contd)

Ref. No. Annex II to CD	Chemical Name / INCI - Name	CAS No.
1289	3-(*N*-Methyl-*N*-(4-methylamino-3-nitrophenyl)amino)propane1,2-diol and its salts	93633-79-5
1290	4-Ethylamino-3-nitrobenzoic acid (*N*-Ethyl-3-Nitro-PABA) and its salts	2788-74-1
1291	(8-[(4-Amino-2-nitrophenyl)azo]-7-hydroxy-2-naphthyl)trimethylammonium and its salts, except Basic Red 118 (CAS 71134-97-9) as impurity in Basic Brown 17	
1292	5-((4-(Dimethylamino)phenyl)azo)-1,4-dimethyl-1H-1,2,4-triazolium and its salts	
1293	*meta*-Phenylenediamine, 4-(phenylazo)-, and its salts	495-54-5
1294	1,3-Benzenediamine, 4-methyl-6-(phenylazo)- and its salts	
1295	2,7-Naphthalenedisulfonic acid, 5-(acetylamino)-4-hydroxy-3((2-methylphenyl)azo)- and its salts	
1296	4,4'-[(4-Methyl-1,3-phenylene)bis(azo)]bis[6-methyl-1,3-benzenediamine] (Basic Brown 4) and its salts	4482-25-1
1297	Benzenaminium, 3-[[4-[[diamino(phenylazo)phenyl]azo]-2-methylphenyl]azo]-*N,N,N*-trimethyl- and its salts	
1298	Benzenaminium, 3-[[4-[[diamino(phenylazo)phenyl]azo]-1-naphthalenyl]azo]-*N,N,N*-trimethyl- and its salts	
1299	Ethanaminium, N-[4-[(4(diethylamino)phenyl)phenylmethylene]-2,5-cyclohexadien-1-ylidene]-*N*-ethyl- and its salts	
1300	9,10-Anthracenedione, 1-[(2-hydroxyethyl)amino]-4(methylamino)- and its derivatives and salts	86722-66-9
1301	1,4-Diamino-2-methoxy-9,10-anthracenedione (Disperse Red 11) and its salts	2872-48-2
1302	1,4-Dihydroxy-5,8-bis[(2-hydroxyethyl)amino]anthraquinone (Disperse Blue 7) and its salts	3179-90-6
1303	1-[(3-Aminopropyl)amino]-4-(methylamino)anthraquinone and its salts	
1304	*N*-[6-[(2-Chloro-4-hydroxyphenyl)imino]-4-methoxy-3-oxo-1,4-cyclohexadien-1-yl]acetamide (HC Yellow No. 8) and its salts	66612-11-1
1305	[6-[[3-Chloro-4-(methylamino)phenyl]imino]-4-methyl-3-oxocyclohexa-1,4-dien-1-yl]urea (HC Red No. 9) and its salts	56330-88-2
1306	Phenothiazin-5-ium, 3,7-bis(dimethylamino)- and its salts	
1307	4,6-Bis(2-Hydroxyethoxy)-*meta*-Phenylenediamine and its salts	
1308	5-Amino-2,6-Dimethoxy-3-Hydroxypyridine and its salts	104333-03-1
1309	4,4'-Diaminodiphenylamine and its salts	537-65-5
1310	4-Diethylamino-*ortho*-toluidine and its salts	148-71-0
1311	*N,N*-Diethyl-*para*-phenylenediamine and its salts	93-05-0
1312	*N,N*-Dimethyl-*para*-phenylenediamine and its salts	99-98-9
1313	Toluene-3,4-Diamine and its salts	496-72-0
1314	2,4-Diamino-5-methylphenoxyethanol and its salts	141614-05-3
1315	6-Amino-*ortho*-cresol and its salts	17672-22-9

Table 1.9 (contd)

Ref. No. Annex II to CD	Chemical Name / INCI - Name	CAS No.
1316	Hydroxyethylaminomethyl-*para*-aminophenol and its salts	110952-46-0
1317	2-Amino-3-nitrophenol and its salts	603-85-0
1318	2-Chloro-5-nitro-*N*-hydroxyethyl-*para*-phenylenediamine and its salts	50610-28-1
1319	2-Nitro-*para*-phenylenediamine and its salts	5307-14-2
1320	Hydroxyethyl-2,6-dinitro-*para*-anisidine and its salts	122252-11-3
1321	6-Nitro-2,5-pyridinediamine and its salts	69825-83-8
1322	Phenazinium, 3,7-diamino-2,8-dimethyl-5-phenyl- and its salts	
1323	3-Hydroxy-4-[(2-hydroxynaphthyl)azo]-7-nitronaphthalene-1-sulphonic acid and its salts	16279-54-2
1324	3-[(2-nitro-4-(trifluoromethyl)phenyl)amino]propane-1,2-diol (HC Yellow No. 6) and its salts	104333-00-8
1325	2-[(4-chloro-2-nitrophenyl)amino]ethanol (HC Yellow No. 12) and its salts	59320-13-7
1326	3-[[4-[(2-Hydroxyethyl)methylamino]-2-nitrophenyl]amino]-1,2-propanediol and its salts	173994-75-7
1327	3-[[4-[Ethyl(2-hydroxyethyl)amino]-2-nitrophenyl]amino]-1,2-propanediol and its salts	114087-41-1
1328	Ethanaminium, *N*-[4-[[4-(diethylamino)phenyl][4-(ethylamino)-1-naphthalenyl]methylene]-2,5-cyclohexadien-1-ylidene]-*N*-ethyl- and its salts	

2. Studies of Cancer in Humans

2.1 Occupational exposures of hairdressers and barbers

2.1.1 *Cohort studies* (Table 2.1) [Only studies not included in the previous IARC Monograph (Volume 57) are listed in the Table].

Alderson (1980) followed a sample of 1831 male hairdressers identified at the 1961 census of England and Wales until 1978. Mortality from all cancers was similar to that expected (134 obs., 126.1 exp.), and no specific cancer showed a significant excess: oesophagus, 5 obs., 3.4 exp.; lung, 52 and 50.8; bladder, 7 and 5.6; leukaemia, 3 and 2.7.

Kono *et al.* (1983) followed the mortality of a cohort of 7736 registered female beauticians from 1948 to 1960 in Fukuoka Prefecture, Japan, for an average of 22.5 years. Among the site-specific cancers examined, only stomach cancer occurred in significant excess (61 observed, 45.59 expected; 95% CI, 1.02–1.72). They found no case of bladder

Table 2.1. Cohort studies of occupational exposure to hair dyes

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	Relative risk (95% CI)*	Adjustment factors	Comments
Lynge (1990-1991)	4874 male and 9497 female hairdressers at the 1970 census aged 25–64 years from Denmark; follow-up from 1970–1980				**SIR**	NR	
			Bladder				
			Men	41	205 (151–278)		
			Women	7	176 (71–363)		
Skov & Lynge (1994)	1177 male and 4160 female hairdressers at the 1970 census aged 25–64 years from Denmark; follow-up from 1970–1987	Census data	*Bladder*				Includes data from Lynge (1990-1991) and possibly Skov & Lynge (1991)
			Men	67	158 (124–201)		
			Women	12	123 (64–215)		
			Lung				
			Men	127	120 (101–143)		
			Women	31	097 (68–138)		
			NHL				
			Men	12	118 (61–206)		
			Women	16	192 (110–312)		
			HD				
			Men	6	200 (73–435)		
			Women	3	90 (19–264)		
			Leukemia				
			Men	13	102 (54–174)		
			Women	8	94 (40–185)		

Table 2.1 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	Relative risk (95% CI)*	Adjustment factors	Comments
Boffetta *et al.* (1994)	29 279 female hairdresser at the 1970 census aged 25–64 years from Denmark, Sweden, Norway and Finland; follow-up from 1971–1985; follow-up started in 1987 for Denmark	Census data	*Ovarian* Female *NHL* Female	 127 36	 1.18 (0.98–1.40) 1.20 (0.84–1.66)	NR	
Pukkala *et al.* (1992)	3637 female and 168 male hairdressers born in or before 1946; followed up between 1970–1987; members of the Finnish Hairdressers' Association	Data from National Cancer Registry	**SIR** *Overall* Female *Breast* Female *Urinary bladder* Female *Multiple Myeloma* Female *Leukemia* Female	 247 70 1 1 4	 1.27 (1.11–1.42) 1.24 (0.97–1.57) 0.4 (0.01–2.35) 0.42 (0.01–2.35) 0.96 (0.26–2.47)		

Table 2.1 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	Relative risk (95% CI)*	Adjustment factors	Comments
Morton (1995)	2052 women with usual occupation as beauticians among residents in the Portland-Vancouver area of Oregon; age 16–68 years; diagnosed between 1963–1977	Hospital records and death certificates	Breast	28	**SIR** 125.2		
Calle *et al*. (1998)	Main lifetime occupation as beauticians, among 563 395 female participants of Cancer Prevention Study II; 46 433 person-years accrued in 1982–1991	Questionnaire	Breast	16	1.02 (0.62–1.69)	Age, race, family history of breast cancer, body mass index, education, smoking, alcohol, exercise, breast cysts, age at menarche, age at menopause, oral contraceptive use, estrogen replacement therapy, number of livebirths, age at first livebirth	Housewives used as reference

Table 2.1 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	Relative risk (95% CI)*	Adjustment factors	Comments
Andersen *et al.* (1999)	10 298 male and 26 545 female hairdressers at the 1970 census aged 25–64 years from Denmark, Sweden, Norway and Finland; follow-up from 1971–1991	Census data			**SIR**		
			Breast				
			Male	4	204 (56–523)		
			Female	643	105 (97–113)		
			Bladder				
			Male	147	147 (125–173)		
			Female	37	89 (63–123)		
			Lung				
			Male	249	121 (107–137)		
			Female	122	122 (102–146)		
			Ovary				
			Female	164	118 (101–138)		
			HD				
			Male	7	97 (39–199)		
			Female	8	88 (40–166)		
			NHD				
			Male	33	101 (69–142)		
			Female	48	106 (78–141)		
			MM				
			Male	18	100 (59–158)		
			Female	19	80 (48–125)		
			Acute Leukemia				
			Male	11	91 (46–163)		
			Female	18	94 (56–148)		
			Other Leukemia				
			Male	25	123 (80–182)		
			Female	18	91 (54–143)		

Table 2.1 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	Relative risk (95% CI)*	Adjustment factors	Comments
Pollán & Gustavsson, (1999)	1 101 669 women with a gainful occupation at the 1970 census, age 25–64 years. from Sweden; follow-up from 1971–1989	Record linkage between the Swedish cancer registry and a population registry comprising all individuals included in the 1970 census	*Breast* Female	258	**SIR** 110 (98–124)	Age, geographical category, period, town size	Comparisons within occupation and with other occupations reported as well. Total number employed as hairdresser or beauticians not given
Vasama Neuvonen *et al.* (1999)	892 591 economically active women in Finland, with occupation as reported in the 1970 census, born between 1906 and 1945; follow-up from 1971–95	Finnish Cancer Registry and exposures based on Finnish job-exposure matrix (FINJEM) developed at the Finnish Institute of Occupational Health	*Ovary* Hairdressers and barbers Beauticians	57 3	**SIR** 1.3 (1.0–1.7) 1.0 (0.2–2.9)	Birth cohort, follow-up period, social status	Total number employed as hairdresser or beauticians not given

Table 2.1 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	Relative risk (95% CI)*	Adjustment factors	Comments
Mutanen & Hemminki, (2001)	Swedish children born from 1935 to 1996 with a father (2.7 million) or a mother (1.0 million) with active occupation in the 1960 census; follow up from 1958–96 for the age group 0–14 years	Census data			Not reported	Not reported	Four cases of kidney cancer among children of male hairdressers: SIR=10.6 (2.9–27.2) and 2 cases among children of female hairdressers: SIR=1.0 (0.1–3.7)
Shields *et al.* (2002)	1 670 517 women with a gainful occupation at the 1960 or 1970 censuses, years from Sweden. follow-up from 1971–89	Swedish Cancer Environment Register (CER III) and census data	*Ovary* 1970 data 1960 data Both censuses	 14 36 51	 0.56 (0.3–0.9) 0.87 (0.6–1.2) 1.21 (0.9–1.6)	5-year age grouping	Total number employed as barbers, beauticians etc not given

Table 2.1 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	Relative risk (95% CI)*	Adjustment factors	Comments
Czene *et al.* (2003)	38 866 women and 6866 men from Sweden who declared to be employed as "hairdressers, barbers, beauticians and others" in at least one of the four censuses of 1960, 1970, 1980 and 1990; follow-up from 1960–1998	Census data	**Males**				
			Any census				
			Bladder	87	1.22 (0.98–1.51)		
			Lung	141	1.38 (1.16–1.63)		
			NHL	29	0.91 (0.61–1.31)		
			HD	8	1.17 (0.50–2.32)		
			MM	18	1.17 (0.69–1.85)		
			Leukemia	29	0.97 (0.65–1.39)		
			1960 census				
			Bladder	82	1.25 (1.01–1.55)		
			Lung	133	1.41 (1.18–1.68)		
			NHL	24	0.86 (0.55–1.28)		
			HD	7	1.34 (0.53–2.78)		
			MM	17	1.19 (0.69–1.92)		
			Leukemia	25	0.94 (0.61–1.38)		
			Females				
			Any census				
			Breast	913	1.02 (0.95–1.09)		
			Bladder	51	1.09 (0.81–1.43)		
			Lung	160	1.35 (1.15–1.58)		
			Ovary	192	1.11 (0.96–1.28)		
			NHL	64	0.94 (0.72–1.20)		
			HD	11	0.58 (0.29–1.03)		
			MM	31	1.30 (0.88–1.84)		
			Leukemia	57	1.01 (0.77–1.31)		

Table 2.1 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	Relative risk (95% CI)*	Adjustment factors	Comments
Czene *et al*. (2003) (contd)			*1960 census*				
			Breast	565	1.01 (0.93–1.09)		
			Bladder	33	0.95 (0.65–1.34)		
			Lung	109	1.22 (1.00–1.47)		
			Ovarian	111	0.97 (0.80–1.16)		
			NHL	41	0.96 (0.69–1.31)		
			HD	6	0.72 (0.26–1.59)		
			MM	19	1.14 (0.69–1.79)		
			Leukemia	41	1.16 (0.83–1.57)		
Ji *et al*. (2005)	4639 male hairdressers at the census of 1960; follow-up from 1960–2000	Census data	**Bladder**		**SIR**	Age, period, socioeconomic status	Same cohort used in all three publications
			SEI-adjusted				
			1960 census	88	1.26 (1.01–1.54)		
			1960–1970 census	62	1.14 (0.88–1.45)		
			1960–1970–1980 census	33	1.35 (0.91–1.84)		
			Smoking corrected				Correction for smoking was done by dividing the SIR by 35% of the excess of lung cancer
			1960 census	88	1.10 (0.88–1.34)		
			1960–1970 census	62	1.00 (0.76–1.26)		
			1960–1970–1980 census	33	1.17 (0.81–1.60)		

Table 2.1 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	Relative risk (95% CI)*	Adjustment factors	Comments
Ji & Hemminki, (2005a)	4639 male hairdressers at the census of 1960 and 16 360 female hairdressers at the census of 1970. Sweden; follow-up from 1960–2000 for males; 1970–2000 for females.	Census, Swedish Family-Cancer Database and Swedish Cancer Registry data	*Lung* Males Females	 144 92	**SIR** 1.42 (1.20–1.66) 1.19 (0.96–1.44)	Age, period, socioeconomic status	**UADT**: *Males*: 49 cases, SIR=1.39 (1.03–1.81) SIR significant also for hairdressers at 1960 & 1970 censuses, and 1960, 1970 & 1980 censuses, and for tongue and larynx. *Females*: 34 cases, SIR=1.45 (1.01–1.98); SIR significant for pharynx.

Table 2.1 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	Relative risk (95% CI)*	Adjustment factors	Comments
Ji & Hemminki, (2005b)	Same as in Ji & Hemminki (2005a); Sweden; follow-up from 1960–2002 for males; 1970–2002 for females	Census, Swedish Family-Cancer Database and Swedish and Swedish Cancer Registry data	*Males*		**SIR**	Age, period, socioeconomic status	
			Leukemia	27	0.85 (0.56–1.21)		
			CLL	9	0.71 (0.32–1.25)		
			AML	6	0.94 (0.34–1.84)		
			CML	3	1.03 (0.19–2.52)		
			PV	4	1.03 (0.27–2.29)		
			Females				
			Leukemia	39	1.02 (0.73–1.37)		
			CLL	8	0.73 (0.31–1.33)		
			AML	14	1.41 (0.77–2.24)		
			CML	3	0.86 (0.16–2.10)		
			PV	7	1.26 (0.50–2.66)		

AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HD, Hodgkin's disease; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NR, not reported; PV, polycythemia vera; RR, relative risk; SEI, socio-economic index; SIR, Standardized Incidence Ratio

cancer (1.01 expected), five cases of breast cancer (8.5 expected) and nine cases of lung cancer (7.4 expected).

Teta *et al.* (1984) examined cancer incidence during 1935–1978 in 11 845 female and 1805 male cosmetologists in Connecticut (USA) who had held licences for five years or more and had begun hairdressing school before 1 January 1966. A significant excess of lung cancer (standardized incidence ratio [SIR], 1.41) and excesses of brain (SIR, 1.68) and ovarian cancer (SIR, 1.34) of borderline significance were observed among women; the SIR for bladder cancer was 1.36 (95% CI, 0.74–2.27), on the basis of 14 cases. No significant cancer risk was evident for female cosmetologists licensed since 1935, even for those with 35 years or more of follow-up, although the SIRs for brain cancer, lymphoma and leukaemia were elevated. Female cosmetologists who had entered the profession between 1925 and 1934, however, experienced a significant overall increase in cancer incidence (SIR, 1.29) and significant excesses of respiratory cancer and cancers of the breast, *corpus uteri* and ovary. Among the men in the cohort, there was no excess of cancers at all sites (77 observed, 73.4 expected), but cancers of the brain occurred more frequently than expected (4 observed, 1.9 expected). [The Working Group noted that no other numbers were given for cancers at specific sites in men.]

Gubéran *et al.* (1985) studied cancer mortality during the period 1942–1982 and incidence in the years 1970–80 in a cohort of 703 male and 677 female hairdressers in Geneva, Switzerland. Increased mortality from bladder cancer was observed among men (10 observed, 3.9 expected; $P < 0.01$) and women (2 observed, 1.0 expected). The corresponding values for incident cases were 11 and 5.3 for men ($P < 0.01$) and 2 and 1.5 for women. Significant ($P < 0.05$) excesses of incident cases of cancer of the buccal cavity and pharynx (6 observed, 2.5 expected) and of prostate cancer (12 observed, 6.1 expected) were seen in men in the period 1970–80. No case of cancer of the buccal cavity and pharynx was seen in women (0.8 expected); for neither of these sites, however, was there an excess in the longer period covered by the mortality analysis (1942–1982). A nested case–control study of 18 cases of bladder cancer among men in this cohort (10 deceased, six incident cases that occurred during 1970–1980 and two incident cases that occurred in 1981) showed a non-significantly longer duration of exposure (measured from the start of apprenticeship) among those who dressed men's hair but not among those who dressed women's hair. Enquiries indicated that the great majority of male hairdressers in this study never dyed men's hair. In the period 1900–1950, application of brilliantines to men's scalps after haircuts was widespread in Geneva. The authors stated that those preparations may have contained colouring agents that are bladder carcinogens, such as *para*-dimethylaminoazobenzene, chrysoidine and auramine, which have been found in brilliantines in other countries. They also mentioned that 2–naphthylamine has been found as an impurity in Yellow AB and Yellow OB, which have been used in cosmetics.

In a brief note, Shibata *et al.* (1990) reported three deaths from leukaemia (3.84 expected) and two from lymphoma (3.01 expected) in a cohort of 8316 male and female barbers surveyed in the period 1976–1987 in the Aichi Prefecture, Japan.

In a cohort study of 248 046 US male veterans who served during 1917–1940 and were interviewed in 1954 or 1957 on smoking habits and occupations, Hrubec *et al.* (1992) analysed the mortality pattern of 740 barbers through 1980. Smoking-adjusted relative risks were 1.2 for all cancers (110 deaths; 95% CI, 1.06–1.45), 1.6 for respiratory cancers (95% CI, 1.22–2.20), 1.5 for prostate cancer (95% CI, 1.03–2.15) and 2.5 for multiple myeloma (95% CI, 1.08–5.63). No excess was found for bladder cancer (3 deaths; OR, 0.7).

Morton (1995) estimated breast-cancer incidence by compiling all cases first diagnosed during the period 1963–1977 among residents of the Portland-Vancouver Standard Metropolitan Statistical Area by searching records of all 24 hospitals (16 of which had tumour registries) in the four counties. An additional 1.8% of total cases were identified through death certificates. The total number of breast-cancer cases identified was 7368. For resident women aged 16–68 the usual occupation was retrieved from census data, and mean age-standardized incidence and mortality rates per 100 000 women were computed for each occupational category. The mean annual incidence rate among beautician was 125.2/100 000, not significantly different from that for all women. The mortality rate was 55.2/100 000, significantly higher than the rate for all women.

In a cohort of 563 395 female participants in Cancer Prevention Study II, a prospective mortality study enrolling volunteers from all US states interviewed in 1982 and followed up until 1991, 1780 fatal breast cancers were identified. Among women whose main lifetime occupation was beautician, the rate ratio, adjusted for age and several known or potential risk factors, was 1.02 (95% CI: 0.62–1.89), based on 16 cases (Calle *et al*., 1998).

(a) Scandinavian cohorts

Several cohort studies were conducted in the Scandinavian countries, often based on overlapping populations. Consequently, their results are not always independent from each other. They have been grouped by country to better understand these interdependencies.

(i) *Denmark*

Bladder-cancer incidence was investigated in a cohort of 4874 men and 9497 women aged 20–64 years from Denmark, who declared "hairdresser" as occupation in the 1970 census. Follow-up was performed up to 1980 through record linkage with national mortality and migration databases. The observed number of cases of bladder cancer was obtained through record linkage with the national Danish Cancer Registry, which also provided incidence rates to compute the expected number of cases. In men, there were 41 observed cases, as compared with 19.97 expected ones (SIR, 2.05; 95% CI, 1.51–2.78). In women, the observed and expected numbers of cases were 7 and 3.97, respectively, thus giving a SIR of 1.76 (95% CI, 0.71–3.63) (Lynge, 1990-1991).

As a follow-up of the previous study the cohort was then updated for the period 1981–1987 and extended to several other cancer sites. During this period, 26 further cases

of bladder cancer occurred among men (SIR, 1.17, 95% CI, 0.77–1.72) and 5 among women (SIR, 0.88; 95% CI, 0.28–2.04). Thus, for the overall period 1970–1987, the SIRs were 1.58 (95% CI, 1.24–2.01) in men and 1.23 (95% CI, 0.64–2.15) in women. In males during 1970–97 there were one case of cancer of the oral cavity (SIR = 0.37, 95% CI: 0.01–2.07), one of pharynx cancer (SIR, 0.29; 95% CI, 0.01–1.64), 10 of larynx cancer (SIR, 1.06; 95% CI, 0.51–1.95), 127 of lung cancer (SIR,,1.20; 95% CI, 1.01–1.43), 12 of NHL (SIR, 1.18; 95% CI, 0.61–2.06), 6 of Hodgkin disease (SIR, 2.00; 95% CI, 0.73–4.35), 13 of leukaemia (SIR, 1.02; 95% CI, 0.54–1.74) and 520 of all cancers (SIR, 1.12; 95% CI, 1.02–1.22). In females there were no cases of cancer of the oral cavity (SIR, 0; 95% CI, 0.00–2.29), three of pharynx cancer (SIR, 2.01; 95% CI, 0.42–5.89), one of larynx cancer (SIR, 0.58; 95% CI, 0.01–2.33), 31 of lung cancer (SIR, 0.97; 95% CI, 0.68–1.38), 16 of NHL (SIR, 1.92; 95% CI, 1.10–3.12), three of Hodgkin disease (SIR, 0.90; 95% CI, 0.19–2.64), eight of leukaemia (SIR, 0.94; 95% CI, 0.40–1.85) and 507 of all cancers (SIR, 1.05; 95% CI, 0.96–1.15) (Skov & Lynge, 1994).

(ii) *Finland*

In a study not entirely independent of that of Skov *et al.* (1990), a cohort of 3637 female and 168 male hairdressers, born in or before 1946, who were members of the Finnish Hairdressers' Association between 1970 and 1982, were followed-up for cancer incidence through the National Cancer Registry between 1970 and 1987 (Pukkala *et al.*, 1992). Expected numbers of cases were calculated by multiplying the number of person-years in each age group by the corresponding overall cancer incidence in Finland during the period of observation. Among women, there were 247 cases of cancer, versus 195.0 expected. Non-significant excesses were seen for breast cancer (70 cases, 56.3 expected), cervical cancer (11 cases, 7.1 expected), lung cancer (13 cases, 7.6 expected) and ovarian cancer (21 cases, 12.8 expected). Risks were not elevated for cancers at other sites, including the bladder (1 and 2.5), leukaemia (4 and 4.2) and multiple myeloma (1 and 2.4). The risk for all cancers was higher during the period 1970–1975 ($P < 0.05$) than during 1976–1981 ($P > 0.05$) or 1982–1987 ($P > 0.05$). Among men, 25 cases of cancer were observed (17.9 expected; 95% CI, 0.90–2.06); nonsignificantly elevated risks were found for cancers of the lung and pancreas, on the basis of seven and three cases, respectively.

The incidence of ovarian cancer was studied in a cohort that included all 892 591 economically active women in Finland, with occupations as reported in the 1970 census, who were born between 1906 and 1945. The follow-up period was 1971–1995. The National Cancer Registry was used for the identification of ovarian cancer cases ($n = 5072$). The expected numbers of cases were standardized by age, time period and social status, using rates of the entire cohort as the standard. The SIR for hairdressers and barbers was 1.3 (95% CI, 1.0–1.7), based on 57 cases, and that for beauticians was 1.0 (95% CI, 0.2–2.9), based on three cases (Vasama-Neuvonen *et al.*, 1999).

(iii) *Sweden*

Pollán and Gustavsson (1999) studied the incidence of breast cancer in a cohort of 1 101 669 Swedish women, alive and 25–64 years of age on 1 January 1971, who were gainfully employed at the time of the 1970 census and had also been present in the country during the 1960 census. The follow-up period was 1971–1989. Vital status was ascertained from a population registry, while emigration was not considered. Linkage to the Swedish Cancer Environment registry was used to identify breast cancer cases ($n = 29\,284$). Information on occupation was extracted from the 1970 census. For each occupation, expected numbers of cases were computed by use of age- and period-adjusted rates from the whole cohort. Among women employed as hairdressers or beauticians (total number not given), there were 284 observed and 258 expected cases of breast cancer, yielding a SIR of 1.10 (95% CI, 0.98–1.24). When further adjustment was made for area of residence and town size, defined from data extracted from the 1970 census, the relative risk (RR) was 1.09 (95% CI, 0.97–1.23) when the reference was set to all women in the cohort, and 1.21 (95% CI, 1.08–1.37) when the reference was set to women in other occupations of the same group (services and military work). Among women who reported hairdresser or beautician as their occupation in the 1970 census only, there were 85 cases of breast cancer, and the RR compared with women in other occupations of the same group was 1.09 (0.88–1.35). Among women reporting this occupation in both censuses (1960 and 1970), the number of breast cancers was 199, and the RR was 1.27 (95% CI: 1.11–1.47).

Mutanen & Hemminki (2001) studied the incidence of childhood cancer in a cohort that comprised all Swedish children born between 1935 and 1996 with a father (2.7 million) or a mother (1.0 million) with active occupation in the 1960 census, registered in the Swedish Family Cancer Database. The follow-up was performed between 1958 and 1996 for the age group 0–14 years. Cancer data were obtained from the Swedish Cancer Registry. Expected numbers of cases were calculated from reference incidence rates specific for 5-year age, area and socioeconomic status. The total active population was used as the reference population. Among the children of all economically active fathers there were 3376 childhood-cancer cases, eight of which were among hairdressers. Among children with economically active mothers there were 1408 childhood-cancer cases, 37 of which among hairdressers. Expected numbers for the whole group were not presented. There were four cases of kidney cancer among children of male hairdressers, compared with 0.4 expected (SIR, 10.6; 95% CI, 2.9–27.2). Among children of female hairdressers, there were 2 and 1.9 observed and expected cases, respectively, for a SIR of 1.0 (0.1–3.7).

All 1 670 517 women in Sweden who participated in both the 1960 and the 1970 censuses, who were gainfully employed in 1960 or 1970, were followed-up until 1989 with regards to ovarian cancer incidence, through linkage to the Swedish Register of Causes of Death. The Swedish Cancer Register was used to identify 9591 cases of ovarian cancer occurring during follow-up. The total numbers of women in the cohort employed as "barbers, beauticians, etc.," or in haircutting and beauty salons are not given.

The relative risk associated with various occupations was calculated by Poisson regression, stratified by time categories based on the census when employment was reported (1960 only, 1970 only, or both). Adjustment was performed for age. Among women who reported being employed as "barbers, beauticians etc." in 1970 only, there were 14 cases of ovarian cancer (RR, 0.56; 95% CI, 0.3–0.9), there were 36 cases among women reporting it in 1960 only (RR, 0.87; 95% CI, 0.6–1.2) and 51 cases among women reporting it in both censuses (RR, 1.21, 95% CI, 0.9–1.6). Among women who reported being employed in haircutting and beauty salons in 1970 only, 1960 only, and in both censuses, there were 12 (RR, 0.50; 95% CI, 0.3–0.9), 37 (RR, 0.88; 95% CI, 0.6–1.2), and 52 (RR, 1.26; 95% CI, 0.96–1.7) cases of ovarian cancer, respectively (Shields *et al.*, 2002).

Czene *et al.* (2003) studied the incidence of various cancers in a cohort comprising 38 866 women and 6866 men in Sweden who declared being employed as "hairdressers, barbers, beauticians and others" in at least one of the four censuses of 1960, 1970, 1980 and 1990. Of these, 67% of male and 41% of female hairdressers kept their occupation for at least two censuses. The follow-up period was 1960–1998. Tumour data were retrieved from the Swedish Cancer Registry. Expected numbers of cases were computed with reference to those who were economically active at least during one of the censuses, for those who were hairdressers in at least one census, and to those economically active in 1960 for those who were hairdressers in 1960. The rates used were sex-, period (5 years)- and age (5 years)-specific. For male hairdressers at any census, direct significant associations were found for cancers of the upper aerodigestive tract (51 cases; SIR, 1.51; 95% CI, 1.13–1.99), colorectal adenocarcinoma (135 cases; SIR, 1.24; 95% CI, 1.04–1.47) and lung cancer (141 cases; SIR, 1.38; 95% CI, 1.13–1.99), and a borderline association for bladder cancer (87 cases; SIR, 1.22; 95% CI, 0.98–1.51). No significant associations were found for other cancers of the digestive tract, urinary tract, skin, nervous system, thyroid, endocrine glands, connective tissue or for haematopoietic neoplasms. Results for male hairdressers at the 1960 census were similar. For female hairdressers at any census, direct significant associations were found for cancer of the pancreas (68 cases; SIR, 1.33; 95% CI, 1.03–1.68), lung cancer (160 cases; SIR, 1.35; 95% CI, 1.15–1.58), cancer of the cervix (213 cases; SIR, 1.28; 95% CI, 1.13–1.48), and cancer of the skin *in situ* (110 cases; SIR, 1.30; 95% CI, 1.07–1.55). No significant associations were found for other cancers, including in the breast, ovaria, and lung and for haematopoietic neoplasms, where the estimated SIRs were below 1.10 (except for multiple lyeloma (MM)). Results for female hairdressers at the 1960 census were largely similar, although the associations with pancreas cancer (38 cases; SIR, 1.01; 95% CI, 0.71–1.38) and cervical cancer (97 cases; SIR, 0.99; 95% CI, 0.80–1.21) were no longer evident.

Using the Swedish Family Cancer Database, a cohort was formed of all 1 644 958 Swedish men economically active at the 1960 census and all 1 154 091 women economically active at the 1970 census. In the cohort there were 4639 male and 16 360 female hairdressers. Follow-up ended in 2000. Linkage to the Swedish Cancer Registry

identified 24 041 bladder, 35 776 lung and 11 627 upper aerodigestive tract (UADT) cancers in men, and 3405, 8352 and 1767 in women, respectively. Expected numbers of cases were computed using sex-, age (5 years)-, period (10 years)- and socioeconomic status (6 groups)- specific rates from the whole cohort. Among male hairdressers there were 144 cases of lung cancer (SIR, 1.42; 95% CI, 1.20–1.54) and 92 (SIR, 1.19; 95% CI, 0.96–1.44) among female hairdressers (Ji & Hemminki, 2005a). A significant increase in risk for bladder cancer was found in men (SIR, 1.26; 95% CI, 1.01–1.54; 88 cases). The authors tried to adjust for the effect of smoking by dividing the SIR by 35% of the excess of lung cancer. The smoking-adjusted SIR was 1.10 (95% CI, 0.88–1.34). Among hairdressers in two consecutive censuses (1960 and 1970) there were 62 bladder-cancer cases, and the SIR was 1.14 (95% CI, 0.88–1.45) before and 1.00 (0.76–1.26) after adjustment for smoking. The corresponding values for those who were hairdressers at the censuses of 1960, 1970 and 1980 were 1.35 (95% CI, 0.91–1.84) and 1.17 (95% CI, 0.81–1.60), based on 33 cases. For women, data for bladder cancer were not presented, because no significant association was found (Ji *et al.*, 2005). Among male hairdressers, there were 49 UADT cancers (SIR, 1.39; 95% CI, 1.03–1.81). When subsites were considered, the SIR was significantly increased for cancers of the tongue (9 cases; SIR, 2.41; 95% CI, 1.09–4.25) and larynx (21 cases; SIR, 1.78; 95% CI, 1.10–2.62). The excess in UADT cancers was still significant when analysis was restricted to men who were employed as hairdressers in both the 1960 and the 1970 censuses (34 cases; SIR, 1.45; 95% CI, 1.01–1.98), or in all three censuses of 1960, 1970 and 1980 (16 cases; SIR, 1.96; 95% CI, 1.12–3.04). For female hairdressers the SIR of UADT cancers was 1.57 (95% CI, 1.02–2.23), based on 26 cases. When subsites were considered, the observed numbers were small, and a significant increase was found for cancer of the pharynx only (nine cases; SIR, 2.49; 95% CI, 1.13–4.39) (Ji & Hemminki, 2005a).

A subsequent cohort study was based on the same data, and had the same design as that described above (Ji & Hemminki, 2005b), and although the number of hairdressers was not given, it appears to be the same as mentioned before (4639 male and 16 360 female hairdressers). In this case, the follow-up was extended to 2002, and the neoplasms investigated were leukaemias. In the whole cohort of economically active men in 1960 there were 11 002 leukaemia cases, and in economically active women in 1970 there were 4040. No excess was found for all leukaemias for male (27 cases; SIR, 0.85; 95% CI, 0.56–1.21) or female (39 cases; SIR, 1.02; 95% CI, 0.73–1.37) hairdressers. When major leukaemia subtypes were considered separately, no excess was seen for CLL, AML, CML or PV in either sex. When analysis was restricted to women who were hairdressers in both censuses of 1960 and 1970, the SIR for PV was significantly elevated (7 cases; SIR, 3.54; 95% CI, 1.40–6.64) (Ji & Hemminki, 2005b).

(iv) *More than one Scandinavian country*

Following a report by Lynge and Thygesen (1988) on Danish hairdressers, Skov *et al.* (1990) carried out an analysis of the incidence of bladder cancer and lung cancer in men

and women employed as hairdressers and beauticians in 1960 in Norway and Sweden and as hairdressers and barbers in 1970 in Denmark and Finland.

Lynge and Thygesen (1988) found an increased risk for bladder cancer in hairdressers in Denmark: the RR was 2.05 for men, on the basis of 41 cases (95% CI, 1.51–2.78), and 1.76 for women, on the basis of seven cases (95% CI, 0.71–3.63). No corresponding increase in lung cancer was observed. In Finland, Norway and Denmark, the expected numbers of cancer cases were calculated by multiplying the person-years at risk for each of the five-year birth cohorts of hairdressers by the sex-specific incidence rate for the equivalent five-year birth cohort of all people who were economically active at the time of the census. In Sweden, the expected number of cancer cases was calculated by multiplying the number of hairdressers in a given region of Sweden in each five-year birth cohort at the time of the census by the sex-specific estimated cancer probability for the equivalent five-year birth cohort of all people in the region. National figures were obtained by aggregating the observed and the expected numbers across the 27 Swedish regions. The pattern of excess bladder-cancer incidence without a corresponding increase in lung-cancer incidence was not found in any of the other Nordic countries (Skov *et al.*, 1990).

In Sweden (Malker *et al.*, 1987; Skov *et al.*, 1990), the incidence of lung cancer was increased in male (98 cases; RR, 1.5; 95% CI, 1.2–1.8) and female (31 cases; 1.6; 1.1–2.2) hairdressers, and bladder-cancer incidence was increased in men (54 cases; 1.5; 1.1–1.9) but not in women (six cases; 0.4; 0.2–1.0). The authors noted that a national survey of smoking in Sweden carried out in 1963 had found that 74% of male barbers and beauticians aged 50–69 were regular smokers, compared with 46% of all men aged 50–69 years. In Norway, the incidences of bladder cancer and lung cancer were increased in hairdressers (RR, 1.4–1.6), but the increase was significant only for lung cancer in men. In the data from Finland, no case of bladder cancer was recorded among male hairdressers in the period 1971–80 (expected, 0.3), but three cases occurred in women (1.8 expected). The incidence of lung cancer was not increased: three observed, 2.0 expected in men and two observed, 4.4 expected in women (Skov *et al.*, 1990). The incidence of non-Hodgkin lymphoma was examined in Denmark (1970–80) by occupational category by Skov and Lynge (1991) using a similar method. No significant excess was observed in female hairdressers (RR, 1.98; 95% CI, 0.24–7.15; two cases); no case was recorded among male hairdressers. When all groups of hairdressers were included (self-employed/barber, work in beauty shops and hairdresser), the RRs were 1.3 (0.48–2.83; six cases) for men and 2.0 (0.81–4.14; seven cases) for women.

Boffetta *et al.* (1994) studied the incidence of ovarian cancer and NHL in a cohort of 29 279 women from Denmark, Sweden, Norway and Finland, aged 20–64 years in 1970, who declared being employed as a hairdresser in the 1970 census questionnaire. They were followed-up between 1970 and 1985 (1987 for Denmark). Date of death or emigration was obtained through linkage to appropriate population registries; linkage to the four national cancer registries identified cases of ovarian cancer and NHL in the cohort. The observed incidence was compared with the expected one using national

5-year age-specific rates in the overall female population at the censuses. SIRs were calculated as the ratio of observed and expected cases, and 95% CIs by use of Byar approximation. Overall, 127 ovarian cancer cases were observed in the cohort, compared with 107.8 expected (SIR, 1.18; 95% CI, 0.98–1.40). The SIRs were 1.4 (95% CI, 1.0–1.9), 1.1 (95% CI, 0.0–1.6) and 1.1 (95% CI, 0.8–1.4) for the periods 1971–1975, 1976–1980 and 1981–1985, respectively. The overall SIR for NHL was 1.20 (95% CI, 0.84–1.66), from 36 observed cases.

Using the same methods as Boffetta *et al.*, Andersen *et al.* (1999) conducted a systematic analysis of cancer risk in 10 298 male and 26 545 female hairdressers from Denmark, Finland, Norway and Sweden. In men, there was a significant increase for all sites combined (SIR, 1.12; 95% CI, 1.06–1.18; 1302 cases). Significant increases were found for lung cancer (SIR, 1.21; 95% CI, 1.07–1.37; 249 cases), bladder (SIR, 1.47; 95% CI, 1.25–1.73; 147 cases) and skin cancers other than melanoma (SIR, 1.22; 95% CI, 1.01–1.48; 105 cases). No association was found for NHL (SIR = 1.01), multiple myeloma (SIR = 1.00) or other haemolymphopoietic malignancies, while the SIR for lip cancer was significantly decreased (SIR, 0.34; 95% CI, 0.11–0.76; 5 cases). For women, the SIR for all sites was 1.05 (95% CI, 1.00–1.09) based on 2178 cases. Significant increases were found for cancers of the pharynx (SIR, 2.16; 95% CI, 1.18–3.62; 14 cases), lung (SIR, 1.22; 95% CI, 1.02–1.46; 122 cases), *cervix uteri* (SIR, 1.21; 95% CI, 1.03–1.43) and ovary (SIR, 1.18; 95% CI, 1.01–1.38). No increase in risk was found for bladder (SIR, 0.89; 95% CI, 0.63–1.23; 37 cases), breast (SIR, 1.05; 0.97–1.13; 643 cases) or haemolymphopoietic cancers (SIR 1.06 for NHL, 0.80 for multiple myeloma).

2.1.2 *Case–control studies* (Tables 2.2–2.6)

(a) Bladder cancer (Table 2.2) [Only studies not included in the previous IARC Monograph (Volume 57) are listed in this Table]

In a case–control study, Glashan and Cartwright (1981) interviewed all patients with bladder cancer presenting in three Yorkshire (United Kingdom) centres over a 3-year period (744 men and 247 women). Controls were 993 men and 345 women without malignant disease, age- and sex-matched to cases. Mantel-Haenszel ORs adjusted for age, sex and year of diagnosis were computed; the OR for "hairdressers" was 0.9 (95% CI, 0.3–3.2).

Schoenberg *et al.* (1984) conducted a population-based case–control study in 1978–79 in New Jersey, USA, on 706 white male patients aged 21–84 years with newly diagnosed, histologically confirmed cancer of the bladder or papilloma not specified as benign, and 1392 controls selected with random-digit dialling (<65 yrs) or from Medicare lists (age 65–84). Participation rates were 89.7% for cases, 86.6% for controls. Twenty cases and 38 controls were excluded from the analysis because of incomplete or unreliable interview. ORs were estimated by multiple logistic regression models adjusted for age, smoking and 19 employment categories. Twelve cases and 17 controls were ever employed as barbers or hairdressers, and the corresponding OR was 1.27 (0.59–2.73).

Table 2.2. Case–control studies of bladder cancer and occupational exposure of hair dyes

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Glashan & Cartwright (1981)	744 male and 247 female bladder cancer cases admitted to 3 centres in Yorkshire, UK	993 men and 345 women; matched on age and sex	Interview	Employed as a hairdresser	NR	0.9 (0.3–3.2)	Sex, age, year of diagnosis	
Schoenberg *et al.* (1984), New Jersey, USA, 1978–79	686 white male cases of histologically confirmed carcinoma of the urinary bladder; aged 21–84	1354 population controls; aged 21–84; matched on age; selected through random digit dialing or HCFA/Medicare lists	Interview	Ever employed as a barber/ hairdresser	12	1.27 (0.59–2.73)	Age, smoking, occupation	
Kunze *et al.* (1992), Northern Germany, 1977–84	531 male and 144 female cases of histologically confirmed benign or malignant epithelial tumors of the urinary bladder, ureters, renal pelves, and urethra; selected from four urologic wards in three cities	675 hospital controls with benign urological diseases; matched on age (±5 years), sex	Interview	Ever employed as a hairdresser	10	1.7 (0.6–4.5)	Age, smoking	Same study population as reported in Claude *et al.* (1988)

Table 2.2 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Cordier *et al.* (1993), France, 1984–1987	658 male and 107 female cases of histologically confirmed bladder cancer; aged <80 years; Five French Regions.	658 male and 107 female hospital controls randomly selected in the same hospital among patients admitted for causes other than cancer, respiratory disease or symptoms suggestive of bladder cancer; controls were matched with cases for sex, age (±5 years), ethnic origin and place of residence	Interviews	Having worked as a hairdresser for ≥6 months (males only)	5	2.21 (0.41–11.94)	Sex, age, ethnicity, residence, smoking.	Data for female hairdressers not reported
Bolm-Audorff *et al.* (1993) Northern Germany 1989–1992	300 histologically confirmed cases of lower urinary tract cancer	300 hospital-based controls admitted for non-malignant diseases of the urinary tract matched on sex, age, residence	Interviews	*Employed as hairdresser* Men Women Total	 5 2 7	 4.05 (0.63–26.09) Not calculated 6.48 (1.15–36.51)	Smoking	

Table 2.2 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Teschke *et al.* (1997), British Columbia, Canada, 1990–1992	88 male and 17 female cases of histologically confirmed bladder cancer registered by the British Columbia Cancer Agency	112 male and 27 female population controls selected from provincial voters lists; frequency matched on age (± 2 years) and sex	Interview	Ever employed as hairdresser or barber	3	3.2 (0.2–176)	Sex, age, smoking	For nasal cancer: 1 case, OR=2.5 (0–225)
				Most recent 20 years removed	2	2.6 (0.1–159)		
Sorahan *et al.* (1998), West Midland Region, UK 1991–1993	Primary analysis: 624 male and 179 female cases of urothelial cancer; Secondary analysis: 1106 male and 321 female cases of urothelial cancer born in 1915–70	*Primary analysis:* 2135 population controls; *Secondary analysis:* 2199 controls; controls were matched on sex, year of birth and GP	Interview	Ever employed as a hairdresser	11	Primary analysis 1.70 (0.74–3.89), Secondary analysis 1.63 (0.86–3.12)	Sex, year of birth, GP, smoking.	Two types of analyses performed: a matched/paired analysis and group analysis comparing all cancer cases and controls
				Ever employed as a hairdresser	22			

Table 2.2 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Kogevinas *et al.* (2003), Germany, France, Italy, Spain, Denmark, Greece,1976–1996	Pooled analysis of 3346 male incident cases of bladder cancer, from 11 case–control studies; aged 30–79 years	6840 male controls identified through hospitals and the general population; controls individually or frequency matched to cases on age (within 5 years) and geographic area	Job exposure matrix was used to calculate the prevalence of exposure and average levels of exposure were evaluated for each occupation in different time periods	Ever employed as a hairdresser	37	1.09 (0.70–1.70)	Age, smoking study centre	Same study population as reported in 't Mannetje *et al.* (1999); Reference: for males not employed in 8 a priori defined high risk occupation (including hairdressers), for females never employed as hairdresser.
Gago-Dominguez *et al.* (2001a), Los Angeles, USA, 1987–1996	1514 incident cases of bladder cancer; aged 25–64	1514 neighborhood controls; matched by sex, date of birth (within 5 years), ethnicity and neighborhood of residence at the time of cancer diagnosis	In-person interview	*Employed as hairdresser or barber* Never Ever *Duration of employment* <10 years ≥10 years	 1494 20 6 14	 1.0 1.5 (0.7–3.2) 0.5 (0.2–1.6) 5.1 (1.3–19.2)	Age, sex, smoking, ethnicity, residence.	

Table 2.2 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Zheng *et al.* (2002), Iowa, USA, 1986–1989	1135 male and 317 female cases of histologically confirmed cases of bladder cancer; identified by the State Health Registry of Iowa; between 1986 to 1989	1601 male and 833 female population controls; frequency-matched by gender and 5-year age group to all cases in a larger study, which also included cancers of the brain, kidney, pancreas, colon, and rectum.; randomly selected from computerized state driver's license records or HCFA lists	Self-administered mailed questionnaire	Employed in a barber shop for ≥5 years	5	1.8 (0.4–8.0)	Age, smoking, family history of bladder cancer	Data for occupational exposure for women not given.
Gaertner *et al.* (2004), Canada, 1994–1997	535 male and 352 female cases, with incident, histologically confirmed bladder cancer; aged 20–74 were identified through the provincial cancer registries in seven Canadian provinces	1430 male and 1417 female population controls; frequency matched on age and gender; identified through the National Enhanced Cancer Surveillance System (NECSS)		**Employed as hairdresser** *Male* *Female* >1–5 years >5–15 years >15 years	 8 6 1 4 3	 3.42 (1.09–10.8) 0.75 (0.28–2.01) NR (no exposed controls) 4.7 (0.79–27.9) 1.98 (0.4–9.7)	Age, province, race, smoking, consumption of fruit, fried food and coffee, employment in potentially hazardous occupations	

Table 2.2 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Dryson *et al.* (2008), New Zealand, 2003–2004	165 male and 48 female incident cases of bladder cancer; aged 25–70; reported to the New Zealand Cancer Registry	221 male and 250 female population controls; randomly selected from the New Zealand Electoral Roll; frequency matched by age	Interviews	*Employed as hairdresser for >1 year* Total Men Women	 6 2 4	 9.15 (1.60–52.22) NR 9.95 (1.37–72.21)	Age, sex, smoking	Risk ratio not reported for men because no controls were identified
Golka *et al.* (2008), North Rhine-Westphalia, Germany, 1988–95	156 male cases with histologically confirmed urinary bladder cancer	336 prostate cancer cases	Mail questionnaire	Employed as hairdresser for >1 year	4	4.90 (0.85–28.39)	Age, smoking	There were less than 10 cases and/or 10 controls available for analysis

CI, confidence interval; NR, not reported; OR, odds ratio

Kunze *et al.* (1992) conducted a hospital-based case–control study in northern Germany (1977–1984), including 531 male patients with an epithelial neoplasm of the lower urinary tract and an equal number of controls admitted to urological wards with benign urological diseases (64% with prostatitis or prostatic hyperthropy) individually matched by age to cases. Two percent of the cases refused to participate. The smoking-adjusted conditional OR for having ever worked as a hairdresser was 1.7 (95% CI, 0.6–4.5), based on 10 exposed cases and six exposed controls.

Cordier *et al.* (1993) conducted a hospital-based case–control study in seven French hospitals between 1984 and 1987. Cases were 765 patients (658 men and 107 women) below age 80 years, with a histologically confirmed bladder cancer diagnosed after 1 January 1982 (527 (69%) were interviewed less than one year after diagnosis) and no previous history of cancer. Controls were patients with no history of cancer admitted to the same hospitals for causes other than cancer, respiratory disease or symptoms suggestive of bladder cancer, individually matched to cases by sex, age, ethnic origin and place of residence. Participation rates were not given. ORs were estimated by unconditional logistic regression including the matching variables and smoking. For subjects who had worked at least six months as hairdressers (five cases and two controls) the OR was 2.21 (95% CI, 0.41–11.94).

Bolm-Audorff *et al.* (1993) conducted a hospital based case–control study on 239 male and 61 female histologically confirmed cases of lower urinary tract cancers (90% of the bladder) identified in four clinics in two areas of Germany between 1989 and 1992, and an equal number of controls admitted to the same clinics for non-malignant diseases of the urinary tract, individually matched to cases by sex, age and residence. Response rate was 93% for cases and 98% for controls. Among men, five cases and three controls were employed as hairdressers, and the smoking-adjusted OR was 4.05 (95% CI, 0.63–26.09). Among women, two cases and no controls were exposed. The OR for both sexes combined was 6.48 (95% CI, 1.15–36.51).

Teschke *et al.* (1997) conducted a population-based case–control study in British Columbia, Canada, between 1990 and 1992, including 105 cases of bladder cancer (88 men and 17 women) and 48 cases of cancer of the nasal cavity or sinus (33 men and 15 women), all histologically confirmed. Controls were 128 men and 31 women randomly selected in age and sex strata from the provincial voters list. Since recruitment of bladder-cancer cases was restricted to those born after 1915, only 112 male and 27 female controls were used for this cancer. Participation rates were 89% for nasal cancer, 88% for bladder cancer, and 81% for controls, and next-of-kin interviews were conducted for 15%, 18% and 14%, respectively. ORs were adjusted for sex, age and smoking. Three bladder-cancer cases and one control had ever worked as a hairdresser or barber; the OR was 3.2 (95% CI, 0.2–176). When the more recent 20 years were removed, two cases and one control were exposed (OR 2.6; 95% CI, 0.1–159). One nasal cancer case and one control were exposed (OR 2.5; 95% CI, 0–225).

Sorahan *et al.* (1998), in a population-based case–control study from the West Midland Region, United Kingdom, interviewed 1427 cases (1106 males and 321 women)

born in 1915–70 and diagnosed with a primary urothelial tumour between 1991 and 1993. A first set of controls was selected by asking general practitioners (GP) of the cases to each select three patients matched on sex and year of birth. Of the 908 GPs contacted, 55% accepted to participate, representing a total of 615 cases. Out of 1845 potential controls, identified 1147 (62%) filled in the questionnaire. A further set of 1768 potential controls matched to cases on age, sex and GP were selected through the Family Health Service Authorities, 1052 (60%) of whom returned the questionnaire. [Note: sex distribution of controls not given]. The primary analysis was performed on the 803 cases (624 men and 179 women) for which at least one matched control was available, and 2135 controls correctly matched to cases. A further analyses was conducted on all 1427 cases and 2199 controls. The conditional OR adjusted for smoking and for ever having been employed as a hairdresser in the primary analysis was 1.70 (95% CI, 0.74–3.89), based on 11 cases and 18 controls. When all cases and controls were considered, there were 22 exposed cases and 19 exposed controls, and the OR adjusted for age, year of birth and smoking was 1.63 (95% CI, 0.86–3.12).

Data from 11 case–control studies on bladder cancer conducted between 1976 and 1996 were combined, and results were published separately for women (’t Mannetje *et al.*, 1999) and men (Kogevinas *et al.*, 2003). Subjects outside the age range 30–79 years and prevalent cases were excluded. Among women, 700 cases of bladder cancer and 2425 controls (761 hospital and 1664 population controls) were included. Eleven cases and 56 controls had worked as hairdresser, barber, or beautician, and the OR adjusted for age, smoking, study centre and centre-age interaction was 0.8 (95% CI, 04.–1.7), compared with those never employed as a hairdresser. Among men, 3346 cases and 6840 controls were used for the analyses, of whom 37 and 62, respectively, had ever been employed as a hairdresser. Compared with men never employed in eight previously defined high-risk occupations (including hairdressers), the OR adjusted for age, smoking and study centre of those ever employed as a hairdresser was 1.09 (95% CI, 0.70–1.70) (’t Mannetje *et al.*, 1999; Kogevinas *et al.*, 2003).

Gago-Dominguez *et al.* (2001a) conducted a population-based case–control study in Los Angeles, California, USA, which involved 1514 (72%) non-Asian patients aged 25–64 years with incident histologically confirmed bladder cancer diagnosed between 1987 and 1996, identified through the SEER cancer registry of Los Angeles County. For each case a neighbourhood control was matched on sex, date of birth, ethnicity and neighbourhood of residence (69% were the first eligible control) [Sex distribution of cases and controls was not given]. Twenty cases and 13 controls were employed as hairdressers or barbers for at least one year, and the smoking-adjusted OR was 1.5 (95% CI, 0.7–3.2). The OR was 0.5 (95% CI, 0.2–1.6) for those employed for less than 10 years, based on six cases and 10 controls, and 5.1 (95% CI, 1.3–19.2) for those employed for 10 or more years, based on 14 cases and three controls.

Zheng and colleagues (2002) conducted a population-based case–control study on 1452 histologically confirmed incident bladder-cancer cases (1135 men and 317 women) aged 40–85 years identified by the State Health Registry of Iowa, US, between 1986 and

1989, and 2434 (1601 men and 833 women) population controls, frequency-matched by sex and age to cases of cancers at several organ sites. Participation rate was 85% for cases and 80–82% for controls. For 156 cases, proxy interviews were conducted. Among men, five cases and three controls were exposed for at least five years in barber shops, giving an OR (adjusted for age, smoking, family history of bladder cancer) of 1.8 (95% CI, 0.4–8.0). All exposed subjects had worked for 10 or more years in barber shops. No data were presented for women.

Gaertner *et al.* (2004) conducted a population-based case–control study in seven Canadian provinces, including 535 male and 352 female patients aged 20–74 years with incident, histologically confirmed bladder cancer between 1994 and 1997, identified through cancer registries. Controls were 1430 men and 1417 women randomly selected either by random-digit dialling (two provinces) or from the provincial health insurance database (five provinces) in 1996. Participation rates were 58% for male cases, 61% for female cases, 59% for male controls and 65% for female controls. ORs were computed by means of unconditional logistic regression models and adjusted for age, province, race, smoking, consumption of fruit, fried food and coffee, and employment in potentially hazardous occupations (as printers, rubber workers, metal workers, truck drivers, painters, dry cleaners, mechanics and machinists). Occupations held for at least one year full-time equivalent were considered relevant. Among men, eight cases and six controls had worked as hairdressers (OR, 3.42; 95% CI, 1.09–10.8): one case and no controls for less than five years, four cases and two controls for 5–15 years (OR 4.7; 95% CI, 0.79–27.9) and three cases and four controls for over 15 years (OR 1.98; 95% CI, 0.4–9.7; *P* for trend, 0.24). Among women there were six cases and 34 controls exposed (OR 0.75; 95% CI, 0.28–2.01).

Dryson *et al.* (2008) interviewed 213 out of all incident cases of bladder cancer aged 25–70, reported to the New Zealand Cancer Registry in 2003–2004 (64%; 165 men and 48 women), together with 471 population controls (48% of eligible controls; 221 men and 250 women) in a population-based case–control study. ORs were adjusted for age, sex, ethnicity and smoking. Six cases and three controls had worked as a hairdresser for more than one year; the OR was 9.15 (95% CI, 1.60–52.22). Among men, two cases and no controls were exposed, and among women four cases and three controls (OR 9.95; 95% CI, 1.37–72.21). Similarly, for the industrial classification "hairdressing and beauty salon" the OR was 5.35 (95% CI, 1.37–20.9), based on seven cases and five controls, three and none respectively among males, and four and five among women (OR, 4.79; 95% CI, 0.90–25.32). No consistent pattern by duration of employment was seen, but numbers were small. For hairdressers, the OR was 2.87 (95% CI, 0.59–13.89) in ever-smokers and 9.66 (95% CI, 0.62–151.42) in non-smokers.

A mailed questionnaire was sent to 332 male subjects with histologically ascertained bladder cancer, and as controls 566 with prostate cancer, who requested an after-care treatment in Bochum, Germany between 1992 and 1995. Of these, 63% of bladder and 72% of prostate cancer cases responded. After further exclusion of 53 bladder and 69 prostate cancer cases because they either were not resident in North-Rhine Westphalia,

had both bladder and prostate cancer, were first diagnosed before 1988 or did not specify first diagnosis, had asked for aftercare for another disease, or did not complete the questionnaire, 156 bladder and 336 prostate cancer cases were available for analysis. Four bladder and two prostate cancer cases had worked as a hairdresser for more than one year, and the corresponding age- and smoking-adjusted OR was 4.90 (95% CI, 0.85–28.39) (Golka *et al.*, 2008).

(b) Childhood cancers (Table 2.3)

The association between parental occupation and the risk for neuroblastoma was evaluated in a population-based case–control study conducted in 139 hospitals in the United States and Canada from 1992 to 1996. Of 741 eligible cases, information was obtained for 538 (73%) case mothers and 472 (64%) case fathers (directly for 405 and from the mother for 67). Controls were selected by random-digit dialling (RDD), and individually matched to cases on date of birth. The response rate for the RDD screening phase was 74%. Of 708 eligible controls, information was obtained for 504 (71%) mothers and 446 (64%) fathers (directly for 304 and from the mother for 142). Conditional logistic regression was used to obtain the OR adjusted for age, mother's age, race and education, and household income in birth year. Exposed subjects were defined as those who had worked as a barber or hairdresser for at least six months. Two case fathers and one control father had worked as a barber or hairdresser; the OR was 3.3 (95% CI, 0.2–45.7). There were 24 exposed case mothers and 10 control mothers, giving an OR of 2.8 (95% CI, 1.2–6.3) (Olshan *et al.*, 1999).

(c) Breast cancer (Table 2.4)

Band *et al.* (2000) conducted a population-based case–control study on occupational risk factors and breast-cancer risk by menopausal status in British Columbia, Canada. Cases were women below age 75 years with Canadian citizenship, residing in British Columbia, English-speaking and without previous history of breast cancer, diagnosed with histologically-confirmed breast cancer between June 1, 1988 and June 30, 1989, identified through the British Columbia Cancer Registry. Controls were women randomly selected from the 1989 British Columbia Provincial Voters List, matched to the cases by 5-year age group, with no diagnosis of breast cancer before. For breast-cancer cases, permission from the physician was requested before contacting the patient. A questionnaire eliciting information on lifetime job descriptions, occupation and industry titles, duration and period of work was mailed to cases and controls. The questionnaire collected information also on socio-demographic, anthropometric, menstrual and reproductive factors, smoking and drinking habits, exogenous estrogen use and family history of breast cancer. If the questionnaire was incomplete, subjects were contacted by telephone to collect missing data. Of 1489 eligible breast-cancer cases identified, 1018 (68.4%) returned a completed questionnaire (for 58 cases the physician did not grant

Table 2.3. Case-control studies of childhood cancer and occupational exposure to hair dyes

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Olshan *et al*., (1999), United States and Canada, 1992–1996	504 newly diagnosed cases of neuroblastoma; aged <19 years; 538 case mothers and 405 case fathers were identified	504 control mothers and 446 control fathers of children selected by RDD, individually matched on date of birth	Interview	*Employed ≥6 months as barber or hairdresser* Men Women	 2 24	 3.3 (0.2–45.7) 2.8 (1.2–6.3)	Race, age, education, household income in birth year	

CI, confidence interval; OR, odds ratio; RDD, random-digit dialling

Table 2.4. Case-control studies of breast cancer and occupational exposure to hair dyes

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Band *et al*. (2000) British Columbia, Canada, 1988–1989	995 female breast cancer cases; aged <75 years; identified through the British Columbia Cancer Registry	1020 population controls; no diagnosis of breast cancer before 1989; randomly selected from the 1989 British Columbia Provincial Voters List	Mailed questionnaire	*Employed as barber/hairdresser* Ever Usual occupation	 22 12	 1.92 (1.04–3.56) 1.02 (0.53–2.11)	Age, weight, smoking, alcohol, family history of breast cancer, history of breast biopsies, menopausal status.	Reported 90% CI
	Pre-menopausal 297 cases	332 controls		*Employed as barber/hairdresser* Ever usual occupation	 14 7	 5.45 (1.85–16.09) 2.71 (0.84–8.74)	Age, smoking, history of breast biopsies, and family history of breast cancer	
	Post-menopausal 690 cases	675 controls		*Employed as barber/hairdresser* Ever usual occupation	 8 5	 0.84 (0.35–2.01) NR	Age, weight, alcohol, family history of breast cancer, history of breast biopsies	
Habel *et al*. (1995) King County, Washington, USA, 1988–1990	537 white female cases of breast cancer; aged 50–64; identified through the SEER program	492 population controls (RDD); stratified by age	Interview	Worked as cosmetologist	7	1.5 (0.5–4.8)	Age, education, parity, BMI, alcohol	

BMI, body mass index; CI, confidence interval; OR, odds ratio; RDD, random-digit dialling; SEER, Surveillance Epidemiology and End Results

permission, 376 cases refused to participate, and 37 had either died or were lost to follow-up). Of 1502 women selected as controls, 359 refused to participate, 10 were deceased, 108 were lost to follow-up and 1025 (68.2%) returned the questionnaire. After further exclusion of cases and controls with no matches or with missing information, 995 cases (297 pre-menopausal and 690 post-menopausal) and 1020 controls (332 pre-menopausal and 675 post-menopausal) were available for the analysis. Conditional logistic regression models were used to estimate ORs and 90% CIs for occupational variables. At first, potential confounders to be included in the model were selected from several factors by keeping the ones significantly associated with breast-cancer risk in a forward selection procedure. Then the ORs for each occupation and industry type for which at least three cases were exposed were estimated in turn, for all women and separately for pre- and post-menopausal women. Usual occupation/industry (job held for the longest period) and ever occupation/industry (job ever held) were investigated. Overall, 22 breast-cancer cases reported to have ever worked as a barber or hairdresser, for an OR of 1.92 (90% CI, 1.04–3.56) and 12 cases reported barber/hairdresser as their usual occupation, for an OR of 1.02 (90% CI, 0.53–2.11). Among pre-menopausal women, 14 cases had ever been a barber or hairdresser (OR, 5.45; 90% CI, 1.85–16.09) and 7 cases reported barber or hairdresser as their usual occupation (OR, 2.71; 90% CI, 0.84–8.74). In post-menopause, there were eight cases who had ever been a barber/hairdresser (OR, 0.84; 90% CI, 0.35–2.01) and five cases whose usual occupation was barber/hairdresser (OR not given).

Habel *et al.* (1995) conducted a population-based case–control study of breast cancer in King County, Washington, USA. Cases were 537 white women aged 50–64 years, resident in King County, who were diagnosed with histologically confirmed first primary invasive or *in situ* carcinoma of the breast between January 1988 and June 1990. Controls were 492 women selected by random-digit dialling, stratified by age, without history of breast cancer. Participation rate was 81% for cases and 73% for controls. ORs were computed by means of logistic regression models and adjusted for age, education, parity, body-mass index, and alcohol. The three longest-held occupations were recorded for each woman. Seven cases and five controls reported having worked as a cosmetologist, and the OR was 1.5 (95% CI, 0.5–4.8). For all exposed women exposure began at least 10 years before diagnosis, while four cases and five controls had had the occupation for at least 5 years (OR, 0.9; 95% CI, 0.2–3.4).

(d) Cancers of the haemolymphopoietic system (Table 2.5)

Herrinton *et al.* (1994) conducted a population-based case–control study on 681 patients (321 women and 360 men) with incident multiple myeloma diagnosed from 1977 to 1981, identified through cancer registries in four geographical areas in the USA (Seattle, Utah, Detroit, Atlanta), and 1679 population controls (746 women and 933 men) frequency-matched to cases on sex, age and race. Participation rate was 89% for cases and 83% for controls. Proxy interviews were conducted for 36% of cases and 1% of controls. ORs were adjusted for age, sex, race, study centre and education. Among women, 12 cases and 22 controls had been employed as a hairdresser for six months or more, and

Table 2.5. Case–control studies of haemolymphopoietic malignancies and occupational exposure to hair dyes

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Herrinton *et al*. (1994), Seattle, Utah, Detroit, Atlanta, USA, 1977–1981	360 male and 321 female incident cases of multiple myeloma identified through cancer registries participating in the SEER program in four geographic areas; aged <82 years	933 male and 746 female population controls were matched on age, sex, and race; identified using area sampling methods and random-digit dialing	Interview	**Employed as hairdresser for >6 months** *Men* Never Ever *Women* Never Ever *Duration (Women)* <2 years 2–5 years >5 years	 359 1 309 12 3 5 4	 1.0 1.5 (0.12–17) 1.0 1.3 (0.60–2.7) 1.2 (0.25–5.3) 6.6 (1.2–36) 0.66 (0.21–2.0)	Age, sex, race, study centre, education	Results were similar when only self-responders were included
Mele *et al.* (1994), Rome, Bologna, Pavia, Italy, 1986–1990	619 cases (273 women, 346 men) of newly diagnosed acute myeloid leukemia, acute lympocytic leukemia, chronic myeloid leukemia and RAEB; aged ≥15 years; identified through hematology departments at selected hospitals in Rome, bologna and Pavia	1 161 outpatients from the same hematology departments as the cases; randomly selected; aged ≥15 years	Interview	*Women employed as hairdresser* AML ALL RAEB CML	 [2] [2] [3] [8]	 0.8 (0.1–6.8) 0.9 (0.1–8.0) 3.9 (0.3–45.3) 5.8 (1.3–26.1)	Sex, age, education, residence, selected occupations	Data for males not given.

Table 2.5 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Miligi *et al.* (1999), Italy	1217 female cases of newly diagnosed NHL, HD, leukemia and MM; aged 20–74 years who resided in the areas under study; cases were identified through periodic surveys of the hospital and pathology departments, the archives of Cancer Registries and cancer institutes	861 population controls; random sample of the general population, ages 20–74 residing in each of the areas under study; stratified by sex and 5-year groups	Interview	*Employed as "hairdresser, barber, beautician and related workers" for at least 5 years, excluding the 5 years before diagnosis* NHL Leukemias MM HD	 9 5 3 5	 1.9 (0.7–5.8) 2.2 (0.7–7.1) 11.1 (1.8–67.0) 2.1 (0.7–6.5)	Age	
Costantini *et al.* (2001), Italy, 1991–1993	1520 newly diagnosed male cases of: NHL, 811 HD, 193 Leukaemia, 383 MM, 133; among residents; aged 20–74 years; cases were identified through periodic surveys of the hospital departments.	918 population controls; random sample residents in each of the areas under study; stratified by sex and 5-year age groups.	Interviews	*Employed as "hairdresser, barber, beautician and related workers" for at least 5 years, excluding the 5 years before diagnosis* NHL Leukemias MM	 5 5 5	 0.6 (0.2–1.6) 1.0 (0.3–3.2) 2.2 (0.7–6.9)	Age	

Table 2.5 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
't Mannetje *et al.* (2008), New Zealand, 2003–2004	157 male and 134 female incident cases of NHL; aged 25 to 70 years; notified to the New Zealand Cancer Registry	221 male and 250 female cases; randomly selected from the New Zealand Electoral Roll for 2003, frequency matched by age according to the age distribution of New Zealand cancer registrations for NHL, bladder cancer and leukaemia in 1999	Interview	*Employed as hairdresser, beauty therapist or related activity for ≥1 year* Total Men Women	 4 0 4	 1.09 (0.27–4.35) - 0.94 (0.22–3.98)	Gender, age group, smoking status, Maori ethnicity, occupational status	
Coté *et al*. (1993), USA 1987–1989	2153 dead cases of NHL and AIDS	8612 persons who died of AIDS without NHL frequency matched on sex, age and race	Death certificate	Worked as beautician or cosmetologist	9	0.65 (0.3–1.13)	Sex, age, race	

AIDS, acquired immunodeficiency syndrome; ALL acute lymphocytic leukaemia; AML, acute myeloid leukaemia; CI, confidence interval; CML, chronic myeloid leukaemia; HD, Hodgkin disease; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; OR, odds ratio; RAEB, refractory anaemia with excess blasts

the OR was 1.3 (95% CI, 0.60–2.7). Of these, four cases and 15 controls were employed for longer than five years (OR, 0.66; 95% CI, 0.21–2.0). Only one male case and two male controls had worked as a hairdresser, yielding an OR of 1.5 (95% CI, 0.12–17). Results were similar when the analysis was restricted to self-responders (OR 1.1 for women and 2.2 for men ever employed as a hairdresser).

Mele *et al.* (1994) carried out a hospital based case–control study on leukaemia and pre-leukaemia in three hospitals located in Rome, Bologna and Pavia, Italy, between 1986 and 1990. Cases were 15 years or older, and included 252 patients with acute myeloid leukaemia (AML) (129 men and 123 women), 100 with acute lymphoblastic leukaemia (ALL) (48 men and 52 women), 111 with refractory anaemia with excess of blasts (72 men and 111 women) and 156 with chronic myelogenous leukaemia (CML) (97 men and 59 women). Controls were 1161 patients (399 men and 762 women) identified in outpatient departments on their first visit. ORs were adjusted for sex, age, education, residence and selected occupations. Among female controls, 1.6% had worked as a hairdresser. The percentage among female cases were: 0.8% (OR, 0.8; 95% CI, 0.1–6.8) for AML, 1.9% (OR, 0.9; 95% CI, 0.1–8.0) for ALL, 2.6% (OR, 3.9; 95% CI, 0.3–45.3) for refractory anaemia with excess of blasts, and 4.1% (OR, 5.8; 95% CI, 1.3–26.1).

A population-based case–control study on haemolymphopoietic neoplasms was conducted in 12 areas of Italy. Included were all newly diagnosed cases that occurred between 1991 and 1993 among residents, aged 20–74 years, identified through periodic survey of the relevant hospital departments in the study areas and in regional cancer institutes or university-affiliated haematology departments. Controls were random samples of the general population resident in the study areas, stratified by sex and age. Of 3357 eligible cases and 2391 eligible controls, an interview was obtained for 2737 (82%; 1520 men, 1217 women) cases and 1779 (74%; 918 men and 861 women) controls. Proxy interviews were conducted for 19% of cases and 5% of controls. The diagnosis of cases was NHL for 811 men and 639 women, Hodgkin disease (HD) for 193 men and 172 women, leukaemia for 383 men and 269 women, and multiple myeloma (MM) for 133 men and 137 women. Mantel-Haenszel ORs adjusted for age were computed. Subjects were considered exposed if they had worked as "hairdressers, barbers, beauticians and related workers" for at least five years, excluding the five years before diagnosis. For women, there were nine exposed cases with NHL/CCL (OR, 1.9; 95% CI, 0.7–7.1), five exposed leukaemia cases (OR, 2.2; 95% CI, 0.7–7.1), three exposed MM cases (OR, 11.1; 95% CI, 1.8–67.0) and five exposed HD cases (OR, 2.1; 95% CI, 0.7–6.5) (Miligi *et al.*, 1999; Costantini *et al.*, 2001).

Coté *et al.* (1993) conducted a study to investigate whether beauticians and cosmetologists with AIDS had an increased risk for NHL compared with other persons with AIDS. Cases were 2153 persons who died between 1987 and 1989 in 23 US states and had both AIDS and NHL listed as cause of death. Controls were 8612 subjects selected among persons who died of AIDS without NHL listed as a cause of death, frequency-matched to cases by sex, age and race. For nine (0.42%) cases and 56 (0.65%)

controls lifetime occupation on the death certificate was beautician or cosmetologist, and the OR was 0.65 (95% CI, 0.3–1.13).

(e) Other cancers

(i) *Cancer of the upper aerodigestive tract* (Table 2.6)

Boffetta *et al.* (2003) conducted a multicentre population-based case–control study of cancer in the larynx and hypopharynx in the early 1980s in six high-incidence areas: Calvados in France, the province of Varese and the city of Turin in Italy, the canton of Geneva in Switzerland, and the provinces of Zaragoza and Navarra in Spain. All of these the areas were covered by cancer registration. Cases were 1010 men with histologically-verified incident epidermoid carcinomas of the larynx and hypopharynx (ICD-9 146.4, 146.5, 148, 149.8 and 161). Participation rate was around 75% in Spain and Italy, > 90% in Geneva and lower in Calvados, where recruitment was limited to the main cancer hospital. Controls were 2176 men who were a representative sample from the general population, selected by use of different sources in the different areas, frequency-matched to the age and sex distribution of controls. Participation rate for controls was > 75% in Spain, Varese and Calvados, 64% in Geneva and 56% in Turin. The occupational section of the questionnaire elicited the list of jobs held for at least one year since 1945. Unconditional logistic regression models were used to estimate ORs, which were adjusted for age, study area, and tobacco and alcohol use. Thirteen cases and 18 controls had worked as a barber or hairdresser, and the estimated OR was 2.33 (95% CI, 1.00–5.40). The ORs were 2.7, 2.2 and 2.2 for duration of employment of 1–10, 11–20 or 21 or more years, respectively (*P* for trend, 0.09).

Swanson & Burns (1997) conducted a population-based case–control study in the three-county Detroit area, USA between 1984 and 1991, including 163 (84 men and 79 women) incident salivary gland cancer cases aged 40–84 years, and 3751 controls (1807 men and 1944 women) who were population referents selected by random-digit dialling. Response rates were 96% and 97%, respectively, and proxy interviews were conducted for 23% of the cases and 8% of the controls. ORs were estimated with multiple logistic regression models, adjusted by age, race and smoking status. Exposed subjects were those ever employed as a hairdresser or in a beauty shop, and were compared with those only employed in occupations with little or no exposure to carcinogens. For men, too few cases were exposed to calculate ORs, while for women, seven cases and 56 controls had ever worked as a hairdresser (OR, 2.7; 95% CI, 1.1–6.5) and eight women and 61 controls had worked in a beauty shop (OR, 3.4; 95% CI, 1.4–7.9).

(ii) *Lung*

Two studies reported results on the association between occupational exposure to hair dyes and lung cancer (Schoenberg *et al.*, 1987; Jahn *et al.*, 1999). Both had small numbers of exposed cases and exposed controls and were considered uninformative.

Table 2.6. Case-control studies of cancer of the upper aerodigestive tract and occupational exposure to hair dyes

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Swanson & Burns (1997), Detroit, USA, 1984–1991	84 male and 79 female cases of salivary gland cancer, identified through the SEER program	1807 male and 1944 female population controls selected via RDD	Telephone interview	Ever employed as hairdresser	7	2.7 (1.1–6.5)	Age, race, smoking.	For males too few exposed subjects to compute ORs. Reference category: subjects only employed in occupations with little or no exposure to carcinogens.
				Ever worked in a beauty shop	8	3.4 (1.4–7.9)		
Boffetta *et al.* (2003), France, Italy, Switzerland and Spain, 1980–1983	1010 males with histologically verified incident epidermoid carcinomas of the larynx and hypopharynx	2176 male population controls selected from census lists, electoral rolls, or population registries	Interviews	Employed as barber/hairdresser for 1+ years since 1945	13	2.33 (1.00–5.40)	Age, study area, alcohol, tobacco	95% CI not reported
				Duration of employment				
				1–10 years	5	2.7		
				11–20 years	2	2.2		
				≥21 years	6	2.2		
						p trend=0.09		

CI, confidence interval; OR, odds ratio; RDD, random-digit dialling; SEER, Surveillance Epidemiology and End Results

2.2 Personal use of hair colourants

2.2.1 *Cohort studies* (see Table 2.7 for studies of urinary bladder, breast and haematopoietic cancers)

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; $P = 0.02$). These associations weakened but remained significant after adjustment for smoking habits. There was no consistent trend of cancer risk with increasing interval from first use of hair dyes, although women who had used permanent dyes during 21 years or more before the onset of cancer had a significant increase in risk for cancers at all sites combined (RR, 1.38 adjusted for smoking; $P = 0.02$), largely because of an excess of breast cancers (RR, 1.48), which, however, was balanced by a decrease of similar magnitude 16–20 years before the onset of cancer. Among the other cancer sites evaluated, no significant associations were found that were related to personal use of hair dyes and lymphoma (RR, 0.59; $P = 0.102$) or urinary cancer (RR, 0.62; $P = 0.296$). Analyses of cases of cancer that had occurred only after 1972 (the year the study population was defined from the nurses' register) and were reported by surviving cases in 1976 yielded essentially the same results, thus indicating that self-selection for the study, early retirement and loss from the professional register were not sources of bias in this study.

Green *et al.* (1987) examined hair-dye use in relation to breast cancer in a follow-up study of a subgroup of the population described above, comprising 118 404 nurses who had no cancer in 1976 and were followed up to 1982. No relationship was detected: the rate ratio for ever-use was 1.1 (95% CI, 0.9–1.2) on the basis of 353 cases, compared with 505 for never-use. The risk for breast cancer did not increase with frequency or duration of use.

Another prospective cohort study from the Nurse's Health Study (Grodstein *et al.*, 1994) examined the relationship between permanent hair-dye use and risks for incident lymphoma, leukaemia, and multiple myeloma. A total of 99 067 women aged 30–55 years were followed through 1990. After eight years of follow-up, 244 incident haematopoietic cancers were identified, including 24 cases of Hodgkin lymphoma, 144 of non-Hodgkin lymphoma, 44 of leukaemia and 32 of multiple myeloma. No positive associations were observed between ever-use of permanent hair dyes and risk for all haematopoietic cancers (OR, 0.9; 95% CI, 0.7–1.2) or specific types, including Hodgkin lymphoma (OR, 0.9: 95% CI, 0.4–2.1), non-Hodgkin lymphoma (OR, 1.1; 95% CI, 0.8–1.6), multiple myeloma (OR, 0.4; 95% CI, 0.2–0.9), chronic lymphocytic leukaemia

Table 2.7. Cohort studies of personal use of hair dye

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Adjustment factors	Comments
Hennekens *et al*. (1979) USA 1972–76	120 557 active female nurses, aged 30–55 yrs; living in 11 U.S. states and registered in the American Nurses' Association	Self-administered questionnaire	*Breast cancer*			Age at first hair dye use, total number of years used, smoking	30% non-respondents
			Never used	861	1.0		
			1–5 years	102	1.10		
			6–10 years	79	1.02		
			11–15 years	49	1.05		
			16–20 years	16	0.64		
			>21 years	24	1.48		
			Bladder cancer				
			Never used	32	1.0		
			1–5 years	2	0.8		
			6–10 years	1	0.43		
			11–15 years	1	0.67		
			16–20 years	1	1.43		
			>21 years	0	0		
			Lymphoma				
			Never used	22	1.0		
			1–5 years	1	0.18		
			6–10 years	2	0.38		
			11–15 years	6	2.07		
			16–20 years	0	0		
			>21 years	1	1.67		

Table 2.7 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Adjustment factors	Comments
Green *et al*. (1987) USA 1976–82	118 404 active female nurses, aged 30–55 yrs; living in 11 U.S. states and registered in the American Nurses' Association; followed prospectively for 6 years	Self-administered questionnaire	*Breast cancer* Never used Ever used 1–5 years 6–10 years 11–15 years 16–20 years >21 years	 505 353 98 66 66 49 40	 1.0 1.1 (0.9–1.2) 1.3 (1.0–1.6) 0.9 (0.7–1.2) 1.0 (0.8–1.3) 1.2 (0.9–1.6) 1.2 (0.9–1.6)	Age, smoking, age at first birth, maternal history of breast cancer, menopausal status, benign breast disease	Nurses enrolled in this study are from the same cohort as Hennekens *et al*. (1979)
Thun *et al*. (1994) USA 1982–89	573 369 women aged 30 and older enrolled from the ACS Cancer Prevention Study II (CPS-II); follow-up through 1989	Self-administered questionnaire	*Breast cancer* Never used Ever used 1–9 years 10–19 years ≥20 years *Bladder cancer* Never used Ever used 1–9 years 10–19 years ≥20 years	 	 1.0 1.0 (0.8–1.1) 0.9 (0.8–1.1) 0.9 (0.8–1.1) 0.9 (0.7–1.2) 1.0 0.6 (0.3–1.0) 0.8 (0.4–1.7) 0.5 (0.2–1.5) 0.3 (0.1–1.1)	Age, hair dye colour	Assessed risk based on very few exposed cases

Table 2.7 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Adjustment factors	Comments
Thun *et al*. (1994) (contd)			*Lymphoma*				
			Never used	263	1.0		
			Ever used	87	1.0 (0.7–1.2)		
			1–9 years	28	0.8 (0.5–1.3)		
			10–19 years	35	1.1 (0.8–1.6)		
			≥20 years	24	1.0 (0.7–1.5)		
			Urinary system				
			Never used		1.0		
			Ever used		0.7 (0.5–0.9)		
			1–9 years		0.9 (0.6–1.3)		
			10–19 years		0.6 (0.4–0.9)		
			≥20 years		0.5 (0.3–0.9)		
			Multiple myeloma				
			Never used	144	1.0		
			Ever used	51	1.1 (0.8–1.5)		
			1–9 years	18	0.9 (0.5–1.5)		
			10–19 years	15	1.0 (0.6–1.9)		
			≥20 years	18	1.4 (0.9–2.3)		
			All hematopoietic cancers				
			Never used	714	1.0		
			Ever used	227	0.9 (0.8–1.1)		
			1–9 years	81	0.9 (0.7–1.2)		
			10–19 years	88	1.0 (0.8–1.3)		
			>20 years	58	0.9 (0.7–1.2)		

Table 2.7 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Adjustment factors	Comments
Grodstein *et al*. (1994) USA 1976–90	99 067 active female nurses, aged 30–55 yrs; living in 11 U.S. states and registered in the American Nurses' Association	Self-administered questionnaire	*All cancers*				Same cohort as Hennekens *et al*. (1979)
			Never used	140	1.0		
			Ever used	104	0.9 (0.7–1.2)		
			Hodgkin lymphoma				
			Never used	14	1.0		
			Ever used	10	0.9 (0.4–2.1)		
			Non-Hodgkin lymphoma				
			Never used	74	1.0		
			Ever used	70	1.1 (0.8–1.6)		
			CLL				
			Never used	15	1.0		
			Ever used	8	0.6 (0.3–1.5)		
			Multiple myeloma				
			Never used	24	1.0		
			Ever used	8	0.4 (0.2–0.9)		

Table 2.7 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	Relative risk (95% CI)*	Adjustment factors	Comments
Altekruse *et al*. (1999) USA 1982–94	547 586 women enrolled in the ACS Cancer Prevention Study II (CPS II)	Self-administered questionnaire	*All cancers*			Age, race, cigarettes smoked per day, age at quitting smoking, education and blue collar occupation, BMI, reproductive factors, dietary factors, alcohol consumption, exercise, aspirin use, X-ray exposure, treatment with radium, coal tar/pitch/asphalt, diesel engine exhaust, dyes, gasoline exhaust, pesticides/herbicides, textiles fibres/dust, wood dust, coal or stone dust, X-rays/radioactive isotopes	
			Never used	13 420	1.0		
			Ever used	5179	0.9 (0.9–1.0)		
			Breast				
			Never used	1894	1.0		
			Ever used	782	0.9 (0.9–1.0)		
			Bladder				
			Never used	154	1.0		
			Ever used	48	1.0 (0.7–1.4)		
			All hematopoietic cancers				
			Never used	1417	1.0		
			Ever used	574	1.1 (1.0–1.2)		
			All leukemias				
			Never used	511	1.0		
			Ever used	207	1.1 (0.9–1.3)		
			Non-Hodgkin lymphoma				
			Never used	536	1.0		
			Ever used	227	1.1 (1.0–1.3)		
			Multiple myeloma				
			Never used	329	1.0		
			Ever used	131	1.0 (0.8–1.3)		

Table 2.7 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	Relative risk (95% CI)*	Adjustment factors	Comments
Henley & Thun (2001)	547 571 women enrolled in the ACS Cancer Prevention Study II (CPS II)	Self-administered questionnaire	**Bladder cancer** *Total cohort* Never used Ever used *Never smokers* Never used Ever used	 244 92 128 28	 1.0 1.1 (0.8–1.4) 1.0 0.9 (0.6–1.4)		

ACS, American Cancer Society; BMI, body mass index; CLL, chronic lymphocytic leukemia

(RR, 0.6; 95% CI, 0.3–1.5), and other leukemias (RR, 0.8; 95% CI, 0.3–1.9). In the absence of information on non-permanent hair-dye use and without repeated assessment of exposure in the follow-up period may introduce misclassification of exposure, but the exposure misclassification is more likely to be non-differential and drives the association towards the null, because the exposure assessment was done before disease onset.

Thun *et al.* (1994) examined prospectively the relationship between hair-dye use and the development of fatal cancer in 573 369 women. Women who had ever used permanent hair dyes showed a reduced risk for all fatal cancer combined (RR, 0.9; 95% CI, 0.9–1.0) and of urinary system cancers (RR, 0.7; 95% CI, 0.5–0.9), and no increase in risk for any type of haematopoietic cancer. Women who had used black hair dyes for 20 years or more had an increased risk for fatal non-Hodgkin lymphoma (RR, 4.4; 95% CI, 1.3–15.2) and multiple myeloma (RR, 4.4; 95% CI, 1.1–18.3); however, these results are based on a very few exposed cases. No relationship was found between the use of permanent hair dyes and fatal cancers of the mouth, breast, lung, bladder or cervix.

Altekruse *et al.* (1999) examined cancer deaths linked to use of permanent hair dye in a cohort of 547 586 women in the USA. Exposure was assessed at the start of the follow-up period. A small increase in risk for death from haematopoietic cancers (RR, 1.1; 95% CI, 1.0–1.2) and leukemias was observed in association with more than 20 years of use (RR, 1.3; 95% CI, 1.0–1.7). However, patterns by duration of use of dyes and type of colour were inconsistent.

Henley & Thun (2001) analysed the mortality associated with hair-dye use based on a sample of 547 571 women from the ACS Cancer Prevention Study (CPS II). After 16 years of follow-up, the death rate from bladder cancer was similar among women who reported ever using permanent hair dye to that of never-users (RR, 1.1; 95% CI, 0.8–1.4) and restricted to lifelong nonsmokers (RR, 0.9; 95% CI, 0.6–1.4). Among women who had used permanent hair dyes, no consistent increase was seen in either the death rate from bladder cancer or the rate ratio associated with hair-dye use.

2.2.2 *Case–control studies* (see Tables 2.8–2.11)

The Working Group systematically reviewed studies dealing with exposures of cases of cancer of the urinary bladder and breast (sites that have been studied extensively), lymphatic and haematopoietic neoplasms and childhood cancer. No systematic review was made of studies of other cancer sites.

(a) Cancers of the urinary bladder and renal pelvis (Table 2.8)

Lockwood (1961) performed a case–control study of bladder tumours in Copenhagen, Denmark. All patients diagnosed with bladder tumours from 1942 until 1 March 1956 and able to be interviewed in 1956–57 were eligible for inclusion. Of the 428 patients, 369 (282 men) were interviewed, together with 369 population controls (282 men) selected from the electoral rolls and matched for sex, age, marital status, occupation and residence, and interviewed in 1956–59. Later in the study, a question on use of brilliantine

Table 2.8. Case–control studies of urinary bladder and renal pelvis cancer and personal hair dye use

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Lockwood (1961) Copenhagen, Denmark 1942–56	369 patients with bladder tumors reported to the Danish Cancer Registry between 1942 and 1956 who were residents of Kobenhavn and the Borough of Frederiksberg; follow-up until June 1959	369 population-based controls were selected from election rolls and matched on age, sex, marital status, occupation and residence	Interview	**Daily brilliantine use** *Men* Yes *Women* Yes	 51 2	 1.7 (1.1–2.6) 1.1 (0.2–6.6)	Matched on sex, age, marital status, occupation, residence	
Dunham *et al*. (1968) New Orleans, USA 1958–64	487 patients with a bladder cancer identified between 1958 and 1964; cases selected through physician and hospital records and through the Tumor Registry. Office of Vital Statistics	527 control patients diagnosed with conditions unrelated to genitor-urinary tract or to neoplastic disease; controls selected from the same hospitals as the patients	Interview	*Preparations for hair and scalp* Not used Used	 87 42	 1.0 [0.9]	Not reported	

Table 2.8 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Howe *et al.* (1980) Canada 1974–76	480 male and 152 female patients diagnosed with bladder cancer in 3 provinces between 1974 and 1976	480 male and 152 female neighbourhood controls matched on age (± 5 years) and sex	Interview	*Use of hair dyes* *Males* No Yes Females No Yes	 472 8 136 16	 1.0 Not calculated 1.0 0.7 (0.3–1.4)	History of bladder and kidney conditions,analgesic use, cigarette smoking, other tobacco products, exposure to a priori suspect industries, exposure to dust and fumes in occupations other than those expected a priori, exposure to specific chemicals, age, coffee and other beverage use, nitrate and nitrite sources in the diet, fiddlehead greens, diabetes, education, use of non-public water supply	Hair dye use not included in the analysis of male patients due to no exposed male controls

Table 2.8 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Hartge *et al.* (1982) USA 1977–78	2982 incident cases of histologically confirmed bladder cancer among residents living in 10 geographic areas within the USA; aged 21–84; cases identified through cancer registries	5782 randomly selected population controls stratified by age, sex and geographical area; random digit dialing (RDD) used to select controls; aged 21–64	Interview	**History of hair dye use**			Age, sex, race and cigarette smoking	No trend with frequency or duration in either sex
				Males				
				Never dyed hair	2065	1.0		
				Ever dyed hair	172	1.1 (0.9–1.4)		
				Unknown	12			
				Females				
				Never dyed hair	288	1.0		
				Ever dyed hair	443	0.9 (0.8–1.1)		
				Unknown	2			
				Duration of hair dye use				
				Males				
				Never dyed hair	2065	1.0		
				<5 years	115	1.4		
				5–10 years	27	0.8		
				10–19 years	23	1.1		
				≥20 years	6	0.7		
				Unknown	13	NR		
				Females				
				Never dyed hair	288	1.0		
				<5 years	109	1.1		
				5–10 years	68	0.9		
				10–19 years	149	1.1		
				≥20 years	104	0.8		
				Unknown	15	NR		

Table 2.8 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Ohno *et al.* (1985) Nagoya, Japan 1976–78	Male and female cases of urinary cancer selected through the Nagoya Bladder Tumor Registry; aged >20 years; residents of metropolitan Nagoya	Controls randomly selected from the general population through electoral registries; aged 20 and older; frequency matched on age, sex and residence	Interview	**Frequency of hair dye use** *Non smokers* Not tinted <1 time/month ≥1 time/month *Smokers* Not tinted <1 time/month ≥1 time/month	 21 12 12 2 8 10	 1.0 0.84 (0.37–1.92) 0.97 (0.42–2.23) 1.0 10.0 (1.56–63.97) 25.0 (3.48–179.9)		Analysis for men not conducted. Only crude RR presented.
Claude *et al.* (1986) Northern Germany 1977–82	431 cases admitted to 3 hospitals in northern Germany; cases with an initial diagnosis of bladder cancer were included in the study	431 hospital controls matched on age (± 5 years) and sex	Interview	Personal hair dye use		Not reported	Not reported	No association was observed with urinary tract tumours for use of hair dyes.

Table 2.8 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Nomura *et al*. (1989) Hawaii, USA 1977–86	261 patients diagnosed with urinary tract cancer from 7 hospitals on the island of Oahu; aged 30–93	522 population controls 2:1 matched on age (± 5 years), sex, race and residence; controls selected through the Hawaii State Department of Health's surveillance program	Interview	**Hair dye use** *Male* Nonuser User 1–5 years 6+ years *p* trend *Female* Nonuser User 1–5 years 6+ years *p* trend	 180 15 12 3 25 41 15 26 	 1.0 1.3 (0.6–2.8) 2.1 (0.9–4.8) 0.7 (0.2–2.4) 1.00 1.0 1.5 (0.8–2.9) 2.4 (1.0–6.0) 1.2 (0.6–2.4) 0.64	Pack-years of cigarette smoking	No trend with frequency or duration for either sex

Table 2.8 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Gago-Dominguez *et al*. (2001a) California, USA 1987–1996	897 incident cases histologically confirmed non-Asian cases of bladder cancer; aged 25–64 years; cases identified through the Los Angeles County Cancer Surveillance Program (SEER Los Angeles County) between 1987–1996	1:1 matched 897 neighborhood controls for each interviewed case; controls matched on date of birth (within 5 years), sex, ethnicity, place of residence at the time of diagnosis	Interview	**Hair dye use** *Male* Regular use No Yes Duration of use (years) Non-users <15 15–<30 30+ *p* for trend *Female* Regular use No Yes Duration of use (years) Non-users <15 15–<30 30+ *p* for trend	 655 39 670 9 2 2 79 124 105 22 38 22 	 1.0 0.8 (0.5–1.3) 1.0 0.7 (0.2–1.9) 1.1 (0.2–7.1) - 0.99 1.0 1.3 (0.8–2.2) 1.0 1.1 (0.5–2.5) 1.7 (0.8–3.6) 3.7 (1.2–11.2) 0.01	Age, sex, ethnicity, neighborhood, smoking status, number of cigarettes smoked per day, number of years smoking	For exclusive use of permanent hair dyes in women: OR=1.8 (1.01–3.3) with dose response relationship.

Table 2.8 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Gago-Dominguez *et al*. (2001b) California, USA 1987–1996	203 cases of bladder cancer from Los Angeles County; NAT2 analysis on 124 cases and 122 controls	203 matched controls		**Hair dye use** *NAT2 Slow* Non-users Exclusive use* Number of times per year <12 12+ *p* for trend Number of years of use <15 15+ *p* for trend *NAT2 Fast* Non-users Exclusive use* Number of times per year <12 12+ *p* for trend Number of years of use <15 15+ *p* for trend	 31 27 15 12 6 21 20 20 10 10 4 16 	 1.0 2.7 (1.01–7.2) 2.1 (0.7–6.5) 4.3 (0.9–20.0) 0.04 1.1 (0.3–4.7) 4.2 (1.3–14.1) 0.02 1.0 1.1 (0.4–2.7) 0.8 (0.3–2.4) 1.3 (0.4–4.5) 0.79 0.3 (0.07–1.3) 1.7 (0.6–5.0) 0.42	Age, ethnicity, current smoking status, number of cigarettes smoked per day and number of years smoking	*, exclusive users of permanent hair dyes

Table 2.8 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Gago-Dominguez *et al*. (2003) California 1992–1996	363 non-Asian women; aged 25–64 with histologically confirmed cases of bladder cancer; cases identified through the Los Angeles County Cancer Surveillance Program (SEER Los Angeles County) between 1992–1996	1:1 matched neighborhood controls; controls matched on sex, date of birth (within 5 years), ethnicity and neighborhood	Interview	**Hair dye use** *NAT2 Rapid* Non-users Exclusive use* Number of times per year <12 12+ *p* for trend Number of years of use <15 15+ *p* for trend *NAT2 Slow* Non-users Exclusive use* Number of times per year <12 12+ *p* for trend Number of years of use <15 15+ *p* for trend	 28 32 15 17 7 25 36 33 18 15 7 26 	 1.0 1.3 (0.6–2.8) 1.0 (0.4–2.6) 1.6 (0.6–4.6) 0.39 0.5 (0.2–1.7) 2.0 (0.8–5.0) 0.20 1.0 2.9 (1.2–7.5) 2.2 (0.8–6.5) 5.3 (1.2–23.2) 0.02 1.1 (0.3–4.5) 4.9 (1.6–15.4) 0.008	Age, ethnicity, smoking variables	*, exclusive use of permanent hair dyes. Sub-analysis by *NAT1* genotype among non-smokers, exclusive use of permanent hair dyes: NAT1*10, 1.0 (0.2–4.3); non-NAT1*10, 6.8 (1.7–27.4)

Table 2.8 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Gago-Dominguez *et al*. (2003) California 1992–1996 (contd)				*CYP1A2 Rapid*			Age and ethnicity, current smoking status (Yes/No), number of cigarettes smoked per day, number of years of smoking	
				Non-users	36	1.0		
				Exclusive use*	26	1.2 (0.6–2.7)		
				Number of times per year				
				<12	10	1.2 (0.4–3.5)		
				12+	16	1.2 (0.5–3.4)		
				p for trend		0.63		
				Number of years of use				
				<15	6	0.4 (0.1–1.3)		
				15+	20	2.3 (0.9–6.2)		
				p for trend		0.19		
				CYP1A2 Slow				
				Non-users	27	1.0		
				Exclusive use*	37	2.5 (1.04–6.1)		
				Number of times per year				
				<12	21	1.6 (0.6–4.2)		
				12+	16	7.6 (1.5–39.4)		
				p for trend		0.01		
				Number of years of use				
				<15	7	0.8 (0.2–2.8)		
				15+	30	4.4 (1.5–13.0)		
				p for trend		0.01		

Table 2.8 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Andrew *et al*. (2004) New Hampshire, USA 1994–1998	459 cases of bladder cancer diagnosed among residents of New Hampshire; ages 25–74; from 1994–1998	Control subjects from a study on non-melanoma skin cancer; controls frequency matched on age and gender; all controls less than 65 years were selected by using population lists obtained from the New Hampshire Department of Transportation; controls 65 year of age and older were chosen from data files provided by the Centers for Medicare and Medicaid Services (CMS) of New Hampshire	Interview	**Hair dye use** *Men* Any dye use No Yes *Women* Any dye use No Yes **Duration of use** *All Dyes* Nonuser 1–11 years >11 years *p* trend *Permanent dyes* Nonuser 1–11 years >11 years *p* trend	 332 19 29 69 29 43 26 0.17 57 16 16 0.72	 1.0 0.5 (0.3–0.8) 1.0 1.1 (0.6–1.9) 1.0 1.4 (0.8–2.5) 1.0 (0.5–1.9) 1.0 1.7 (0.8–3.7) 1.5 (0.7–3.2)	Age, smoking, education	

Table 2.8 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Kelsey *et al*. (2005) New Hampshire, USA 1994–1998	330 cases of bladder cancer identified through the New Hampshire State Cancer Registry between 1994–1998; aged 25–74;	Controls were selected from the population	Pathological and cytological samples; personal interview	**Hair dye use** *TP53 mutation* Never Ever *TP53 immunohisto-chemistry (IHC) inactivation* Never Ever *TP53 mutation/IHC inactivation* Never Ever	 282 73 282 73 282 73	 1.0 1.4 (0.4–4.4) 1.0 3.2 (1.4–7.2) 1.0 4.1 (1.0–17.0)	Age, sex, stage	TP53 mutation negative served as the "control" group in the analysis

Table 2.8 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Lin *et al*. (2006) Texas, USA 1999–2001	712 incident cases of bladder cancer identified through the University of Texas MD. Anderson Cancer Center and Baylor College of Medicine	Controls were recruited in collaboration with the Kelsey-Seybold clinics; controls were frequency matched to cases by age (±5 years), gender, and ethnicity; controls have no prior history of cancer (except non-melanoma skin cancer)	Interview	**Regular hair dye use** *Overall* Non users Permanent *Men* Nonusers Regular users *Women* Nonusers Regular users **Duration of use (years)** *Women* <15 15–29 ≥30 *Lifetime use (total number of times)* <100 100–200 ≥200 *Frequency of use (number of times per year)* <6 6–11 ≥12	 523 100 489 59 34 127 33 18 26 40 20 17 26 6 18	 1.0 0.81 (0.50–1.30) 1.0 0.71 (0.47–1.07) 1.0 1.0 (0.54–1.85) 0.75 (0.26–2.12) 1.31 (0.43–3.98) 0.86 (0.34–2.17) 0.78 (0.29–2.14) 1.56 (0.54–4.48) 0.66 (0.23–1.88) 0.26 (0.03–2.18) 0.76 (0.07–8.59) 8.88 (0.65–121.42)	Age, gender, ethnicity, smoking status	Duration, lifetime and frequency of use not analysed separately in men

Table 2.8 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Kogevinas *et al*. (2006) Spain 1998–2001	128 newly diagnosed and histologically confirmed cases of bladder cancer from 18 hospitals in 5 areas of Spain between 1998–2001	131 patients hospitalized with diagnoses believed to be unrelated to the exposures of interest; 1:1 matched on age (±5 yrs), gender, ethnicity and study hospital; controls included subjects who were mainly hospitalized for trauma or minor surgery	Computer-aided personal interviews	*Hair dye use* Never used hair dyes Used hair dyes at least 10 times Only permanent hair dye use at least 10 times Only dark colour use Self applying without gloves *Duration of use* Never users <10 years 11–24 years 25–32 years >32 years *NAT2 genotype* slow fast	 42 78 60 23 4 42 15 20 15 20 32 24	 1.0 0.8 (0.5–1.4) 0.8 (0.5–1.5) 1.1 (0.5–2.5) 1.2 (0.2–6.1) 1.0 0.4 (0.2–0.9) 1.0 (0.4–2.4) 0.5 (0.2–1.2) 1.2 (0.5–2.7) 0.6 (0.3–1.4) 0.9 (0.3–2.6)	Age, region, smoking, socio-economic status	Sub-analysis by *NAT1* genotype: NAT1*10, 2.9 (0.7–11.6); non-NAT1*10, 0.6 (0.2–1.6)

CI, confidence interval; OR, odds ratio; RR, relative risk

was added, and this question was answered by 51% of the male and female patients and by 93% of male and 80% of female controls. The crude OR for brilliantine use, relative to those reporting no use, was [1.7] for men (51 exposed patients; 95% CI, 1.1–2.6) and [1.1] for women (two exposed patients; 95% CI, 0.2–6.6).

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). [The Working Group noted that the choice of controls was unusually limited and may have introduced a detection bias.]

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.

In a study that examined bladder cancer and occupational exposure of hairdressers and barbers, 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-use *vs* never-use).

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 whom 615 cases and 1164 controls had ever 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. ORs by frequency or duration of use ranged for both sexes from 1.0 to 1.7, with no clear relationship with increasing duration or frequency among 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 (OR, 1.4; 95% CI, 1.0–1.9; 68 exposed cases).

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 (RR, 1.31; 95% CI, 0.64–2.71). There was a positive relationship between smoking and hair-dye use more than once a month (RR, 25; 95% CI, 3.48–179.86); after adjustment for smoking, no significant effect of hair dyes remained (RR, 1.7; 95% CI; 0.82–3.52; 22 exposed cases).

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.

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, non significant association with hair-dye use was found for both men and women, but there was no positive trend with increasing duration of use.

Gago-Dominguez *et al.* (2001a) studied 897 incident cases of bladder cancer and 897 matched controls in a population-based case–control study conducted in Los Angeles between 1987 and 1996. In a cigarette-smoking-adjusted model based on 82 exposed female cases and 56 exposed female controls, exclusive use of permanent hair dyes was related to an increased risk for bladder cancer (OR, 1.9; 95% CI, 1.01–3.3). The longest female users of permanent hair dyes (i.e. > 30 years) had a 4-fold increase in the risk for bladder cancer. Men exposed to hair dyes were not at an increased risk for bladder cancer, although the estimates were based on small numbers. Based on a subset of the population, Gago-Dominguez *et al.* (2001b) found a higher bladder-cancer risk among NAT-2 slow acetylators than among fast NAT-2 acetylators (OR, 2.7; 95% CI, 1.01–7.2 and OR, 1.1; 95% CI, 0.4–2.7, respectively). In an extension of the study, Gago-Dominguez *et al.* (2003) confirmed this association and also found indications of an interaction between CYP1A2 slow metabolizers and permanent hair-dye use in relation to bladder-cancer risk.

In a population-based case control study conducted in New Hampshire in 1994–1998 that included 459 incident bladder cancer cases and 665 controls, Andrew *et al.* (2004) found no overall indication of an increased bladder-cancer risk among hair-dye users, after adjustment for age, smoking and education level. However, women exposed to permanent hair dyes who had started their use before age 37 were at a 2.3-fold increased risk for bladder cancer (95% CI, 1.1–4.6), based on 22 exposed cases and 32 exposed controls. Women with greater frequency of use and prolonged time since first use of permanent hair dyes were also at an increased risk for bladder cancer. Subjects exposed for less than 11 years to permanent dyes had a 1.7-fold excess in risk (95% CI, 0.8–3.7), and among those exposed for more than 11 years the risk was 1.5 (95% CI, 0.7–3.2, *P*-value for linear trend, 0.72). In an extension of the New Hampshire study, Kelsey *et al.* (2005) found that among bladder-cancer cases, hair-dye use was significantly associated to TP53 immunohisto-chemistry inactivation (OR, 3.2; 95% CI, 1.4–7.2), but not to *TP53* mutation (OR, 1.4; 95% CI, 0.4–4.4), based on 282 cases who were never-users of hair dyes and 73 cases who had ever used hair dyes.

In a case–control study conducted in Texas among 712 incident bladder-cancer cases and 712 hospital-based controls, Lin *et al.* (2006) found no indication of an increased risk for bladder cancer among users of permanent hair dyes after adjustment for age, sex, race and smoking, based on 100 exposed cases and 115 exposed controls (OR, 0.81; 95% CI, 0.50–1.30). No increased risks were found for other types of hair dyes or when

duration variables were assessed. Restriction of the analyses to women only also showed no significant increase in risks.

In a case–control study conducted in Spain between 1998 and 2001 among 152 female bladder-cancer cases and 166 female controls, Kogevinas *et al.* (2006) found no overall or specific indication of an elevated risk for bladder cancer among hair-dye users (OR, 0.8; 95% CI, 0.5–1.4), based on 78 exposed cases after adjustment for age, region and smoking. No increase in risk was observed for only permanent users for at least 10 times (OR, 0.8; 95% CI, 0.5–1.5), among users of only dark colour (OR, 1.1; 95% CI, 0.5–2.5), or for self-applying of the dyes with no gloves (95% CI, 0.2–6.1). Users for more than 32 years showed a non-significantly increased risk of 1.2 (95% CI, 0.5–2.7). ORs were below 1.0 for high cumulative exposure. There was no indication of an increased risk for bladder cancer associated with the *NAT2* genotype.

Takkouche *et al.* (2005) published a meta-analysis evaluating the association between use of hair dyes and risk for cancer. This meta-analysis of 10 studies (9 case–control and 1 cohort) reached an overall risk estimate for bladder cancer of 1.01 (95% CI, 0.89–1.14). The pooled OR for permanent dye use was 1.13 (95% CI, 0.93–1.38) and 1.0 (95% CI, 0.82–1.22) for intensive exposure using fixed effects models. For random effects models the estimates were 1.13 (95% CI, 0.93–1.38) and 1.33 (95% CI, 0.69–2.56), respectively.

(b) Breast cancer (Table 2.9)

Shafer & Shafer (1976) reported on 100 consecutive breast-cancer patients in a clinical practice in New York, USA, 87% of whom had been long-term users of hair-colouring agents, and a group of age-comparable controls, 26% of whom were regular users of permanent hair dyes over prolonged periods. [The Working Group noted the dissimilarity of the exposure definitions for the two groups and the lack of information on the number of controls or the manner of eliciting details on the use of hair dyes.]

Kinlen *et al.* (1977) reported a study of 191 breast-cancer patients interviewed in the hospital in 1975 and 1976 in Oxford, United Kingdom, and 561 controls without cancer, matched to the patients by age (within three years), marital status and social class. Seventy-three cases and 213 controls had used permanent or semi-permanent hair dyes, giving an OR of 1.01. There was no evidence of an increasing risk for breast cancer with increasing duration of use of hair dyes or with use beginning more than four or more than nine years before diagnosis. Stratification by age at first pregnancy showed a deficit of cases in which hair-dye use was reported among women whose first pregnancy occurred at ages 15–19 (33.3% of cases used hair dyes, compared with 64.7% of controls) and an excess of cases with use of hair dyes among women whose first pregnancy had occurred at 30 years of age or older (38.3% of cases and 25.5% of controls). There were two hairdressers among cases (1.0%) and 10 among controls (1.8%).

Shore *et al.* (1979) compared the hair-dye use of 129 breast-cancer patients and 193 control subjects aged 25 and over, identified from the records of a multiphasic screening clinic in New York City, USA. Adjusted ORs for use of permanent hair dyes

Table 2.9. Case–control studies of breast cancer and personal hair dye use

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Kinlen *et al.* (1977) Oxford, UK 1975–76	191 women with breast cancer; interviewed in hospital between 1975–1976	561 matched controls; 506 inpatients/outpatients from the same hospitals and did not have malignant disease as the cases and 55 women selected from an age-sex register in a general practice and interviewed at home; matched on age (within three years), marital status, and social class	Interview	**Anytime before diagnosis** *Length of use* <1 year 1–4 years 5–9 years 10–14 years 15–19 years ≥20 years **More than 4 years before diagnosis** *Length of use* <1 year 1–4 years 5–9 years 10–19 years ≥20 years	 10 31 17 11 2 2 10 23 12 7 0	 0.67 1.34 0.88 1.25 0.66 0.74 0.87 1.17 1.04 0.86 -	Age, social status, parity, age at menopause, smoking	No trend with duration of use

Table 2.9 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Kinlen *et al*. (1977) (contd)				**More than 9 years before diagnosis**				
				Length of use				
				<1 year	5	0.56		
				1–4 years	15	1.37		
				5–9 years	2	0.53		
				10–19 years	5	1.12		
				≥20 years	0	-		
Shore *et al*. (1979) New York, USA 1964–76	129 breast cancer cases identified through a breast cancer clinic registry.	193 controls comprised a sequential sample of women who attended the clinic in 1968–1969; aged ≥25 years old	Interview	**Use of oxidative hair dye**				
				Number of years used before diagnosis				Cases and controls selected from a previous study of breast cancer (Thiessen 1974)
				0 years	43	1.08		
				5 years	35	1.31		
				10 years	23	1.58		
				15 years	15	1.44		

Table 2.9 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Stavraky *et al.* (1979) Ontario, Canada 1976–79	All patients with breast cancer admitted to one of two hospital clinics located in Toronto and London, Ontario Canada. 50 cases of breast cancer were identified in London, Ontario and 35 cases were identified in Toronto; aged 30-69 years	A total of 170 controls were indentified; 70 controls from Toronto and 100 controls from London, Ontario	Interview	**Use of hair dyes** *London, Ontario* Any hair dye use Unexposed Exposed Permanent hair dye use Unexposed Exposed Semi-permanent hair dye use Unexposed Exposed Color rinse used Unexposed Exposed Streaking product used Unexposed Exposed	 14 36 22 28 46 4 33 17 45 5	 1.0 1.5 (0.7–3.1) 1.0 1.3 (0.6–2.5) 1.0 1.7 (0.4–6.5) 1.0 1.2 (0.6–2.5) 1.0 1.0 (0.3–3.2)	Education, income, place of residence, family history of cancer, age at menarche and first pregnancy, use of other household products	

Table 2.9 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Stavraky *et al.* (1979) (contd)				*Toronto, Ontario*				
				Any hair dye use				
				Unexposed	16	1.0		
				Exposed	21	0.7 (0.3–1.7)		
				Permanent hair dye use				
				Unexposed	21	1.0		
				Exposed	16	1.1 (0.5–2.4)		
				Semi-permanent hair dye use				
				Unexposed	33	1.0		
				Exposed	2	0.3 (0.1–1.7)		
				Color rinse used				
				Unexposed	31	1.0		
				Exposed	4	0.8 (0.1–2.7)		
				Streaking product used				
				Unexposed	33	1.0		
				Exposed	2	0.5 (0.1–2.7)		

Table 2.9 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Nasca *et al*. (1980) New York, USA 1975–76	118 breast cancer cases identified through diagnostic index files of hospitals from 3 upstate New York hospitals between 1975–1976; aged 20–84, with a diagnosis of primary tumor of the breast	233 population controls select through random digit dialing; 2:1 matched on age and county	Interview	**Use of any hair dye** *Total times used* Never used <50 50–99 100–149 150–199 ≥200	 60 26 12 4 7 7	 1.0 1.11 (0.67–1.84) 1.19 (0.57–2.41) 0.87 (0.24–2.68) 1.53 (0.56–3.98) 1.70 (0.61–4.57)	Previous benign breast disease (BBD), parity, age at first pregnancy, menopause induced by operation, age at menarche, education	
Wynder & Goodman (1983) New York, USA 1979–81	401 breast cancer patients admitted to Memorial Sloan-Kettering Cancer Center between 1979–1981; white women, aged 20–80 years	625 controls admitted to the Cancer Center within 2 months of the cases; hospitalized without a primary diagnosis of breast cancer or a history of the disease; 1;1 or 2:1 matched on age of diagnosis	Interview	**Any hair dye use** *Overall* Never Ever *Smoker* Never used Ever used *Ex-smoker* Never used Ever used *Never smoker* Never used Ever used	 132 267 32 82 33 60 67 125	 1.0 1.02 (0.78–1.32) 1.0 0.87 (0.52–1.45) 1.0 0.76 (0.43–1.36) 1.0 1.32 (0.90–1.93)	Age at diagnosis, smoking, religion, age at first menarche, oral contraceptive use, age at first pregnancy, age at menopause, age, history of BBD, family history of breast cancer	No dose–response relationship

Table 2.9 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Koenig *et al.* (1991) New York, USA 1977–1981	398 cases of breast cancer were identified through breast cancer screening at Guttman Breast Diagnostic Institute between 1977–1981	790 randomly selected controls screened during the same study period but without breast cancer	Telephone interview	**Hair dye use** No hair dye use Ever use *Permanent dye* 1–9 10–49 50–149 150–906 *Semi-permanent dye* 1–9 10–49 50–776 *Temporary dye* 1–49 50–1 824	 97 294 50 44 65 41 24 8 17 23 14	 1.0 0.8 (0.6–1.1) 0.9 (0.6–1.3) 0.8 (0.6–1.2) 0.9 (0.6–1.3) 0.8 (0.5–1.2) 1.3 (0.8–2.3) 0.4 (0.2–1.0) 0.8 (0.4–1.4) 1.2 (0.7–2.0) 0.7 (0.4–1.4)	Age, family history of breast cancer, age at first full-term birth, height, Latin American birth place, history of receiving Medicaid, race, average darkness of dye color, religion	No trend with number of uses; models not adjusted for smoking
Boice *et al.* (1995), USA, 1926–1982	528 breast cancer cases; identified through the American Registry of Radiologic Technologists; certified between 1926 and 1982;	2628 controls; 5:1 matched on sex, date of birth (+ 5 years), calendar year of certification, length of time between certification and diagnosis	Interview	*Hair dye use* Never Yes	 368 155	 1.0 1.08 (0.87–1.33)	age, age at menarche, menopause, first birth, family history of breast cancer	

Table 2.9 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Cook *et al*. (1999) Western Washington, USA 1983–1990	844 cases identified from records of the population-based Cancer Surveillance System (CSS)/ (SEER) Program; cases were white women born after 1944 who were diagnosed between 1983 and 1990 and who resided in three counties of western Washington	960 control subjects identified through random digit dialing; frequency matched on age (within 5 years)	Interviews	*Hair coloring use* None Any use Any rinse Any semi-permanent dye use Any permanent dye use Any bleach then dye	 315 529 92 172 282 69	 1.0 1.3 (1.0–1.6) 1.7 (1.2–2.5) 1.4 (1.0–1.8) 1.2 (1.0–1.6) 2.5 (1.6–3.9)	Age, parity, weight in kg, family history of breast cancer in first degree relative	

Table 2.9 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Zheng *et al.* (2002) Connecticut, USA 1994–1997	608 cases of histologically-confirmed breast cancer; between 1994 and 1997; aged 30–80 years; with no previous diagnosis of cancer, with the exception of non-melanoma skin cancer; cases had breast-related surgery at the Yale-New Haven Hospital (YNHH), in New Haven County, or who were residents of Tolland County, Connecticut	609 population-based controls were recruited using RDD methods, from Health Care Finance Administration files or from computerized files of patients who had breast surgery but were histologically confirmed to be without breast cancer.	Interview	**Hair dye use** *Permanent dye use* Never Ever *Semi-permanent dye use* Never Ever	 163 237 163 102	 1.0 0.9 (0.7–1.2) 1.0 1.2 (0.9–1.8)	Age, race and at age at menopause, study site	

Table 2.9 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Petro-Nustas *et al*. (2002) Jordan 1996	100 Jordanian women with breast cancer listed in the Jordan Cancer Registry	100 controls were identified through a convenience proportionate sample based on the percentages of cases from each area of the country; controls were selected to match the cases based on age, parity, level of education, and place of residence	Interview	**Hair dye use** *Within 5 years of diagnosis* No Yes	 5 95	 1.0 8.62 (3.33–22.28)	History of cancer in the family, trauma to the breast, environmental and pollutant factors, abnormal breast size, breast cancer screening, reproductive history, lifestyle	Increased risk of breast cancer among older women.

BBD, benign breast disease; CI, confidence interval; OR, odds ratio; RDD, random-digit dialling

for 0, 5, 10 and 15 years were, respectively, 1.08, 1.31, 1.58 and 1.44 (none significantly different from 1.0). A significant relationship ($P = 0.01$) was noted between a measure of cumulative hair-dye use (number of years times frequency per year) and breast cancer. This relationship also held if the analysis was limited to cases in which the patient herself had responded to the telephone interview. Among women who had used hair dyes 10 years before developing breast cancer, the relationship held only for women at low risk (as assessed from the distribution of a multivariate confounder score) and for those 50–79 years old. [The Working Group noted that the use of a multivariate confounder score for the control of confounding may produce misleading results.]

To follow-up on these findings, Koenig *et al.* (1991) carried out a case–control study of 398 women with breast cancer and 790 controls identified at the same screening centre. For ever-use, the adjusted OR was 0.8 (95% CI, 0.6–1.1), and there was no trend with increased use.

Stavraky *et al.* (1979) compared 50 breast-cancer cases at a cancer-treatment centre with 100 hospitalized controls in London, Ontario, Canada and 35 breast-cancer cases with 70 neighbourhood controls in Toronto, Ontario, Canada, with respect to hair-dye use. The ORs for breast cancer from use of permanent hair dyes (at any time) were 1.3 (95% CI, 0.6–2.5) in London and 1.1 (0.5–2.4) in Toronto. Further statistical analyses, allowing for smoking habits, family history of cancer and age at first birth, showed no significant relationship between hair-dye use and breast-cancer incidence.

Nasca *et al.* (1980) reported a study of 118 patients with breast cancer and 233 controls matched to the patients by age and county of residence (115 matched triplets and three matched pairs) in upper New York State, USA. In the study overall, there was no significant association between breast cancer and use of permanent or semi-permanent dyes (OR, 1.11), nor was an increase in risk seen with increasing numbers of times hair dyes were used or with increasing time since first use. The authors commented that women who dyed their hair to change its colour, as distinct from those who dyed their hair to mask greyness, had a significantly increased risk for breast cancer (OR, 3.13; 95% CI, 1.50–6.54). In this group, there was a significant trend towards increasing risk with increasing numbers of exposures to hair dyes. Examination of risk for hair-dye use in subgroups of women defined by other risk factors for breast cancer showed an OR of 4.5 (95% CI, 1.20–16.78) for women with a past history of benign breast disease, an OR of 1.75 ($P = 0.03$, one-tailed test) for 12 or more years of schooling, and an OR of 3.33 (95% CI, 1.10–10.85) for women aged 40–49 years; the OR was near unity for all other age groups. These effects appeared to be independent of one another and were not explained by confounding by past pregnancy, age at first pregnancy, history of artificial menopause or age at menarche. The authors stressed that the associations observed in the subgroups should be considered as newly generated hypotheses, requiring further testing. In a larger, subsequent study (Nasca *et al.*, 1990) (reported as an abstract) of 1617 cases of breast cancer in New York State and 1617 controls, these authors found no relationship with hair-dye use (OR, 1.04; 95% CI, 0.90–1.21), no significant difference in the ORs for

women with a history of benign breast disease (1.15; 95% CI, 0.86–1.53) and those without (0.98; 95% CI, 0.83–1.16) and no association with duration of hair-dye use.

Wynder and Goodman (1983) carried out a hospital-based case–control study of 401 cases of breast cancer in New York City in 1979–1981. No association was found with hair-dye use (OR, 1.02; 95% CI, 0.78–1.32) and there was no dose–response relationship.

Cook *et al.* (1999) carried out a case–control study in Western Washington (USA) using the Cancer Surveillance System (CSS) to recruit 844 cases of breast cancer (747 invasive and 97 *in situ*). The 960 controls were frequency-matched to cases by age. The aim was to evaluate use of hair colouring and hair-spray application and breast-cancer risk among women in their reproductive age. An increased risk was identified for ever-use of hair dyes (OR, 1.3; 95% CI, 1.0–1.6) adjusted by age, parity, weight and history of breast cancer in first-degree relatives. No relation to breast cancer risk was found for hair-spray application.

In 2002, Petro-Nustas *et al.* evaluated exposure to chemical hair dyes and the risk for breast cancer among Jordanian women. One hundred breast-cancer cases identified through the Jordan cancer registry and 100 population-based controls were included, matched to age, parity, education level and place of residence. A high prevalence in the use of chemical hair dyes was observed among cases compared with controls (95% *vs* 51%) with an eightfold increased risk for breast cancer among users (OR, 8.62; 95% CI, 3.33–22.28). Information about frequency, colour, type and years of exposure was not available.

Zheng *et al.* in 2002 carried out a case–control study in Connecticut, USA to evaluate personal use of hair dyes and risk for breast cancer. A total of 608 incident breast-cancer cases and 609 population controls were included. No increase in risk associated with personal use of hair dyes was observed (OR, 0.9; 95% CI, 0.7–1.2) after adjustment for age, race, study site and age at menopause. Detailed information on duration, frequency, type and colour allowed quantitative study of risk; none of the ORs related to these factors was statistically significant.

A meta-analysis by Takkouche *et al.* (2005) included 12 case–control and two cohort studies, and reached an overall risk estimate for breast cancer of 1.04 (95% CI, 0.98–1.09) with use of hair dyes. When restricted to a population-based framework, the analysis showed an OR of 1.12 (95% CI, 1.01–1.23). No association with use of permanent dyes (OR, 1.00; 95% CI, 0.94–1.05) or intensity of exposure (OR, 0.99; 95% CI, 0.89–1.11) was identified under the assumptions of the fixed effects model, and no differences in estimates were found under the hypothesis of random effects.

(c) Lymphatic and haematopoietic cancers (Table 2.10)

In a further report of the study of Stavraky *et al.* (1979) in Canada, these authors found no significant increase in risk for leukaemia or lymphoma (70 cases) (Stavraky *et al.* (1981). [The Working Group noted that it was not possible to distinguish different haematopoietic malignancies.]

Table 2.10. Case–control studies of lymphatic haematopoietic cancer and personal hair dye use

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Stavraky *et al*. (1981) Ontario, Canada 1976–1979	A total of 70 cases of lymphoma and leukaemia were identified from two hospital clinics located in Toronto and London, Ontario, Canada; cases were identified between 1976 and 1979	In London, Ontario, 314 hospital controls were identified from women hospitalized with illnesses other than cancer; in Toronto, Ontario, 470 neighborhood controls were identified; in both cities 2 controls were matched for each case	Interview	**Use of semi-permanent and permanent hair dyes** *Toronto* Yes *London* Yes	 45 25	 0.7 (0.3–1.6) 1.2 (0.4–3.8)	Oral contraceptives, smoking, use of hair spray	
Cantor *et al*. (1988) Iowa and Minessota, USA 1980–1983	578 cases of leukaemia and 622 cases of non-Hodgkin lymphoma living in Iowa and Minnesota between 1980-1983; cases were male, aged >30 years	1245 controls were selected from the general population and frequency matched to cases on state of residence, five-year age category, and vital status; controls were selected using random digit dialing methods or using a random listing provided by the Federal Health Care Financing Administration.	Interview	**Use of hair dyes** *Leukaemia* Never used Ever used *Non-Hodgkin lymphoma* Never used Ever used	 534 43 569 53	 1.0 1.8 (1.1–2.7) 1.0 2.0 (1.3–3.0)	Age, state of residence	

Table 2.10 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Zahm *et al*. (1992) Nebraska, USA 1983–1986	650 histologically confirmed cases of non-Hodgkin lymphoma, Hodgkin's disease, multiple myeloma, chronic lymphocytic leukaemia were identified Nebraska Lymphoma Study Group and area hospitals; White men and women aged >21 years	1655 controls were selected from residents of the same 66-county area as the cases; 3: 1 frequency matched by race, sex, vital status, and age(± 2 years)	Interview	**Use of hair colouring products**			Age	
				NHL				
				Female				
				Never used	74	1.0		
				Ever used	106	1.5 (1.1–2.2)		
				Male				
				Never used	190	1.0		
				Ever used	11	0.8 (0.4–1.6)		
				HD				
				Female				
				Never used	19	1.0		
				Ever used	16	1.7 (0.7–4.0)		
				Male				
				Never used	32	1.0		
				Ever used	3	1.7 (0.4–6.3)		
				MM				
				Female				
				Never used	14	1.0		
				Ever used	24	1.8 (0.9–3.7)		
				Male				
				Never used	27	1.0		
				Ever used	4	1.8 (0.5–5.7)		
				CLL				
				Female				
				Never used	10	1.0		
				Ever used	9	1.0 (0.3–2.6)		
				Male				
				Never used	34	1.0		
				Ever used	3	1.0 (0.1–28.6)		

Table 2.10 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Brown *et al.* (1992) Iowa, USA 1981–1984	173 histologically confirmed cases of multiple myeloma; White men; aged ≥30; diagnosed between 1981 and 1984; cases were identified from the Iowa Health Registry	650 population-based White male control subjects without lymphatic or hematopoietic cancer; identified from three sources: random-digit dialing, Medicare records provided by the Health Care Financing Administration and state death certificate files; frequency matched by 5-year age group and vital status at time of interview	Interview	*Hair dye use* Never Ever Used <1 year or <1 time /month Used ≥1 year or ≥1 time /month	 159 14 10 4	 1.0 1.9 (1.0–3.6) 1.5 (0.7–3.3) 4.3 (0.9–19.7)	Vital status (alive, dead), age	Analysis restricted to Whites. Lack of detailed questions on hair dyes usage.

Table 2.10 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Herrinton *et al*. (1994) USA 1977–1981	689 case patients aged <82 years with incident multiple myeloma; diagnosed from 1977 to 1981; identified through cancer registries participating in the Surveillance, Epidemiology, and End Results program (SEER) in four geographic areas	1681 control subjects, matched on age, sex, and race; identified using area sampling methods and random-digit dialing	Interview	**Ever regularly used hair dyes** *Men* No Yes *Women* No Yes	 343 17 205 114	 1.0 1.3 (0.7–2.3) 1.0 1.1 (0.83–1.5)	Age, race, study center, educational attainment	No information about type and colouring
Markovic-Denic *et al*. (1995) Yugoslavia, 1989	130 patients with histologically confirmed chronic lymphocytic leukaemia (CLL); selected from Departments of Hematology, Faculty of Medicine in Belgrade and Nis	130 control patients treated at the Department of Orthopedics and Traumatology, Faculty of Medicine in Belgrade and Nis; matched on age (2 years), sex, place of residence and area of residence	Interview	*Hair dye use* Yes	 11	 1.97 (1.08–3.59)	Age, sex, place of residence	

Table 2.10 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Mele *et al*. (1995) Italy 1986–1990	Cases were aged ≥15-year with newly diagnosed leukaemias or pre-leukaemias (refractory anemias with excess of blasts, RAEB) between 1986 and 1990	Controls were recruited in the region of the study hospital during the study period from among outpatients with no hematologic malignancy, and they were seen in the same hospitals in which the cases had been identified	Standard questionnaire	**Hair dye use** *APL* No Yes *Other AML* No Yes	 [25] [9] [169] [47]	 1.0 1.5 (0.6–3.7) 1.0 0.8 (0.5–1.3)	Age, sex, education, residence outside the study town	
Mele *et al*. (1996) Italy 1986–1990	39 cases aged >20 years or older with newly diagnosed ET between 1986 and 1990 in each hospital, diagnoses were verified by chart review	156 controls; outpatients without neoplastic hernatologic disorders in the same hospitals as identified cases; frequency matched to the patients (4:l) after stratification by hospital, sex, age (+ 1 year), and closest diagnosis date	Standard questionnaire	**Use of hair dyes** *Ever used* No Yes *Duration of dark color use* <10 years >10 years	 [24] [15] [33] [6]	 1.0 1.5 (0.7–3.2) 1.0 5.3 (1.4–19.9)	Education, living outside the study area	

Table 2.10 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Ido *et al*. (1996) Japan 1992–93	116 (69 male and 47 female) cases of myelodysplastic syndromes (MDS) were selected from the patients treated at 32 hospitals between 1992 and 1993.	116 hospital-based controls matched on age (within 5 years), sex, and hospital was recruited	Self-administered questionnaire	*Hair dye use* No Yes	 78 38	 1.0 1.77 (0.90–3.49)	Cigarette smoking, alcohol drinking, exposure to organic solvents	
Nagata *et al*. (1999) Japan 1995–1996	111 cases of MDS treated at 28 institutes in Japan, between 1995 and 1996, cases diagnosed within 3 years prior to the date of the survey; aged between 20 and 74 years old	830 neighborhood controls recruited from residents in the same prefecture of cases; aged 20–74 years old	Questionnaire	*Hair dye use* No hair dye use Ever used *Duration of use (years)* 9 10+	 75 34 17 16	 1.0 1.99 (1.17–3.38) 1.58 (0.83–3.00) 2.99 (1.43–6.24)	Age, sex, living area (prefecture)	No information about colour and type

Table 2.10 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Holly *et al*. (1998) USA 1991–1995	1593 patients recently diagnosed with non-Hodgkin lymphoma were identified and interviewed; between age 21 and 74 years within 1 month of primary diagnosis from hospitals in the 6 San Francisco Bay area counties	2515 population-based controls were identified with random-digit dialing; frequency matched to cases on gender, by age within 5 years and by county of residence	Interview	**Hair dye use** *Men* Never used Ever used *Women* Never used Ever used	 348 37 143 185	 1.0 1.3 (0.86–2.00) 1.0 1.0 (0.77–1.30)	Age (for women); sexual preference, age (for men)	Study period was from 1988-1995. Questions about hair dyes use were included in the questionnaire in 1991

Table 2.10 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Miligi *et al*. (1999) Italy	1183 newly diagnosed cases of non-Hodgkin lymphomas (ICD IX 200, 202), Hodgkin disease (ICD IX 201), leukaemias (ICD IX 204–208), and multiple myeloma (ICD IX 203), aged 20–74 years old who resided in the areas under study.	828 controls randomly selected from the general population; aged 20–74 residing in each of the areas under study; stratified by sex and 5-year groups; 1:1 matched to cases for NHL and CLL only	Interviews	**Hair dye use** *Ever used* NHL & CLL No Yes MM No Yes Leukaemia No Yes HD No Yes *Use of dark permanent hair dye* No Yes	622	 1.0 1.0 (0.8–1.2) 1.0 0.8 (0.5–1.2) 1.0 0.9 (0.7–1.3) 1.0 0.7 (0.5–1.1) 1.0 2.00 (1.1–3.8)	Age	Analyses restricted to women.

Table 2.10 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Björk *et al*. (2001) Southern Sweden 1976–1993	255 adult patients with Ph+CML from southern Sweden, cytogenetically analyzed between 1976–1993 at the Department of Clinical Genetics, Lund, Sweden	Population-based controls 3:1 matched on sex, age, and county of living from the study population of southern Sweden at the calendar year each case was diagnosed; controls selected by the Swedish national bureau of statistics (Statistics Sweden)	Structured telephone interview	*Regular use of personal hair dye* No Yes Uncertain	 195 25 6	 1.0 0.35 (0.18–0.68) NR		
Schroeder *et al*. (2002) Iowa and Minessota USA 1980–1982	68 t(14;18)-positive and 114-negative cases of non-Hodgkin's lymphoma identified through the National Cancer Institute's Factors Affecting Rural Men (FARM) study	1245 population-based controls; white men aged <30 years without hemolymphatic cancer; identified through the FARM study; frequency-matched to cases on state, vital status, and age within 5-year age groups	Structured in-person interviews	Any hair dye use	26	0.9 (0.4–2.1)	Age, vital status, age	70% of cases were not classifiable

Table 2.10 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Zhang *et al*. (2004) Connecticut USA 1995–2001	601 histologically confirmed cases of incident, non-Hodgkin lymphoma in Connecticut, diagnosed between 1995 and 2001; cases were women aged 21–84 years at diagnosis with no previous diagnosis of cancer, with the exception of non-melanoma skin cancer; cases identified through the Yale Cancer Center's Rapid Case Ascertainment Shared Resource (RCA).	717 population-based controls with Connecticut addresses were recruited using random digit dialing methods or Health Care Finance Administration files; frequency matched on age (+5 years)	Interviews	*Hair dye use* Never used Ever used Started use before 1980 Started use after 1980	 152 449 295 154	 1.0 1.1 (0.9–1.5) 1.3 (1.0–1.8) 0.9 (0.7–1.2)	Age, family history of NHL in first-degree relative	Increased risk for follicular and B-Cell lymphoma who used permanent hair dyes (OR=1.9; 1.1–3.2 and OR=1.6; 1.2–2.3, respectively)

Table 2.10 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Rauscher *et al*. (2004) USA and Canada 1986–1989	769 incident cases of adult acute leukaemia were recruited through Cancer and Leukaemia Group B (CALGB), a multi-institutional cooperative cancer treatment group located throughout the United States and Canada; between 1986 and 1989	623 population-based controls selected using a two-stage random digit dialing procedure; controls identified within 6 months of case accrual; frequency matched to cases by age in 10-year intervals, sex, race and region of residence within the United States and Canada	Interview	*Hair dye use* No use Any use Exclusive permanent dye use	 584 185 87	 1.0 1.3 (0.99–1.8) 1.6 (1.1–2.4)	Age, race, sex, geographic region, education	.
Benavente *et al*. (2005) Spain 1998–2002	574 incident cases of lymphoma recruited at four centres in Spain served by three pathology departments: Barcelona, Tortosa-Reus, and Madrid; between 1998 and 2002	616 hospital-based controls were frequency matched to cases by age, sex, and hospital; selected from admission lists excluding hospitalizations for cancer, organ transplant, systemic infection, or severe immunosuppression.	Structured interview	**Hair dye use** *All lymphomas* Never used Ever used *CLL* Use of permanent dye Started use before 1980	 395 179 35 27	 1.0 1.2 (0.9–1.7) 3.4 (1.4–7.8) 3.5 (1.5–7.8) .	Age, sex, center of recruitment, house ownership	Significant linear trend for years exposed among CLL cases

Table 2.10 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Tavani *et al*. (2005) Northern Italy 1985–1997	158 patients with histologically confirmed incident HD, 446 with NHL, 141 with MM, 221 with STS; between 1985 and 1997; aged 14–79 years	1295 hospital-based control patients with acute non-neoplastic conditions; aged 17–79 years	Interviews	**Any use of hair dye** *HD* Never Ever *NHL* Never Ever *MM* Never Ever *STS* Never Ever *Use of semi-permanent dyes* Never Ever	 129 26 336 93 97 36 166 39 110 23	 1.0 0.68 (0.4–1.18) 1.0 1.03 (0.73–1.44) 1.0 1.17 (0.7–1.97) 1.0 0.73 (0.45–1.17) 1.0 1.78 (1.02–3.12)	Age, sex, area of residence, education, smoking	No information about duration, shade, age at first use
de Sanjosé *et al*. (2006) Spain, Germany, France, Ireland, Finland, Italy, Czech Republic 1998–2003	2 302 incident lymphoma cases with an initial diagnosis of lymphoid malignancy between 1998 and 2003;	2 417 controls were identified from the general population from census lists or were recruited from the same hospitals as the cases; controls were matched to the cases by age (+5 years), gender, and study center	Structured face-to-face interview	*Lymphoma* Never use Ever use *Used prior to 1980* Never use Ever use *CLL* Never use Ever use	 1436 866 1436 340 280 127	 1.0 1.19 (1.01–1.53) 1.0 1.37 (1.09–1.72) 1.0 1.43 (1.01–2.03)	Age, sex, center of recruitment, house ownership	The risk of lymphoma increased with increasing years of using dark hair dyes

Table 2.10 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Morton *et al*. (2007) USA 1988–2000	1321 cases with a histologically confirmed, first primary diagnosis of NHL; aged 20–74 years, diagnosed between 1998 and 2000; identified among residents of four SEER registries in Iowa, Los Angeles County, metropolitan Detroit and metropolitan Seattle	1057 population-based controls were selected from residents of the same four SEER areas; frequency matching to the cases by age (within 5-year age groups), sex, race and SEER area.	In person interviews	**Use of any hair dye** *Men* Yes *Women* Yes *Use of permanent intense colors for more than 15 years* Yes	 113 509 17	 0.9 (0.6–1.2) 1.2 (0.9–1.6) 3.9 (1.2–12.5)	Age, race, SEER area	.

Table 2.10 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Chiu *et al*. (2007) Eastern Nebraska, USA 1983–1986	426 cases of NHL, Hodgkin's disease, multiple myeloma, and chronic lymphocytic leukaemia diagnosed between 1983 and 1986 among White men and women aged 21 years or older who resided in one of 66 counties in eastern Nebraska	1655 population-based controls without hematopoietic cancer; randomly selected from the same 66-county area; 3:1 frequency matched on sex, vital status, and age (5-year age groups)	Telephone interviews	**Any use of hair dye products** *t(14;18)-negative*			Age, type of respondent, farming status	Analysis restricted to 175 cases of NHL; ORs for t(14;18)-positive and t(14;18)-negative NHL did not differ significantly. Information on exposures from proxies for about 40% of cases and controls
				Men				
				Never	39	1.0		
				Ever	4	1.2 (0.4–3.4)		
				Women				
				Never	31	1.0		
				Ever	33	1.1 (0.6–1.8)		
				Semi-permanent	24	1.1 (0.6–1.8)		
				Permanent	15	1.4 (0.7–2.7)		

APL, acute polymyelocytic leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myelogenous leukaemia; HD, Hodgkin disease; ICD-IX, International Classification of Diseases, Volume 9; NHL, non-Hodgkin lymphoma; MDS, myelodysplastic syndromes; MM, multiple myeloma; OR, odds ratio; SEER, Surveillance Epidemiology and End Results programme; STS, soft tissue sarcoma

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).

Cantor *et al.* (1988) carried out a population-based case–control study of hair-dye use among 578 men with leukaemia, 622 with non-Hodgkin lymphoma and 1245 population controls in Iowa and Minnesota, USA, in 1980–83. Significantly increased ORs were found for leukaemia (OR, 1.8; 95% CI, 1.1–2.7) and non-Hodgkin lymphoma (OR, 2.0; 1.3–3.0) in association with personal use or other potential exposure to hair tints, any hair colouring product or hair dyes. The authors stated that the ORs did not substantially change after exclusion of the 10 men with other potential exposure to hair-colouring products (e.g., occupational exposure), but detailed results were not presented. [The Working Group noted that, although the authors suggested an increased risk with increasing extent of hair-dye use, examination of the paper could not verify this.]

A population-based case–control study carried out in eastern Nebraska, USA, during 1983–1986 investigated use of hair-colouring products among a total of 201 male and 184 female cases of non-Hodgkin lymphoma, 35 male and 35 female cases of Hodgkin disease, 32 male and 40 female cases of multiple myeloma, 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). Telephone interviews were conducted with cases, controls or their next of kin; response rates were 81–96% for cases and 84% for controls. Among women, use of any hair-colouring product was associated with an increased risk for non-Hodgkin lymphoma (OR, 1.5; 95% CI, 1.1–2.2), Hodgkin disease (OR, 1.7; 0.7–4.0) and multiple myeloma (OR, 1.8; 0.9–3.7), and women who used permanent hair dyes had high ORs for all three neoplasms (non-Hodgkin lymphoma, (OR, 1.7; 95% CI, 1.1–2.8), Hodgkin disease (OR, 3.0, 95% CI, 1.1–7.9) and multiple myeloma (OR, 2.8; 95% CI, 1.1–7.1); all $P < 0.05$). For non-Hodgkin lymphoma and multiple myeloma, the risks were highest among women who used dark permanent dyes. Long duration and early age at first use tended to increase the risk among men, use of any hair-colouring product was associated with nonsignificantly increased ORs for Hodgkin disease (OR, 1.7), and multiple myeloma (OR, 1.8), on the basis of three and four exposed cases, respectively; no increase was found for non-Hodgkin lymphoma (OR, 0.8). Use of any hair dye was not associated with chronic lymphocytic leukaemia in either women or men (OR, 1.0).

A population-based case–control study of 173 white men with multiple myeloma and 650 controls was carried out in Iowa, USA. The risk for multiple myeloma was significantly elevated (OR, 1.9; 95% CI, 1.0–3.6; 14 exposed cases) among users of hair dyes. For men who had used hair dyes for one year or more at a frequency or one or more times per month, the OR was 4.3 (95% CI, 0.9–19.7; four exposed cases) (Brown *et al.*, 1992).

Herrinton *et al.* (1994) carried out a case–control study to evaluate the relation between both personal exposure to hair dyes and the risk for multiple myeloma (MM) in the USA. Six hundred eighty-nine MM cases and 1681 controls were included. Among women, no significant increase in risk was observed for personal use (OR, 1.1; 95% CI, 0.83–1.5). Results for males were also non-significant and based on small numbers of exposed cases. Information about colour and type was not collected.

Mele *et al.* (1995) carried out a case–control study in Italy to evaluate exposure to hair dyes and risk for acute promyelocytic leukaemia (APL) and acute myeloid leukaemia (AML). A total of 254 cases and 1161 hospital controls were included. No significant associations were found for APL (OR, 1.5; 95% CI, 0.6–3.7) or AML (OR, 0.8; 95% CI, 0.5–1.3). No data were available for colour or frequency.

In 1996, Ido *et al.* carried out a case–control study in Japan. A total of 116 myelodysplastic syndromes (MDS) cases from among hospital members of the Idiopathic Disorders Organs Research Committee, and 116 hospital controls were included to evaluate exposure to hair dyes. An increased risk for MDS was observed among users of hair-dye products (OR, 1.77; 95% CI, 0.90–3.49), although it did not reach statistical significance. The odds ratio among women was 2.50 (95% CI, 0.97–6.41). Although information about duration and frequency of hair-dye use was collected, no results about these associations were reported.

Mele *et al.* (1996) carried out another case–control study in Italy. Thirty-nine thrombocythemia cases and 156 hospital controls were included to evaluate both personal use of hair dye and occupational exposure. The prevalence of hair-dye exposure among cases was 38.2%. A non-significantly increased risk was reported (OR, 1.5; 95% CI, 0.7–3.2), although association between dark hair-dye use and increased risk was statistically significant (OR, 5.3; 95% CI, 1.4–19.9) when the duration of exposure exceeded 10 years.

Nagata *et al.* (1999) evaluated the risk for myelodysplastic syndromes (MDS) and personal use of hair dyes using a case–control study carried out in Japan. A total of 111 MDS cases and 830 controls randomly selected from the same prefecture as the cases responded to a health questionnaire. The risk for MDS for ever having used hair dyes was 1.99 (95% CI, 1.17–3.38). A statistically significant trend was observed in risk with increasing years of exposure and number of hair-dye applications ever used.

Holly *et al.* (1998) carried out a case–control study in the San Francisco Bay area (USA) to evaluate the association of hair-dye use and the risk for non-Hodgkin lymphoma (NHL). A total of 713 NHL cases and 1604 population controls were asked about type, colour, number of years of exposure for each product, age at first and last use, and frequency of use. Stratified results by gender were reported. No increases in risk were found for ever-use of hair dyes (OR, 1.00; 95% CI, 0.77–1.30 for women and OR, 1.3; 95% CI, 0.86–2.00 for men) or for years of use, lifetime frequency of use, colour or type.

Miligi *et al.* (1999) carried out a case–control study in Italy to study the role of hair-dye exposure and occupation as a hairdresser in the etiology of haematolymphopoietic malignancies. A total of 1170 cases (611 NHL, 260 leukaemia, 165 Hodgkin lymphoma, and 134 multiple myeloma) and 828 population controls were enrolled. The overall

estimation of OR for ever-exposure to hair dyes was not reported, but for none of the studied diseases was a significant risk observed. Among those women who had used dark permanent products, an increased in risk was observed for leukaemia (OR, 2.0; 95% CI, 1.1–3.8).

In 2001, Björk *et al.* conducted a case–control study in Southern Sweden to evaluate the risk for Philadelphia chromosome-positive chronic myeloid leukaemia associated with the regular use of hair dyes. Among the 226 cases included, the prevalence of exposure to hair dyes was 11.1%, whereas that among the 251 population controls was 26.4%. The estimated risk for ever-use of hair dyes was less among cases compared with controls (OR, 0.35; 95% CI, 0.18–0.68). Information about dose-response was not provided.

Schroeder *et al.* (2002) carried out a population-based NHL study in Iowa and Minnesota (USA) to evaluate non-occupational exposures. A total of 622 cases and 1245 controls were included. The study also considered the presence of the t(14;18) translocation in the tumours. An increased risk for NHL with ever-use of hair dyes was observed independently of the t(14;18) translocation (OR, 2.0; 95% CI, 1.3–3.4). An excess in risk was observed both among subjects with the t(14;18) translocation (OR, 1.8; 95% CI, 0.9–3.7) and without the translocation (OR, 2.1; 95% CI, 1.3–3.4). A large proportion of NHL (> 70%) could not be evaluated in histological subtypes due to lack of histological information.

Pu *et al.* (2003) carried out a case–control study (114 cases and 114 controls) on haematological cancer and reported increased risks associated with ever-use of hair dyes (OR, 3.3; 95% CI, 1.59–7.18) and with increasing frequency of use (OR, 3.28; 95% CI, 1.99–7.34). [The Working Group noticed that the study did not provide enough methodological and statistical details to fully evaluate the results; these data are not included in Table 2.10].

Rauscher *et al.* (2004) carried out a population-based acute leukaemia study evaluating the risk from hair-dye exposure. A total of 769 cases and 623 controls were interviewed in the USA and Canada. A slight increase in risk was observed for those ever exposed to hair dyes (OR, 1.3; 95% CI, 0.99–1.80). In addition, the use of permanent dye only, for 15 years or more, was associated with an increased acute leukaemia risk (OR, 1.9; 95% CI, 1.1–3.6). The OR was marginally elevated for use of permanent dyes that had started in the 1970s (OR, 1.7; 95% CI, 0.98–3.0).

Zhang *et al.* (2004) carried out a case–control study in Connecticut, USA to evaluate the association between hair dyes and risk for NHL among females. A total of 601 cases and 717 population controls were included. The OR associated with hair-dye use was 1.1 (95% CI, 0.9–1.5). Additionally, no evidence of a dose-response with the total number of applications, duration of use, years since first use, colour or type was observed. However, the OR for permanent dark-colour users for more than 25 years was 2.1 (95% CI, 1.0–4.0) and it was 1.2 (95% CI, 0.6–2.1) if the duration of use was less than 15 years. Considering lifetime dose, those with more than 200 applications had an OR of 1.7 (95% CI, 1.0–2.8). An increase in risk was observed for those starting use before 1980 (OR, 1.3; 95% CI, 1.0–1.8). By NHL subtypes, a significant increase in risk was seen for follicular

lymphoma and B-Cell NHL among women who used permanent hair-colouring products (OR for follicular lymphoma, 1.9; 95% CI, 1.2–3.2; OR for B-cell NHL, 1.6; 95% CI , 1.2–2.3).

Benavente *et al.* (2005) carried out a case–control study in Spain to evaluate the risk for lymphoma associated with hair-dye exposure. A total of 574 lymphoma cases and 616 hospital controls were included in the study. The prevalence of hair-dye exposure was 79% among females and 8% among males. A non-significant increase in risk was observed for ever-use (OR, 1.2; 95% CI, 0.9–1.7). No association was observed for colour, type, frequency, or lifetime dose. By specific lymphoma subtypes, a twofold increase in risk for ever-use was observed for CLL (95% CI, 1.1–4.7). A significant linear trend by years of use was also observed for CLL ($P = 0.04$) among those exposed for 10 years or less (OR, 1.1; 95% CI, 0.4–3.0), from 11 to 24 years of use (OR, 3.2; 95% CI, 1.3–8.2) and for 24 years or more (OR, 3.7; 95% CI, 1.5–8.9). In this group of cases, those who started hair-dye use before 1980 had a 3.5-fold increased risk (95% CI, 1.5–7.8) compared with non-users. Use of dark colour and permanent hair-dye types were both associated with an increased risk for CLL (OR, 2.3; 95% CI, 1.1–4.9 for dark colour and OR, 3.4; 95% CI, 1.4–7.8 for permanent).

Tavani *et al.* (2005) carried out a case–control study in northern Italy aimed at evaluating the relationship between lymphoid neoplasm and tissue sarcoma and use of hair dyes. A total of 966 cases and 1295 hospital controls were interviewed. No significant association with hair-dye use was seen for any of the lymphoma subtypes. An increased risk for multiple myeloma among semi-permanent dye users was observed (OR, 1.78; 95% CI, 1.02–3.12). Information about colour was not included in the study.

De Sanjosé *et al.* (2006) carried out a multicentric case-control study including seven countries in Europe. A total of 2302 lymphoma cases and 2417 controls were pooled to study the relationship between hair dyes and the risk for lymphoma. A slight increase in risk for lymphoma was observed for ever-use of hair dyes (OR, 1.19; 95% CI, 1.00–1.41). The risk for lymphoma for those starting use before 1980 was 1.37 (95% CI, 1.09–1.72). Among all lymphoma categories, a statistically significant increase in risk for CLL was seen (OR, 1.43; 95% CI, 1.01–2.03). The risk for lymphoma increased with the number of years of use of dark hair dyes (*P* for linear trend, 0.07): four years or less: OR, 1.11 (95% CI, 0.84–1.46); from 4.5 to 13 years: OR, 1.28 (95% CI, 0.96–1.70) and for 14 years or more: OR, 1.45 (95% CI, 1.09–1.94). This study included the data of Benavente *et al.* (2005), but sensitivity analysis showed that results were not explained by any of the individual studies.

Morton *et al.* (2007) carried out a population-based NHL study in the USA among 1321 cases and 1057 controls, examining NHL risk in relation to reported hair-dye use and genetic variation in *NAT1* and *NAT2*. No increased in risk was observed for ever-exposure among either males or females (OR, 1.2; 95% CI, 0.9–1.6). The OR for females exposed to 100 or more lifetime applications was 1.4 (95% CI, 1.0–2.0). Among females, a fourfold increase in risk was observed for those using permanent and intense tones for more than 15 years before 1980 (OR, 3.9; 95% CI, 1.2–12.5). Concerning *NAT1* and

NAT2 variation, an increase in risk was observed for the use of dark or intense permanent hair dyes before 1980 among women if they had the NAT2 rapid/intermediate phenotype (OR, 3.3; 95% CI, 1.3–8.6) or if they had one or two copies of the *NAT*10* allele (OR, 3.0; 95% CI, 1.1–8.1).

Chiu *et al.* (2007) carried out a case–control study in Eastern Nebraska (USA) to evaluate the relationship between personal use of hair dyes and the risk for t(14;18)-defined subtypes of Non-Hodgkin lymphoma. A total of 385 cases and 1432 population controls were interviewed. No relation was observed for ever-use of hair dyes and the risk for NHL for either t(14;18)-negative or -positive translocation cases.

A meta-analysis by Takkouche *et al.* (2005) included 40 studies on non-Hodgkin lymphoma, Hodgkin lymphoma and multiple myeloma. All haematopoietic cancers were significantly increased among ever-users of hair dyes (RR, 1.13; 95% CI, 1.06–1.20). The combined OR estimated for permanent hair-dye use was 1.14 (95% CI, 0.99–1.29) and for intensive use it was 1.12 (95% CI, 0.98–1.28). The different sensitivity analyses provided a range of estimates from 0.87 for Hodgkin-lymphoma studies to 1.57 for those studies including men only. No evaluation of the period of exposure was included in this analysis.

(d) Childhood cancer (see Table 2.11; only studies since 1993 are shown in the Table)

Kramer *et al.* (1987) reported a matched case–control study of maternal exposures during pregnancy and neuroblastoma diagnosed during the period 1970–1979 in the Greater Delaware Valley, USA. Of the 181 cases identified, 139 met the eligibility criteria, and interviews were completed with 104 case families (75%). Control subjects were selected by random-digit dialling and were matched with cases on age, race and the first five digits of their telephone number at the time of diagnosis; the response rate among those eligible was 57% (101 of 177). In addition, the authors compared 86 patients who had at least one sibling with a randomly selected sibling. Mothers were asked about six main exposures, specified for hypothesis testing, and about a variety of other exposures, including the use of hair-colouring products. The OR associated with maternal exposure to hair dye was 3.00 (90% CI, 1.64–5.48; one-sided *P*-value, 0.002; 36 discordant pairs) in comparison with controls selected by telephone and 2.20 (90% CI, 0.93–5.22; one-sided *P*-value, 0.07; 16 discordant pairs) in comparison with siblings.

Bunin *et al.* (1987) conducted a case–control study of Wilms' tumour diagnosed in children under 15 during the period 1970–1983 in the Greater Philadelphia (USA) area in relation to use of hair dyes by their mothers during pregnancy. Of 152 white cases, 28 were ineligible for a variety of reasons. Interviews were completed with the parents of 88 (71%) of the 124 eligible cases and 88 of 159 (55%) controls, on average 10 years after the relevant pregnancy. For Wilms tumour overall, the OR associated with maternal hair-dye use was 3.6 (95% CI, 1.4–10.2; based on 32 discordant pairs). A total of 68 cases could be classified as genetic (26 cases) (if they were bilateral or had nephroblastomatosis) or non-genetic (42 cases) (if they were unilateral without nephroblastomatosis or

Table 2.11. Case–control studies of childhood cancer and personal hair dye use

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Olshan *et al*. (1993) USA,Canada 1984–86	200 cases were identified throught the National Wilms Tumor Study (NWTS) between 1984 and 1986; aged ≤15 years	200 control subjects 1:1 matched on age (± 2 years) and geographical area; controls identified through a modified random digit dialing procedure	Interview	**Hair dye use during pregnancy** *Wilms Tumor* No Yes	 180 20	 1.0 1.37 (0.66–2.85)	Household income and father's education	Discrepancy between risk estimated for cases diagnosed < 2 years old in results section and in discussion section (OR = 1.23, 95% CI = 0.16 –9.45 and OR = 2.92, 95% CI = 0.91 –9.33, for results and discussion, respectively)

Table 2.11 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Bunin *et al*. (1994) USA, Canada 1986–89	322 cases with astrocystic glioma or PNET were identified through the Children Cancer group; eligible cases were diagnosed before 6 years of age between 1986 and 1989	321 controls; 1:1 matched on race, birth year, telephone area code and prefix; controls selected through random digit dialing procedure	Interview	**Use of hair dyes during pregnancy** *Astrocystoma* Not used Colouring products Permanent procucts *PNET* Not used Colouring products Permanent procucts	 305 16 59 305 16 64	 1.0 0.7 (0.3–1.6) 0.9 (0.5–1.5) 1.0 1.1 (0.4–2.6) 1.2 (.07–2.0)	Income level	

Table 2.11 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Holly *et al*. (2002) San Francisco, Seattle, Los Angeles 1984–1991	540 cases were recruited from three areas in California and Washington state; aged <20 years at the time of diagnosis between 1984 and 1991 and had a benign or malignant primary tumour of the brain, cranial nerves or cranial meninges of any histological type. USA cancer registry	Random digit dialing telephone methods were used to select control subjects without CBT who were frequency matched to patients by sex and birth year in Seattle and San Francisco and individually matched on sex and birth year in Los Angeles	Interview	**Use of hair dye during pregnancy** *Astrocystic tumor* Never used Ever used *PNET* Never used Ever used *Other glioma* Never used Ever used	 265 40 94 12 113 12	 1.0 1.0 (0.69–1.5) 1.0 0.97 (0.51–1.9) 1.0 0.76 (0.40–1.4)	Child age and sex	

Table 2.11 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
McCall *et al*. (2005) USA, Canada 1992–94	538 cases identified through hospitals participating in the Children's Cancer Group or the Pediatric Oncology Group between 1992 and 1994; aged <19 years with newly diagnosed neuroblastoma	504 controls were identified through random-digit dialing; controls were 1:1 matched based on date of birth (±6 months for cases <3 years old and ±1 year for cases >3-years old) and telephone number	Interview	**Maternal hair dye use the month before and/or during pregnancy** *Any hair dye use* Unexposed Exposed *Permanent hair dye use* Unexposed Exposed *Temporary hair dye use* Unexposed Exposed	 124 410 98 436 33 501	 1.0 1.6 (1.2–2.2) 1.0 1.4 (1.0–2.0) 1.0 2.0 (1.1–3.7)	Child's age	Risk persists when restricted to exposure during pregnancy. No differences by age at diagnosis. Stronger effect among smokers for any and permanent hair dye

Table 2.11 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Adjustment factors	Comments
Chen *et al*. (2006) USA 1993–2001	273 cases were recruited through the Children's Oncology Group (COG); aged <15 years newly diagnosed with a GCT (germinoma (dysgerminoma/seminoma/germinoma), embryonal carcinoma, yolk sac tumor, choriocarcinoma, immature teratoma, and mixed GCT between 1993 and 2001	418 controls were selected by random-digit dialing; frequency matched on the child's sex, year of birth ±1 year and geographic location at diagnosis. The matching ratio was 1:2 for males and 1:1 for females	Interview	**Maternal hair dye use** *Total* Exposed *Boys* Exposed *Girls* Exposed	 79 30 49	 1.3 (1.0–1.7) 1.4 (0.9–2.3) 1.2 (0.9–1.7)	Child gender, age, maternal education, race, age at index pregnancy and family income	

CBT, childhood brain tumours; CI, confidence interval; GCT, germ-cell tumours; OR, odds ratio; PNET, primitive neuroectodermal tumour

a Wilms tumour-associated congenital anomaly). The OR associated with maternal use of hair-colouring agents was 5.5 (95% CI, 1.0–71.9; on the basis of 13 discordant pairs out of 42) for non-genetic cases and 3.3 (95% CI, 0.7–22.1; on the basis of 13 out of 26 discordant pairs) for genetic cases. The ORs associated with exposure to hair dyes were similar for an interval of 2–10 years and for an interval of 11–24 years between pregnancy and interview.

Kuijten *et al.* (1990), in an earlier report of the study of Kuijten *et al.* (1992), found no association between astrocytoma and maternal use of hair-colouring products during pregnancy (OR, 0.9; 95% CI, 0.4–1.8; 37 discordant pairs).

Olshan *et al.* (1993) carried out a case–control study in the USA and Canada using the National Wilms Tumor Study to recruit 200 cases of Wilms tumours to evaluate parental exposures during pregnancy, including hair-colouring products. Cases were matched to 233 controls living in the same neighbourhood and having the same age, selected using random-digit dialling. A non-significant increased risk was observed for ever-use of hair dyes during pregnancy (OR, 1.37; 95% CI, 0.66–2.85). There is a discrepancy in this paper between the risk estimated for cases diagnosed younger than 2 years in the Results section and in the Discussion section (OR, 1.23; 95% CI, 0.16–9.45 and OR, 2.92; 95% CI, 0.91–9.33, for Results and Discussion sections, respectively). The study had a moderate inclusion rate (61% of the selected cases and 52% of the controls) and exposure was assessed by interview.

Bunin *et al.* (1994) carried out a case–control study, in the USA and Canada, based on the Children's Cancer Group to evaluate several exposures occurring during the pregnancy and breastfeeding periods. The exposures included hair dyes, hair sprays and makeup in association with astrocytic glioma ($n = 155$) and primitive neuroectodermal tumours (PNET) ($n = 166$) diagnosed before age 6. Controls ($n = 321$) were selected via random-digit dialling and matched to the cases by neighbourhood, race and age. No association was identified for astrocytoma with use of make-up (OR, 1.2; 95% CI, 0.7–1.9), hair spray (OR, 1.2; 95% CI, 0.7–2.0), hair colouring (OR, 0.7; 95% CI, 0.3–1.6) or use of permanent hair dye (OR, 0.9; 95% CI, 0.5–1.5) or for PNET (OR for make–up, 0.8; 95% CI, 0.5–1.2; for hairspray, 1.0; 95% CI, 0.6–1.7; for hair-colouring products, 1.1; 95% CI, 0.4–2.6; for permanent hair-dye use 1.2; 95% CI, 0.7.-2.0). The analysis was fully adjusted for income level for the astrocytoma analysis. Participation was around 65%, and exposure was assessed by interview.

McCredie *et al.* (1994) conducted a case–control study of incident primary malignant brain tumours diagnosed during 1985–1989 in children below 14 years old in Sydney, Australia, and evaluated several hypotheses among which ever-use of hair dyes by the mothers. No association was shown (OR, 0.8; 95% CI, 0.4–1.6).

Holly *et al.* (2002) carried out a case–control study to evaluate childhood brain tumours (CBT) and maternal use of hair colouring one month before pregnancy and during pregnancy. The study used cancer registries from Los Angeles County, the San Francisco Bay area and the Seattle area, USA. It included 540 biological mothers of CBT children diagnosed during 1984–1991 and 801 control mothers matched to cases by birth

year and sex of the index child. Exposure was assessed through interview. A non-statistically significant increase in risk was identified for those mothers using exclusively semi-permanent dyes one month before pregnancy or during the first trimester of pregnancy (OR, 2.5; 95% CI, 0.58–10.0). Exclusive use of permanent dyes, temporary dyes or hair darkeners was not related to an increased risk. Exclusive use of semi-permanent dyes was related to an increased risk (OR, 2.0; 95% CI, 0.83–4.7) for users before or during pregnancy. No differences by histological tumour type were observed. Participation rates were over 70% for cases and controls.

McCall *et al.* (2005) carried out a case–control study on neuroblastoma in association with exposure to hair-dye use before and during pregnancy. The study recruited 538 cases from the USA and Canadian Children's Cancer Group or the Pediatric Oncology Group. A total of 504 controls were selected using telephone random-digit sampling. Controls were matched to the cases by sex, year of birth and neighbourhood. Participation rates were over 70% for both cases and controls. Use of temporary hair dyes was associated with a twofold increased risk for neuroblastoma (OR, 2.0; 95% CI, 1.1–3.7). Use of hair dyes in the month before pregnancy showed a 60% increase in risk (OR, 1.6; 95% CI, 1.2–2.2). Ever smokers were more likely to have an increased risk for neuroblastoma in their offspring if mothers used hair dyes (OR, 2.2; 95% CI, 1.3–3.8) or permanent dyes (OR, 2.2; 95% CI, 1.2–4.1). No dose-responses were reported for permanent dyes.

Chen *et al.* (2006) reported a case–control study that explored the association between childhood germ-cell tumours and hair-dye use by the mother before and during pregnancy and during breastfeeding, among 273 cases diagnosed between 1993 and 2001 from the Children's Oncology Group in the USA. A total of 418 controls were selected via random-digit dialling and matched to the cases by sex, age and geographical area. Maternal use of hair dyes one month before pregnancy was related to a 1.7-fold increased risk for boys (95% CI, 1.0–2.8). For mothers who used hair dyes during breastfeeding the overall OR was 1.5 (95% CI, 1.0–2.2) and 1.7 among girls (95% CI, 1.1–2.6).

(e) Other cancer sites

Ahlbom *et al.* (1986) carried out a case–control study in Stockholm and Uppsala, Sweden, of 78 patients with astrocytoma diagnosed in 1980–1981, 197 hospital controls (with meningioma, pituitary adenoma or cerebral aneurysm) and 92 population controls. The ORs for the 23 astrocytoma patients who had dyed their hair were 0.8 (95% CI, 0.4–1.8) relative to 83 hospital controls and 1.5 (95% CI, 0.6–3.7) when compared with 46 population controls who had dyed their hair.

Burch *et al.* (1987) found that significantly more adults with brain cancer diagnosed in Canada in 1977–1981 than hospital controls reported having used hair dye or hair spray (OR, 1.96; $P = 0.013$; 43/22 discordant pairs). No data by histology were provided, but 133 of 215 were astrocytomas and 67 of 215 had a glioma or related histology.

Heineman *et al.* (2005) evaluated the risk for glioma in the female white population of Nebraska associated to use of hair dyes. Cases were diagnosed between 1988 and 1993, and controls were retrieved from a previous study, were population-based and were

matched to the case by age. Adjustment by year of birth and educational level was done throughout the study. Questions about exposures from hair-dye use before 1985 were assessed by personal or proxy interview (79% of the cases). The study identified an increased risk for glioma for ever-use of hair dye (OR, 1.7; 95% CI, 1.0–2.9) and a 2.4-fold risk from use of permanent hair dyes (95% CI, 1.3–4.5). The risk for glioblastoma multiforme increased 4.9-fold (95% CI, 1.6–15.7) with exposure to dark colours for those reporting use during 20 years or less.

Bluhm *et al.* (2007) explored the association between use of synthetic hair dyes and risk for brain tumours in a hospital-based case–control study, including 489 patients with glioma, 197 with meningioma, 96 with acoustic neuroma, and 799 controls. The study, carried out in 1994–1998, identified no increase in risk for these tumours from ever-use among exposed women or exposed men, including in evaluations of frequency, lifetime number of doses, or colour. There was only one positive association linked to use of brown colour for more than 20 years for all glioma cases and use of red colour during less than 20 years. Both ORs were stronger for acoustic neuroma. [The Working Group was concerned about data stratification resulting in very small numbers and high ORs]

A meta-analysis by Takkouche *et al.* (2005) included 15 studies on a wide range of cancer sites other than breast, bladder or non-Hodgkin lymphoma. The pooled RR was 1.83 (95% CI, 1.16–2.89) for brain cancer; 1.71 (95% CI, 1.15–2.53) for ovarian cancer; 0.74 (95% CI, 0.51–1.07) for skin cancer; and 0.89 (95% CI, 0.53–1.90) for cervical cancer.

Stavraky *et al.* (1981), in a case–control study, found no significant increase in crude or adjusted risks for cancer of the cervix (38 cases), cancer of the ovary (58 cases), cancer of the lung (70 cases), cancers of the kidney and bladder (35 cases) or endometrial cancers (36 cases) among ever-users of hair-colouring agents in either Toronto or London, Ontario, Canada.

Holman & Armstrong (1983) examined hair-dye use in a population-based case–control study of 511 patients with malignant melanoma and individually matched controls in Western Australia in 1980–1981. No relationship was found with ever-use of permanent hair dyes. The ORs obtained from a conditional logistic regression analysis with adjustment for solar exposure, reaction to sunlight and hair colour (Armstrong & Holman, 1985) for 86 cases of Hutchinson's melanotic freckle associated with use of semi-permanent and temporary dyes were: never used, 1.00; used 1–9 times, 1.5 (95% CI, 0.3–6.8); used ≥ 10 times, 3.3 (95% CI, 1.0–11.5; *P* for trend, 0.05). The OR for Hutchinson's melanotic freckle in relation to use of permanent dyes was not elevated. [The Working Group noted that the number of exposed subjects was not reported.]

Osterlind *et al.* (1988a,b) found a negative association with use of permanent or semi-permanent hair dyes among women with malignant melanoma in Denmark in 1982–1985 (OR for hair dye use, 0.6; 95% CI, 0.5–0.9; 136 exposed cases). Cases of Hutchinson's melanotic freckle were not included in this population-based study.

Spitz *et al.* (1990) examined hair dye use in a case–control study of 37 male and 27 female patients with salivary gland cancer in Texas, USA, in the period 1985–1989.

Controls were patients with other malignancies. Among ever-users of hair dyes, an increased OR was found for women (OR, 4.1; 95% CI, 1.5–11.5; 14 cases). There was no difference between female cases and controls with respect to frequency of use, except that the OR for use during more than 15 years (OR, 3.5; 95% CI, 0.9–12.8) was higher than that for shorter duration of use (OR, 2.3; 95% CI, 0.9–6.2).

2.2.3 *Pooled analysis* (Tables 2.12–2.16)

A recent analysis (Zhang *et al.*, 2008) pooled original data from four previously reported case–control studies that were part of the International Lymphoma Epidemiology Consortium (InterLymph), including a total of 4461 NHL cases (2123 men and 2338 women) and 5799 controls (2837 men and 2962 women) to investigate the relationship between personal hair-dye use and risk for NHL. Three studies were from the USA, the Connecticut Women's NHL Study, the National Cancer Institute (NCI)/Surveillance, Epidemiology, and End Results (SEER) MultiCenter Case-Control Study (NCI/SEER), and the Epidemiology of NHL Study from the University of California at San Francisco (UCSF). The three US studies collectively represent a total of six sites from the SEER programme (Connecticut, San Francisco-Oakland, Iowa, Detroit, Seattle-Puget Sound, and Los Angeles). The other case–control study, from Europe (the EpiLymph International Case-Control Study of Lymphomas), represents geographic sites from six countries (Czech Republic, France, Germany, Ireland, Italy, and Spain). Each study collected detailed information on hair-dye use (including duration of use, total number of applications, year of use, and type and colour of hair-dye) and included histologically-confirmed incident NHL cases. Among women, 75% of the cases and 70% of the controls reported ever having used hair dyes. An increased risk for NHL was observed among women who started using hair dyes before 1980, compared with non-users (OR, 1.3; 95% CI, 1.1–1.4). After stratification by NHL subtype, hair-dye use was associated with an increased risk for follicular lymphoma (FL) and chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) but not other NHL subtypes. The increased risk for FL (OR, 1.4; 95% CI, 1.1–1.9) and CLL/SLL (OR, 1.5; 95% CI, 1.1–2.0) associated with hair-dye use was mainly observed among women who started use before 1980, with a significant trend in risk with duration of use ($P < 0.01$, 0.02 respectively). For women who began using the products in 1980 or later, a higher risk for FL was limited to users of dark-coloured hair dyes (OR, 1.5; 95% CI, 1.1–2.0) with ORs of 1.5 (95% CI, 1.1–2.1) for permanent dark-coloured hair dyes and 1.7 (95% CI, 1.1–2.4) for non-permanent dark-coloured dyes. Among men, approximately 10% of cases and 10% of controls had ever used hair dyes. Risk for NHL was not associated with hair-dye use before or after 1980 among men. The results indicate that personal hair-dye use may play a role in the risk for FL and CLL/SLL in women who started use before 1980, and that an increased risk for FL in women starting use in 1980 or later cannot be excluded.

Table 2.12. Characteristics of case–control studies included in pooled analysis

Reference, study, period[†]	Location	Year	Age (years)	Cases (n=4461)[*]			Controls (n=5799)[*]			
				n	Source	Participation rate (%)	Matching Criteria	n	Participation rate (%)	Source
Zhang *et al*. (2004) Yale	Connecticut, USA	1996–2000	21–84	601	Population-based	72	Frequency matched by age within 5-year groups	717	RDD: 69 CMMS: 47	<65 years: RDD, >=65 years: random, selection from CMMS files
Morton *et al*. (2007) NCI-SEER	Detroit, Los Angeles, Seattle, and Iowa State, USA	1998–2001	20–74	1321 (1319)	Population-based	76	Frequency matched by age within 5-year groups, sex, and study site	1057 (1056)	52	<65 years:RDD, >=65 years:random, selection from CMMS files
Holly *et al*. (1998) UCSF	San Francisco Bay Area, CA, USA	1988–1993	21–74	1304 (837)	Population-based	72	Frequency matched by 5-year age groups, sex, and county of residence within 5 years	2402 (1609)	78	RDD and random selection from CMMS files for >=65 years old

Table 2.12 (contd)

Reference, study, period[†]	Location	Year	Age (years)	Cases (n=4461)[*]			Controls (n=5799)[*]			
				n	Source	Participation Rate (%)	Matching Criteria	n	Participation Rate (%)	Source
De Sanjosé *et al*. (2006) EpiLymph	Italy, Spain, Germany, France, Finland, Ireland, and Czech Republic	1998–2003	18+	2480 (1704)	Population-based (Italy, Germany), Hospital-based (Spain, France, Finland, Ireland, Czech Republic)	87	Age, sex, geographical area	2540 (2417)	75	Population-based (Italy, Germany), hospital-based (Spain, France, Finland, Ireland, Czech Republic)

From Zhang *et al*. (2008)

[†] Yale = Yale University Connecticut Women's NHL Study; NCI/SEER = National Cancer Institute (NCI)/Surveillance, Epidemiology, and End Results (SEER) Multi-Center Case-Control Study; UCSF = the Epidemiology of NHL Study from the University of California at San Francisco; EpiLymph = European multi-center case-control study coordinated by the International Agency for Research on Cancer.

CMMS, Centers for Medicare and Medicaid Service; RDD, random digit dialing.

[*] The numbers of cases and controls shown in parentheses are reported in the respective cited reference.

Table 2.13. Characteristics of non-Hodgkin lymphoma cases and controls

Characteristics	Cases (n=4461)		Controls (n=5799)	
	#	%	#	%
Study center				
Yale	601	13.5	717	12.4
NCI/SEER	1319	29.5	1056	18.2
UCSF	837	18.8	1609	27.7
EpiLymph	1704	38.2	2417	41.7
Gender				
Male	2123	47.6	2837	48.9
Female	2338	52.4	2962	51.1
Race				
White	4108	92.1	5347	92.2
Black	175	3.9	248	4.3
Others	178	4.0	204	3.5
Age (years)				
<30	147	3.3	309	5.3
30–39	362	8.1	599	10.3
40–49	644	14.4	798	13.8
50–59	971	21.8	1183	20.4
60–69	1330	29.8	1631	28.1
70–79	912	20.5	1159	20.0
80+	95	2.1	120	2.1
NHL subtype				
DLBCL	1543	34.6		
Follicular lymphoma	908	20.3		
CLL/SLL	736	16.5		
Marginal zone lymphoma	146	3.3		
T-cell lymphoma	298	6.7		
Others	830	18.6		

From Zhang *et al.* (2008)
DLBCL = diffuse large B-cell lymphoma ; CLL/SLL = small lymphocytic lymphoma/chronic lymphocytic leukemia; NHL = Non-Hodgkin lymphoma; NCI/SEER = National Cancer Institute/Surveillance, Epidemiology and End Results; Epylymph = European multicenter case-control study coordinated by the International Agency for Research on Cancer

Table 2.14. Risk of non-Hodgkin lymphoma and hair-dye use by year started and gender

	Total				Women				Men			
	Controls	Cases	OR (95%CI)	p	Controls	Cases	OR (95%CI)	p	Controls	Cases	OR (95%CI)	p
Hair-Dye Use												
Never	3432	2433			874	576			2558	1857		
Ever	2365	1915	1.0(0.9–1.2)	0.38	2087	1711	1.1(1.0–1.3)	0.04	278	204	0.9(0.7–1.1)	0.38
Type												
Permanent	1561	1217	1.0(0.9–1.2)	0.60	1433	1131	1.1(1.0–1.3)	0.09	128	86	0.9(0.6–1.2)	0.33
Non-permanent	997	854	1.1(1.0–1.3)	0.11	884	765	1.2(1.0–1.4)	0.02	113	89	1.1(0.8–1.4)	0.72
Color												
Dark color	1405	1158	1.0(0.9–1.1)	0.82	1252	1033	1.1(1.0–1.3)	0.12	153	125	0.9(0.7–1.1)	0.27
Light color	939	763	1.0(0.9–1.2)	0.54	879	734	1.1(1.0–1.3)	0.07	60	29	0.7(0.4–1.1)	0.15
Type & Color												
Permanent dark	898	697	1.0(0.9–1.1)	0.95	813	637	1.1(0.9–1.3)	0.22	85	60	0.8(0.6–1.2)	0.27
Permanent light	715	551	1.1(0.9–1.2)	0.35	671	530	1.2(1.0–1.4)	0.07	44	21	0.8(0.5–1.4)	0.48
Non-permanent dark	580	565	1.1(1.0–1.3)	0.17	525	507	1.2(1.0–1.5)	0.02	55	58	1.0(0.7–1.5)	0.87
Non-permanent light	158	144	1.0(0.8–1.3)	0.74	153	142	1.2(0.9–1.5)	0.20	5	2	0.5(0.1–2.6)	0.42
Started Use Before 1980												
Never	3432	2433			874	576			2558	1857		
Ever	1169	1053	1.2(1.0–1.3)	0.01	1102	997	1.3(1.1–1.4)	<0.01	67	56	1.0(0.7–1.5)	0.90
Type												
Permanent	778	678	1.2(1.0–1.4)	0.02	746	658	1.3(1.1–1.5)	<0.01	32	20	0.8(0.4–1.4)	0.45
Non-permanent	444	392	1.2(1.0–1.4)	0.06	413	365	1.2(1.0–1.5)	0.02	31	27	1.3(0.7–2.2)	0.41
Color												
Dark color	644	579	1.1(1.0–1.3)	0.07	607	547	1.2(1.1–1.5)	0.01	37	32	0.9(0.6–1.5)	0.69
Light color	479	462	1.2(1.1–1.5)	<0.01	469	457	1.3(1.1–1.6)	<0.01	10	5	0.7(0.2–2.2)	0.58
Type & Color												
Permanent dark	435	372	1.2(1.0–1.4)	0.05	413	356	1.3(1.0–1.5)	0.01	22	16	0.9(0.4–1.7)	0.67
Permanent light	363	328	1.3(1.1–1.5)	<0.01	354	326	1.3(1.1–1.6)	<0.01	9	2	0.4(0.1–2.0)	0.28
Non-permanent dark	226	232	1.1(0.9–1.4)	0.28	213	217	1.2(1.0–1.6)	0.06	13	15	1.1(0.5–2.3)	0.89
Non-permanent light	72	76	1.2(0.8–1.7)	0.32	72	76	1.3(0.9–1.9)	0.12	0	0		

Table 2.14 (contd)

	Total				Women				Men			
	Controls	Cases	OR (95%CI)	p	Controls	Cases	OR (95%CI)	p	Controls	Cases	OR (95%CI)	p
Started Use in 1980 or Later												
Never	3432	2433			874	576			2558	1857		
Ever	1157	844	1.0(0.9–1.1)	0.67	966	703	1.1(0.9–1.2)	0.40	191	141	0.9(0.7–1.1)	0.32
Type												
Permanent	709	480	0.9(0.8–1.1)	0.35	616	415	1.0(0.9–1.2)	0.86	93	65	0.9(0.6–1.3)	0.51
Non-permanent	486	401	1.1(0.9–1.3)	0.23	406	342	1.2(1.0–1.5)	0.05	80	59	1.0(0.7–1.4)	0.85
Color												
Dark color	716	548	1.0(0.8–1.1)	0.76	604	459	1.1(0.9–1.3)	0.32	112	89	0.8(0.6–1.1)	0.24
Light color	390	262	0.9(0.8–1.1)	0.35	341	238	1.0(0.8–1.3)	0.83	49	24	0.7(0.4–1.2)	0.20
Type & Color												
Permanent dark	421	288	0.9(0.8–1.1)	0.29	362	246	1.0(0.8–1.2)	0.97	59	42	0.8(0.5–1.2)	0.32
Permanent light	288	185	0.9(0.8–1.2)	0.58	254	166	1.0(0.8–1.3)	0.88	34	19	0.9(0.5–1.7)	0.84
Non-permanent dark	314	294	1.2(1.0–1.4)	0.13	272	254	1.3(1.0–1.6)	0.02	42	40	1.0(0.6–1.5)	0.84
Non-permanent light	71	52	0.9(0.6–1.3)	0.65	66	50	1.1(0.7–1.6)	0.77	5	2	0.5(0.1–2.6)	0.42

From Zhang *et al.* (2008)

Table 2.15. Risk of non-Hodgkin lymphoma and hair-dye use by NHL subtype and year started hair dye use among women

	DLBCL			Follicular			CLL/SLL			MZL			T-cell		
	Cases	OR (95%CI)	p	Cases	OR (95%CI)	p	Cases	OR (95%CI)	p	Cases	OR (95%CI)	p	Cases	OR (95%CI)	p
Hair-Dye Use															
Never	224			117			80			20			40		
Ever	564	1.0(0.9–1.2)	0.69	400	1.3(1.0–1.6)	0.02	244	1.3(1.0–1.6)	0.10	74	1.1(0.7–1.9)	0.69	109	1.0(0.7–1.5)	0.91
Type															
Permanent	351	1.0(0.8–1.2)	0.64	274	1.3(1.1–1.7)	0.02	163	1.2(0.9–1.6)	0.15	52	1.2(0.7–2.1)	0.42	65	0.9(0.6–1.4)	0.61
Non-permanent	261	1.1(0.9–1.4)	0.36	180	1.3(1.0–1.7)	0.03	101	1.3(0.9–1.7)	0.14	32	1.0(0.6–1.8)	0.97	58	1.3(0.8–2.0)	0.24
Color															
Dark color	314	0.9(0.8–1.2)	0.61	249	1.3(1.0–1.7)	0.02	148	1.2(0.9–1.7)	0.14	53	1.2(0.7–2.0)	0.57	65	1.0(0.6–1.4)	0.83
Light color	251	1.1(0.9–1.3)	0.4	173	1.3(1.0–1.7)	0.06	104	1.3(0.9–1.8)	0.12	29	1.0(0.6–1.8)	0.96	40	0.9(0.6–1.4)	0.58
Type & Color															
Permanent dark	185	0.9(0.7–1.1)	0.24	164	1.4(1.1–1.8)	0.01	96	1.3(0.9–1.7)	0.14	35	1.4(0.8–2.4)	0.3	38	0.9(0.6–1.4)	0.68
Permanent light	175	1.0(0.8–1.3)	0.76	124	1.3(1.0–1.7)	0.05	75	1.3(0.9–1.8)	0.18	22	1.3(0.7–2.5)	0.4	30	0.9(0.6–1.5)	0.69
Non-permanent dark	155	1.1(0.9–1.4)	0.43	118	1.4(1.0–1.8)	0.03	64	1.3(0.9–1.8)	0.18	24	1.0(0.5–1.8)	0.96	35	1.1(0.7–1.8)	0.61
Non-permanent light	45	1.1(0.8–1.6)	0.57	31	1.2(0.8–1.9)	0.34	27	1.7(1.0–2.7)	0.04	7	1.1(0.4–2.6)	0.86	11	1.3(0.7–2.7)	0.44
Started Use Before 1980															
Never	224			117			80			20			40		
Ever	311	1.1(0.9–1.3)	0.47	236	1.4(1.1–1.9)	<0.01	159	1.5(1.1–2.0)	<0.01	47	1.1(0.7–2.0)	0.64	55	1.0(0.6–1.5)	0.93
Type															
Permanent	204	1.1(0.9–1.3)	0.57	151	1.4(1.1–1.9)	<0.01	105	1.5(1.1–2.0)	0.01	33	1.4(0.8–2.4)	0.3	36	1.0(0.6–1.5)	0.9
Non-permanent	114	1.0(0.8–1.3)	0.78	84	1.4(1.0–1.9)	0.05	56	1.5(1.0–2.1)	0.04	18	1.1(0.6–2.1)	0.79	23	1.1(0.7–2.0)	0.62
Color															
Dark color	161	1.0(0.8–1.3)	0.94	124	1.4(1.0–1.8)	0.02	90	1.5(1.1–2.1)	0.01	31	1.3(0.7–2.3)	0.4	33	1.0(0.6–1.7)	0.86
Light color	145	1.2(0.9–1.5)	0.17	115	1.6(1.2–2.1)	<0.01	73	1.6(1.1–2.2)	<0.01	21	1.2(0.6–2.3)	0.59	19	0.8(0.4–1.4)	0.38

Table 2.15 (contd)

	DLBCL			Follicular			CLL/SLL			MZL			T-cell		
	Cases	OR (95%CI)	p	Cases	OR (95%CI)	p	Cases	OR (95%CI)	p	Cases	OR (95%CI)	p	Cases	OR (95%CI)	p
Started Use Before 1980 (contd.)															
Type & Color															
Permanent dark	111	1.0(0.8–1.3)	0.77	80	1.4(1.0–1.9)	0.03	58	1.5(1.0–2.2)	0.03	21	1.6(0.8–3.0)	0.15	23	1.2(0.7–2.0)	0.58
Permanent light	102	1.1(0.9–1.5)	0.32	80	1.6(1.2–2.2)	<0.01	51	1.5(1.0–2.2)	0.03	15	1.5(0.8–3.1)	0.23	14	0.8(0.4–1.5)	0.5
Non-permanent dark	58	1.0(0.7–1.4)	0.99	44	1.2(0.8–1.8)	0.34	36	1.6(1.0–2.5)	0.03	12	1.0(0.5–2.1)	0.94	13	1.0(0.5–1.9)	1
Non-permanent light	19	1.0(0.6–1.7)	1	20	1.7(1.0–3.0)	0.05	15	1.9(1.1–3.6)	0.03	4	1.1(0.4–3.3)	0.9	5	1.2(0.4–3.2)	0.72
Started Use in 1980 or Later															
Never	224			117			80			20			40		
Ever	246	1.0(0.8–1.2)	0.89	163	1.3(1.0–1.7)	0.07	84	1.1(0.8–1.5)	0.63	27	1.0(0.6–1.9)	0.93	52	1.0(0.7–1.6)	0.93
Type															
Permanent	128	0.8(0.6–1.1)	0.12	104	1.3(1.0–1.8)	0.06	50	1.1(0.7–1.6)	0.8	18	1.2(0.6–2.5)	0.52	29	0.9(0.5–1.5)	0.66
Non-permanent	124	1.1(0.9–1.5)	0.3	80	1.4(1.0–2.0)	0.03	41	1.3(0.8–1.9)	0.24	12	0.9(0.4–2.0)	0.85	33	1.5(0.9–2.6)	0.09
Color															
Dark color	149	0.9(0.7–1.2)	0.65	114	1.5(1.1–2.0)	0.02	54	1.1(0.8–1.6)	0.6	22	1.2(0.6–2.2)	0.66	31	0.9(0.6–1.6)	0.82
Light color	88	1.0(0.7–1.3)	0.98	51	1.1(0.8–1.6)	0.58	28	1.1(0.7–1.7)	0.75	5	0.6(0.2–1.6)	0.28	20	1.1(0.6–1.9)	0.8
Type & Color															
Permanent dark	69	0.7(0.5–1.0)	0.05	69	1.5(1.1–2.1)	0.02	32	1.1(0.7–1.8)	0.62	14	1.4(0.7–2.9)	0.36	14	0.7(0.4–1.4)	0.35
Permanent light	60	1.0(0.7–1.3)	0.77	38	1.2(0.8–1.8)	0.35	17	0.9(0.5–1.7)	0.82	3	0.6(0.2–2.2)	0.45	16	1.2(0.6–2.2)	0.62
Non-permanent dark	85	1.2(0.9–1.6)	0.28	61	1.7(1.1–2.4)	<0.01	27	1.3(0.8–2.1)	0.35	11	1.0(0.5–2.3)	0.9	22	1.4(0.8–2.5)	0.23
Non-permanent light	19	1.1(0.6–1.9)	0.75	9	1.0(0.5–2.1)	0.98	11	1.8(0.9–3.7)	0.09	1	0.5(0.1–4.0)	0.52	5	1.4(0.5–3.8)	0.48

From Zhang *et al.* (2008)
DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MZ, marginal-zone lymphoma; T-cell, T-cell lymphoma.
Adjusted for age (continuous), race (white, black, others), and study site.

Table 2.16. Associations between hair dye use and risk of follicular lymphoma and CLL/SLL among women by duration, frequency, and total applications

	Follicular lymphoma						SLL/CLL					
	Overall		Started use before 1980		Started use in 1980 or later		Overall		Started use before 1980		Started use in 1980 or later	
	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
DURATION (in years)												
Any hair-dye use												
<8	1.2(0.9–1.6)	0.23	1.4(0.9–2.1)	0.11	1.2(0.9–1.7)	0.21	1.2(0.8–1.6)	0.40	1.5(1.0–2.4)	0.08	1.1(0.7–1.7)	0.61
8–19	1.3(1.0–1.7)	0.09	1.3(0.9–1.9)	0.11	1.4(1.0–1.9)	0.08	1.3(0.9–1.8)	0.16	1.6(1.0–2.4)	0.03	1.2(0.8–1.8)	0.46
20+	1.5(1.1–1.9)	0.01	1.5(1.1–2.0)	<0.01	1.5(0.6–4.0)	0.41	1.3(1.0–1.8)	0.08	1.5(1.1–2.0)	0.02	0.3(0.0–2.0)	0.20
p for trend	0.01		<0.01		0.06		0.07		0.02		0.90	
Type												
Permanent												
<8	1.3(0.9–1.7)	0.13	1.6(1.0–2.5)	0.03	1.2(0.8–1.7)	0.35	1.0(0.7–1.5)	0.96	1.2(0.7–2.2)	0.53	1.0(0.6–1.6)	0.95
8–19	1.3(1.0–1.8)	0.08	1.2(0.8–1.8)	0.44	1.5(1.0–2.2)	0.03	1.3(0.9–1.9)	0.17	1.5(0.9–2.5)	0.09	1.2(0.7–2.0)	0.43
20+	1.4(1.1–1.9)	0.02	1.5(1.1–2.0)	0.01	1.9(0.6–5.6)	0.26	1.4(1.0–2.0)	0.05	1.5(1.1–2.2)	0.02	0.4(0.1–3.3)	0.42
p for trend	0.02		0.02		0.02		0.03		0.01		0.75	
Non-permanent												
<8	1.3(0.9–1.9)	0.14	1.2(0.7–1.9)	0.54	1.5(0.9–2.4)	0.09	1.0(0.6–1.7)	0.94	1.1(0.6–2.1)	0.81	1.1(0.6–2.3)	0.71
8–19	1.3(0.8–2.1)	0.31	1.5(0.7–3.2)	0.28	1.3(0.7–2.4)	0.49	2.0(1.1–3.4)	0.02	2.3(1.0–5.2)	0.04	1.9(0.9–3.9)	0.08
20+	1.3(0.9–1.7)	0.12	1.3(0.9–2.0)	0.13	1.4(0.9–2.2)	0.13	1.2(0.8–1.8)	0.34	1.6(1.0–2.5)	0.03	0.9(0.5–1.7)	0.84
p for trend	0.11		0.13		0.10		0.15		0.02		0.90	
Color												
Dark color												
<8	1.3(1.0–1.8)	0.05	1.3(0.8–2.0)	0.27	1.4(1.0–2.1)	0.05	1.2(0.8–1.7)	0.43	1.3(0.8–2.3)	0.29	1.1(0.7–1.8)	0.59
8–19	1.2(0.9–1.7)	0.22	1.0(0.6–1.7)	0.87	1.6(1.1–2.3)	0.02	1.2(0.8–1.8)	0.28	1.6(0.9–2.7)	0.08	1.2(0.7–2.0)	0.46
20+	1.5(1.1–2.2)	0.01	1.6(1.1–2.3)	0.01	1.5(0.4–5.2)	0.53	1.4(1.0–2.1)	0.08	1.6(1.1–2.4)	0.02	0.4(0.1–3.3)	0.42
p for trend	0.02		0.01		0.04		0.08		0.01		0.74	

Table 2.16 (contd)

	Follicular Lymphoma						SLL/CLL					
	Overall		Started use before 1980		Started use in 1980 or later		Overall		Started use before 1980		Started use in 1980 or later	
	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
DURATION (in years)												
Light color												
<8	1.2(0.9–1.7)	0.22	1.6(1.1–2.6)	0.03	1.2(0.8–1.9)	0.41	1.0(0.7–1.7)	0.84	1.2(0.6–2.2)	0.66	1.1(0.6–2.0)	0.82
8–19	1.1(0.8–1.6)	0.56	1.7(1.1–2.8)	0.03	0.9(0.5–1.6)	0.69	1.2(0.7–1.8)	0.50	1.7(0.9–3.1)	0.08	1.2(0.7–2.2)	0.55
20+	1.5(1.1–2.1)	0.02	1.5(1.1–2.1)	0.02	2.7(0.7–10.1)	0.13	1.6(1.1–2.4)	0.01	1.7(1.2–2.6)	0.01	–	
p for trend	0.02		0.01		0.60		0.02		<0.01		0.91	
FREQUENCY (# of applications per year)												
Any hair-dye use												
<5	1.3(1.0–1.7)	0.09	1.4(1.0–2.0)	0.05	1.3(0.9–1.8)	0.21	1.1(0.7–1.5)	0.78	1.2(0.8–1.9)	0.42	1.0(0.6–1.7)	0.86
5–8	1.2(0.9–1.6)	0.17	1.4(1.0–2.0)	0.05	1.1(0.8–1.7)	0.49	1.2(0.8–1.7)	0.30	1.7(1.2–2.5)	0.01	0.7(0.4–1.3)	0.27
9+	1.3(1.0–1.8)	0.03	1.4(1.0–1.9)	0.04	1.5(1.0–2.2)	0.04	1.6(1.1–2.1)	0.01	1.7(1.2–2.4)	<0.01	1.6(1.0–2.5)	0.04
p for trend	0.05		0.03		0.06		<0.01		<0.01		0.19	
NUMBER OF TOTAL APPLICATIONS												
Any hair-dye use												
<31	1.2(0.9–1.6)	0.20	1.4(0.9–2.0)	0.10	1.2(0.9–1.7)	0.25	1.1(0.8–1.6)	0.58	1.3(0.8–2.1)	0.22	1.1(0.7–1.7)	0.77
31–138	1.2(0.9–1.6)	0.15	1.2(0.9–1.8)	0.24	1.4(1.0–1.9)	0.08	1.2(0.8–1.7)	0.31	1.6(1.1–2.5)	0.02	0.9(0.6–1.5)	0.75
139+	1.4(1.1–1.9)	0.01	1.5(1.1–2.0)	0.01	1.3(0.8–2.3)	0.33	1.5(1.1–2.1)	0.01	1.6(1.1–2.2)	0.01	1.8(1.0–3.2)	0.04
p for trend	0.02		0.01		0.07		0.01		<0.01		0.24	

From Zhang *et al.* (2008)
CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma
Adjusted for age (continuous), race (white, black, others), and study sites

3. Studies of Cancer in Experimental Animals

3.1 Occupational use of hair dyes: Hair-dye formulations and some of their components

3.1.1 *Skin application*

(a) Mouse

Groups of 50 male and 50 female Swiss Webster mice, 6–8 weeks of age, received applications of one of three oxidation (permanent) hair-dye formulations, PP-7588, PP-7586 or PP-7585 (all three contained 2,5-toluenediamine sulfate, *para*-phenylenediamine and resorcinol; PP-7586 also contained 2,4-diaminoanisole sulfate, PP-7585 contained *meta*-phenylenediamine, and PP-7588 contained 2,4-toluene-diamine) [see reference for additional details on composition], mixed with an equal volume of 6% hydrogen peroxide just before use; 0.05 mL of the mixture in acetone was applied to the shaved skin of the interscapular region. Controls were given acetone or were left untreated. For each formulation and for the vehicle control, one group was treated once weekly and another group once every other week for 18 months. Survival at 18 months varied from 58% to 80%. No sign of systemic toxicity was found in any of the dye-treated groups. Average body weights were comparable in all groups throughout the study. The incidence of tumours at all sites, including lung tumours, was not statistically different between treated and control groups. No skin tumours were observed at the site of application (Burnett *et al.*, 1975).

The chronic toxicity of 2,4-toluenediamine (2,4-TDA) alone [purity not specified] or in combination with a hair-dye complex (2,5-toluenediamine, *para*-phenylenediamine, and resorcinol) [see reference for additional details on composition] was studied in groups of 28 male and 28 female Swiss Webster mice, 4–7 weeks of age, and weighing 15–20 g by use of a skin-painting technique, whereby a 6% solution of the study materials in a water/isopropanol solvent were mixed with equal volumes of either 6% peroxide or distilled water at doses of 50, 150 or 1500 μg 2,4-TDA per week. Additional groups of vehicle and untreated controls were used. No information on survival was provided. The predominant neoplasms seen in these mice were primary pulmonary adenomas and adenocarcinomas. Skin neoplasms were seen in most groups of mice, including untreated controls. Statistical analysis of the incidences of skin neoplasms among the various groups of mice did not show any significant differences. The 2,4-TDA, alone or mixed with the hair-dye complex, did not produce any abnormal proliferation and maturation of the squamous epithelium of the skin (Giles *et al.*, 1976). [The Working Group noted the lack of information on survival, and the use of water as the skin-painting solvent.]

Groups of 26 male and 22 female DBAf and 26 male and 26 female strain-A mice, 6–7 weeks of age, received skin applications of 0.4 mL (reduced to 0.2 mL at 24 weeks for

DBAf mice) of a 10% solution of a commercially available semi-permanent hair dye ('GS'), containing, among other constituents [unspecified], 1,4-diamino-2-nitrobenzene (2-nitro-*para*-phenylene-diamine) and 1,2-diamino-4-nitrobenzene (4-nitro-*ortho*-phenylenediamine) in 50% aqueous acetone twice a week on the clipped dorsal skin. Groups of 16 male and 16 female control mice of each strain received applications of acetone alone. When the experiment was terminated at 80 weeks, four (18%) lymphomas and six (27%) tumours of the reproductive tract (four ovarian cystadenomas and two uterine fibrosarcomas) had developed in the 22 treated female DBAf mice within 37–80 weeks, and one (4%) lymphoma had developed by week 26 among the 26 treated males. In control DBAf mice, 1 lymphoma and 1 lung adenoma were found in females and 1 hepatoma in males. No difference was observed in the incidence of lymphomas or liver or lung tumours between treated and control strain-A mice. No skin tumour at the site of application was observed in either strain. Of the treated animals, 27 DBAf mice and 32 strain-A mice survived 60–80 weeks without tumours (Searle & Jones, 1977). [The Working Group noted that this study was conducted with a low concentration of the formulation used in this study.]

In the same study, groups of 17 male and 15 female DBAf and 16 male and 16 female strain-A mice, 6–7 weeks of age, received skin applications of 0.4 mL (reduced to 0.2 mL at 24 weeks for DBAf mice) of a 10% solution of a commercially available semi-permanent hair dye ("RB"), containing, among other constituents [unspecified], 4-amino-2-nitrophenol and CI Acid Black 107, in 50% aqueous acetone twice a week on the clipped dorsal skin. The experiment was terminated at 80 weeks. No significant difference was observed in the incidence of tumours at any site between treated and control animals of either strain, and no skin tumour at the site of application was observed in either strain (Searle & Jones, 1977). [The Working Group noted the low concentration of the formulation used in this study.]

In an interim report of the Searle and Jones (1977) study mentioned above, it was noted that the tumours arose consistently earlier in the treated than in the control mice, notably in the DBAf strain, in which the first lymphoma was detected after 26 weeks. Apart from the early appearance, there was also an increased tumour incidence in this strain, due mainly to uterine and ovarian tumours that were not seen in the control group (Venitt & Searle, 1976).

Twelve groups of 50 male and 50 female random-bred Swiss Webster mice, 6–8 weeks of age, were exposed dermally, once per week for 21–23 months, to different hair-dye formulations by placing a 0.05-mL sample on a 1-cm^2 area of the interscapular region, which had been clipped free of hair 24 hours before treatment. Nine oxidative hair dyes (7401, 7402, 7403, 7404, 7405, 7406, P-21, P-25, and P-26) were mixed with an equal volume of 6% hydrogen peroxide and 0.025 ml was applied within 15 minutes. Three semi-permanent hair-dye formulations (P-22, P-23, and P-24) were applied in 0.05 ml within 30 minutes after opening the bottle. In an earlier study, the composition of these hair-dye formulations was given in an extensive table (Burnett *et al.*, 1976). Three groups of 50 males and 50 females served as controls that had their backs shaved but were not

further treated. After seven and nine months, groups of 10 females and 10 males were randomly selected from each group, necropsied and examined by histopathology. The experiment was terminated after 21–23 months. The treatments had no effect on survival. The incidences of skin tumours and liver and lung lymphomas were not greater than in control mice (Burnett *et al.*, 1980).

Groups of 60 male and 60 female Swiss Webster mice, eight weeks of age, received topical applications of two oxidative and 12 non-oxidative hair-dye formulations supplied by five cosmetic companies. The composition of the hair-dye formulations was described. Two groups of 60 male and 60 female Swiss Webster mice served as controls. Each oxidative formulation was applied at 0.05 mL/mouse once weekly for 20 months. Each non-oxidative dye was applied at a dose of 0.05 mL per mouse three times weekly for 20 months. The mice were shaved 24 hours before treatment as needed. Control animals were shaved only and received no treatment. The application of hair dyes did not have an adverse effect on average body-weight gain or survival of any group. There was no significant increase in the incidence of malignant lymphomas in male mice or in liver hemangiomas or lung adenomas of both sexes in these studies. Significant increases in numbers of malignant lymphomas over those in one of the untreated control groups were observed in female mice in the hair dye-formulation groups treated with formulation 7602A (19/60 (32%) treated *vs* 7/60 (12%) control, $P < 0.01$), formulation 7605 (18/60 (30%) treated *vs* 7/60 (12%) control, $P < 0.05$) and formulation 7610 (23/60 (38%) treated *vs* 7/60 (12%) control, $P < 0.01$). The authors pointed out that the incidence in each treated group is not significantly different from the incidence in the second control group in this study, and is within the range of control values previously reported for this strain of mouse. They concluded that these tumours were probably not treatment-related (Jacobs *et al.*, 1984).

(b) Rat

Groups of 50 male and 50 female Sprague-Dawley rats, approximately 14 weeks of age, received topical applications of 0.5 mL of permanent hair-dye mixtures containing [purity unspecified] either 4% *para*-toluenediamine or 3% *para*-toluenediamine, 0.75% resorcinol and 0.75% *meta*-diaminoanisole in vehicle solution (4% Tylose HT, 0.5% sodium sulfite, 8.5–13% ammonia (25%), 3.7% ammonium sulfate or as formed by neutralization and deionized water to 100.0%), with 6% hydrogen peroxide added immediately before use on a 3-cm^2 area of shaved dorsal skin twice a week for two years. The animals were then observed for a further six months. Control groups of 25 males and 25 females of the same strain and age received topical applications of 0.5 mL vehicle alone, to which 6% hydrogen peroxide was added immediately before use. Another group of 50 males and 50 females of the same strain served as untreated controls. No difference in survival was observed between treated, vehicle control and untreated control groups. The skin at the application site, and the liver, kidney, lung and gross lesions were studied histologically. No skin tumour was observed at the site of application, and there was no

significant difference in the incidence of tumours, including those of the skin, between treated, vehicle control and untreated control groups (Kinkel & Holzmann, 1973).

Groups of 10 male and 10 female Wistar rats weighing 120–140 g received topical applications of 0.5 mL oxidized *para*-phenylenediamine [purity unspecified] (1:1 mixture of 5% *para*-phenylenediamine and 2% ammonium hydroxide) and 6% hydrogen peroxide on shaved dorsal skin once a week for 18 months. Control rats were shaved and treated with the corresponding vehicle. Treated and control groups did not differ significantly in body weight gain or survival. All surviving rats were killed after 21 months. Treated rats had a significantly increased incidence of mammary tumours (5/10 (50%); $P < 0.05$ [incidental tumour test]) in comparison with female vehicle-controls (0/9). The first mammary tumour observed was a fibrosarcoma, which occurred at week 47; the others were three adenomas and one fibroadenoma. No skin tumour was observed at the site of application (Rojanapo *et al.*, 1986).

Groups of 60 male and 60 female Sprague-Dawley rats (aged 6–8 weeks) received topical applications of an oxidative hair-dye formulation (7406) containing 0.5% 2-amino-5-nitrophenol, 4.0% *para*-phenylenediamine, 0.7% *para*-aminophenol, 2.0% 4-chlororesorcinol, 5.0% oleic acid, 15.0% isopropanol, 0.2% sodium sulfite, 6.0% ammonia and water to 100%. The formulation was diluted in an equal volume of 6% hydrogen peroxide before application, and 0.5 mL were applied to a shaved area of the back (approx. 2.5 cm in diameter) twice a week up to week 117. Three separate, similarly treated, concurrent control groups of 60 rats received applications of the vehicle alone. Mean body weights and survival were similar in treated and control groups. No skin tumours were observed. The incidence of pituitary adenomas was increased in females in comparison with all three control groups (45/51 (88%) *vs* 34/50 (65%), 36/51 (71%) and 35/50 (70%); $P < 0.05$, χ^2-test). The incidence of mammary gland adenomas was increased in comparison with one control group (6/53 (11%) *vs* 0/49; $P < 0.05$, χ^2-test). The authors concluded that the tumours were probably not treatment-related (Burnett & Goldenthal, 1988).

In the same study, groups of 60 male and female Sprague-Dawley rats, 6–8 weeks of age, received topical applications of an oxidative hair-dye formulation (7405) containing 0.4% 2-amino-4-nitrophenol, 6.0% 2,5-diaminoanisole sulfate, 2.0% resorcinol, 0.3% *ortho*-aminophenol, 5.0% oleic acid, 3.0% isopropanol, 0.2% sodium sulfite, 6.0% ammonia (29%) and water to 100%. The formulation was diluted in an equal volume of 6% hydrogen peroxide, and 0.5 mL was applied to a shaved area of the back (approx. 2.5 cm in diameter) twice a week up to week 117. Mean body weights and survival were similar in treated and control groups. No skin tumours were observed. The incidence of pituitary adenomas was increased in males in comparison with one of the control groups 35/52 (67%) *vs* 14/49; $P < 0.01$; χ^2-test), and no increase in the incidence of tumours at any other site was observed in treated rats compared with control animals. The authors concluded that the tumours were probably not treatment-related (Burnett & Goldenthal, 1988).

In the same study, groups of 60 male and female Sprague-Dawley rats, 6–8 weeks of age, received topical applications of an oxidative hair-dye formulation (7403) containing 6.0% *para*-toluenediamine sulfate, 0.7% *meta*-aminophenol, 1.0% *para*-aminophenol, 0.25% 4-nitro-*ortho*-phenylene diamine, 0.50% 1-naphtol, 15% oleic acid, 10% isopropanol, 4.5% glycerine, 9.0% propylene glycol, 0.2% sodium sulphite, 9.0% ammonia and water to 100%. The formulation was diluted in an equal volume of 6% hydrogen peroxide before application, and 0.5 mL was applied to a shaved area of the back (approx. 2.5 cm in diameter) twice a week until week 117. Mean body weights and survival were similar in treated and control groups. The incidence of mammary gland adenomas was increased in comparison with one control group (10/52 (19%) *vs* 0/49; $P < 0.01$, χ^2-test). There was no significant increase in the incidence of tumours at any site, and no skin tumour was observed. The authors concluded that the tumours were probably not treatment-related (Burnett & Goldenthal, 1988). [The Working Group wondered why the tumours were assumed not to be treatment-related.]

3.1.2 *Subcutaneous injection*

(a) Rat

Groups of 10 male and 10 female rats weighing 120–140 g received subcutaneous injections of 0.5 mL oxidized *para*-phenylenediamine (5% *para*-phenylenediamine in 2% ammonium hydroxide and 1.8% sodium chloride) in an equal volume of 6% hydrogen peroxide in the hip area every other week for 18 months. Controls were injected similarly with vehicle only. There was no significant difference between treated and control groups in body-weight gain or survival. All survivors were killed after 21 months. The incidence of mammary lesions [duct ectasia or adenosis] was significantly increased (4/7 (57%); $P < 0.05$ incidental tumour test) in females in comparison with vehicle controls (0/10). Two uterine tumours, an adenocarcinoma and an endometrial polyp were observed in females; no such tumours were observed in controls. Two sarcomas [not otherwise classified] at the injection site and two lipomas were also observed in treated animals (Rojanapo *et al.*, 1986). [The Working Group noted the small number of animals used in this study.]

3.2 Personal use of hair dyes

No data were available to the Working Group

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, elimination

No data were available to the Working Group.

4.2 Genetic and related effects

4.2.1 *Occupational use of hair dyes*

(a) Humans

Chromosomal aberrations in peripheral lymphocytes were examined in a study of 60 professional hair colourists (28 men, 28.4 ± 9.4 years old; 32 women, 23.3 ± 5.1 years old) and 36 control subjects matched for age and sex (17 men, 28.1 ± 7.3 years old; 19 women, 25.3 ± 6.5 years old) (Kirkland *et al.*, 1978) in the United Kingdom. Information was recorded on smoking habits, alcohol consumption, medical history, use of medicinal drugs and drugs of abuse, infections, vaccinations and exposure to X-rays. Details of occupational exposure to hair dyes were also collected: women had done an average of 11 000 permanent and 5000 semipermanent hair-tinting operations and men had done 15 000 permanent and 6000 semi-permanent operations, over periods ranging from 1 to 15 years. Blood samples were taken at the time of interview, but the time since the last hair-tint application (to themselves or clients) was not recorded. Among the chromosomal aberrations, more gaps were found per cell among female tinters than in controls (0.065 *vs* 0.048; $P < 0.02$) but not among male tinters (0.064 *vs* 0.063). The number of breaks per cell (assumed from the observed aberrations) was not altered among women (0.028 *vs* 0.031) but was lower among men (0.034 *vs* 0.047; $P < 0.05$). After exclusion of subjects exposed to high doses of diagnostic X-rays or who recently had viral infections these differences disappeared (breaks in tinters *vs* controls: women, 0.023 *vs* 0.027; men, 0.036 *vs* 0.038). Reallocation of this smaller set of subjects according to whether or not their own hair was dyed revealed that the number of breaks per cell was higher among women who dyed their hair (dyed *vs* not dyed, 0.031 *vs* 0.018; $P < 0.02$) and lower among men who dyed their hair (0.023 *vs* 0.044; $P < 0.01$). The women had given themselves an average of 90 permanent and 10 semi-permanent tints and the men an average of 30 permanent tints [semi-permanent tints not indicated] over a period similar to their occupational exposure. The authors stated that there was no association between chromosomal damage and the duration and/or frequency of hair dyeing in the women. [The Working Group noted the absence of data to substantiate this statement.] They reported that 20/23 female and 11/18 male tinters wore protective gloves for all applications of permanent and semi-permanent hair tints and deduced that most of the subjects would receive greater exposure to hair-dye components when their own hair was treated. The finding that the number of breaks per cell was lower among men who dyed their hair than among those who did not was explained by the age difference between the group with tinted hair (22.7 ± 5.1 years, $n = 10$) and the group with non-tinted hair (31.8 ± 10.1, $n = 17$). Kirkland *et al.* (1978) based their argument on the observation of Brown *et al.* (1965) that there was much less chromosomal damage of all types in 48-hour blood cultures from men aged 15–24 than from men aged 25–34, whereas there was no difference among women in these age ranges.

Babish *et al.*, (1991) conducted a study in New York State, USA, on cosmetologists (91 women, 7 men) who were occupationally exposed to a wide range of chemicals, including hair dyes, and who had reported a prevalence of skin rashes that was twice as high as that of a control group of 87 female dental personnel (29% *vs* 15%). The two groups were matched for median age, smoking status and proportion of subjects (13–16%) who had had their hair permed or dyed within seven days of the study. At the end of a normal working day, subjects from each group provided a urine sample, which was later concentrated and tested for mutagenicity in *S. typhimurium* TA100 in the presence and absence of S9. In the presence of S9, there was no difference between the groups, but in tests conducted without S9 the frequency of mutagenic urine samples was 15% higher among cosmetologists (39%) than among dental personnel (24%). Multivariate analysis, with adjustment for age and smoking habits, revealed an OR of 2.0 (95% CI, 1.1–3.8) for the presence of urinary mutagens in cosmetologists compared with dental personnel. [The Working Group noted the inadequate reporting of the results.]

Sardaş *et al.* (1997) assessed the cytogenic effects of occupational exposure to oxidation hair dyes by using three assays in professional hair colourists. The assays were analysis of sister chromatid exchange (SCE) in circulating lymphocytes to evaluate the interchange of DNA-replication products at apparently homologous chromosomal loci, the single-cell gel electrophoresis assay to detect the presence of DNA strand-breaks/alkali-labile damage, and the Ames assay with *Salmonella typhimurium* strain TA98 to detect the mutagenicity of the urine. The ability of these assays to detect genetic damage caused by oxidation hair dyes compared with closely matched controls produced the following findings: (i) The SCE assay could not detect an effect in lymphocytes of exposed subjects from whom complete data were obtained. However, subjects (controls and exposed) with a history of smoking had a slightly higher frequency of SCE than the non-smokers in both groups. (ii) The extent of DNA migration (single-cell gel electrophoresis assay) did not distinguish between the samples of exposed and control subjects. Like the SCE results, the exposed smokers and control smokers showed a greater proportion of damaged lymphocytes with apparent change in migration of DNA in the single-cell gel electrophoresis assay. (iii) No clear differences in the mutagenic activity of the urine samples were observed between the exposed and control subjects.

(b) Experimental systems

Wang *et al.* (1991) showed that of 169 commercial oxidative-type (hydrogen peroxide) hair-dye formulations, 150 (89%) were mutagenic in the *Salmonella* mutagenicity assay. Of the 18 components of these hair dyes, nine showed various degrees of mutagenicity: 2,4-diaminoanisole, 4-nitro-*ortho*-phenylenediamine, 2-nitro-*para*-phenylenediamine, 2,5-diaminoanisole, 2-amino-5-nitrophenol, *meta*-phenylene-diamine, *ortho*-phenylenediamine, 2-amino-4-nitrophenol, and 2,5-diaminotoluene. Three hair-dye components (*para*-phenylenediamine, 2,5-diaminotoluene and 2,5-diamino-anisole) became strongly mutagenic after oxidation by hydrogen peroxide: the mutagenic product of *para*-phenylenediamine was identified as the known trimer Bandrowski's base.

[The Working Group considered formation of this mutagenic product unlikely to happen under practical hair-dyeing conditions.] 2,4-Diaminotoluene, a hair-dye component, was also mutagenic: this compound has been shown to be a carcinogen in rats and is used in large amounts in the polyurethane-foam industry. [The Working Group noted that this compound has been taken off the market in the early 1970s] (Ames *et al.*, 1975).

A total of 13 commercial hair-dye products made in China were tested for mutagenicity in two short-term assays, the *Salmonella typhimurium* mutagenicity test in strains TA98 and TA100 and the in-vivo micronucleus assay with mouse bone-marrow polychromatic erythrocytes. The results showed that the 13 hair dyes were not mutagenic in strains TA98 and TA100 with or without S9. In the micronucleus test, no effect was observed (Wang *et al.*, 1991).

Albano *et al.* (1982) found that of 25 commercial permanent hair-dye formulations containing *para*-phenylenediamine, resorcinol and aminophenols incubated with hydrogen peroxide, 12 were mutagenic to *S. typhimurium* TA98 only in the presence of S9. Without the addition of hydrogen peroxide, mutagenicity was reduced for three dyes and disappeared for three others. Four of six formulations, with degrees of mutagenicity varying from zero to high, administered topically with 3% hydrogen peroxide to male rats, induced urine that was mutagenic to *S. typhimurium* TA98 in the presence of S9.

Ferguson *et al.* (1990) tested 40 products, chosen from among 12 brands of commercially available hair colourants used in New Zealand, for mutagenicity in *S. typhimurium* TA98 and TA100 without S9; activators were added when recommended. Twenty-three of these products were mutagenic in one or both strains. When 10 mutagenic hair-dye preparations were tested in the presence of the drug verapamil, used for treating cardiac conditions (Ferguson & Baguley, 1988), the mutagenic activity of four was decreased and that of two was increased (Ferguson *et al.*, 1990).

Watanabe *et al.* (1990) found that two of four commercial hair-dye formulations containing phenylenediamines and aminophenols (two of which also contained 2,5-diaminophenol), when oxidized with 6% hydrogen peroxide, were mutagenic to *S. typhimurium* TA98 in the presence of Kanechlor 500-induced S9. When toxicity was reduced by adsorbing bactericidal products on blue rayon, peroxide treatment increased the mutagenicity of all preparations to different extents; in the two preparations with markedly increased mutagenicity, activity was attributed to the oxidation of *meta*-phenylenediamine to 2,7-diaminophenazine, itself a potent mutagen.

Ammenheuser and Warren (1979) applied two commercial oxidative hair-colouring products at 10–30 mL, both with and without hydrogen peroxide, to the backs of male Sprague-Dawley rats [number unspecified]. Both colourants contained 1,4-diamino-2-nitrobenzene and 1,2-diamino-4-nitrobenzene (4-nitro-*ortho*-phenylenediamine). The solutions were left on the hair for 20 min and then removed by shampooing and rinsing. Urine was collected before and every 24 hours after product application for four days and tested on *S. typhimurium* TA1538, the volumes of urine applied to each plate varying from 3.4 to 11.5% of the total volume. Urine samples collected during the first 24 hours from rats treated with either of the preparations were mutagenic (two to three times

background); no significant mutagenicity was observed in urine samples collected two to four days after application. Prior reaction with hydrogen peroxide had little or no effect on the mutagenicity of the urine.

Stamberg *et al.* (1979) tested henna and its active colouring ingredient, 2-hydroxy-1,4-naphthoquinone, for mutagenicity in *S. typhimurium* TA98, TA100, TA1535, TA1537 and TA1538. Henna was not mutagenic to any strain, but 2-hydroxy-1,4-naphthoquinone was mutagenic to TA98, in the absence of S9 only.

Matsuki *et al.* (1981) isolated 2-amino-5-methoxy-2′(or 3′)-methylindamine and 2-amino-5-methoxy-2′(or 3′)-methylindoaniline from an oxidative reaction mixture of 2,5-diaminotoluene and 2,4-diaminotoluene. These compounds were found to be highly mutagenic to *S. typhimurium* TA98 in the presence of an exogenous metabolic system.

Burnett *et al.* (1981), in a study of heritable translocation, painted groups of 25 male Sprague-Dawley CD rats twice weekly for 10 weeks on the shaved dorsal skin with 0.5 mL of a semi-permanent dye formulation (comprising base ingredients plus 0.12% CI Disperse Blue 1, 0.04% CI Disperse Black 9, 0.01% HC Red No. 3, 0.21% HC Yellow No. 3, 0.50% HC Blue No. 1, 0.06% Acid Orange No. 3, 0.07% CI Disperse Violet No. 11 and 0.01% HC Yellow No. 2), or with 0.5 mL of an oxidative dye formulation (comprising base ingredients plus 2.2% *para*-phenylenediamine, 3.1% *N,N*-bis(2-hydroxyethyl)-*para*-phenylenediamine sulfate, 1.0% resorcinol and *meta*-aminophenol, mixed 1:1 with 6% hydrogen peroxide just before use). The animals were then mated with untreated female rats. Male F_1 progeny were subsequently mated with other untreated females, and the resulting pregnancies were arrested at day 16 of gestation. No difference in average litter size or frequency of successful matings at the F_1 mating was seen between controls and the two exposed groups. Furthermore, there was no effect on the number of live fetuses, implantations or resorptions at the F_2 (total litters analysed: 275 controls, 261 in the oxidation dye group and 271 in the semi-permanent dye group).

4.2.2 *Personal use of hair dyes*

Hofer *et al.* (1983) studied chromosomal aberrations in lymphocytes from six women and four men who volunteered to have their hair dyed and a similar group of 10 controls matched for age (men: hair-dyed, 35.7 ± 6.7; controls, 30.8 ± 6.4; women: hair-dyed, 30.3 ± 5.7; controls, 35.0 ± 5.8). Records were taken of smoking habits, alcohol consumption and medical drug use and, during the experiment, exposure to X-rays, illness and vaccinations. There were more smokers in the test group. None of the volunteers had used hair dyes or shades for at least one year before entering the study, and the control group did not use hair colourants during the study. The treated group had their hair dyed 13 times at intervals of three to six weeks with commercial preparations containing mixtures of aminotoluenes, aminophenols and hydroxybenzenes and, in some cases, naphthol, as active ingredients; the colouring product used was chosen according to each subject's hair colour, and the same material was used throughout the study. The colouring preparations were mixed (1:1) with 3–6% hydrogen peroxide. Nine blood samples were

taken: three weeks before the first treatment (control sample), 24 hours after a sham dyeing (no dye or hydrogen peroxide) and 24 hours after each of the first three and last four dyeing procedures. No difference was observed between the control and treated groups in the percentage of cells with one or more structural aberrations (excluding gaps) before treatment, after sham-dyeing or after treatment. Subdivision of the groups according to sex revealed no difference. A significant increase in aberration rate with age was observed among the male but not the female subjects. Neither smoking nor X-ray exposure had an effect. In conjunction with this study, sister chromatid exchange was examined in peripheral lymphocytes; no evidence was found of an effect on the frequency (Turanitz *et al.*, 1983).

Kirkland *et al.* (1981) studied sister chromatid exchange in the peripheral lymphocytes of a small group of volunteers comprising 13 women and one man immediately before and 6 hours and seven days after one normal application of four semi-permanent and 10 permanent hair dyes, all of which were mutagenic to *Salmonella typhimurium* TA1538 and TA98 in the presence of metabolic activation. There was no consistent increase in the frequency of sister chromatid exchange per cell.

In a study in the USA involving 30 women aged 45–65 years, Burnett *et al.*, (1979) determined mutagenicity in urine specimens collected before and during a 24-hour period immediately after application of dark shades of several hair-colouring products containing high levels of dyes and dye intermediates. Many of the women had used hair dyes regularly for over 20 years. Concentrated (XAD-2 resin) urine samples did not increase the number of reverse mutations in *S. typhimurium* TA1538 in the presence of an exogenous metabolic system from rat liver (S9). [The Working Group noted the inadequate reporting of the results.]

Espinoza *et al.* (2008) evaluated micronuclei in urothelial cells to determine the possible association between genetic damage and use of hair dyes in 128 Spanish women. In addition, 72 women who participated as controls in a bladder cancer case–control study in Spain were included as controls. To avoid any kind of bias, only those cells with a typical morphology corresponding to the urothelial cells were scored. The mean micronucleus frequency in the overall study group was 9.72 ± 0.82 micronclei/1000 cells and did not vary by hair-dye exposure: 9.90 micronuclei/1000 cells (± 0.78) observed in women using hair dyes during the preceding month *vs* 9.50 micronuclei/1000 cells (± 2.45) observed in women who did not use hair dye in the preceding month. Use of hair dyes in recent months was associated with a higher frequency of micronuclei, but the association was not statistically significant ($P = 0.536$).

4.3 Mechanistic considerations

Hair dyes are difficult to evaluate as a group. On the one hand, the exposure situation is different for hairdressers and personal users, and on the other hand it seems particularly difficult to obtain information about a causal relationship. Significant associations can hardly be expected from epidemiological investigations. The experience with aromatic

amines somehow directed the attention from the beginning towards genotoxicity, and towards the bladder as the target tissue. Since bladder tumours are not uncommon in the general population, one would expect the tumour incidence to increase significantly only if exposures to hair dye-derived agents are relatively high, i.e. significantly above the background of other "bladder-specific" agents, for instance from smoking. Moreover, since bladder tumours seem to be the result of genotoxic as well as acute toxic effects, it is difficult to assess how (frequently changing) hair-dye components and other exogenous factors contribute to various biological effects. A monocausal approach seems to be particularly questionable in this case. The heterogeneous results of the many epidemiological studies reflect this dilemma. Bolt & Golka (2007) concluded from an extensive review of the literature that there seems to be no relevant bladder-cancer risk associated with the use of hair dyes that are available today. In other words, the potency is considered to be low. On the other hand, the epidemiological results from studies among hairdressers indicate that—with all reservations—the potential of occupational exposure to contribute to the overall cancer risk cannot be excluded.

More recently, other possible target tissues have been taken into account. Ambrosone *et al.* (2007) looked for effect markers of aromatic and heterocyclic amines as well as polycyclic aromatic hydrocarbons in exfoliated breast ductal epithelial cells from breast milk as etiological factors for breast-cancer risk. DNA adducts for each class were detected, and the presence of 4-aminobiphenyl adducts was associated with the use of hair-colouring products. Although this finding does not prove a causal relationship, it underlines the view that environmental exposures contribute to lesions in many tissues and thereby add to the risk. The suspicion of a relationship between hair dyes and cancer developed when some of the components were found to be genotoxic in in-vitro tests, and subsequently also carcinogenic in rodents after oral administration. The results were negative however, if the amines or commercial mixtures containing carcinogenic components were tested via topical application. Although the latter route of administration is more analogous to the current use of hair dyes, the other experiments indicate a carcinogenic potential under certain circumstances. If comparable exposure conditions would be strenuously required in carcinogen testing, the relevance of the results of many if not most animal experiments becomes questionable. However, it is important to keep in mind the difference between hazard and risk.

A particular aspect with permanent hair colourants is that the colourant is generated by oxidation of an amine and the structure of the oxidation product is normally not known from the peer-reviewed literature. Primary intermediates are for instance *para*-phenylenediamine or *para*-aminophenol, and couplers are *meta*-aminophenols or *meta*-hydroxyphenols. In the presence of peroxide, the primary intermediate and the coupler react with each other and coloured oligomers are formed. By itself, *para*-phenylene-diamine is only weakly genotoxic, but a mutagenic trimer (Bandrowski's base) is formed under oxidizing conditions. Moreover, additional activating pathways must be considered with diamines and phenolic amines: quinoid structures are involved, which react with cellular proteins. In this context it is interesting to note that *para*-phenylendiamine is an

established contact sensitizer, which indicates that relevant amounts penetrate the skin and are biologically active. The incidence of contact sensitization is increased particularly among beauticians and hairdressers (Iorizzo *et al*., 2002).

In the light of the above, it seems difficult to differentiate between different exposure situations on the basis if epidemiological observations. If there are hazardous components involved in exposure to hair colourants, they would probably contribute to the background exposure of aromatic amines. For practical purposes, and in line with the ALARA principle, established carcinogens should be avoided, omitted or exchanged for less hazardous components, and biological effect markers should be used to establish to what extent the professional handling of hair dyes and their personal use contribute to the background or total load of aromatic amine exposure.

5. Summary of Data Reported

5.1 Exposure data

5.1.1 *Hair Dyes: Production, use, occupational exposure and exposure after personal use*

Modern hair dyes may be classified as a) oxidative (permanent) hair dyes, b) semi-permanent and c) temporary dyes. Oxidative hair dyes represent approximately 80% of the market and consist of colourless primary intermediates (*para*-substituted aromatic amines) and couplers (*meta*-substituted aromatic amines and other compounds) that, in the presence of peroxide, form the dye by a chemical reaction. The concentration of oxidative hair-dye ingredients is approximately proportional to their degree of shade: dark colours tend to contain the highest concentrations of colouring ingredients (up to 3% primary intermediates during use) whereas light shades (blond) contain lower concentrations. Semi-permanent (direct) hair dyes contain colour molecules of low molecular weight, such as nitro-phenols, nitro-aminophenols and nitro-phenylene-diamines. Temporary dyes contain direct hair dyes of high molecular weight, such as azo, triphenylamine and indamine colourants. A worldwide survey in 2005 showed the presence of 50 ingredients in oxidative, 43 in semi-permanent and 88 ingredients in temporary hair dyes. The most frequently used oxidative hair-dye ingredients are *para*-phenylenediamine, resorcinol, 2,5-diaminotoluene, *para*- and *meta*-aminophenol, 4-amino-2-hydroxytoluene, 4-amino-*meta*-cresol and 2-methyl-5-hydroxyethylamino-phenol. The majority of oxidative hair-dye ingredients have been on the market since the 1930s. Most semi-permanent or temporary hair dyes have a much more limited use.

Occupational exposure studies found no or only traces of hair-dye ingredients in the air of hair salons, whereas measurable amounts were detected on hairdressers' hands. The major occupational exposure pathway appears to be via skin contact, followed by dermal absorption. The same exposure pathway applies to personal (consumer) use of hair dyes.

Hair dyes have been subject to regulations in many countries, and the number of substances permitted for use in hair dyes has been restricted during the past 40 years; in 2007, 135 individual ingredients were no longer allowed in the European Union for use in hair dyes.

5.2 Human carcinogenicity data

5.2.1 *Professional use of hair colourants*

The Working Group reviewed the literature on cancer at several sites in hairdressers, barbers and beauticians. Many additional studies have been published since the previous review in 1993 (IARC Monograph 57). These include several case–control studies and a few cohort studies. Most data from cohort studies derive from linkage between census data and cancer registries in Scandinavian countries, with limited potential to adjust for confounding by important correlates of cancer risk, e.g., lifestyle and reproductive factors. The Working Group noted that the evidence mainly concerned exposures that occurred before 1980s, and often much earlier.

(a) Bladder cancer

The cohort studies indicated an increased risk for cancer of the urinary bladder among male hairdressers, but not among female hairdressers. In a large Scandinavian cohort of hairdressers, barbers, beauticians and other related workers identified in the 1970 census and followed-up for 20 years, there was a significant 50% increase in risk for bladder cancer in men and a non-significant 10% decrease in risk in women. Allowance for smoking was generally not possible, although results for lung cancer suggest that higher exposure to tobacco in hairdressers could not totally account for the bladder cancer excess.

More than 20 case–control studies were available for evaluation. Most of these, including three of the larger studies, reported increased risks in the range of 1.3–1.7 in male hairdressers. A pooled analysis of 11 studies conducted in six European countries found no significant increase in risk among male or female hairdressers. Overall, risks appeared generally lower for women than for men. The number of exposed subjects was generally small, and did not allow a reliable assessment of the risk by duration and period of exposure.

In view of the consistent yet modest increase in risk reported in studies of hairdressers and barbers, especially men, and in the absence of solid data on the relation between duration and period of exposure, the Working Group concluded that there was *limited evidence* of an increased risk for bladder cancer in hairdressers.

(b) Haematological malignancies

With regards to cancers of the haematological system, the heterogeneity in the diseases included and the differences in the classification used often hampered

comparison between the results of different studies. Although one cohort study of barbers among male US veterans and an Italian case–control study reported significant increases in risk for multiple myeloma based on only few exposed cases, these results were not replicated in other studies. In the large Scandinavian cohort, no excess was found in either sex for multiple myeloma or for other haematological malignancies.

(c) Breast cancer

Many studies on breast cancer, including the largest case–control and cohort studies, did not show any increased risk for breast cancer associated with professional use of hair colourants.

(d) Childhood cancers

One cohort study and five case–control studies investigated the risk for childhood cancers in the offspring of hairdressers and barbers. Although some positive associations were reported, an overall evaluation is difficult because of the different sites and/or histologies investigated in various studies and the problems in the identification of the relevant period of exposure (before or around conception, or during pregnancy).

(e) Other sites

(i) *Ovarian cancer*

A modest increase in risk for ovarian cancer was reported in two cohorts of US cosmetologists and Scandinavian hairdressers, which was significant only in the latter study. The excess in risk appeared stronger in—or limited to—women exposed in earlier periods. No case–control study was available for evaluation. The lack of adjustment for potential confounders, especially reproductive history and oral contraceptive use, does not allow confounding to be ruled out.

(ii) *Lung cancer*

Small increases in lung cancer risk of the order of 20–40% were found in most cohort studies, which did not, however, adequately adjust for smoking. A higher prevalence of smokers among hairdressers than in the general population was reported in Scandinavia and the USA. No informative case–control study was available for evaluation. The Working Group concluded that tobacco smoking cannot be excluded as a likely cause of the modest excess in lung cancer observed in hairdressers.

5.2.2 *Personal use of hair colourants*

The Working Group revised and evaluated the epidemiological evidence of an association between cancer at several sites and personal use of hair dyes.

(a) Bladder cancer

Several studies with contradictory results have been published. Increased risks for bladder cancer were reported in two studies in the USA, while no association was found in three larger studies, two from the USA and one from Spain. These recent studies had similar characteristics in design and methodology.

One study from the USA suggested an increased risk for bladder cancer among users of hair colourants, in particular among those who exclusively used permanent hair dyes. Further, this study showed that exclusive use of permanent dyes among subjects with slow acetylation (*NAT2* genotype) or among CYP1A2 slow metabolizers was associated with an increased risk for bladder cancer. The other studies did not confirm these results. In the Spanish study, there was no indication of an increased risk for bladder cancer associated with the *NAT2* genotype, but there was a non-significant association with *NAT1*10*. The available cohort studies were largely negative for bladder cancer. The available meta-analyses did not show an association.

The Working Group considered that the available evidence for cancer of the bladder was overall *inadequate*.

(b) Haematological malignancies

The results for this tumour type were difficult to interpret: many different malignancies are involved, and many of the studies do not provide analyses for the different disease entities. Historically, the results have been inconsistent in identifying an increased risk. While cohort studies were largely negative for haematological malignancies, the results of case–control studies varied greatly. In those that showed an increased risk, the increase tended to be moderate. A recent pooled analysis was evaluated with particular interest because it was a large study evaluating hair-dye exposure in relation to single lymphoma entities including case–control data derived from Canada, the USA and six countries in Europe. The study showed an overall increased risk of 1.1 among women who were regular users, and of 1.3 among those women who had started regular hair-dye use before 1980. The risk was consistently elevated for follicular lymphoma and chronic lymphocytic leukaemia, but not for other types. For these lymphoma subtypes, the risk did not vary by intensity, years of use or type of exposure, remaining generally of the order 1.2–1.4. When the period of first use was considered, the increased risk for chronic lymphocytic leukaemia was mainly observed among those who started use before 1980, with a statistically significant increase in risk among those reporting use for more than 20 years. For follicular lymphoma, increased risks were observed throughout the two study periods. Overall, the Working Group considered this evidence to be *inadequate*.

(c) Breast cancer

For breast cancer the Working Group considered the evidence as *inadequate* based on several studies, none of which except one showed an association.

(d) Childhood cancers

For childhood cancers, the studies evaluated dealt with childhood brain tumours and Wilms tumours. The Working Group discussed in depth the potential biases and study limitations that could explain some of the increased risks observed for some brain tumours, and considered that some of the reported associations could not be simply explained by recall bias, as mothers may not have known about this hypothesis at the time of the studies. The Working Group considered that the evidence presented in the studies was *inadequate*.

(e) Other sites

Only a few studies were available to the Working Group, and no evaluation was made.

5.3 Animal carcinogenicity data

Various commercially available hair-dye formulations and various laboratory preparations of hair dyes were tested for carcinogenicity in mice or rats by skin application in 11 studies and by subcutaneous injection in a single study in rats.

In three studies by skin painting in mice, all using different formulations, increased incidences of lymphomas were observed in female mice compared with concurrent controls, for five different formulations. The increased incidences were not significant when compared with historical controls. In three studies by skin painting in rats, a significant increase in the incidence of mammary adenomas in females was observed for two formulations, and a significant increase in pituitary adenomas was seen in females for one formulation and in males for a different formulation. In the single subcutaneous injection study in rats, an increased incidence in mammary and uterine tumours was observed. The other studies either showed no increased incidence of tumours at any site or were inadequate for evaluation.

5.4 Other relevant data

Studies that investigated the induction of chromosomal aberrations in peripheral blood lymphocytes of professional hair-colourists or in volunteers who had their hair dyed reported no effect. The same is true for two studies that investigated sister chromatid exchange in lymphocytes of hairdressers. Two studies on the mutagenicity of urine collected from hair-dye users and cosmetologists were inadequate for evaluation. One study assessed sister chromatid exchange, DNA breakage (measured by single-cell gel electrophoresis) in lymphocytes and mutagenicity in urine in professional hair-colourists. No effect was seen for any of these three endpoints. A study on micronucleus formation in hair-dye users did not show a difference with non-user controls.

In an early study, 90% of a large number of commercial oxidative hair-dye formulations were mutagenic in bacteria. In later studies, this percentage dropped to 0–50%. The hair-colouring product henna did not show bacterial mutagenicity in one study. When tested separately, its active ingredient was mutagenic.

The urine of rats skin-painted with oxidative hair-colouring products was mutagenic when collected during the first 24 hours. The mutagenicity disappeared afterwards.

No effects were seen in a heritable translocation assay in rats skin-painted twice weekly for ten weeks with a semi-permanent dye formulation.

6. Evaluation

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of occupational exposures as a hairdresser or barber.

There is *inadequate evidence* in humans for the carcinogenicity of personal use of hair colourants.

6.2 Cancer in experimental animals

There is *limited evidence* in experimental animals for the carcinogenicity of hair colourants.

6.3 Overall evaluation

Occupational exposures as a hairdresser or barber are *probably carcinogenic to humans (Group 2A)*.

Personal use of hair colourants is *not classifiable as to its carcinogenicity to humans (Group 3)*.

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