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

## 1. Exposure Data

### 1.1 Historical perspective

The history of the development and use of cosmetics has been reviewed (Zviak, 1986a,b). The dyeing of human hair can be traced back at least 4000 years: evidence from Egyptian tombs indicates the use of henna, from *Lawsonia inermis*, for dyeing hair, nails and skin, and there is evidence in other early eastern Mediterranean cultures of the use of henna and indigo for dyeing hair. During the time of the Roman civilization, a number of methods were used for colouring hair; one was the use of lead combs dipped in vinegar (presumably producing lead acetate), and another was the use of walnut stain. Pliny cited more than 100 recipes for colouring hair with vegetable and mineral materials.

In England, the Elizabethans treated hair with potash alum (aluminium potassium sulfate) followed by a concoction of rhubarb in order to produce a red tone, which was popular because of the colour of the Queen's hair. At the time of the French Revolution, 24 million pounds [11 000 tonnes] of starch were sold each year in France for use in colouring hair. In this technique, starch, a binder and, possibly, small amounts of colouring material were applied to the hair.

Bleaching of hair has also been popular for many centuries. In order to mimic the appearance of their Anglo slaves, Roman women devised a method of bleaching their hair using a mixture of tallow soap and the ashes of burnt beech wood. In sixteenth-century Venice, women treated their hair with a caustic soda solution and spent many hours sitting in the sun to decolorize the melanin. In 1867, the French chemist, Léon Hugot, and the British chemist, E.H. Thiellay, demonstrated the use of hydrogen peroxide for bleaching hair at the Paris Exhibition. Cora Pearl, mistress of Napoleon III, is reputed to have bleached her hair with hydrogen peroxide.

Of the hair colouring products currently on the market, only henna and lead acetate have a history of more than 100 years. The modern hair colouring industry was born in the nineteenth century with the development of organic chemistry. In 1863, Haussman observed that a mixture of *para*-phenylenediamine and an oxidizing agent produced a coloured material. In 1883, the first patent for the exploitation of this observation in hair dyeing was acquired by Monnet, who actually used 2,5-diaminotoluene and hydrogen peroxide. Shortly thereafter, patents were obtained by H. and E. Erdmann over the period 1888–97 for the use as hair dyes of a wide variety of *para*-phenylenediamines and aminophenols with hydrogen peroxide (Anon., 1966).

## 1.2 Characterization of the exposures of hairdressers, beauticians and users of hair colourants

Professional hairdressers and beauticians who work in beauty salons (parlours) and barber shops typically shampoo, cut and style hair and apply hair colourants, waving and straightening preparations and conditioners. They may also be manicurists, trimming finger and toe nails and applying nail care products. The term 'barber' has traditionally been applied to professionals who cut men's hair; they may also apply hair sprays and other styling preparations and may shave men's facial hair. The terms 'hairdresser', 'beautician' and 'cosmetologist' appear to be used interchangeably. In the USA, for example, the terms 'hairdresser' and 'beautician' apply to people involved in the care of hair, primarily women's hair, in beauty salons; they exclude barbers. In the United Kingdom, the term 'hairdresser' is more inclusive: it is used to denote ladies' hairdressers, and it may also mean barbers.

In the USA in 1937, there were about 60 000 to 70 000 salons and close to 200 000 professional hairdressers and beauticians (McDonough, 1937). Today, there are about 150 000 salons and between 500 000 and 750 000 professional hairdressers and beauticians, of whom approximately 80–85% are women (Cosmetic, Toiletry, and Fragrance Association, undated). In Europe, there are between 350 000 and 400 000 salons in which about 1 200 000 professional personnel work, not including manicurists.

Over 5000 different chemicals are currently used to make beauty products worldwide (Cosmetic, Toiletry, and Fragrance Association, 1991). Beauty products are manufactured by a few large companies, which make the majority of products used personally and professionally, and by many small companies which formulate products for professional trades. The various categories of products used by hairdressers are described in general terms below. The products are principally hair preparations but also include nail care products and, occasionally, skin care products. Although one of the focuses of this monograph is hair colourants, an enormous range of chemical substances may be present in beauty salons. Rather than attempting to list all of the chemicals that are or have been used in beauty products, this section gives the general composition of each type of product and examples of typical chemicals or chemical classes. Those compounds that have been evaluated in the *IARC Monographs* series are listed in Table 1.

Few actual measurements of the exposures of professional hairdressers are available. Use patterns provide a qualitative picture of the potential exposures of both hairdressers and clients. Information on skin penetration and inhalation is mentioned (see also section 4.1), although many hairdressers now use gloves for some operations, to reduce dermal exposure. In Finland, however, it was estimated that only about one-third of hairdressers currently use protective gloves when dyeing hair (Pukkala *et al.*, 1992). The method of dye application may affect exposures; for example, permanent cream dyes are commonly applied with a brush, whereas other dyes are more often worked into the hair by hand.

### 1.2.1 *Hair preparations*

The term 'hair preparations' covers all compounds used on the scalp and hair. The most important of these are hair colouring preparations (bleaches, dyes), cleansing and conditioning products (shampoos, conditioning agents), hair-styling preparations (setting

**Table 1. Compounds used by hairdressers, beauticians and consumers that have been evaluated in the *IARC Monographs* series**

| Compound | Product in which found | Overall evaluation of carcinogenicity to humans[a] | IARC Monographs | |
|---|---|---|---|---|
| | | | Volume | Year |
| 2-Amino-4-nitrophenol | Semi-permanent hair dyes | 3 | 57 | 1993 |
| 2-Amino-5-nitrophenol | Semi-permanent hair dyes | 3 | 57 | 1993 |
| 4-Amino-2-nitrophenol | Semi-permanent hair dyes | 3 | 16 | 1978 |
| Auramine | Brilliantines | 2B | 1 | 1972[b] |
| Butylated hydroxyanisole | Skin products | 2B | 40 | 1986 |
| Carbon blacks | Nail products | 3 | 33 | 1984[b] |
| Chlorodifluoromethane | Hair sprays | 3 | 41 | 1986[b] |
| Chromium oxides | Nail products | 1 or 3 | 49 | 1990 |
| Chrysoidine | Brilliantines | 3 | 8 | 1975[b] |
| CI Disperse Blue 1 | Semi-permanent hair dyes | 2B | 48 | 1990 |
| Coal-tars | Shampoos | 1 | 35 | 1985[b] |
| Cobalt salts | Temporary hair dyes | 2B | 52 | 1991 |
| D&C Red No. 9 | Temporary hair dyes | 3 | 57 | 1993 |
| 2,4-Diaminoanisole | Permanent hair dyes | 2B | 27 | 1982 |
| 2,4-Diaminotoluene | Permanent hair dyes | 2B | 16 | 1978 |
| 2,5-Diaminotoluene | Permanent hair dyes | 3 | 16 | 1978 |
| Dichloromethane | Hair sprays | 2B | 41 | 1986[b] |
| *para*-Dimethylaminoazobenzene | Brilliantines | 2B | 8 | 1975 |
| 1,4-Dioxane | Other exposures | 2B | 11 | 1976[b] |
| Ethanol | Setting lotions; hair sprays; nail products; skin products | Inadequate in experimental animals | 44 | 1988 |
| Formaldehyde | Shampoos; nail products | 2A | 29 | 1982[b] |
| HC Blue No.1 | Semi-permanent hair dyes | 2B | 57 | 1993 |
| HC Blue No. 2 | Semi-permanent hair dyes | 3 | 57 | 1993 |
| HC Red No. 3 | Semi-permanent hair dyes | 3 | 57 | 1993 |
| HC Yellow No. 4 | Semi-permanent hair dyes | 3 | 57 | 1993 |
| Hydrogen peroxide | Bleaching agents; permanent-wave preparations | 3 | 36 | 1985 |
| Hydroquinone | Permanent hair dyes | 3 | 15 | 1977 |
| Iron oxide | Nail products | 3 | 1 | 1972[b] |

**Table 1 (contd)**

| Compound | Product in which found | Overall evaluation of carcinogenicity to humans[a] | IARC Monographs | |
|---|---|---|---|---|
| | | | Volume | Year |
| Isopropanol | Permanent hair dyes; nail products | 3 | 15 | 1977[b] |
| Lead acetate | Temporary hair dyes | 2B | 23 | 1980[b] |
| Methyl methacrylate | Skin products | 3 | 19 | 1979 |
| Mineral oils | Conditioning treatments | 1 | 33 | 1984[b] |
| Nickel salts | Temporary hair dyes | 1 | 49 | 1990 |
| 2-Nitro-*para*-phenylenediamine | Permanent hair dyes; semi-permanent hair dyes | 3 | 57 | 1993 |
| *N*-Nitrosodiethanolamine | Other exposures | 2B | 17 | 1978 |
| Phenacetin | Bleaching agents; permanent-wave preparations | 2A | 24 | 1980[b] |
| *meta*-Phenylenediamine | Permanent hair dyes | 3 | 16 | 1978 |
| *para*-Phenylenediamine | Permanent hair dyes | 3 | 16 | 1978 |
| Polyacrylic acid | Setting lotions | 3 | 19 | 1979 |
| Polyvinylpyrrolidone | Setting lotions; hair sprays | 3 | 19 | 1979 |
| Potassium bromate | Permanent-wave preparations | 2B | 40 | 1986 |
| Resorcinol | Permanent hair dyes | 3 | 15 | 1977 |
| Selenium disulfide | Shampoos | 3 | 9 | 1975 |
| Sodium bisulfite | Permanent hair dyes | 3 | 54 | 1992 |
| Sodium sulfite | Permanent hair dyes | 3 | 54 | 1992 |
| Titanium oxide | Nail products; skin products | 3 | 47 | 1989 |
| Toluene | Nail products | 3 | 47 | 1989 |
| Vinyl chloride | Hair sprays | 1 | 19 | 1979[b] |
| Xylene | Nail products | 3 | 47 | 1989 |

[a]For definitions of the groups represented by numbers and letters, see Preamble, pp. 28–30.
[b]Also evaluated in Supplement 7 to the *Monographs* series

lotions, hair sprays), permanent-wave preparations and hair-straightening preparations. In recent years, fashion trends have spurred the development of new products, such as high-hold hair lacquers and styling gels and dyes that give brilliant colours. Toxicological considerations have also become increasingly important in product formulation (Lang, 1989a,b).

(*a*) *Hair colouring preparations*

(i) *Bleaching*

Bleaching has two objectives: to give hair a lighter look or, more often, to prepare it for application of a dye preparation, generally yielding a shade lighter than the natural one (Zviak, 1986a).

The chemistry of bleaching is described in detail by Zviak (1986a). All of the bleaching methods used currently are oxidation processes. Hydrogen peroxide is the commonest oxidant and is used usually as a 6 or 9% solution or, rarely, as a 12% solution. Solutions are normally preserved with phosphoric acid, quinine sulfate, pyrophosphates, acetanilide, phenacetin, *ortho*-oxyquinoline sulfate, ethylene diaminetetraacetic acid and certain stannates. Hydrogen peroxide can be used alone to bleach hair, but in hairdressing salons it is mixed with an alkaline solution, typically ammonia, before use, in order to accelerate the process.

Persulfates are often used in the formulation of bleaching powders that are mixed with hydrogen peroxide just before use, particularly as the sodium, potassium and ammonium salts; sodium percarbonate is used occasionally, diluted in water or hydrogen peroxide just before use; sodium perborate and magnesium perborate are rarely used; and magnesium dioxide and barium dioxide are sometimes present in bleaching powders. Bleaching formulations are available in several forms: hydrogen peroxide solutions and emulsions, creams, shampoos, powders, pastes and oils (Zviak, 1986a).

In order to remove permanent and semi-permanent hair colourings, hairdressers use reducing agents (sodium hydrosulfite or sodium or zinc formaldehyde sulfoxylate dissolved just before use in acidified water) or high-strength oxidants such as those mentioned above (Zviak, 1986a).

(ii) *Dyeing*

The world market for hair colouring products is in excess of US$ 2500 million in factory sales. About one-third is bought by salon owners and the remainder by retail outlets for home use. The major markets are North America, Europe and Japan, each having US$ 300–900 million in factory sales. Retail sales represent 50–75% of the total business, being highest in North America and the United Kingdom and lowest in Italy, Spain and Australia.

The types of hair colourants are classified according to the permanence of the effect, i.e., temporary, semi-permanent or permanent, or to the type of ingredients that they contain. Only permanent and semi-permanent hair colourants are used to a significant extent in the hairdressing trade, whereas all three classes are used extensively by consumers.

In Europe and in North and South America, permanent dyes dominate the market, representing about 70% of the dollar volume of the retail market (Corbett, 1988) and 85% of the professional market. In Japan and parts of Asia, permanent dyes comprise an even

greater share of the market. Semi-permanent dyes were introduced into Europe about 40 years ago and into the USA some 35 years ago. Temporary hair colourants are somewhat older but have rarely represented more than 5% of the market.

*Permanent dyes* (Zviak, 1986c): Permanent hair dyes, otherwise known as oxidation dyes, represent the major segment of the hair dye market. The hair is dyed by oxidation of dye precursors which penetrate the hair fibre, where they react with hydrogen peroxide to produce coloured indo dyes. Since hydrogen peroxide is an excellent decolorizing agent for melanin, the hair's natural colouring matter, manufacturers can balance the amounts of hydrogen peroxide and of dye precursors in such a way as to produce lightening, darkening or matching of the natural colour of the hair.

The dye precursors used in the permanent hair colour are of two types: 'primary intermediates', generally *para*-phenylenediamines or *para*-aminophenols, which undergo oxidation to produce highly reactive benzoquinoneimines; and compounds known as 'couplers' which react with these imines to produce a variety of indo dyes. Compounds used as couplers include resorcinol, *meta*-aminophenol, *meta*-phenylenediamine and certain other reactive intermediates such as 1-naphthol and phenylmethylpyrazolone. Permanent hair colouring preparations may contain as many as 15 different dyes and dye precursors so that they will produce the desired shade. Dye precursors are formulated in ammoniacal or detergent solutions. Two typical formulations of permanent hair colours are presented in Table 2, and oxidation dye precursors used in the USA and Europe are listed in Table 3.

**Table 2. Ingredients of two typical hair colouring products**

| *Light blond* | *Bronze (reddish)* |
|---|---|
| Water | Water |
| Coconut acid diethanolamide | Oleic acid |
| Butoxyethanol | Isopropanol |
| Polyethyleneglycol-2 tallow amide | Nonoxynol-1 |
| Ethanol | Propylene glycol |
| Polyglyceryl-4 oleyl ether | Ethoxydiglycol |
| Oleyl alcohol | Nonoxynol-4 |
| Polyglyceryl-2 oleyl ether | Ammonium hydroxide |
| Propylene glycol | Linoleic acid diethanolamide |
| Oleic acid | Sodium lauryl sulfate |
| Sodium monodiethylaminopropyl cocoaspartamide | Sulfated castor oil |
| | Ethoxylated cetylalcohol-24 |
| Ammonium hydroxide | Ethoxylated cholesterol-24 |
| Pentasodium diethylenetriamine-pentaacetic acid | Fragrance |
| | Sodium sulfite |
| Ammonium acetate | Ethylene diaminetetraacetic acid |
| Sodium bisulfite | Erythorbic acid |
| Fragrance | *N,N*-Bis(2-hydroxyethyl)-*para*-phenylenediamine sulfate |
| Phenylmethylpyrazolone | |
| Hydroquinone | 2-Methylresorcinol |
| *para*-Phenylenediamine | 4-Amino-2-hydroxytoluene |
| Resorcinol | *para*-Aminophenol (4-aminophenol) |

**Table 2 (contd)**

| *Light blond* (contd) | *Bronze (reddish)* (contd) |
|---|---|
| *para*-Aminophenol (4-aminophenol) | *para*-Phenylenediamine (1,4-diaminobenzene) |
| *meta*-Aminophenol (3-aminophenol) | Resorcinol |
| 2,4-Diaminophenoxyethanol HCl | 1-Naphthol |

From Cosmetic, Toiletry, and Fragrance Association (1992)

**Table 3. Major oxidation dye precursors used in the USA and Europe**

5-Amino-2-methylphenol
2-Aminophenol (*ortho*-Aminophenol)
3-Aminophenol (*meta*-Aminophenol)
4-Aminophenol (*para*-Aminophenol)
*N*,*N*-Bis(2-hydroxyethyl)-*para*-phenylenediamine
2-Chloro-*para*-phenylenediamine
4-Chlororesorcinol
1,3-Diaminobenzene (*meta*-Phenylenediamine)
1,4-Diaminobenzene (*para*-Phenylenediamine)
2,4-Diaminophenol
2,4-Diaminophenoxyethanol
2,5-Diaminotoluene
*N*,*N*-Dimethyl-*para*-phenylenediamine
3-*N*-Ethylamino-4-methylphenol
7-Hydroxybenzomorpholine
5-*N*-(2-Hydroxyethyl)amino-2-methylphenol
*N*-Methyl-4-aminophenol
2-Methylresorcinol
1-Phenyl-3-methylpyrazolone-5
*N*-Phenyl-*para*-phenylenediamine
2-Nitro-*para*-phenylenediamine
Resorcinol

From Cosmetic, Toiletry, and Fragrance Association (1992)

Most of the more important ingredients in permanent dyes have been in use for over 50 years, although a few new ones were introduced during the last 20 years. The use of some ingredients has been discontinued, usually simultaneously in North America, Europe and Japan, as a result of findings in assays of carcinogenicity in rodents. For example, use of 2,4-diaminotoluene (4-methyl-*meta*-phenylenediamine) was discontinued in 1970–71 and that of 2,4-diaminoanisole (4-methoxy-*meta*-phenylenediamine) some six years later. For other reasons, *para*-phenylenediamine was not used in France or Germany from about 1905 to 1980-85, during which time 2,5-diaminotoluene (2-methyl-*para*-phenylenediamine) was used in its place.

The usual conditions of use for permanent hair colours involve the mixing of equal volumes of the hair colouring lotion containing the dye precursors and a hydrogen peroxide solution with a strength of 3 or 9%. About 100 g of this mixture (containing 0.1–3 g of dye precursors and 2–4 g hydrogen peroxide) are then applied to the hair and left in contact for 20–40 min. During that time, the colour develops and the natural hair pigment is lightened. The residual product is then removed from the hair by rinsing.

Permanent colouring materials occur in a number of different forms: liquids, creams, gels, shampoos and powders. The first oxidation dyes were simple, aqueous solutions, but they were replaced by aqueous alcoholic dyes (15–20% alcohol), as the added alcohol enhanced penetration of dye precursors into the hair fibre. Liquid dyes have been replaced by cream- or gel-based formulae. Cream dyes are emulsions formed from self-emulsifying raw materials, such as fatty oxyethyleneated alcohols (partially sulfated or not), fatty amides and oxyethylated vegetable oils. Emollients such as lanolin derivatives, fatty alcohols and cation-active compounds may be added. Gel dyes (or, more properly, gelling dyes) offer the advantages of both liquids and creams. A number of formulations exist, but the following are typical: (i) soap solutions, generally ammonium oleate; (ii) solutions of low oxyethylated nonionic surfactants, most often polyoxyethylated alkylphenols; and (iii) anion–cation complexes in solution. 'Shampoo-in colours' are a simplified form of the usual permanent dye products, except that the vehicle is, or acts like, a shampoo. These materials colour and bleach less than other permanent dye products. Shampoo-in colours are the permanent dyes intended particularly for home use; they are also used in hairdressing salons, as fast-acting, permanent dye products, especially for producing dark shades or for 'tone-on-tone' shading. Powder dyes contain very stable oxidizing agents, such as sodium perborate, in powder form, and only non-lightening shades can be formulated. This type of product is offered for domestic use in countries where the people's natural hair colouring is very dark, e.g., for black Africans and Japanese (Zviak, 1986c; Clausen, 1989).

Owing to the rate of hair growth (about 1.25 cm per month), regrowth of undyed hair becomes evident after about four to six weeks. Permanent hair colouring products are therefore used about six to nine times per year in Europe and North America. More frequent applications, 'touch-ups' around the hair line and parting, are common in Asian countries.

Potential exposures to *para*-phenylenediamine by inhalation in some hairdressing parlours in Italy were assessed recently by air sampling; all samples contained less than the detection limit of 1 $\mu g/m^3$ (Gagliardi *et al.*, 1992). Measurements of skin penetration of some oxidation dye precursors are discussed in section 4.1 of this monograph.

*Semi-permanent dyes*: The term 'semi-permanent' is used to define hair colouring products that last through 6–12 washings and do not involve the use of an oxidizing agent in colour development. That level of wash fastness is achieved by using low-molecular-weight dyes capable of penetrating the hair cortex. Semi-permanent hair colours contain direct dyes, which are generally nitro derivatives of phenylenediamines or aminophenols, together with a selected number of azo dyes and aminoanthraquinone dyes. Because the dyes in semi-permanent hair colours are preformed and do not require added oxidant, such products cannot lighten the natural hair colour.

Some typical formulations are presented in Table 4; semi-permanent dyes used in the USA and Europe are listed in Table 5. Henna, an orange-red hair colouring derived from the powdered leaves and stems of *Lawsonia inermis*, a tropical shrub, has been used since antiquity and is still used, by both professional hairdressers and consumers (Feinland *et al.*, 1980). The active colouring matter in henna is 2-hydroxy-1,4-naphthoquinone (Farris, 1979).

**Table 4. Ingredients of typical semi-permanent hair colouring products**

*Light blond*

Water
Ethoxydiglycol
Polyethyleneglycol-50 tallow amide
Hydroxyethylcellulose
Lauric acid diethanolamide
Aminomethyl propanol
Erythorbic acid
Fragrance
Oleic acid
Triethanolammonium dodecylbenzenesulfonate
CI Disperse Black 9
CI Disperse Blue 3
CI Disperse Violet 1
FD&C Yellow No. 6
HC Blue No. 2
HC Orange No. 1
HC Red No. 3
HC Yellow No. 2
HC Yellow No. 4

*Red*

Water
Ethoxydiglycol
Polyethyleneglycol-50 tallow amide
Hydroxyethylcellulose
Lauric acid diethanolamide
Aminomethyl propanol
Erythorbic acid
Fragrance
Oleic acid
Triethanolammonium dodecylbenzenesulfonate
CI Disperse Black 9
HC Orange No. 1
HC Red No. 1
HC Red No. 3
HC Yellow No. 2

*Reddish brown*

Water
Butoxyethanol
Coconut acid diethanolamide
Hydroxyethylcellulose
Lauric acid
*N*-Methylaminoethanol
HC Blue No. 2
2-Nitro-5-glyceryl methylaniline
Fragrance
Butylparaben
Ethylparaben
Methylparaben
Propylparaben
3-Methylamino-4-nitrophenoxyethanol
3-Nitro-*para*-hydroxyethylaminophenol
HC Yellow No. 6
CI Disperse Violet 1
2-Amino-3-nitrophenol
4-Amino-3-nitrophenol
CI Disperse Blue 1

*Dark brown*

Water
Butoxyethanol
Polyglyceryl-2 oleyl ether
Coconut acid diethanolamide
Hydroxyethylcellulose
HC Blue No. 2
Lauric acid
*N*-Methylaminoethanol
2-Nitro-5-glyceryl methylaniline
Fragrance
HC Violet No. 2
CI Disperse Blue 1
Butylparaben
Ethylparaben
Methylparaben
Propylparaben
HC Yellow No. 7

**Table 4 (contd)**

| | |
|---|---|
| | *Dark brown* (contd) |
| | 3-Methylamino-4-nitrophenoxyethanol |
| | CI Disperse Violet 1 |
| | 3-Nitro-*para*-hydroxyethylaminophenol |

From Cosmetic, Toiletry, and Fragrance Association (1992)

**Table 5. Semi-permanent dyes used widely in the USA and Europe**

| |
|---|
| 2-Amino-3-nitrophenol |
| 4-Amino-3-nitrophenol |
| CI Disperse Black 9 |
| CI Disperse Blue 1 |
| CI Disperse Blue 3 |
| CI Disperse Violet 1 |
| HC Blue No. 2 |
| HC Orange No. 1 |
| HC Red No. 1 |
| HC Red No. 3 |
| HC Red No. 7 |
| HC Violet No. 2 |
| HC Yellow No. 2 |
| HC Yellow No. 4 |
| HC Yellow No. 6 |
| HC Yellow No. 7 |
| HC Yellow No. 10 |
| HC Yellow No. 11 |
| 2-(N-Hydroxyethylamino)-5-nitroanisole |
| 4-β-Hydroxyethylamino-3-nitrophenol |
| 3-Methylamino-4-nitrophenoxyethanol |
| 3-Methylamino-4-nitrophenoxypropan-1,2-diol |
| 2-Nitro-*para*-phenylenediamine |
| Sodium picramate |

From Cosmetic, Toiletry, and Fragrance Association (1992)

The dyes used in semi-permanent colourants have been used for 30 years or less, which is shorter than for permanent dyes, except for a few of the direct dyes that were used as toners in permanent colourants (the unsubstituted nitrophenylenediamines and nitroaminophenols). Use of HC Blue No. 1 (see monograph, p. 129) was discontinued in 1985 and that of 4-amino-2-nitrophenol somewhat earlier. 2-Amino-4-nitrophenol and 2-amino-5-nitrophenol were prohibited from use in cosmetic products, including hair dyes, in the countries of the European Economic Community in 1990 (Commission of the European Communities, 1990, 1991).

Semi-permanent colouring products come in several forms. Colour rinses are the simplest means for altering hair colour: The hair is rinsed with a dilute aqueous or aqueous alcoholic dye solution. The dyes are generally cationic and are adsorbed by the hair surface. Coloured or tint setting lotions are also used as rinses and usually contain cationic, disperse and/or nitro dyes. More pronounced colour changes are possible with tints, which are formulated with direct dyes; intense colours can be obtained, especially with nitro dyes. With foam tints, a surfactant solution is dispensed as a foam from an aerosol. Tints can be also thickened with cellulose derivatives, natural mucilage or synthetic polymers. Concentrated solutions with intense colouring action can be obtained by using co-solvents (e.g., alcohols and ethylene glycol ethers) and vehicles (e.g., urea derivatives and benzyl alcohol). In emulsion tints, the dye base consists of an emulsion (Clausen, 1989).

Semi-permanent colours are applied at 35–60 g to the hair for 10–30 min, followed by rinsing. The colouring lotion contains 0.1–5% of dye and generally less than 1% of any individual dyestuff. Users either apply such products at least monthly or use them only on special occasions, for example, three to four times a year. Measurements of skin penetration of some semi-permanent dyes are discussed in section 4.1 of this monograph.

*Temporary dyes*: Temporary hair colouring products, often referred to as 'colour rinses', are products that produce colour that is removed by a single shampoo. They are normally formulated with water-soluble acid or basic dyes of the type used in wool dyeing, which have a molecular size too great to penetrate the cortex of the hair. As a result, the dye is deposited on the surface, from which it is easily removed by washing. Temporary colourants may also comprise systems which produce insoluble complexes of an acid dye as a quaternary ammonium or metal salt. One of the compounds included in this volume, D&C Red No. 9 (see monograph, p. 203), is used in temporary hair dye formulations as a pigment in the form of its barium salt (Corbett, 1988). A commercial dye formulation may contain between 0.5 and 2.0% of the permitted colour, together with surface-active agents. Temporary dye formulations may also contain nitro aromatics as colourants, together with anionic detergents and urea to increase the solubility. Temporary colourants are occasionally used in the hairdressing trade but are more commonly used directly by consumers at home. While there are few data on skin absorption, very little of such materials will pass through the skin owing to the relatively high molecular weight of the dyes.

Virtually no metal salt (e.g., lead acetate) is used for hair colouring in the hairdressing trade, as coloration with such products occurs gradually and they must be applied daily. Furthermore, the selection of colours available is limited, and the shades look metallic and unnatural. Metal salts are also incompatible with permanent waving and bleaching of hair (Clausen, 1989).

### (*b*) *Hair cleansing and conditioning preparations*

#### (i) *Shampoos*

Shampoos are cosmetic products for cleaning the hair and scalp. The word 'shampoo' is derived from a Hindi word meaning massage. Shampoos are the cosmetic products most often applied to the hair. Some of the characteristics considered in formulating modern shampoos are their ability to clean, to lather and to make the hair easy to comb, their capacity

to condition the hair, mildness (compatibility with skin, eyes and mucosa; no burning on the scalp or in the eyes), colour, appearance and fragrance (Lang, 1989a).

The principal constituents and most important raw materials of shampoos are surfactants, and nearly all modern shampoos are aqueous surfactant preparations. Surfactants break the bonds between dirt and hair components and suspend the dirt in the aqueous medium (Lang, 1989a).

Bar soaps were probably used for washing hair from about 1800, when they first became available, until the 1930s and 1940s, when liquid soaps and cream shampoos were introduced. The first surfactants used for hair cleansing were fat soaps. In hard water, however, soaps create a deposit of calcium and magnesium fatty acid salts on the hair, so their use must be followed by treatment with an organic acid, such as citric or acetic acid. Another drawback is the alkaline pH of soap, which may increase the swelling of hair. In order to meet the requirements of high cleansing power, good lathering and safety (for the user and for the environment), modern shampoos are formulated mainly with anionic surfactants. Amphoteric surfactants are also used, whereas nonionic and cationic surfactants play only secondary roles in special-purpose formulations (Lang, 1989a).

The most important anionic surfactants used in shampoos are alkyl sulfates (ammonium lauryl sulfate), alkyl and alkylaryl sulfonates, olefin sulfonates, secondary alkyl sulfonates, alkyl ether sulfates, sulfosuccinates (disodium lauryl ether sulfosuccinate) and protein-fatty acid condensates (potassium coco-hydrolysed animal protein) (Lang, 1989a). Sulfonated oils, such as sulfonated castor, mineral and olive oils, were introduced for use in shampoos in the 1930s; their use continued into the 1950s, with declining popularity. Sulfated fatty alcohols were first introduced in Europe in the 1930s and in the USA late in the 1930s in salon products and some retail products. By 1957, 70% of the shampoos used in the USA were based on synthetic detergents such as sodium lauryl sulfate and triethanolamine lauryl sulfate, and those two detergents are still commonly found in salon shampoos (McDonough, 1937; Wall, 1954; Powers, 1972). The trend in the late 1950s was to increase the use of liquid shampoos over that of creams, and there was then a movement to use of ammonium lauryl sulfate, introduced in the early 1970s, and laurylether sulfates. Laurylether sulfates are the preferred detergents in Europe.

Amphoteric surfactants used in shampoos can be divided into two classes: betaines (coco-amidopropylbetaine) and alkyl amphoglycinates and alkyl amphopropionates (coco-amphocarboxyglycinates and coco-amphocarboxypropionates). Cationic surfactants have a positive charge and are strongly absorbed by the hair. Only a few special-purpose shampoos, especially those for the treatment of severely damaged hair, contain these compounds. The nonionic surfactants in use are polysorbates (Polysorbate 20, Polysorbate 80) and fatty alcohol ethoxylates and polyglycerides (Lang, 1989a).

Another important class of constituents of shampoos is foam builders, typified by the fatty acid mono- and dialkanolamides (Lang, 1989a) introduced in the late 1930s. By the mid 1950s, virtually all liquid shampoos based on lauryl sulfates contained alkanolamides. Two types of amides are used. Condensation of 1 mol of fatty acid with 1 mol of an alkanolamine such as diethanolamine gives a water-soluble product; condensation of 1 mol of fatty acid with 2 mol of diethanolamine gives a more water-soluble product. The 2:1 types of alkanolamides can have appreciable levels of free alkanolamine, fatty acid amide and free

fatty acids. Some of the commonest examples of these constituents are the amides derived from reaction of diethanolamine with lauric acid and with coconut oil fatty acids (Kritchevsky, 1937; Barker, 1985).

Other constituents of shampoos include: refatting agents, conditioning additives (cationic polymers such as quaternary hydroxyalkyl celluloses), thickeners (salts such as sodium and ammonium chloride in combination with amphoteric surfactants), opacifiers (fatty acid alkanolamides in mixtures with ethylene glycol monostearate and distearate or cetyl alcohol and stearyl alcohol), colouring agents, fragrances and buffers (pH stabilizers, such as citric, tartaric, adipic and phosphoric acids and their salts). The preservatives added to shampoos today include formaldehyde and its donors and isothiazolinones, introduced in the 1980s. From the 1930s to the mid-1960s, the main preservatives were parabens and phenylmercuric acetate (Liem, 1977), which was banned in the late 1960s (Feinland *et al.*, 1980; Lang, 1989a).

Shampoos may be clear, opaque or pearly liquids, gels or aerosols. Shampoos with special additives include those for frequent use and for babies, conditioning shampoos, antidandruff preparations, shampoos for oily hair, tinting shampoos and those containing insecticides. Shampoos for frequent use and for babies contain especially mild surfactants (e.g., sulfosuccinate esters, magnesium ethyl ether sulfates) or mixtures of anionic, amphoteric and sometimes nonionic surfactants. Conditioning shampoos are used to make the hair easy to comb in the wet state and glossy and soft when dry. These effects are provided chiefly through the addition of cationic polymers; addition of amphoteric surfactants or refatting agents can improve the conditioning qualities of anionic surfactant formulations. Antidandruff shampoos contain agents that reduce excessive scalp flaking to a normal level. The most important antidandruff ingredients are zinc pyrithione, Octopirox (1-hydroxy-4-methyl-6-[2,4,4-trimethylpentyl]-2[1*H*]-pyridone) and Climbazole (Baypival; 1-[4-chlorophenoxy]-1-[1-imidazolyl]-3,3-dimethyl-2-butanone) (Lang, 1989a). Coal-tar formulations (Weinberg, 1980) and selenium disulfide have also been used extensively, but their use is regulated in some countries.

### (ii) *Conditioning agents and treatments*

Hair can be damaged in a number of ways: by climatic effects such as humidity and temperature extremes (weathering); by exposure to sunlight; by washing with products containing surfactants; by cosmetic treatments, such as bleaching, dyeing, permanent waving and straightening; and by combing and brushing. These processes alter the physical, chemical and morphological properties of hair as well as its reaction to cosmetic treatments such as dyeing and permanent waving. They lead to perceptible roughening of the hair surface, difficulty in combing, tangling, increased static charge, formation of split ends and loss of natural lustre. Hair conditioning agents prevent, retard or mask such changes. Their action is restricted largely to modifying the surface qualities of the hair and making it glossy. Nearly all modern shampoos, permanent wave lotions, setting lotions and dyes contain conditioning additives that prevent excessive mechanical damage to the hair. This simple type of conditioning may not be sufficient for severely damaged or long hair, and special conditioning treatments are available for such cases (Lang, 1989a).

The earliest conditioning treatments were waxes and oils (vegetable and mineral oils, petrolatum), which provided lubrication and enhanced lustre, and acid rinses (lemon juice, vinegar), which counteracted the undesirable effects of soap shampoos. During the 1940s and 1950s, these ingredients were combined with surfactants in anionic emulsions as after-shampoo rinses. Alkaline rinses included water-softening ingredients such as borax and trisodium phosphate (Wall, 1954).

In the mid-1940s, the quaternary ammonium compound, stearyl dimethyl benzyl ammonium chloride, began to be investigated for use as an after-shampoo treatment. By the early 1960s, almost all after-shampoo conditioners contained quaternary ammonium compounds as cationic surfactants. Typical quaternary compounds in current use include cetyldimethylammonium chloride and cetyltrimethylammonium chloride, sometimes in formulations with fatty alcohols such as cetylstearyl alcohol or with simethicone (Lang, 1989a).

Cationic polymers can also be used in conditioning treatments, together with special ingredients such as antidandruff additives. The addition of special wax components yields pearly preparations; if water-insoluble components are omitted and cationic polymers are added, the formulae obtained are transparent and clear. Conditioning treatments are generally rinsed out after they have been allowed to work for a defined time; however, some newer products with a lower content of active ingredients can be left on the hair without rinsing (Lang, 1989a).

### (c) *Hair-styling preparations*

Styling preparations stabilize a hair-style during or after its creation with comb, brush or rollers, usually as a temporary set. Styling products may also make hair easier to manage, for example, by facilitating wet combing and brushing. The products are mainly setting lotions and hair sprays. Newer products developed in response to fashion changes are 'wet gels' and 'hair waxes', which were developed from the brilliantines, pomades and hair creams used formerly. Styling preparations are generally left on the hair and are not rinsed out. Their active ingredients are usually dissolved polymers, known as film-forming agents, which are deposited on the hair after evaporation of a solvent (Lang, 1989b).

#### (i) *Setting lotions*

Setting lotions make a hair-style more durable and prevent hair from 'flying' away, reduce the amount of charge during combing and brushing, improve wet or dry combing and improve its feel and lustre. They may be applied before hair is wound on rollers and dried (wave sets) or before use of a hair dryer, brush or comb to style the hair (blow-dry sets) (Lang, 1989b).

The first preparations comparable to modern setting lotions were aqueous or aqueous alcoholic solutions and gels of natural substances, such as egg white, sugar solutions, plant mucilage (pectins, alginates, carrageenan, karaya gum, tragacanth) and beer. These products simply 'glued' the hairs together. They had the drawback of forming opaque, brittle residues which created dust during combing or brushing and became sticky in the presence of moisture. Modern setting lotions contain polymers (film-forming agents), solvents, agents to

facilitate combing, plasticizers, fragrances, colouring agents, ultra-violet radiation stabilizers, preservatives (if necessary) and other special ingredients (Lang, 1989b).

Film-formers are nonionic, anionic or cationic polymers dissolved in water or water-alcohol mixtures. Nonionic film-forming polymers include polyvinylpyrrolidone, the first polymer used for this purpose, and vinylpyrrolidone-vinyl acetate copolymers. Anionic film formers are vinyl acetate-crotonic acid copolymers or copolymers of methyl vinyl ether and maleic acid semi-esters. Both types of polymer are usually neutralized with organic amines such as 2-amino-2-methyl-1,3-propanediol, 3-amino-2-methylpropanol or triisopropanolamine. Other anionic polymers are terpolymers of vinyl acetate, crotonic acid and vinyl esters and graft polymers of vinyl acetate, crotonic acid and poly(ethylene oxide). Cationic polymers have an affinity for keratin, thus making the hair easier to untangle; they also prevent the accumulation of static charge during combing and brushing. The most important cationic film-forming polymers are quaternary vinylpyrrolidone–dimethylaminoethyl methacrylate copolymers (CTFA Polyquaternium 11), vinylpyrrolidone–vinylimidazole copolymers (CTFA Polyquaternium 16), cationic hydroxyethyl cellulose (CTFA Polyquaternium 10), poly(dimethyldiallylammonium chloride) (CTFA Polyquaternium 6), poly-(dimethyl–diallylammonium chloride) copolymers (CTFA Polyquaternium 7) and chitosan (obtained from chitin by alkali treatment) or its derivatives (Lang, 1989b).

The solvents used in setting lotions are water, ethanol, 2-propanol and their mixtures. Agents that facilitate combing include the cationic film-forming polymers listed above and cationic surfactants such as cetyltrimethylammonium chloride or bromide. Plasticizers enhance the flexibility of films formed on the hair. They include esters such as diethyl phthalate, diethyl citrate, adipates, silicones and polyglycols (Lang, 1989b).

Setting lotions are usually marketed as dilute, aqueous alcoholic solutions in single- or multiple-application packages. Depending on intended use, they contain 0.5–4% of polymers or polymer mixtures and up to 50% ethanol. Setting lotions for waving have a higher polymer content than those for blow-drying. Gels thickened by the addition of higher-molecular-mass polymers of the poly(acrylic acid) type are used far less frequently. Liquid lotions can also be packaged as aerosol sprays (propellant or pump spray). A novel form is the aerosol foam (mousse). Addition of adsorptive or penetrating dyes to setting lotions allows simultaneous hair colouring (Lang, 1989b).

(ii) *Hair sprays*

Aerosol spray-can products first came into widespread use in about 1948, on the basis of technology developed for insecticide applications during the Second World War. Hair sprays did not become practical until 'liquefied' gases with low vapour pressures became available. By virtue of the propellant liquid–gas equilibrium in the pressurized can, the pressure remains roughly constant during spraying. Pump sprays ('nonaerosol' sprays) do not use a propellant gas; the energy needed to swirl and atomize the concentrate is supplied by a manual pump. The ingredients of 'nonaerosol' hair sprays are generally the same as those of aerosol products, but the propellant content is replaced by additional solvent (Lang, 1989b).

The most important ingredients of hair sprays today are concentrates (film-forming agents, solvents, plasticizers, agents for lustre and fragrances) and propellants (Lang, 1989b). Hair spray products can be subdivided into six types on the basis of the hair fixative or

film-forming component: polyvinylpyrrolidone, a copolymer of polyvinylpyrrolidone and polyvinyl acetate, shellac, dimethylhydantoin–formaldehyde resin, modified polyacrylic acid resin and lanolin (Draize *et al.*, 1959).

The first film-forming agent, shellac, was superseded in the 1950s by polyvinylpyrrolidone. Better results are obtained with vinylpyrrolidone–vinyl acetate copolymers, the harder, more hydrophobic types being used for hair sprays. Still harder films can be obtained with vinyl acetate–crotonic acid copolymers. Copolymers of methyl vinyl ether and ethyl or butyl maleate and polyvinyl methyl ether/maleic anhydride–ethyl half-ester copolymers are used most often in the USA. More recently, acrylate–acrylamide copolymers (such as *tert*-butylacrylamide–ethyl acrylate–acrylic acid copolymers and octylacrylamide–acrylate copolymers), vinyl acetate–crotonic acid–vinyl neodecanate copolymers and vinylcaprolactam–vinylpyrrolidone–dimethylaminoethyl methacrylate copolymers have been used.

Ethanol, 2-propanol and acetone are the most important solvents in hair sprays. Dichloromethane has been used for many years (1965–89 in the USA) but is no longer used in some countries (including the USA) because of its toxicological properties (Lang, 1989b). Vinyl chloride was reportedly used to a limited extent as a solvent-propellant (US Consumer Product Safety Commission, 1974) before it was found to be a carcinogen (see IARC, 1979).

Until recently, the most common propellants in aerosol hair sprays were chlorofluorocarbons. Those most frequently used were trichlorofluoromethane (F-11), trichlorotrifluoroethane (F-113), dichlorotetrafluoroethane (F-114) and chlorodifluoromethane (F-22). By 1979, controversy about the possible action of these compounds on the Earth's ozone layer led to a ban on their use as propellants in the USA. International agreements and national legislation have led to a gradual abandonment of chlorofluorocarbons as propellants in Europe and elsewhere. Alternatives are the hydrocarbons propane, butane, isobutane, pentane and their mixtures, although they are highly inflammable and poor solvents for most polymers (Lang, 1989b).

Exposures to hair spray components in beauty salons have been estimated on the basis of both use patterns and direct measurements. The average spray release time per application is 10 sec, and about 10 g of spray are emitted during a spray period (Gerkens *et al.*, 1989). About 65% of the unimpinged spray has a particle diameter less than or equal to 10 μm, making the aerosol highly respirable. Half of the particle weight is solvent. It was estimated that 0.03–0.4 mg were inhaled over a 5-min period following 10 sec of spraying (Draize *et al.*, 1959).

Concentrations of dichloromethane in the air of beauty salons were reported in three studies: 8-h time-weighted average exposures were in the range of 1–6 ppm ($cm^3/m^3$) (Hoffman, 1973 (USA); Sayad *et al.*, 1976 (USA); Gerkens *et al.*, 1989 (Italy)). Average exposure to dichloromethane while spraying from an aerosol can during one 219-min period was 18 ppm in the breathing zone (Sayad *et al.*, 1976). Peak exposure concentrations up to 130 ppm (Hoffman, 1973) and more (< 400 ppm) were measured (Sayad *et al.*, 1976). Total particulate levels in personal samples in beauty salons ranged from 0.3 to 0.6 $mg/m^3$ (Palmer *et al.*, 1979).

Trace quantities of airborne polyvinylpyrrolidone (< 7 $\mu g/m^3$ to 0.07 $mg/m^3$), ethanol (< 7 $\mu g/m^3$ to 3 $mg/m^3$) and trichlorofluoromethane (3–41 $mg/m^3$) were found to be

associated with hair spray use in a beauty salon. Isobutane concentrations ranged from 373 to 1935 mg/m$^3$ (Gunter *et al.*, 1976).

(iii) *Other hair-styling preparations*

Brilliantine (pomade) is the oldest preparation for stabilizing styled hair. Colourants added to brilliantine in the past were reported to have included *N*,*N*-dimethyl-4-amino-azobenzene (*para*-dimethylaminoazobenzene; butter yellow), auramine and chrysoidine (Clemmesen, 1981; Gubéran *et al.*, 1985). 2-Naphthylamine has been found as an impurity in yellow AB and yellow OB, which have been used in cosmetics (Conway & Lethco, 1960; Gubéran *et al.*, 1985). Brilliantines consist mainly of vaseline and paraffin or other oils. The viscosity of the product and the hydrophobic layer with which it coats the hair are responsible for stabilization. These and similar formulations have reappeared on the market as hair waxes.

Setting gels are a new form of hair fixative. Fat-based gels are generally of the micro-emulsion type; aqueous gels are aqueous solutions thickened with poly(ethylene glycol), cellulose derivatives or polyacrylates and contain film-forming substances. They allow the creation of 'wet-look' hairstyles (Lang, 1989b).

Changes in fashion have meant that hair creams have lost much of their commercial importance. These products facilitate combing, add lustre and help to hold hair-styles. Creams include oil-in-water and water-in-oil types. Hair tonics refresh the scalp and serve as simple styling aids. They may also contain disinfectants, soothing, cooling or hair growth-promoting ingredients and anti-oil and antidandruff agents (Lang, 1989b).

(*d*) *Permanent-wave preparations*

In permanent waving, intermolecular and intramolecular bonds in the hair are broken and then reformed after the hair has been shaped (curled). The strongest bonds that are broken and reformed are the disulfide bonds of cystine; approximately 25% of the cystine bridges are reduced to cysteine. After the hair has been reshaped, this reaction is reversed with an oxidant. Hydrogen bonds, salt bridges and hydrophobic and van der Waals interactions between individual amino acids are also involved but are of lesser importance (Kohler, 1989a).

Modern permanent waving traces its roots to a London hairdresser named Nessler who in 1906 introduced heat treatment of hair soaked in borax. The treatment required a whole day and often resulted in burns and hair loss. During the next 35 years, the use of heat, with and without alkaline solutions, was perfected. The image from the 1920s and 1930s of a person sitting under a salon hair dryer represents the classic picture of someone receiving a salon wave. Alkaline solutions in combination with heat were developed, and special pads with strong exothermic reactions when moistened were introduced. In the early 1940s, sulfides were tried but were discontinued because of toxicity (Winkel, 1936; Willat, 1939; Thomssen, 1947; Gershon *et al.*, 1972; Zviak, 1986d).

It was also in the 1940s that thioglycolates were introduced. These preparations were called cold waves to differentiate them from earlier processes (Gershon *et al.*, 1972). Since the 1950s, most waving preparations have involved salts of thioglycolic (mercaptoacetic) acid as the principal reducing agents. Ammonium thioglycolate (concentration, 6–11%) has been

in constant use in salons since the late 1940s. In 1972, glyceryl or glycerol monothioglycolate was introduced in the USA and Canada. It was first used with heat (from a hair dryer), but by 1980 most such waves were processed without heat at a concentration of about 13%, expressed as thioglycolic acid (about 23% as glyceryl thioglycolate). Today glyceryl monothioglycolate waves account for about one-half of the 200 million waves done in salons in the USA each year. In Japan, cysteine is used in some waves, but the predominant waving material is still ammonium thioglycolate (concentrations up to 7%), as it is in Europe and elsewhere (Kohler, 1989a).

Ammonia and monoethanolamine are most commonly used for pH control (alkalinization) in waving preparations. Combinations of ammonium hydrogen carbonate and ammonium carbonate, or urea and the enzyme urease, are also used. Other additives include surfactants, fragrances, agents to facilitate combing (poly(dimethyldiallylammonium chloride), cetyltrimethylammonium chloride), thickeners (cellulose derivatives, polyacrylate salts), opacifiers (styrene–vinylpyrrolidone copolymers), colouring agents, carriers (urea, ethanol, 2-propanol) and complexing agents (Kohler, 1989a).

Waves must be 'neutralized' with an oxidizing agent. During 1940–70, potassium and sodium bromate were the chief agents used, at concentrations of 6–12%. Since then, hydrogen peroxide (at 0.5–3.0%) has been used in most parts of the world. In Asia, bromate-based neutralizers are used mainly, because they do not greatly lighten dark hair. Percarbamide (urea–hydrogen peroxide), sodium perborate and melamine peroxide hydrate have been used occasionally (Kohler, 1989a).

The most widely used preparations are those containing hydrogen peroxide, stabilized with inorganic phosphates, phenacetin, 4-acetaminophenol or α-bisabolol (a constituent of chamomile oil). The 'foam neutralizer' that is applied to curlers with a sponge and lathered into a foam is commonest; however, rinse and aerosol foam neutralizers are becoming increasingly popular (Kohler, 1989a).

A survey in the United Kingdom in 1992 of exposures of hairdressers during permanent waving showed ethanol at 2–30 mg/m$^3$, isopropanol at none detected to 9 mg/m$^3$ and ammonia at 5–25 mg/m$^3$. Dichloromethane was not detected (Rajan, 1992).

(*e*) *Hair-straightening preparations*

Preparations similar to those employed for permanent waving can be used to straighten naturally wavy or curly hair. Hair-straightening products are usually gels or creams rather than lotions. They contain strong bases such as alkali hydroxides (1.5–4.0 wt% lithium or sodium hydroxide) and other active ingredients such as guanidinium hydroxide and tetra-alkylammonium hydroxides. Lye-based products are so strong that they do not require oxidative post-treatment; however, improper use can easily make the hair brittle, and skin burns may even occur. In order to reduce such hazards, formulations have a high content of mineral oil (Kohler, 1989b).

### 1.2.2 *Nail products*

Nail-care products fall into three categories: coloured products; colourless products that include base coats, top coats and strengthener/hardener coats; and lacquer/enamel removers. The main ingredients of coloured and colourless nail-care products are:

nitrocellulose (10–15%), resins (5–15%), solvents (30–40%), diluents (20–30%), plasticizers (1–6%), suspending agents for colourants (0.7–3%) and colourants (3–5%). Nitrocellulose is used as a film-former in conjunction with a plasticizer to avoid shrinkage and brittleness; it is usually wetted with isopropanol for safety reasons. The function of resins is to produce adhesion to the nail and a glossy surface. Those most commonly used are toluene-sulfonamide/formaldehyde resin, polyester, polyamide (e.g., nylon) and acrylates and acrylics. The most commonly used solvents are ethyl acetate, butyl acetate, isopropanol and ethanol. Diluents help stabilize the viscosity of the formula. Those most commonly used are alcohols (ethyl, isopropyl, butyl), aromatic hydrocarbons (toluene, xylene) and aliphatic hydrocarbons (heptane). Plasticizers are used to achieve flexibility in the nitrocellulose film; the commonest are dibutyl phthalate and camphor. Dispersing agents help to keep colourants suspended; the commonest is stearalkonium hectorite. Colourants may be organic or inorganic and may include natural or synthetic pearl. The pigments used in nail lacquer formulations are carbon black, iron oxides, chromium oxides, ultramarines, metallic powders (gold, bronze, aluminium, copper), aluminium and calcium lakes of FD&C and D&C blue, red, yellow and orange, and titanium oxide. Transparent systems require the use of solvent-soluble colourants such as D&C red, green, yellow and violet. A typical nail lacquer formulation contains (% by weight): toluene, 30.5; *n*-butyl acetate, 12.8; *n*-amyl acetate, 11.1; ethyl acetate, 11.1; nitrocellulose, 10.0; aryl sulfonamide–formaldehyde resin, 10.0; isopropanol, 5.0; bentonite, 3.0; camphor, 2.5; dibutyl phthalate, 2.5; and ethanol, 1.5 (Isacoff, 1979). Nail hardeners usually contain an 'active' ingredient to strengthen the nail plate and include isobutyraldehyde, glutaraldehyde and sometimes formaldehyde.

A typical nail treatment, at home or in a salon, includes application of a base coat, two coats of lacquer (coloured product) and then a top coat. For added durability, an additional layer of each coat might be added. Typical drying time for a single layer is about 7 min; more time is needed between successive layers, because barriers to evaporation are created. A total nail treatment takes 1 h or more.

Lacquer/enamel removers may be made from any number of solvents, including any of those used in the formulation of the enamels. The fastest acting is acetone, but ethyl acetate is also used. Various oils and emollient compounds added to lacquer removers include castor oil, lanolins and lanolin derivatives. The formula of a typical nail polish remover is (% by weight): ethyl acetate, 40; acetone, 30; carbitol, 19; dibutyl phthalate, 10; sesame oil, 1; and a small amount of perfume. Cuticle removers and cuticle softeners usually consist of a dilute solution of alkali in water with some glycerol or other humectant added to keep the water from evaporating too rapidly. Potassium hydroxide, trisodium phosphate, triethanolamine and some quaternary ammonium salts have been used (Isacoff, 1979).

A quantitative evaluation of the exposure of manicurists during the production of synthetic fingernails showed 8-h time-weighted average exposures of 5.3 ppm methyl methacrylate, 7.3 ppm ethyl methacrylate and 1.6 ppm isobutyl methacrylate. Intermittent exposure to 9–48 ppm (average, 20 ppm) methyl methacrylate was measured during application, with peak exposures to up to 137 ppm (average peak, 54 ppm); intermittent exposure to ethyl methacrylate was 7–18 ppm (average, 13 ppm) and that to isobutyl methacrylate, 5–8 ppm (average, 6 ppm). The average time to create a full set of artificial

nails was 40 min (Froines & Garabrant, 1986). In another investigation of artificial nail application, personal exposures to methyl methacrylate were 15–25 ppm (Kronoveter, 1977).

### 1.2.3 *Skin products*

Skin preparations used in beauty salons comprise various lotions, creams, perfumes, colours, powders and soaps intended to beautify and improve the complexion of the skin, including colouring foundation creams, concealers/blemish-covering creams and solids, eyeliners, eyeshadows, face powders, facial colouring products (blush, powders, liquid make-up), facial masks and beauty packs, hair removers (depilatories), lipstick, mascara, moisturizing creams and lotions, skin cleansing creams and lotions and skin fresheners/-toners.

The typical chemical content of a clay mask is (%): water, 50–80; fillers (bentonite clay, kaolin, titanium oxide), 10–40; thickeners (algin, potassium alginate, magnesium aluminium silicate, carbomers), 0–10; humectants (glycerol, propylene glycol, lanolin, polyethylene glycol, sorbitol), 5–10; astringents and healing agents (zinc oxide, witch hazel extract), 0–5; emulsifiers (beeswax, magnesium aluminium silicate, polysorbates), 0–5; preservatives (citric acid, methyl and propyl parabens), 0–1.5; fragrance (essential oils), 0–1; and colourants, 0–0.1. The typical chemical content of paste and peel-off facial masks is (%): water, 50–75; film formers (hydroxyethylcellulose, polyvinylpyrrolidone–vinyl acetate, gums), 10–25; ethanol, 5–12; humectants and emollients (glyceryl stearate, polyethylene glycol stearate, glycerol, sorbitol, polysorbates, cetyl alcohol, stearyl alcohol, lanolin, beeswax), 0–5; clay (bentonite, kaolin), 0–5; preservatives (butylated hydroxyanisole, citric acid, methyl and propyl parabens), 0–0.1; fragrance (essential oils), 0–1; aloe plant gel; and colourants.

### 1.2.4 *Other exposures in beauty salons*

Nitrosamines have been found in a wide variety of cosmetic and toiletry products, including hair dyes, shampoos, rinses, conditioners and fragrance preparations. The use of 2-bromo-2-nitropropane-1,3-diol as an antibacterial and antifungal agent was associated with the highest concentrations, since it may act as a source of nitrosation of amines or amides (Fan *et al.*, 1977; US Food and Drug Administration, 1991). The commonest nitrosamine found is *N*-nitrosodiethanolamine. Between 1978 and 1980, the US Food and Drug Administration analysed more than 300 cosmetic samples for this compound and found concentrations of < 30 ppb in 7% of the samples, 30 ppb to 2 ppm in 26% and 2–150 ppm in 7% (US Food and Drug Administration, 1991). In 1986, 40% of samples of cosmetics and shampoos in Germany were found to be contaminated with *N*-nitrosodiethanolamine (up to 275 μg/kg) and *N*-nitrosobis(2-hydroxy-propyl)amine (20–30 μg/kg). The introduction of official recommendations by the German Federal Health Office in 1987 to stop use of secondary amines in cosmetic products led to a reduction in such contamination; only 15% of the products were contaminated in a 1987–88 survey (Eisenbrand *et al.*, 1991). These nitrosamines may be absorbed appreciably through human skin (US Food and Drug Administration, 1979; Marzulli *et al.*, 1981).

Formaldehyde is added to many cosmetic products, particularly shampoos, as an antibacterial agent and preservative. It is also used in processes for hair setting that employ

urea– or melamine–formaldehyde condensation products (Walker, 1975). Formaldehyde can also form during storage as a degradation product of materials containing polyethylene glycol (Fregert, 1986). Formaldehyde and formaldehyde donors, such as 1-hydroxymethyl-5,5-dimethylhydantoin, were found at levels of up to 0.5% in cosmetics (Liem, 1977). Concentrations of formaldehyde found in some specific products were: shampoo, up to 0.03%; hair rinse, 0.41%; bubble bath, 0.61%; and nail hardener, 7% (Wilson, 1974). Although formaldehyde is known to penetrate the skin and is volatile, no study was found that reported levels of exposure during the use of cosmetic products (Lodén, 1986a,b).

Paraformaldehyde may be used as a fumigant in towel cabinets, equipment drawers and cosmetic kits in beauty parlours and barber shops. Such use was found at one site to contribute to general air concentrations of formaldehyde of between 0.01 and 0.03 ppm [0.012 and 0.037 mg/m$^3$] (Almaguer & Blade, 1990). In area air samples in a high-school cosmetology laboratory, levels of 0.01–0.9 ppm [0.012–1.1 mg/m$^3$] formaldehyde were detected over a 6-h period (Almaguer & Klein, 1991). Short-term exposure to several parts per million of formaldehyde may be experienced when opening cabinets containing paraformaldehyde.

1,4-Dioxane is a common trace component of cosmetic products containing polyethoxylated surfactants, such as some shampoos and conditioners, hair dyes and skin conditioners. Of the cosmetic products tested, including shampoos, hair and body gels, liquid soaps, balms and foam preparations, 82% contained 1,4-dioxane in the range of 0.3–96 ppm [mg/kg or l] (Rastogi, 1990). In other evaluations, 48% of commercially available cosmetic products containing polyethoxylated surfactants contained 7–86 ppm [mg/kg] 1,4-dioxane (Scalia & Menegatti, 1991), and up to 613 ppm [mg/kg] was found in shampoo (Beernaert *et al.*, 1987). 1,4-Dioxane penetrates the skin (Marzulli *et al.*, 1981).

### 1.3 Consumer use of hair dyes

While permanent hair colours have been in use since the late nineteenth century, they were first applied only by professionals; retail consumer use became significant in the years following 1945. Subsequently, total use of hair colourings increased, until by about 1965 35–40% of women in the USA and Europe aged 18–60 were using them, and that prevalence has remained stable. Permanent hair colouring constituted > 90% of use until the introduction of semi-permanent dyes in the late 1950s. In Europe and the USA, semi-permanent dyes now represent about 20% of use, permanent dyes about 75% and temporary dyes about 5%. In Japan, mainly permanent colourants are used; the prevalence of use among women is similar to that in Europe and the USA.

In the USA and Europe, use of hair colourants among men is almost completely for grey coverage and is mainly among men over 40 years of age. No published data are available, but it is unlikely that more than 10% of men aged 35–60 use hair colourants. Progressive colourants (see below) have been used by about 80% of male users (Zahm *et al.*, 1992). Use of hair colouring materials is believed to be greater among Japanese men than among US and European men.

The products used by hairdressers and beauticians are, with few exceptions, similar to the retail products sold for home use. Thus, consumers are exposed potentially either in

beauty salons or during home use of the products to a similar range of chemical substances as are hairdressers and beauticians. The frequency and duration of exposure, however, may be quite different for consumers and professionals.

As noted above, one class of hair colouring products that is not used in beauty salons is the metal salts used as temporary hair colourants. This practice is as ancient as the use of vegetable dyes, but metal salts are rarely used today except by people who do 'progressive' colouring, involving daily applications of the product. Metal salts used as temporary hair colourants are, for the most part, lead and silver salts; occasionally, copper, nickel, bismuth, cobalt and manganese salts are added to solutions to vary shades. While there is still some uncertainty about how these dyes work, it is thought that the hair shaft is coloured by reaction of the metallic salt with keratin sulfur, depositing a metallic sulfide. In addition, it is thought that some of the colour is attributable to slow formation of metallic oxide. Lead salts commonly used for this purpose are the acetate and the nitrate. Sometimes, finely divided sulfur is added to formulations. Silver nitrate, used since the beginning of the nineteenth century, has a dual mode of action, in that the silver salts darken when exposed to light, and silver combines with protein, yielding a dark-coloured proteinate. A rapid colouring process has also been used (e.g., on eyelashes and eyebrows) in which a solution of trihydroxybenzene is applied, followed by ammoniacal silver nitrate (Zviak, 1986b).

### 1.4 Regulatory aspects

A detailed discussion of the laws and regulations related to toiletry and cosmetic products is presented by Zviak and Camp (1986). In order to authorize, restrict or ban the use of substances in cosmetic products, some countries have set up negative and positive lists or derogatory and restrictive lists. A negative list comprises substances that cannot be part of a cosmetic composition; a positive list includes only substances authorized for a definite purpose. When a positive list is adopted, any other substance is banned for the said purpose. A derogatory and restrictive list covers substances outside the scope of negative lists for certain types of use and/or within certain concentration limits, or a list of substances the use of which is permitted only under certain conditions (e.g., ingredient warning labelling).

General provisions for cosmetic products, including hair-care products, are compiled in the Council Directive of the European Economic Community (EEC) of 27 July 1976 on the Approximation of the Laws of the Member States Relating to Cosmetic Products (Commission of the European Communities, 1976), which is amended constantly. Hair-care products include hair tints and bleaches; products for waving, straightening and fixing; setting products; cleansing products (lotions, powders, shampoos); conditioning products (lotions, creams, oils); and hairdressing products (lotions, lacquers, brilliantines). The Directives include: lists of substances that must not form part of the composition of cosmetic products; lists of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down; lists of colouring agents allowed for use in cosmetic products; lists of colouring agents provisionally allowed for use in cosmetic products; lists of preservatives which cosmetic products may contain; and lists of ultraviolet radiation filters which cosmetic products may contain. Oxalic acid, its esters and alkaline products, hydrogen peroxide, 1,3-bis(hydroxymethyl)imidazolidine-2-thione, quinolin-8-ol, bis(2-hydroxyquinolium) sulfate

and etidronic acid and its salts are permitted in hair-care products with restrictions on concentrations (Commission of the European Communities, 1990). Some countries of the EEC, however, such as France, Denmark and Italy, depart from the EEC Directive regarding restrictions and labelling requirements. In Greece, cosmetics must be registered. Spain requires government notification before a product is marketed. In Germany, hair preparations are classified as cosmetics and subject to legal provisions (Liebscher & Spengler, 1989). Under the EEC Cosmetics Directive, cosmetics must not be liable to endanger human health when applied under normal conditions of use (Commission of the European Communities, 1990, 1991, 1992). The cosmetic regulations in Norway, Finland and Turkey are closely modelled on the EEC Directive (Liebscher & Spengler, 1989).

In the USA, certain cosmetics are subject to registration as over-the-counter drugs. The list of cosmetic colour additives is very limited, and stringent purity standards must be observed. In preparations sold directly to the consumer, all ingredients must currently be listed on the label. Registration is required for cosmetics in Canada and in most countries of Latin America and Southeast Asia. In Japan, cosmetics are classified as quasi-drugs or cosmetics. New raw materials must be registered and extensive toxicological data submitted; human tests from other countries are not recognized (Liebscher & Spengler, 1989).

### 1.4.1 *Hair dyes*

2,4-Diaminoanisole and 2,5-diaminoanisole, 1,2-diaminobenzene (*ortho*-phenylenediamine) and 2,4-diaminotoluene (4-methyl-*meta*-phenylenediamine) and their salts, 2-amino-4-nitrophenol and 2-amino-5-nitrophenol, are banned in the EEC. Other diaminobenzenes and diaminotoluenes, as well as their *N*-substituted derivatives and their salts, diaminophenols, hydroquinone, α-naphthol and resorcinol are permitted, with restrictions on concentrations. With the exception of α-naphthol, these substances may be used for dyeing eyelashes and eyebrows by professionals only. Lead acetate is permitted for hair dyeing only at a concentration of 0.6% calculated as lead; it is not allowed for dyeing eyelashes, eyebrows or moustaches. Warning labels are also prescribed (Commission of the European Communities, 1990, 1992). In addition to the EEC provisions, 1,4-diamino-2-nitrobenzene and 1,2-diamino-4-nitrobenzene are banned in Italy and Denmark, and 1,3-diaminobenzene is also banned in Denmark. The USA requires a special warning label; with the label, any hair dye can be used without restriction. In Japan, a list of permissible hair dyes is issued; new dyes must be registered (Liebscher & Spengler, 1989).

### 1.4.2 *Shampoos*

The general provisions stated above apply to shampoos in the EEC countries. Furthermore, phenol and its alkali salts, quinine and its salts and selenium disulfide are permitted with restriction on concentrations (Commission of the European Communities, 1990). Antidandruff shampoos are classified as over-the-counter drugs in the USA and as quasi-drugs in Japan (Liebscher & Spengler, 1989). Quinine and its salts are permitted in hair lotions at a concentration of 0.2% calculated as quinine base in the finished product (Commission of the European Communities, 1990).

1.4.3 *Bleaching preparations*

In the EEC, persulfates can be used without restriction. Argentina and Thailand limit their concentration, and in Finland a warning label is required for ammonium persulfate. The USA does not have any specific regulations for this group (Liebscher & Spengler, 1989).

1.4.4 *Permanent-wave preparations*

The EEC Directive restricts the pH range of permanent-wave preparations and hair straighteners based on thioglycolic acid, its salts and esters (pH 7–9.5 or 7–12.7 for the acid and salts, 6–9.5 for esters). The maximal concentration (calculated as thioglycolic acid) is 8% by weight for general use, and 11% by weight at pH 7–9.5, 5% at pH 7–12.7 for the acid and salts and 11% at pH 6–9.5 for esters for professional use. A special warning label is required. Potassium and sodium hydroxide are permitted with a restriction on concentration in hair straighteners (Commission of the European Communities, 1990). France further restricts permanent-wave and straightening preparations made from thioglycolic acid, its salts and esters to professional use only. In the USA, no legal restriction is known. Because of self-imposed industry restrictions, however, the thioglycolic acid content does not exceed 14% by weight at a pH of not more than 9.5. In Japan, permanent-wave products are classified as quasi-drugs. Thioglycolic acid and its salts are permitted, as is cysteine, with restrictions on concentration and pH. Thioglycolate esters are not allowed. Concentration limits also apply to neutralizers (Liebscher & Spengler, 1989).

1.4.5 *Hair sprays*

In the EEC, dichloromethane is allowed as a solvent up to a concentration of 35% by weight in the finished product. When dichloromethane is mixed with 1,1,1-trichloroethane, a total concentration of both is limited to a maximum of 35% by weight (Commission of the European Communities, 1990). Chlorofluorocarbons are now being phased out in most parts of the world in accordance with the 'Montreal Protocol', as amended in London in 1990 and in Copenhagen in 1992 (see US Environmental Protection Agency, 1993).

1.4.6 *Nail hardeners*

Formaldehyde is permitted at a concentration of 5% in the finished product. Potassium and sodium hydroxide are permitted in nail cuticle solvent at the same concentration (Commission of the European Communities, 1990).

## 2. Studies of Cancer in Humans

The available studies relate to exposures that occurred at different times over the last 30 years or more, during which period there were changes in both the types and quantities of products used by hairdressers and barbers and by the consumer (Wall, 1972).

### 2.1 Occupational exposure

2.1.1 *Descriptive studies*

Cancer mortality among men and single women in England and Wales was examined for the period 1949–53 (Registrar General, 1958). For male barbers and hairdressers, the sites

examined were all sites, stomach, lung and leukaemia. Lung cancer occurred in excess (standardized mortality ratio [SMR], 1.15; 114 observed, 99 expected); for cancers at all sites, there were 257 observed and 273 expected. For single female hairdressers and manicurists, the numbers of observed deaths exceeded those expected for cancers at all sites combined (43 observed, 37 expected) and for cancers of the lung and bronchus (4 and 2), breast (13 and 9) and cervix uteri (4 and 1).

Similar data from the Registrar General (1971) for the period 1959–63 showed no significant excess mortality from cancers at all sites or from lung or stomach cancers or leukaemia among male hairdressers and barbers. Among single female hairdressers and manicurists, there were 21 observed deaths from breast cancer, with 12 expected ($p < 0.05$); for cancers of the cervix uteri and other parts of the uterus the ratios of observed to expected deaths were 3:2 and 4:2, respectively. A further report from England and Wales (Office of Population Censuses and Surveys, 1978), in which occupational mortality for the period 1970–72 was analysed, did not indicate a significant excess of any of the above cancers in men or in women in those occupations, including breast cancer among single female hairdressers and manicurists (eight observed, seven expected).

In the latest report in this series (Office of Population Censuses and Surveys, 1986), covering the years 1979–80 and 1982–83, male barbers in England and Wales were reported to have had increased mortality from cancers at all sites at ages 15–64 (45 deaths, 21.6 expected) and from lung cancer (21 deaths, 7.9 expected). Nonsignificant increases were seen for cancers of the lip, oesophagus, stomach, colorectum, prostate and bladder and for Hodgkin's disease and leukaemia, all based on five cases or fewer. Single female hairdressers also showed a significant excess of cancers at all sites at ages 15–64 (22 observed, 9.2 expected; $p < 0.01$) and of cancer of the breast (7 observed, 1.6 expected; $p < 0.05$). Nonsignificant excesses were seen for cancers of the stomach, colorectum, cervix, ovary and brain and for malignant melanoma, which were based on few cases.

Clemmesen (1977) studied the incidence of malignant neoplasms in the period 1943–72 among hairdressers in Denmark on the basis of the numbers recorded with this occupation in successive censuses. Among male hairdressers, 447 malignant neoplasms were observed, with 517.4 expected (Clemmesen, 1981). There was no excess in any of 13 groupings of cancer sites. In women, there was a large overall excess, with 872 malignant neoplasms observed and only 475.4 expected, which appeared in each five-year period and for each of 14 site groups. [The Working Group noted that the consistent excess of cancers at markedly different sites in women in this study suggests use of different criteria for reporting women's occupation as hairdresser at the census and in hospital records.]

Garfinkel *et al.* (1977) analysed a series of death certificates with mention of cancer covering Alameda County, California, USA, in the period 1958–62. Of 3460 such deaths in females, 24 occurred in beauticians, at the following sites: lung (6), breast (5), cervix (4), ovary (3), brain (1), bladder (1), stomach (1), synovium (1) and unspecified (2). An expected number of 21.8 cancers was calculated for beauticians on the basis of 1000 death certificates for women of similar age and race which had no mention of cancer (24 observed; $p = 0.43$). When women who had died from causes other than cancer were matched to those who had died from lung cancer by age, race, date of death and county of residence, of 176 lung cancer

cases, six were in beauticians, compared with one among the 176 controls. The relative risk (RR) was 6.0, with a one-tailed $p = 0.06$.

Menck *et al.* (1977) used data on 15 230 men and 22 792 women, aged 20–64, white and with non-Spanish names, from the Los Angeles County (USA) Cancer Surveillance Program in 1972–75 to investigate the association of cancer with occupation reported at hospital admission. Of 135 cases of cancer found in female beauticians, 20 were of the lung. Proportionate incidence ratios (PIR) and standardized incidence ratios (SIR) were computed, the latter being derived from the sex-specific populations at risk by occupation as ascertained in a 2% sample census of Los Angeles County. Both the PIRs and SIRs for lung cancer among beauticians were significantly increased (about two-fold; $p < 0.05$). No data on smoking habits were available. The authors mentioned parenthetically, without giving details, that a case–control study of 199 lung cancer cases and 187 controls had shown a RR of 0.94 for beauticians, on the basis of six cases.

In a study of cancers registered in the Los Angeles (USA) Tumor Registry, in 1972–78, which partially overlaps with the above study, Guidotti *et al.* (1982) noted an excess of multiple myeloma in the category of cosmetologists, hairdressers and manicurists. The PIR was 4.67 in women, on the basis of eight cases, and 3.47 in men, on the basis of one case.

Milham (1983) studied the occupations of 429 926 men in Washington State, USA, who had died during 1950–79 and of 25 066 women who had died during 1974–79. Among male barbers (3014 deaths), the proportionate mortality ratio (PMR) was elevated for multiple myeloma. Among female hairdressers and cosmetologists (409 deaths), the PMRs were elevated for stomach cancer, other lymphomas, multiple myeloma, acute leukaemias and neoplasms at other and unspecified sites. [The Working Group noted that detailed figures were not given.]

Dubrow and Wegman (1982, 1983, 1984) analysed mortality by occupation among 34 879 white men in Massachusetts, USA, who had died during 1971–73. Overall, there were 179 deaths among barbers. Nonsignificantly elevated odds ratios (ORs) were found for cancers of the pancreas (1.46) and lung (1.34), on the basis of six and 29 deaths, respectively. For hairdressers and cosmetologists, an elevated OR was found for bladder cancer (11.56; four deaths).

Baxter and McDowall (1986) conducted a study of death certificates analysed as a case–control study of bladder cancer among men in six boroughs of London (United Kingdom), in the period 1968–78, using as controls all other causes of death, including cancer. There were four deaths in hairdressers, giving a RR of 2.0.

Pearce and Howard (1986) examined male cancer mortality by occupation in New Zealand in the period 1974–78 in relation to census-based estimates of the relevant populations. The RR for bladder cancer, adjusted for social class, was 12.94 (95% confidence interval [CI], 1.45–46.7; two cases). The adjusted RR for 'other urinary' cancers was 12.85 (1.44–46.4; two cases) and that for lung cancer was 2.54, on the basis of five cases (0.82–5.93).

Gallagher *et al.* (1989) analysed the death certificates of 320 423 male residents of British Columbia, Canada, who had died during 1950–84. There were 1209 deaths among barbers: cancer mortality was slightly reduced from that expected (PMR, 0.95; 95% CI, 0.82–1.08; 224 deaths), and PMRs were not elevated for any cancer site. The PMRs were 1.34

for bladder cancer, 1.33 for all non-Hodgkin's lymphomas and 0.58 for multiple myeloma, on the basis of 12, 8 and 2 deaths, respectively. In a similar analysis of mortality among female cosmetologists and hairdressers in 1950–78 in British Columbia, a significantly increased PMR was found for multiple myeloma (6.19; 95% CI, 1.27–18.11; three deaths) (Spinelli *et al.*, 1984). A nonsignificant excess of ovarian cancer was also noted (PMR, 2.04; 95% CI, 0.88–4.03; eight deaths), which reached statistical significance ($p < 0.05$) in the age group 20–65 years.

Neuberger *et al.* (1991) examined 375 industries and occupations that were associated with five or more deaths from brain cancer in Missouri, USA, between January 1983 and October 1984. Seven deaths were observed in the beauty shop industry against 1.49 expected (standardized proportionate mortality ratio, 4.7; $p < 0.005$). Among hairdressers and cosmetologists, there were eight deaths with 1.50 expected (5.3; $p < 0.005$).

### 2.1.2 *Cohort studies*

The studies summarized below are also presented in Table 6, with the results for the sites at which cancer occurred most commonly. Bias may have been introduced in the case of certain malignancies (other than bladder and breast cancers), owing to failure to present relevant results in some of the studies.

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 observed, 126.1 expected), and no specific cancer showed a significant excess: oesophagus, 5 observed, 3.4 expected; lung, 52 and 50.8; bladder, 7 and 5.6; and 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 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 in 1935–78 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 prior to 1 January 1966. A significant excess of lung cancer (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, breast, corpus uterine and ovarian cancers. 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 in the period 1942–82 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 prostatic 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 (1942–82). A nested case–control study of 18 cases of bladder cancer among men in this cohort (10 deceased, six incident cases that occurred during 1970–80 and two incident cases that occurred in 1981) showed a non-significantly greater 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 1900–50, 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 study linking 1960 census and 1961–79 cancer incidence in Sweden, 11 cases of multiple myeloma were found in people classified as beauticians (SIR, 1.3; $p > 0.05$) (McLaughlin *et al.*, 1988).

In a brief note, Shibata *et al.* (1989) 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 1976–87 in Aichi Prefecture, Japan.

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 was reported by Skov *et al.* (1990). 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 to 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: 3 observed, 2.0 expected in men and 2 observed, 4.4 expected in women (Skov *et al.*, 1990). The incidence of non-Hodgkin's 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.

In a study not entirely independent of the study of Skov *et al.* (1990), a cohort of 3637 female and 168 male hairdressers, born in or before 1946 and 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 and 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 1970–75 ($p < 0.05$) than during 1976–81 ($p > 0.05$) or 1982–87 ($p > 0.05$). 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.

In a cohort study of 248 046 US male veterans who served during 1917–40 and were interviewed during 1954 or 1957 on smoking habits and occupations, Hrubec *et al.* (1992) analysed the mortality pattern of 740 barbers through 1980. Smoking-adjusted RRs were 1.2 for all cancers (110 deaths; 95% CI, 1.06–1.45), 1.6 for respiratory cancers (31; 1.22–2.20), 1.5 for prostatic cancer (20; 1.03–2.15) and 2.5 for multiple myeloma (4; 1.08–5.63). No excess was found for bladder cancer (3 deaths; OR, 0.7).

### 2.1.3 *Case–control studies* (Table 7)

The Working Group systematically reviewed studies dealing with occupational risk factors for 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. Many of the case–control studies that have been published did not present results for all of the occupational categories covered in the

**Table 6. Occupational exposure: results of cohort studies on cancers at selected sites**

| Reference | Study population | Sex | Breast cancer | | | Bladder cancer | | | Lung cancer | | | Ovarian cancer | | | Lymphatic and haematopoietic neoplasms | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | O | E | RR | O | E | RR | O | E | RR | O | E | RR | Type | O | E | RR | |
| Alderson (1980) | 1831 male hairdressers at 1961 census, England and Wales, follow-up (M), 1961–78 | M | | | | 7 | 5.6 | 1.25 | 52 | 50.8 | 1.02 | | | | Leu | 3 | 2.7 | 1.1 | |
| Kono *et al.* (1983) | 7736 female beauticians, Fukuoka, Japan, registered, 1948–60, follow-up (M), 1953–77 | F | 5 | 8.46 | 0.59 | 0 | 1.01 | – | 9 | 7.41 | 1.21 | 5 | 3.69 | 1.36 | Leu | 6 | 4.38 | 1.37 | Excess of stomach cancer (RR, 1.34*) |
| Teta *et al.* (1984) | 11 845 female cosmetologists, Connecticut, USA licensed, 1925–74, follow-up (I), 1935–78 | F | 204 | 199.59 | 1.02 | 14 | 10.33 | 1.36 | 49[a] | 34.83 | 1.41* | 48 | 35.83 | 1.34 | Leu<br>MM<br>Lym | 14<br>3<br>22 | 11.62<br>4.33<br>17.07 | 1.20<br>0.69<br>1.29 | Higher RRs for women licensed during 1925–34 than among those licensed since 1935. |
| Gubéran *et al.* (1985) | 677 female and 703 male hairdressers, Geneva, Switzerland, employed 1900–64, follow-up (I), 1970–80 | F<br>M | 7 | 12.5 | [0.6] | 2<br>11 | 1.5<br>5.3 | [1.3]<br>[2.1*] | 3<br>8 | 1.6<br>10.3 | [1.9]<br>[0.78] | 1 | 2.0 | [0.5] | All<br>All | 4<br>0 | 2.0<br>2.3 | [2.0]<br>– | The only excess in a parallel analysis of 1942–82 mortality was bladder cancer among males (10 observed [RR, 2.6*]) |
| McLaughlin *et al.* (1988) | 3067 male MM cases, Swedish Cancer Registry, 1961–79, employed at 1960 census as beautician | M | | | | | | | | | | | | | MM | 11 | | 1.3 | |
| Shibata *et al.* (1989) | 3701 female and 4615 male barbers, Aichi Prefecture, Japan, employed in 1976, follow-up (M), 1976–87 | F<br><br>M | | | | | | | | | | | | | Leu<br>Lym<br>Leu<br>Lym | 0<br>1<br>3<br>1 | 1.26<br>0.73<br>2.58<br>2.29 | –<br>1.37<br>1.16<br>0.44 | |
| Skov *et al.* (1990) | 4356 female and 2149 male hairdressers and beauticians, Norway, employed at 1960 census, follow-up (I), 1961–84 | F<br>M | | | | 11<br>23 | 7.2<br>15.1 | 1.5<br>1.5 | 16<br>47 | 11.1<br>29.2 | 1.4<br>1.6* | | | | | | | | |
| Malker *et al.* (1987); Skov *et al.* (1990) | 16 942 female and 6522 male hairdressers and beauticians, Sweden, employed at 1960 census, follow-up (I), 1961–79 | F<br>M | | | | 6<br>54 | 13.5<br>36.6 | 0.4<br>1.5* | 31<br>98 | 20.0<br>67.2 | 1.6*<br>1.5* | | | | | | | | |

**Table 6 (contd)**

| Reference | Study population | Sex | Breast cancer | | | Bladder cancer | | | Lung cancer | | | Ovarian cancer | | | Lymphatic and haematopoietic neoplasms | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | O | E | RR | O | E | RR | O | E | RR | O | E | RR | Type | O | E | RR | |
| Skov *et al.* (1990) | 9138 female and 428 male hairdressers and barbers, Finland, employed at 1970 census, follow-up (I), 1971–80 | F<br>M | | | | 3<br>0 | 1.8<br>0.3 | 1.7<br>– | 2<br>3 | 4.4<br>2.0 | 0.5<br>1.5 | | | | | | | | Partially overlapping with the study of Pukkala *et al.* (1992) |
| Lynge & Thygesen (1988; Skov *et al.* (1990); Skov & Lynge (1991) | 9497 female and 4874 male hairdressers and barbers, Denmark, employed at 1970 census, follow-up (I), 1970–80 | F<br>M | | | | 7<br>41 | 4.0<br>20.0 | 1.8<br>2.1* | 12<br>56 | 11.0<br>50.5 | 1.1<br>1.1 | | | | NHL<br>NHL | 7<br>6 | | 2.01<br>1.30 | For all hairdressers and barbers. For hairdressers only, RR, 1.98 in women |
| Pukkala *et al.* (1992) | 3637 female hairdressers, Finland, employed 1970–82, follow-up (I), 1970–87 | F | 70 | 56.3 | 1.24 | 1 | 2.5 | 0.40 | 13 | 7.6 | 1.72 | 21 | 12.8 | 1.64* | Leu<br>MM | 4<br>1 | 4.2<br>2.4 | 0.96<br>0.42 | Higher RRs during 1970–75 than in subsequent periods. Excess incidence of all cancers (1.27*). Partially overlapping with the study of Skov *et al.* (1990). |
| Hrubec *et al.* (1992) | 740 male barbers, beauticians and manicurists, serving in the US Army during 1917–40, follow-up (M), 1954–80 | M | | | | 3 | [4.3] | 0.7 | 31 | [19.4] | 1.6* | | | | NHL<br>HD<br>MM<br>Leu | 4<br>1<br>4<br>5 | [3.1]<br>[0.7]<br>[1.6]<br>[4.6] | 1.3<br>1.4<br>2.5*<br>1.1 | Smoking-adjusted RRs. Excess mortality from all cancers (RR, 1.2*) |

O, observed cases/deaths; E, expected cases/deaths; RR, relative risk; M, mortality; I, incidence; Leu, leukaemias; Lym, lymphomas; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; HD, Hodgkin's disease. Numbers in square brackets, calculated by the Working Group.

[a]Respiratory and intrathoracic neoplasms

*, $p < 0.05$

analysis, including barbers, hairdressers and cosmetologists. A possible reporting bias derives from the fact that occupations associated with an elevated cancer risk are more likely to be reported than those that are not.

(*a*) *Bladder cancer*

Wynder *et al.* (1963) carried out a case–control study of smoking habits and occupations among 300 male patients with bladder carcinoma and 300 hospital controls in New York City, USA, during the period 1957–61; 93% of cases and 82% of controls were smokers. Four of the patients (all smokers) and none of the controls had worked as hairdressers.

Dunham *et al.* (1968) compared the most recent occupations of 265 white, male patients with bladder cancer (mostly transitional-cell carcinomas) with those of 272 comparable controls in New Orleans, Louisiana, USA, during 1958–64. They found four barbers in the case group, while 1.45 were expected (OR, 2.76).

Anthony and Thomas (1970) interviewed 812 men and 218 women with bladder papillomas and carcinomas in Leeds, United Kingdom, in the period 1959–67; 47% had known smoking histories. Of several alternative analyses presented by the authors, the most reliable appears to be based upon a comparison of the male cases with a control group comprising cases of non-malignant surgical disease matched by sex, age and number of cigarettes smoked. Among the cases, four were hairdressers, of whom three had worked more than 20 years in the occupation; one control was a hairdresser. The ORs for bladder cancer among hairdressers were 4.1 (predominant occupation), 4.0 (occupation ever undertaken) and 3.0 (20 or more years in the occupation). None of the female cases was in a hairdresser (0.6 expected). None of the differences was significant.

Cole *et al.* (1972) studied occupation in a systematic sample of patients (356 men, 105 women) aged 20–89 with transitional- or squamous-cell carcinoma of the lower urinary tract in a defined population in Boston, Massachusetts, USA, during an 18-month period in 1967–68 (Cole *et al.*, 1971). Controls were comparable with respect to age and sex. There was no increased risk for barbers (men: 4 observed cases, 7.2 expected; women: 1 observed case, 0.9 expected).

A hospital-based study of many types of cancer in males was conducted in Buffalo, New York, in the period 1956–65 (Viadana *et al.*, 1976). In an unspecified number of cases of bladder cancer and controls out of a total of 11 591 white men, the RR for bladder cancer associated with occupation as a barber was 1.49 (five cases; $p > 0.05$). Restriction to those with five or more years of exposure (still five cases) increased the RR to 1.77 ($p > 0.05$).

Howe *et al.* (1980) reported a population-based study of all 480 men and 152 women with bladder cancer diagnosed in 1974–76 in three Canadian provinces and of individually matched controls. Among men, three cases but no control were barbers; and among women, two cases but no control were hairdressers.

Vineis and Magnani (1985) conducted a case–control study of 512 male cases of bladder cancer in northern Italy in the period 1978–83. An OR of 0.9 was recorded for barbers and hairdressers on the basis of nine cases (95% CI, 0.4–2.3).

Morrison *et al.* (1985) conducted case–control studies in 1976–78 of cancer of the lower urinary tract among men in Boston, USA, Manchester, United Kingdom, and Nagoya, Japan.

No increased risk was recorded among barbers in Boston (OR, 1.00; 90% CI, 0.4–2.6; seven cases); only two cases were recorded in Manchester and one in Nagoya.

Jensen *et al.* (1988) reported a case–control study on incident cases of renal pelvis and ureter cancer. Cases were identified from hospitals in the eastern part of Denmark in 1979–82, and a total of 97 patients were included, corresponding to some 80% of those eligible. Three matched hospital controls were selected for each case, excluding patients with urinary tract and smoking-related diseases. A personal interview was obtained for 94% of cases and controls. A total of 36 female cases and 108 controls were interviewed, of whom two in each group reported occupation as a hairdresser (OR, 3.0; 95% CI, 0.3–33.0). Data were not reported on occupation as a hairdresser among men.

Risch *et al.* (1988) carried out a case–control study of 826 male and female cases of bladder cancer in Canada in 1979–82. The OR among barbers or hairdressers was not increased (men, 0.66, 11 cases; women, 1.00, nine cases). No significant trend was noted with increasing duration of employment.

The US National Bladder Cancer study is a population-based case–control study carried out in 10 areas of the USA during 1977–78. In 2100 white male cases and 3874 population controls, an OR of 1.3 (95% CI, 0.8–2.3; 28 exposed cases) was found for hairdressers and barbers and an OR of 2.8 (95% CI, 0.7–11.6; seven exposed cases) was found for hairdressers alone (Silverman *et al.*, 1989). For 652 white female bladder cancer patients and 1266 controls, an OR of 1.4 (95% CI, 0.7–2.9; 17 exposed cases) was found for hairdressers (Silverman *et al.*, 1990).

(*b*) *Lymphatic and haematopoietic cancers*

In a case–control study in Sweden, Persson *et al.* (1989) recorded crude ORs in hairdressers of 2.6 (one case) for Hodgkin's disease and 1.3 (one case) for other lymphomas. The logistic odds ratios were 2.7 and 2.2, respectively. [The Working Group noted that the two sexes cannot be distinguished.]

A case–control study of 622 white male cases of non-Hodgkin's lymphoma and 1245 controls was carried out in Iowa and Minnesota, USA. Case identification was population based; for living cases, living population-based controls were selected, while for the deceased, dead controls were identified from state vital records. Employment in a barber-shop was associated with a 2.7-fold risk (95% CI, 0.9–8.7; six exposed cases). The occupation of barber/cosmetologist showed an OR of 2.1 (95% CI, 0.7–5.9; seven exposed cases) (Blair *et al.*, 1993).

Four case–control studies on multiple myeloma analysed the risk among hairdressers or barbers. In a study from Sweden, cases diagnosed between 1973 and 1983 were collected as survivors into the period 1981–83; one case and one control were employed as hairdresssers (OR, 3.3; 95% CI, 0.24–45.7) (Flodin *et al.*, 1987). In a study nested in a large American Cancer Society cohort, no case and four controls were classified as beauticians, cosmetologists or barbers (Boffetta *et al.*, 1989). In another study from Sweden, of 256 cases and 256 population controls, two cases and three controls were employed as hairdressers or cosmetologists (OR, 0.67; 90% CI, 0.15–2.71) (Eriksson & Karlsson, 1992). Finally, in a study on the incidence of multiple melanoma among women in the Danish Cancer Registry,

one case and six controls were classified as hairdressers (OR, 0.7; 95% CI, 0.0–5.8) (Pottern *et al.*, 1992).

A case–control study conducted in Tasmania, Australia, included 51 female cases of acute nonlymphoblastic leukaemia, 27 of chronic lymphoblastic leukaemia, 32 of Hodgkin's disease, 116 of non-Hodgkin's lymphoma and 59 of multiple myeloma diagnosed during 1972–80, as well as population controls. Five cases of non-Hodgkin's lymphoma and no control were employed as hairdressers ($p < 0.05$); all five cases had been employed for more than five years. For none of the remaining neoplasms was there a significant difference between cases and controls for employment as a hairdressr (Giles *et al.*, 1984).

(*c*) *Cancers at other sites*

Viadana *et al.* (1976) reported an increase in the incidence of laryngeal cancer among barbers in the study described on p. 74. Barbers had an age-adjusted OR of 2.83 for laryngeal cancer (10 cases); this excess persisted in men who had been barbers for five or more years (OR, 2.49; eight cases). The overall OR after adjustment for tobacco use was 3.39 ($p < 0.05$).

Osorio *et al.* (1986) noted a PIR of 1.44 for lung cancer among female cosmetologists aged 20–65 in the Los Angeles (USA) Tumor Registry in 1972–82, on the basis of 81 cases. In a case–control study of 50 cases and 56 non-pulmonary cancer controls, no occupational exposure factor was identified that could explain the lung cancer excess.

Koenig *et al.* (1991) carried out a case–control study of 398 women with breast cancer and 790 controls identified from the records of a multiphasic screening clinic in New York City, USA. They noted a three-fold excess (95% CI, 1.1–7.9) among beauticians with five or more years of exposure, on the basis of 12 cases.

(*d*) *Childhood cancer*

Kuijten *et al.* (1992) carried out a case–control study of astrocytoma diagnosed in children under 15 in the period 1980–86 in Pennsylvania, New Jersey and Delaware, USA. Controls were recruited by random-digit dialling and pair-matched with cases on age, race and telephone exchange. Mothers and fathers of cases and controls were interviewed separately by telephone. A total of 217 eligible cases were identified; a maternal occupational history was obtained for 163 case–control pairs (75%) and a paternal one for 158 pairs (73%). Of the 163 controls, 115 (71%) were the first eligible control identified. A complete occupational history was obtained for each parent. Maternal employment as a hairdresser in the period before conception was associated with an OR of 2.5 (95% CI, 0.4–26.2, seven discordant pairs), employment during pregnancy with an OR of 1.5 (95% CI, 0.2–18.0, five discordant pairs) and employment postnatally with an OR of 3.0 (95% CI, 0.2–157.7, four discordant pairs). [The Working Group noted that cases and controls could have been exposed during more than one period.]

**Table 7. Occupational exposure: results of case–control studies on cancers at selected sites**

| Reference | Study population | Controls | Exposure | Control for smoking (when relevant) | Sex | Type of cancer | Exposed cases | Odds ratio | Comments |
|---|---|---|---|---|---|---|---|---|---|
| **Bladder cancer** | | | | | | | | | |
| Wynder *et al.* (1963) | 300 male cases, 2 hospitals, New York, USA, 1957–61 | Hospital controls | Ever employed as hairdresser | No | M | | 4 | NR | No exposed control |
| Dunham *et al.* (1968) | 265 male cases, hospital in New Orleans, USA, 1958–64 | 272 hospital controls | Employed as barber | No | M | | 4 | 2.76 | NS |
| Anthony & Thomas (1970) | 812 male, 218 female cases, Leeds, UK, 1959–67 | Non-malignant surgical diseases (340 men, 50 women) | Hairdresser as predominant occupation | No | M | | 4 | 4.1 | |
| Cole *et al.* (1972) | 356 male, 105 female cases, Boston, USA, 1967–68 | 485 population controls | Ever employed as barber or hairdresser | No | M<br>F | | 4<br>1 | 0.56 | 0.9 expected cases |
| Viadana *et al.* (1976) | Male cases, Buffalo, USA, 1956–65 | Non-neoplastic hospital controls | Ever employed as barber | No | M | | 5 | 1.49 | RR 1.77 for ≥ 5 years of employment |
| Howe *et al.* (1980) | 480 male, 152 female cases, 3 Canadian provinces, 1974–76 | 480 male, 152 female neighbourhood controls | Ever employed as barber or hairdresser | No | M<br>F | | 3<br>2 | | No exposed control of either sex |
| Gubéran *et al.* (1985) | 18 male cases nested in a cohort of hairdressers in Geneva, Switzerland, 1970–80 | 54 cohort members | Duration of employment | | | | | | Nonsignificant association with men's hairdressing, no association with women's hairdressing |
| Vineis & Magnani (1985) | 512 male cases, Turin, Italy, 1978–83 | 596 hospital controls | Ever employed as barber or hairdresser | No | M | | 9 | 0.9 | |
| Morrison *et al.* (1985) | 430 male cases, Boston, USA, 1976–78 | 397 population controls | Employed as barber | Yes | M | | 7 | 1.00 | |
| Morrison *et al.* (1985) | 399 male cases, Manchester, UK, 1976–78 | 493 population controls | Employed as barber | No | M | | 2 | [1.3] | |
| Morrison *et al.* (1985) | 226 male cases, Nagoya, Japan, 1976–78 | 443 population controls | Employed as barber | No | M | | 1 | [1.0] | |

**Table 7 (contd)**

| Reference | Study population | Controls | Exposure | Control for smoking (when relevant) | Sex | Type of cancer | Exposed cases | Odds ratio | Comments |
|---|---|---|---|---|---|---|---|---|---|
| **Bladder cancer (contd)** | | | | | | | | | |
| Risch *et al.* (1988) | 826 male and female cases, Canada, 1979–82 | 792 population controls | Ever employed as barber or hairdresser | Yes | M<br>F | | 11<br>9 | 0.66<br>1.00 | No trend with duration of exposure in either sex |
| Silverman *et al.* (1989) | 2100 white male cases, 10 US areas, 1977–78 | 3874 population controls | Ever employed as barber or hairdresser | Yes | M | | 28 | 1.3 | |
| | | | Ever employed as hairdresser | | M | | 7 | 2.8 | |
| Silverman *et al.* (1990) | 652 white female cases, 10 US areas, 1977–78 | 1266 population controls | Ever employed as hairdresser | Yes | F | | 17 | 1.4 | |
| **Lymphatic and haematopoietic neoplasms** | | | | | | | | | |
| Persson *et al.* (1989) | 54 HD and 106 NHL cases, hospital in Sweden, 1964–86 | 275 population controls | Employed as hairdresser | | Both | HD<br>NHL | 1<br>1 | 2.7<br>2.2 | Logistic odds ratio |
| Blair *et al.* (1993) | 622 white male NHL cases, Iowa and Minnesota, USA 1980–83 | 1245 population controls | Ever employed in barbershop | | M | NHL | 6 | 2.7 | |
| | | | Ever employed as barber/cosmetologist | | M | NHL | 7 | 2.1 | |
| Flodin *et al.* (1987) | 131 MM cases, 6 hospitals in Sweden, 1981–83 | 431 population controls | Employed as hairdresser | | Both | MM | 1 | 3.3 | Surviving cases included |
| Boffetta *et al.* (1989) | 128 MM incident cases, American Cancer Society cohort, 1982–86 | 512 controls from the cohort | Employed as beautician, cosmetologist or barber | | Both | MM | 0 | – | Four exposed controls |
| Eriksson & Karlsson (1992) | 256 MM cases, northern Sweden, 1982–86 | 256 population controls | Employed as hairdresser or cosmetologist | | Both | MM | 2 | 0.7 | |
| Pottern *et al.* (1992) | 607 female MM cases, Denmark, 1970–84 | 2596 population controls | Most recent employment as hairdresser | | F | MM | 1 | 0.7 | |
| Giles *et al.* (1984) | 116 female NHL cases, Tasmania, Australia, 1972–80 | Population controls | Employed as hairdresser | | F | NHL | 5 | * | No exposed control |
| Giles *et al.* (1984) | 32 female HD cases, Tasmania, Australia, 1972–80 | Population controls | Employed as hairdresser | | F | HD | 2 | | No exposed control |

**Table 7 (contd)**

| Reference | Study population | Controls | Exposure | Control for smoking (when relevant) | Sex | Type of cancer | Exposed cases | Odds ratio | Comments |
|---|---|---|---|---|---|---|---|---|---|
| **Lymphatic and haematopoietic neoplasms (contd)** | | | | | | | | | |
| Giles *et al.* (1984) | 51 female ANLL cases, Tasmania, Australia, 1972–80 | Population controls | Employed as hairdresser | | F | ANLL | 1 | | No exposed control |
| Giles *et al.* (1984) | 27 female CLL cases, Tasmania, Australia, 1972–80 | Population controls | Employed as hairdresser | | F | CLL | 0 | - | No exposed control |
| Giles *et al.* (1984) | 59 female MM cases, Tasmania, Australia, 1972–80 | Population controls | Employed as hairdresser | | F | MM | 0 | - | One exposed control |

NR, not reported; NS, not significant; RR, relative risk; HD, Hodgkin's disease; NHL, non-Hodgkin's lymphoma; MM, multiple myeloma; ANLL, acute nonlymphocytic leukaemias; CLL, chronic lymphocytic leukaemias. Numbers in square brackets, calculated by the Working Group

*$p < 0.05$

## 2.2 Use of hair colourants

### 2.2.1 *Cohort studies* (Table 8)

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 were reduced 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 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. 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 the study. [The Working Group noted the low response rate and the fact that information on both cancer and exposure to hair dyes was derived from participants.]

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 to 505 for never use. The risk for breast cancer did not increase with frequency or duration of use.

### 2.2.2 *Case–control studies* (Table 9)

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*

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 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,

**Table 8. Hair dye users: Results of cohort studies on cancers at selected sites**

| Reference | Study population | Sex | Breast cancer | | | Bladder cancer | | | Lymphatic and haematopoietic neoplasms | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | O | E | RR | O | E | RR | Type | O | E | RR | |
| Hennekens *et al.* (1979) | 120 557 female nurses, aged 30–55, 11 US states, active in 1972, follow-up (I), 1972–76 | F | 270 | 258.2 | 1.06 | 5 | 7.4 | 0.62 | Lym | 10 | 15.7 | 0.59 | 30% non-respondents; similar results after adjustment for smoking; excess of breast cancer for hair dye use ≥ 21 years before cancer; excess for all cancer sites (1.10*), cervix (1.44*) and lower genital tract (2.58*) |
| Green *et al.* (1987) | 1976–82 follow-up (M) of 118 404 nurses enrolled in the study above | F | 353 | | 1.1 | | | | | | | | No trend with duration of use |

M, mortality; I, cancer incidence; Lym, lymphomas
*, $p < 0.05$

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]). [The Working Group noted that the reported data do not allow control for age or tobacco smoking and that the cases were surviving patients.]

In the study reported on p. 74, Dunham *et al.* (1968) compared 132 cases of bladder cancer with 136 controls for history of 'use of tonics, lotions and other preparations for the hair and scalp'. The percentage of cases who used such preparations (32%) was slightly lower than that of controls (36%).

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.]

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 the study described on p. 74, Howe *et al.* (1980) found that eight male cases (including two of the barbers) and no male control had a history of personal use of hair dyes ($p = 0.004$, one-tailed test); only one of them had used hair dyes for more than six years before diagnosis of bladder cancer. There was no evidence in women of an increased risk for bladder cancer associated with personal use of hair dyes (OR, 0.7; 95% CI, 0.3–1.4 for ever *versus* never use).

Hartge *et al.* (1982) examined hair dye use among participants in the US National Bladder Cancer Study (see p. 75) in a case–control study of bladder cancer involving 2982 incident cases and 5782 controls, of which 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. No trend with frequency or duration of use was seen in people of either sex. Use of black hair dye was associated with elevated ORs in both men and women; the OR was of borderline significance for the two sexes combined (1.4; 95% CI, 1.0–1.9; 68 exposed cases).

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

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

(*b*) *Breast cancer*

Shafer and Shafer (1976) reported that, of 100 consecutive breast cancer patients seen in a clinical practice in New York, USA, 87% had been long-term users of hair colouring agents, compared with 26% of age-comparable controls, who 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 that no information was provided on the number of controls nor the manner of eliciting information on use of hair dyes.]

Kinlen *et al.* (1977) reported a study of 191 breast cancer patients interviewed in 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 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 use of a multivariate confounder score for the control of confounding may produce misleading results.]

In order to follow up 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, and 35 breast cancer cases with 70 neighbourhood controls in Toronto, Ontario, 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 State New York, 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 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 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, they 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 1979–81. No association was found with hair-dye use (OR, 1.02; 95% CI, 0.78–1.32) and there was no dose–response relationship.

(*c*) *Lymphatic and haematopoietic cancers*

In a further report of the study of Stavraky *et al.* (1979) in Canada, p. 83, Stavraky *et al.* (1981) found no significant increase in risk for leukaemia or lymphoma (70 cases). [The Working Group noted that it was not possible to distinguish different haematopoietic malignancies.]

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

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's lymphoma and 1245 population controls in Iowa and Minnesota, USA, in 1980–83. Significantly raised ORs were found for leukaemia (1.8; 95% CI, 1.1–2.7) and for non-Hodgkin's lymphoma (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 were not substantially changed 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, an examination of the paper could not verify this.]

A population-based case–control study carried out in eastern Nebraska, USA, during 1983–86 investigated use of hair colouring products among a total of 201 male and 184 female cases of non-Hodgkin's lymphoma, 35 male and 35 female cases of Hodgkin's 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's lymphoma (OR, 1.5; 95% CI, 1.1–2.2), Hodgkin's disease (1.7; 0.7–4.0) and multiple myeloma (1.8; 0.9–3.7), and women who used permanent hair dyes had high ORs for all three neoplasms (non-Hodgkin's lymphoma, 1.7, 1.1–2.8; Hodgkin's disease, 3.0, 1.1–7.9; and multiple myeloma, 2.8, 1.1–7.1; all $p < 0.05$). For non-Hodgkin's 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, but the patterns were not consistent. Among men, use of any hair colouring product was associated with nonsignificantly increased ORs for Hodgkin's disease (1.7) and multiple myeloma (1.8), on the basis of three and four exposed cases, respectively; no increase was found for non-Hodgkin's lymphoma (0.8). Use of any hair dye was not associated with chronic lymphocytic leukaemia in either women or men (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).

*(d) Cancers at other sites*

Stavraky *et al.* (1981) (see p. 84) 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.

Holman and 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 1980–81. 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 $\geq$ 10 times, 3.3 (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.]

Østerlind *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 1982–85 (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.

Ahlbom *et al.* (1986) carried out a case-control study in Stockholm and Uppsala, Sweden, of 78 patients with astrocytoma diagnosed in 1980–81, 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) in relation to 83 hospital controls and 1.5 (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 1977–81 than hospital controls reported having used hair dye or hair spray (OR, 1.96; $p = 0.013$; 43/22 discordant pairs).

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 1985–89. 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 for more than 15 years (OR, 3.5; 95% CI, 0.9–12.8) was higher than that for shorter duration of use (2.3; 0.9–6.2).

(*e*) *Childhood cancer*

Kramer *et al.* (1987) reported a matched case–control study of maternal exposures during pregnancy and neuroblastoma diagnosed during the period 1970–79 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) did a case–control study of Wilms' tumour diagnosed in children under 15 during the period 1970–83 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 'nongenetic' (42 cases) (if they were unilateral without nephroblastomatosis or 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 nongenetic cases and 3.3 (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 an interval of 11–24 years between pregnancy and interview.

Kuijten *et al.* (1990), in an earlier report of the study of Kuitjen *et al.* (1992) (p. 76), found no association between astrocytoma and maternal use of hair-colouring products during pregnancy (OR, 0.9; 95% 0.4–1.8; 37 discordant pairs).

## 3. Studies of Cancer in Experimental Animals

### 3.1 Skin application

#### 3.1.1 *Mouse*

Groups of 50 male and 50 female Swiss Webster mice, six to eight weeks old, received applications of one of three oxidation (permanent) hair dye formulations, PP-7588, PP-7586 or PP-7585 (all three formulations 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-toluenediamine), mixed with an equal volume of 6% hydrogen peroxide just prior to use; 0.05 ml of the mixture in acetone was applied to the shaved skin of the mid-scapular 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 lung tumours was not statistically different between treated and control groups. No skin tumour was observed at the site of application (Burnett *et al.*, 1975).

Groups of 26 male and 22 female DBAf and 26 male and 26 female strain A mice, six to seven weeks old, 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, 1,4-diamino-2-nitrobenzene (2-nitro-*para*-phenylenediamine) 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 lymphomas and six 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 lymphoma at week 26 among the 26 treated males. In control DBAf mice, one lymphoma and one lung adenoma were found in females and one 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 the small number of animals used in the study.]

**Table 9. Hair colourant users: results of case–control studies on cancers at selected sites**

| Reference | Study population | Controls (case: control ratio) | Exposure | Sex | Type of cancer | Exposed cases | Odds ratio | Comments |
|---|---|---|---|---|---|---|---|---|
| **Bladder cancer** | | | | | | | | |
| Lockwood (1961) | 282 male and 87 female cases, Copenhagen, Denmark, 1942–56 | Population controls (1:1) | Use of brilliantine | M<br>F | | 51<br>2 | [1.7*]<br>[1.1] | |
| Dunham *et al.* (1968) | 132 male cases, hospital in New Orleans, USA, 1958–64 | 136 hospital controls | Use of tonics, lotions and other preparations for hair and scalp | M | | 42 | [0.9] | |
| Howe *et al.* (1980) | 480 male, 152 female cases, 3 Canadian provinces, 1974–76 | Neighbourhood controls (1:1) | Use of hair dye | F<br>M | | NR<br>8 | 0.7<br>* | No exposed male control |
| Hartge *et al.* (1982) | 2249 male and 733 female cases, 10 US areas, 1977–78 | 4282 male and 1500 female population controls | Use of hair dye | M<br>F | | 172<br>443 | 1.1<br>0.9 | No trend with frequency or duration in either sex |
| Ohno *et al.* (1985) | 65 female cases, Nagoya, Japan, 1976–78 | 143 population controls | Use of hair dye | F | | [42] | [1.6] | RRs higher among smokers<br>Crude<br>10.0* for < 1/month,<br>25.0* for ≥ 1/month<br>Adjusted for smoking<br>1.3 for < 1/month<br>1.7 for ≥ 1/month |
| Claude *et al.* (1986) | 340 male cases, 91 female cases, northern Germany, 1977–82 | Hospital controls (1:1) | Use of hair dye | Both | | | | No association |
| Nomura *et al.* (1989) | 195 male, 66 female cases, Hawaii, USA, 1977–86 | Population controls (2:1) | Use of hair dye | M<br>F | | 15<br>41 | 1.3<br>1.5 | No trend with duration of exposure for either sex |
| **Breast cancer** | | | | | | | | |
| Shafer & Shafer (1976) | 100 cases, New York, USA | No information | Use of hair dye | F | | 87 | [19] | Limited reporting |
| Kinlen *et al.* (1977) | 191 cases, Oxford, UK, 1975–76 | 561 hospital controls | Use of permanent or semi-permanent hair dye | F | | 73 | 1.01 | No trend with duration of use |

**Table 9 (contd)**

| Reference | Study population | Controls (case: control ratio) | Exposure | Sex | Type of cancer | Exposed cases | Odds ratio | Comments |
|---|---|---|---|---|---|---|---|---|
| **Breast cancer (contd)** | | | | | | | | |
| Shore *et al.* (1979) | 129 cases, New York, USA, screening centre, 1964–76 | 193 clinic controls | Use of permanent hair dye | F | | [43] | 1.08 | Higher RRs for use ≥ 5 years (1.31), ≥ 10 years (1.58) or ≥ 15 years (1.44) before diagnosis. Significant association with cumulative hair dye exposure |
| Stavraky *et al.* (1979) | 50 cases, London, Canada, 1976–< 1979 | Hospital controls (2:1) | Use of permanent hair dye | F | | 28 | 1.3 | |
| | 35 cases, Toronto, Canada, 1976–< 1979 | Neighbourhood controls (2:1) | Use of permanent hair dye | F | | 16 | 1.1 | |
| Nasca *et al.* (1980) | 118 cases, 3 counties in New York State, USA, 1975–76 | 233 random-digit dialling controls | Use of permanent or semi-permanent hair dye | F | | NR | 1.11 | No trend with frequency of use or latency. Excess for use of hair dye to change colour (3.1*). |
| Wynder & Goodman (1983) | 401 cases, New York, USA, 1979–81 | 625 cancer controls | Use of hair dye | F | | 267 | 1.02 | No dose–response relationship |
| Koenig *et al.* (1991) | 398 cases, New York, USA, screening centre, 1977–81 | 790 screening centre controls | Use of hair dye | F | | 294 | 0.8 | No trend with number of uses |
| **Lymphatic and haematopoietic neoplasms** | | | | | | | | |
| Stavraky *et al.* (1981) | 45 female cases, Toronto, Canada, 1976–< 1979 | Neighbourhood controls (2:1) | Use of permanent or semi-permanent dye | F | All | | 0.7 | |
| | 25 female cases, London, Canada, 1976–< 1979 | Hospital controls (2:1) | Use of permanent or semi-permanent dye | F | All | | 1.2 | |
| Cantor *et al.* (1988) | 578 male cases of leukemia and 622 male NHL cases, Iowa and Minnesota, USA, 1980–83 | 1245 population controls | Use of hair tints, colouring products or dyes | M<br>M | Leu<br>NHL | 43<br>53 | 1.8*<br>2.0* | |
| Zahm *et al.* (1992) | 201 male and 184 female NHL cases, Nebraska, USA, 1983–86 | 725 male and 707 female population controls | Use of any hair dye | F<br>M | NHL<br>NHL | 106<br>11 | 1.5*<br>0.8 | ORs higher among women using permanent dark hair dye. No trend with duration or frequency of use of permanent hair dye |
| | | | Use of permanent hair dye | F | NHL | 41 | 1.7* | |

**Table 9 (contd)**

| Reference | Study population | Controls (case: control ratio) | Exposure | Sex | Type of cancer | Exposed cases | Odds ratio | Comments |
|---|---|---|---|---|---|---|---|---|
| **Lymphatic and haematopoietic neoplasms (contd)** | | | | | | | | |
| Zahm *et al.* (1992) (contd) | 35 male and 35 female HD cases, Nebraska, USA, 1983–86 | 725 male and 707 female population controls | Use of any hair dye | F | HD | 16 | 1.7* | Trend with duration and not with frequency of use of permanent hair dye |
| | | | | M | HD | 3 | 1.7 | |
| | | | Use of permanent hair dye | F | HD | 12 | 3.0* | |
| | 32 male and 40 female MM cases, Nebraska, USA, 1983–86 | 725 male and 707 female population controls | Use of any hair dye | F | MM | 24 | 1.8 | ORs higher among women using permanent dark hair dye. Trend with duration and frequency of use of permanent hair dye |
| | | | | M | MM | 4 | 1.8 | |
| | | | Use of permanent hair dye | F | MM | 11 | 2.8* | |
| | 37 male and 19 female CLL cases, Nebraska, USA, 1983–86 | 725 male and 707 female population controls | Use of any hair dye | F | CLL | 9 | 1.0 | |
| | | | | M | CLL | 3 | 1.0 | |
| | | | Use of permanent hair dye | F | CLL | 2 | 0.8 | |
| Brown *et al.* (1992) | 173 white male MM cases, Iowa, USA, 1981–84 | 650 population controls | Use of hair dye | M | MM | 14 | 1.9 | Higher OR for high frequency |

NR, not reported; RR, relative risk; Leu, leukaemia; NHL, non-Hodgkin's lymphoma; OR, odds ratio; HD, Hodgkin's disease; MM, multiple myeloma; CLL, chronic lymphocytic leukaemia. Numbers in square brackets, calculated by the Working Group

*$p < 0.05$

In the same study, groups of 17 male and 15 female DBAf and 16 male and 16 female strain A mice, six to seven weeks old, received skin aplications 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, 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 small number of animals used in the study.]

Groups of 60 male and 60 female Swiss Webster mice, eight weeks of age, received topical applications of a semi-permanent hair dye formulation (7611) containing 0.15% 2-amino-5-nitrophenol, 0.11% 4-amino-2-nitrophenol, 0.85% 2-nitro-*para*-phenylenediamine, 0.30% CI Solvent Blue 6, 0.95% CI Solvent Blue 7, 0.06% CI Solvent Blue 16, 0.45% CI Solvent Blue 18, 0.35% CI Solvent Orange 9, 0.15% CI Solvent Red 26, 0.11% CI Solvent Green 3, 0.76% CI Basic Orange 1, 0.50% CI Basic Blue 3, 0.15% CI Basic Blue 47, 0.12% CI Basic Red 2, 0.10% CI Basic Violet 1, 0.10% CI Basic Violet 2, 0.10% CI Basic Violet 13, 0.15% CI Basic Violet 14, 2.76% hydroxyethyl cellulose, 7.78% phenoxyethanol, 5.00% ethoxydiglycol, 4.60% Amphoteric 1, 4.60% Polysorbate 20, 4.12% propylene glycol, 2.70% methacrylamide, 0.42% Quarternium 4 and 0.41% tetrasodium EDTA in water. The formulation was applied at 0.05 ml/mouse three times a week for 20 months to a 1-$cm^2$ area of clipped shaved skin. Control animals were shaved only and received no treatment. Body weights of treated animals were depressed by no more than 10% of those of controls; all mice survived until termination of the experiment. The incidences of liver haemangiomas, lung adenomas and malignant lymphomas, which occur spontaneously in this strain of mice, were no greater than in controls. No skin tumour was observed at the site of application (Jacob *et al.*, 1984).

### 3.1.2 *Rat*

Groups of 50 male and 50 female Sprague-Dawley rats, about 14 weeks of age, received topical applications of 0.5 ml of permanent hair dye mixtures containing 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 and untreated control groups. Skin at the application site, 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). [The Working Group noted the limited histopathology undertaken in the study.]

Groups of 10 male and 10 female Wistar rats, weighing 120–140 g, received topical applications of 0.5 ml oxidized *para*-phenylenediamine (1:1 mixture of 5% *para*-phenylenediamine in 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 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; $p < 0.05$ [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). [The Working Group noted the small number of animals used in this study and the fact that only selected organs were examined histologically.]

Groups of 60 male and 60 female Sprague-Dawley rats, six to eight weeks of age, 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 (approximately 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 vehicle alone. Mean body weights and survival were similar in treated and control groups. No skin tumour was observed. The incidence of pituitary adenomas was increased in females in comparison with all three control groups (45/51 *versus* 34/50, 36/51 and 35/50; $p < 0.05$, $\chi^2$ test) (Burnett & Goldenthal, 1988).

In the same study, groups of 60 male and female Sprague-Dawley rats, six to eight 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 were applied to a shaved area of the back (approximately 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 tumour was observed, and no increase in the incidence of tumours at any site was observed in treated as compared with control animals (Burnett & Goldenthal, 1988).

In the same study, groups of 60 male and female Sprague-Dawley rats, six to eight weeks of age, received topical applications of an oxidative hair dye formulation (7401) containing 1.1% 1,4-diamino-2-nitrobenzene (2-nitro-*para*-phenylenediamine), 3.0% *para*-phenylenediamine, 2.0% 2,4-diaminoanisole sulfate, 1.7% resorcinol, 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 before application, and 0.5 ml were applied to a shaved area of the back (approximately 2.5 cm in diameter) twice a week up until week 117. Mean body weights and survival were similar in treated and control groups. There was no significant increase in the incidence of tumours at any site, and no skin tumour was observed (Burnett & Goldenthal, 1988).

### 3.2 Subcutaneous injection

*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; $p < 0.05$ 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 tumour was 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 and the fact that only selected organs were examined histologically.]

## 4. Other Relevant Data

### 4.1 Absorption, distribution, metabolism and excretion

Many factors influence skin absorption. The upper layer of the epidermis (stratum corneum) is the primary barrier, but this protective layer can be affected by changes in humidity, temperature and pH. Skin damage, irritation and inflammation can also influence permeability. Many hair colouring formulations contain detergents and organic solvents, which at low concentrations may damage the skin barrier and thus facilitate uptake by the skin (Malkinson & Gehlmann, 1977). The absorption of different substances varies between species; generally, the skin of humans is less permeable than that of experimental animals (Bartek *et al.*, 1972), although the permeability of the skin of the back of rats is similar to that of the human scalp (Ammenheuser & Warren, 1979). [The Working Group noted that very little information was available on absorption by men and women following exposure to hair dyes.]

#### 4.1.1 *Occupational exposure*

2,4-Toluenediamine, one possible diamino constituent of permanent hair dyes, was detected in five of 30 urine samples from professional hairdressers who had been exposed professionally for four to five years and who reportedly did not usually wear gloves when applying hair dyes. The range of detectable concentrations was 16–67 µg/l (Şardaş *et al.*, 1986).

Differences in the mutagenicity of the urine of cosmetologists exposed to hair dyes and of those without exposure (Babish *et al.*, 1991; see pp. 102–103) suggest that the exposed cosmetologists absorbed hair-dye components systemically.

#### 4.1.2 *User exposure*

Kiese and Rauscher (1968) studied the absorption of 2,5-diaminotoluene (*para*-toluenediamine) through human scalp skin, applying a formulation containing the dye, resorcinol

and hydrogen peroxide for 40 min and then washing. Urinary excretion was followed in aliquots over the next 48 h. The highest rate of excretion occurred 5–8 h after dyeing, and traces were found 36 h later. The average total amount of metabolite excreted after application of 2.5 g of the sulfate was 3.7 mg *N,N'*-diacetyl-2,5-diaminotoluene (0.09%), equivalent to 2.17 mg 2,5-diaminotoluene. Other metabolites were not identified.

Scalp penetration of four semi-permanent dyes (HC Blue No. 1, HC Blue No. 2 (see monographs, pp. 129 and 143), 1,4-diamino-2-nitrobenzene [2-nitro-*para*-phenylenediamine] and 4-amino-2-nitrophenol) and of three ingredients of oxidative dyes (1,4-diaminobenzene [*para*-phenylenediamine], resorcinol and 4-amino-2-hydroxytoluene), under conditions similar to those of use of oxidative hair dyes, was studied in humans and rhesus monkeys. The absorption of [ring-$^{14}$C]-labelled compounds [radiochemical purity not specified] was quantified in urinary assays. The two species showed a similar pattern of dye absorption. Slightly more of the semi-permanent dyes penetrated the scalp, but in neither case did penetration exceed 1% of the applied dose. Metabolites were not identified in the urine (Maibach & Wolfram, 1981; Wolfram & Maibach, 1985).

Marzulli *et al.* (1981) investigated skin penetration of 2,4-diaminoanisole in humans and rhesus monkeys. [Ring-$^{14}$C]-labelled 2,4-diaminoanisole [radiochemical purity not specified] in acetone solution was applied to the abdomens of monkeys and to the ventral forearms of male subjects. The remaining substance was removed after 24 h by washing with soap and water. Urine was collected over a five-day period and analysed for radiolabel. Men absorbed 3.9% and monkeys 4.7% of the applied dose. Metabolites were not identified in the urine.

Application of a commercial hair colouring formulation containing 2% lead acetate to the hair of the head of nine men for 90 days led to increasing lead concentrations in axillary, pubic and capillary hair, indicating systemic uptake of lead (Marzulli *et al.*, 1978). Two hair dye formulations containing lead acetate were spiked with lead-203 acetate and applied to the foreheads of eight men for 12 h. Absorption was estimated by measuring lead-203 activity in blood, urine and the whole body. Absorption through the skin was low: 0–0.3% of the dose (Moore *et al.*, 1980). [The Working Group noted that such small increments cannot be measured by conventional methods such as those used in other studies.] In a study of 53 adult volunteers and 13 controls, the hair of the head was treated 63 times over a six-month period with preparations containing 0.6 or 1.8% lead acetate. No difference in lead concentration in whole blood or in urine was found between exposed and control volunteers, nor in a number of other blood parameters (Ippen *et al.*, 1981).

## 4.2 Toxic effects

### 4.2.1 *General exposures of hairdressers*

The principal occupational hazards for hairdressers are irritant and allergic contact dermatitis. The irritants used include soap, detergents, shampoos, rinse solutions, bleaches and water. Two predisposing risk factors for the development of irritant contact dermatitis in hairdressers and beauticians are atopic status (defined as allergies, hay fever, asthma or atopic eczema) and nickel allergy (Cronin & Kullavanijaya, 1979; Landthaler *et al.*, 1981; Lindemayr, 1984; Holness & Nethercott, 1990). The various agents and their uses that induce

allergic contact dermatitis in hairdressers have been described (Marks, 1986), and a number of reviews on the chemistry and toxicology of hair dyeing are available (Corbett, 1976; Iyer *et al.*, 1985; Corbett, 1988). The most important group of sensitizers are synthetic organic dyes (Lynde & Mitchell, 1982; Stovall *et al.*, 1983; Nethercott *et al.*, 1986; Matsunaga *et al.*, 1988), which contain dyes, couplers and an oxidizing agent—usually a hydrogen peroxide solution. Ammonium persulfate, which is used for bleaching, has been reported to cause asthma (Pepys *et al.*, 1976; Blainey *et al.*, 1986; Schwaiblmair *et al.*, 1990), contact dermatitis and urticaria (Fisher & Dooms-Goossens, 1976; Kleinhans & Rannederg, 1988).

Application of henna has also been associated with the development of asthma in hairdressers (Pepys *et al.*, 1976; Starr *et al.*, 1982).

### 4.2.2 *Personal use of hair dyes*

[The Working Group noted that very little information was available on toxic effects associated with the use of hair dyes.]

Hair dyeing was the procedure associated with the highest risk of sensitization in a group of patients with contact dermatitis who were hairdresser clients. *para*-Phenylenediamine dihydrochloride was the most frequent sensitizer (Guerra *et al.*, 1992).

Case reports linking the use of hair dyes with bone-marrow suppression and aplastic anaemia (which occurs in about four people per million population) have appeared occasionally in the medical literature (Hopkins & Manoharan, 1985). The postulated etiological agent, a hair dye, contained 2,5-diaminotoluene, which is suspected of causing aplastic anaemia (Cavignaux, 1962).

A case–control study (Freni-Titulaer *et al.*, 1989) of 44 cases of connective tissue disease, comprising 23 cases of systemic lupus erythematosus, 10 of scleroderma, two of polymyositis and nine cases of undifferentiated disease, and of 88 controls selected by random-digit dialling, was carried out in Georgia, USA. Significant associations were found between the occurrence of connective tissue disease and use of hair dyes (crude OR, 6.5; 95% CI, 2.4–17.4; 21 exposed cases).

A US study involved 218 cases of systemic lupus erythematosus; 178 first- and second-degree relatives and 186 friends were identified by the patients as being close to them in age, race and sex and served as controls. No excess risk was found for hair dye use during the five years prior to diagnosis (OR compared to friends, 0.92; 95% CI, 0.59–1.45; OR compared to relatives, 1.33; 95% CI, 0.83–2.12) (Petri & Allbritton, 1992). [The Working Group noted that the choice of controls may have biased the frequency of hair dye use.]

### 4.2.3 *Hair lacquers and pulmonary disease*

Ameille *et al.* (1985) reviewed the evidence for possible associations between respiratory lesions of various types and inhalation of hair lacquers. The link was first suggested by Bergmann *et al.* (1958), who considered that the pulmonary findings in two cases were secondary to thesaurosis, which involves storage of nonbiodegradable macromolecules in the reticuloendothelial system. A further 15 case reports on about 30 individuals showed similar associations, with pulmonary radiological anomalies and associated symptoms regressing six months on average after cessation of exposure. McLaughlin *et al.* (1963)

observed that in a case of interstitial pulmonary disease in a hairdresser, clinical and radiological signs resolved after cessation of exposure to shellac-based hair spray but reappeared after recommencement of exposure. Valeyre *et al.* (1983) reported a case of diffuse interstitial pulmonary disease in a woman aged 66, which regressed after cessation of use of hair lacquer. The presence of the lacquer was demonstrated in a lung biopsy. No case of thesaurosis, however, was diagnosed in more than 1500 hairdressers surveyed in a number of countries (Ameille *et al.* (1985).

Palmer *et al.* (1979) compared the prevalence of respiratory disease in 213 licensed, practising beauticians, 262 student cosmetologists and 569 women who were not exposed to hair sprays as part of their occupation, in Utah, USA, using a respiratory symptom questionnaire, chest x ray and forced expiratory spirogram. The prevalences of radiological abnormality and/or reduced forced vital capacity, which were considered to be signs of possible thesaurosis or sarcoidosis, were 6.1% in practising beauticians, 1.1% in student cosmetologists and 2.8% in controls. The prevalences of a third sign, reduced diffusing capacity of the lung, which was assessed only in every tenth person, were 16.2, 10.5 and 11.4%, respectively. Some 12% of cosmetologists and 8% of controls reported 'abnormal' respiratory symptoms, the percentages being adjusted for smoking habits and geographical area. None of the differences was significant, but the authors reported that the difference was significant when the two categories of symptoms were combined. Among cosmetologists, particulate concentrations (as determined by personal samplers) were 0.48 mg/m$^3$ for those considered to have 'abnormal' symptoms on the basis of a questionnaire and 0.51 mg/m$^3$ for those with 'borderline' symptoms; each of those levels is significantly higher than the 0.36 mg/m$^3$ for cosmetologists who had 'normal' respiratory function. No difference in the prevalence of abnormal chest x rays was found between cosmetologists and controls, and there was no substantial difference between the groups in the frequency of restrictive or large-airway obstructive disease. Employees working in small salons, however, which the investigators found had more limited ventilation than large salons, had significantly reduced forced expiratory flow rates, suggesting some obstructive effect in the small airways. For all cosmetologists, the forced expiratory flow rate decreased with increasing number of years worked in cosmetology. In the subsamples for which lung closing volume measurements were obtained, a higher prevalence of abnormality was observed among beauticians, but none of the differences was significant. In the 40% of subjects from whom sputum samples were obtained, 42% of the cosmetologists had atypia, which is significantly higher than the 22% in control subjects. The major contribution to the difference was employees working in small salons. Particulate concentrations were similar in cosmetologists with normal and abnormal sputum cytology.

The cosmetologists in the study of Palmer *et al.* (1979) who were suspected to have thesaurosis were re-examined two years later (Renzetti *et al.*, 1980). The radiological anomalies and anomalies of pulmonary function had regressed in the majority of subjects (5% compared to 4% in controls), all but one of whom had continued working as a cosmetologist.

#### 4.2.4 *Experimental data*

Pulmonary granulomas were found in albino rats after prolonged inhalation of various types of hair lacquers (Vivoli, 1966). Thesaurosis was not induced in rabbits (Draize *et al.*,

1959), rats (Brunner *et al.*, 1963; Lowsma *et al.*, 1966; Ameille *et al.*, 1984), guinea-pigs (Calendra & Kay, 1958; Brunner *et al.*, 1963) or dogs (Giovacchini *et al.*, 1965) after repeated inhalation of hair sprays. Chronic exposure of mice, rats, rabbits and dogs to hair dye formulations by various routes gave no indication of adverse effects on haematopoiesis or other systemic effects (Kinkel & Holzmann, 1973; Burnett *et al.*, 1975, 1977, 1980; Burnett & Goldenthal, 1988).

In a chronic feeding study, a composite test material containing 0.24% Acid Orange 3, 1.63% HC Blue No. 2, 0.64% Celliton Fast Navy Blue BRA (mixture of Disperse Yellow 1, Disperse Blue 1, Disperse Violet 4, Disperse Red 17), 0.24% 2-nitro-*para*-phenylenediamine, 0.16% 4-nitro-*ortho*-phenylenediamine, 0.05% 2-amino-4-nitrophenol, 0.31% HC Yellow No. 4, 0.4% Disperse Violet 11, 0.61% Disperse Blue 1, 0.13% Disperse Black 9, 1.54% HC Blue No. 1, 0.02% HC Red No. 3, 0.65% HC Yellow No. 3, 0.28% HC Yellow No. 2 plus base, representative of commercial semi-permanent hair dyes, was incorporated into the diets of male and female beagle dogs (Wernick *et al.*, 1975). Groups of six dogs of each sex were fed the composite at doses of 0, 19.5 or 97.5 mg/kg bw per day for two years. Physical examinations and clinical analyses of blood and urine were performed after 3, 6, 12, 18 and 24 months of the study. One dog of each sex was necropsied at 6, 12 and 18 months, and all survivors were necropsied at 24 months. All dogs fed the composite material excreted blue–brown urine, indicating systemic absorption of the dyes. The weight gain and physical, clinical and histological indices were normal.

In 13-week dermal toxicity studies, nine oxidative and three semi-permanent composite test materials, representative of commercial hair dye formulations, were applied twice weekly to the shaved dorsolateral skin of six male and six female New Zealand rabbits (Burnett *et al.*, 1976). The semi-permanent formulations were applied without dilution, while the oxidative formulations were mixed 1:1 with 6% hydrogen peroxide immediately prior to application. The applied dose in each case was 1 ml/kg bw. Application sites were abraded on three rabbits of each sex; all rabbits were restrained for 1 h after treatment, then were shampooed, rinsed and dried. Haematological and clinical chemical tests were performed at weeks 0, 3, 7 and 13: no toxic sign was noted, and there was no meaningful change in haematological or clinical parameters. Slight epidermal hyperplasia associated with some of the oxidative formulations was seen in 25 tissues collected at necroscopy for microscopic examination.

One commercial non-oxidative colouring formulation, containing 0.3% HC Blue No. 1, several other colouring agents and 23% of 40% active sodium lauryl sulfate, was applied at 50 µl to the skin of random-bred Swiss Webster mice of each sex three times a week for 20 months. Survival and mean body weights were similar in dosed and control animals. Haematological analyses (haemoglobin, haematocrit, red blood cells, total or differential white blood cells) and urinary tests indicated no toxic effect, but significant increases in the degree of chronic inflammation of the skin were observed in all treated animals in comparison with controls (Jacobs *et al.*, 1984).

## 4.3 Reproductive toxicity and developmental effects

### 4.3.1 *Humans*

Vaughan *et al.* (1984) noted a small excess of spontaneous abortions among hairdressers from the 1980–81 birth records of Washington State, USA (RR, 1.4; 95% CI, 1.2–1.7).

In the 1980 US National Natality and National Fetal Mortality Survey, no difference in the prevalence of malformations (1.9%) or of fetal deaths (1.6%) was found among offspring of women employed in beauty and barber shops from that in the whole sample. A nonsignificant difference was noted in the prevalence of low-birth-weight infants (2.5%) (Shilling & Lalich, 1984).

A total of 40 346 congenital malformations routinely notified during 1980–82 in England and Wales were analysed with regard to parental occupation (McDowall, 1985). Paternal occupation was reported for 62% and maternal occupation for 28%: 298 mothers and 49 fathers were categorized as hairdressers, barbers and hairdressing supervisors, managers and proprietors. The rates of all malformations and of specific malformations were not significantly different from those in the overall group.

A survey was carried out of spontaneous abortion and maternal occupation during pregnancy in Montréal, Canada (McDonald *et al.*, 1986), in maternity units in which 90% of births in the city are estimated to occur. Interviews were done with 51 885 hospitalized women who delivered at term (participation rate, 90%) and 4127 hospitalized women who were undergoing a spontaneous abortion (participation rate, < 75%). The interviews identified 48 608 previous pregnancies, 10 910 of which had terminated spontaneously in abortion whether in hospital or elsewhere. The expected numbers of abortions were adjusted for maternal age, parity, history of previous abortion, smoking habits and educational level reached. Hairdressers were represented by 458 current pregnancies, of which 34 ended in spontaneous abortion, and 417 previous pregnancies, of which 102 ended in spontaneous abortion; the observed:expected ratios were 1.05 and 1.08 ($p > 0.1$), respectively. A subsequent analysis for spontaneous abortion, low birth weight and congenital defects among women who had worked at least 30 h per week at the beginning of their pregnancies showed no excess risk among 688 hairdressers (McDonald *et al.*, 1987).

In another analysis (McDonald *et al.*, 1988a), the 22 613 previous pregnancies in which the woman had been employed for at least 30 h a week at the time of conception were evaluated with regard to the period of pregnancy at which fetal death occurred. Of 354 pregnancies among hairdressers, 83 had terminated in fetal death, 76 before the 16th week, six between the 16th and the 27th week and one after the 27th week; the corresponding observed: expected ratios were 1.1, 0.6 and 0.3 (none was significant). Similar ORs were estimated in a separate case–control analysis of the same study (Goulet & Thériault, 1991), which included 227 fetal deaths of 20 weeks' gestation or more without major malformations and a similar number of live-born controls matched on maternal age and gravidity. The OR associated with maternal employment in hairdressing was 0.3 (95% CI, 0.1–1.7; 2/6 discordant pairs) for fetal deaths at 20–27 weeks' gestation and 0.1 (95% CI, 0.0–1.4; 1/6 discordant pairs) for fetal deaths at ≥ 28 weeks' gestation. The combined OR was 0.1 (95% CI, 0.0–0.3).

In the same data base, the association between congenital defects in index and previous births and maternal occupation for at least 15 h per week at the time of conception was investigated. Of 714 pregnancies among hairdressers, 17 resulted in offspring with congenital malformations, comprising three chromosomal errors, seven 'developmental defects probably arising in the first few weeks of gestation' and seven 'musculoskeletal defects and hernias perhaps related to influences after the first trimester'. The corresponding observed:expected ratios were, respectively, 2.3, 0.9 and 0.8; none was statistically significant (McDonald *et al.*, 1988b).

Tikkanen *et al.* (1988) analysed data on cardiovascular anomalies for the period 1980–81 from the Finnish Register of Congenital Malformations; 160 infants with specific anomalies confirmed by a paediatric cardiologist were compared with 160 controls. 'Substantial' exposure to 'hairdresser's chemicals' was reported for no case and six controls. A previous analysis of the same data base identified 34 children with hypoplastic left ventricle; regular maternal use of aerosols (deodorant or hair sprays) was reported for 44.1% of case mothers and 23.9% of 752 control mothers (Tikkanen, 1986).

A report on all 6166 naturally terminated pregnancies in the district of Gottwaldov in Czechoslovakia in 1981–83 described an increased proportion of reproductive losses, but not premature births, in an unspecified number of hairdressers (Mareš & Baran, 1989).

### 4.3.2 *Experimental systems*

No evidence of teratogenicity was seen when hair dye formulations were applied to the skin of pregnant rats and rabbits (Wernick *et al.*, 1975; Burnett *et al.*, 1976) or when individual hair dye components were administered by gavage or subcutaneous injection to pregnant rats and mice (Marks *et al.*, 1981; DiNardo *et al.*, 1985). Similarly, topical application of hair dye formulations produced no adverse reproductive effect in rats in a multigeneration study (Burnett & Goldenthal, 1988) or in a test for heritable translocation (Burnett *et al.*, 1981; see p. 104 for a detailed description).

#### (*a*) *Reproduction*

In a study of fertility and reproductive performance, a composite test material, representative of commercial semi-permanent hair dye formulations (see p. 97), was incorporated into the diets of Sprague-Dawley rats at 0, 1950 or 7800 ppm (Wernick *et al.*, 1975). Groups of 10 male rats fed the test diet for eight weeks prior to and throughout the mating period were mated with groups of 20 females fed the basal diet. Groups of 10 male rats fed the basal diet were mated with groups of 20 females fed the test diet for eight weeks prior to mating and throughout mating, gestation and lactation. One female made pregnant by each male was killed in mid-pregnancy in order to evaluate the status of the uterine contents. The remaining dams were allowed to deliver litters normally and to maintain pups until 21 days of age. Systemic absorption of dyes was indicated by the production of blue–brown urine by all animals receiving the treated diet, but no reduction in food consumption or body weight gain was associated with exposure. Similarly, there was no evidence of an adverse effect on fertility or other reproductive parameters in exposed male or female rats.

Six composite test materials, representative of commercial oxidative hair dye formulations, were evaluated in rats in a two-generation study of reproduction (Burnett & Goldenthal, 1988). Test materials were mixed 1:1 with 6% hydrogen peroxide and then applied at 0.5 ml twice weekly to the clipped backs of 20 male and 20 female Sprague-Dawley rats. The $F_0$ rats began treatment at six to eight weeks of age, and rats of the second litter ($F_{1b}$) began treatment at weaning. Breeding for both generations began at 100 days of age, and skin applications continued throughout mating, gestation and lactation periods. Occasional mild dermatitis was the only adverse effect noted. Body weight gain, food consumption, survival and reproductive indices (fertility, gestation, live birth and survival, weaning weight) in $F_{1a}$, $F_{1b}$, $F_{2a}$ and $F_{2b}$ litters were unaffected by the treatments.

(*b*) *Teratogenesis*

A composite test material, representative of commercial semi-permanent hair dye formulations (see p. 97), was evaluated for teratogenic potential in rats and rabbits (Wernick *et al.*, 1975). Groups of 20 pregnant CFE-S rats were fed diets containing 0, 1950 or 7800 ppm of the material on gestation days 6–15, and groups of 12 pregnant New Zealand rabbits were dosed by gavage on gestation days 6–18 with 0, 19.5 or 97.5 mg/kg bw. All animals receiving the composite produced blue–brown urine, indicating systemic absorption of dyes, but food consumption and body weight gain were unaffected in both species. Similarly, there was no evidence in rats or rabbits of an adverse effect on intrauterine growth or development or of treatment-related gross, visceral or skeletal malformation.

The teratogenicity of nine oxidative and three semi-permanent composite test materials, representative of commercial hair dye formulations, was tested by Burnett *et al.* (1976). The materials were applied to the shaved dorsoscapular area of pregnant Charles River CD rats in groups of 20 on every third day of gestation (days 1, 4, 7, 10, 13, 16 and 19). The semi-permanent formulations were applied without dilution, while the oxidative formulations were mixed 1:1 with 6% hydrogen peroxide immediately prior to application. The applied dose in each case was 2 ml/kg bw per day. No maternal toxicity was observed, there was no effect of treatment on implantation or untrauterine growth or survival, and there was no evidence of external, visceral or skeletal malformation.

Five oxidative dyes (12.5, 25 or 50 mg/kg bw 4,4′-diaminodiphenylene sulfate, 50, 100 or 200 mg/kg bw *N*′-(2-hydroxyethyl)-4-nitro-*ortho*-phenylenediamine, 110, 220 or 450 mg/kg bw 2,3-dihydroxynaphthalene, 50, 100 or 150 mg/kg bw *N*,*N*-dimethyl-*para*-phenylenediamine and 125, 250 or 500 mg/kg bw resorcinol) used in hair colouring formulations were evaluated for teratogenicity in Sprague-Dawley rats (DiNardo *et al.*, 1985). Groups of 10–13 pregnant rats were administered the low, intermediate or high doses by gavage on days 6–15 of gestation. Significant reductions in maternal body weight gain during days 6–16 of gestation were seen in rats treated with the high doses of 4,4′-diaminodiphenylene sulfate, *N*′-(2-hydroxyethyl)-4-nitro-*ortho*-phenylenediamine and 2,3-dihydroxynaphthalene; the high doses of *N*,*N*-dimethyl-*para*-phenylenediamine and resorcinol reduced maternal body weight gain during treatment, but not significantly. There was a significant compensatory increase in maternal body weight gain after treatment (on days 16–20) with the high doses of 4,4′-diaminodiphenylene sulfate and *N*′-(2-hydroxyethyl)-4-nitro-*ortho*-phenylenediamine. None of the dyes impaired implantation, intrauterine growth or survival or external, visceral

or skeletal malformation. [The Working Group noted the small number of animals used in the study.]

## 4.4 Genetic and related effects

### 4.4.1 *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.*, 1978a,b) in the United Kingdom. Information was recorded on smoking habits, alcohol consumption, use of medicinal drugs and drugs of abuse, infections, vaccinations and exposure to x rays; details of occupational exposure to hair dyes were collected: women had done an average of 11 000 permanent and 5000 semi-permanent tinting operations and men, 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 last hair tint application (to themselves or clients) was not recorded. More gaps were found per cell among female tinters than controls (0.065 *versus* 0.048; $p < 0.02$) but not among male tinters (0.064 *versus* 0.063). The number of breaks per cell (assumed from the observed aberrations) was not altered among women (0.028 *versus* 0.031) but was lower among men (0.034 *versus* 0.047; $p < 0.05$). Exclusion of subjects exposed to high doses of diagnostic x rays or who had recently had viral infections removed these differences (breaks in tinters *versus* controls: women, 0.023 *versus* 0.027; men, 0.036 *versus* 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 *versus* not dyed, 0.031 *versus* 0.018; $p < 0.02$) and lower among men who dyed their hair (0.023 *versus* 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 stated] 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 record that 20/23 female and 11/18 male tinters wore protective gloves for all applications of permanent and semi-permanent tints and deduced that most of the subjects would receive greater exposure to hair-dye components when their own hair was treated. [The Working Group noted that most aberrations were of the chromatid type and were, therefore, likely to have occurred recently; the absence of information on the actual dyes used recently by the subjects is regrettable, since some components are relatively potent clastogens while others are not.] The finding that the number of breaks per cell was lower among men who dyed their hair 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.* (1978a) based their argument on the observation of Court Brown *et al.* (1966) that there was much less chromosomal damage of all types in 48-h blood cultures from men aged 15–24 than from men aged 25–34, whereas there was no difference among women in these age ranges. [The

Working Group noted that the results of subsequent studies, by Hedner *et al.* (1982) and Ivanov *et al.* (1978), do not confirm the latter observations.]

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 ± 67; 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, 24 h after a sham dyeing (no dye or hydrogen peroxide) and 24 h 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 aberration (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).

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

In a study in the USA involving 30 women aged 45–60 years, mutagenicity was determined in urine specimens collected prior to and during a 24-h period immediately after application of dark shades of several hair colouring products containing high levels of dyes and dye intermediates (Burnett *et al.*, 1979). 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.]

A study was conducted 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 twice that of a control group of 87 female dental personnel (29% *versus* 15%) (Babish *et al.*, 1991). The two groups were matched for median age, smoking status and proportion of subjects (13–16%) who had had their hair permanent-waved 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 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 to dental personnel. [The Working Group noted the inadequate reporting of the results.]

### 4.4.2 *Experimental systems*

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 eliminated 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 (Albano *et al.*, 1982).

Forty products chosen from among 12 brands of commercially available hair colourants used in New Zealand were tested for mutagenicity in *S. typhimurium* TA98 and TA100 without S9; activators were added when recommended (Ferguson *et al.*, 1990). Twenty-three 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).

Two of four commercial hair dye formulations containing phenylenediamines and aminophenols (two of which also contained 2,5-diaminophenol) and 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 (Watanabe *et al.*, 1990).

Two commercial oxidative hair colouring products were applied at 10–30 ml, both with (10–30 ml) and without hydrogen peroxide, to the backs of male Sprague-Dawley rats [number unspecified]. Both colourants contained 1,4-diamino-2-nitrobenzene (see monograph, p. 185) 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 h after product application for four days and tested in *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 h 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 (Ammenheuser & Warren, 1979).

Henna and its active colouring ingredient, 2-hydroxy-1,4-naphthoquinone, were tested 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, only in the absence of S9 (Stamberg *et al.*, 1979).

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

In a study of heritable translocation, groups of 25 male Sprague-Dawley CD rats were painted 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 to 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 prior to use). 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 observed between controls and the two exposed groups. Furthermore, there was no effect on the number of live fetuses, implantations or resorptions at the $F_2$ mating (total litters analysed: 275 controls, 261 oxidation dye group and 271 semi-permanent dye group) (Burnett *et al.*, 1981).

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Since the early twentieth century, hairdressers have made use of a wide range of products, including hair colourants and bleaches, shampoos and conditioners, hair styling preparations and nail and skin care products. Several thousand chemicals are found in formulations of these products. Barbers generally cut only men's hair and make limited use of some of the above products, such as hair dyes, in their work.

Hair colourants are classified as permanent (primarily aromatic amines and aminophenols with hydrogen peroxide), semi-permanent (nitro-substituted aromatic amines, aminophenols, aminoanthraquinones and azo dyes) and temporary (high-molecular-weight or insoluble complexes and metal salts, such as lead acetate). The numerous individual chemicals used in hair colourants have varied over time. Only permanent and semi-permanent hair colourants are used to a significant extent by hairdressers, while consumers at home use any of the three types.

Hairdressers may also be exposed to volatile solvents, propellants and aerosols (from hair sprays), formaldehyde (an antibacterial agent), methacrylates (in nail care products) and trace quantities of nitrosamines, which have been reported in many hair care products.

It is estimated that there are several million hairdressers and barbers worldwide. Few exposure measurements are available. Approximately 35% of women and 10% of men in Europe, Japan and the USA use hair colourants.

### 5.2 Human carcinogenicity data

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

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

Personal use of hair colourants has been studied in seven case–control studies of cancer of the urinary bladder. Overall, these do not indicate an excess risk; however, one study from Denmark found an association with personal use of briliantine, although it had methodological limitations. Following a report in 1976 of an excess of breast cancers among hair dye users in New York, USA, six case–control studies and one cohort study examined this subject. None found evidence of a significant excess among hair dye users overall. One case–control study of non-Hodgkin's lymphoma from Iowa and Minnesota showed a significantly increased risk among male users of hair colouring products. A second case–control study, from Nebraska, showed an excess risk for this malignancy among female users of hair colourants but showed no excess among a smaller number of male users. The case–control study from Nebraska also found a significant excess of multiple myeloma among female users of permanent hair dyes, and another study from Iowa reported a nonsignificant excess of this malignancy in male users of hair colourants. One cohort study in the USA showed no excess risk among hair dye users for all lymphomas combined. One case–control study of neuroblastoma and one of Wilms' tumour showed significantly increased risks for the offspring of mothers who had used hair dyes during pregnancy. Single studies have reported significant excess risks for Hutchinson's melanotic freckle, Hodgkin's disease, leukaemia, malignant tumours of the brain and cancers of the salivary gland, cervix and lower female genital tract. Other studies showed no such excesses.

The higher prevalence of smokers reported among male hairdressers and barbers in some studies is consistent with the overall excess of lung cancer but cannot readily explain the

magnitude of the increase in risk for cancer of the urinary bladder in the European cohort studies. In particular, studies in Switzerland and Denmark have shown significant excesses of cancer of the urinary bladder unaccompanied by appreciable excesses of lung cancer, which further weigh against smoking as the sole explanation for the overall excess. Specific exposures of hairdressers and barbers have not been evaluated in epidemiological studies.

### 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 many studies and by subcutaneous injection in a single study in rats. In one study by skin application in rats, a particular formulation was associated with an increased incidence of pituitary adenomas in females. The other studies either showed no increased incidence of tumours at any site or were inadequate for evaluation.

### 5.4 Other relevant data

Contact dermatitis is a common clinical dermatological problem in hairdressers. Because hairdressers use a wide variety of multicomponent chemical products, it is difficult to determine the specific etiology of their dermatitis, although cutaneous nickel allergy and atopic status have been suggested to play a role. Moreover, many of the products used contain both irritants and sensitizers. Pulmonary toxicity has been associated with the use of hair lacquer by consumers and hairdressers.

No study has reported a significant excess of congenital malformations, early or late fetal death or low birth weight among the offspring of male or female barbers or hairdressers.

No increase was observed in chromosomal aberration frequencies in the lymphocytes of humans exposed to commercial hair colourants which included hydrogen peroxide application. In this and another study, no increase in sister chromatid exchange frequency was found.

A number of different commercial permanent and semi-permanent hair colourants were tested for their mutagenic activity *in vitro*. Many were mutagenic to bacteria. Less than half of the preparations applied to rats resulted in the excretion of bacterial mutagens in urine. Application of a semi-permanent and an oxidation dye colourant topically to male rats had no effect on the reproductive performance of the treated rats and did not induce heritable translocations, as judged by a mating protocol.

### 5.5 Evaluation[1]

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

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[1]For definition of the italicized terms, see Preamble, pp. 26–30.

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

### Overall evaluations

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

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

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