PRINTING PROCESSES AND PRINTING INKS

1. Exposure Data

1.1 Historical overview

The origins of printing can be traced back several centuries. Pictorial prints were produced from cut wood blocks in Japan during the tenth century and probably earlier in China. The first movable type, moulded in clay, can be traced to China in the eleventh century, and wooden type appeared in China in the fourteenth century. In Europe, book production from wood blocks was seen early in the fifteenth century, and Gutenberg introduced cast metal type in the middle of the fifteenth century. These inventions were the basis of the original printing method, namely letterpress printing.

As the first printing was a development from writing and drawing/painting, it was natural that the first printing inks would be based on writing inks and paints. They were composed of lampblack or coloured minerals dispersed in water-soluble gum. However, Gutenberg soon found that the aqueous gum solution-based inks did not wet metal type surfaces satisfactorily. The composition of the inks developed by Gutenberg is not known with certainty but was probably derived from the artists' paints of the time. These were based upon vegetable oils, such as linseed or nut oil, which were heated to increase their viscosity and fortified with natural rosin; to accelerate drying, metal salts were added. The first clear records of compositions of printing inks date from the seventeenth century and are of this nature (Wood, 1994).

Until the middle of the eighteenth century, printers made their own inks. When the specialist industry of ink manufacture began to develop, the ink supplied was little more than a concentrated pigment dispersion. Any skilled printer considered that he was a craftsman and would modify the ink that he purchased with his own 'secret' additives to give the printing properties that he wanted.

During the eighteenth century, there were many publications of printing ink formulations. They all followed the same basic composition but included the use of other vegetable oils and natural resins, gave more details about the pigments used and focused on the details of the manufacturing methods. Throughout this period, a significant hazard to the ink makers (in terms of fires, vapours and spills) was in the heating of the various oils. Some of the processing even required the hot oils to be ignited and then extinguished with a metal cover.

The lithographic (or litho) process was introduced in 1796 in Germany by Alois Senefelder. This process relied upon a particular type of hydrophilic limestone upon which images were drawn with greasy inks. These images were then receptive to oil-based inks, while the remainder of the surface was not. The first lithographic inks were

composed of beeswax, tallow soap and lampblack, again produced by heating and burning.

Gradually, the basic composition of letterpress and litho inks began to converge, with rosin-fortified linseed oil being the basis of most coloured inks and rosin oil or mineral oils being the basis of blacks. The difference between the inks for the two processes was minor, but important; the litho inks contained additives and had a substantially higher viscosity.

The invention of phenol–formaldehyde resins and the introduction of oil-soluble formulations in the 1920s initiated the era of synthetic resin media. Then in 1936, petroleum distillates were introduced to create the two-phase quick-setting mechanism that is the basis of the majority of conventional letterpress and litho inks used today (Wood, 1994).

Although printing was carried out by letterpress for many centuries, this process has declined rapidly in the last two decades and is now limited to a few specialist applications and those sectors where older equipment has yet to be replaced.

Rotary letterpress printing from rubber printing plates (stereos) originated around 1890 and took the name 'aniline printing' from the aniline-derived dyes that were dissolved in water or alcohol to make the ink. The crude process has been refined since then, particularly over the last 30 years, and has developed into a discrete process in its own right under the name of flexographic (or flexo) printing. The basic dyes still have limited use but modern inks are based upon synthetic pigments in a wide range of synthetic media dissolved in volatile solvents, such as industrial methylated spirits (denatured ethanol).

The intaglio process, in which the image is engraved as a recess in a metal plate, was probably first used for printing purposes in the fifteenth century. A very viscous ink, which was likely to be similar to the letterpress inks of the time, was wiped over the surface so that it filled the recesses but was removed from the surface. A much refined form of this basic process is still in limited use for high-security printing such as the printing of bank notes.

An evolution of the intaglio process occurred in 1852 with the introduction of a method of etching the image into the plate rather than relying on the highly skilled art of engraving. This has led to the rotogravure or gravure process of today. A coating of dichromated gelatine was exposed to sunlight and then etched with a solution of ferric chloride. A variety of techniques were used over the years to control the depth of the etching and thus the strength of the print produced. Modern production is by mechanical or laser engraving so that the light-sensitive coatings and etchants have largely fallen out of use.

In the early days, the gravure inks were similar to those of intaglio printing. By the end of the eighteenth century, metal 'doctor blades' had been introduced to replace the wiping of the surplus ink with a cloth, but the inks remained the same. It was not until the end of the nineteenth century that the 'liquid' inks were introduced. The earliest of these were water-based and probably similar to the aniline inks of the time. These were

later abandoned in favour of inks containing hydrocarbon solvents and natural or synthetic resins.

Screen printing is a small segment of the printing industry, for which the history is less well recorded. As a development of stencilling, the process has been in use for many centuries, primarily for the decoration of textiles. In the 1920s, it started to attract attention as a convenient way of producing short runs of posters and for printing on difficult surfaces such as glass. The process has developed as a means of depositing heavy films of ink upon a wide variety of substrates, often of difficult shape. In the early days, no suitable inks were available for screen printing, and use was made of ordinary decorative paints. Modern screen printing inks are based on a wide range of synthetic resins and polymers in a range of solvents with suitable volatility.

At the end of the 1960s, a totally new technology, ultraviolet (UV) (see IARC, 1992) curing, was introduced into printing ink formulation (Carlick, 1971; Hargreaves, 1995). These 100%-solids systems polymerize by mechanisms of free radicals or acid catalysis initiated by irradiation with suitable wavelengths of UV radiation. The technology was initially developed for litho and letterpress printing but soon spread to screen ink formulations and is now being introduced to flexo and gravure printing.

Although the smallest companies and industries in lesser developed regions may still use older technologies, the printing and printing ink industries today are generally very different from those of 50 years ago. Rapidly changing technologies, automation and computer control, and safer materials and processes characterize the industries today in the developed countries.

For reviews on historical overview, see Leach and Pierce (1993), Wood (1994) and Taggi and Walker (1996).

1.2 Description of the industry

The manufacture of printing inks and the major printing processes have been described in several reviews (National Association of Printing Ink Manufacturers, 1988; Williams, 1992; Leach & Pierce, 1993; Taggi & Walker, 1996).

1.2.1 *Printing ink manufacture*

The development of printing inks followed somewhat different paths, depending upon the printing process. Letterpress and litho printing use high-viscosity inks that are formulated using low-volatility materials and are generically known as 'paste' or 'oil' inks. The flexo and gravure processes use low-viscosity inks formulated with volatile solvents and are known collectively as 'liquid' inks. Screen printing inks generally are of intermediate viscosity. Ink manufacturers tend to specialize in one of these three areas, with only the largest companies covering a broader field.

The companies in the industry range from large international groups (of which Japanese-based Dainippon Ink & Chemicals and French-based Coates Lorilleux (The Freedonia Group, 1995) are the biggest) to small companies with less than 10 employees. For example, there are thought to be over 200 ink manufacturers each in the United

States of America (National Association of Printing Ink Manufacturers, 1988) and in Europe.

Generally, the large groups have associations with chemical companies that provide resin or pigment manufacturing resources. It is usually these groups that develop the new technology that drives the industry forward; they manufacture their products from the raw materials of pigments, resins, oils and solvents, and supply the largest printing companies or groups. The smaller companies focus upon products of established technology supplied to small- to middle-sized users. Commonly, manufacture of their inks is from partly processed intermediates, such as varnishes and pigment dispersions, which are bought from specialist manufacturers. Their business is generally based upon providing good service in areas where the major ink manufacturing groups find it uneconomical to do so.

1.2.2 *The printing processes*

The printing industry itself is equally varied with a limited number of very large groups and many small printers. Whatever the size, there is a tendency to concentrate on one, or at the most two, of the different printing technologies described below. Each of the processes has its own characteristics, summarized in Table 1.

(*a*) *Lithography*

Lithography is the most widespread of the printing processes and is probably used by more individual companies than all the other processes combined.

The litho process depends upon the ability to make the non-image areas of the planar printing plate hydrophilic, and thus readily wetted by water, and to make the image areas oleophilic, and thus readily wetted by oil-based inks. The plate is then wetted with a water-based fountain (damping) solution and inked with the oil-based ink. The development of the modern litho process has been made possible by the introduction of 'offsetting', in which the ink film is transferred from the printing plate onto a rubber blanket and then offset onto the substrate. This offsetting process prolongs plate life, particularly when printing on metal, and also improves the quality of print on substrates of poor smoothness.

The printing plate most commonly consists of a thin flat sheet of aluminium that has been treated to make the surface hydrophilic. Onto this is placed a light-sensitive polymer coating that is exposed to UV radiation through a film (which is positive or negative depending on the coating). The non-image areas are then developed away to expose the hydrophilic surface. Modern processing is usually in self-contained equipment that restricts any exposure of the operator to the developing solutions involved. Aqueous developers are replacing solvent-based systems. The metal plate is replaced by paper or polyester materials for some short-run small-format printing.

The paper or other substrate being printed can be fed into the press as individual sheets and delivered as a pile of sheets (sheet-fed litho) or as a continuous reel (web offset) that is converted to the finished publication after printing. Web offset printing can be further subdivided into cold-set web offset (with inks drying by penetration) and heat-

set web offset (with inks drying by evaporation in gas-heated ovens). The sheet-fed process is generally used for printing a wide variety of commercial/advertising print and cartons whereas web offset is used for newspapers and magazines.

Table 1. Main characteristics of the printing processes

Printing process		Ink film thickness (μm)	Substrate types	Typical applications
Offset litho	Sheet-fed	< 2	Wide range of paper and board, plastic sheet and metal	All general print, business forms, technical documentation, packaging, promotional, magazines, credit cards
	Web-fed			
	Heat-set	< 2	Wide range of coated and uncoated paper	Magazines and similar format products
	Cold-set	< 2	Newsprint	Newspapers
Letterpress	Rotary	3–4	Newsprint, self-adhesive materials	Newspapers, labels
	Offset	< 2	Plastic containers, metals	Dairy product and drinks containers
Flexography	Narrow web	0.75–2	Paper and plastic film	Labels, flexible packaging
	Wide web	0.75–2	Newsprint	Newspapers
		0.75–2	Wide range of plastic film, paper, corrugated cardboard	Boxes and many other types of packaging, sacks
Gravure	Large web	< 6	Coated or uncoated paper	Magazines and similar products, mail order catalogues, wood grain patterns
	Smaller web	< 6	Coated or uncoated paper, plastic films, board	Packaging (especially flexible), cigarette cartons, postage stamps
	Sheet	< 6	Paper	Fine art reproductions
Screen		< 30	Card, fabric, wide range of plastic, shaped containers	Point-of-sale displays, plastic containers, labels, T-shirts
Intaglio		< 30	Paper	Bank notes, security documents

From Leach & Pierce (1993), except letterpress data which have been compiled by the Working Group

The inks used are high-viscosity products based upon low-volatility resins and oils. The printing press is cleaned after use with solvent washes using volatile organic solvents, usually hydrocarbons, although there is now a move towards vegetable oil-based cleansers and even water-based cleansers (Searle, 1993).

A major segment of the lithographic printing industry is the cold-set web offset printing of newspapers using lower-viscosity inks that run on high-speed presses and are prone to misting, but less so than with rotary letterpress.

(*b*) *Letterpress*

Letterpress is a 'relief' printing process — that is, the image area is raised above the non-image area. The raised image area is inked before being brought into direct or indirect contact with the substrate to be printed. The more specialized applications that have developed over the last two decades have made greater use of offset letterpress, where the image is transferred via a rubber blanket.

Traditionally, the raised image was a lead alloy type or etched metal plates, but these have largely been replaced by photopolymer plates that are exposed to either negative or positive film and developed in dedicated equipment. Aqueous developers are replacing solvent-based systems.

Sheet-fed letterpress has declined to such a degree that it is of little more than historic interest today in industrialized countries. The same is true of the use of rotary letterpress in the printing of newspapers. The one sector in which letterpress is still of major importance is the printing of reel-fed self-adhesive labels, but even there its use is now in decline. The inks most widely used for rotary label printing are UV-cured, although there is still some use of heat-set inks. The inks used for letterpress printing are very similar, and sometimes identical, to those used for lithography.

(*c*) *Flexography*

Although the newest of the major print processes, flexography (or flexo) is now the most important process for the production of flexible packaging. A number of other applications include corrugated cases, tickets, forms, directories, paperback books, comics and newspapers.

The process is similar to letterpress in that the image area is raised above the non-image area. An inking roller is positioned in an ink duct and runs in contact with an engraved metering roller known as the 'anilox'. This controls the amount (film weight) of ink that is transferred to the surface of the printing plate. At one time, the two processes were easily differentiated because letterpress used metal type plates and flexo used rubber stereos. Now both may use photopolymer plates. Although the distinction between letterpress and flexo is becoming blurred in some areas, this is not the case in the most important sector, namely flexible packaging, where the use of letterpress is insignificant. The dry ink film weight deposited in flexo is similar to that of litho and thus generally lower than that of letterpress.

The majority of flexo printing is web-fed with the main exception being the printing of corrugated cartons that are fed in as sheets.

The inks used for flexo are of low viscosity and are based upon a wide range of synthetic resins dissolved in low-boiling solvents. The drying process requires the removal of these solvents, usually by evaporation. However, there is a rapidly increasing

interest in UV-cured (Atkinson, 1995) and water-based inks (Williams, 1994a,b) in an effort to reduce the emissions of volatile organic compounds.

(*d*) *Gravure*

The printing image for gravure consists of recessed cells engraved in a metal cylinder. This image cylinder runs directly in the ink duct so that both the cells and the surface of the cylinder are flooded with ink. A reciprocating metal doctor blade held against the rotating cylinder scrapes the surplus ink from the non-image surface of the cylinder. The substrate, usually in web form, is held against the cylinder by an impression roller so that transfer of the ink takes place. The printed substrate then passes through a heated drying oven to remove the solvent by evaporation.

Until the mid 1980s, chemical etching of the copper cylinder through a gelatine image resist with ferric chloride solution was the usual process. Because of the difficulty in maintaining consistent quality and the potential hazard of ferric chloride, this has now been largely replaced by electromechanical or laser engraving.

The cells in the image vary in surface area according to the screen ruling being used. However, with a typical 60-lines/cm screening, the cells will be about 125 μm across and the depth will vary from 2 μm in the highlights to 40 μm or more in the shadows. The result is an ink film that varies in thickness according to the density of colour and can be up to three times as thick as that deposited by litho or flexo.

There are two sectors in the gravure printing industry: production of flexible packaging similar to that of flexo, and publication gravure that produces long-run magazines. With flexible packaging, gravure is generally preferred to flexo, since higher print quality is required and longer runs are used, and the high set-up costs can be recovered. In publication, gravure is again preferred to web offset for the long runs where it is more cost-effective.

The inks used are similar to those of flexo printing, although hydrocarbon solvents can be used as there are no rubber parts in the printing unit.

(*e*) *Screen process*

Unlike those used in other mainline printing processes, screen printing (sometimes called silk screen or screen process) inks do not have to transfer from an image surface to the substrate but actually pass through the image, which is the stencil on the screen.

The screen consists of a fine mesh, usually nylon or polyester, but sometimes stainless steel, stretched over a metal frame. The stencil is produced by coating the mesh with a photosensitive coating, exposing it to UV radiation through a positive film and developing away the unexposed image areas. The open areas of the screen around the stencil are blocked with screen filler, using volatile solvents such as xylene (see IARC, 1989a) or dichloromethane (see IARC, 1987a).

The inks used are intermediate in viscosity between those used for litho and those used for flexo or gravure. Evaporation, oxidation, chemical curing and UV curing methods are all used for drying in screen printing. As with the other printing processes, there is growing use of UV- and water-based inks (Pfirrmann, 1994).

Screen printing is the most versatile process and can cover much work that is impossible by other means — it can print on curved surfaces, even those that are not totally regular or symmetrical; it can deposit a heavy ink film that is very much more durable than those applied by other processes; and it can be used on a wide range of surfaces including fabrics, plastics, metals, glass and printed circuit laminates as well as on paper and board. Above all, origination costs and set-up times can be very low so that short-run work is economically viable. As a result, the importance of the process has grown steadily over recent years.

1.3 Chemistry and uses of printing inks

The chemistry and composition of printing inks have been reviewed (National Association of Printing Ink Manufacturers, 1988; Williams, 1992; Kübler, 1993; Leach & Pierce, 1993; Bassemir *et al.*, 1995).

Among other factors, the formulation of a printing ink must take into account the printing process, the type and speed of the press, the characteristics of the substrate (the base material which is coated or printed) and the end use and desired appearance of the final printed product. For this reason, most printing inks are custom-made for specific applications. It is estimated that nearly a million new ink formulae are prepared each year and that several millions are in use (National Association of Printing Ink Manufacturers, 1988).

Printing inks are broadly distinguished by the printing process in which they are used. Letterpress and lithographic inks are known as paste inks and are of higher viscosity than the flexographic and gravure inks, which are called liquid inks. Printing inks are mixtures of three basic types of ingredients: pigments, vehicles and additives. Pigments determine the colour of the ink, including its hue (shade) and strength, and also affect physical properties, such as flow characteristics (rheology), opacity (or transparency), fastness and bleed resistance. Vehicles serve as carriers for the pigment during the printing process and bind the pigment to the substrate. Additives may include any of a very large number of ingredients needed to impart specific characteristics to the ink, such as driers, waxes, plasticizers, antioxidants, lubricants, rheological agents and curing agents.

1.3.1 *Pigments*

Pigments used in printing inks include both inorganic and organic pigments. Opaque pigments reflect light from their surface and therefore can cover or hide the surface on which they are printed. Transparent pigments transmit the light and allow the background on which they are printed to be seen through the film. Some of the most commonly used pigments are described below (National Association of Printing Ink Manufacturers, 1988; Williams, 1992; Kübler, 1993; Bassemir *et al.*, 1995).

(*a*) *Inorganic pigments*

The only black pigment used to an appreciable extent is carbon black (Pigment Black 7), mainly furnace black and thermal black (see separate monograph, this volume). It is used in newsprinting and in publication, commercial and packaging printing, and is

therefore used in large quantities. Different grades of carbon black, varying in particle size, surface condition and structure, are required depending on the application.

Titanium dioxide (Pigment White 6) (see IARC, 1989b) is by far the most commonly used opaque white pigment. Other opaque whites used in printing inks include zinc oxide, zinc sulfide and lithopones (mixtures of zinc sulfide and barium sulfate).

Transparent white pigments, in order of decreasing transparency, include alumina hydrate, magnesium carbonate, calcium carbonate (chalk), blanc fixe (precipitated barium sulfate), talc and clays. Transparent white pigments are also known as extenders, because they are used to reduce the colour strength of inks, as well as to modify ink dispersion and flow characteristics.

Inorganic colour pigments are generally complex mixtures of inorganic salts or minerals, manufactured to meet colour, rheological and other specifications for the particular application. In printing inks, some of these pigments include chrome yellow and chrome orange (mixtures of lead chromate (see IARC, 1990) and other lead compounds (see IARC, 1987b)), iron blue (a series of precipitated complex ferriferrocyanide compounds) and several iron oxide (see IARC, 1987c) and iron silicate pigments (Pigment Red 101 and 102, Pigment Brown 6 and 7). Cadmium (see IARC, 1993a) yellow, orange and red (selenides) and cadmium-mercury red have been used in printing applications where their high stability to light and alkali are advantageous, although their use has reportedly been almost completely eliminated except where extreme chemical resistance properties are required (National Association of Printing Ink Manufacturers, 1988).

Metallic powders (bronzes) also find some use in producing 'silver' (aluminium powder) and 'gold' (copper-zinc alloy powder) inks for packaging and advertising.

(*b*) *Organic pigments*

The printing ink industry uses more organic pigments than any other industry. Approximately 100 organic pigments are suitable for use in printing inks. Most of these pigments are prepared from azo, anthraquinone and triarylmethane dyes, phthalocyanines and vat dyes. Organic pigments are characterized by their high colouring strength, pure shades and transparency. However, as with the inorganic pigments, they are seldom pure chemicals and are classified by colour rather than by chemical composition. Organic pigments known as 'lakes' may be insoluble organic salts or may be produced by depositing organic dyes on one of the transparent inorganic white pigments, usually alumina hydrate.

Yellows are mainly diarylide yellows, Hansa yellows and lake yellows. These yellows are frequently used in place of the chrome yellows to avoid the use of lead and chromate compounds. Diarylide yellows are the principal yellow pigments currently used in printing inks. Pigment Yellow 12, one of the most common diarylide yellows, is a *bis*-azo dye based on 3,3′-dichlorobenzidine (see IARC, 1987d). Hansa yellows are also azo pigments based on toluidine and β-naphthol (Lewis, 1993a).

The most common orange pigment in printing inks is Pigment Orange 34, a diarylide orange. Others include dianisidine orange and Persian orange lakes.

There are more red pigments used in inks than any other organic colour. Some of the more common are the para reds (lakes based on the azo dye from *para*-nitroaniline and β-naphthol), lithol reds (e.g. Pigment Red 57:1, a calcium salt of an azo dye, which is the most important magenta colourant in inks), rhodamine reds (e.g. Pigment Red 81, which is rhodamine 6G laked by precipitation with phosphotungstic and phosphomolybdic acids) and Red Lake C (Pigment Red 53:1 (see IARC, 1993b), which is the barium salt of the azo dye obtained from 2-amino-4-methyl-5-chlorobenzenesulfonic acid and β-naphthol).

Phthalocyanine blues, such as Pigment Blue 15, are the most common organic blue pigments in inks. Peacock blues (Lewis, 1993b) (salts of certain sulfonated triarylmethane dyes, sometimes laked on alumina hydrate) were used in the past. Other organic blue pigments include the victoria blues and the alkali blues.

Phthalocyanines also form green pigments (for example, Pigment Green 7, a chlorinated phthalocyanine). Triarylmethane dyes, the salts of which are used as pigments, include malachite green and methyl violet. Pigment Violet 19, a quinacridone structure, is an example of the anthraquinone-type pigments used in printing inks.

1.3.2 *Vehicles and ink drying*

In a printing ink, the fluid vehicle in which the pigments are dispersed serves not only as a carrier for the pigments but also effects the binding of the pigments to the printed surface ('drying'). The vehicle is also the primary determinant of the tack[1] and flow characteristics of the ink. The drying of printing inks is accomplished in most cases by one or more of the following physical/chemical processes: absorption, evaporation, precipitation, oxidation, quick-setting and radiation curing.

Table 2 gives an overview of the types of vehicles used for various drying systems and printing processes (National Association of Printing Ink Manufacturers, 1988; Williams, 1992; Kübler, 1993; Bassemir *et al.*, 1995). In practice, drying often involves a combination of these physical/chemical processes. For example, so-called quick-setting inks, currently used in most letterpress and offset litho processes where rapid drying is essential, contain a balanced combination of resin, drying oil and solvent; the solvent is rapidly absorbed by the paper, leaving a partially dry or set ink film of resin and oil that subsequently hardens by oxidation (National Association of Printing Ink Manufacturers, 1988).

1.3.3 *Printing inks and processes*

(*a*) *Lithographic (offset) inks*

The broad spectrum of applications for lithography requires a wide variety of inks to serve the needs of the offset printing industry (National Association of Printing Ink Manufacturers, 1988; Kübler, 1993; Bassemir *et al.*, 1995; Pardoen, 1995).

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[1] Tack is a relative measurement of the cohesion of an ink film which is responsible for its resistance to splitting between two rapidly separating surfaces.

Table 2. Printing ink drying systems and vehicles

Drying system	Printing process	Type of vehicle	Examples
Absorption	Newspaper printing (letterpress or cold-set web offset)	Non-drying oil	High-boiling petroleum oils (mineral oil, b.p. 280–350 °C)
Solvent evaporation	Heat-set web offset	Solvent/resin	Lower-boiling petroleum distillates (b.p. within 240–300 °C) with resins and drying oils
	Gravure	Solvent/resin	Toluene (publication gravure), or ethyl acetate and alcohols (packaging gravure) with resins
	Flexography	Solvent/resin	Alcohol, ethyl acetate or water and resins
Oxidation	Letterpress, offset, intaglio	Drying oil/resin	Linseed oil varnish with resins and driers (cobalt or manganese soaps)
Precipitation	Letterpress (specialty)	Glycol/resin	Moisture-set inks (glycol solvent with water-insoluble resin binder)
Radiation curing (UV or electron beam)	All processes	Monomers	Acrylate or vinyl ether/epoxy resins for the oligomers, reactive resins and monomers (with photoinitiators for UV curing)
Quick-setting	Litho, letterpress	Drying oil/resins/ distillate	Linseed oil/resin with petroleum distillate (b.p. 260–280 °C)

Adapted from National Association of Printing Ink Manufacture (1988), Williams (1992), Kübler (1993) and Bassemir *et al.* (1995)
b.p., boiling point

Newspaper offset (cold-set) printing inks are typically very simple. Blacks are carbon black in a high-boiling mineral oil with asphaltic material (bitumen (see IARC, 1987e), gilsonite). Such inks could consist of up to 70% mineral oil (see IARC, 1987f) which, in the past, might have contained up to 15% aromatic hydrocarbons. During the last decade, these mineral oils have been replaced with grades that have about 5% aromatics, of which less than 0.1% are polycyclic aromatic hydrocarbons (PAHs) (see IARC, 1983). Coloured inks generally have a soya bean oil vehicle instead of mineral oil. For recycling of newsprint, the ink must be removable and therefore these inks do not contain binders that undergo significant oxidative cross-linking.

Heat-set web offset inks are designed to produce high-gloss printed images (magazines, books). They contain lower-boiling mineral oils that are removed (within 1 sec) as the printed roll (web) passes through a hot air oven. A typical formulation might be: organic pigments (15–25 wt %), hard resins (25–35 wt %), soft resins and drying oils (5–15 wt %), mineral oil (b.p. 240–260 °C; 25–40 wt %) and additives (5–10 wt %) (Williams, 1992; Kübler, 1993).

Sheet-fed offset inks are used in commercial litho presses for printing, for example, advertising brochures, business papers and packaging, on individual sheets rather than long rolls. Inks are based on phenolic or maleic acid-modified rosin ester and alkyd resins in vegetable drying oils (linseed, soya, tung) diluted with mineral oil. Inks dry by quick-setting, i.e. by absorption and oxidation. A typical formulation would be: organic pigments (12–20 wt %), hard resins (20–25 wt %), soft resins and drying oils (20–30 wt %), mineral oil (b.p. 250–300 °C; 20–30 wt %) and additives (5–10 wt %) (Kübler, 1993).

Radiation-cured offset inks, which are based on acrylate or vinyl/ether monomers, are becoming very important in both sheet-fed and web offset processes. The printed substrate is exposed to UV radiation or an electron beam at the end of the press, and the ink sets within a fraction of a second.

To exclude the oil-based ink from the hydrophilic areas of the printing plate, all offset litho printing processes require water-based fountain or dampening solutions. These solutions are typically slightly acidic aqueous solutions (pH 3.5–5.5) containing small amounts of buffers, alcohols, surfactants, hydrophilic polymers (gum arabic or cellulose derivatives), complexing agents (EDTA, ethylenediamine tetraacetic acid) and preservatives.

(*b*) *Letterpress inks*

While letterpress is being replaced by other printing processes, it is still used to a limited extent to produce newspapers, magazines, self-adhesive labels, packaging and other printed products (National Association of Printing Ink Manufacturers, 1988; Williams, 1992; Kübler, 1993; Bassemir *et al.*, 1995).

Letterpress news ink is similar to web offset inks used to print newspapers.

Moisture-set inks have been used for food packaging printing and contain maleic or fumaric acid-modified rosin products or modified phenolics as binders in glycol solvents. The printed surface is treated with steam or a fine mist of water, and the water-insoluble acidic binders precipitate, setting the ink.

Water-miscible inks maintain the stability of the ink through an organic base that evaporates or is neutralized to induce drying.

A variety of other ink types have been used in letterpress printing, including heat-set, quick-set, water-washable and high-gloss inks (National Association of Printing Ink Manufacturers, 1988).

(*c*) *Flexographic inks*

Flexographic inks are liquid inks, rather than pastes, and are designed to dry quickly primarily by evaporation. Both solvent- and water-based ink systems are used extensively in flexography.

Common solvents in the solvent-based inks include the lower alcohols (ethyl, *n*-propyl, isopropyl (see IARC, 1987g)), usually mixed with esters and sometimes small amounts of higher glycol ethers or aliphatic hydrocarbons to obtain optimum resin solubility, viscosity and drying speed. A wide variety of resins are used in solvent-based

flexo inks, such as nitrocellulose, polyamides, cellulose esters, acrylics and various modified rosins. Although pigments are the most common colourants, there is some use of both basic and metal-complex dyes in flexographic inks. Because much of the flexographic printing is on non-absorbent flexible packaging (polyethylene (see IARC, 1987h), polypropylene (see IARC, 1987i), poly(vinyl chloride) (see IARC, 1987j)), ink additives may include plasticizers to promote formation of a flexible ink film and waxes to add rub resistance (National Association of Printing Ink Manufacturers, 1988; Kübler, 1993; Bassemir *et al.*, 1995).

For environmental reasons, the solvents in ink are being increasingly replaced by water. Approximately 50% of all flexographic inks have water as their primary solvent (Bassemir *et al.*, 1995). Resins in these water-based formulations are generally acidic acrylates or fumaric acid-modified rosin or shellac, neutralized with ammonia or volatile amines, which evaporate from the printed substrate and thereby set the ink film. A typical water-based flexographic ink for paper or paperboard contains: organic pigments (12–15%), resins (10–25%) and additives (5–7%); the remainder is water. For printing on plastics, the ink usually contains a small amount of alcohol (2–5%) and more additives (6–10%) (Kübler, 1993).

Water-based flexographic printing also finds some application in newspaper printing, but it still represents only a small segment of the market (6–7% in the United States in 1992) (Bassemir *et al.*, 1995), and removal of the ink from newsprint before recycling the paper remains a problem.

UV-cured inks are also beginning to be used in flexographic printing. Their composition is similar to the UV-cured offset litho inks although they are less viscous (Kübler, 1993; Atkinson, 1995).

(*d*) *Gravure inks*

Gravure inks are similar to flexographic inks except that ketones and aromatic hydrocarbons can be used as solvents, providing a much greater latitude in the selection of binders (Bassemir *et al.*, 1995). In the United States, gravure inks are divided into 10 categories according to the type of binder or solvent. For example, aliphatic hydrocarbons (hexane, VM&P (varnish makers' and painters') naphtha, mineral spirits) are used mainly in type A, B and D inks; aromatic hydrocarbons (toluene (see IARC, 1989c), xylene) are used in types B, D, M and T; and ketones (acetone, methyl ethyl ketone) and esters (ethyl, isopropyl, *n*-propyl and butyl acetates) are required for type C inks (Bassemir *et al.*, 1995).

Gravure inks also are classified according to the printed product. 'Publication gravure' (magazines, catalogues) utilizes hard resins dissolved in toluene and/or aliphatic solvents. Resins include maleic acid-modified rosin and phenolic resins, calcium and zinc resinates, hydrocarbon resins and others. Polyethylene-based waxes are often added to improve abrasion resistance. A typical publication gravure ink might contain: pigments (8–15 wt %), resins (15–20 wt %), solvent (60–70 wt %) and additives (0.5–5 wt %) (Kübler, 1993).

'Packaging gravure' does not use hydrocarbon solvents but rather uses esters and alcohols (type C inks in the United States nomenclature). For various packaging substrates, resins may include cellulose nitrate, maleic resins, acrylate resins, polyurethane resins and polyamide resins, or mixed polymers of vinyl chloride/vinyl acetate/vinyl alcohol. Plasticizers (phthalates, citrates, adipates) also may be required, especially with cellulose nitrate. Basic dyes are used occasionally, in addition to pigments, in gravure inks. More recently, water-based gravure inks (type W), with formulations very similar to the water-based flexographic inks, are finding increasing use in packaging gravure (National Association of Printing Ink Manufacturers, 1988; Kübler, 1993; Bassemir *et al.*, 1995).

A special application of gravure (as well as other processes) is in printing with transfer inks. Aqueous inks containing selected textile-disperse dyes are printed and dried on special papers. The printed image can then be transferred by sublimation to the textile materials (e.g. polyester fabric) by pressing at approximately 200 °C (Kübler, 1993).

Intaglio is another specialized process using a higher-viscosity ink in which a high-quality image is engraved on a steel plate. Inks often contain special high-durability pigments, fillers to increase viscosity, drying oil vehicle and a number of additives. This process is used in printing paper currency (bank-notes), postage stamps, stock certificates and similar products (Kübler, 1993; Bassemir *et al.*, 1995).

(*e*) *Screen process inks*

Screen printing is a highly versatile process that can apply a thicker film of ink to the substrate than other printing processes. A very wide range of ink formulations is available, depending on the substrate and the requirements for the printed product. Drying may be by evaporation, oxidation, radiation-curing or other processes. Any of the resin types found in litho, flexo and gravure inks may be used, and the solvents can be of almost any type as long as they evaporate at a suitable rate, which is slower than that required for flexo and gravure. Solvents (propylene glycol ethers, aromatic and aliphatic hydrocarbons and cyclohexanone) typically have somewhat higher boiling-points than those used in gravure printing, and inks are more viscous (Kübler, 1993; Leach & Pierce, 1993; Bassemir *et al.*, 1995).

Although newly introduced product ranges are usually lead-free, screen printing is the one process that still makes significant use of lead chromate pigments. The use of *N*-vinyl pyrrolidone (see IARC, 1987k) in UV-cured inks has declined.

1.4 Production

The manufacture of printing inks traditionally has been a batch process, and the large majority of all printing inks are still made in batches. Only a few high-volume, standardized inks (e.g. news inks) are made by continuous processes (National Association of Printing Ink Manufacturers, 1988; Williams, 1992).

Ink vehicles are usually produced in separate resin/varnish plants and may be received by the ink manufacturer as solid resins or fluid varnishes (Bassemir *et al.*, 1995).

Pigments and other ink components are normally purchased by ink manufacturers from suppliers. Pigments are available as presscake, flushed colours (in which the water has been replaced by vehicle), dry colours (with virtually all of the water removed) and colour concentrates (liquids or pastes with 35–65% pigment). In paste inks, flushed colours are the principal form of colourant used in the United States. In Europe, dry colours are generally used because of the greater choice of vehicles available to the formulator (Bassemir *et al.*, 1995).

If very finely ground (predispersed) pigments or flushed pigment concentrates are used, paste inks can often be prepared simply by mixing pigment thoroughly with vehicles, solvents, oils and additives. Many sizes (5–1000 gallons [20–3790 L]) and types of mixers are used. Inks are sometimes filtered in a final step to remove residual particles (National Association of Printing Ink Manufacturers, 1988; Bassemir *et al.*, 1995).

Dry pigments or resin-coated pigments usually require a two-stage process — the pigments are first mixed with the other ink components and then thoroughly ground and dispersed using various types of ink mills. Milling may be done in three-roll mills, ball mills, sand mills, shot mills and others. Fluid inks (flexographic, gravure) must be milled in closed systems because of the volatility of the solvents, and, appropriately, controlled shot or sand mills, colloid mills and ball mills all are in use. Some large-volume inks, such as web offset process colours and coloured news inks, are manufactured by pump-filtration, in which a flushed colour is dispersed in the vehicle by high-speed high-shear mixers and then pumped through a series of filters (National Association of Printing Ink Manufacturers, 1988; Bassemir *et al.*, 1995). The major ink suppliers will carry out most or all of these processes themselves.

Inks can be packaged and shipped in metal cans, in metal or plastic pails or in metal or fibre drums. Large-volume fluid inks (news, flexo, gravure) may be delivered directly to the printer in tank trucks. Flexo, gravure and screen inks are shipped at higher viscosity, and solvent is added by the printer (National Association of Printing Ink Manufacturers, 1988; Bassemir *et al.*, 1995).

Worldwide printing ink production in 1994 was approximately 2.7 million tonnes, with the 15 largest producers accounting for 85% and the remaining 15% produced by several hundred smaller manufacturers (Table 3). European production levels in 1993 are shown by country in Table 4.

The importance of lithographic (offset) printing and the decline in market share for letterpress are evident from the data in Table 5. Table 6 shows the estimated worldwide distribution of printing inks by process.

1.5 Occupational exposures in printing processes and to printing inks

Occupational exposures in the printing industry and processes are discussed below according to their occurrence in printing ink manufacture and in printing operations such as letterpress, lithography, flexography, gravure and screen printing. Occupational exposure measurements from several of the studies described herein are presented in Table 7.

Table 3. 1994 World production of printing inks

Country/region	Thousands of tonnes	Percentage of total
United States	1020	38.0
Europe	730	27.0
Japan	500	18.5
Rest of the world	450	16.5
Total	2700	100.0

From European Confederation of Paint, Printing Ink and Artists' Colours Manufacturers' Association (1995)

Table 4. 1993 European production of printing inks

Country/region	Thousands of tonnes	Percentage of total
Germany	276	40.0
United Kingdom	114	16.5
Italy	72	10.5
France	70	10.5
Belgium	30	4.5
Netherlands	30	4.5
Others	93	13.5
Total	685	100.0

From European Confederation of Paint, Printing Ink and Artists' Colours Manufacturers' Association (1995)

Table 5. Percentage distribution of printing ink use by process in the United States in 1981–1994

Process	1981[a]	1985[b]	1989[b]	1994[b]
Lithography and offset	44	44.5	45	49
Flexography	14	19	21	22
Gravure	17	20	19	16
Letterpress	20	7.5	6	5
Screen printing and other	5	9	9	8

[a] From Bruno (1982)
[b] From The Freedonia Group (1995)

Table 6. Estimated worldwide distribution of printing ink use by process

End-use market	Printing process	Thousands of tonnes	Market (%)
Newspapers	Letterpress	30	1
	Web offset	350	13
Publications and magazines	Gravure	590	22
	Heat-set/offset	300	11
Packaging and commercial	Offset (Litho)	385	14
	Gravure	390	14
	Flexo (solvent)	150	5.5
	Flexo (water)	150	5.5
Others (posters, plastic containers)	Screen	85	3
Miscellaneous	All processes	270	11
Total		2700	100

From European Confederation of Paint, Printing Ink and Artists' Colours Manufacturers' Association (1995)

Some common job categories in printing operations include the following: typesetters (compositors), photoengravers and plate makers who set type or transfer images to plates; press room or machine room operators who operate and tend the printing machines and presses that produce the printed product; and publishing room workers, folding machine operators or collators who bundle or fold the printed product.

1.5.1 *Exposures in printing ink manufacture*

During manufacture of liquid and paste inks, powder pigments are transferred from drums or bags into rotary mixing vessels and mixed and blended with resins and solvents in a batch process. In the past, mixers were often operated open; however, closed systems have replaced many open mixers. Dust exposures to raw pigments may occur if bags or drums are emptied into the mixer by hand. Solvents are usually piped into the mixture and exposure to solvents during mixing depends on whether the mixer is closed or open.

Crude ink mixtures are then milled or dispersed for thorough mixing of pigments. Once crude ink has been prepared, potential for inhalation of pigment dust is lessened, although dermal contact with paste ink provides continued opportunity for exposures.

Liquid inks are further diluted with solvents by the printer for some applications where low-viscosity inks are required such as for flexography. Common solvent components of liquid inks include: toluene, ethanol, isopropanol, methyl ethyl ketone, ethyl acetate, xylene, isobutanol and acetone (Sakurai, 1982; Leach & Pierce, 1993). In addition, the use of methanol, dichloromethane, ethyl ether and 2-methoxyethanol has been reported (Sakurai, 1982). Benzene (see IARC, 1987l) was withdrawn from significant use in printing inks in Europe in 1950, although substantial contamination of

Table 7. Occupational exposures in printing processes and to printing inks

Industry	Process/operation	Sample type	No. of samples	Analyte	Air concentration				Year	Reference Country
					Mean		Range (or SD)			
					ppm	mg/m³	ppm	mg/m³		
Printing ink manufacture (Flexography)	NR	Personal	22	Ethanol	21	39.5	< 1–89	< 2–167	1983	Winchester (1985) New Zealand
			3	MIBK	23	94	1–59	4–236		
			24	*n*-Propylacetate	8	33	2–18	8.4–75		
			6	Isopropyl acetate	7	29.3	< 1–14	< 4–58.5		
			12	*n*-Propanol	4	9.8	< 1–10	< 2.5–25		
			14	Isopropanol	4	9.8	< 1–11	< 2.5–27		
			27	Toluene	4	15	< 1–21	< 4–79		
			27	Higher aromatics[a]	2		< 1–6			
			7	MEK	1	3	< 1–2	< 3–6		
			3	Cyclohexanone	1	4	≤ 1	≤ 4		
			12	*n*-Hexane	1	3.5	< 1–3	< 3.5–10.5		
			18	2-Ethoxyethanol	1	3.7	< 1–5	< 3.7–18.5		
Printing ink manufacture	Liquid ink department	Personal	10	Toluene		> 735		27–4595	1988	Lewis (1994) South Africa
			3	Xylene		> 314		< LD–> 783		
			8	Ethyl acetate		183		< LD–464		
			9	Ethanol		> 164		< LD–> 366		
			4	Isopropanol		> 11		< LD–> 22		
			1	*n*-Hexane		4		NA		
	Paste ink department	Personal	9	Toluene		27		< LD–42		
			3	Xylene		24		< LD–58		
			1	Ethanol		16		NA		
Printing industry	Various	NR	94	EGMEA		4.3 (GM)		3.9–4.7	1983–86	Veulemans *et al.* (1987) Belgium
				EGEE		9.8 (GM)		0.7–182.0		
				EGEEA		16.4 (GM)		0.3–186.8		
				EGBE		4.1 (GM)		1.5–17.7		
				EGBEA		12.7 (GM)		4.6–26.5		
Printing facility	Various	Personal	90	Isopropanol		208		8–647	Early 1980s	Brugnone *et al.* (1983) Italy

Table 7 (contd)

Industry	Process/operation	Sample type	No. of samples	Analyte	Air concentration				Year	Reference Country
					Mean		Range (or SD)			
					ppm	mg/m³	ppm	mg/m³		
Printing facility	Between press lines	Area	1	Aliphatic hydrocarbons	117		NA		1970	FIOH (1995) Finland
	Box lacquering and printing	Area	1	Acetone	15	35	NA	–	1970	
		Personal	18	Acetone	23	54	7–98	16–232	1970	
	Gravure	Area	5	Benzene	5	16	2–7	6–22	1962	
	Printing press	Personal	4	Butanol	28	84	ND–64	ND–192	1970	
	Silk screen printing	Personal	3	Hydrocarbons	41	–	18–82	–	1970	
	Gravure	Area	14	Xylene	19	82	2.5–70	11–304	1960–62	
	Lacquering	Personal	7	Xylene	3	13	ND–5	ND–22	1970	
	Printing press	Personal	3	Lead		0.113		0.05–0.17	1970	
	Printing press	Personal	3	Antimony		0.04		ND–0.09	1970	
	Silk screen	Personal	5	Toluene	16	60	7–28	26–105	1970	
	Printing press	Personal	21	Toluene	20	75	8–53	30–200	1970	
Printing facility	Rotogravure	Area	NR	Benzene	288	922	125–532	400–1702	1953	Forni *et al.* (1971) Italy
	Rotogravure	Area	NR	Toluene	NR	NR	0–240	0–905	1954–56	
	Rotogravure	Area	NR	Toluene	264	995	56–824	211–3106	1957–67	
Printing facility	Rotogravure	Area	NR	Toluene	100–200	377–754	NR–700	NR–2640	< 1977	Funes-Cravioto *et al.* (1977) Sweden
Printing facility	Rotogravure	Area	NR	Toluene	NR	NR	200–300	754–1130	1970s	Bauchinger *et al.* (1982) Germany
Printing facility	Rotogravure	Personal	NR	Toluene	NR	NR	7–112	26–422	< 1979	Mäki-Paakkanen *et al.* (1980) Finland
Printing facility	Rotogravure	Personal	30	Toluene		128		42–253	1980s	De Rosa *et al.* (1986) Italy

Table 7 (contd)

Industry	Process/operation	Sample type	No. of samples	Analyte	Air concentration				Year	Reference Country
					Mean		Range (or SD)			
					ppm	mg/m³	ppm	mg/m³		
Printing facility	Rotogravure	Personal	NR	Toluene		NR		30–600	< 1993	Monster *et al.* (1993) Netherlands
Newspaper printing	Rotary letterpress	Area	NR	Dust		1.1		NR	1979	Lynge *et al.* (1995) Denmark
	Rotary letterpress	Area	NR	Dust		NR		1–4 (65–90% ink mist)	1986–87	
	Offset lithography	Area	NR	Dust		0.28		NR	1979	
	Offset lithography	Area	NR	Dust		NR		0.1–0.7 (25% ink mist)	1986–87	
Newspaper printing	Press operation	Personal	5	Oil mist		0.5		0.1–1.0	1976	Kronoveter & Gill (1977) USA
	Press operation	Personal	4	Stoddard solvent		6.5		5–9		
Newspaper printing	Press operation	Personal	2	Cyclohexanone	0.1	0.4	0.05–0.15	0.2–0.6	1981	Daniels (1981) USA
	Plate photocuring	Personal	2	Acetic acid	0.08	0.2	0.04–0.12	0.1–0.3		
Paper box printing	Colour offset printing, UV curing, press operation	Personal	2	DPGME	3.7	22.2	1.8–5.5	10.8–33.6	Early 1980s	Cullen *et al.* (1983) USA
Screen printing	Printing press	Personal	18	Isophorone	23	115	5.4 (SD)	27 (SD)	< 1982	Samimi (1982) USA
				Cyclohexanone	28	112	5 (SD)	20 (SD)		
				Cellosolve acetate	18.5	100	4 (SD)	22 (SD)		
				Butyl acetate	11.5	55	0.8 (SD)	3.8 (SD)		
				Xylene	15	65	6.8 (SD)	29.5 (SD)		
				Diacetone alcohol	14	66	6.2 (SD)	29.5 (SD)		
				Petroleum distillate	85	–	14.5 (SD)	–		
Screen printing	Automatic dryer	Personal	19	Isophorone	9.5	48	3.3 (SD)	17 (SD)		
				Cyclohexanone	11	44	3 (SD)	12 (SD)		
				Cellosolve acetate	11	59	2.5 (SD)	13.5 (SD)		
				Butyl acetate	2.5	12	1.3 (SD)	6.2 (SD)		
				Xylene	4.5	19.5	1.5 (SD)	6.5 (SD)		
				Diacetone alcohol	3.5	16.6	1.5 (SD)	7.1 (SD)		
				Petroleum distillate	28.4	–	7.6 (SD)	–		

Table 7 (contd)

Industry	Process/operation	Sample type	No. of samples	Analyte	Air concentration				Year	Reference Country
					Mean		Range (or SD)			
					ppm	mg/m³	ppm	mg/m³		
Screen printing	Manual drying	Personal	15	Isophorone	15	75	4.1 (SD)	21 (SD)		Samimi (1982) USA (contd)
				Cyclohexanone	18	72	3.8 (SD)	15 (SD)		
				Cellosolve acetate	18	97	3.5 (SD)	19 (SD)		
				Butyl acetate	4.5	21	1.5 (SD)	7 (SD)		
				Xylene	8.5	37	3.8 (SD)	16.5 (SD)		
				Diacetone alcohol	12	57	4.8 (SD)	23 (SD)		
				Petroleum distillate	49.5	–	12 (SD)	–		
Screen printing	Paint mixing	Personal	12	Isophorone	17.8	89	5.5 (SD)	28 (SD)		
				Cyclohexanone	8.5	34	4.1 (SD)	16.4 (SD)		
				Cellosolve acetate	10	54	2.1 (SD)	11.3 (SD)		
				Butyl acetate	3.4	16	1.1 (SD)	5 (SD)		
				Xylene	3.5	15	1.8 (SD)	7.8 (SD)		
				Diacetone alcohol	2.8	13	1.3 (SD)	6.2 (SD)		
				Petroleum distillate	56.5	–	18 (SD)	–		
Screen printing	Screen wash	Personal	14	Isophorone	8.3	42	5.6 (SD)	28 (SD)		
				Cyclohexanone	6	24	4.5 (SD)	18 (SD)		
				Cellosolve acetate	5	27	0.5 (SD)	2.7 (SD)		
				Butyl acetate	85	404	17 (SD)	81 (SD)		
				Xylene	35	152	8.9 (SD)	39 (SD)		
				Diacetone alcohol	6.8	32	1.5 (SD)	7 (SD)		
				Petroleum distillate	39	–	15.5 (SD)	–		

NR, not reported; MIBK, methyl isobutyl ketone; MEK, methyl ethyl ketone; LD, limit of detection; NA, not applicable; EGMEA, ethylene glycol monomethyl ether acetate; GM, geometric mean; EGEE, ethylene glycol monoethyl ether; EGEEA, ethylene glycol monoethyl ether acetate; EGBE, ethylene glycol monobutyl ether; EGBEA, ethylene glycol monobutyl ether acetate; UV, ultraviolet; DPGME, dipropylene glycol monomethyl ether; SD, standard deviation

[a]Higher aromatics, largely ethyl benzene and trimethylbenzenes

toluene with benzene remained until about 1960 (European Confederation of Paint, Printing Ink and Artists' Colours Manufacturers' Associations, 1995).

Few studies of exposures during ink manufacture have been published. In a 1983 study of 27 workers in five plants manufacturing colour flexographic ink, the highest personal solvent exposures occurred during the mixing of ingredients, the production of resin and quality control (Winchester, 1985). The most common solvents were ethanol (56% of total solvent volume), toluene (6.5%) and *n*-propyl acetate (5.4%). Full-shift average exposures to these and 14 other solvents ranged from 15% to 38% of their respective threshold limit values (TLV). The highest mean personal exposures were to ethanol (21 ppm [39.5 mg/m^3]) and methyl isobutyl ketone (23 ppm [94 mg/m^3]). Relatively lower exposures were found during dispersing, diluting and ink packing operations.

In a survey of a South African printing ink manufacturing plant in 1988, exposures to solvents were measured for 27 workers (Lewis, 1994). Personal partial-shift average exposures were higher in the liquid ink department than in the paste ink department and are shown in Table 7. Job titles in the liquid ink department include the mixer/weigher who operated the mixer for varnishes and inks, the pot washer who cleaned mixing drums with solvents and the weigher who weighed ingredients. Job titles in the paste ink department include the millhand who operated and cleaned the mill with solvents, the mixer/weigher who mixed and transported inks to the milling machine and the storeman who ran the pigment and varnish stockroom. This survey was conducted during a summer heat wave and the exposures probably represented their annual peak. Skin contact with solvents occurred in the liquid ink department during batch mixing, weighing and pouring of liquid inks into containers and during pot washing, where workers climbed into drums and scrubbed them with toluene-soaked rags. Gloves and paper filter masks were provided to the workers but were not used. At the time of this study, only general dilution ventilation was in use in the liquid ink department; however, local exhaust ventilation hoods over the mixing vessels to remove pigment dust existed in the paste ink department.

In the formulation of printing ink, estimated exposures to ink pigments were ranked for different job titles (Kay, 1976). These ranks were based on professional judgement rather than actual monitoring results. Exposures for weighers, mixers and laboratory staff were estimated to be the highest, followed by container washers, maintenance workers, millhands, porters, utility men and working foremen.

1.5.2 *Exposures in printing operations*

In newspaper production, exposures in the early twentieth century included lead dust and fumes, due to the use of lead stereotype plates. Lead alloy type contributed to exposures of manual typesetters (Hamilton, 1925). Mechanical typesetting somewhat reduced lead exposures in the printing industry, followed by further reduction in exposure potential with the introduction of the linotype. By the mid-1970s, computerized typesetting had eliminated these lead exposures arising from the handling of lead type (Michaels *et al.*, 1991; Kristensen & Anderson, 1992).

Other common exposures besides lead in older letterpress newspaper printing operations include noise, carbon tetrachloride (see IARC, 1987m), benzene, toluene, xylene and oil mist containing ink. Ink mist can be generated in the press room by high-speed rollers. The mean of 106 press room area samples taken in the 1970s was 1.1 mg/m^3 total aerosol, with 45% of the mass distribution of these particles as respirable particulates. Ink mist particulate may contain ink and oil mist and cellulose paper dust (Beaulieu & Anderson, 1978). The newspaper industry made a gradual process shift in the 1970s–80s and now primarily uses offset lithography rather than letterpress, resulting in lower lead and ink mist exposures (American Newspaper Publishers Association, 1988). Modern printing presses are fitted with closed ink-feed systems and point source extraction, and provide a higher level of automation and computerized control than previously.

Benzene was a common solvent in rotogravure processes from the 1930s up to the beginning of the 1960s in the United States but was eventually replaced by other solvents, primarily toluene (Greenburg *et al.*, 1939; Lloyd *et al.*, 1977; Svensson *et al.*, 1990; European Confederation of Paint, Printing Ink and Artists' Colours Manufacturers' Associations, 1995). Benzene was used exclusively as an ink solvent and diluent in an Italian rotogravure plant up to 1953, when it was replaced by toluene following an epidemic of benzene poisoning (Forni *et al.*, 1971). In a Swedish study of two rotoprinting factories [probably rotogravure], benzene was used as a solvent in the 1940s up to 1950, when toluene replaced it, and was a probable contaminant of toluene up to 1958 (Funes-Cravioto *et al.*, 1977). In two Finnish rotogravure printing factories, benzene concentration in the toluene solvent has been controlled since 1962 and averaged 0.006% (always < 0.05%) (Mäki-Paakkanen, 1980). In a German rotogravure plant in the 1970s and early 1980s, the toluene printing ink solvent contained < 0.3% benzene (Bauchinger *et al.*, 1982).

Polycyclic aromatic hydrocarbons (PAHs) such as benzo[*a*]pyrene adsorb onto the surface of carbon black particles and have been found in press room atmospheres (Casey *et al.*, 1983). Although some yellow, red and orange pigments are manufactured from 3,3′-dichlorobenzidine and substituted derivatives of toluidine, laboratory analysis of 16 samples as part of a renal cancer study among paperboard printing workers did not detect either 3,3′-dichlorobenzidine or *ortho*-toluidine (see IARC, 1987n) in the bulk pigment (Sinks *et al.*, 1992).

In newspaper plant surveys prior to 1976, Kay (1976) observed that ink was heavily dispersed into the air during printing and black ink oil mist readily settled on surfaces within the room. Higher-viscosity vegetable oil-based inks were introduced in the late 1980s to replace colour mineral oil inks, although black inks still contain mineral oil to disperse the darker pigments and carbon black (American Newspaper Publishers Association, 1988)

In a study of total dust concentrations in British press rooms between 1967 and 1981, ink mist droplet and cellulose paper fibre concentrations ranged from 0.62 to 2.16 mg/m^3 for 'particles < 60 μm' and from < 0.06 to 0.9 mg/m^3 for respirable particles of < 7 μm diameter (Casey *et al.*, 1983). A study of a newspaper plant press room in the United

States detected air concentrations of oil mist ranging from 5 to 21 mg/m^3 in the 1960s, with 15% of the mass distribution of particles in the respirable size range (Goldstein *et al.*, 1970).

With the introduction of UV-cured acrylic resins and inks into colour offset printing in the 1970s, the use of high concentrations of glycol ethers increased. However, the trend has been towards the use of higher relative molecular mass glycol ethers, such as propylene and dipropylene glycol mono alkyl ethers (Cullen *et al.*, 1983; Williams, 1992).

In a colour offset printing operation in a paper box printing company in the early 1980s, inks were both UV-cured and air-dried, the former accounting for 20–50% of the press operation time (Cullen *et al.*, 1983). Solvent exposures occurred due to evaporation during both curing and mixing of solvents with inks. Exposure to inks and resins occurred by splashing and misting from press rollers, but the highest solvent exposures occurred during clean-up (25% of the work time), when rollers were wiped with press wash solutions. This latter operation provided the opportunity for dermal exposure as well as inhalation. Respiratory protection and gloves were seldom used. Solvents used in the printing process included substituted benzenes, dichloromethane, dichloroethane, 1-hexanol 2-terpinol, 1,2-dichloromethylene, 1,1,1-trichloroethane, methyl ethyl ketone and glycerol triacetate. UV-cured wash solutions contained glycol ethers diluted in *n*-propanol. Wash solutions for air-dried inks contained glycol ethers, mixed with aliphatic and aromatic hydrocarbons.

The use of gasoline (see IARC, 1989d) as a cleaning agent in typographic printing shops and by rotogravure pressmen, when cleaning rollers, has been reported in Finland (Partanen *et al.*, 1991).

In a Taiwan colour printing factory examined in 1985, carbon tetrachloride was used to clean a machine pump associated with the printing machine, resulting in estimated levels of 300–500 ppm [1890–3150 mg/m^3] carbon tetrachloride vapour (Deng *et al.*, 1987).

An Italian study of rotogravure workers in the 1980s (when the printing ink was diluted with pure toluene) showed mean toluene personal exposures of 128 mg/m^3, with no full-shift average exposure over the TLV of 375 mg/m^3 (De Rosa *et al.*, 1986). Personal toluene exposures correlated with post-shift urinary hippuric acid and *ortho*-cresol levels for six subjects over five days.

A Swedish study of the rotogravure industry found median toluene concentrations of 33 ppm [124 mg/m^3] in two plants and 7 ppm [26 mg/m^3] in a third, more modern plant between 1983 and 1986. Toluene concentrations ranged from 300 to 450 ppm [1130–1695 mg/m^3] between 1920 and 1965 in six rotogravure factories, but dropped to average concentrations of less than 50 ppm [190 mg/m^3] by 1985. Benzene concentrations (from contamined toluene) in one plant in 1960–62 ranged from 0 to 61 ppm [0–195 mg/m^3] and averaged 3 ppm [9.6 mg/m^3] (Svensson *et al.*, 1990).

In a Danish study of 52 printers in six printing factories (letterpress and newspaper printing, offset printing and flexopress and rotogravures) in the late 1980s, personal time-weighted average (TWA) concentrations of toluene averaged 5.4 ppm [20 mg/m^3] and

were found in 88% of the samples (Baelum, 1990). An average of seven different solvents were found in the air samples (range, 3–16) with decane, ethanol, xylene and isopropanol following toluene in frequency of detection [actual concentrations not given].

In a Japanese study of solvent exposures in 169 workers in 52 printing facilities in the 1980s, 24% of area air concentrations of solvents were greater than their occupational exposure limits, although actual concentrations were not given (Ukai *et al.*, 1986).

A Belgian study of ethylene glycol ethers and other solvent exposures in 24 printing plants during 1983–86 found detectable levels of several glycol ethers and other solvents (see Table 7; Veulemans *et al.*, 1987). The most common solvents detected were toluene (in 26% of samples), xylenes (24%), ethanol (35%), *n*-butanol (31%), isopropanol (31%), *iso*- and *tert*-butanol (26%), ethyl acetate (66%), *n*-butyl acetate (32%) and methyl ethyl ketone (45%). Actual solvent concentrations were not reported except for the glycol ethers.

In a large Canadian study of seven commercial printing operations and two newspaper plants, exposure to total particulate and polycyclic aromatic hydrocarbons (PAHs) was determined (Purdham *et al.*, 1993). Total particulate exposures for press room workers ranged from 0.1 to 4.7 mg/m^3 (mean, 0.63 mg/m^3) for lithographic and rotagravure commercial printers and from 0.14 to 0.31 mg/m^3 for newspaper plants. Personal PAH exposures ranged from none to 0.39 mg/m^3 (mean, 0.0165 mg/m^3), with no detectable PAH in 45% of samples. Naphthalene was the greatest constituent of PAH exposures. Companies classified as having poor ventilation had the greatest particulate and PAH exposures. The authors observed that second and third pressman (less senior) had the greatest exposure to oil and ink mist, whereas rollmen and catchers (at the end of the line) had particulate exposures comprised mostly of paper dust. The newspaper plants had lower particulate and PAH exposures than the other printing operations due to high-speed offset presses and relatively better ventilation.

In the same study, particulate exposures appeared to be inversely related to press speed, although the method of paper feeding may be part of the reason (sheet was dustier than roll or 'web'). The authors concluded that job category within the press rooms was not a factor in predicting total particulate exposure, while printing process type and impression area were. Gravure printing produced higher particulate exposures than lithography, and, the larger the image area, the more particulates were produced. Other important determinants of particulate exposure were effectiveness of ventilation, paper type and feed method.

In a Dutch study in the 1980s, substantial opportunity for dermal exposure to PAHs on the hands and through clothing was observed among press operators exposed to black offset ink from a newspaper printing industry during bulk material transfer (Jongeneelen *et al.*, 1988). Urinary 1-hydroxypyrene was examined as a marker of exposure (see monograph on Carbon Black, this volume).

Acrylates and methacrylates are often found in printing processes, as a component of UV-cured inks (Krishnan *et al.*, 1987; McCammon *et al.*, 1987a,b). Various acrylates are used for the production of photoprepolymer relief printing plates, as are other contact

sensitizers such as isocyanates and epoxy resins. It was well recognized by the 1970s that press operators had become sensitized to acrylates (Malten, 1982).

Samimi (1982) reported exposures to isophorone (3.5.5-trimethyl-Δ^2-cyclohexanone) and other solvents during screen printing in the United States. Isophorone was the most widely used ink thinner in the plant (comprising 75%), followed by cyclohexanone, petroleum distillates, butyl acetate, diacetone alcohol, cellosolve acetate (2-ethoxy ethylacetate) and xylene. Exposures for each of these solvents are listed in Table 7 for five different job classifications. Screen press operators had the highest exposures to organic vapours, followed by manual drying, paint mixing, screen washing and automatic drying. Workers involved in press operations, drying operations, ink formulations and screen washing all handled inks, solvents and freshly printed sheets, and were exposed more highly than workers in die cutting, finishing, packing and stencil making. The major exposure determinant was proximity of the solvent evaporating surfaces to the workers' breathing zones.

The National Occupational Exposure Survey conducted by the United States National Institute for Occupational Safety and Health (1995) between 1981 and 1983 indicated that 190 900 employees in the United States were potentially exposed to printing ink, with 29 300 employees potentially exposed specifically to lithographic inks and 8300 to screen process inks. These estimates were based on a survey of companies and did not involve measurements of actual exposures.

In industrial hygiene surveys conducted in the United States by the United States Occupational Safety and Health Administration (1995) between 1979 and 1994, the 12 most commonly monitored exposures in the printing industry were noise, toluene, isopropanol, xylenes, petroleum distillates, acetone, Stoddard solvent, methyl ethyl ketone, methylene chloride (dichloromethane), carbon monoxide, lead and benzene.

1.6 Regulations and guidelines

Exposures in the printing industry are regulated on a component-specific basis for some solvents and ink constitutents and also using non-specific measurements such as the measurement of aerosols and total hydrocarbons.

Oil mist, ink mist (a mist of ink dispersed in oil) and paper dust levels are all characterized in the occupational environment by measuring either total or respirable particulates. Although further analysis of the particulate filter sample for specific components such as PAHs and dyes is possible, it is generally not possible to differentiate between the individual components such as oil, ink solids and paper dust as fractions of the total particulate. Although analytical methods for solvent-soluble fractions of the particulate sample have been developed (such as the cyclohexane-soluble fraction), occupational exposure limits do not exist for these measurements.

Occupational exposure limits have been set for many individual substances found in printing ink manufacture and in printing processes. Examples include alcohols, esters, glycol ethers, ketones, aliphatic hydrocarbons, aromatic hydrocarbons, acrylates, carbon black and organic dyes. Standard compilations of occupational exposure limits may be

consulted for individual chemicals (International Labour Office, 1991; American Conference of Governmental Industrial Hygienists, 1995).

2. Studies of Cancer in Humans

Many epidemiological studies contain some evidence concerning cancer risk in printing trades and printing industries. However, several problems compromised the value of these studies for the purpose of this monograph. The first major problem relates to so-called publication bias. Because of pressures relating to the publication of scientific results, it cannot be assumed that all of the evidence that exists concerning cancer risks for printing processes or printing inks would have been published and therefore available to the Working Group. Indeed, for many of the possible associations reviewed in this monograph, the published evidence is probably a biased sample. Namely, it is much more probable that so-called positive findings are published than so-called non-positive or negative findings. This is a particular problem for the evidence regarding occupation or industry titles. Many studies have collected data on the whole range of occupations or industries in a community (from death certificates or from questionnaires) and related these to occurrence of one or many types of cancer. The large mass of possible associations that can be analysed usually precludes the publication of all findings. Thus, there is often a tendency to publish results for a given occupation, printer for example, only if the association is statistically suggestive. In industrial cohort studies also, it is often the practice not to publish the results found for each site of cancer, but only for prominent sites (e.g. lung) and a selection of other sites based on statistical significance.

The magnitude of the problem varies both by site of cancer and by type of study design. Once there is a controversy about a topic, there is a greater tendency for results to be published irrespective of whether the evidence is positive or negative. Thus, because there has been some discussion in the literature of risks of urinary bladder cancer related to inks, but less of risks of lung cancer, the Working Group believed that, among community-based case–control studies of urinary bladder cancer that collected data on job histories, complete reporting of results on printers was more probable than among analogous studies of lung cancer. Therefore, the Working Group tended to consider the body of evidence from case–control studies of urinary bladder cancer as being more representative and valid than the body of evidence from case–control studies of lung cancer. On the other hand, when evaluating cohort studies of printers, the Working Group believed that it is more probable that investigators report their lung cancer results, irrespective of their being positive or negative, than that they report their urinary bladder cancer results. This is because the incidence of lung cancer is much higher and the results on urinary bladder cancer are often considered to be based on too few numbers of cases to be of interest, unless the result is statistically significant. The same problem holds for most rare sites of cancer in relation to cohort studies. For instance, studies on printers reported their results for renal cancer much more probably if the standardized mortality ratio (SMR) was positive than if it was negative.

Another major problem in the review of the epidemiological literature on printers and the printing industry is the poor specificity of the occupational information available for epidemiological analysis. As described in Section 1 of this monograph, there is a wide variety of printing processes and a wide variety of jobs in the printing industry. Each process and each job is associated with different types of exposures. The bulk of the epidemiological evidence for this monograph is based on broad and often poorly defined employment categories, such as printers or printing industry. Where community-based studies have been carried out using such broad categories, irrespective of whether the studies were based on interviews, record linkage or abstraction from death certificates, it is clear that the exposure variable encompassed a large variety of exposure circumstances. This detracts significantly from the ability of the study to detect any risk, should one be present in the printing industry, since it is improbable that the same risk would occur across the whole range of exposure circumstances. In addition to compromising the power to detect risks, however, this problem also subverts the opportunity to seek consistency of findings between studies, since it is quite possible that the group of printers in one study has a quite different distribution of processes and precise job titles than a group of printers in another study. Even among cohort studies, many of them were described as taking place among printers with no further specification of types of printing processes or precise job titles. This problem of lack of specificity also applied to those studies that attempted to attribute exposure to printing inks.

2.1 Ecological studies

Blot and Fraumeni (1978) correlated 3056 United States county urinary bladder cancer mortality rates for the period 1950–69 with demographic, socioeconomic, ethnic and industrial data at the county level. Using data derived from the 1963 Census of Manufacturers, counties were categorized into three groups (high, mid, low) according to the proportion (> 1%; 0.1–1%; < 0.1% of the total county population) of employees engaged in each of 18 selected industrial productions. Using multiple regression models, average age-adjusted rates were estimated for each county as functions of other variables in the models. For white men, there was a positive correlation between the proportion of workers in the printing industry in each county and the rate of urinary bladder cancer.

Greene *et al.* (1979a) evaluated 211 pathologically verified cases of mycosis fungoides that were reported to the Mycosis Fungoides Cooperative Study Group during 1973–76 and 1948 deaths from mycosis fungoides occurring between 1950 and 1975 in 3056 United States counties. Analysis by specific industries was presented for 1665 white male deaths. For each county, the population distribution by age, race and sex was obtained from the 1960 United States census. Using data derived from the 1963 Census of Manufacturers, counties were categorized as in Blot and Fraumeni (1978). For each group of counties, age-standardized rates were computed based on the 1960 United States population distribution; in addition, SMRs were calculated using the total population rates as reference. The SMRs were 0.9, 1.0 and 1.2 respectively for those counties with < 0.1%, 0.1–1% and > 1% of their population employed in printing industries. [The Working Group noted that numbers of observed deaths were not given.]

2.2 Community-based studies

2.2.1 *Death certificate studies*

Kennaway and Kennaway (1947) selected the death certificates for lung cancer (23 549 deaths) and laryngeal cancer (14 869 deaths) occurring in men aged 20 years or more in England and Wales between 1921 and 1938 and compared the observed distribution of occupations recorded on the certificates to those expected on the basis of the occupational groupings in the 1931 census. The SMRs for lung cancer were 1.2 ([95% confidence interval (CI), 1.0-1.4]; 177 observed deaths) among printers and 0.7 ([95% CI, 0.3–1.4]; 7 observed deaths) among lithographic and process engravers; the SMRs for laryngeal cancer were 1.1 ([95% CI, 0.9-1.4]; 104 observed deaths) and 1.4 ([95% CI, 0.6–2.7]; 8 observed deaths), respectively.

Menck and Henderson (1976) examined lung cancer rates in Los Angeles County, United States, by occupation and industry. The study included 2161 death certificates mentioning lung cancer in white men aged 20–64 for the period 1968–70 and 1777 incident cases of lung cancer in white men of the same age reported to the Los Angeles County Cancer Surveillance Program for 1972–73. Mortality and morbidity data were pooled. Occupations and industries of employment were abstracted from death certificates for deceased cases and from hospital admission records for living cases. No occupation was reported for 17.5% and no industry for 31% of the study population. The white male population at risk by age, occupation and industry was obtained from the 1970 census. Expected number of deaths and incident cases in each occupation were computed using the rates of lung cancer in the 1970 census population. Significantly increased SMRs were found among men classified as photoengravers (SMR, 3.2 [95% CI, 1.4–6.3] based on four deaths and four incident cases) and pressmen (SMR, 2.8 [95% CI, 1.7–4.3] based on 10 deaths and 10 incident cases). For the printing and newspaper industry, the SMR was 1.0 [95% CI, 0.7–1.3] (30 observed deaths and 16 incident cases). [The Working Group noted the high proportion of study subjects without information on occupation or industry.]

Petersen and Milham (1980) investigated the occupational and mortality patterns of white male residents in California, United States, for the period 1959–61, using the occupation reported on death certificates. The total number of deaths from all causes among pressmen and plate printers was 1144. No increased risk (proportionate mortality ratio [PMR]) was reported for any cancer site [specific figures not given].

Dubrow and Wegman (1984) examined cancer mortality patterns by occupation for white men in Massachusetts, United States, in the period 1971–1973. Using age-standardized mortality odds ratios (sMORs), 397 occupational categories derived from death certificate information were assessed for their association with 62 malignancies. Statistically significant increased sMORs were reported for cancer of the buccal cavity and pharynx in the printing industry (sMOR, 2.5; $p < 0.001$; 15 deaths), and for cancer of the trachea, bronchus and lung (sMOR, 2.2; $p < 0.05$; 12 deaths) and cancer of the prostate (sMOR, 3.8; $p < 0.01$; 6 deaths) in compositors and typesetters.

In an occupational mortality surveillance study, Dubrow (1986) examined cause-specific mortality patterns by occupation and industry among Rhode Island, United States, residents (≥ 16 years old) who died during the period 1968–78. He used age-standardized PMRs stratified by sex and race. Expected numbers of deaths within specific occupations and industries were calculated using the total Rhode Island mortality experience. Information on usual (longest) occupation and usual industry was derived from death certificates. Results for skin melanoma deaths were presented. Out of a total of 577 white male decedents whose usual industry was printing, six died from melanoma (PMR, 4.6 [95% CI, 2.1–10.2]). When the analysis was restricted to occupations in the printing industry, four melanoma deaths were observed (PMR, 5.7 [95% CI, 2.1–15.2]). Examination of death certificates revealed that three of the four decedents either were lithographers or had worked at companies where lithography was performed.

Mortality by occupation was studied in British Columbia, Canada (Gallagher *et al.*, 1989). Cause of death and occupation were abstracted from death certificates from 1950 through to 1984. A total of 320 423 male and 216 213 female deaths were available for the analysis. Age-standardized PMRs were calculated. During the study period there were 1314 deaths in all printers. A larger number of deaths from colonic cancer was observed than that which was anticipated (PMR, 1.5; 95% CI, 1.1–2.1; 34 deaths). Mortality from lung cancer did not differ from expectation in printers (PMR, 1.0; 95% CI, 0.8–1.3; 71 deaths). The PMR for Hodgkin's disease was nonsignificantly elevated in all printers (PMR, 2.5; 95% CI, 0.8–5.8; 5 deaths). Four cases of pancreatic cancer occurred among printing press operators (PMR, 2.6; 95% CI, 0.7–6.7).

A proportionate mortality study using occupational data recorded in death certificates was conducted on 588 090 Washington State, United States, white male deaths between the years 1950 and 1989, and 88 071 white female deaths during 1974–89 (Milham, 1992). The PMRs were standardized for age and year of death. In men, there were 2775 deaths in printing pressmen, plate printers and typesetters. A significant excess from all cancers was observed for these occupations (PMR, 1.1 [95% CI, 1.0–1.1]; $p < 0.05$; 606 cases). Excesses for specific cancer sites were observed for malignancies of the oral mesopharynx (PMR, 4.4 [95% CI, 2.2–13.1]; $p < 0.01$; 6 cases), for rectal cancer (PMR, 1.7 [95% CI, 1.1–2.5]; $p < 0.01$; 27 cases) and for cancer of the bronchus, trachea and lung (PMR, 1.2 [95% CI, 1.1–1.4]; $p < 0.01$; 191 cases). No excess was found for urinary bladder cancer (PMR, 1.0 [95% CI, 0.7–1.5]; 21 cases), leukaemia (PMR, 1.2 [95% CI, 0.7–1.7]; 27 cases) or Hodgkin's disease (PMR, 0.7 [95% CI, 0.1–0.8]; 3 cases). Seven cases of malignant melanoma of the skin were observed (PMR, 1.3 [95% CI, 0.5–2.4]. In women, 153 deaths occurred in printers and typesetters; there was a significant excess of colonic cancer (PMR, 2.0 [95% CI, 0.9–4.0]; $p < 0.05$; 8 cases). No significant PMR was found either for cancer of the bronchus, trachea and lung (PMR, 0.9 [95% CI, 0.4–1.8]; 7 cases) or for malignancies of lymphatic and haematopoietic tissue (PMR, 1.5 [95% CI, 0.5–3.9]; 5 cases).

2.2.2 *Record-linkage studies*

A number of studies have been carried out linking job or industry titles derived from census data with subsequent cancer morbidity or mortality. Compared with studies based on information derived from death certificates alone, record-linkage studies provide higher-quality occupational data and follow-up data on identified cohorts. However, since the occupational data are collected at one point in time, this may not reflect accurately lifetime employment histories, particularly in occupationally mobile populations. In addition, the lack of longitudinal data precludes estimation of employment duration.

Malker and Gemne (1987) evaluated cancer risk among printing industry workers (24 652 men and 6450 women) using the Swedish Cancer-Environment Registry, which linked national cancer incidence for the period 1961–73 to 1960 census-derived data on occupation and industry. Standardized incidence ratios (SIRs) were based on birth cohort-specific incidence rates. Three different reference populations were used: the total Swedish population, all employed persons and blue-collar workers. Among male printing workers, the age- and region-adjusted SIR for lung cancer was 1.5 ([95% CI, 1.3–1.8]; 190 cases). The risk was similar (SIR, 1.6 [95% CI, 1.4–1.9]; 149 cases) in blue-collar workers employed in printing enterprises (newspaper, journal, book printing and other graphic enterprises). The excess risk for lung cancer, adjusted by region, was mainly evident in those born around 1900 (for birth cohort 1900–04: SIR, 1.9 [95% CI, 1.4–2.5]; 45 cases). Among female printing workers, an excess risk for cervical cancer was observed (age- and region-adjusted SIR, 1.3 [95% CI, 1.1–1.5]; 162 cases), but this disappeared when employed persons and blue-collar workers were used as reference. No other site was found to be at excess risk.

To describe the occurrence of cancer in occupational groups, Olsen and Jensen (1987) examined 90 651 primary tumours identified in the Danish Cancer Registry in 1970–79. Occupations were derived from computer-based national registries such as the Supplementary Pension Fund and the Central Population Registry. The risk for specific cancer sites by occupation or industry was estimated as the standardized proportionate incidence ratio (SPIR). Among men employed in the printing and publishing industries, statistically significantly increased risks were found for cancers of the renal pelvis and ureter (SPIR, 2.5; 95% CI, 1.4–4.7; 10 cases) and for urinary bladder cancer (SPIR, 1.4; 95% CI, 1.1–1.8; 55 cases). Slightly increased risks were also found for cancers of the lung and trachea (SPIR, 1.1; 95% CI, 0.9–1.3; 107 cases), pancreas (SPIR, 1.3; 95% CI, 0.9–2.1; 20 cases), testis (SPIR, 1.2; 95% CI, 0.8–1.8; 22 cases) and for non-melanoma skin cancer (SPIR, 1.2; 95% CI, 0.9–1.5; 58 cases). No increased risk was found for other cancer sites. In women employed in the printing, publishing and allied industries, a statistically significantly increased risk was found for cancer of the lung and trachea (SPIR, 1.4; 95% CI, 1.0–1.9; 44 cases).

Based on an extended follow-up of the aforementioned Swedish Cancer-Environment Registry, McLaughlin *et al.* (1988) investigated the risk for melanoma of the skin among male printing workers for the period 1961–79; a significantly elevated SIR was observed in the printing industry (SIR, 1.4 [95% CI, 1.1–1.7]; 91 cases). Men employed in newspaper printing (SIR, 1.9 [95% CI, 1.3–2.6]; 39 cases) and newspaper publishing

(SIR, 3.1 [95% CI, 1.2–6.4]; 7 cases) industries seemed to account for much of the association. Analysis by occupation within industry revealed a statistically significantly increased risk for typographers in the newspaper printing industry (SIR, 2.0 [95% CI, 1.2–3.1]; 19 cases), whereas the risk for this occupational group in any of the other printing industries was not increased. Risks were also significantly raised for other occupations within the printing industries: machine repairers (SIR, 14.5 [95% CI, 1.6–52.3]; 2 cases), journalists and editors (SIR, 2.4 [95% CI, 1.4–3.9]; 16 cases) and business executives (SIR, 9.1 [95% CI, 2.9–21.2]; 5 cases).

Aronson and Howe (1994) examined cancer-specific mortality patterns by occupation or industry in a cohort of 242 196 Canadian women identified through an employment survey of approximately 10% of the Canadian labour force between 1965 and 1971 in which employers were asked to provide information (name, surname, year of birth, current occupation and industry) for each of their workers. The mortality of the cohort in the period 1965–79 was determined by a computerized record-linkage to the Canadian National Mortality Data Base. SMRs by occupation or industry were computed using age- and calendar year-specific rates for the entire female cohort. The results were only published for significantly elevated SMRs. The only finding related to the printing and publishing industry concerned breast cancer in women under 64 years of age (SMR, 2.2; 95% CI, 1.1–3.9; 11 deaths).

A cohort of the residents of Turin, Italy, enrolled on the basis of the 1981 census record, was followed up until the end of 1989 (73 606 deaths recorded among 1 056 102 persons; 10 798 deaths among persons employed and aged 18–64 at the 1981 census) (Costa *et al.*, 1995). SMRs were computed by applying age- and sex-specific death rates of the whole active population to the person-years accrued by the 'exposed' group under study. In men employed in printing and publishing, nonsignificant increases were shown for malignancies of the pleura (SMR, 6.0; 95% CI, 0.7–21.6; 2 cases), for colonic cancer (SMR, 2.1; 95% CI, 0.9–4.4; 7 deaths) and for malignancies of the haematopoietic system (SMR, 1.6; 95% CI, 0.6–3.3; 7 deaths). The SMR for lung cancer was 1.1 ([95% CI, 0.7–1.7]; 22 deaths) and that for urinary bladder cancer was 1.0 ([95% CI, 0.1–3.6]; 2 deaths). In women employed in printing and publishing, risks were raised for lung cancer (SMR, 2.6; 95% CI, 0.5–7.6; 3 deaths), colonic cancer (SMR, 2.7; 95% CI, 0.3–9.7; 2 deaths), ovarian cancer (SMR, 3.2; 95% CI, 0.6–9.3; 3 deaths) and haematopoietic system malignancies (SMR, 2.0; 95% CI, 0.2–7.2; 2 deaths). In male printers, an increased risk of liver cancer (SMR, 1.7; 95% CI, 0.3–5.0; 3 deaths), colonic cancer (SMR, 1.8; 95% CI, 0.4–5.3; 3 deaths) and lung cancer (SMR, 1.2 [95% CI, 0.6–2.1]; 12 deaths) was shown; there were also two deaths from multiple myeloma [SMR, 9.7; 95% CI, 1.1–33.1], but no death from urinary bladder cancer.

All Italian residents aged 18–74, identified through the 1981 census (which included 94 163 deaths, 15 734 of which were among employed individuals aged 18–64) were followed up from November 1981 to April 1982 (Costa *et al.*, 1995). Cause-specific relative risks by occupation were estimated as age-adjusted Mantel-Haenszel odds ratios. An excess risk of renal cancer was found among male printing and publishing workers (odds ratio, 4.8; 95% CI, 1.7–13.4; 3 cases). The odds ratios in men were 1.1 ([95% CI,

0.8–1.4]; 11 cases) for lung cancer and for urinary bladder cancer 2.9 ([95% CI, 0.8–11.1]; 2 cases).

Lynge *et al.* (1995) examined the cancer risk of 15 534 men and 3593 women, 20–64 years old, living in Denmark and working in the printing and bookbinding industry according to the 1970 Census. Incident cancer cases were identified by linkage with the Danish Cancer Registry for the period 1970–87, 1970 being the year in which the change from rotary letterpress to offset lithography took place in newspaper production in Denmark. Measurements undertaken in Denmark in 1979 and 1986–87 detected dust concentrations of 1.1 mg/m^3 and 1–4 mg/m^3 (65–90% being ink mist), respectively, for rotary letterpress and 0.28 mg/m^3 and 0.1–0.7 mg/m^3 (25% being ink mist), respectively, for offset. Age-adjusted SIRs were calculated using the cancer incidence rates of all employed persons as reference. Male workers had significantly increased risks for all cancers (SIR, 1.2; 95% CI, 1.1–1.2; 1095 cancers) and for cancers of the liver (SIR, 1.9; 95% CI, 1.1–3.0; 19 cases), lung (SIR, 1.3; 95% CI, 1.1–1.4; 248 cases), renal pelvis (SIR, 1.9; 95% CI, 1.1–3.1; 15 cases) and urinary bladder (SIR, 1.3; 95% CI, 1.1–1.6; 109 cases). Excess risks of borderline statistical significance were found for cancers of the oral cavity (SIR, 1.9; 95% CI, 0.9–3.4; 11 cases) and colon (SIR, 1.2; 95% CI, 1.0–1.6; 80 cases) and non-melanoma skin cancer (SIR, 1.2; 95% CI, 1.0–1.4; 148 cases). The SIR for melanoma was 1.1 (95% CI, 0.8–1.6; 28 cases). Based on census-derived data on occupation and industry, analysis by occupational groups was performed. The risk for lung cancer was significantly increased in factory workers in the printing industry (SIR, 1.5; 95% CI, 1.1–1.9; 62 cases) and particularly among operators of rotary letterpress machines in newspaper and magazine production (SIR, 2.0; 95% CI, 1.3–3.0; 26 cases). An excess of borderline statistical significance was found among photo-engravers (SIR, 1.7; 95% CI, 0.9–2.8; 15 cases). The risk for urinary bladder cancer was elevated among typographers (SIR, 1.5; 95% CI, 1.1–2.0; 40 cases) and among factory workers in printing establishments (SIR, 1.6; 95% CI, 0.9–2.7; 14 cases). The risk for cancer of the renal pelvis was elevated in typographers both in printing establishments (SIR, 2.3; 95% CI, 0.8–5.0; 6 cases) and newspaper and magazine production (SIR, 2.2; 95% CI, 0.6–5.5; 4 cases); two cases among lithographers yielded a SIR of 3.4 (95% CI, 0.4–12.2), whereas three cases were observed in factory workers in the printing industry (SIR, 1.8; 95% CI, 0.4–5.3). Several occupational subgroups contributed to the excess risk for primary liver cancer, the risk being high among lithographers (SIR, 6.7; 95% CI, 2.2–15.8; 5 cases). Statistically significantly increased SIRs for cancer of the gall-bladder (SIR, 3.4; 95% CI, 1.1–7.9; 5 cases) and for male breast cancer (SIR, 7.9; 95% CI, 1.6–23.1; 3 cases) were found among typographers in newspaper and magazine production. Female workers showed significantly increased risks for all cancers (SIR, 1.2; 95% CI, 1.0–1.3; 284 cancers), lung cancer (SIR, 1.7; 95% CI, 1.2–2.5; 32 cases) and breast cancer (SIR, 1.4; 95% CI, 1.1–1.7; 88 cases). Cervical cancer was also elevated (SIR, 1.4; 95% CI, 0.9–2.0; 29 cases). No increased risk was found for melanoma (SIR, 1.1; 95% CI, 0.5–2.0; 9 cases). Smoking and drinking habits reported by members of the printing trade unions at a survey in 1972 were compared with habits reported by members of other trade unions. Based on the reported patterns of smoking and alcohol

consumption in this population, the authors stated that the observed elevated risks were unlikely to be entirely attributable to confounding by these factors.

In Finland, the 1970 Population Census file was linked with the Finnish Cancer Registry file for the period 1971–85 (Pukkala, 1995). Crude occupation-specific SIRs and social class-adjusted SIRs were calculated. Expected numbers were based on the incidence for the total employed, active, Finnish population of the same sex during the same period. The total number of cases included in the analyses was 47 178 men and 46 853 women aged 35–64 years. A significant excess of colonic cancer in men was found for printing occupations (adjusted SIR, 2.2; 95% CI, 1.2–3.5; 16 cases). The excess was nonsignificant in women (adjusted SIR, 1.4; 95% CI, 0.7–2.5; 10 cases). No significant excess was observed in lung cancer incidence either in male (adjusted SIR, 0.8; 95% CI, 0.6–1.1; 50 cases) or in female printing occupations (adjusted SIR, 1.8; 95% CI, 0.9–3.2; 12 cases). The analysis by job title in men confirmed the results. A significant excess of breast cancer was observed in female printers (adjusted SIR, 1.4; 95% CI, 1.1–1.8; 74 cases), and there was also a statistically significant increase in ovarian cancer for the same group (adjusted SIR, 2.2; 95% CI, 1.5–3.1; 30 cases). No increase was shown for cancer of the urinary bladder in male printers (adjusted SIR, 1.1; 95% CI, 0.5–2.0; 9 cases), for cancer of the lung in male printers (adjusted SIR, 1.1; 95% CI, 0.7–1.7; 19 cases), for skin melanoma in printers of either sex (adjusted SIR, 1.1; 95% CI, 0.5–2.4; 7 male cases; adjusted SIR, 1.1; 95% CI, 0.3–2.5; 5 female cases) or for leukaemia in male printers (adjusted SIR, 0.4; 95% CI, 0.1–1.4; 2 cases). Female lithographers had a significant excess of basal-cell carcinoma of the skin (adjusted SIR, 4.4; 95% CI, 1.2–11.2; 4 cases).

A cancer registry-based study in Tianjin, China (Wang *et al.*, 1995) identified 4806 male and 3595 female cases of incident lung cancers and 14 685 male and 13 010 female controls (all other cancers) ≥ 20 years old during 1981–87. The subjects' most-recent occupation and industry were abstracted from cancer notifications. For printers and related occupations, the odds ratio, when roughly adjusted for smoking, was 1.1 (95% CI, 0.6–1.8; 20 cases) in men and 1.5 (95% CI, 0.7–3.3; 9 cases) in women.

These studies are summarized in Table 8.

2.2.3 *Case–control studies*

Case–control studies are summarized in Tables 9–11.

(*a*) *Cancer at multiple sites*

Cancer cases (17 sites) and patients with non-neoplastic diseases admitted to the Roswell Park Memorial Institute in Buffalo, New York, United States, from 1956 to 1965 were compared with regard to occupations associated with either inhalation of combustion products or chemicals (Viadana *et al.*, 1976). Information on lifetime occupational history, educational level and smoking habits was collected at the time of hospital admission. A total of 11 591 white male patients (cancer cases and non-cancer cases) were included in the analysis. Workers ever employed in specific occupations were compared with those in an unexposed clerical group. Eleven cases of cancer of the

Table 8. Record linkage studies among workers in the printing industry

Reference, country	Study subjects	Period of follow-up	Occupation/exposure	Cancer site/ cause of death	No. obs.	RR	95% CI	Comments
Malker & Gemne (1987) Sweden	24 652 men and 6450 women registered at 1960 census as printing workers	1961–73	Printing workers (M)	Lung	190	1.5	[1.3–1.8]	Morbidity
			Blue-collar workers (M) in printing enterprises (newspaper, journal/book printing, others)		149	1.6	[1.4–1.9]	
			Birth cohort around 1990 (M)		45	1.9	1.4–2.5	
				Urinary bladder	76	1.3	NG	$p > 0.01$
				Kidney	48	1.1	NG	$p > 0.01$
				Skin melanoma	27	1.2	NG	$p > 0.01$
			Printing workers (F)	Lung	9	1.3	NG	$p > 0.01$
				Urinary bladder	5	0.8	NG	$p > 0.01$
				Kidney	7	1.1	NG	$p > 0.01$
				Skin melanoma	8	1.2	NG	$p > 0.01$
				Cervix/uteri	162	1.3	[1.1–1.5]	
Olsen & Jensen (1987) Denmark	90 651 primary tumours	1970–79	Printing and publishing industries (M)	Renal pelvis	10	2.5	1.4–4.7	Standardized proportionate incidence ratio
				Urinary bladder	55	1.4	1.1–1.8	
				Lung and trachea	107	1.1	0.9–1.3	
				Pancreas	20	1.3	0.9–2.1	
				Testis	22	1.2	0.8–1.8	
				Non-melanoma skin cancer	58	1.2	0.9–1.5	
			Printing, publishing and allied industries (F)	Lung and trachea	44	1.4	1.0–1.9	

Table 8 (contd)

Reference, country	Study subjects	Period of follow-up	Occupation/exposure	Cancer site/ cause of death	No. obs.	RR	95% CI	Comments
McLaughlin *et al.* (1988) Sweden	Male printing workers at 1960 census; 91 melanomas	1961–79	Printing industry	Skin melanoma	91	1.4	[1.1–1.7]	Morbidity
			Newspaper printing industry		39	1.9	[1.3–2.6]	
			Newspaper publishing industry		7	3.1	[1.2–6.4]	
			Typographers in newspaper printing industry		19	2.0	[1.2–3.1]	
			Machine repairers in newspaper printing industry		2	14.5	[1.6–52.3]	
			Journalists/editors in newspaper printing industry		16	2.4	[1.4–3.9]	
			Business/executives in newspaper printing industry		5	9.1	[2.9–21.2]	
Aronson & Howe (1994) Canada	242 196 women identified through employment survey	1965–79	Printing and publishing industry	Breast	11	2.2	1.1–3.9	Mortality; other sites not significantly elevated
Costa *et al.* (1995) Italy	1981 population census of Turin, Italy, residents; 10 798 deaths among persons employed	1981–89	Printing and publishing industry	M Pleura	2	6.0	0.7–22	Mortality
				Colon	7	2.1	0.9–4.4	
				Lung	22	1.1	[0.7–1.7]	
				Urinary bladder	2	1.0	[0.1–3.6]	
				Haematopoietic	7	1.6	0.6–3.3	
				F Lung	3	2.6	0.5–7.6	
				Colon	2	2.7	0.3–9.7	
				Ovarian	3	3.2	0.6–9.3	
				Haematopoietic	2	2.0	0.2–7.2	
			Printers	M Liver	3	1.7	0.3–5.0	
				Colon	3	1.8	0.4–5.3	
				Multiple myeloma	2	[9.7]	[1.1–33.1]	
				Lung	12	1.2	[0.6–2.1]	
				Urinary bladder	0	–	–	

Table 8 (contd)

Reference, country	Study subjects	Period of follow-up	Occupation/exposure	Cancer site/ cause of death	No. obs.	RR	95% CI	Comments
Costa *et al.* (1995) Italy	1981 population census of Italian residents; 15 734 deaths among persons employed	1981–82	Printing and publishing industry	M Kidney	3	4.8	1.7–13.4	Mortality
				Lung	11	1.1	[0.8–1.4]	
				Urinary bladder	2	2.9	[0.8–11.1]	
Lynge *et al.* (1995) Denmark	15 534 men and 3593 women working in printing and bookbinding industry based on 1970 Census	1970–87	*Men*					(SIR)
			Whole printing and book binding industry	All cancers	1095	1.2	1.1–1.2	
				Lung	248	1.3	1.1–1.4	
			Factory workers in printing industry		62	1.5	1.1–1.9	
			Factory workers in newspaper and magazine production		26	2.0	1.3–3.0	
			Photoengravers		15	1.7	0.9–2.8	
			Whole industry[a]	Liver	19	1.9	1.1–3.0	
			Lithographers		5	6.7	2.2–15.8	
			Whole industry[a]	Urinary bladder	109	1.3	1.1–1.6	
			Typographers in printing establishment		40	1.5	1.1–2.0	
			Factory workers in printing establishment		14	1.6	0.9–2.7	
			Whole industry[a]	Colon	80	1.2	1.0–1.6	
				Renal pelvis	15	1.9	1.1–3.1	
			Typographers in printing establishments		6	2.3	0.8–5.0	
			Typographers in newspaper and magazine production		4	2.2	0.6–5.5	
			Whole industry[a]	Oral cavity	11	1.9	0.9–3.4	

Table 8 (contd)

Reference, country	Study subjects	Period of follow-up	Occupation/exposure	Cancer site/ cause of death	No. obs.	RR	95% CI	Comments
Lynge *et al.* (1995) Denmark (contd)			Whole industry[a]	Skin melanoma	28	1.1	0.8–1.6	
				Non-melanoma skin cancer	148	1.2	1.0–1.4	
				Women				
				All cancers	284	1.2	1.0–1.3	
				Lung	32	1.7	1.2–2.5	
				Breast	88	1.4	1.1–1.7	
				Cervix uteri	29	1.4	0.9–2.0	
				Skin melanoma	9	1.1	0.5–2.0	
Pukkala (1995) Finland	1970 population census 47 178 men, 46 853 women	1971–85	Printing occupations	M Colon	16	2.2	1.2–3.5	Morbidity
				F Colon	10	1.4	0.7–2.5	
				M Lung	50	0.8	0.6–1.1	
				F Lung	12	1.8	0.9–3.2	
			Printers	F Breast	74	1.4	1.1–1.8	
				F Ovarian	30	2.2	1.5–3.1	
				F Skin melanoma	5	1.1	0.3–2.5	
				M Skin melanoma	7	1.1	0.5–2.4	
				M Urinary bladder	9	1.1	0.5–2.0	
				M Leukaemia	2	0.4	0.1–1.4	
				M Lung	19	1.1	0.7–1.7	
			Lithographers	F Skin basal-cell carcinoma	4	4.4	1.2–11.2	

RR, relative risk estimated by SMR (for mortality) or SIR (for morbidity); M, male; F, female
[a] Means whole printing and book binding industry

buccal cavity and pharynx among printers yielded a statistically significant age-adjusted odds ratio of 2.6 ($p < 0.05$), while the odds ratio adjusted for smoking was 2.1 ($p > 0.05$). A nonsignificant ($p > 0.05$) increased age-adjusted odds ratio of 1.5 was found for lung cancer (7 cases).

As part of the United States Third National Cancer Survey, 7518 incident cancer cases, representing a 57% response rate, were interviewed on lifestyle factors and main lifetime industry and occupation (Williams *et al.*, 1977). Respondents and non-respondents were comparable in age, race, sex, marital status, method of diagnosis, country of birth and cancer site distributions. The proportions of specific main-lifetime industries and occupations among patients with cancer at one site were compared (separately for men and women) to those of patients having cancer at other sites combined, controlling for age, race, education, tobacco use and alcohol consumption. The total numbers of cancer cases in printing, publishing and allied products industries were 59 among men and 33 among women. The only significantly increased relative risk was found for cancer of the oral cavity in males (odds ratio, 4.5; $p < 0.05$; 7 cases). Nonsignificant excesses were observed for cancer of the pancreas both in men (odds ratio, 7.0; 3 cases) and women (odds ratio, 8.2; 2 cases). Among men, there were four urinary bladder cancer cases (odds ratio, 2.0) and two cases of melanoma (odds ratio, 3.0). [The Working Group noted the low response and the resultant possibility of bias.]

In a population-based case–control study of cancer at 19 sites (Siemiatycki, 1991), described in detail in the monograph on Carbon Black in this volume, pp. 188–189, analyses were carried out relating to the printing and publishing industry, employment as a printer and employment as a printing press worker. For the printing and publishing industry, the odds ratio for lung cancer was 2.0 ([95% CI, 1.2–3.5]; 35 cases); no significant excess was noted for any other site. In printers, significant excesses were found for lung cancer (odds ratio for any exposure, 2.1 [95% CI, 1.1–4.1]; 26 cases; odds ratio for over 10 years' exposure, 1.7 [95% CI, 0.7–4.1]; 13 cases) and pancreatic cancer (odds ratio for over 10 years' exposure, 3.7 [95% CI, 1.2–11.2]; 4 cases); for French printers, a significant excess for renal cancer was observed (odds ratio for any exposure, 3.4 [95% CI, 1.2–9.5]; 5 cases; odds ratio for over 10 years' exposure, 3.6 [95% CI, 1.0–10.6]; 3 cases). In the more narrowly defined category of printing press workers, the odds ratio for lung cancer was 3.1 ([95% CI, 1.1–8.7]; 15 cases), and, when this association was further analysed by histological type of lung cancer, the odds ratio for adenocarcinoma of the lung was 7.0 ([95% CI, 1.8–27.9]; 6 cases).

One of the substances assessed by the occupational hygienists in the Montréal (Canada) study (Siemiatycki, 1991) was inks, including printing inks. Nearly 4% of the total study sample exposure was attributed to inks in one or another of their jobs. The most common job titles in which it was attributed were: typesetters and printers, draftsmen and business machine repairmen. In analyses using cancer controls adjusting for age, smoking, ethnic groups and socioeconomic status, the following sites of cancer were not associated with exposure to inks: oesophagus (odds ratio, 0.9; 3 cases), stomach (odds ratio, 0.9; 7 cases), colon (odds ratio, 0.5; 9 cases), rectum (odds ratio, 1.2; 12 cases), pancreas (odds ratio, 1.3; 5 cases), prostate (odds ratio, 1.3; 13 cases), urinary bladder (odds ratio, 1.2 [95% CI, 0.7–2.1]; 18 cases), melanoma of the skin (odds ratio,

1.0; 5 cases) and lymphoma (odds ratio, 0.8; 6 cases). For lung cancer, there was an indication of excess among all those considered to be exposed (odds ratio, 1.6 [95% CI, 1.0–2.7]; 37 cases) but no greater risk among the subset considered to be substantially exposed (odds ratio, 1.5 [95% CI, 0.7–3.1]; 18 cases). For renal cancer, there was an indication of excess risk for those considered to be substantially exposed (odds ratio, 2.5 [95% CI, 1.0–5.4]; 7 cases).

In a reanalysis of the above data focusing on urinary bladder cancer (Siemiatycki *et al.* 1994), having worked in the printing and publishing industry for less than 10 years yielded an odds ratio of 0.3 (95% CI, 0.1–1.2; 2 cases), while for 10 or more years in the industry, the odds ratio was 1.9 (95% CI, 0.9–3.9; 11 cases). An elevated odds ratio of 3.0 (95% CI, 0.9–10.1; 4 cases) was found for substantial exposure to photographic products among photoengravers and photographic processors.

(*b*) *Urinary bladder cancer* (see Table 9)

Wynder *et al.* (1963) examined occupation and other risk factors associated with urinary bladder cancer risk in 300 male and 70 female cases and an equal number of controls from seven New York hospitals in 1957–61. Controls, matched by age and sex, were selected among patients of the same hospitals excluding subjects with cancers of the respiratory system and of the upper alimentary tract and those with myocardial infarction. Information on possible risk factors was collected through interviews. Three cases had ever worked as printers, engravers or lithographers [crude odds ratio, 2.2; 95% CI, 0.4–13.2].

A case–control study was conducted in eastern Massachusetts, United States (Cole *et al.*, 1972), on 510 male and female histologically confirmed cancers of the lower urinary tract (94% were urinary bladder cancer) diagnosed between January 1967 and June 1968 (Cole *et al.*, 1971). Each case was matched by sex and age to a general population control; 92% of the cases and 91% of the controls were interviewed and usable occupational history was collected for 461 cases (356 men and 105 women) and 485 controls (374 men and 111 women). The age-adjusted odds ratio for men whose 'usual' occupation was printing was 0.8 (95% CI, 0.3–1.9; 5 cases). Men ever employed in printing had an age- and smoking-adjusted odds ratio of 1.3 (95% CI, 0.7–2.5; 14 cases).

Sixty-five male and 10 female white patients with histologically confirmed urinary bladder cancer, admitted in 1978 to two community hospitals in northern New Jersey, United States, and 142 (123 men, 19 women) controls matched by age, race, place of birth, sex, hospital and residence were investigated by Najem *et al.* (1982). Controls were selected from patients treated for other conditions in the same hospitals, excluding those with a history of neoplasms or tobacco-related heart diseases. Lifetime occupational histories and a variety of other personal factors were collected through interviews. Among subjects employed in the printing industry for at least one year, the crude odds ratio was 2.7 (95% CI, 0.8–9.6; 7 cases). [The Working Group noted that these were prevalent cases and that this was a hospital-based series.]

Cartwright (1982) conducted a case–control study on urinary bladder cancer in three hospital districts of West Yorkshire, United Kingdom. A total of 625 prevalent cases were identified in October 1978 (472 men, 153 women) and 366 incident cases (272 men, 94 women) were identified between 1978 and 1980. Prevalent cases were matched to one hospital control and incident cases with two controls. Controls were selected randomly among patients without malignant diseases and matched by age, sex and health district. Information on a variety of personal habits and occupational history was derived from interviews. A significant odds ratio, adjusted by sex and type of case (incident or prevalent), of 3.1 (95% CI, 1.4–6.8; 18 cases) was detected for subjects working for at least six months as printers (defined as those exposed to ink-fly from high-speed presses).

Four papers are available giving results on urinary bladder cancer risks in printers based on various subsets of the United States National Bladder Cancer Study (Silverman *et al.*, 1983; Schoenberg *et al.*, 1984; Silverman *et al.*, 1989, 1990). This population-based case–control study was carried out in 10 areas of the United States during 1977–78. Age frequency-matched population controls were selected for each geographical area. Employment was considered as 'ever' or 'usual' in each occupation or industry; subjects never employed in the industry served as referents.

In the Detroit, MI, United States, area, out of 420 male subjects with carcinomas, or papillomas not specified as benign, of the lower urinary tract (95% being urinary bladder cancer) were identified and 339 (81%) were interviewed (Silverman *et al.*, 1983). Analysis was restricted to 303 white male cases and 296 white male population controls. Subjects ever employed in the printing industry did not show an increased risk (crude odds ratio, 1.1; 95% CI, 0.7–1.7; 50 cases). A nonsignificant elevation was seen for subjects who ever worked as printers (odds ratio, 3.0; 95% CI, 0.6–14.8; 6 cases).

In the New Jersey area, United States, 658 incident male cases of urinary bladder cancer and 1258 general population male controls were studied by Schoenberg *et al.* (1984). Age- and smoking-adjusted odds ratios were presented for each employment/-material category in the multiple regression model. The findings suggested no increased risk for men ever employed in the printing industry (odds ratio, 0.9; 95% CI, 0.5–1.5; 20 cases). However, self-reported exposure to printing inks yielded an odds ratio of 1.6 (95% CI, 1.0–2.5; 42 cases).

In the latter two of this group of four papers, Silverman *et al.* (1989) reported on 2100 white male cases with urinary bladder cancer and 3874 population controls. The smoking-adjusted odds ratio was 0.8 for white men who had ever worked as printers (95% CI, 0.5–1.2; 37 cases). There were 652 cases of urinary bladder cancer and 1266 controls among white women (Silverman *et al.*, 1990). The smoking-adjusted odds ratio for women who had ever worked as printers was 0.2 (95% CI, < 0.1–1.4; 1 case).

A death certificate-based case–control study included 291 urinary bladder cancer deaths occurring in England and Wales in the period 1975–79 among males under the age of 50 years (Coggon *et al.*, 1984). For each case, two controls were selected among men who had died from any other causes, matched by sex, year of birth, year of death and residence. Based on occupation recorded on the death certificate, exposure to four

known and five putative carcinogens was evaluated and graded (high, low, none), applying a job–exposure matrix. No increased risk was found for those occupations involving exposure to printing inks (odds ratio, 1.1; 95% CI, 0.5–2.3; 12 cases). However, the risk was elevated for occupations with high exposure to printing inks (odds ratio, 5.0; 95% CI, 1.0–25.8; 5 cases). [The Working Group noted the young age of the study subjects and that occupational status was derived from death certificates.]

Vineis and Magnani (1985) conducted a hospital-based study of 512 male cases of urinary bladder cancer diagnosed between 1978 and 1983, and 596 male hospital controls, matched by age, having benign urological (other than haematuria, cystitis and benign polyps of the urinary tract; Vineis *et al.*, 1984) and surgical conditions. All cases and controls lived in the province of Turin, Italy. Information on lifelong smoking habits and a complete occupational history were collected through interviews. The age-adjusted odds ratio for subjects ever employed in the broad category of the printing and publishing industry for at least six months was 1.8 (95% CI, 0.8–4.0; 17 cases). Adjustment for smoking (and not for age) resulted in a significant odds ratio of 1.7. When incident cases only were considered, the age-adjusted odds ratio was 1.2 (95% CI, 0.5–3.3) [number of incident cases not given].

Baxter and McDowall (1986) examined the association between occupation and urinary bladder cancer risk using death certificate information in the six London boroughs that had the highest mortality from this disease in England and Wales. Cases comprised 1080 deaths from urinary bladder cancer between 1968 and 1978 among male residents of the six boroughs. Two controls for each case were chosen: one selected randomly from male deaths from all other cancers and another from male deaths from all causes. Both were matched to the cases by residence, year of death and age. Odds ratios for printers were 1.5 (controls from all other cancers) and 1.2 (controls from all other causes including cancers) ($p > 0.05$; 21 cases). [The Working Group noted that the number of exposed controls was not given, that the method used to calculate the odds ratios was not clearly stated, and that occupational status was derived from death certificates.]

Using data derived from a large case–control study of smoking and cancer among hospitalized patients in six cities in the United States, Kabat *et al.* (1986) examined the potential risk factors for urinary bladder cancer for reported lifetime nonsmokers in a series of 76 male and 76 female cases and 238 male and 254 female controls. Controls, matched by age, sex, race, hospital and year of interview, were selected among patients with non-tobacco-related cancers (67% in men, 59% in women) or non-neoplastic diseases (33% in men, 41% in women). All subjects were interviewed between 1976 and 1983 and the usual (longest-held) occupation recorded. The study failed to detect an increased risk for male printers: two cases and six controls yielded a nonsignificant odds ratio of 1.1. [The Working Group noted the small number of exposed cases in this study.]

The Missouri Cancer Registry has been collecting data on cancer cases since 1972. Data on smoking, alcohol consumption and occupation (the longest-held job) are routinely derived from a standardized form administered to each cancer patient. Brownson *et al.* (1987) selected 823 histologically confirmed urinary bladder cancers diagnosed among white males between 1984 and 1986. For each case, three white male

controls, frequency matched by age, were chosen among other patients in the registry, excluding smoking-related cancers. Analysis by occupational history was performed using low-risk employment categories as reference. The low-risk occupations included professionals, managers and sales and clerical workers. Printing machine operators had a statistically significant age-, smoking- and alcohol-adjusted odds ratio of 3.1 (95% CI, 1.1–8.9; 7 cases).

Iscovich *et al.* (1987) reported on a case–control study of 117 histologically confirmed urinary bladder cancer cases diagnosed between 1983 and 1985 in the La Plata area, Argentina. Cases were individually matched by age and sex to one neighbourhood control and one non-neoplastic hospital control. Information on smoking, demographic, socioeconomic and medical variables and occupational history for the three occupations of longest duration and the most recent occupation were collected from subjects by questionnaire. Three cases and two controls had ever been employed in printing industries, which yielded a nonsignificant age- and smoking-adjusted odds ratio of 2.7. Seven subjects (5 cases, 2 controls) working as printers either in the printing industry or elsewhere gave a statistically significant age-adjusted odds ratio of 5.4; after adjustment for smoking, the odds ratio was 5.6 but no longer significant.

As part of a methodological investigation of data sources for occupational studies, Steenland *et al.* (1987) conducted a case–control study of male urinary bladder cancer deaths in Hamilton County, OH, United States. A total of 731 urinary bladder cancer cases, deceased during 1960–82, were matched on age, sex, race, date of death and residence at death to two controls per case. Controls were chosen from among all other deaths with the exclusion of deaths from urinary tract tumours and pneumonia. Commercial city directories report yearly occupation and employer for all residents in the county over the age of 18, making it possible to reconstruct occupational lifetime histories. Occupational data from city directories were available for 648 cases and 1275 controls. Odds ratios, conditional on matched sets, were calculated by occupation, industry and employer. The odds ratio for having ever been employed as a press machine operator was 5.0 ([95% CI, 1.3–19]; 5 cases). For employment over 20 years in the printing industry, the odds ratio was 1.3 ($p > 0.05$; 12 cases).

A case–control study of occupation and urinary bladder cancer was carried out by González *et al.* (1989) in five provinces of Spain. Cases of histologically confirmed urinary bladder cancer were recruited from the registers of 12 hospitals between 1985 and 1986. A total of 497 (438 men and 59 women) cases, alive at the time of interview, resident in the province where the hospital was located and below the age of 79, were interviewed (71 were not traced or refused interview). The proportion of incident cases was 51%. For each case, two controls, matched by sex and age, were selected. The first was selected from the same hospital as the case, excluding patients with diagnoses possibly associated with the risk factors under study. Among hospital controls, 583 (62 women) were interviewed; 159 were not traced or refused interview. A second control was randomly selected from the same section of the census or municipality register as that of the case. Of the population controls, 530 (65 women) were interviewed; 200 were not traced or refused interview. A questionnaire on lifestyle and occupational history was administered to each subject. The age- and sex-adjusted odds ratio was 2.1 for male

printers (95% CI, 1.0–4.3; 15 cases). The odds ratio was slightly lower (1.8; 95% CI, 0.8–4.1) after further adjustment for tobacco consumption and employment in other high-risk occupations. In the analysis by occupational subgroups, typesetters and linotypists were associated with an odds ratio of 2.0 (95% CI, 0.5–7.5; 9 cases) after adjusting for smoking and employment in other high-risk occupations.

Using data derived from an on-going case–control study conducted in the area of Milan, Italy, La Vecchia *et al.* (1990) examined the relationship between occupation and urinary bladder cancer. The case series included 263 (219 men, 44 women) histologically confirmed invasive urinary bladder cancers diagnosed between 1985 and 1988. The controls were 287 patients (210 men, 77 women) with acute medical and surgical conditions and non-neoplastic and non-urinary tract diseases. The proportion of cases ever employed in the printing industry (2.3%) was similar to that among controls (2.4%) [crude odds ratio, 0.9; 95% CI, 0.3–2.8].

Steineck *et al.* (1990) examined the relationship between urothelial cancer and exposure to benzene and exhaust in a population-based case–control study in Sweden. The study was based on men born between 1911 and 1945 and living in the county of Stockholm for all or part of the observation period of September 1985 to November 1987. Incident cases of urothelial cancers and/or squamous-cell carcinoma in the lower urinary tract were identified from the regional Cancer Registry and the urological departments (320 subjects). Controls (363 subjects) were selected by stratified (gender and year of birth) random sampling during the observation period from a computerized register covering the population of Stockholm. Information on exposure was collected by a postal questionnaire and all subjects were contacted at their homes. An industrial hygienist classified the subjects as having been exposed or unexposed to 38 agents and groups of substances. The adjusted odds ratio among men classified as having been exposed to carbon black (including printing inks) was 2.0 (95% CI, 0.8–4.9; 14 cases). The odds ratios were 3.2 (95% CI, 0.4–27.1) for low exposure to printing inks, 0.5 (95% CI, 0.1–2.1) for moderate exposure and 3.6 (95% CI, 0.8–12.1) for high exposure.

A population-based case–control study was conducted in the United States to examine the relationship between urinary bladder cancer, usual occupation and industry, and cigarette smoking (Burns & Swanson, 1991a). Cases and controls were selected through the Metropolitan Detroit Cancer Surveillance System, which had collected population-based cancer data for the three-county metropolitan Detroit area since 1973. Incident cases occurring among white and black subjects of each sex between the ages 40 and 84 were enrolled into the study. Subjects, or their surrogate respondents, were interviewed by telephone; the response rate for cases and controls was 94% and 95%, respectively. A total of 2160 urinary bladder cancer cases and 3979 controls with cancers of the colon and rectum, with complete histories of occupation and tobacco use, were included in the analysis. The analysis by usual occupation did not reveal an increased risk for printers (adjusted odds ratio, 0.9; 95% CI, 0.4–1.9; 12 cases). Nor was there an excess risk found for the printing industry (adjusted odds ratio, 0.7; 95% CI, 0.4–1.2; 22 cases). Case series in this study partly overlapped with the United States National Bladder Cancer Study (see Silverman *et al.*, 1983, 1989, 1990). [The Working Group was concerned that only colonic and rectal cancers were used as controls.]

A hospital–based case–control study of 531 male matched pairs was conducted in South Lower Saxony, Germany (Claude *et al.*, 1988; Kunze *et al.*, 1992). Of the cases, 93% had histologically confirmed benign or malignant epithelial tumours of the urinary bladder; the remainder had tumours of the lower urinary tract. The cases were ascertained between 1977 and 1985 from three hospitals. Controls were patients with non-neoplastic diseases of the lower urinary tract from the same hospitals, individually matched by age to the cases. Among controls, 64% had hyperplasia of the prostate and 19% infection of the lower urinary tract. All subjects were interviewed on lifestyle, familial occurrence of urinary bladder cancer and occupational history. Cases and controls were compared according to whether they were ever employed in specific industries or occupations or ever exposed to selected agents. A significantly increased crude odds ratio of 5.0 (95% CI, 1.3–19.6; 11 cases) was observed among men ever employed in the printing industry. Analysis by occupation showed an elevated, although statistically nonsignificant, risk for printing workers (odds ratio, 3.0; 95% CI, 0.7–13.8; 7 cases). Analysis by length of employment was not performed due to the small numbers. [The Working Group noted that the definition of printing workers was unclear.]

Urinary bladder cancer and occupational exposures were investigated in a multicentre hospital-based case–control study in France between 1984 and 1987 (Cordier *et al.*, 1993). Incident and prevalent cases, diagnosed after 1982, of histologically verified urinary bladder cancers in patients under 80 years of age were collected in urology departments of seven university hospitals in five regions of France. There was a total of 658 male cases. For each case, one hospital control was selected; controls were matched for age, ethnic origin and place of residence and had been admitted to other departments of the same hospital for diseases other than cancer, respiratory diseases or symptoms suggestive of urinary bladder cancer. Detailed interview data were collected for jobs held for at least six months. Occupational industrial titles were classified by a team of industrial hygiene experts. An unconditional logistic regression model was employed, controlling for age, hospital, place of residence and smoking status. The adjusted odds ratio for men ever employed in the printing and publishing industry for at least six months was 0.9 (95% CI, 0.5–1.5; 26 cases). The odds ratio for men who, based on job title, were classified as printers was 1.5 (95% CI, 0.6–3.5; 14 cases); the subgroup classified as printing pressmen had an odds ratio of 4.2 (95% CI, 0.8–20.8; 8 cases).

(*c*) *Lung cancer* (see Table 10)

Coggon *et al.* (1984), in a case–control study described on pp. 73–74, examined the relationship between lung cancer and occupation, based on information derived from death certificates. The study included 598 lung cancer deaths occurring in the period 1975–79 among males under the age of 40 in England and Wales. For each case, two controls were selected among men who had died from any other causes (matched by year of birth, year of death and residence). Information on occupation was obtained as described previously. A nonsignificant excess was found in occupations involving exposure to printing inks (odds ratio, 1.6; 95% CI, 0.9–2.7; 28 cases). The odds ratio for

Table 9. Case–control studies of urinary bladder cancer among workers in the printing industry

Reference, country	Type of controls	Exposure	Sex	No of exposed cases/controls	Odds ratio	95% CI	Comments
Wynder *et al.* (1963) USA	Hospital-based, excluding cancers of the respiratory system and upper alimentary tract, myocardial infarction	Printers, engravers, lithographers (ever)	M	3/2	[2.2]	[0.4–13.2]	–
Cole *et al.* (1972) USA	Population-based	Printing (usual)	M	5/7.7 (exp.)	0.8	0.3–1.9	Adjusted for age
		Printing (ever)	M	14/15.1 (exp.)	1.3	0.7–2.5	Adjusted for age and smoking
Williams *et al.* (1977) USA	Population-based, other cancers	Printing, publishing and allied products industry	M	4/NG	2.0	NG	Not significant. Adjusted for smoking
Najem *et al.* (1982) USA	Hospital-based, tobacco-related heart diseases and neoplasms excluded	Printing industry (≥ 1 year)	M+F	7/5	2.7	0.8–9.6	Crude odds ratio
Cartwright (1982) United Kingdom	Hospital-based, non-malignant diseases	Printers (exposed to ink-fly from high-speed presses)	M+F	18/NG	3.1	1.4–6.8	Adjusted for type of case (incident or prevalent) and sex
Silverman *et al.* (1983) USA	Population-based	Printing industry (ever)	M	50/45	1.1	0.7–1.7	Crude odds ratio
		Printers (ever)	M	6/2	3.0	0.6–14.8	
Coggon *et al.* (1984) United Kingdom	Deaths from other causes	Printing inks	M	12/21	1.1	0.5–2.3	Job exposure matrix applied to occupations recorded on death certificates; age < 50 years, cases and controls
		Printing inks (high exposure)	M	5/2	5.0	1.0–25.8	
Schoenberg *et al.* (1984) USA	Population-based	Printing workers (ever)	M	20/38	0.9	0.5–1.5	Adjusted for age, smoking and other employments
		Printing ink (self-reporting)	M	42/53	1.6	1.0–2.5	

Table 9 (contd)

Reference, country	Type of controls	Exposure	Sex	No of exposed cases/controls	Odds ratio	95% CI	Comments
Vineis & Magnani (1985) Italy	Hospital-based, benign urological and surgical conditions	Printing and publishing industry (ever)	M	17/12	1.8	0.8–4.0	Adjusted for age
					1.7	NG	Adjusted for smoking; significant ($p < 0.05$)
			M	NG	1.2	0.5–3.3	Only incident cases, adjusted for age
Baxter & McDowall (1986) United Kingdom	Other cancers	Printers (stated on death certificates)	M	21/NG	1.5	$p > 0.05$	Against other cancers; matched on residence, year of death, age
	All causes of death				1.2	$p > 0.05$	
Kabat *et al.* (1986) USA	Hospital-based, nonsmoking-related diseases	Printers	M	2/6	1.1	NG	Not significant. Nonsmoking cases and controls; blue-collar industrial occupations under-represented in the study population
Brownson *et al.* (1987) USA	Population-based, other nonsmoking-related cancers	Printing machine operators (longest-held job)	M	7/8	3.1	1.1–8.9	All controls
			M	7/6	2.3	0.8–7.2	Prostate cancer excluded from controls. Adjusted for age, smoking and alcohol
Iscovich *et al.* (1987) Argentina	Neighbourhood and hospital-based, non-neoplastic diseases	Printing industry (ever)	M+F	3/2	2.7	NG	Not significant, adjusted for age and smoking
		Printers (either in printing industry or elsewhere)	M+F	5/2	5.6	NG	

Table 9 (contd)

Reference, country	Type of controls	Exposure	Sex	No of exposed cases/controls	Odds ratio	95% CI	Comments
Steenland *et al.* (1987) USA	Other deaths, excluding urinary tract tumours and pneumonia	Pressing machine operator (ever)	M	5/2	5.0	[1.3–19]	Data from city directories
		Printing industry > 20 years	M	12/19	1.3	$p > 0.05$	Data from city directories. All matched on age, sex, race, date of death, residence at death
Gonzáles *et al.* (1989) Spain	Hospital- and population-based	Printers	M	15/19	1.8	0.8–4.1	Adjusted for smoking and exposure in other at-risk occupations
		Typesetters, linotypists	M	9/10	2.0	0.5–7.5	Adjusted for smoking and exposure in other at-risk occupations
Silverman *et al.* (1989, 1990) USA	Population-based	Printer (ever)	M (white)	37/77	0.8	0.5–1.2	Adjusted for smoking; frequency matching for age and geographic area
			F (white)	1/10	0.2	< 0.1–1.4	
La Vecchia *et al.* (1990) Italy	Hospital-based, other non-neoplastic, non-urinary diseases	Printing (ever)	M + F	[6/7]	[0.9]	[0.3–2.8]	Crude odds ratio
Steineck *et al.* (1990) Sweden	Population-based	Carbon blacks (including printing inks)	M	14/9	2.0	0.8–4.9	Adjusted for smoking; frequency matching for sex and year of birth
		Printing ink, low exposure	M	NG	3.2	0.4–27.1	
		Printing ink, moderate	M	NG	0.5	0.1–2.1	
		Printing ink, high	M	NG	3.6	0.8–12.1	

Table 9 (contd)

Reference, country	Type of controls	Exposure	Sex	No of exposed cases/controls	Odds ratio	95% CI	Comments
Burns & Swanson (1991a) USA	Colonic and rectal cancers	Printers (usual)	M + F	12/19	0.9	0.4–1.9	Adjusted for smoking, race, sex, age at diagnosis
		Printing industry	M + F	22/41	0.7	0.4–1.2	
Kunze *et al.* (1992) Germany	Hospital-based, non-neoplastic diseases of the lower urinary tract	Printing industry (ever)	M	11/3	5.0	1.3–19.6	Crude odds ratios
		Printing workers (ever)	M	7/3	3.0	0.7–13.8	
Cordier *et al.* (1993) France	Hospital-based, neoplastic, respiratory and urological conditions excluded	Printing and publishing industry (ever)	M	26/28	0.9	0.5–1.5	Adjusted for age, hospital, residence, smoking
		Printers	M	14/9	1.5	0.6–3.5	
		Printing pressmen	M	8/2	4.2	0.8–20.8	
Siemiatycki (1991) Canada	Hospital-based, other cancers	Inks (any)	M	18/NG	1.2	[0.7–2.1]	Adjusted for age, smoking
		Inks (substantial)		6/NG	0.9	[0.4–2.3]	
Siemiatycki *et al.* (1994) Canada	Population and hospital-based, other cancers, excluding lung and kidney sites	Printing and publishing industry	M				Adjusted for age, family income, smoking, coffee consumption, ethnicity, respondent status
		< 10 years		2/NG	0.3	0.1–1.2	
		≥ 10 years		11/NG	1.9	0.9–3.9	
		Photographic products (substantial exposure)		4/NG	3.0	0.9–10.1	

M, males; NG, not given; F, females

occupations with high exposure was 2.0 (95% CI, 0.8–5.0; 9 cases). [The Working Group noted the young age of the study subjects and that occupational status was derived from death certificates.]

Occupational risk factors for lung cancer were investigated in a case–control study in France (Benhamou *et al.*, 1985, 1988). The data were collected during the period 1976–80 in 16 hospitals, 13 of which were in Paris. A total of 1260 male cases with histo-ogically confirmed lung cancer and 2084 matched (by age at diagnosis, hospital of admission, and interviewer) controls hospitalized for non-tobacco-related diseases were included. Complete occupational histories were recorded in personal interviews. The smoking-adjusted matched odds ratio for printers and related workers was 1.2 (95% CI, 0.7–1.9; 32 cases). There was no evidence of an increase in risk with duration of exposure.

A case–control study of lung cancer in Florence, Italy, was conducted to investigate occupational risk factors (Buiatti *et al.*, 1985). All histologically confirmed cases of primary lung cancer admitted during 1981–83 to the regional general hospital (referral centre for all lung cancers) were selected for the study. For each case, one or two controls were selected from the same hospital by sex, age (plus or minus five years), date of admission and smoking status. All cases and controls were interviewed after their first admission to the hospital; in total, 592 cases (547 men, 45 women) and 1036 controls (955 men, 81 women) were interviewed. After restricting both series to residents of metropolitan Florence, 376 cases (340 men, 36 women) and 892 controls (817 men, 75 women) were available for the analysis. The odds ratio (adjusted for age, smoking and place of birth) for men having ever worked in paper or printing occupations was 1.6 (95% CI, 0.7–3.5; 11 cases). In women, two cases and four controls had ever worked in paper and printing occupations.

The association between occupation and lung cancer risk was examined in a population-based case–control study in New Mexico, United States (Lerchen *et al.*, 1987). Cases included Hispanic white and other white residents of New Mexico, aged 25–84 years, with primary lung cancer, other than bronchiolar/alveolar carcinoma, diagnosed between January 1980 and December 1982. Cases were identified through the New Mexico Tumor Registry. Controls were selected by random-digit dialling for persons aged 65 and older from the Health Care Financing Administration's roster of Medicare participants. The controls were frequency matched to cases for sex, ethnicity and 10-year age category. A personal interview was used to obtain lifetime occupational and smoking histories and self-reported history of exposure to specific agents. The overall case interview rate was 89%, half of which were conducted with next-of-kin. The analysis was based on data from 333 male cases and 499 male controls. The odds ratio adjusted for age, ethnicity and smoking was 0.8 (95% CI, 0.4–1.8; 11 cases) for workers in the printing industry. Five cases had ever been employed as printers (odds ratio adjusted for age, ethnicity and smoking, 0.8; 95% CI, 0.3–2.6).

The association between lung cancer risk and occupation was examined in a case–control study in six areas of New Jersey, United States (Schoenberg *et al.*, 1987). The study included 763 histologically confirmed incident lung cancers in white males and

900 general population white male controls between September 1980 and October 1981. The response rates were 70% among cases and 64% among controls. A total of 429 cases and 334 next-of-kin were interviewed. For self-respondent cases, controls were selected from State Drivers License files and frequency matched by race, age and residence. For deceased or incapacitated cases, controls, individually matched by race, age, residence and closest date of death or diagnosis, were selected from State mortality files, excluding deaths from lung cancer and respiratory diseases. Among controls, 564 were self-respondents. The smoking-adjusted odds ratio for subjects ever employed as printing workers (printing pressmen, compositors, typesetters, photoengravers, lithographers, printing engravers, printing trade apprentices) was 2.5 (95% CI, 1.0–6.1; 20 cases). After adjustment for additional variables (age, area, respondent type, education, vegetable consumption), the odds ratio was 2.3 (95% CI, 1.0–5.3). A significant crude odds ratio of 8.4 (7 cases) was found for duration of employment of 10 or more years as a printing worker.

The association between lung cancer risk and occupation was studied in a case–control study in Missouri, United States (Hoar Zahm *et al.*, 1989). Study subjects were identified through the Missouri Cancer Registry. Cases were all white male Missouri residents who had been diagnosed with histologically confirmed lung cancer from January 1980 through to November 1985; controls were white male Missouri residents diagnosed with cancer, excluding cancers of the lip, oral cavity, oesophagus, lung, urinary bladder, ill-defined sites and unknown sites. The study involved 4431 cases and 11 326 controls. Occupation at the time of diagnosis was abstracted from questionnaires administered to the cancer patients at the hospitals. Forty-eight percent of lung cancer cases and 55% of controls had unknown occupation on the records. The age- and smoking-adjusted odds ratio for printing occupations was 1.1 (95% CI, 0.6–1.9; 21 cases). An excess of adenocarcinoma was found for printing occupations (odds ratio, 1.8; 95% CI, 0.7–4.2; 7 cases). [The Working Group noted that many cases and controls had no known occupation.]

Occupational risk factors for lung cancer were assessed in a population-based case–control study in the Detroit Metropolitan Area, United States (Burns & Swanson, 1991b). Incident cancers occurring among white and black men and women between the ages of 40 and 84 were enrolled into the study through a rapid reporting system within two to six weeks of diagnosis. There were 5935 lung and bronchial cancer patients in the case group and 3956 colonic and rectal cancer patients in the control group. Subjects or their surrogate respondents were interviewed by telephone. Interviews with surrogates for deceased subjects were conducted with 39% of lung cancers, compared to 13% of the colonic and rectal cancer controls. The overall response rate was 93%. No elevated risk was found for printers (odds ratio adjusted for age at diagnosis, race, smoking and gender, 0.8; 95% CI, 0.4–1.7; 18 cases). The adjusted odds ratio for the printing industry was 0.7 (95% CI, 0.4–1.1; 54 cases). [The Working Group was concerned that only colonic and rectal cancers were used as controls and noted that the series of controls used in this study is probably the same as that in Burns & Swanson (1991a).]

Morabia *et al.* (1992) reported on a multicentre case–control study involving 1793 histologically confirmed male lung cancer cases at 24 hospitals in nine metropolitan

Table 10. Case–control studies of lung cancer among workers in the printing industry

Reference, country	Type of controls	Exposure	Sex	No of exposed cases/controls	Odds ratio	95% CI	Comments
Viadana *et al.* (1976) USA	Hospital-based, non-neoplastic diseases	Printing workers	M	7/NG	1.5	NG	Not significant
Coggon *et al.* (1984) United Kingdom	Deaths from other causes	Printing inks Printing inks (high exposure)	M M	28/36 9/9	1.6 2.0	0.9–2.7 0.8–5.0	Job exposure matrix applied to occupations recorded on death certificates; age < 40 years, cases and controls
Buiatti *et al.* (1985) Italy	Hospital-based	Paper or printing occupations (ever)	M F	11/16 2/4	1.6	0.7–3.5	Adjusted for age, smoking, place of birth; matched on sex, age, date of admission
Lerchen *et al.* (1987) USA	Population-based	Printing industry (ever) Printers	M M	11/17 5/7	0.8 0.8	0.4–1.8 0.3–2.6	Adjusted for age, ethnicity, smoking; matched on age, ethnicity and sex
Schoenberg *et al.* (1987) USA	Population-based	Printing workers ≥ 10 years Printing industry	M M M	20/11 7/1 37/31	2.5 8.4 1.3	1.0–6.1 NG 0.8–2.3	Adjusted for smoking ($p < 0.05$, crude) Adjusted for smoking
Benhamou *et al.* (1988) France	Hospital-based, non-tobacco-related diseases	Printers and related workers	M	32/51	1.2	0.7–1.9	Matched for sex, age at diagnosis, hospital, interviewer; adjusted for smoking
Hoar Zahm *et al.* (1989) USA	Selected cancer sites	Printing occupations	M	21/41 7/[4] (adeno-carcinoma)	1.1 1.8	0.6–1.9 0.7–4.2	Adjusted for age, smoking. Occupations unknown for about half of cases and controls
Burns & Swanson (1991) USA	Colonic and rectal cancers	Printers (usual) Printing industry	M+F	18/19 54/41	0.8 0.7	0.4–1.7 0.4–1.1	Adjusted for age at diagnosis, race, smoking, sex

Table 10 (contd)

Reference, country	Type of controls	Exposure	Sex	No of exposed cases/controls	Odds ratio	95% CI	Comments
Siemiatycki (1991) Canada	Hospital-based, other cancers	Printing and publishing industry	M	35/NG	2.0	[1.2–3.5]	Smoking-adjusted
		Printers	M	26/NG	2.1	[1.1–4.1]	Smoking-adjusted
		Printers (> 10 years)	M	13/NG	1.7	[0.7–4.1]	Smoking-adjusted
		Printing process workers	M	15/NG	3.1	[1.1–8.7]	Smoking-adjusted
			M	6/NG (adeno-carcinoma)	7.0	[1.8–27.9]	Smoking-adjusted.
		Inks (any)	M	37/NG	1.6	[1.0–2.7]	Smoking-adjusted
		Inks (substantial)	M	18/NG	1.5	[0.7–3.1]	Smoking-adjusted
Morabia *et al.* (1992) USA	Hospital-based	Bookbinders and related printing trade workers	M	11/6	3.3	1.2–8.9	Adjusted for age, race, smoking, geographical area

M, male; NG, not given; F, female

areas in the United States during 1980–89. Information on sociodemographic characteristics, cigarette smoking and occupational history (usual job title and 44 specific exposures) were collected through a standardized questionnaire. For each case, one or two controls were selected from among patients without lung cancer, individually matched by race, age, hospital and cigarette smoking habits. Out of 3228 controls, 69% had a diagnosis of cancer other than of the lung and 31% had a diagnosis of non-neoplastic diseases. Unconditional logistic regression was used to compute odds ratios adjusted for matching variables. A statistically significantly increased risk was found for bookbinders and related printing trade workers (odds ratio, 3.3; 95% CI, 1.2–8.9; 11 cases).

(*d*) *Lymphohaematopoietic neoplasms* (see Table 11)

Occupational risks of leukaemia were investigated using the data from the Tri-State Leukemia Survey collected in New York, Baltimore and Minnesota, United States, during the period 1959–62 (Viadana & Bross, 1972). A subsample of 1345 white adult leukaemia cases and 1237 controls randomly selected from households in the same area as the cases were interviewed and included in the analysis. No relationship was found between leukaemia and occupation among women. Men reporting employment as printers in any of the five most recent jobs prior to interviews had a nonsignificant excess when compared to either non-printers (age-adjusted odds ratio, 1.5 [95% CI, 0.6–3.7]; 17 cases) or to clerks (age-adjusted odds ratio, 1.9 [95% CI, 0.7–5.0]).

Blair *et al.* (1993) examined the relationship between non-Hodgkin's lymphoma and occupation in a population-based case–control study in Iowa and Minnesota, United States. Cases were 715 white men with histologically confirmed non-Hodgkin's lymphoma reported to the Iowa State Health Registry during 1981–83 and patients identified through a surveillance network of hospitals in Minnesota during 1980–82. Controls were selected by random-digit dialling from the medical files of the Health Care Finance Administration and state vital records. All controls were frequency matched by state, age (15-year categories) and by year of death for deceased cases. A total of 622 cases and 1245 controls were interviewed on lifestyle and occupational history. The proportion of next-of-kin interviews was 30% for cases and 34% for controls. Subjects employed only as farmers were excluded, which left 546 cases and 1087 controls in the study. Odds ratios adjusted for age, state, smoking, type of respondent, family history of lymphoma and agricultural exposure to pesticides were computed. Six cases employed in printing press occupations yielded an odds ratio of 1.5 (95% CI, 0.4–5.1). A significant excess was found among workers with a duration of employment in the printing and publishing industry longer than 10 years (odds ratio, 2.5; 95% CI, 1.1–5.7); a decreased odds ratio of 0.5 was found for duration of employment less than 10 years (95% CI, 0.2–1.3).

(*e*) *Oropharyngeal cancer* (see Table 11)

Huebner *et al.* (1992) conducted a population-based case–control study of oropharyngeal cancers in four areas of the United States (Atlanta, New Jersey, Los Angeles and San Francisco). A total of 1114 black and white incident cases (762 males and 352 females) of primary histologically confirmed cancers of the oral cavity and pharynx

(salivary glands and nasopharynx excluded) were identified from population-based cancer registries during 1984–85. A total of 1268 controls were obtained through random-digit dialling (aged 18–64 years) and from Health Care Financing Administration files (aged 65–79). These were frequency matched to the cases by race, sex, five-year age group and study area. Interviews on personal habits and occupation were conducted with the subjects or with next of kin for 75% of cases and 76% of controls. Surrogate respondents constituted 22% of cases and 2% of controls. The odds ratio adjusted for smoking, alcohol consumption, study location, age and race for men ever employed in the printing industry was 0.8 (95% CI, 0.5–1.5; 28 cases) and that for women was 2.9 (95% CI, 0.7–11.6; 8 cases). Analysis by job category revealed an odds ratio of 0.7 (95% CI, 0.3–1.4; 16 cases) for male printers/pressmen.

(*f*) *Testicular cancer* (see Table 11)

Coldman *et al.* (1982) examined the relationship of testicular seminoma to several risk factors in a case–control study of 128 histologically confirmed cases diagnosed between 1970 and 1977 in a regional treatment centre in Vancouver, Canada. One-hundred-and-twenty-eight controls were matched by age and year of diagnosis, and selected from other patients with skin cancers or Hodgkin's disease. A detailed occupational history was obtained for 89% of cases and 88% of controls. Seven cases had ever worked in the printing industry (odds ratio, 7.2; 95% CI, 0.9–162.3). No significant differences between cases and controls for exposure to inks were noted [actual results not reported].

The risk for testicular cancer associated with socioeconomic status and occupation was examined by Swerdlow *et al.* (1991) in England. A total of 259 cases of primary testicular cancer, incident between January 1977 and February 1981 and aged at least 10 years, were enrolled in six radiotherapy and oncology centres. Two control groups were selected from the same centres: 238 patients with other cancers (35% represented Hodgkin's disease, 13% non-Hodgkin's lymphoma, 10% brain cancer, 8% urinary bladder cancer) and, in other departments, 251 hospital inpatients with a wide range of non-malignant conditions. The subjects were interviewed on education, lifetime occupational history and father's occupation. Odds ratios adjusted for age and region of residence were estimated using conditional logistic regression models. When the results of the analyses for each control group were similar, the two sets of controls were combined. The risk was examined for occupation at age 20, at age 30, for the longest held occupation, for ever held occupation and for that most recently held. The only substantially increased odds ratio was reported for subjects ever employed in paper and printing (odds ratio, 2.1; 95% CI, 0.8–5.0; 10 cases).

(*g*) *Other cancer sites* (see Table 11)

The Missouri Cancer Registry identified 1993 white male cases of histologically confirmed colonic cancer and 9965 age-matched cancer controls, diagnosed between 1984 and 1987 (Brownson *et al.*, 1989). Two control groups were selected. The first contained all other cancers, the second excluded cancer sites known to be related to occupations (leukaemia, peritoneum, nasal cavity, lung, pleura, urinary bladder). Data on

occupation and industry were collected routinely from hospital medical records at the time of diagnosis. Age-adjusted odds ratios were computed. Since odds ratios were generally of similar magnitude using each of the two control groups, all other cancers were used as controls. Excesses were found for printing machine operators (odds ratio, 1.9; 95% CI, 1.0–3.3; 18 cases) and workers employed in the printing and publishing industry (odds ratio, 1.8; 95% CI, 1.2–2.7; 33 cases).

Using the above-mentioned Missouri Cancer Registry, Brownson *et al.* (1990) evaluated the risk of brain cancer in relation to employment history in white males in a study of 312 histologically confirmed brain and other central nervous system cancers (ICD codes 191–192) and 1248 other cancer controls, frequency matched by age. Controls excluded cancers of ill-defined or unknown primary sites. The study covered the period 1984–88. Data on occupation and tobacco smoking habits were collected as in Brownson *et al.* (1989). Of the eligible subjects, 34% of cases and 38% of controls were excluded due to missing occupational information. [The Working Group was concerned by this high proportion of missing information.] The age- and smoking-adjusted odds ratio for workers in the printing and publishing industry was 2.8 (95% CI, 1.0–8.3; 7 cases). The elevated risk was equally distributed between astrocytic- and 'other'-cell type cancers [odds ratios not reported].

The role of occupational risk factors in the occurrence of pancreatic cancer was investigated in a case–control study conducted in France (Pietri *et al.*, 1990), with 171 cases (105 men, 66 women) enrolled in seven public hospitals in Paris between 1982 and 1985. For each case, two controls, matched by sex, age at interview (within five years), hospital and interviewer, were selected: one among patients with cancers other than neoplasms of the biliary tract, liver, stomach and oesophagus and the other among patients with non-neoplastic diseases. The total number of controls was 317 (196 men, 121 women). All subjects agreed to be interviewed. Odds ratios were derived from unconditional logistic regression models adjusting for age, sex, foreign origin, education, coffee, cigarette and alcohol consumption using the two sets of controls combined. Cases and controls did not significantly differ in having been employed for at least one year in the printing industry (odds ratio, 1.3; 95% CI, 0.5–3.4; 8 cases). Among manual workers, three cases had ever been employed in printing occupations (odds ratio, 0.8; 95% CI, 0.2–3.4).

A case–control study of renal-cell cancer was conducted in Finland (Partanen *et al.*, 1991). A total of 672 primary incident cases of renal-cell adenocarcinoma were identified through the Finnish Cancer Registry in 1977–78. Two population controls were matched to each case for year of birth, gender and survival status at the time of data collection; they were randomly selected from the population register, and the total number of controls was 1344 (280 alive, 1064 deceased). Data were collected by questionnaire, which had response rates for self-respondents of 76% for cases and 79% for controls; for next-of-kin respondents, the rates were 67% for cases and 65% for controls. The analyses were based on 338 matched sets of cases and controls, 192 cases having one control and 146 cases having two controls. An ad-hoc scoring system (three levels) was developed based on exposure level (background, low, high), the proportion of annual work time spent in the higher level of exposure and the period and duration of exposure for nine

Table 11. Case–control studies of other cancer sites among workers in the printing industry

Reference, country	Cancer type	Type of controls	Exposure	Sex	No of exposed cases/controls	Odds ratio	95% CI	Comments
Viadana & Bross (1972) USA	Leukaemia	Population-based	Printers (any of five most recent jobs)	M	17/814	1.5	[0.6–3.7]	In comparison with non-printers
				M	17/114	1.9	[0.7–5.0]	In comparison with clerks. Adjusted for age
Blair *et al.* (1993) USA	Non-Hodgkin's lymphoma	Population-based	Printing press occupations	M	6/5	1.5	0.4–5.1	Adjusted for age, state, smoking, family, history of malignant lympho-proliferative diseases, agricultural exposure to pesticides, use of hair dyes, direct or surrogate respondent
			Printing and publishing industry	M	NG	0.5	0.2–1.3	Duration < 10 years
					NG	2.5	1.1–5.7	Duration > 10 years
Huebner *et al.* (1992) USA	Oral cavity and pharynx, excluding salivary glands and nasopharynx	Population-based	Printing industry (ever)	M	28/36	0.8	0.5–1.5	Adjusted for age, race, smoking, alcohol, study location
				F	8/4	2.9	0.7–11.6	
			Printers/pressmen (ever)	M	16/27	0.7	0.3–1.4	
Coldman *et al.* (1982) Canada	Testicular seminoma	Hospital-based, patients with melanoma, other skin cancers and Hodgkin's diseases	Printing industry (ever)	M	7/1	7.2	0.9–162.3	Adjusted for age

Table 11 (contd)

Reference, country	Cancer type	Type of controls	Exposure	Sex	No of exposed cases/controls	Odds ratio	95% CI	Comments
Swerdlow *et al.* (1991) United Kingdom	Testis	Hospital-based, other cancers and non-neoplastic diseases	Paper and printing workers (ever)	M	10/12	2.1	0.8–5.0	Adjusted for age, residence
Brownson *et al.* (1989) USA	Colon	Population-based, other cancers	Printing and publishing industry	M	33/92	1.8	1.2–2.7	Adjusted for age
			Printing machine operators	M	18/49	1.9	1.0–3.3	
Brownson *et al.* (1990) USA	Brain and other central nervous system	Population-based, other cancers, excluding ill-defined or unknown primary site	Printing and publishing industry	M	7/10	2.8	1.0–8.3	Adjusted for age, smoking
Pietri *et al.* (1990) France	Pancreas	Hospital-based, non-neoplastic diseases and other cancers, excluding biliary tract, liver, stomach, oesophagus	Printing industry, all workers (at least 1 year)	M+F	8/12	1.3	0.5–3.4	Adjusted for age, sex, foreign origin, education, coffee, alcohol, smoking
			Printing industry, manual workers only (ever)	M+F	3/7	0.8	0.2–3.4	
Partanen *et al.* (1991) Finland	Renal-cell adenocarcinoma	Population-based	Printing and publishing industry, duration of employment ≥ 5 years	M	6/NG	4.6	0.9–23.5	Adjusted for obesity, smoking, coffee
				F	5/NG	8.0	0.9–69.8	
			Printers, duration of employment ≥ 5 years	M	4/NG	6.0	0.7–54.5	

Table 11 (contd)

Reference, country	Cancer type	Type of controls	Exposure	Sex	No of exposed cases/controls	Odds ratio	95% CI	Comments
Sinks *et al.* (1992) USA	Renal-cell cancer	Controls selected from paperboard printing plant workers (nested case–control study)	Duration of employment in finishing departments ≥ 5 years	M	3/3	16.6	1.7–453	Adjusted for age
Mandel *et al.* (1995) Australia, Denmark, Germany, Sweden, USA	Renal-cell cancer	Population-based	Printing or graphic industry (ever/never)	M	39/41	1.3	0.8–2.0	Adjusted for age, smoking, body mass index, education, study center
Multisite case–control studies								
Viadana *et al.* (1976) USA	Buccal cavity and pharynx	Hospital-based, non-neoplastic diseases	Printing workers	M	11/NG	2.6	NG	In comparison with clerical workers; significant ($p < 0.05$), adjusted for age. Not significant when adjusted for smoking (odds ratio 2.1)
Williams *et al.* (1977) USA	Oral cavity	Population-based, other cancers	Printing, publishing and allied products industry	M	7/NG	4.5	NG	Significant ($p < 0.05$)
	Pancreas			M	3/NG	7.0	NG	Not significant
	Pancreas			F	2/NG	8.2	NG	Not significant
	Melanoma			M	2/NG	3.0	NG	Not significant
								Adjusted for age, race, education, smoking, alcohol

Table 11 (contd)

Reference, country	Cancer type	Type of controls	Exposure	Sex	No of exposed cases/controls	Odds ratio	95% CI	Comments
Siemiatycki (1991)	Pancreas	Hospital-based, other cancers	Printers (> 10 years exposure)	M	4/NG	3.7	[1.2–11.2]	Smoking-adjusted
Canada	Kidney	Hospital-based, other cancers	Printers (any exposure)	M	5/NG	3.4	[1.2–9.5]	Smoking-adjusted
			Printers (> 10 years exposure)	M	3/NG	3.6	[1.0–10.6]	

M, male; F, female; NG, not given

selected exposures. For men and women, conditional logistic models were used to calculate separately odds ratio estimates adjusted for smoking status, coffee consumption and obesity. The odds ratio associated with employment for at least five years in the printing and publishing industry was 4.6 (95% CI, 0.9–23.5; 6 cases) in men and 8.0 (95% CI, 0.9–69.8; 5 cases) in women. Analysis by occupation revealed an increased risk among male printers who had worked for at least five years (odds ratio, 6.0, 95% CI, 0.7–54.5; 4 cases). Out of 10 cases with a high level of exposure to gasoline (odds ratio, 7.4; 95% CI, 1.6–35), three worked as operators of a relief-printing press and one as a rotogravure pressman who cleaned the press cylinders with gasoline; one of the two controls with high exposure was a press operator and foreman in a relief-printing shop.

A population-based multicentric international case–control study investigated the relationship between renal-cell adenocarcinoma and occupation (men and women) (Mandel *et al.*, 1995). Study centres in Australia, Denmark, Germany, Sweden and the United States interviewed 1732 incident cases and 2309 population controls (about 60% were men). The elicited occupational data were coded as ever/never in an occupation and industry. Ever employment in the printing or graphic industry was associated with an odds ratio of 1.3 (95% CI, 0.8–2.0; 39 cases) for men, adjusted for age, smoking status, body mass index, education and study centre.

2.2.4 *Cohort studies*

Cohort studies (industry- and community-based) are summarized in Table 12.

Mortality by occupation and industry among men who had served in the United States Armed Forces at some time between 1917 and 1940 was studied (Hrubec *et al.*, 1992). Information on tobacco use, occupation and industry was obtained through a mailed questionnaire sent in 1954 or 1957. The response rate was 84%. Included in the analysis were 248 046 respondents, who accumulated 4 530 604 person-years. A total of 164 785 deaths occurred during the period 1954–80. Mortality experience of this cohort during 1954–69 has been reported by Rogot and Murray (1980). Relative risks (RRs) for 1954–80 were calculated using a Poisson regression model adjusted for age at observation, calendar time, type of smoking and number of cigarettes smoked. Mortality from respiratory cancer was increased in printing pressmen and plate printers (adjusted RR, 1.6 [95% CI, 0.5–3.1]; 9 cases), in electrotypers and stereotypers (adjusted RR, 2.2; non-significant; 4 cases) and in bookbinders (adjusted RR, 2.5; nonsignificant; 3 cases; 1 case in nonsmokers). The risk of urinary bladder cancer was significantly increased in printing pressmen and plate printers (RR, 3.4 [95% CI, 1.3–9.0]; 4 cases). Two cases of renal cancer yielded a RR of 3.4 [95% CI, 0.6–18.7] in printing pressmen and plate printers. There were two cases of leukaemia in printing pressmen and plate printers (RR, 1.6), two cases in photoengravers and lithographers (RR, 1.7) and one case in other engravers (RR, 3.1).

2.3 **Industry-based studies** (see Table 12)

To evaluate lung cancer risk associated with occupations, Dunn and Weir (1968) carried out a prospective mortality study among 68 153 men, aged 35–64 years,

Table 12. Cohort studies (industry- and community-based) among workers in the printing industry

Reference, country	Study subjects	Period of follow-up	Occupation/exposure	Cancer site/ cause of death	No. obs.	RR	95% CI	Comments
Dunn & Weir (1968) USA	68 153 male members of union organizations in 1954	1954–65	Printers	Lung	30	[0.8]	[0.5–1.1]	SMR, adjusted for age and smoking
Goldstein *et al.* (1970) USA	About 460 pressroom workers and 700 compositors in a newspaper plant	1947–62	Mineral oil mist	Lung				Crude RR, pressmen versus compositors
			Pressmen		3	[0.9]	[0.2–3.7]	
			Compositors		6			
Pasternack & Ehrlich (1972) USA	778 pressmen and 1207 compositors in a newspaper plant	1958–69	Pressmen	Mouth and respiratory system	6	[1.2]	[0.4–3.4]	Crude RR, pressmen versus compositors
			Compositors		8			
Moss *et al.* (1972) United Kingdom	3485 deaths among male workers in London and Manchester newspaper printing companies	1952–66	Printing trade workers	Lung	365	1.3	[1.2–1.5]	PMR
			Machine-room men (London)	Lung	71	1.2	[1.0–1.6]	
			Machine-room men (Manchester)	Lung	38	2.0	[1.5–2.8]	
			Publishing-room men (London)	Lung	91	1.4	[1.1–1.7]	
			Publishing-room men (Manchester)	Lung	22	1.6	[1.1–2.5]	
Greenberg (1972) United Kingdom	670 deaths among newspaper printing workers in London	1954–66		All cancers	195	1.2	[1.0–1.4]	PMR
				Lung	93	1.3	[1.1–1.6]	
				Stomach	29	1.4	[1.0–2.0]	
				Leukaemia	4	1.2	[0.5–3.2]	
				Urinary tract	6	0.7	[0.3–1.5]	Based on national reference
				Tonsil	2	6.7	[1.7–26.8]	Based on national reference

Table 12 (contd)

Reference, country	Study subjects	Period of follow-up	Occupation/exposure	Cancer site/ cause of death	No. obs.	RR	95% CI	Comments
Lloyd *et al.* (1977) USA	2604 deaths among members of the International Printing Pressmen and Assistants' Union	1966–68	Newspaper pressmen	All cancers	138	1.1	[0.9–1.3]	PMR
				Buccal cavity and pharynx	9	[2.4]	[1.2–4.6]	
				Lung	41	[1.1]	[0.8–1.5]	
				Leukaemia	8	[1.6]	[0.8–3.1]	
				Pancreas	9	[1.2]	[0.6–2.3]	
				Rectum	7	[1.6]	[0.7–3.3]	
			Commercial pressmen	All cancers	336	1.0	[0.9–1.1]	
				Lung	97	[1.0]	[0.8–1.3]	
				Buccal cavity and pharynx	13	[1.3]	[0.8–2.3]	
				Leukaemia	12	[0.9]	[0.5–1.5]	
Greene *et al.* (1979b) USA	347 cancer deaths at Government Printing Office in Washington DC	1948–77	Whole cohort	All haematopoietic	40	1.4	1.1–1.9	PCMR using age-, race- and time period-specific mortality proportions in Washington DC for 1950–69
				Multiple myeloma	10	2.2	1.2–4.0	
				Hodgkin's disease	7	2.3	1.1–4.7	
				Leukaemia	16	1.4	0.9–2.2	
				Colon	42	1.4	1.1–1.8	
				Liver/biliary tract	13	1.5	0.9–2.5	
				Urinary bladder	17	1.4	0.9–2.2	
				Melanoma	5	1.8	0.8–4.1	
				Lung	84	0.9	0.7–1.1	
				Kidney	8	1.1	0.6–2.2	
				Prostate	15	1.7	1.1–2.6	Non-white subjects
			Compositors	Multiple myeloma	8	5.3	2.7–10.1	White subjects
			Binders	Leukaemia	4	3.2	1.2–7.2	White subjects

Table 12 (contd)

Reference, country	Study subjects	Period of follow-up	Occupation/exposure	Cancer site/ cause of death	No. obs.	RR	95% CI	Comments
Bertazzi & Zocchetti (1980) Italy	700 male workers employed for at least 5 years in a newspaper plant between 1940 and 1955	1956–75	Whole cohort	All causes	199	1.1	[0.9–1.2]	SMR
				All cancers	51	1.2	[0.9–1.6]	
				Lung	13	1.5	[0.8–2.5]	
				Larynx	3	2.0	[0.4–5.8]	
				Lymphohaemato-poietic	3	1.2	[0.2–3.4]	
			Packers and dispatch workers	All causes	66	1.5	[1.1–1.8]	
				All cancers	19	1.8	[1.1–2.8]	
				Lung	6	2.5	[0.9–5.4]	
Paganini-Hill *et al.* (1980) USA	1361 white newspaper pressmen, members of the Los Angeles Pressmen's Union for at least 1 year between 1949 and 1965	1949–78		All cancers	68	1.0	[0.8–1.2]	SMR
				Buccal cavity and pharynx	2	0.9	[0.1–3.3]	
				Lung	22	1.5	[0.9–2.3]	
				Kidney	5	3.0	[1.0–7.1]	
				Leukaemia	7	2.5	[1.0–5.1]	
Zoloth *et al.* (1986) USA	1401 deaths among white male commercial pressmen members of a labour union	1958–81		All cancers	315	1.3	1.1–1.4	PMR; 14% of this population overlaps with that of Lloyd *et al.* (1977)
				Colon	40	1.6	1.2–2.2	
				Rectum	19	2.1	1.3–3.2	
				Non-Hodgkin's lymphoma	11	2.1	1.2–3.8	
				Lung	79	1.2	0.9–1.5	
				Leukaemia	9	0.9	0.5–1.7	
				Urinary bladder	11	1.1	0.6–2.0	
				Kidney	8	1.5	0.7–2.9	Membership ≥ 20 years
				Liver	9	2.2	[1.1–4.1]	Membership ≥ 20 years
				Pancreas	18	1.6	[1.0–2.6]	

Table 12 (contd)

Reference, country	Study subjects	Period of follow-up	Occupation/exposure	Cancer site/ cause of death	No. obs.	RR	95% CI	Comments
Svensson *et al.* (1990) Sweden	1020 male workers employed for at least 3 months in eight rotogravure plants	1952–86 (mortality) 1958–85 (morbidity)	Rotogravure printers	All causes	129	1.0	0.9–1.2	SMR; mortality
				Stomach	7	2.7	1.1–5.6	Mortality
					7	2.3	0.9–4.8	Morbidity
				Colon-rectum	7	2.2	0.9–4.5	Mortality
					9	1.5	0.7–2.8	Morbidity
				Respiratory system	11	1.4	0.7–2.5	Mortality
					16	1.8	1.0–2.9	Morbidity
					9	1.3	0.6–2.4	Morbidity, ≥ 5 yrs of exposure and > 10 yrs of latency
				Leukaemia, lymphoma	3	1.0	0.2–2.8	Mortality
				Leukaemia	3	1.7	0.3–4.9	Morbidity
				Urinary organs	1	0.5	0.01–2.5	Mortality
					4	0.6	0.2–1.7	Morbidity
Michaels *et al.* (1991) USA	1261 male members of the International Typographical Union employed by two newspaper plants in 1961, New York city	1961–84	Newspaper printers	All causes	498	0.7	0.7–0.8	SMR
				All cancers	123	0.8	0.7–1.0	
				Buccal cavity and pharynx	5	1.1	0.4–2.7	
				Lung	37	0.9	0.6–1.2	
				Urinary bladder	8	1.5	0.7–3.0	
				Leukaemia and aleukaemia	5	1.0	0.3–2.4	
Hrubec *et al.* (1992) USA	248 046 veterans	1954–80	Printing pressmen and plate printers	Respiratory system	9	1.6	[0.5–3.1]	Adjusted for smoking
				Kidney	2	3.4	[0.6–18.7]	
				Urinary bladder	4	3.4	[1.3–9.0]	

Table 12 (contd)

Reference, country	Study subjects	Period of follow-up	Occupation/exposure	Cancer site/ cause of death	No. obs.	RR	95% CI	Comments
Sinks *et al.* (1992) USA	2050 white male workers in a paper-board printing plant	1957–89		All causes	141	1.0	0.9–1.2	SMR; mortality
				All cancers	16	0.6	0.3–0.9	
				Respiratory system	5	0.5	0.2–1.2	
				Renal-cell cancer	6	3.7	1.4–8.1	SIR; morbidity
				Urinary bladder	3	1.1	0.2–3.1	
Leon (1994) United Kingdom	9232 full-time male members of NGA and NATSOPA trade unions, between 1949 and 1963	1950–83	NATSOPA members (unskilled workers)	All cancers	509	1.2	1.1–1.3	SMR; national reference
						1.0	0.9–1.1	SMR; local reference
				Lung	242	1.4	1.2–1.6	National reference
						0.9	0.8–1.1	Local reference
				Urinary bladder	18	1.1	0.7–1.8	National reference
						1.0	0.6–1.6	Local reference
			NATSOPA newspaper machine assistants	Lung	94	1.8	1.4–2.2	National reference
						1.2	1.0–1.5	Local reference
			NATSOPA publishing room men	Brain and other CNS	4	3.7	1.0–9.5	National reference
						3.7	1.0–9.6	Local reference
			NATSOPA editorial workers	Buccal cavity and pharynx	2	10.5	1.3–38.0	National reference
						6.7	0.8–24.1	Local reference
			NATSOPA clerical staff	Buccal cavity and pharynx	3	6.4	1.3–18.6	National reference
						4.1	0.8–11.8	Local reference
			NGA members	Lung	150	0.8	0.7–1.0	National reference
						0.6	0.5–0.7	Local reference
				Urinary bladder	11	0.6	0.3–1.1	National reference
						0.6	0.3–1.0	Local reference

RR, relative risk; PMR, proportionate mortality ratio; PCMR, proportionate cancer mortality ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; NGA, National Graphical Association; NATSOPA, National Society of Operative Printers, Graphical and Media Personnel; CNS, central nervous system

identified through their 1954 membership in union organizations in California, United States. Data on occupational and smoking histories (daily consumption and years of smoking) were collected through questionnaires mailed during 1954 and 1957. Causes of death during 1954–65 were identified. The expected numbers of deaths were derived from age- and smoking-specific rates in the union population. A nonsignificant deficit of lung cancer ([SMR, 0.8; 95% CI, 0.5–1.1]; 30 observed cases) was reported for printers. No relationship was found with duration of employment.

Goldstein *et al.* (1970) compared the mortality from respiratory diseases during the years 1947–62 among about 460 actively employed and retired male pressroom workers in a large newspaper plant in New York City, United States, with that of about 700 compositors in the same plant. Environmental exposure to mineral oil mist in the pressroom ranged from 5 to 21 mg/m^3. The particle size of the mineral oil mist showed a mass median diameter of 'about' 15 μm with about 15% of the material in droplets generally considered to be 'respirable'. The particle size of carbon black in the ink used was about 0.1–0.2 μm. There were three deaths from pulmonary carcinoma out of 2797 person-years at risk among pressmen (crude rate, 1.1 per thousand) and six among compositors with 5127 person-years at risk (crude rate, 1.2 per thousand), giving a crude RR of [0.9; 95% CI, 0.2–3.7] for pressmen versus compositors. [The Working Group noted that the age distribution of the subjects in the exposed groups and the degree of completeness of death ascertainment were not given. The interpretation of this study is limited by the absence of an external comparison group]

Pasternack and Ehrlich (1972) expanded the study of Goldstein *et al.* (1970) examining the mortality of 778 pressmen and a comparison group of 1207 compositors employed in the same plant in the years 1958–69. Mortality data for active full-time employees and pensioners were available through health records maintained in the newspaper plant medical department. Observed and expected (on the basis of age- and period-specific mortality of compositors) deaths were compared. Cause-specific mortality was not analysed. Six cases of malignant neoplasms of the mouth and respiratory system among pressmen (5841 person-years) and eight cases among compositors (9189 person-years) yield a crude RR of [1.2; 95% CI, 0.4–3.4] for pressmen versus compositors. [The Working Group noted the possibility of under-ascertainment of deaths because of the type of information used, even when an internal comparison of cancer cases was performed.]

Moss *et al.* (1972) and Moss (1973) examined the mortality experience of 3485 full-time male workers from 16 newspaper printing companies in London and Manchester, United Kingdom, who died in 1952–66. Age- and calendar period-standardized PMRs were computed using regional statistics as the referent. Based on the occupational status supplied by the employers, workers were subdivided into five categories: compositors, readers and foundrymen; machine-room men; publishing-room men; other manual production workers; and office and white-collar workers. Significant excesses of deaths from lung cancer were observed for all manual printing trade workers (i.e. the first four categories above) (PMR, 1.3 [95% CI, 1.2–1.5]; 365 cases). Among machine-room men, a significant excess was found in Manchester (PMR, 2.0 [95% CI, 1.5–2.8]; 38 cases), whereas 71 lung cancer deaths were observed in London (PMR, 1.2 [95% CI, 1.0–1.6]).

Statistically significant excesses were also found among publishing-room men both in London (PMR, 1.4 [95% CI, 1.1–1.7]; 91 cases) and in Manchester (PMR, 1.6 [95% CI, 1.1–2.5]; 22 cases). Lung cancer mortality among non-manual workers did not differ from expectations. No information on smoking status was available. Observed deaths from bronchitis did not differ from the number expected among printing trade workers either in London or in Manchester.

Greenberg (1972) conducted a proportionate mortality study of male newspaper printing workers in London, United Kingdom, who died in the years 1954–66 based on 670 death certificates obtained from company death benefit fund records. Expected numbers of deaths by age group and calendar period were computed using regional statistics. Significant excesses of deaths from all neoplasms (PMR, 1.2 [95% CI, 1.0–1.4]; 195 cases) and cancer of the lung and bronchus (PMR, 1.3 [95% CI, 1.1–1.6]; 93 cases) were detected. There were 29 deaths from gastric cancer (PMR, 1.4 [95% CI, 1.0–2.0]) and four deaths from leukaemia (PMR, 1.2 [95% CI, 0.5–3.2]). Using national rates as reference, six deaths from cancer of the urinary organs (bladder and kidney) (PMR, 0.7 [95% CI, 0.3–1.5]) and two from cancer of the tonsil (PMR, 6.7 [95% CI, 1.7–26.8]) were observed. Low mortality from bronchitis and emphysema was observed, whereas the number of observed deaths from arteriosclerotic and degenerative heart disease did not differ from expectation. This study included workers from one of the factories studied by Moss *et al.* (1972).

A total of 2604 deaths occurring between 1966 and 1968 among white male members of a labour union representing printing pressmen in the United States were identified from death benefit fund records and examined for proportionate mortality (Lloyd *et al.*, 1977). Age-adjusted numbers of expected deaths by cause were computed using the mortality experience of white males in the United States in 1967. Among 676 deaths of newspaper pressmen, a significant excess of cancers of the buccal cavity and pharynx emerged ([PMR, 2.4; 95% CI, 1.2–4.6]; 9 deaths), which was mainly confined to men aged 20–54 years ([PMR, 10.0; 95% CI, 4.8–21.0]; 7 deaths). Mortality from lung cancer did not differ from expectation ([PMR, 1.1; 95% CI, 0.8–1.5]; 41 deaths). There were eight leukaemia deaths [PMR, 1.6; 95% CI, 0.8–3.1], nine deaths from pancreatic cancer [PMR, 1.2; 95% CI, 0.6–2.3] and seven rectal cancer deaths [PMR, 1.6; 95% CI, 0.7–3.3]. A total of 1840 deaths were observed among commercial pressmen; none of the specific cancer sites showed statistically significant differences between the observed and expected deaths in the whole group. Mortality from arteriosclerotic heart diseases was slightly elevated among commercial pressmen and newspaper pressmen.

Greene *et al.* (1979b) selected 347 cancer deaths occurring between 1948 and 1977 in former male United States Government Printing Office (GPO) employees in Washington DC whose last job was with the GPO and who had a survivor receiving death annuity payments. Proportionate cancer mortality ratios by specific cancer sites were computed using the age-, race- and time period-specific mortality proportions in the Washington DC area for the period 1950–69. A significant (44%) excess from all haematopoietic neoplasms (proportionate cancer mortality ratio (PCMR), 1.4; 95% CI, 1.1–1.9; 40 cases) was observed, with statistically significant increases for multiple myeloma (PCMR, 2.2; 95% CI, 1.2–4.0; 10 cases) and Hodgkin's disease (PCMR, 2.3; 95% CI, 1.1–4.7;

7 cases). Sixteen leukaemia deaths were found (PCMR, 1.4; 95% CI, 0.9–2.2). There was a statistically significant (36%) increase in the relative frequency of colonic cancer (95% CI, 1.1–1.8; 42 cases). Nonsignificantly elevated PCMRs related to cancers of the liver and biliary tract (PCMR, 1.5; 95% CI, 0.9–2.5; 13 cases) and urinary bladder (PCMR, 1.4; 95% CI, 0.9–2.2; 17 cases) and melanoma (PCMR, 1.8; 95% CI, 0.8-4.1; 5 cases) were observed. The observed number of lung cancers (84) did not exceed the expected number (PCMR, 0.9; 95% CI, 0.7–1.1), nor did that of renal cancers (PCMR, 1.1; 95% CI, 0.6–2.2; 8 cases). A significant increase in mortality from prostatic cancer was found among non-white subjects (PCMR, 1.7; 95% CI, 1.1–2.6; 15 cases). Analysis by occupation (composers, binders, pressmen, other) was performed only for multiple myeloma, leukaemia and colonic cancer. The excess of multiple myeloma was restricted to white compositors (PCMR, 5.3; 95% CI, 2.7–10.1; 8 cases); deaths from leukaemia occurred in excess among white bindery workers (PCMR, 3.2; 95% CI, 1.2–7.2; 4 cases), whereas the colonic cancer excess was not attributable to any specific occupation. Benzene had been used at the GPO on a limited basis for specialized processes, particularly in the bindery, while the main exposure of compositors was to inorganic lead.

Bertazzi *et al.* (1979) and Bertazzi and Zocchetti (1980) conducted a mortality study to investigate the reportedly high occurrence of cancer in a large newspaper plant in Milan, Italy. A total of 700 male workers employed between 1940 and 1955 with at least five years' service and alive on 31 December 1955 were admitted to the study. Mortality was studied in the period 1956–75. Expected deaths were computed from national mortality rates. Vital status ascertainment was 97% successful. Overall mortality was higher than expected (SMR, 1.1 [95% CI, 0.9–1.2]; 199 deaths). A total of 51 cancer deaths were observed in the whole cohort (SMR, 1.2 [95% CI, 0.9–1.6]). There were 13 deaths from lung cancer (SMR, 1.5 [95% CI, 0.8–2.5]), three deaths from laryngeal cancer (SMR, 2.0 [95% CI, 0.4–5.8]) and three from lymphatic and haematopoietic neoplasms (SMR, 1.2 [95% CI, 0.2–3.4]). None of the cancer site-specific SMRs was statistically significant. No clear-cut pattern of cancer mortality according to length of employment, duration of follow-up or time since first employment emerged. Analysis by subcategory showed a statistically significant excess among packers and dispatch workers for all causes (SMR, 1.5 [95% CI, 1.1–1.8]; 66 deaths) and all neoplasms (SMR, 1.8 [95% CI, 1.1–2.8]; 19 cases). Nonsignificant increases in lung cancer were found in packers and dispatch workers (SMR, 2.5 [95% CI, 0.9–5.4]; 6 cases) as well as in other workers (SMR, 1.6 [95% CI, 0.5–3.8]; 5 cases). With regard to non-malignant diseases, mortality from ischaemic heart diseases did not differ from expectation in the whole cohort, whereas packers and dispatch workers experienced a particularly elevated mortality from these causes (SMR, 2.1 [95% CI, 1.2–3.5]; 16 cases).

Paganini-Hill *et al.* (1980) carried out a mortality study of 1361 white newspaper web pressmen who were members of the Los Angeles Pressmen's Union for at least one year between 1949 and 1965. Of the subjects, 65% had worked for 20 or more years as pressmen, and most began employment before the age of 35. Vital status as of 1978 was determined for 1261 (91%), and death certificates were obtained for 344 of the 354 decedents. SMRs, adjusted for age and calendar period, were computed based on the general United States white male population. Overall mortality among web pressmen

was 8% less than expected (SMR, 0.9 [95% CI, 0.8–1.0]; 344 cases); 68 deaths from all cancers were observed compared to 69 expected. Elevated SMRs were seen for renal cancer (SMR, 3.0 [95% CI, 1.0–7.1]; 5 cases) and leukaemia (SMR, 2.5 [95% CI, 1.0–5.1]; 7 cases). None of the other specific cancer sites showed statistically significant differences between observed and expected deaths, including lung cancer (SMR, 1.5 [95% CI, 0.9–2.3]; 22 deaths).

Following a report of a cluster of urinary bladder cancer, Zoloth *et al.* (1986) conducted a proportionate mortality study based on 1401 death certificates of white male members of a labour union of commercial printers in New York City, Long Island and New Jersey, United States, who died between 1958 and 1981. Expected numbers of deaths were calculated using age-, sex-, calendar- and time-specific United States population rates. Based on the amount of death benefit paid to the survivors of deceased members, the length of membership (< 20 years; > 20 years) was established for 1264 members (90% of the cohort). Only 164 members had length of membership less than 20 years. Mortality from all cancers was significantly elevated (PMR, 1.3; 95% CI, 1.1–1.4; 315 cases). Excesses at specific cancer sites were statistically significant for cancers of the colon (PMR, 1.6; 95% CI, 1.2–2.2; 40 cases) and rectum (PMR, 2.1; 95% CI, 1.3–3.2; 19 cases) and for non-Hodgkin's lymphoma (PMR, 2.1; 95% CI, 1.2–3.8; 11 cases). All deaths from liver (9 cases) and pancreatic cancer (18 cases) occurred among the longest-working population and these yielded significant excesses (PMRs, 2.2 [95% CI, 1.1–4.1] and 1.6 [95% CI, 1.0–2.6], respectively); there were 79 deaths from lung cancer (PMR, 1.2; 95% CI, 0.9–1.5). No excess was found for either deaths from leukaemia (PMR, 0.9; 95% CI, 0.5–1.7; 9 cases) or urinary bladder cancer (PMR, 1.1; 95% CI, 0.6–2.0; 11 cases). Three deaths due to myelofibrosis, a very rare myeloproliferative disease, were observed. With regard to nonmalignant diseases, the most notable excesses were found for arteriosclerotic and chronic rheumatic heart disease. [The data of this study are not fully independent from that of Lloyd *et al.* (1977); at most, 14% of this population potentially overlap with that study.]

Svensson *et al.* (1990) examined mortality (1952–86) and cancer incidence (1958–85) in a cohort of 1020 male workers employed for at least three months during 1925–85 in eight rotogravure plants in Sweden. Age-standardized mortality and incidence ratios were computed using mortality rates of the geographical area where the factories were located; cancer incidence rates for the same areas were obtained from the Swedish Tumour Registers. Vital status was ascertained for 99% of the cohort members. In 1983 and 1986, air concentrations of toluene were measured in three plants: the median concentrations were 33 ppm [124 mg/m^3] in two plants and 7 ppm [26 mg/m^3] in the third. The yearly average air concentrations of toluene were estimated in each plant; they reached a maximum of about 450 ppm [1665 mg/m^3] in the 1940s and 1950s, while later, there was a sharp fall. Cumulative doses (ppm-years) of toluene were calculated. Benzene was known to have been used in the 1940s, while its use decreased in the 1950s and 1960s. In one plant, the mean level of benzene in the air was 3 ppm [9.6 mg/m^3] ranging from 0.3 to 25 ppm [1–80 mg/m^3] in 1960, and from 0 to 61 ppm [0–195 mg/m^3] in 1962. Other aromatic and aliphatic hydrocarbons (such as 'naphtha') were used in decreasing proportions. After 1969, only toluene had been used in all plants, except one

where substantial amounts of ethanol and ethyl acetate were used in addition to toluene. Mortality from all causes did not differ from that expected (SMR, 1.0; 95% CI, 0.9–1.2; 129 cases). A total of 41 cancer deaths were observed (SMR, 1.4; 95% CI, 1.0–1.9). Increases in deaths from cancer of the stomach (SMR, 2.7; 95% CI, 1.1–5.6; 7 cases) and colon/rectum (SMR, 2.2; 95% CI, 0.9–4.5; 7 cases) were detected; five out of seven cancers of the stomach and six out of seven cancers of the colon/rectum were found among the subcohort of workers with at least five years of exposure and more than 10 years of latency (SMR, 2.5; 95% CI, 0.8–5.9, for stomach; SMR, 2.4; 95% CI, 0.9–5.3, for colon and rectum). Eleven respiratory cancer deaths (7.9 expected) and three lymphohaematopoietic cancer deaths (3.1 expected) were observed. When cancer morbidity was analysed, only cancers of the respiratory tract were significantly increased (SMR, 1.8; 95% CI, 1.0–2.9; 16 cases); however, when a minimal employment period of five years and a latency period of 10 years were applied, the increase was no longer statistically significant (SMR, 1.3; 95% CI, 0.6–2.4; 9 cases). There were seven cancers of the stomach compared to three expected, nine cancers of the colon and rectum against six expected and three leukaemias versus 1.8 expected. Both mortality and morbidity for urinary tract cancers were nonsignificantly lower than expected. There were no associations between cumulative doses of toluene and SMRs for all tumour sites, gastrointestinal cancers or respiratory cancers. The authors cautioned about the overall accuracy of estimates of the exposure to toluene.

To investigate the effects of low-level exposure to lead, Michaels *et al.* (1991) examined the mortality experience (1961–84) of 1309 male members of the International Typographical Union employed in two New York City newspapers on 1 January 1961. The cohort was composed primarily of linotypists and slug makers; there was also a small group of mechanics and proof-readers. Although direct measurements of exposure were not available, historical industrial hygiene studies in the United States suggest that the typographers in this study had been exposed to airborne lead levels below the United States Occupational Safety and Health Administration permissible exposure level of 50 $\mu g/m^3$. Forty-eight subjects (4%) were excluded since date of birth was unavailable. Out of 1261 workers, vital status was unknown for 39 cohort members (3%; assumed alive at the end of the study period). Age-, calendar time-, sex- and race-specific standardized mortality ratios were computed using the mortality rates of New York City as the comparison population. A surrogate measure of years of lead exposure was computed using the number of years between enrolment into the Union and last year of employment or until the end of 1976, which ever was earlier. The year 1976 was chosen since the use of hot lead in the plants ended during 1974–78. A significant deficit for overall mortality was observed (SMR, 0.7; 95% CI, 0.7–0.8; 498 cases). Mortality from all cancers was lower than expected (SMR, 0.8; 95% CI, 0.7–1.0; 123 cases). Five deaths from cancer of the buccal cavity and pharynx were observed (4.4 expected); 37 lung cancer deaths (SMR, 0.9; 95% CI, 0.6–1.2), eight urinary bladder cancers (SMR, 1.5; 95% CI, 0.7–3.0) and five leukaemias (SMR, 1.0; 95% CI, 0.3–2.4) occurred.

Following a physician's alert about one renal and one urinary bladder cancer in workers employed in the finishing department of a paperboard printing plant in Georgia, United States, Sinks *et al.* (1992) investigated mortality and cancer morbidity of 2050

subjects employed for more than one day between 1957 and 1988 in the facility. Vital status was successfully ascertained for 90% of the cohort. Out of 141 deceased subjects, death certificates were unavailable for 26 (18%). Expected numbers of deaths were computed based on United States mortality rates. The total number of person-years at risk accrued during the study period was 36 744; 71% had a duration of employment of less than four years and years-since-first-employment of less than 19 years. Age-standardized SIRs for urinary bladder and renal cancer were calculated using reference rates from the Atlanta-SEER (Surveillance, Epidemiology and End Results) Registry for the years 1973–77. Mortality from all causes did not differ from expectation (SMR, 1.0; 95% CI, 0.9–1.2; 141 cases), while a statistically significant deficit was observed for all cancer deaths (SMR, 0.6; 95% CI, 0.3–0.9; 16 cases). There were five deaths from cancer of the digestive organs (6.1 expected) and five from cancer of the respiratory system (9.4 expected), the remaining sites being represented by one or no cases. Six incident renal-cell cancers were identified (SIR, 3.7; 95% CI, 1.4–8.1). The excess risk persisted when the index case was excluded from the analysis (SIR, 3.1; 95% CI, 1.1–6.8). No increased risk for urinary bladder cancer was found (SIR, 1.1; 95% CI, 0.2–3.1; 3 cases). The review of the company safety data-sheets led to the identification of three potential carcinogens in the plant: methylene chloride (dichloromethane), formaldehyde (see IARC, 1995a) and trichloroethylene (see IARC, 1995b). The supplier information that several coloured inks had been manufactured from 3,3′-dichlorobenzidine and derivatives of toluidine was not confirmed by the analysis of 16 bulk pigment samples. The authors discussed possible limitations in the mortality study related to the high percentage of subjects lost to follow-up and of unknown causes of deaths. They also noted that the number of renal cancer cases could have been underestimated; moreover, a potential for selection bias exists due to the fact that four of the six renal cancer cases had been identified through employee interviews.

A nested case–control study was conducted for the six renal cancer cases identified in the above cohort of workers employed in a paperboard printing plant (Sinks *et al.*, 1992) (see Table 11). Forty-eight controls, matched by age and sex, were selected according to incidence density sampling. Controls were required to be of a younger age at first employment than the case's age at diagnosis. Conditional maximum likelihood odds ratio estimates were computed. Analysis by length of employment in each department (cut and crease, finishing, maintenance, office, press operators) was performed. Five out of six cases (83%) had worked in the plant for five years or more, whereas only 19% of the controls had a duration of employment greater then five years. Employment in the finishing department for five years or more was associated with a statistically significant increased risk (odds ratio, 16.6; 95% CI, 1.7–453.1; 3 cases). The odds ratio did not change when employment during the most recent five or 10 years was not included in the calculation. Time since first employment, date of hire and age at hire were added to the model; these covariates did not alter the odds ratio.

A retrospective cohort mortality study (Leon, 1994) of printing workers was undertaken after an anecdotal report of a cluster of urinary bladder cancers (three cases between 1971 and 1979 against 0.7 expected based on national rates) in a newspaper plant in Manchester, United Kingdom. The cohort included 9232 men born in 1890 or

later who had been full-time members for at least six months in 1949–63 in two trade unions (National Graphical Association (NGA) and National Society of Operative Printers, Graphical and Media Personnel (NATSOPA)) in the Manchester area. The plant from which the cluster of urinary bladder cancers originated was not included. Mortality was examined from 1950 to 1983 and follow-up was 98% complete for NGA members and 97% complete for NATSOPA members. SMRs were computed. Expected numbers of deaths were obtained using age- and calendar-specific mortality figures for men in England and Wales. SMRs for Manchester County Borough in the period 1968–78 were applied as correction factors. Among NATSOPA members, significant elevations were found in SMRs for 'all causes of death' (SMR, 1.1; 95% CI, 1.1–1.2), all cancers (SMR, 1.2; 95% CI, 1.1–1.3), lung cancer (SMR, 1.4; 95% CI, 1.2–1.6) and ill-defined or secondary cancers (SMR, 1.6; 95% CI, 1.1–2.4). When adjustment for local rates was applied, all SMR values decreased and none of the above remained elevated; for lung cancer, the adjusted SMR was 0.9 (95% CI, 0.8–1.1). Mortality from urinary bladder cancer did not differ from expectation based on either national (SMR, 1.1; 95% CI, 0.7–1.8) or locally adjusted rates (SMR, 1.0; 95% CI, 0.6–1.6). For NGA members, mortality from all causes, from all cancers and from urinary bladder and lung cancer was lower than expected based on both national and locally adjusted rates. When workers were subdivided into four major occupational groups (NGA machine managers, NGA compositors, NATSOPA machine assistants and NATSOPA publishing-room men), the risk of lung cancer was elevated among NATSOPA machine assistants (SMR, 1.8; 95% CI, 1.4–2.2, based on national rates; SMR, 1.2; 95% CI, 1.0–1.5, based on locally adjusted rates; 94 cases). The only other statistically significant SMR was for malignant neoplasms of the brain and other sites in the central nervous system among NATSOPA publishing room men, although this was based on only four cases (SMR, 3.7; 95% CI, 1.0–9.5). Among NATSOPA non-production workers, two cancers of the buccal cavity and pharynx were found in the editorial group and three among clerical staff — the SMRs based on national rates were 10.5 (95% CI, 1.3–38.0) and 6.4 (95% CI, 1.3–18.6), respectively; adjustment for local rates reduced both mortality ratios (SMR, 6.7; 95% CI, 0.8–24.1, for editorial group; SMR, 4.1; 95% CI, 0.8–11.8, for clerical workers). RRs of NATSOPA versus NGA members were calculated via Poisson regression, controlling for age and calendar period. RRs were high for most of the causes. In particular, the RR for lung cancer was 1.7 (95% CI, 1.4–2.1). The authors noted that a strong socioeconomic component can explain the differences: NATSOPA members were mainly semiskilled or unskilled workers whereas NGA members had higher skills.

To evaluate the risk of lung cancer, a case–control study was nested within the above cohort of printing workers (Leon *et al.*, 1994) (see Table 10). A total of 110 lung cancer deaths were identified between 1949 and 1986 in machine assistants who were members of NATSOPA and who had entered the union after 1915. For each case, five controls were selected at random from all other machine assistants with a similar work record, born within 2.5 years of the corresponding case and alive at the date of the case's death. A complete occupational history was collected for all cases and 316 controls. Conditional logistic regression was used to compute odds ratio estimates. Duration of union membership was taken as an indicator of duration of work. Duration of work (< 10, 10–

19, 20–29, 30–39, > 40 years) in newspaper machine rooms was positively associated with the risk of lung cancer (odds ratios, 1; 1.2; 95% CI, 0.5–3.0; 1.4; 95% CI, 0.6–3.3; 2.0; 95% CI, 0.8–4.9; and 2.0; 95% CI, 0.7–5.8; p for trend = 0.07). Adjustment for period of first exposure gave similar results. When an analysis was carried out restricted to workers with a minimum of 15 years of latency, the duration–response relationship was not apparent; however, this analysis was hampered by small numbers and low precision. An analysis for period of first entry failed to show any clear pattern.

2.4 Childhood cancer in relation to parental exposure

Many case–control studies have been conducted to assess whether occupation of the father or of the mother at the time of conception constitutes a risk factor for malignant diseases in offspring. In the majority of the studies, the grouping of occupations is too broad to make it possible to evaluate the risk specific for printing-related occupations.

Kwa and Fine (1980) compared the parental occupation for 692 children who died of cancer before the age of 15 in Massachusetts, United States, and who were born during the periods 1947–57 and 1963–67 with that of 1384 population controls. For each case, two controls were selected among children whose birth registration immediately preceded or followed that of the case subject. Parental occupations were extracted from the birth certificates. Fifteen cancer cases had 'printer' as father's occupation at the time of birth [crude odds ratio, 1.8; 95% CI, 0.9–3.6]. The crude odds ratio for children with leukaemia and lymphoma and with printers as father's occupation was [1.7 (95% CI, 0.8–3.9; 9 cases)].

In a study designed to test hypotheses that paternal occupational exposure to lead and hydrocarbons is associated with Wilms' tumour in offspring, Wilkins and Sinks (1984) compared paternal occupation recorded on birth certificates of 62 cases identified through the Columbus Children's Hospital Tumor Registry in Ohio, United States, during the period 1950–81 with that of 124 controls matched on sex, year of birth and ethnic group. Half of the controls were also matched on the mother's county of residence when the child was born. None of the fathers of the cases was a printer; two of the fathers of the control children worked as printers at the time of birth of their children.

In the inter-regional epidemiological study of childhood cancer in the Northwest, West Midlands and Yorkshire regions of the United Kingdom during the period 1980–83, 555 cases of newly incident childhood cancer were identified in paediatric oncology centres and through cancer registries (Birch *et al.*, 1985). Two groups of age- and sex-matched controls were recruited: 555 through the general practitioners or group practices with whom the cases were registered and 555 selected from among children in hospital for reasons other than neoplastic disease and who did not have either a genetic or other constitutional disease or malformation known to be associated with increased risk of cancer, or any other major malformation or chronic disease. Information on parental occupation was obtained by interview with the parents. No association was found between leukaemia or lymphoma (234 cases) and paternal employment classified as 'paper and printing workers' (McKinney *et al.*, 1987). No association was apparent between central nervous system tumours (78

cases) and paternal employment in the year before pregnancy and during pregnancy in 'paper and printing' (Birch *et al.*, 1990).

Cole Johnson *et al.* (1987) conducted a case–control study in Texas, United States, to evaluate paternal occupational exposure to hydrocarbons and the risk of childhood cancer of the nervous system. Cases included 499 children born in Texas, who had died of intracranial or spinal cord tumours with a birth year distribution from 1950 through 1979 at 0–14 years of age. A total of 998 controls, matched by sex, race and year of birth, were selected from live births in Texas during the same period. Paternal occupation was abstracted from the birth certificates. Nine cases had paternal occupation defined as 'printing workers' yielding a statistically significant odds ratio of 4.5 (95% CI, 1.4–14.7); the odds ratio for father's occupation in 'newspaper and printing industries' was 5.1 (95% CI, 1.6–16.3; 10 cases).

In a mortality-based case–control study in Ohio, United States, during the period 1959–78, information on paternal occupation was obtained from the birth certificates of the children (Wilkins & Koutras, 1988). A total of 491 deaths due to brain tumours at ages of 19 and under were ascertained and 491 controls were selected randomly after matching for sex, ethnic group and year of birth. The odds ratio associated with the father being employed in 'printing occupations' was 0.9 (95% CI, 0.3–2.8; 6 exposed cases), adjusted for parental age, birth order, birth weight, mother's residence at the time of birth of the index child, the sex of the child and the year of the child's birth.

In a study of the occupational exposure of parents of 204 children diagnosed with acute non-lymphoblastic leukaemia under 18 years of age during the period 1980–84, ascertained through the registration files of a cooperative clinical trial groups in the United States and Canada, and a similar number of controls selected by random-digit dialling, no association with reported exposure to printing inks of either parent was found (Buckley *et al.*, 1989). [The Working Group noted that no details were given of the association other than the inclusion of this occupational exposure in the questionnaire]

Olsen *et al.* (1991) identified 1747 cases of childhood cancer from the Danish Cancer Registry and 8630 controls randomly selected from the Central Population Register after matching for sex and date of birth and survival without cancer until the date of diagnosis of the case. Employment histories of parents were established by record linkage with the files of the nationwide Supplementary Pension Fund. Eight fathers of cases with childhood cancer of any type were printers, and the odds ratio associated with this job title was 1.0; there was no significant association in any specific cancer sites.

Kristensen and Andersen (1992) investigated the occurrence of cancer in offspring of male members of the Oslo (Norway) printers' unions during the period 1930–74. Children born between 1950 and 1987 were traced for cancer in the Norway Cancer Registry. The study population comprised 12 440 children who were followed until 1987. Age-, gender- and calendar period-SIRs were computed based on incidence rates in Oslo. Using the employment description in the union records, each worker was categorized as exposed to lead (compositors, monotype casters and stereotype workers) or lead and solvents (rotary press printers and assistants) or solvents (all other printers). The total observed number of offspring cancers was 33 compared to 39.2 expected. After

restricting the analysis to children whose father joined the union before the child's birth (10 829), seven cancer cases were identified in children younger than 14 years of age (SIR, 0.5; 95% CI, 0.2–1.0); 20 cancers occurred in those of older age (SIR, 1.0; 95% CI, 0.6–1.6). Among children aged 0–14 years, there were two acute leukaemia cases (4.5 expected cases) and two tumours of the central nervous system (4.1 expected cases); four cases of tumours of the central nervous system were observed among older children (3.0 expected). Since lead was abandoned in Oslo printing shops in the mid-1970s, all fathers were reclassified as lead-exposed only until 1975. Among 3221 children of these fathers, none developed cancer before the age of 15 (3.7 expected cases).

In a study of 163 cases of astrocytoma diagnosed under the age of 15 years during the period 1980–86 in eight hospitals in Pennsylvania, New Jersey and Delaware, United States, information on parental occupation was obtained by telephone interview (Kuijten *et al.*, 1992). Controls were selected by random-digit dialling. For the pre-conceptional period, the odds ratio associated with paternal employment as a printing worker was 4.0 (95% CI, 0.4–195.1, based on 5 discordant pairs); for paternal employment in this category during the index pregnancy, the odds ratio was 3.0 (95% CI, 0.2–158, based on 4 discordant pairs); and for the period between birth and one year prior to diagnosis, the odds ratio was 2.5 (95% CI, 0.4–26.2, based on 7 discordant pairs).

3. Studies of Cancer in Experimental Animals

Subcutaneous injection

Mouse: Groups of 20 male CB stock mice, 11 weeks of age, received 15–22 weekly injections into the right flank of unknown amounts of one of 22 different printing inks of unknown composition diluted or suspended in distilled water or arachis oil. Three groups of 40 mice each received 80 injections of distilled water or arachis oil alone or were untreated and served as controls. Survival at 18 months ranged from 7/20 to 14/20 in all groups with the exception of the group treated with Medium Sepia, which had no survivors by that time. No other toxic effect was reported. Local sarcomas developed at the injection site in 1/20 mice in each of five experimental groups: as early as at seven months in a mouse given Medium Sepia and from 18 to 19 months in mice receiving Process Black, Bronze Blue L/P, Concentrated Brown and Brown No. 3. The neoplasms that developed later were spindle-cell tumours, while the earlier tumour was more anaplastic. No tumour developed at the injection site in control mice (Carter *et al.*, 1969). [The Working Group noted many inadequacies in study design and reporting, and the small numbers of animals used.]

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, excretion and metabolism

In two press operators exposed to black offset ink during bulk material transfer, 1-hydroxypyrene levels were measured in pre- and post-shift urine. In one of the operators, post-shift urine 1-hydroxypyrene was elevated by about 60%. The other operator exhibited only a very slight increase (~ 5%) (Jongeneelen *et al.*, 1988).

4.2 Toxic effects

4.2.1 *Humans*

The first systematic study on the health effects of working in printing trades was carried out by Ramazzini at the end of the seventeenth century, who noted that there was a high prevalence of visual and respiratory symptoms (Ramazzini, 1933).

No excess mortality from all causes was observed among printing industry workers in the studies described in Section 2.3 (Paganini-Hill *et al.*, 1980; Svensson *et al.*, 1990; Michaels *et al.*, 1991; Sinks *et al.*, 1992; Leon, 1994).

No excess mortality from diseases of the circulatory system (Zoloth *et al.*, 1986; Svensson *et al.*, 1990) or from cardiovascular diseases (Greenberg, 1972; Paganini-Hill *et al.*, 1980; Sinks *et al.*, 1992; Leon, 1994) was observed among printing industry workers in the studies described in Section 2.3.

A small but significant excess mortality from arteriosclerotic heart disease (PMR, 1.09; $p < 0.01$) was observed among commercial pressmen, and a similar, but non-significant excess among newspaper pressmen (PMR, 1.05) and paper handlers (PMR, 1.04) (Lloyd *et al.*, 1977). An excess in mortality of ischemic heart disease (SMR, 3.0; $p < 0.01$) was reported among newspaper printing workers 25–54 years of age, which was associated with length of employment, age at the time of hiring and duration of follow-up (Bertazzi *et al.*, 1979; Bertazzi & Zocchetti, 1980). [No increase was observed in the 55–74-year and > 74-year age groups.]

Elevated mortality from cerebrovascular disease, which was of borderline statistical significance, was observed among typesetters in a study in the United States (Michaels *et al.*, 1991). The SMR for cerebrovascular disease mortality was 1.1 in an early British study (Greenberg, 1972) and 1.0 in a more recent study (Leon, 1994). The PMR for vascular lesions of the central nervous system was 0.76 ($p < 0.05$) among commercial pressmen in the United States (Zoloth *et al.*, 1986). A deficit of mortality from cerebrovascular lesions was also observed among commercial pressmen (PMR, 0.84; $p < 0.05$) and paper handlers (PMR, 0.41; not significant), but not among newspaper pressmen (PMR, 1.02) (Lloyd *et al.*, 1977).

No excess mortality from nonmalignant diseases of the respiratory tract was observed among printing industry workers in the studies described in Section 2.3 (Greenberg, 1972; Lloyd *et al.*, 1977; Zoloth *et al.*, 1986; Svensson *et al.*, 1990; Michaels *et al.*,

1991; Leon, 1994). Mortality from bronchitis was not elevated among men who worked full-time in the newspaper printing industry in London and Manchester (see Section 2.3) (Moss *et al.*, 1972).

Five-year mortality from respiratory diseases among newspaper pressmen (11 deaths in 2797 man-years at risk, i.e. 3.9/1000 man-years) was not statistically significantly different from the mortality experience of compositors (17/5127; 3.3/1000 man-years) in the same company (Goldstein *et al.*, 1970).

When occupational causes of asthma were sought in a case–control study in a community-based outpatient clinic in Singapore, an elevated odds ratio (2.2; 95% CI, 1.2–4.3) was observed for printers, after adjusting for age, sex, race, smoking and clinical atopy (Ng *et al.*, 1994). The frequency of dyspnoea was not elevated among former printers in a prospective study of the relationship between main lifetime occupation and dyspnoea after the age of 65 (Nejjari *et al.*, 1993). Several outbreaks of humidifier lung disease have been reported among printing workers (Hauck & Baur, 1990; Jost & Lehmann, 1990; Mamolen *et al.*, 1993).

No excess mortality from gastrointestinal tract diseases was observed among printing industry workers in the studies described in Section 2.3 (Svensson *et al.*, 1990; Michaels *et al.*, 1991; Leon, 1994).

Excess mortality from liver cirrhosis was observed among newspaper web pressmen (Paganini-Hill *et al.*, 1980) and newspaper pressmen (Lloyd *et al.*, 1977). A nonsignificant increase in the mortality from liver cirrhosis was observed in a subcohort of British printing industry union members (Leon, 1994).

Hepatic function has been studied among printers, mostly with emphasis on exposure to toluene. Although a high prevalence (55/181) of abnormalities in biochemical tests of liver function was observed among workers at a rotogravure plant, this was mostly explained by alcohol abuse and overweight (Boewer *et al.*, 1988). Similarly, in a four-year follow-up study of printers, no association was observed between occupational solvent exposure and biochemical markers of hepatic damage (Nasterlack *et al.*, 1994). The prevalence of abnormal serum alanine, aspartate transaminase or alkaline phosphatase was not different among printing factory workers and its job applicants (Guzelian *et al.*, 1988). Mild pericentral fatty change was observed in liver biopsies from six workers, in whom no cause other than work exposure could be identified for their elevated serum enzyme activities. An elevated urinary excretion of D-glucaric acid (the end-product of the glucuronic acid pathway and proposed as a marker substance for microsomal enzyme induction) was reported among printing plant workers, but was not correlated to levels of toluene exposure (Moretto & Lotti, 1990). In another printing plant, toluene-exposed workers had higher D-glucaric acid excretion than those not exposed to toluene [toluene concentrations not mentioned] (Sandstad *et al.*, 1993).

No excess mortality from urinary tract diseases was observed among printing industry workers in studies described in Section 2.3, in which the indicators of exposure were toluene (Svensson *et al.*, 1990) and lead (Michaels *et al.*, 1991).

Creatinine clearance or urinary excretion rates of albumin or β2-microglobulin were not different among 43 flexoprint or rotogravure printers and 43 controls not exposed to

organic solvents (Krusell *et al.*, 1985). In the same subjects, urinary excretion of albumin and β2-microglobulin was not significantly elevated by 6.5-h exposure to toluene (382 mg/m^3) in an exposure chamber (Nielsen *et al.*, 1985). A 31% prevalence of haematuria (dipstick) was observed among workers at a printing company compared to 25% in the control group from other industries. The authors noted that both the prevalences from exposed and control groups were higher than those reported in earlier studies (Sinclair *et al.*, 1993). Hashimoto *et al.* (1991) reported that the prevalence of microscopic haematuria, leukocyturia and albuminuria was elevated among solvent-exposed newspaper pressworkers in comparison to compositors not exposed to organic solvents.

Prompted by a case of aplastic anaemia in a printer in a printing shop, where most of the work involved five-colour printing with UV-cured and air-cured offset ink, Cullen *et al.* (1983) investigated the blood-forming organs of seven workers exposed to a variety of solvents and resins. The solvents used were chemically analysed for benzene; none was detected. All workers examined were clinically healthy and none showed any abnormalities in the cellular elements of the peripheral blood. However, all workers had one or more findings in the bone-marrow aspirate that was considered to be pathological. No concurrent healthy controls were examined.

UV-cured inks and printing plates (often containing acrylates) are frequent causes of allergic contact dermatitis among printing workers (Magnusson & Mobacken, 1972; Wahlberg, 1974; Beurey *et al.*, 1976; Pye & Peachey, 1976; Calas *et al.*, 1977; Emmett, 1977; Malten, 1977); sensitized people have shown positive reactions on patch testing toward alkyl acrylates (Björkner & Dahlquist, 1979; Björkner, 1981), multifunctional acrylic monomers such as tripropylene glycol diacrylate (Smith, 1977; Whitfeld & Freeman, 1991), pentaerythritol triacrylate (Emmett, 1977; Emmett & Kominsky, 1977; Smith, 1977; Nethercott, 1978; Björkner & Dahlquist, 1979; Nethercott *et al.*, 1983), trimethylol propane triacrylate (Emmett, 1977; Emmett & Kominsky, 1977; Smith, 1977; Nethercott, 1978; Björkner & Dahlquist, 1979; Björkner *et al.*, 1980; Nethercott *et al.*, 1983) or hexanediol diacrylate (Emmett & Kominsky, 1977), 2-hydroxyethyl methacrylate, different secondary acrylamides (Pedersen *et al.*, 1982, 1983) as well as toward urethane, epoxy or polyester acrylate resins and oligomers (Emmett & Kominsky, 1977; Malten, 1977; Björkner & Dahlquist, 1979; Björkner *et al.*, 1980; Nethercott, 1981; Nethercott *et al.*, 1983). During a two-year period in Toronto, Canada, 21 printing tradesmen with contact dermatitis were evaluated. Of these, 14 (67%) had allergic contact dermatitis (positive patch testing) and seven (33%) had an irritant contact dermatitis (negative patch testing). The irritant contact dermatitis was attributed to solvent exposure. Six of the cases of allergic contact dermatitis and one of the cases of irritant contact dermatitis had exposure to UV-cured ink components (Nethercott & Nosal, 1986).

Single cases of allergic contact dermatitis, caused by ethoxylated phenol surfactant (Ashworth & White, 1991) and colophony (used for paper sizing) (Castelain *et al.*, 1980; Bergmark & Meding, 1983), have also been described among printers.

Allergic contact dermatitis has been described in a female silk-screen printer in the manufacture of circuit boards; patch testing was positive toward diaminodiphenylmethane, 2-hydroxyethyl methacrylate and triglycidyl isocyanurate (Jolanki *et al.*, 1994).

No excess mortality from nervous system diseases was observed among printing industry workers in the studies described in Section 2.3 (Svensson *et al.*, 1990; Leon, 1994).

Mucous membrane irritation, neurological symptoms and neurophysiological and neuropsychological findings have been described among printers; these have usually been linked to exposure to different solvents or to lead (Baelum *et al.*, 1982; Ruijten *et al.*, 1991; Matsumoto *et al.*, 1993; Sinha *et al.*, 1993; Uchida *et al.*, 1993). The solvents most often incriminated have been hexane, toluene, xylene and chlorinated solvents, but often the exposure has been mixed.

n-Hexane-induced polyneuropathy has been observed among printing factory workers (Wang *et al.*, 1986; Chang, 1987; Chang *et al.*, 1993).

The frequency of neurasthenic symptoms was higher among rotogravure printers (mainly exposed to toluene) than among controls not exposed to solvents; the printers also had slightly lower scores in psychometric tests (Ørbaek & Nise, 1989). Changes in auditory, visual and somatosensory evoked potentials (Urban & Lukás, 1990; Abbate *et al.*, 1993; Stêtkárová *et al.*, 1993) and nerve conduction velocities (Stêtkárová *et al.*, 1993) have been suggested. However, in other studies, no relationship between exposure to toluene and reported central nervous system symptoms, clinical central nervous system signs, cardiovascular reflexes, psychological tests, electroencephalography or computerized tomography has been observed among rotogravure printers (Antti-Poika *et al.*, 1985; Juntunen *et al.*, 1985; Hänninen *et al.*, 1987) or in neuropsychological test performance among offset printers mainly exposed to either isopropanol, naphtha, acetone, xylene and hexane (Maizlish *et al.*, 1985) or acetone, isopropanol, toluene, xylene and 2-ethoxyethanol (Baird *et al.*, 1994). No deterioration of neuropsychological test performance or increase in subjective symptoms was observed in a two-year follow up study of screen printing workers exposed to a variety of solvents (toluene, methyl ethyl ketone, mineral spirits, dichloromethane, 'β-cellosolve' [probably 2-ethoxyethanol]) (White *et al.*, 1995). Decreases in the plasma concentrations of luteinizing and follicle-stimulating hormones and testosterone (Svensson *et al.*, 1992a,b) have also been reported among rotogravure printers.

Solvent-exposed printers were reported to have acquired colour vision deficit (Mergler *et al.*, 1988); however, these findings were not corroborated in another study comparing printers with binders (Baird *et al.*, 1994).

Noise-induced hearing loss was accentuated among rotogravure workers, who were exposed to toluene and high noise levels (88–98 dBA) in comparison to workers exposed to noise only (Morata *et al.*, 1993).

4.2.2 *Experimental systems*

In 30-day toxicity studies with Fischer 344/N rats and C3H mice, five males and five females of each species were given daily dermal applications (100 μL for mice, 250 μL

for rats) of five different letterpress and five different offset newsprint inks on five days per week for a total of 21–22 applications. In female rats treated with either undiluted or a 3 : 1 diluted composite mixture of the letterpress inks, a decrease in body weight gain (12–14%) was observed. No such change was observed after treatment with the other inks. Scaliness at the site of application was observed in mice treated with letterpress inks (Mahler, 1992).

In a subsequent experiment, rats and mice (10 males and 10 females of each species) were given dermal applications (20 μL for mice, 50 μL for rats) twice a week for 13 weeks of the letterpress ink mixture, offset ink mixture, mineral oil used as printing ink extender, USP mineral oil (rats) or the four individual lots (mice only) of both letterpress and offset inks. Decreased body weight gain was observed in female rats treated with the printing ink mineral oil (5%) or letterpress ink mixture (9%), and increased relative liver and kidney weights (12–15%) in both male and female rats treated with USP mineral oil. In mice, body weight gain was not affected, but liver weight was increased in most groups treated with either inks or mineral oils. No histological changes were observed in the liver. Dermal scaliness and/or irritation were observed in male and female mice treated with USP mineral oil or one of the letterpress inks (Mahler, 1992). Microscopically, skin lesions were observed at the site of application in all treated groups of mice.

Potent sensitizers identified in tests with guinea pigs were trimethylol propane triacrylate, pentaerythritol triacrylate, hexanediol diacrylate, tripropylene glycol diacrylate and the prepolymers, epoxy and urethane diacrylate (Nethercott, 1978; Björkner, 1980, 1981; Nethercott *et al.*, 1983; Björkner *et al.*, 1984). Oligomeric methacrylated polyester was a moderate sensitizer in a similar experiment (Björkner, 1982).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

(*a*) *Cohort study*

Kristensen *et al.* (1993) investigated the offspring of a cohort of 10 992 men who had been members of the Oslo (Norway) unions of compositors, lithographers and bookbinders between 1 January 1930 and 31 December 1974, and who were alive at the time of the 1960 census. A total of 6251 infants born during the period 1967–86 was identified by linking records from the printers' unions and the Norwegian Medical Births Registry. The reference group was all 118 403 births to married Oslo couples during the period 1967–86. The morbidity ratio, standardized for maternal age, year of birth, sex and birth order for total birth defects (ICD-8 codes 740–759.9) was 0.9 (95% CI, 0.8–1.0). When specific congenital anomalies were considered, the highest morbidity ratio was 1.6 (95% CI, 1.0–2.5) for cleft lip and/or palate. Further analyses in this study related to exposure to lead and solvents on the basis of job classification. On the basis of 69 job codes in the union records, each worker was categorized *a priori* into one of four exposure groups: lead only, solvents only, lead and solvents or 'other' exposure. The father's job category one year prior to the child's birth was considered in the allocation

of exposures, as the a-priori hypothesis was that exposure acts on the developing paternal germ cells, that is up to three months prior to conception. None of the paternal exposure categories was associated with the risk of total birth defects. However, boys whose fathers had been exposed to lead were at increased risk of cleft lip (using the reference population of total births to married couples in Oslo, the SMR was 4.1; 95% CI, 1.8–8.1). The authors noted that they did not have an a-priori hypothesis about cleft lip, and the possibility of a chance cluster could not be excluded.

In addition to congenital anomalies, the authors considered fetal growth and birth weight, gestational age and perinatal death. A higher proportion (67/1000 births) of printers' children than that of total births in Oslo (54/1000 births) was small for gestational age; there was no consistent association with exposure category between internal analysis and analysis using the external reference group. There was no association with birth weight, and the overall distribution of gestational age was similar between printers' children and total births in Oslo. The proportion of printers' children that were delivered as early pre-term births was 6.5/1000, as compared to 8/1000 for total births to married couples in Oslo. Compared with 'other' exposures, the RR for early pre-term births (16–27 weeks) was 5.4 (95% CI, 1.7–17.4) for infants with paternal exposure to solvents and 8.6 (95% CI, 2.7–27.3) for infants with paternal exposure to lead and solvents; these RRs were adjusted for fathers' occupational status, year of birth, twin births, maternal age, birth order and sex. Compared with the external reference group, the elevated risk associated with external exposure to lead and solvents was still apparent (SMR, 2.1; 95% CI, 1.2–3.3). The corresponding SMR for exposure to solvents only was 1.3 (95% CI, 0.6–2.3). The rate of late abortion (still-born infants with gestational age of less than 28 completed weeks) was 2.7/1000 births to printers, compared with 5.3/1000 for the reference population. The rate of still births and early neonatal deaths was 16.0/1000 infants born to printers, as compared to 12.6/1000 for the reference population. The RR for total perinatal deaths was 2.4 (95% CI, 1.2–4.9) for children with fathers exposed to lead and 1.9 (95% CI, 0.96–3.7) for children with fathers exposed to lead and solvents. The association with lead only was not apparent in the comparison with the external reference group, but the SMR for paternal exposure to lead and solvents was 1.6 (95% CI, 1.2–2.2) (Kristensen *et al.*, 1993). [The Working Group noted that the parents' smoking behaviour was unknown.]

(*b*) *Case–control studies of congenital anomalies*

In the Metropolitan Atlanta Congenital Defects Programme (United States), parents of infants with a variety of anomalies have been interviewed since 1970n about a range of exposures three to six months after the birth of their children (Edmonds *et al.*, 1981). The occupational distribution of parents of babies with one malformation was compared with that of parents with babies with all other malformations (Erickson *et al.*, 1979). [The period of study was not specified]. In general, the mother was the sole informant; some 85% of eligible mothers were interviewed. Information adequate for coding the industry of paternal employment at the time of conception was obtained from 76% of the total 989 women interviewed. Eleven (1.6%) of the 705 fathers for whom this information was available worked in the printing and publishing industry at the time of conception; this

proportion is similar to that of all employed persons aged 16 or more as determined in the 1970 census. Analyses were made by industry, occupation and occupation–industry cross classification. Results were presented if the RR was greater than or equal to 2, associated with a p value of less than 0.05 and the exposure of at least two fathers. The only category involving paternal employment in printing for which a result was presented was for cleft palate; two fathers of affected births were clerical personnel in the printing industry. Both were mailers and handled freshly printed material. None of the fathers of infants with other types of malformations had this category of employment. In regard to maternal occupation, the reference period during which exposure was considered was the first trimester and during the period up to and including the time of conception. Two mothers of infants with Down's syndrome were managers in printing firms; none of the mothers of infants with other types of malformations were so employed. Three mothers of babies with omphalocele and gastroschisis were also employed in the printing industry (RR, 7.7; $p < 0.05$); two operated printing presses while one worked both as a binder and a press operator. Another mother employed in the printing industry operated a press and her baby was affected by microcephaly, cleft palate and limb defects.

In a large study based on the national congenital malformation system in England and Wales during the period 1974–79, information on the occupations of both mothers and fathers of births with congenital anomalies was obtained from the notification form which is completed by Area Health Authority staff (Office of Population Consensus and Surveys, 1982). About 60% of births with malformations notified had a father's and mother's occupation stated. In a total of 47 352 births with notified malformations, the father's occupation was stated; 20 778 births with malformations had a mother's occupation stated. In the analysis of paternal occupation, the analysis was performed for two separate periods — 1974–76 and 1977–79 — and births with malformations notified in those periods were compared with total births in the middle year of each period (i.e. 1975 and 1978, respectively) to produce prevalence rates at birth by father's occupation. The distribution of paternal occupation for total births was obtained from birth certificate data, so the sources of information for cases and total births differ. The malformation ratio (observed cases/expected cases) associated with paternal employment in the paper and printing industries was 0.92 in 1974–76 and 0.86 in 1977–79. Data were presented on three groups of malformations — neural tube defects, cleft lip and/or palate and Down's syndrome. No increase in the malformation ratio was apparent for any of these groups. When analysis was made according to a smaller subdivision of types of occupations, the malformation ratio associated with the father being a printer was 1.6 in the first period and 1.4 in the second period. These excesses were not statistically significant. This information was not presented for the three selected groups of malformation. As noted by the authors, the differences in sources of information for cases and total births are a potentially serious source of bias as, at birth registration, details of occupation are collected by the Registrar with the aid of several questions whereas, at notification, details of occupation are derived either from a record obtained by health workers during pregnancy or from an enquiry made to the mother by a health visitor. Thus, the information obtained from birth registration tends to be more precise than that obtained from notification, and this may cause certain occupations to be

classified differently between the sources, with a differential effect on numerator and denominator. This bias may account for the nonsignificant excess of malformations in the offspring of printers. As there are no comparable data on maternal occupation from birth registration, the analysis by maternal occupation was limited to a study of the proportions of different malformations in births delivered to mothers of certain occupational groups, compared to the overall distribution of total births with malformations. For neural tube defects, the proportionate malformation ratio associated with the mother being a paper or printing worker was 1.4 during the period 1974–76, and 1.2 during the period 1977–79. For cleft lip and/or palate, the corresponding ratios were 1.2 and 1.7; for Down's syndrome, the ratios were 1.0 and 1.7, respectively. These ratios were not statistically significant.

A study of similar design was made for births with malformations notified in the period 1980–82 (McDowall, 1985). Notification may be made of malformations recorded in still-births and in live-births during the first week of life. Of a total of 40 346 births with malformation notified in England and Wales during this period, 62% (24 922) had a father's occupation stated and 28% (11 115) a mother's occupation. Standardized congenital malformation ratios for paternal occupations were calculated as the ratio of observed notifications to expected notifications, the former being adjusted for each specific type of malformation to account for the under-reporting of paternal occupation at notification. The effect of this adjustment was to make the standardized congenital malformation ratio equal to 1 rather than about 0.6 for a paternal occupation that had the same malformation notification rate as all cases for which an occupation was recorded. The number of expected notifications was derived by applying maternal age-specific rates of notified malformations to the number of births in each paternal occupation unit as determined from live- and still-birth registration. A significant positive association (standardized congenital malformation ratio, 1.4 based on 159 exposed cases) between total malformations and paternal employment as a printer was found, but the author noted that this would have been affected by the bias arising from the use of different sources of information for the numerator and the denominator. With regard to anomalies of specific types, a significant excess was found for rectal and anal atresia and stenosis (standardized congenital malformation ratio, 3.5 based on five exposed cases). No excess was found for related occupations; the standardized congenital malformation ratio was 0.4 for 'compositors', based on 11 exposed cases, 0.4 for 'electrotypers, stereotypes, printing plate and cylinder preparers' based on four exposed cases, 0.6 for 'printing machine minders and assistants' based on 26 exposed cases and 0.8 for 'screen and block printers' based on six exposed cases. As in the earlier analysis (Office of Population Censuses and Surveys, 1982), only standardized proportionate congenital malformation ratios could be calculated for maternal occupation. A significant excess was found for reduction deformities associated with maternal employment as a printer (standardized proportionate congenital malformation ratio, 10.1 based on three exposed cases). No excess was apparent for related occupations.

A large survey assessing the effect of occupational factors on pregnancy outcome in employed workers was conducted in Montréal, Canada, during the period 1982–84. A sample of 56 067 women who had just given birth or been treated for a spontaneous

abortion in 11 hospitals, in which about 90% of deliveries in the city take place, were interviewed about their index pregnancies and all previous pregnancies (McDonald *et al.*, 1987, 1988). In the main analyses relating to the women's occupation, 60 occupational groups were considered; none of the groups was related specifically to printing and related occupations. However, noting the findings of Erickson *et al.* (1979) relating to omphalocele or gastroschisis in employees in the printing industry, McDonald *et al.* (1988) noted that there was no evidence of such an association in the Montréal data. The only malformations in printing workers were two cases of Fallot's tetralogy. The women in the Montréal study were also asked about the husband's or partner's employment at the time of the first missed menstrual period for both current and past pregnancies (McDonald *et al.*, 1989). For spontaneous abortion, the analysis was limited to those in which the women were employed for 30 h a week or more at the time of conception; there were 47 326 such pregnancies — 24 711 index and 22 615 previous. The RR of spontaneous abortion associated with the father working in 'printing operations' was 0.9 ([95% CI, 0.7–1.1]; 81 exposed cases). The analysis relating to congenital anomalies was based on 47 822 pregnancies (27 472 index and 30 350 prior) of women employed 15 h a week or more at the time of conception. This total excluded spontaneous abortions of less than 20 weeks gestation but included therapeutic abortions following prenatal diagnosis of fetal abnormality. These RRs were adjusted for maternal age, gravidity, previous miscarriage, ethnic group, educational level, smoking and alcohol consumption. Two pregnancies associated with chromosomal anomalies were observed where the father was employed in printing operations (RR, 1.8 [95% CI, 0.3–9.9]). The RR of developmental defects, defined to include neural tube defects, cleft lip and/or palate and anomalies of the heart and of the respiratory, digestive and urinary tracts, was 0.6 ([95% CI, 0.2–1.8]; 4 exposed cases). In the analysis relating to congenital anomalies, no adjustment was made for confounding variables. No excess was apparent for specific types of congenital anomaly considered and, in particular, none of the fathers of cases with cleft lip and/or palate was a printer.

Olshan *et al.* (1991) reported a study based on 14 415 live births with birth defects recorded in the population-based registry in British Columbia, Canada, in the period 1952–73. Two controls were matched to each case on month, year and hospital of birth. Information on paternal occupation was obtained from the birth-registration record. Potential confounding by parental age, ethnic group and outcome of previous pregnancy was considered. Twenty categories of congenital anomalies were considered in relation to 58 occupational categories. Of the fathers of infants with congenital anomalies, 1.7% (245/14 415) had been employed as printers at the time of birth of the child. This occupation was associated with RRs greater than or equal to 1.5 for five groups of anomalies, and RRs of 0.7 or less for six groups of anomaly. RRs of 2 or more were observed for obstructive renal defects (RR, 2.0; 95% CI, 0.4–9.9; 3 exposed cases), atresia of urethra (RR , 4.5; 95% CI, 1.0–20.8; 7 exposed cases) and clubfoot (RR, 2.2; 95% CI, 1.2–4.1; 19 exposed cases). The RR for cleft palate was 1.6 (95% CI, 0.3-7.1; 3 exposed cases), that for cleft lip was 1.0 (95% CI, 0.1–11.1; 1 exposed case) and that for cleft palate with cleft lip was 1.2 (95% CI, 0.3–4.5; 3 exposed cases).

Fedrick (1976) determined the RRs, defined as the rate in specific categories relative to the rate in a total population, for anencephalus associated with specific paternal occupational orders at the time of birth in a population-based study in Oxfordshire and West Berkshire, United Kingdom, during the period 1965–72. Paternal occupation could be classified to an 'order' for 88% (92 083/104 854) of births in 1965–71 (data on total births in 1972 were not included) and 85% (151/177) of the births with anencephalus. There was a statistically significant increase in risk associated with work in the paper and printing industries (RR, 1.9; 5 exposed cases). All five case fathers employed in the paper and printing industries were printers; the RR for printers was 6.7. [The Working Group noted that although a p value of less than 0.001 was reported, detailed subgroup analysis was not reported for the other occupational groups.]

Using data from a case–control study of neural tube defects in upstate New York, United States, during the period 1968–74 which was aimed primarily at assessing a possible association with oral contraceptive use and included 201 mothers of cases, Polednak and Janerich (1983) analysed parental occupations as reported on the birth records of 171 case–control pairs. The RR associated with paternal employment in the printing industry (other than as a salesman) was 0.5 (not statistically significant, based on three discordant pairs).

Ericson *et al.* (1988) examined the association between neural tube defects and maternal occupation in Sweden, using three sets of data. In all three data sets, the defects were ascertained from the records of the Swedish Medical Birth Registry. In the first data set, the maternal occupation recorded in the 1975 census was determined for 158 infants with neural tube defects identified during the period 1976–77 and 316 controls matched on year of birth, maternal age and parity. In the second data set, the maternal occupation recorded at the 1980 census was determined for 103 infants with neural tube defects born in 1980 and 1981 and 206 randomly selected controls; the age and parity distributions did not differ significantly between cases and controls. In the third data set, maternal occupation recorded at the first antenatal clinic visit was determined for 87 infants with spina bifida born during the period 1982–84 and 174 controls matched on year of birth, maternal age and parity. Anencephalus was not considered in this last period since few cases were born as a consequence of intensive prenatal screening. No statistically significant association with any type of maternal occupation was found in any of the three data sets or in a pooled analysis of these. The RR associated with maternal employment in the 'graphic industry' was 1.0 (1 exposed case and 2 exposed controls in pooled analysis).

Brender and Suarez (1990) examined the association between paternal occupations thought to involve exposures to solvents and anencephalus in Texas, United States, during the period 1981–86. A total of 727 cases were identified by death certificates, live-birth records and records of fetal death. Of these, 528 (72.6%) were included in the analysis, exclusions having to be made either because the record from which the case was ascertained could not be matched with a live birth record from which the information of paternal occupation was obtained, or because the recorded occupation could not be classified. Similarly, only 1160 (79.2%) of 1464 randomly selected live-born controls, frequency matched on ethnic group and year of birth, were included. The RR

associated with the father being employed as a printer was 1.6 (95% CI, 0.4–5.5; 4 exposed cases).

Thus, the only group of congenital anomalies associated with printing-related work in more than one study was cleft lip and/or cleft palate (Erickson *et al.*, 1979; Kristensen *et al.*, 1993). [The Working Group noted that cleft lip with or without associated cleft palate and cleft palate without associated cleft lip are considered to be etiologically distinct.]

(*c*) *Case–control study of infertility*

Rachootin and Olsen (1983) examined the association between infertility and occupation in a case–control study using data collected from medical records and mailed questionnaires. A total of 1069 infertile case couples were identified from records of the Odense University Hospital in Denmark during the period 1977–80 and were compared with 4305 fertile control couples who had a healthy child born at the same hospital during the period 1977–79. Information on occupation was obtained from 927 case and 3728 control couples, representing a response rate of about 87% for each group. The analyses focused on three subgroups: (1) 258 couples in which the male partner was diagnosed as having abnormalities of sperm density, mortality or morphology; (2) 305 couples in which the female partner was diagnosed as having amenorrhoea, anovulation, luteal insufficiency or other endocrine malfunction; and (3) 129 couples with idiopathic infertility. The first two subgroups were not mutually exclusive as 48 couples were diagnosed as having both of these reproductive disorders. Analysis in relation to occupation was made restricting the control group to couples who reported that the index child had been conceived within a year of the decision to have the child and where the female partner was 20 years of age or older at the time the questionnaire was sent out. Statistically significant positive associations were found between sperm abnormalities and the male partner being employed as a typesetter (a) in the year prior to hospital admission of spouse for infertility investigation and (b) as the longest-held occupation prior to hospital admission. Odds ratios were not presented as there were fewer than 20 controls in this occupational category. There was no association with idiopathic infertility or with delayed conception, defined as conceiving more than a year after the decision was taken to have a child. In addition, there were significant positive associations between the female member of the pair having been employed as a typesetter both in the year prior to hospital admission and for whom this was the longest-held occupation prior to hospital admission. There was no association between female employment in typesetting and idiopathic infertility or delayed conception. (Again no odds ratio was presented as fewer than 20 controls were employed in this category.) A total of 55 categories of male employment and 43 categories of female employment were analysed.

(*d*) *Case–control study of mental retardation*

A case–control study of parental employment and mental retardation of unknown etiology was carried out in children referred to the paediatric or child neurology departments of the Nijmegen University Hospital (The Netherlands) or to rehabilitation centres in the vicinity during the period 1979–87 (Roeleveld *et al.*, 1993). A total of 340 cases

with mental and psychomotor retardation (ICD codes 317–319) with an IQ of less than 80 according to the Dutch School Criteria for the Mentally Retarded were compared with 362 children with other congenital handicaps. The main diagnoses of the control children were familial neuromuscular and metabolic disorders and cerebral palsy. Data on parental occupation were obtained by interview with 306 parents of cases (participation rate, 90%) and 322 parents of controls (participation rate, 89%). Using a job–exposure matrix developed for use in England and Wales, the RR, adjusted for primigravidity, prematurity, alcohol consumption and leisure-time activities, associated with maternal occupational exposure to printing inks during the last trimester of pregnancy was 1.6 [95% CI, 0.8–3.0]. The corresponding RR associated with paternal exposure during the three months prior to conception was 0.7 [95% CI, 0.4-1.3]. When the father was asked directly about exposure to printing inks, the associated RR was 0.7 [95% CI, 0.2–2.8]. For 57% of the cases and 47% of the controls, the father provided information about his own exposure; for the remaining subjects, the mother supplied information about the father and the appropriate exposure checklists were left for him to complete. None of the mothers reported exposure to printing inks during the third trimester in response to a direct question about this. The lag time between the critical period and the interview varied from two to 25 years, with an average lag time of 10.7 years. A number of exposures that could not be identified by the job–exposure matrix approach were studied. Among these, maternal exposure in the last trimester to copying machines was associated with a RR of 3.0 [95% CI, 1.1–8.3] and exposure to correction fluid was associated with a RR of 1.7 [95% CI, 0.7–4.1]; these RRs were adjusted for primigravidity, prematurity, alcohol consumption and leisure time activities. Paternal preconceptional exposure to copying machines was associated with a RR of 1.5 [95% CI, 0.8–2.8].

4.3.2 *Experimental systems*

Groups of 10 male and 10 female Fischer 344/N rats, seven to eight weeks of age, were given dermal applications to hair-clipped skin of 50 μL neat letterpress or offset newsprint inks, or of mineral oil vehicles at twice-weekly intervals for 13 weeks (Mahler, 1992). Control rats were hair-clipped but untreated. The letterpress and offset ink mixtures were prepared by mixing four separate lots of each type, each lot representing a batch from each of the four major manufacturers in the United States. There were no effects of any of the applications on epididymal sperm motility, sperm density, testicular spermatid head count, vaginal cytology or oestrus cycle length.

4.4 Genetic and related effects

The genotoxicity of various printing ink components, e.g. solvents, such as toluene and benzene, and dyes, has been reviewed (Dean, 1985; WHO, 1986; IARC, 1987l, 1989b,c, 1993b,c,d; Snyder *et al.*, 1993; WHO, 1993; McGregor, 1994; Snyder & Kalf, 1994).

Azo dyes are used extensively in the printing industry. A review on the mutagenicity of 84 azo dyes has been given by Chung and Cerniglia (1992). Magenta and CI Basic

Red 9 (preparation of printing inks) and CI Pigment Red 53:1 and CI Pigment Red 3 (preparation and in printing ink) have been evaluated by IARC (1993b,c,d).

4.4.1 *Humans*

(*a*) *Urinary mutagenicity*

Crebelli *et al.* (1985) studied urinary mutagenicity in workers employed in the use of an IBM Printing System 3800, which implies exposure to small amounts of 2,4,7-trinitro-9-fluorenone. Urine samples were collected in the morning after at least three workdays from 22 exposed white men (11 smokers, 11 nonsmokers) and 18 white men (7 smokers, 11 nonsmokers) working in the same bank, but only occasionally in contact with the printing system. Analytical measurements showed the presence of 2,4,7-trinitro-9-fluorenone residues in both printed and photocopied sheets (0.4–4 μg in 21 × 27 cm sheets) and in the surrounding air (0–0.4 μg/m^3). Urine samples were concentrated by adsorption onto XAD-2 resin and elution with acetone. Mutagenicity was studied both by the plate incorporation assay and the microtitre fluctuation assay using *Salmonella typhimurium* TA98. Pure 2,4,7-trinitro-9-fluorenone was highly mutagenic, but urine concentrates of both exposed and presumed unexposed workers were mostly negative. A few concentrates were significantly mutagenic but with no relationship to exposure (one among exposed and four among controls). In the presence of an exogenous metabolic activation system, five of eight concentrates from both unexposed and exposed smokers were mutagenic, whereas the urine of nonsmokers was completely inactive.

(*b*) *Cytogenetic damage in lymphocytes*

Forni *et al.* (1971) studied chromosomal aberrations in peripheral lymphocytes in 34 male workers employed in a rotogravure plant, 10 of whom were exposed to both benzene (for 1–22 years) and toluene (for 12–14 years) and 24 to toluene only (for 3–15 years). Each worker was matched with a healthy control of the same sex and approximately the same age with no history of exposure to benzene or its homologues or to therapeutic or occupational X-irradiation. There was no control for tobacco smoking or alcohol consumption, but people having had a recent viral disease or vaccination were excluded. The concentrations of benzene and homologues of benzene expressed as concentrations of benzene were 131 ppm [419 mg/m^3] in the centre of the rotary machine room, 125 ppm [400 mg/m^3] near the windows, 363 ppm [1162 mg/m^3] near a folding machine and 532 ppm [1702 mg/m^3] in the auxiliary room. After a benzene-poisoning epidemic, only toluene was used as an ink diluent. Concentrations of toluene in different parts of the working department varied between 56 and 824 ppm [211 and 3106 mg/m^3] up to 1966, when the plant was moved and better ventilation was obtained (156 ppm [588 mg/m^3] near folding machines and 265 ppm [999 mg/m^3] between machine elements). In the benzene–toluene group, a statistically significant increase in the incidence of unstable chromosomal aberrations was found (1.66% compared with 0.61% in the controls). This was not found in the toluene-exposed group.

Funes-Cravioto *et al.* (1977) examined eight rotoprinting factory workers exposed to benzene during the 1940s and to toluene from 1950 onwards for periods ranging from

two to 26 years. Air concentrations of benzene were not measured. Air concentrations of toluene showed time-weighted average values of 100–200 ppm [377–754 mg/m^3] with occasional rises up to 500–700 ppm [1885–2639 mg/m^3]. The frequency of chromosome breaks was 11.9% (5.6% in controls). No increase in sister chromatid exchange frequency was found in the four workers examined in this group. In 14 other workers exposed to toluene only (1.5–26 years), the frequency of chromosome breaks was 8.9%. [The Working Group noted that statistical evaluations were not made on the separate groups.]

Mäki-Paakkanen *et al.* (1980) studied 32 men working in two different rotoprinting factories and 15 control men from a research institute. Toluene was the only solvent used in the two factories. Concentrations of benzene, which is a contaminant, had been checked regularly since 1962 and had always been below 0.05% (average, 0.006%) as measured by gas chromatography. The personal toluene exposures of the printers were calculated as time-weighted averages for an 8-h work day and were between 7 and 112 ppm [26–420 mg/m^3]. The cytogenetic study showed little difference between the workers and the controls (chromatid type, 1.0 versus 0.7%; chromosome type, 0.5 versus 0.9%; sister chromatid exchange, 8.5 versus 8.9 per cell). A higher frequency of sister chromatid exchange was observed among smokers both in the group of workers and in the controls. No effect of smoking was observed as regards chromosomal aberrations.

Bauchinger *et al.* (1982) examined 20 men working for more than 16 years on a rotogravure machine. The continuously measured toluene concentration in the air of the rotary machine was between 200 and 300 ppm [754 and 1131 mg/m^3]. The toluene used contained < 0.3% benzene. From the same plant, a group of 24 unexposed workers [sex unspecified] was used as controls. There were 12 smokers and eight nonsmokers in the exposed group, and nine smokers and 15 nonsmokers in the control group. In the exposed group, a significantly larger number of peripheral lymphocytes with structural chromosomal changes were found: chromatid breaks (0.0036 versus 0.0019 per cell) and chromatid exchanges (0.0015 versus 0.0004 per cell), but not acentrics or dicentrics. The yield of gaps was also significantly increased (0.0248 versus 0.019 per cell). Significantly higher levels of sister chromatid exchange were observed in the nonsmoking rotogravure workers compared with nonsmoking controls (8.55 versus 7.75 per cell). This was also the case for toluene-exposed smokers compared with control smokers (10.33 versus 8.89 per cell). In both groups, smokers had significantly higher sister chromatid exchange values than nonsmokers.

A second study of chromosomal changes in peripheral lymphocytes was made on 27 workers from the same factory who had not been exposed to toluene for four months to five years (Schmid *et al.*, 1985). These 27 workers were subdivided into two groups: those without exposure for up to two years, and those without exposure for more than two years. They were compared with 26 controls. The exposure conditions had been the same as in the first study. The group of 13 workers without exposure for up to two years still showed a significantly larger number of cells with structural chromosomal aberrations (S-cells; 0.69 versus 0.49%) and chromatid-type aberrations (but not gaps) than the controls (0.39 versus 0.20/100 cells). No significant difference was observed in the group of 14 workers without exposure for more than two years compared with the

controls. In all groups, smokers showed a significantly higher incidence of sister chromatid exchange than nonsmokers, but the two post-exposure groups did not differ from the controls as regards incidence of sister chromatid exchange.

Chromosomal aberrations in peripheral lymphocytes of rotogravure printing plant workers [sex unspecified] were studied in two groups of exposed persons by Pelclová *et al.* (1990): 42 persons (37 smokers, 5 nonsmokers) who had been exposed to highly purified toluene (104–1170 ppm; 390–4380 mg/m^3) and to printing dyes for an average of 12 years; 28 office and technical employees (17 smokers, 11 nonsmokers) of the same printing plant exposed to low levels of toluene (2.1–4.3 ppm; 8-16 mg/m^3) and working on average 2 h per day in the rotary machine room. A control group of 32 persons (17 smokers, 15 nonsmokers) was selected from offices in a nearby brewery and dairy. Exposure was assessed by measuring toluene in blood at the end of the working shift (124.0 and 10.3 μmol/L in the two exposed groups, respectively; not measured in the control group). The percentages of aberrant cells were 3.6 and 3.3 in the exposed groups and 2.1 in the control group. There were significantly higher proportions of chromatid breaks per cell in both exposed groups and gaps and chromosomal exchanges in the low toluene-exposed group only, whereas the proportions of chromosomal breaks per cell were not different between the three groups. A small difference in the percentage of cells with aberrations was seen between smokers and nonsmokers (3.4 versus 2.4%; $p < 0.05$). Smoking printers had 3.8% aberrant cells, smoking office and technical employees had 3.4% and smoking controls had 2.5%. The difference between smoking printers and smoking controls was significant ($p < 0.05$).

Micronuclei and chromosomal aberrations in lymphocytes have been studied in 21 men employed as rotogravure printers by Nise *et al.* (1991). As controls, 21 workers were selected from a margarine factory with no exposure to solvents or other components of the printing trade. The median time of exposure was 25 years; median weekly individual exposure measured in 1986 was 150 mg/m^3 when the median blood toluene content was 1.6 μmol/L (measured between 11.00–14.00 h in the middle of a working week). For lymphocytes stimulated with pokeweed mitogen, there was a significantly increased incidence of micronuclei in the printers compared with the controls, when allowance was made for age and smoking (2.8 versus 1.5/1000 cells). There was also a significant difference in the incidence of small micronuclei for which the size ratio micronucleus:main nucleus was ≤ 0.03 (1.0 versus 0.3/1000 cells) and, in the exposed group, an association between blood toluene and small micronuclei (0.17/1000 cells/-μmol toluene/L blood; $p = 0.0005$). No difference was found with lymphocytes stimulated with phytohaemagglutinin (2.8 versus 2.5/1000 cells). There was no significant difference in chromosome breaks between the exposed and the control group, but there was an association between chromosome breaks and earlier benzene exposure. [The Working Group noted that there is considerable variation in micronucleus frequency in pokeweed mitogen-stimulated lymphocytes. The relevant historical database from the same laboratory gives frequencies of 1.5 (this study), 3.4, 6.0, 7.0 and 2/1000 pokeweed mitogen-stimulated cells (Högstedt *et al.*, 1988; Hagmar *et al.*, 1989; Högstedt *et al.*, 1991; Nise *et al.*, 1991; Holmén *et al.*, 1994).]

Lead concentrations in urine and the frequency of chromosomal aberrations and sister chromatid exchange in lymphocytes were studied in 84 printers exposed to lead (Chen *et al.*, 1992). A linear correlation was found between urinary lead concentrations and the frequency of chromosomal aberrations and sister chromatid exchange.

Richer *et al.* (1993) exposed five male volunteers to 50 ppm [187.5 mg/m^3] toluene, which is a prominent solvent in the printing industry, in a controlled exposure chamber for 7 h per day for three days on three occasions at two-weekly intervals. Blood samples were taken before and after exposure. No effect upon sister chromatid exchange frequencies was observed in peripheral lymphocytes.

4.4.2 *Experimental systems*

Toluene also shows little mutagenic potential *in vitro*, while *in vivo* there have been some reports of the induction of both micronuclei and chromosomal aberrations in rodent bone-marrow cells. These responses may be largely due to contamination of the toluene with benzene, and it has been suggested that no definitive conclusion can be reached at present regarding the genetic activity of toluene in rodents (McGregor, 1994). Most studies have failed to show any mutagenic potential of benzene *in vitro*. Positive responses have been reported in *Salmonella typhimurium* TA100 in a microfluctuation test (Glatt *et al.*, 1989) and in three studies with the Syrian hamster embryo cell transformation assay (IARC, 1987l). The mutagenicity of the benzene metabolites *trans*-1,2-benzene dihydrodiol, benzene diol epoxides, 1,2,4-trihydroxybenzene, hydroquinone, catechol and *trans,trans*-muconaldehyde has been demonstrated (reviewed by Snyder *et al.*, 1993). Many in-vivo studies have demonstrated that benzene is clastogenic in assays for the induction of rodent bone-marrow cell micronuclei and chromosomal aberrations (IARC, 1987l). However, covalent association of benzene with cellular DNA occurs at a very low level, which has been difficult to detect *in vivo* (Snyder *et al.*, 1993).

Co-exposure of BDF1 mice to toluene and benzene has been shown to reduce the DNA damage in peripheral leukocytes, bone-marrow cells and liver cells induced by benzene alone (Plappert *et al.*, 1994). An interaction between benzene and toluene resulting in a reduced response to benzene has also been described with cytogenetic endpoints in mice and rats (reviewed by McGregor, 1994).

Milvy and Kay (1978) studied the mutagenicity of 19 dyes used in the graphic arts and printing industry with the *S. typhimurium*/mammalian microsome reversion test system. Two of these were found to be mutagenic. Para red [1-(4-nitrophenyl)azo-2-naphthol] was mutagenic in TA98 and TA1538 when activated with S9 homogenate. Dinitroaniline orange was a direct mutagen with TA98. No mutagenicity was found with lithol red (CI 15630), alkali blue (CI 42750), cadmium red (CI 77196), naphtol red (CI 12315), phthalocyanine green (CI 74260), elemental aluminium, Red Lake C (CI 15585) (see IARC, 1987o), rhodamine (CI 45160) (see IARC, 1987p), diarylide orange (CI 21110), red 2B (CI 15865), Hansa yellow (CI 11680), phthalocyanine blue (CI 74160), diarylide yellow (CI 21090), fire red (CI 12085), molybdate orange (CI 77605), lithol rubine (CI 15850) or iron blue (CI 77510).

Møller *et al.* (1983) found that extracts of typewriter ribbons and carbon papers were mutagenic in the *Salmonella*/microsome assay with strain TA98. A sample of black ink used for a word-processing system was also shown to be mutagenic. Fractionation of the ribbon extracts indicates that at least two to three different classes of mutagenic components were present in the extracts.

The mutagenicity of letterpress and offset black newsprint ink (see section 1.3) has been tested under the United States National Toxicology Program (Mahler, 1992). The inks were tested in a preincubation protocol at concentrations of 100–10 000 μg/plate in *S. typhimurium* strains TA100 and TA98 with and without rat and Syrian hamster liver S9. In the absence of S9, none of the inks was mutagenic. In the presence of 30% hamster liver S9, both inks were mutagenic in both *Salmonella* strains. In the presence of rat liver S9, both inks were non-mutagenic with strain TA100, but induced mutations in strain TA98.

The azo dye D & C Red No. 9 is used for manufacturing printing inks. It has previously been tested in several in-vitro and in-vivo test systems and has been shown to be non-mutagenic (see IARC, 1993b). Dillon *et al.* (1994) tested the dye in a specific *Salmonella* mutagenicity assay, incubating the test compound with a rat caecal preparation under anaerobic conditions to reduce the azo bond. Ethyl acetate extracts of this incubation mixture gave dose-related mutagenic responses in TA100 and a weak response in TA98 when incubated with rat liver S9. The presumed major reduction product, 1-amino-2-naphtol, was mutagenic to TA100, but not TA98, with S9. The authors suggest that the previous non-mutagenicity of this dye may have been due to insufficient reductive cleavage.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Printing inks are mixtures of three main types of ingredients: pigments, vehicles and additives. Pigments used in printing inks include both inorganic pigments such as carbon black and titanium dioxide and organic pigments, which are frequently dyes rendered insoluble by complexing with a metal ion. Most organic pigments are prepared from azo, anthraquinone and triarylmethane dyes, and phthalocyanines.

There are five main printing processes, and inks are designed for the specific process. Lithography and letterpress are collectively known as the 'paste ink' processes and use inks that are essentially non-volatile at normal temperatures. Flexography and gravure are known as the 'liquid ink' processes and are based upon volatile solvents that evaporate readily at room temperatures. Screen printing uses inks that fall between the other two groups.

Choice of the vehicle (solvent with resins) for a printing ink depends on the printing process, how the ink will be dried, and the substrate on which the image is to be printed. In lithography and letterpress, where inks are dried by absorption and oxidation, vehicles

are generally mixtures of mineral and vegetable oils and resins. Flexographic inks, which are designed to dry quickly by evaporation, can be either water-based or based on organic solvents (such as ethanol, ethyl acetate, *n*-propanol or isopropanol) with a wide variety of resins. Vehicles for gravure inks, which also dry by evaporation, may also contain aromatic or aliphatic hydrocarbons and ketones as solvents. Inks for screen printing use organic solvents that are somewhat less volatile than those used for flexography or gravure (higher glycol ethers and aromatic and aliphatic hydrocarbons). Additives in inks include driers, waxes and plasticizers.

Ultraviolet radiation-cured inks, commonly based on acrylates, are used in all of the printing processes to varying degrees.

The manufacture of inks consists of dissolving or dispersing resins in organic solvents or oils to produce the vehicle (varnish), mixing and dispersing the pigment or dye into the vehicle, introduction of any additives and packaging. Some or all of these stages may be done manually or automatically in a batch process or as a continuous process.

During the manufacture of printing inks, exposure to pigments, vehicles and additives can occur through inhalation or skin contact during mixing and dispersion and during clean-up of mixers. Exposures are higher with liquid inks than with paste inks. During newspaper printing by letterpress or lithography, the major exposure is to ink mist. Rotary letterpress was the dominant process for the production of newspapers until the 1970s. It has now been largely replaced by web offset litho, in which exposures to ink mist are considerably lower than for letterpress. In other lithographic and letterpress printing, the major exposure is to hydrocarbon-based cleaning solvents and isopropanol from damping solutions. In flexographic, gravure and screen printing, exposures are mainly to organic solvents. Historically, some workers in both ink manufacture and printing were exposed to much higher levels of lead, polycyclic aromatic hydrocarbons and benzene than today, and the development and use of modern control technologies have made possible the marked reduction in solvent and ink mist exposures.

5.2 Human carcinogenicity data

A large volume of epidemiological data deals with potential cancer risks in printing processes. Because of the presence of a fairly large number of adequate cohort and case–control studies, it was considered that there was no marginal benefit in considering further the descriptive studies based on simple tabulations of death certificate causes of death and mentions of occupation. In any case, these latter studies did not provide clear patterns of results.

The evaluation of results of case–control and cohort studies, in particular those regarding relatively rare neoplasms, was hampered by the possibility of reporting or publication bias. A second problem was the poor specificity of exposure information. While most studies were based on crude designations of the exposure variable, a few, most notably some of the cohort studies, did describe risks for subgroups of the printing industry that are more homogenous in exposure circumstances. The Working Group tried to identify such subgroup studies with presumably more well-defined common exposure circumstances. In a small number of studies, there was an explicit attempt to identify a

group of workers exposed to printing inks. This, like the designation of exposure on the basis of the job or industry title, is of poor specificity. Further, most of these were in the context of community-based case–control studies, and the attribution of exposure was based on job–exposure matrices, which do not discriminate among subsectors of the printing industry.

A third problem was that most of the cohort and record-linkage studies had no information on some important counfounders, notably cigarette smoking. It has previously been shown that confounding by smoking is unlikely to distort the relative risk estimate between occupation titles and lung cancer by more than 30%. For other sites that are affected by smoking, the maximal bias is likely to be even lower. The Working Group considered these possible biases when interpreting results.

Apart from cancers of the lung, oropharynx, urinary bladder and kidney and leukaemia, which are presented below, the Working Group considered that the findings are not strong or consistent enough to be evaluated.

Lung cancer

Ten community-based case–control studies examined the relationship between lung cancer and occupation and reported results regarding printing industry and/or printing related occupations. Increased relative risks were found in eight studies; smoking was controlled for in six of them and the smoking-adjusted relative risks for 'printing occupations' ranged from 1.1 to 3.3. Two studies reported findings for exposure to printing inks: both found a positive association. A Canadian study found that a small excess of lung cancer detected in printers as a whole was concentrated in printing process workers and was very high for adenocarcinoma of the lung in particular.

Six census-based record-linkage studies reported results for lung cancer. The Swedish study found a statistically significant 60% excess of lung cancer in blue-collar workers in printing enterprises. One study in Denmark showed an increased risk only for women employed in printing, publishing and allied industries. A subsequent Danish study revealed a slight, statistically significantly increased risk in printing and bookbinding industry workers; the risk was higher and still significant in workers employed in newspaper and magazine production. The Finnish study and the two Italian studies did not detect a statistically significant increased risk for lung cancer related to printing occupations.

Among the industry-based studies, five proportionate mortality studies evaluated the risk for lung cancer. In one study, statistically significantly increased risks were found among printing trade workers in two different areas of the United Kingdom. A subsequent, partially overlapping study in London, United Kingdom, reported a statistically significant 30% excess of lung cancer among newspaper printing workers. A third study examined United States newspaper and commercial pressmen separately; neither newspaper nor commercial pressmen showed an increased mortality from lung cancer. The other two proportionate mortality studies in printing workers in the United States failed to show an increased risk for lung cancer.

Among the industry-based studies, seven standardized mortality ratio studies examined lung cancer risk in printing trade workers. Respiratory cancer was elevated in four studies; in none was smoking controlled. An increased risk for lung cancer was found in the Italian cohort of newspaper workers. The historical cohort of trade union members in the United Kingdom printing industry had a statistically significantly increased risk for lung cancer among mainly unskilled workers in newspaper letterpress printing (machine assistants). Newspaper web pressmen in Los Angeles, United States, showed a nonsignificantly increased lung cancer risk. A Swedish study of rotogravure printers revealed increased risk from respiratory cancers.

In addition, in a cohort of United States Army veterans, an increased smoking-adjusted relative risk for respiratory cancer was found in 'printing pressmen and plate printers'.

In some studies, it was possible to separate newspaper printing workers from other less-well defined employment in the printing industries. Seven cohort studies examined lung cancer risk in workers employed in the newspaper printing industry, mainly during the period 1945–1970. Three were proportionate mortality studies, two of United Kingdom newspaper printing companies and one that examined United States newspaper pressmen and commercial pressmen separately. Four were standardized mortality ratio studies of newspaper web pressmen in Los Angeles, United States, of newspaper printers in two plants in New York City, United States, of newspaper workers in one Italian plant and of newspaper machine assistants who were trade union members in the printing industry in the United Kingdom. Five of the seven cohort studies reported increased relative risk estimates ranging from 1.2 to 1.5, of which three were statistically significant. In none of them was smoking taken into account. In addition, a Danish record-linkage study found a two-fold, statistically significantly increased risk for workers in newspaper and magazine production whose typical job was the operation of rotary letterpress machines.

Cancer of the oropharynx

The risk for cancer of the buccal cavity and pharynx was examined in three case–control studies in the United States. One study on multiple cancer sites showed a smoking-adjusted elevated risk in printing workers. Another similar study detected a significantly high smoking- and alcohol-adjusted risk for cancer of the oral cavity in workers in the printing and publishing industry. A third case–control study on oropharyngeal cancer did not find an increased risk among men employed in the printing industries, whereas a nonstatistically significantly increased risk was found for women. A nonstatistically significantly increased risk was found in male workers in printing and bookbinding industries in a Danish record-linkage study.

Four cohort studies reported results for cancer of the buccal cavity and pharynx. The United States study that examined separately newspaper pressmen and commercial pressmen found a higher than two-fold statistically significantly increased risk in newspaper pressmen only. Increased risks were not found in a standardized mortality ratio study of newspaper pressmen in Los Angeles nor in a cohort of newspaper printers in

two plants in New York City. The cohort of trade union members in the United Kingdom printing industry found increased risks in non-production workers (editorial and clerical staff) only.

Urinary bladder cancer

Thirty-five studies have reported findings for urinary bladder cancer and employment in the printing industry. A positive association between urinary bladder cancer and either a printing occupation or employment in the printing industry was reported in 14 of the 23 case–control studies. The range of relative risk estimates derived from these studies was from 1.1 to 5.6. These associations were statistically significant in only three of the case–control studies. Generally, the interpretation of the case–control studies was limited by their use of broad job and industry categories such as printers or the printing industry. One study in Spain reported a nonsignificantly increased relative risk for typesetters and linotypists.

Six cohort studies and six record-linkage studies have also been reported. Increased rate ratios were reported in five of the cohort studies of workers in the printing industry. However, the rate ratios in two of them were close to 1.0 and a statistically significant increase was found only for printing pressmen and plate printers in the cohort of United States Army veterans. Similarly, the relative risk estimates derived from the record-linkage studies were close to unity and the only ones that achieved statistical significance were from the two Danish studies: one study found an increased risk among men employed in printing and bookbinding industries and the other among men employed in printing, publishing and allied industries. Five case–control studies reported results for exposure to printing inks and urinary bladder cancer risk was observed to be elevated in all five studies.

Cancer of the kidney

Slight to moderate excesses of cancer of the kidney have been reported in the printing industry in five industry-based studies in different cohorts in the United States, and in two record-linkage studies in Italy and Sweden. Ten cohort studies did not report results for cancer of the kidney at all. Four case–control studies, one nested in a cohort of paper-board printing workers and three representing different populations in three continents reported odds ratios ranging from 1.3 to 16.6. Most of these were not statistically significant. By far the most powerful case–control study, a multicentric study conducted in Australia, Denmark, Germany, Sweden and the United States, reported a 30% non-significant excess associated with employment in printing and graphic industry.

Leukaemia

Results regarding leukaemia risk in printing workers have been reported in one case–control study and seven cohort studies. The case–control study found a nonstatistically significantly increased risk for printers. Significantly increased risks were found in two cohort studies.

The proportionate mortality study that examined newspaper pressmen and commercial pressmen separately found a 60% excess of leukaemia risk only in newspaper pressmen. In another proportionate mortality study in printing workers in the United States, a statistically significantly increased risk for leukaemia was detected primarily among bindery workers who may have had exposure to benzene. Newspaper web pressmen in Los Angeles, United States, also showed a higher than two-fold increased risk. A Swedish study of rotogravure printers revealed an increased risk for leukaemia, although this was based on a very small number of cases. Both newspaper web pressmen and rotogravure printers may have been exposed to benzene and other organic solvents in the past. Three other cohort studies in newspaper printing workers in London, United Kingdom, commercial pressmen in the United States and newspaper printers in New York City failed to show an increased risk.

Overall, notwithstanding the variability in the results, there are indications of excess risks among printing process workers for some types of cancer. In its evaluation of these data, the Working Group considered the likelihood of publication bias, the possibility of confounding by cigarette smoking, and the imprecision and inconsistency of the designation of exposure groups. Based on these considerations, the Working Group concluded that there is weak evidence of an increased risk of lung and urinary bladder cancers among workers in the printing industry.

While there was a suggestion of an increased risk of lung and urinary bladder cancers in relation to exposure to printing inks, the quality of the data was weak.

The Working Group noted that the vast majority of epidemiological studies covered workers who were in the printing industry in North America or Europe during the middle of the twentieth century. Very few of the studies included workers whose employment was after 1980. Given the rapid technological changes that have gone on in this industry in North America and Europe in the past decade, it is questionable whether the exposure circumstances that were prevalent in the past are still prevalent. However, there may be areas of the world in which the older processes are still prevalent. Where the technologies have substantially changed from those of the past and insofar as this has changed the exposure conditions, the present evaluation may not be relevant.

5.3 Animal carcinogenicity data

Twenty-two different printing inks were tested for carcinogenicity in one study in mice by subcutaneous injection. The study was inadequate for evaluation.

5.4 Other relevant data

No consistent association between employment in printing trades and morbidity from non-malignant diseases has been observed. Solvent-induced central nervous system damage has been observed in several but not all studies on employees in printing trades. Ultraviolet radiation-cured printing inks are a frequent cause of allergic contact dermatitis.

One study suggested that occupational exposures may induce hepatic damage in printers, but several other studies failed to confirm this finding.

An early report of an increased risk of anencephalus associated with paternal employment in printing has not been confirmed in subsequent studies of neural tube defects. In two studies, an association between this exposure and cleft lip and/or palate has been observed. However, in one of these, the association was apparent only for cleft palate, and in the other only for cleft lip, and no noteworthy association has been observed in a further three studies. In a single study in rats, dermal exposure to newspaper inks had no effect on sperm numbers or motility, vaginal cytology or oestrus cycle length.

Several pigments and dyes used in printing inks are mutagenic in *Salmonella typhimurium*: para red, dinitroaniline orange, azo dye D & C Red No. 9.

An increased frequency of chromosomal aberrations in peripheral lymphocytes in printing workers exposed to *inter alia* toluene was found in two studies, but not in two other studies. In one study, an increased frequency of chromosomal aberrations was found in workers exposed to toluene and benzene. In one study of a group exposed to toluene, an increased frequency of sister chromatid exchange was found, but not in two other studies. In one study of printers exposed to lead, increased frequencies of chromosomal aberrations and sister chromatid exchange were found. In one study, an increased frequency of micronuclei was observed in printing workers exposed to toluene. In one study of volunteers exposed to toluene, no increase in sister chromatid exchange was observed in lymphocytes.

5.5 Evaluation[1]

There is *limited evidence* that occupational exposures in printing processes are carcinogenic.

There is *inadequate evidence* for the carcinogenicity in humans of printing inks.

There is *inadequate evidence* for the carcinogenicity in experimental animals of printing inks.

Overall evaluation

Occupational exposures in printing processes are *possibly carcinogenic to humans (Group 2B).*

Printing inks are *not classifiable as to their carcinogenicity to humans (Group 3).*

[1] For definition of the italicized terms, see Preamble, pp. 24–27.

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