OCCUPATIONAL EXPOSURE AS A PAINTER

Occupational exposure as a painter was considered by previous Working Groups in 1988 and 2007 (IARC, 1989, 2010a). Since that time new data have become available, which have been incorporated in this *Monograph,* and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Description of paint products

Paint is a suspension of finely divided pigment particles in a liquid composed of a binder (resin), a volatile solvent or water, and additives that impart special characteristics. The volatile components evaporate from the drying film after application, while the binder holds the pigment in the dry film, causing it to adhere to the substrate. Some high quality, hard gloss paints are referred to as enamels.

The basic components of paints vary widely in terms of chemical composition, depending on the colour, the durability, and other required properties of the paint. Table 1.1 lists the main substances and classes of chemicals present in paints, to which workers may be exposed in the painting trades.

Thousands of chemical compounds are used in paint products as pigments, extenders, binders, solvents, and additives. Azo pigments that contain 3,3′-dichlorobenzidine are common, although free aromatic amines are not present in significant quantities. Asbestos was used as a filler until the early 1990s. The main organic solvents used in paints are toluene, xylene, aliphatic compounds, ketones, alcohols, esters, and glycol ethers. Nowadays, solvent-based paints contain much less solvent – and less hazardous solvents – than a decade ago. In some cases the solvent content is reduced to such an extent that the amounts of volatile organic compounds (VOCs) released from the paint are similar to those from water-based paints.

Several hazardous chemicals (including benzene, phthalates (plasticizers), chromium, and lead oxides) have been reduced or replaced in paint in some countries, although they are still used elsewhere. The increasing use of water-based paints and powder coatings has promoted this trend. New formulations contain lower-toxicity solvents, biocides, and neutralizing agents, such as amines.

1.1.1 Pigments and fillers

Paints may contain pigments, dyes and fillers. Hazardous pigments and fillers, especially chromate- or lead-based substances, are increasingly replaced by other compounds, even though many of the new products have a lower performance in corrosion protection or mechanical properties of the paint layers. Many paints for industrial or individual use are lead- and chromate-free, especially in western Europe, but the situation is extremely diverse and complex across countries worldwide.

Table 1.1 Main substances (and classes of substances) to which workers may be exposed in the painting trades[a]

Material	Principal uses or sources of emissions	Agent evaluated	Evaluation
Acrylates (e.g. ethyl acrylate, methyl methacrylate)	Acrylic resins, ultraviolet curing paints	Ethyl acrylate Acrylic acid Methyl acrylate Methyl methacrylate	2B 3 3 3
Acrylic resins	Binders	As above	
Alcohols, aliphatic (e.g. methanol, isopropanol, *n*-butanol)	Solvents (lacquers), paint removers	Methanol Ethanol Isopropanol *n*-Butanol	– – 3 –
Alkalis (e.g. sodium hydroxide, potassium hydroxide)	Paint removers	–	–
Alkyd resins	Binders	–	–
Aluminium, powder	Pigment	–	–
Amides, aliphatic (e.g. dimethylformamide)	Solvents	Dimethylformamide	2A
Amines (mono), aliphatic (e.g. diethylamine) and alkanolamines (e.g. 2-amino-2-methyl-1-propanol)	Water-based paints	Triethanolamine	3
Amines (poly), aliphatic (e.g. diethylenetriamine)	Curing agents (epoxy resins)	–	–
Amines, aromatic (e.g. *meta*-phenylenediamine, 4,4-methylenedianiline)	Curing agents (epoxy resins)	*meta*-Phenylenediamine 4,4-Methylenedianiline	3 2B
Amino resins (e.g. urea-formaldehyde resins, melamine-formaldehyde resins)	Binders	See formaldehyde	
Ammonia	Water-based paints	–	–
Anhydrides, organic (e.g. maleic anhydride, phthalic anhydride, trimellitic anhydride)	Alkyd resin synthesis, curing agents (epoxy resins)	Succinic anhydride	3
Antimony compounds (e.g. antimony trioxide)	Pigments, fire retardant pigments	Antimony trioxide Antimony trisulfide	2B 3
Arsenic compounds (e.g. copper aceto-arsenate)	Antifouling agents	–	1
Asbestos	Filler, spackling and taping compounds, talc	Asbestos	1
Barium compounds (e.g. barium sulfate, barium carbonate)	Pigments	–	–
Benzoyl peroxide	Catalyst	Benzoyl peroxide	3
Bisphenol A	Epoxy resins		3
Cadmium compounds (e.g. cadmium sulfide, cadmium sulfoselenide)	Pigments	Cadmium and cadmium compounds	1

Table 1.1 (continued)

Material	Principal uses or sources of emissions	Agent evaluated	Evaluation
Calcium compounds (e.g. calcium sulfate, calcium carbonate)	Fillers	–	–
Camphor	Plasticizer	–	–
Carbon black	Pigment	Carbon black	2B
Cellulose ester resins (e.g. cellulose nitrate, cellulose acetate)	Binders	–	–
Chloracetamide	Fungicide (water-based paints)	–	–
Chlorofluorocarbons	Spray-can paint propellants	Chlorofluoromethane	3
Chromium and chromium compounds (e.g. chromic oxide, chromates)	Pigments	Chromium (III) compounds Chromium (VI) compounds Chromium, metallic	3 1 3
Clays (e.g. bentonite)	Fillers	–	–
Coal-tar and asphalt	Special waterproof coatings (ships, tanks, pipes)	Coal tar Coal-tar pitches Bitumen extracts Bitumen refined	1 1 2B 3
Cobalt compounds	Pigments, driers	Cobalt and cobalt compounds Cobalt, metallic	2B 2B
Copper and copper compounds (e.g. bronze powder, cuprous oxide)	Pigments, antifouling agents	–	–
Dyes and pigments, organic (e.g. aromatic azo dyes, phthalocyanines, rhodamine)	Pigments	CI Basic Red 9 } Magenta production } 2-naphthylamine } 4-aminobiphenyl } Auramine production } Benzidine } Benzidine-based dyes }	2B 1 1 1 1 1 1
Epichlorohydrin	Epoxy resins	Epichlorohydrin	2A
Epoxy resin	Binders	–	–
Esters, aliphatic (e.g. ethyl acetate, isopropyl acetate)	Solvents	–	–
Ethers, aliphatic (e.g. isopropyl ether, tetrahydrofuran) and glycol ethers (e.g. methyl cellosolve)	Solvents	2-Butoxyethanol 1-*tert*-Butoxypropan-2-ol	3 3

Table 1.1 (continued)

Material	Principal uses or sources of emissions	Agent evaluated	Evaluation
Formaldehyde	Amino resin varnishes, biocide (water-based paints)	Formaldehyde	1
Gasoline	Solvent	Gasoline	2B
Glycidyl ethers (e.g. *n*-butyl glycidyl ether and bisphenol A diglycidyl ether)	Epoxy resin diluents and constituents	Phenylglycidyl ether Triethylene glycol diglycidyl ether Bisphenol A diglycidyl ether	2B 3 3
Glycols (e.g. ethylene glycol)	Polyester resins, water-based paints	–	–
Hydrocarbons, aliphatic (e.g. hexanes, heptanes)	Solvents (naphthas, white spirits)	–	–
Hydrocarbons, aromatic (e.g. benzene, toluene, xylenes, trimethylbenzene)	Solvents (naphthas, white spirits), paint removers	Benzene Toluene Xylene Ethylbenzene	1 3 3 2B
Hydrocarbons, chlorinated (e.g. dichloromethane, 1,1,1-trichloroethane, carbon tetrachloride, trichloroethylene)	Solvents, paint removers, metal degreasers	Dichloromethane 1,1,1-Trichloroethane Carbon tetrachloride Trichloroethylene	2B 3 2B 2A
Hydrochloric acid (hydrogen chloride)	Catalyst (amino resins)	–	3
Iron compounds (e.g. iron oxides, ferric ferrocyanide)	Pigments	Ferric oxide	3
Isocyanates (e.g. 1,6-hexamethylene diisocyanate, toluene diisocyanate)	Two-component polyurethane resins	Toluene diisocyanate	2B
Isothiazolones (e.g. 1,2-benzisothiazolin-3-one)	Biocides in tinned foods	–	–
Kerosene	Solvent	Jet fuel	3
Ketones, aliphatic (e.g. acetone, methyl ethyl ketone, cyclohexanone, isophorone, diacetone alcohol)	Solvents, lacquers, paint removers	Cyclohexanone	3
Lead compounds (e.g. lead chromate, lead oxides, basic lead carbonate, lead naphthenate)	Primers, pigments, driers	Lead Lead compounds, inorganic	2B 2A
Magnesium compounds (e.g. magnesium carbonate)	Fillers	–	–
Manganese naphthenate	Drier	–	–
Mercury compounds (e.g. mercuric oxide, phenyl mercuric acetate)	Fungicides (water-based paints)	Mercury and inorganic mercury compounds	3
Methyl cellulose	Thickener (water-based paints)	–	–
Mica	Filler	–	–
Molybdenum compounds (e.g. lead molybdate)	Pigments	–	–
Nickel, metal powder	Pigment	Nickel compounds Nickel, metallic and alloys	1 2B 2B

Table 1.1 (continued)

Material	Principal uses or sources of emissions	Agent evaluated	Evaluation
Nitroparaffins (e.g. nitroethane, 2-nitropropane)	Solvents	2-Nitropropane	2B
Oils, vegetable (e.g. linseed oil, tung oil)	Binders	–	–
Oximes (e.g. methyl ethyl ketoxime)	Anti-oxidants, anti-skinning agents	–	–
Petroleum solvents (e.g. Stoddard solvent, VM & P naphtha)	Solvents, paint removers	Petroleum solvents	3
Phenol	Phenol-formaldehyde resins, paint remover (formerly)	Phenol	3
Phenol-formaldehyde resins	Binders	See phenol, and formaldehyde	
Phenols, chlorinated (e.g. pentachlorophenol)	Fungicides (water-based paints)	Polychlorophenols and their sodium salts Pentachlorophenol	2B 2B
Phosphates, organic (e.g. tricresyl-*ortho*-phosphate, tributyl phosphate)	Plasticizers	–	–
Phthalate esters (e.g. dibutyl phthalate, dioctyl phthalate	Plasticizers	Di(2-ethylhexyl)phthalate Butyl benzyl phthalate	3 3
Polychlorinated biphenyls	Plasticizers	Polychlorinated biphenyls	2A
Polycyclic aromatic hydrocarbons	Special waterproof coatings (ships, tanks, pipes)	Selected polycyclic aromatic hydrocarbons	–[b]
Polyester resins	Binders	–	–
Polyurethane resins	Binders	Polyurethane foams	3
Polyvinylacetate resins	Binders	Polyvinyl acetate	3
Pyrolysis fumes	Removal of paint by burning; heat-curing operations	–	–
Rosin	Binder	–	–
Rubber, synthetic (e.g. butyl rubber, styrene-butadiene rubber)	Binders (special paints, water-based paints)	Rubber industry	1
Shellac resin	Binder	–	–
Silica, amorphous (e.g. diatomaceous earth)	Filler	Silica, amorphous	3
Silica, crystalline (e.g. quartz)	Filler, sand-blasting operation	Silica, crystalline	1
Silicates (e.g. sodium silicate, aluminium silicate)	Fillers	–	–
Stearates (e.g. aluminium stearates, zinc stearates)	Soaps, flattening agents	–	–
Strontium compounds (e.g. strontium chromate, strontium sulfide)	Pigments	Strontium chromate see chromium and chromium compounds	
Styrene	Polyester resins	Styrene	2B

Table 1.1 (continued)

Material	Principal uses or sources of emissions	Agent evaluated	Evaluation
Styrene oxide	Diluent (epoxy resins)	Styrene-7,8-oxide	2A
Sulfuric acid	Metal cleaner	–	–
Talc	Filler	Talc containing asbestiform fibres Talc, not containing asbestiform fibres	1 3
Tin, metal powder	Lacquers (tinplate containers)	–	–
Tin, organic compounds (e.g. tri-*n*-butyltin oxide, dibutyltin laurate)	Antifouling agents, catalysts	–	–
Titanium dioxide	Pigment	Titanium dioxide	2B
para-Toluenesulfonic acid	Catalyst (amino resins)	–	–
Turpentine	Solvent	–	–
Vinyl acetate	Polyvinylacetate resins	Vinyl acetate Vinyl chloride – vinyl acetate copolymers	2B 3
Zinc and compounds (e.g. zinc metal powder, zinc oxide, zinc chromate)	Pigments, catalysts, bodying agents	Zinc chromate see chromium and chromium compounds	

[a] Updated from IARC (1989)

[b] Groups 1–3; see (IARC, 2010d) for details

–, not evaluated by IARC

(a) Pigments

Pigments can be classified as inorganic and organic (Bentley & Turner, 1998; Stoye & Freitag, 1998; Brock *et al.*, 2000; Smith, 2002) and they are generally added in considerable proportion (3–60% by weight) to paint formulations to provide colour, opacity, and sheen. Pigments also affect the viscosity, flow, toughness, durability, and other physical or chemical characteristics of the coating (e.g. corrosion-protective properties). The diameter of pigment particles is generally less than 3 μm, but for special performance the particle size can be up to 15 or 20 μm (Oyarzún, 2000).

Today the most common pigment employed in paint is the white pigment titanium dioxide, TiO_2 (IARC, 2010b). It occurs in two different crystal forms – rutile and anatase – with distinct colour properties. The rutile crystal structure has an almost 25% greater opacity than the anatase form. Because of its chemical inertness, extreme whiteness, excellent covering power and lack of toxicity compared with white lead, titanium dioxide is the predominant component in the manufacture of white paint, representing 90% of all pigments on the market worldwide. The most important black pigment in paints is carbon black (micro-crystalline carbon, 10–40 nm, graphite-similar), which belongs to the inorganic pigments (Buxbaum & Pfaff, 2005; IARC, 2010b).

In the 1960s, there were probably more than 200 different organic pigments used in paints. At the time, azo pigments such as Benzidine Yellow were considered to have relatively low toxicity, and were widely used. These pigments have relatively low solubility, and although they are based on the aromatic amine 3,3′-dichlorobenzidine, the free amine is not readily bioavailable. Three 3,3′-dichlorobenzidine-based paint pigments were commonly used in architectural finishes in the mid-to-late 1960s. Benzidine was used as the basis for the paint-pigment pyrazolone maroon (IARC, 2010c). The free aromatic amines used in the synthesis of azo pigments can be found in trace amounts as impurities. The aromatic amines 4-aminobiphenyl, benzidine, 2-naphthylamine and 2-methyl-4-chloroaniline [4-chloro-*ortho*-toluidine] have been found in azo pigments (IARC, 2010c).

(b) Dyes

Dyes, unlike pigments, are soluble in paint medium. Dyes are used only in a few instances or products, because they provide much less long-term stability against light and other influences. Examples of use of dyes are in transparent wood stains (Zollinger & Iqbal, 2003), and as transparent colourants in automobile coatings (Streitberger & Dössel, 2008).

1.1.2 Binders (resins)

The ‘vehicle’ part of paints contains components collectively termed ‘binders’ or film formers. Almost all binders in modern paint films are composed of polymer materials such as resins and drying oils, whose main functions are to provide film hardness, gloss, and surface adhesion, as well as resistance of the film to weather influences, air pollutants that stimulate corrosion through the atmosphere, acids, alkalis, and other agents (Stoye & Freitag, 1998; Brock *et al.*, 2000; Müller & Poth, 2006). A large variety of natural and synthetic binders or resins, mostly synthetic, have been used in paints.

(a) Natural resins and oils

Shellac and insect exudations are natural oleoresins that have been used in paints for centuries. Another useful natural resin is rosin (colophony), which is obtained as a residue after distilling pine oleoresin for the production of turpentine. Vegetable and fish oils have long been used as binders in traditional paints and varnishes. White linseed oil has been the most important oil in standard exterior paints, despite its relatively slow drying rate. Other important

oils include castor oil, tall oil, soya-bean oil, coconut oil, cottonseed oil, tung oil and various fish oils (Brock *et al.*, 2000).

(b) Synthetic resins

A wide variety of synthetic resins have been commercially available since the early 1900s. Those that have been most frequently used in paints, varnishes and lacquers include cellulose-based resins, phenolic, alkyd, vinyl, acrylic and methacrylic resins, polyester and polyurethane resins, chlorinated rubber derivatives, styrene-butadiene, and silicone oils. Mixtures of synthetic resins provide characteristic properties that cannot be obtained from a single resin. While the amount of resin in paint varies, concentrations of 20–60% by weight are not uncommon.

1.1.3 Solvents

Since the early 1900s, the number of solvents in paints has increased considerably to encompass a broad range of petroleum and coal-tar distillates, alcohols, esters, ketones, glycols, synthetic glycol ethers and esters (mainly ethylene-derived), and propylene glycol derivatives, as well as a large variety of mixtures of these chemical classes. The choice of solvent depends on properties such as adequate polarity, possibility of hydrogen-bonding, volatility and vapour pressure, cooling effects during atomization, surface tension, viscosity, flash point, flammability and – more and more importantly – lack of adverse physiological effects. In western Europe, derivatives of ethylene-glycol monoethyl-ether (ethyl glycol) have been removed from many formulations since the 1980s. Since 1990, the use of styrene has been restricted by legislation in the European Union. Water-based coatings generally require water-soluble solvents such as glycol ethers (butyl glycol), *n*-butanol or, less commonly, *N*-methyl-pyrrolidone.

1.1.4 Additives

Additives are defined as chemicals that have a specific function or impart a special property to paints or coatings. They are present at low concentrations (generally 0.1–5% by weight) and include surfactants and dispersing agents, driers, rheological agents, plasticizers, biocides, anti-skinning agents, antifoam agents (de-foamers), corrosion inhibitors, light (UV) stabilizers and catalysts (Stoye & Freitag, 1998; Brock *et al.*, 2000). Many additives are adapted to the new paint systems by modification of existing products rather than by the development of new ones.

(a) Surfactants and dispersing additives

Anionic, cationic, amphoteric or non-ionic surfactants are used in paints as pigment dispersants (in both non-aqueous and aqueous systems), emulsifying agents, protective colloids, wetting agents and antifoaming agents. Dispersants employed in non-aqueous paints include lecithin, zinc or calcium naphthenate or octoate, oleates, oleic acid, polyurethanes, polyamides and other chemicals. Dispersants in aqueous paints include polyphosphates, pyrophosphates, salts of arylalkyl-sulfonic acids and salts of polycarboxylic acids, e.g. polyacrylic acid (Oyarzún, 2000; Müller & Poth, 2006). Surfactants used in water-based paints include aluminium stearate, cellulose ethers, polydimethyl siloxanes, polyethylene, alkali metal phosphates and sodium dioctyl sulfosuccinate.

A variety of other surface-active agents are added to paints to control flow, levelling, sagging, settling and viscosity. These include hydrogenated castor oils, lecithin, metallic soaps (e.g. linoleates, palmitates and stearates), treated montmorillonite clays, peptized oil gels, polyol esters, siloxan-polyester resins, silicas, and soap solutions (Brock *et al.*, 2000; Müller & Poth, 2006). Mineral oils and specially modified siloxanes are used as antifoaming agents.

(b) Driers

Driers (siccatives) used in solvent-based and water-based paints containing unsaturated polymers are principally metal salts – lead, calcium, cobalt, manganese, zirconium, vanadium, barium, zinc, cerium and lanthanum – of naphthenic acid, tall-oil acid, 2-ethylhexanolic acid and neodecanoic acid, generally at concentrations ranging from 0.3 to 0.8% (Brock *et al.*, 2000). Cobalt-based driers are the most commonly used commercially as active catalysts in both air-drying and heat-cure systems. Other metal-containing siccatives serve as auxiliary driers and are generally used in combination with cobalt- and manganese-based driers. Lead-containing products were at one time the major auxiliary driers, but legislation that limits the amount of lead used in coatings has practically eliminated its use during the period 1990–2000 (IARC, 2006). The most suitable replacements for lead are reported to be zirconium, calcium and cobalt-zirconium compounds (Müller & Poth, 2006).

(c) Rheological additives

The rheological properties of a coating material influence its optimal performance during application ('good flow without dripping') as well as its storage life. Water-soluble hydrophilic colloids that are used as rheological additives include agents such as gum arabic, gum tragacanth, starch, sodium alginate, methyl cellulose, hydroxyethyl cellulose, polyvinyl alcohol, ammonium caseinate, polyurethane derivates, and polyacrylates. Acrylate salts, casein and cellulose-derived compounds are widely used in acrylic paints, while the major thickeners for styrene–butadiene paints are alkali-soluble proteins (e.g. soy-bean proteins). Methyl cellulose and hydroxyethyl cellulose are common thickeners for polyvinyl acetate paints (Brock *et al.*, 2000).

Agents used in water-based and solvent-based paints as rheological additives not derived from cellulose include maleic anhydride copolymers, mineral fillers such as colloidal attapulgite (IARC, 1997), treated magnesium montmorillonite clays, pyrogenic silicic acid (SiO_2), natural products (e.g. alginic acid, casein and soya-bean protein), polyacrylamides, polyacrylic acid salts and acid-containing cross-linked acrylic emulsion copolymers (Brock *et al.*, 2000).

(d) Plasticizers

Plasticizers are generally added in quantities of up to about 2% by weight and include dibutyl-, diethyl-, diethylhexyl- and dioctylphthalates. To a lesser extent, plasticizers also contain the low molecular-weight esters of adipic and sebacic acid, tributyl phosphate, and castor oil. Polyester resins, including maleic residues, sulfonamides, tri-*ortho*-cresyl phosphate and chlorinated diphenyls, are used occasionally (Stoye & Freitag, 1998).

(e) Biocides (fungicides, preservatives, and mildew killers)

Water-based paints contain organic substances and represent an ideal growth medium for fungi, algae and bacteria. With the reduced content of residual monomers and organic solvents (which often have anti-microbial action), there is a greater risk for microbial contamination in the new formulations. The growth of microorganisms in the coating or subsequently in the film can be reduced or even prevented by adding chemical biocides to the paint in concentrations below 1% by weight (Brock *et al.*, 2000; Schwartz & Baumstark, 2001).

In-can preservatives protect the paint against microbial growth during production, transportation and storage. Substances commonly used for this purpose are formaldehyde – now less and less common – and its reaction products with alcohols, amines and amides, as well as *N*,*S*-heterocyclic compounds such as isothiazolinones and

chloroacetamide (Brock *et al.*, 2000). *In-film preservatives*, also encompassing *antifouling additives* in marine paints, protect the applied paint against attack by bacteria, moulds, algae or mosses. Substances currently in use for this purpose include several *S*- and *N*-containing chemicals, cyclic compounds such as dithiocarbamates, thiophthalimide derivates, benzimidazole derivates and trialkyl compounds, as well as ecologically harmful substances such as organic mercury compounds (Brock *et al.*, 2000).

(f) Anti-skinning agents

Anti-skinning agents are added to paints to retard the formation of skin on the surface of the liquid coating, in either closed or open cans, without delaying the drying of the product. The principal anti-skinning agents are oximes (e.g. methyl ethyl ketoxime, butyraldoxime, cyclohexanone oxime) and phenol derivatives (methoxyphenol, *ortho*-aminophenol, poly-hydroxyphenol). Small quantities of cresols, guaiacol, hydroquinone (IARC, 1999), isobutoxysafrol and lignocol have also been used as anti-skinning agents.

(g) Corrosion inhibitors

Corrosion inhibitors can be divided into inorganic pigments and organic inhibitors (Brock *et al.*, 2000). Red lead and chromate-containing pigments are both chemically and electrochemically active. Pigments containing red lead are still used in heavy-duty anti- corrosion systems, because they possess excellent protection properties. Some zinc chromates are still essential for the protection of aluminium on aircraft. Lead- and chromate-containing anti-corrosion pigments are increasingly being substituted by phosphates (zinc, chromium(III), aluminium, calcium and magnesium phosphates). Zinc-dust primers are widely used in the protection of steel structures. The synthetic micaceous iron-oxide pigment haematite (Fe_2O_3) acts via a physical mechanism, mainly by the barrier effect of its crystal-lattice structure (platelets). The most important compound in the group of organic inhibitors is the zinc salt of 5-nitrophthalic acid.

(h) Asbestos

In the early twentieth century, asbestos was used as a filler to improve the technical properties of paints, particularly those used in shipyards and on bridges. The paints may have contained up to about 20% asbestos by weight. Usage decreased after about 1950, although special textured paints or coatings continued to be widely used in home decoration until the early 1990s. These paints contained approximately 5% chrysotile asbestos by weight (Williams *et al.*, 2007).

(i) Nanoparticles

The use of 0.5–5% (w/w) nanoparticles (10–100 nm) remarkably improves the properties of paint layers in terms of scratch resistance, hardness, gloss, weather stability, and cross-linking and hardening properties. Nanoparticles are present as single particles only at the time of manufacturing. They increase in effective size by agglomeration and by absorption of polymers and surface-active agents onto their surface. During drying of the paint, the particles continue to agglomerate and are incorporated irreversibly into the polymer matrix.

1.2 Human exposure

Workers in the painting industry are potentially exposed to the chemicals found in paint products during their application and removal. Exposure to dichloromethane occurs during paint stripping from wood and metal surfaces. Diisocyanate is present in some binders and is released during painting. Silica is used in the preparation of surfaces before painting. As bystanders during construction or demolition activities, painters may also be exposed to asbestos or crystalline silica. During the

application of paint, workers are exposed primarily to solvents, whereas the mechanical removal of paint mainly leads to exposure to pigments and fillers. In the past, exposure to hazardous substances frequently exceeded current occupational exposure limits, but exposure levels have generally decreased over time.

Exposure, both by inhalation and via skin contact, occurs specifically in operations that involve manual handling during preparation of the paint, such as weighing ingredients (pigments, extenders, resins, additives), loading them into mixing equipment, adding solvents to mills, and cleaning equipment (mixers, mills, reactors, kettles, tanks, filters). Additional exposure to solvents occurs during thinning, tinting and shading, during filling operations, and during the filtering of varnishes. The cooking of varnishes may produce emissions of various aldehydes such as acrolein, of phenol, ketones, glycerine and fatty acids as well as dusts or vapours of maleic, phthalic and fumaric anhydrides during the loading of kettles. The production of powder coatings can be associated with significant exposure to dust from resin powders, pigments, curing agents and other additives. In the manufacture of radiation-curable coatings, exposures may occur to monomers such as ethyl acrylate, other acrylates, and photo-initiators. While inhalation and cutaneous contact are the major routes of exposure, ingestion related to personal work habits constitutes another potential route of entry.

Bio-monitoring of workers exposed to paints has shown elevated levels of paint compounds or their metabolites in blood and urine. Appropriate selection and use of personal protective equipment can substantially reduce uptake, although painters do not generally wear respirators or gloves.

The main substances to which workers may be exposed are listed in Table 1.1. Quantitative studies of occupational exposure in the major painting trades are summarized in IARC (2010a).

As indicated above, the use of 0.5–5% (w/w) nanoparticles (10–100 nm) remarkably improves several properties of paint. Because these particles agglomerate and become incorporated irreversibly into the polymer matrix, painters are not exposed to single nanoparticles as such. Since nanoparticles are made by special manufacturers and sold as aqueous or solvent-based slurry because of their strong potential for agglomeration, workers in paint manufacture do not come into contact with nanoparticles (Aitken *et al.*, 2006).

2. Cancer in Humans

Occupational exposure as a painter was classified as a Group-1 carcinogen in *IARC Monograph* Volume 47 (IARC, 1989), based on an increased risk for lung cancer, and reaffirmed in *Monograph* Volume 98 (IARC, 2010a), based also on increased risks for mesothelioma and bladder cancer. The recent Working Group noted that there was *limited evidence*, based primarily on studies of maternal exposure, that painting is associated with childhood leukaemia. The epidemiological evidence on occupational exposure as a painter did not allow identification of the specific carcinogenic agent in paint.

2.1 Cancer of the lung

2.1.1 Cohort studies

Eighteen independent cohort studies of painters – excluding reports with substantial population overlap – have investigated the association between occupation as a painter and lung cancer (OPCS, 1958, 1972, 1979, 1986, 1996; Guralnick, 1963; Dunn & Weir, 1965; Menck & Henderson, 1976; Whorton *et al.*, 1983; Dubrow & Wegman, 1984; Gubéran *et al.*, 1989; Hrubec *et al.*, 1995; Alexander *et al.*, 1996; van Loon *et al.*, 1997; Boice *et al.*, 1999; Steenland & Palu,

1999; Pronk *et al.*, 2009; Pukkala *et al.*, 2009; see Table 2.1, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-30-Table2.1.pdf). Overall, these studies have shown a significantly increased incidence or mortality from lung cancer, with a magnitude of effect that was relatively consistent between studies. Several of these studies were adjusted for tobacco smoking (Dunn & Weir, 1965; Hrubec *et al.*, 1995; van Loon *et al.*, 1997; Pronk *et al.*, 2009).

2.1.2 Case–control studies

Thirty independent case–control studies of lung cancer that reported on the association with occupation as a painter demonstrated relatively consistent increased risks for lung cancer (generally ranging between 1.10 and 2.70) (Wynder & Graham, 1951; Breslow *et al.*, 1954; Viadana *et al.*, 1976; Williams *et al.*, 1977; Milne *et al.*, 1983; Kjuus *et al.*, 1986; Lerchen *et al.*, 1987; Levin *et al.*, 1988; Ronco *et al.*, 1988; Vineis *et al.*, 1988; Zahm *et al.*, 1989; Bethwaite *et al.*, 1990; Burns & Swanson, 1991b; Siemiatycki, 1991; Morabia *et al.*, 1992; Notani *et al.*, 1993; Wu-Williams *et al.*, 1993; Finkelstein, 1995; De Stefani *et al.*, 1996, 2005; Muscat *et al.*, 1998; Wünsch-Filho *et al.*, 1998; Jahn *et al.*, 1999; Pezzotto & Poletto, 1999; Brüske-Hohlfeld *et al.*, 2000; Matos *et al.*, 2000; Pohlabeln *et al.*, 2000; Bouchardy *et al.*, 2002; Richiardi *et al.*, 2004; Baccarelli *et al.*, 2005; Zeka *et al.*, 2006; see Table 2.2, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-30-Table2.2.pdf). Twenty-seven of these studies showed positive associations (with statistically significant or borderline significant results in 15 studies) and three studies had odds ratios below 1, but not statistically significant (Morabia *et al.*, 1992; Wünsch-Filho *et al.*, 1998; Baccarelli *et al.*, 2005). All except six studies adjusted for tobacco smoking (Wynder & Graham, 1951; Breslow *et al.*, 1954; Milne *et al.*, 1983; Bethwaite *et al.*, 1990; Finkelstein, 1995; Bouchardy *et al.*, 2002).

2.1.3 Meta-analyses

Two comprehensive meta-analyses of the epidemiological literature on painters and lung cancer have been published since the previous *Monograph* (IARC, 2010a).

One meta-analysis included 39 studies (23 case–control and 16 cohort studies) (Bachand *et al.*, 2010). Summary risk estimates were derived and sensitivity analysis performed to evaluate smoking, socioeconomic status and exposure variables. Overall summary risk estimates for lung cancer were 1.29 (95%CI: 1.10–1.51) for case–control studies, and 1.22 (95%CI: 1.16–1.29) and 1.36 (95%CI: 1.34–1.41) for cohort studies, respectively. The 20 case–control studies that adjusted for smoking gave a summary relative risk (RR) of 1.32 (95%CI: 1.10–1.59). Only one of the cohort studies included in the meta-analysis adjusted for smoking and an external adjustment for smoking demonstrated an increased mortality from lung cancer in painters. [The Working Group noted that the methods for external adjustment for smoking were not clearly described.]

Guha *et al.* (2010a) performed a meta-analysis to assess the association between occupation as a painter and lung cancer. Forty-seven independent studies (18 cohort and 29 case–control studies) were included. Overall, a statistically significant increased risk for lung cancer was observed (meta-relative risk, 1.35; 95%CI: 1.29–1.41). When the analysis was restricted to smoking-adjusted estimates, the summary relative risk was 1.35 (95%CI: 1.21–1.51). On the basis of data from three studies that investigated risk in never smokers, the meta-relative risk was 2.00 (95%CI: 1.09–3.67). The increased risk persisted when the analysis was restricted to studies that adjusted for other occupational exposures (RR 1.57; 95%CI: 1.21–2.04). A duration–response relationship was also identified: the meta-relative risk for < 10 years of exposure was 1.13 (95%CI: 0.77–1.65) and 1.95 (95%CI: 1.26–3.02) for > 10

years of exposure; similarly, the meta-RR was 1.37 (95%CI: 0.89–2.13) for < 20 years of exposure and 2.00 (95%CI: 1.01–3.92) for > 20 years (the reference category was no exposure).

2.2 Mesothelioma

The association between occupation as a painter and mesothelioma was investigated in four cohort studies (Malker *et al.*, 1990; Peto *et al.*, 1995; Brown *et al.*, 2002; Pukkala *et al.*, 2009) and two case–control studies (Teschke *et al.*, 1997a; Pan *et al.*, 2005). An increase in mortality from mesothelioma was observed in each of the four cohort studies, with borderline significant relative risks ranging from 1.31 to 1.70. The two case–control studies on mesothelioma also showed an increased risk (OR, 4.5; 95%CI: 1.0–23.7; 6 exposed cases; and OR, 2.6; 95%CI: 1.3–5.3; 31 exposed cases, respectively) for persons ever employed as painters.

[The Working Group noted that it is improbable that the presence of asbestos would completely explain the excess of lung cancer; if this had been the case, a more pronounced excess of mesothelioma would have been observed.]

2.3 Cancer of the urinary bladder

2.3.1 Cohort studies

The association between occupational exposure as a painter and urinary bladder cancer was investigated in 11 cohort studies, excluding reports with substantial population overlap (OPCS, 1958, 1972, 1979, 1986; Guralnick, 1963; Whorton *et al.*, 1983; Gubéran *et al.*, 1989; Hrubec *et al.*, 1995; Steenland & Palu, 1999; Zeegers *et al.*, 2001; Pukkala *et al.*, 2009) see Table 2.3, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-30-Table2.3.pdf). Two of the cohort and record-linkage studies controlled for tobacco smoking (Hrubec *et al.*, 1995; Zeegers *et al.*, 2001). Overall these studies showed consistent increases in incidence of or mortality from urinary bladder cancer.

2.3.2 Case–control studies

Several case–control studies have investigated the association between urinary bladder cancer and occupation as a painter. Thirty-one independent case–control studies were identified (Wynder *et al.*, 1963; Cole *et al.*, 1972; Decouflé *et al.*, 1977; Williams *et al.*, 1977; Howe *et al.*, 1980; Schoenberg *et al.*, 1984; Morrison *et al.*, 1985; Coggon *et al.*, 1986; Iscovich *et al.*, 1987; Risch *et al.*, 1988; Silverman *et al.*, 1989a, b; Bethwaite *et al.*, 1990; La Vecchia *et al.*, 1990; Burns & Swanson, 1991a; Barbone *et al.*, 1994; Teschke *et al.*, 1997b; Golka *et al.*, 1999, 2008; Bouchardy *et al.*, 2002; Pelucchi *et al.*, 2002; Zheng *et al.*, 2002; Kogevinas *et al.*, 2003; Colt *et al.*, 2004; Gaertner *et al.*, 2004; Band *et al.*, 2005; Reulen *et al.*, 2007; Dryson *et al.*, 2008; Ramanakumar *et al.*, 2008; Kobrosly *et al.*, 2009 ; see Table 2.4, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-30-Table2.4.pdf). Three studies showed no association (Howe *et al.*, 1980; Colt *et al.*, 2004; Ramanakurmar *et al.*, 2007) and six reported odds ratios less than 1.0, although none were statistically significant (Morrison *et al.*, 1985 – the United Kingdom and Japanese populations; Williams *et al.*, 1977; Coggon *et al.*, 1986; Iscovich *et al.*, 1987; Gaertner *et al.*, 2004). Twenty-two case–control studies demonstrated an increased risk for bladder cancer associated with occupation as a painter. Although the results of three studies were statistically significant (Silverman *et al.*, 1989a, b; Golka *et al.*, 1999; Band *et al.*, 2005) and those of six studies were of borderline statistical significance (Wynder *et al.*, 1963; Decouflé *et al.*, 1977; Risch *et al.*, 1988; Bethwaite *et al.*, 1990; Zheng *et al.*, 2002; Kogevinas *et al.*, 2003), all studies that showed an increased risk for bladder cancer among painters were relatively consistent in the magnitude of the effect reported.

2.3.3 Meta-analyses

Five meta-analyses have also demonstrated a significant or borderline significant increased incidence of or mortality from bladder cancer among persons occupationally exposed as a painter (Yamaguchi *et al.*, 1991; Chen & Seaton, 1998; Bosetti *et al.*, 2005; Bachand *et al.*, 2010; Guha *et al.*, 2010b). The two most recent meta-analyses are highlighted below.

The meta-analysis by Bachand *et al.* (2010) included 40 case–control and 11 cohort studies. Overall bladder-cancer summary risk estimates were 1.28 (95%CI: 1.17–1.41) for case–control and 1.14 (95%CI: 1.06–1.22) and 1.27 (95%CI: 1.16–1.38) for cohort morbidity and mortality studies, respectively. The 33 case–control studies that adjusted for smoking gave a summary RR of 1.30 (95%CI: 1.17–1.44). None of the cohort studies adjusted for smoking. When an external adjustment for smoking was applied to the meta-analysis of the cohort studies, an increased incidence of and mortality from bladder cancer persisted. [The Working Group noted that the methods for the external adjustment for smoking were not clearly described.]

A separate meta-analysis of 41 independent studies (11 cohort and record-linkage studies and 30 case–control studies) conducted by Guha *et al.* (2010b) showed a meta-relative risk of 1.25 (95%CI: 1.16–1.34). This association did not change significantly when the analysis was restricted to population-based studies or studies that adjusted for smoking and other potentially confounding occupational exposures. Furthermore, exposure-response analyses suggested that the risk increased with duration of employment: those exposed < 10 years had a lower risk (meta-RR, 1.41; 95%CI: 1.00–2.01) than those exposed > 10 years (meta-RR, 1.81; 95%CI: 1.20–2.75) (reference category was no exposure).

2.4 Childhood leukaemia

2.4.1 Maternal exposure

The association between maternal exposure during painting and childhood leukaemia was evaluated in nine population-based case–control studies (van Steensel-Moll *et al.*, 1985; Lowengart *et al.*, 1987; Buckley *et al.*, 1989; Shu *et al.*, 1999, 2004; Schuz *et al.*, 2000; Freedman *et al.*, 2001; Alderton *et al.*, 2006; Scélo *et al.*, 2009; see Table 2.5, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-30-Table2.5.pdf). Most of the studies presented results for the combined exposure to paints, stains, and lacquers. Shu *et al.* (2004) presented a case-only analysis that examined whether maternal exposure to paint was associated with development of mutation in the *RAS* gene in acute lymphoblastic leukaemia (ALL) cases compared with ALL cases without *RAS* mutation and, therefore, is not directly relevant to the discussion of whether maternal exposure during painting increases the risk for childhood leukaemia compared with healthy controls.

In five studies significant positive associations were found between maternal exposure during painting, either before or during pregnancy, and acute leukaemia (van Steensel-Moll *et al.*, 1985; Lowengart *et al.*, 1987), acute non-lymphoblastic leukaemia (ANLL) (Buckley *et al.*, 1989); and ALL (Shu *et al.*, 1999; Schuz *et al.*, 2000). All these studies controlled for age and/or sex, race, social class (measured through income, socioeconomic status, or degree of urbanization) or other variables. Additionally, borderline significant positive associations were found with ALL (Freedman *et al.*, 2001; Scélo *et al.*, 2009) and non-significantly elevated ORs for ALL and acute myeloid leukaemia (AML) (Alderton *et al.*, 2006). Furthermore, significant exposure-response relationships, according to duration of maternal exposure to paint, were observed in two studies (Buckley *et al.*, 1989; Shu *et al.*, 1999).

2.4.2 Paternal exposure

The association between paternal exposure during painting and childhood leukaemia was considered in 12 population-based case–control studies (Fabia & Thuy, 1974; Hakulinen *et al.*, 1976; Kwa & Fine, 1980; Hemminki *et al.*, 1981; Sanders *et al.*, 1981; Gold *et al.*, 1982; van Steensel-Moll *et al.*, 1985; Lowengart *et al.*, 1987; Buckley *et al.*, 1989; Shu *et al.*, 1999; Schuz *et al.*, 2000; McKinney *et al.*, 2003; (see Table 2.6, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-30-Table2.6.pdf). In three of the four case–control studies on ALL, non-significant positive associations were found (van Steensel-Moll *et al.*, 1985; Schuz *et al.*, 2000; McKinney *et al.*, 2003) and in the only case–control study of ANLL (Buckley *et al.*,1989) a significant, positive association was observed. Of the eight studies that considered combined leukaemia subtypes, positive associations were found in five (either significant or borderline significant) (Fabia & Thuy, 1974; Hemminki *et al.*, 1981; Gold *et al.*, 1982; Lowengart *et al.*, 1987; McKinney *et al.*, 2003), while there was no association in two studies (Kwa & Fine, 1980; Sanders *et al.*, 1981).

2.5 Lympho-haematopoietic cancers

The risk for lymphatic and haematopoietic cancers among painters was evaluated in 21 case–control studies (Persson *et al.*, 1989, 1993; Lindquist *et al.*, 1987; La Vecchia *et al.*, 1989; Bethwaite *et al.*, 1990; Heineman *et al.*, 1992; Scherr *et al.*, 1992; Blair *et al.*, 1993; Demers *et al.*, 1993; Mele *et al.*, 1994; Nordström *et al.*, 1997; Clavel *et al.*, 1998; Persson & Fredrikson, 1999; Blair *et al.*, 2001; Costantini *et al.*, 2001; Adegoke *et al.*, 2003; Dryver *et al.*, 2004; Kato *et al.*, 2005; Colt *et al.*, 2007; Ramanakumar *et al.*, 2008; Purdue *et al.*, 2009). Although increased risks were observed, the results were inconsistent and the data are inadequate to draw a conclusion about the association between occupation as a painter and the risk for lymphatic and haematopoietic cancers.

2.6 Other cancers

A few case–control studies of cancers of the upper aerodigestive tract (oral cavity, nose, pharynx, nasopharynx, larynx, and oesophagus), stomach, pancreas, liver, colon, rectum, kidney, brain, prostate, testis, ovary and breast, and of melanoma and soft–tissue sarcoma have been conducted among painters (Tarvainen *et al.*, 2008; IARC, 2010a). Results were inconclusive for all sites.

2.7 Synthesis

The Working Group reviewed a large body of epidemiological evidence evaluating the association between occupational exposure as a painter and the risk for lung cancer (30 case–control studies, 18 cohort studies), urinary bladder cancer (30 case–control studies, 11 cohort studies) and mesothelioma (2 case–control studies, 4 cohort studies). This evidence demonstrates that occupational exposure as a painter is causally associated with the risk for cancer of the lung and urinary bladder, and for mesothelioma. The Working Group noted that the magnitude of the effect was consistent across studies and the elevated risks persisted after controlling for other occupational exposures and for tobacco smoking. Increased risks for these cancers were also observed in never smokers and current non-smokers. Several studies that demonstrated significant positive duration-response relationships support this evaluation.

The Working Group noted that no particular agent could be identified from epidemiological studies as the specific cause of the excess of lung and urinary bladder cancers. It is improbable that the presence of asbestos in paint would completely explain the excess of lung cancer; if

this had been the case, a more pronounced excess of mesothelioma would have been observed. There is little information from epidemiological studies on the risk associated with the use of paint pigments that are known lung carcinogens, such as chromium or cadmium.

There is evidence suggesting a causal association between maternal exposure during painting and childhood leukaemia in the offspring. Although there were few studies and exposure assessments were relatively poor, all of the studies showed significant positive associations after adjusting for potential confounders such as age and/or sex, race and social class, although confounding or recall bias could not be ruled out.

The evidence is inconclusive for cancer at other sites.

3. Cancer in Experimental Animals

No data were available to the Working Group.

4. Other Relevant Data

The chemicals discussed below are common components of paints: benzene, toluene, chlorinated solvents (dichloromethane, trichloroethylene), xylenes, metals (cadmium, chromium, inorganic lead), styrene, PAHs, and aromatic azo dyes.

4.1 Toxicokinetics and metabolism

4.1.1 Solvents

(a) Aromatic hydrocarbons

The aromatic hydrocarbons present in paints (benzene, toluene, xylenes and styrene) are absorbed mainly through inhalation, although oral or dermal exposure could be important as well. They are metabolized primarily in the liver by oxidation, in a process catalysed mainly by the CYP2E1 enzyme:

(i) Benzene

The toxicokinetics of benzene is reviewed in the *Monograph* on Benzene in this volume.

(ii) Toluene

Toluene is metabolised to benzyl alcohol followed by oxidation to benzoic acids, which are excreted as conjugates with glycine or with UDP-glucuronate (ATSDR, 2000a).

(iii) Xylene

All three isomers of xylene are metabolised to methylbenzyl alcohol and conjugated with glycine to form methylhippuric acid. Aromatic hydroxylation of xylene to xylenol occurs to only a limited extent in humans. About 90% of the absorbed xylene is excreted in the urine as methylhippuric acid, and less than 2% as xylenol. Approximately 5% is eliminated unchanged in exhaled air (ATSDR, 2007b).

(b) Chlorinated solvents

(i) Dichloromethane

Dichloromethane (DCM) is absorbed mainly into the bloodstream after inhalation and is found in highest concentration in adipose tissue and liver. DCM can be metabolised by the cytochrome P450(CYP)-associated enzyme CYP2E1 to form formyl chloride, CO and CO_2, and by GSTT1-1 to carbon dioxide via a postulated glutathione-conjugate (*S*-chloromethyl glutathione), and to formaldehyde. Both pathways can give rise to toxic metabolites. After inhalation exposure, humans eliminate dichloromethane mainly in expired air, but also in the urine (ATSDR, 2000b).

(ii) Trichloroethylene

Trichloroethylene (TCE) is also absorbed mainly into the bloodstream after inhalation and is widely distributed in the liver, kidneys, and the cardiovascular and nervous systems.

Trichloroethylene is mainly metabolized in the liver through an oxidative pathway by CYP isoenzymes and through conjugation with

glutathione (Davidson & Beliles, 1991; Lash *et al.*, 2000a), leading to the formation of major metabolites such as chloral hydrate, trichloroethanol and trichloroacetic acid. Four CYP isoforms play a role in TCE metabolism: CYP2A1/2, CYP2B1/2, CYP2C11/6 and CYP2E1 (Koop *et al.*, 1985; Nakajima *et al.*, 1988; Guengerich & Shimada, 1991; Lash *et al.*, 2000a). The resulting metabolites are thought to be associated with liver toxicity and liver carcinogenesis in animals. The glutathione conjugation pathway leads to the formation of dichlorovinyl glutathione and dichlorovinyl cysteine. The latter can be further metabolized by β-lyase to reactive chemical species that are thought to play a role in the toxicity of TCE in the proximal renal tubules and in the renal carcinogenicity of TCE in animals. The CYP pathway is thought to predominate and formation of reactive species via the glutathione *S*-transferase (GST) pathway is less important (Lash *et al.*, 2000b).

4.1.2 Metals

Metal compounds used as paint pigments such as cadmium, chromium, and inorganic lead, are predominantly absorbed in the lung. Dermal absorption is generally low and depends on the chemical properties of the compound, the vehicle, and the integrity of the skin. Absorbed metals are distributed to the organs and, in the case of lead, are concentrated in the bone. Elimination of metals varies from several days to several years.

(a) Cadmium

Cadmium (Cd) enters the body mainly by inhalation in the working environment, whereas the general population is exposed via food and drinking-water. Fractional intestinal absorption is influenced by dietary factors and increases with dietary Cd concentration, while pulmonary fractional absorption depends partly on the solubility of cadmium. Cd and other agents induce synthesis of metallothionein, a protein that binds to cadmium and transfers it via the blood, primarily to the liver and the kidney. In the kidney, the complex is filtered through the renal glomeruli and then reabsorbed from the filtrate in the proximal tubules where the protein portion is rapidly degraded to release Cd. As a result, most of the body burden of Cd is retained in the liver and kidneys (where the half-life is estimated to be 7–16 years (IARC, 2012). Excretion occurs mainly via the urine and, in individuals without renal dysfunction, primarily reflects the amount of cadmium retained in the kidneys (IARC, 1993).

(b) Chromium

The toxicokinetics of chromium compounds depend on the solubility and particle size, on the valence state of the chromium atom and the nature of its ligands. Absorption of chromium(VI) compounds is higher than that of chromium(III) compounds, the latter occurring via passive diffusion and phagocytosis. Absorption of inhaled chromium compounds takes place in the lung via transfer across cell membranes and in the gastrointestinal tract from particles cleared from the lungs. Absorption after dermal exposure depends on the physical and chemical properties of the compound, the vehicle, and the integrity of the skin. Once taken up in the blood, chromium compounds are distributed to all organs, with highest concentrations in kidney, liver and bone (NTP, 2010).

Particles containing chromium can be retained in the lung for years after occupational exposure (ATSDR, 2000c). After exposure by inhalation, excretion occurs predominantly via the urine, and after oral exposure via the faeces, due to low absorption of chromium compounds from the gastrointestinal tract (ATSDR, 2008).

(c) Lead compounds, inorganic lead

Lead compounds have been used in paints as primers, pigments and driers. Lead can be absorbed after inhalation, oral or dermal exposure. Patterns and rates of particle deposition are highly dependent on size and ventilation rate. However, all lead settled deep in the lung is eventually absorbed. Dermal absorption of inorganic lead is negligible, although slightly increased by high perspiration in humans. Absorption from the gastrointestinal tract in both humans and experimental animals is strongly influenced by age, fasting/fed status, nutrition, solubility, and particles size. Absorbed lead is rapidly distributed from plasma into erythrocytes, soft tissues and – mainly – bone. Bone can be a significant source of endogenous lead, in particular when the resorption rate is increased, such as during pregnancy, lactation, and just after the menopause. After oral ingestion, absorbed lead is primarily excreted in the urine and, via the bile, in the faeces. Inorganic lead that has not been absorbed in the gastrointestinal tract is excreted in the faeces (IARC, 2006).

4.1.3 Other compounds

(a) Styrene

Styrene is used as polyester resin in paints. After inhalation, oral intake, or dermal absorption, styrene is rapidly distributed throughout the body, with the highest concentrations found in adipose tissue (IARC, 1994, 2002). In humans, styrene is metabolised to the predominant first metabolite, styrene-7,8-oxide, principally by CYP2E1, CYP2F, but also by CYP2B6. Isolated erythrocytes are also capable of non-enzymatic conversion of styrene totyrene-7,8-oxide. After its oxidation, a large percentage of styrene is excreted as urinary mandelic and phenylglyoxylic acids; glutathione conjugates represent a minor fraction of the metabolites of styrene-7,8-oxide (IARC, 1994, 2002).

(b) PAHs

PAH exposure during painting occurs through the use of special waterproof coatings or by pyrolysis of paint residues during removal. There are more than 100 different PAHs, which generally occur as complex mixtures rather than single compounds, but their identity is unknown in paints. Therefore, the toxicokinetics is discussed in broad general terms. Little is known about the toxicokinetics of PAH mixtures or individual PAHs in humans and most of the available data come from benzo[*a*]pyrene in experimental studies (described in IARC, 2010d; see also the *Monograph* on Benzene elsewhere in this volume).

(c) Aromatic amines and azo dyes

The toxicokinetics of aromatic amines and azo dyes, such as 4-aminobiphenyl, benzidine, benzidine-based dyes and 2-naphthylamine, are described in *IARC Monograph* Volume 99 (IARC, 2010c) and in the *Monographs* on these agents elsewhere in this volume.

4.2 Genetics and related effects

4.2.1 Genotoxicity

(a) Chromosomal aberrations, micronuclei, and sister chromatid exchange

Six of eight studies on chromosomal aberrations among painters reviewed in *IARC Monograph* Volume 98 (IARC, 2010a) showed consistent and significant elevated frequencies, and three of these studies reported an association with years of employment (Silva & Santos-Mello, 1996; Pinto *et al.*, 2000; Gajalakshmi *et al.*, 2002) while the others did not report analyses on duration of employment (Capomazza & Botta, 1990; Piña-Calva *et al.*, 1991; Testa *et al.*, 2005).

Several chromosomal abnormalities could be detected in the bone marrow of patients with acute myeloid leukaemia (AML). In a study by

Crane *et al.* (1996), routine cytogenetic data from 213 patients (129 enrolled in the period 1976–1983 and 84 enrolled in the period 1986–1990) with AML were correlated with environmental exposures to organic chemicals (e.g. benzene), paints, pesticides, and other substances such as dyes, glues, or varnishes. A suggestive association was found between exposure to paints and the –7/7q chromosomal abnormality but this was non-significant and only observed in the set of patients enrolled between 1986 and 1990.

In a study in Columbia, chromosomal aberrations were evaluated in 200 unexposed control subjects and in 200 car-painters recruited from several workshops. Painters were exposed for at least five years to the same commercial thinners, a complex mixture which contains toluene, isobutane, xylene, hexane, ethyl-benzene, and octane. After exclusion of current smokers, ex-smokers and those under medical treatment, the chromosomal aberration frequency was significantly higher in exposed workers compared with controls. The chromatid-type aberration was the most common aberration found in both groups, and was significantly higher in painters compared with controls, whereas no statistical difference was detected between frequencies of chromosome-type aberration in exposed workers and controls (Hoyos-Giraldo *et al.*, 2009).

Five of six studies reported significant increases in the frequency of micronuclei among painters (Diaz *et al.*, 1990; Di Giorgio *et al.*, 1994; Lemasters *et al.*, 1997, 1999; Pinto *et al.*, 2000; Martino-Roth *et al.*, 2003; Testa *et al.*, 2005). Chromosomal aberrations and micronuclei were found both in cultured lymphocytes and in buccal cells. Significantly increased frequencies of sister chromatid exchange were found in four of seven studies among painters (Haglund *et al.*, 1980; Kelsey *et al.*, 1988, 1989; Cullen *et al.*, 1992; Sardas *et al.*, 1994; Lemasters *et al.*, 1997, 1999; Pinto *et al.*, 2000; Testa *et al.*, 2005). Exposure–response relationships with duration of employment were reported in three of these studies (Sardas *et al.*, 1994; Lemasters *et al.*, 1997, 1999; Pinto *et al.*, 2000).

(b) DNA strand-breaks

Increased levels of DNA single-strand breaks among painters were reported in three of four studies (Oesch *et al.*, 1994; Fuchs *et al.*, 1996a, b; Zhu *et al.*, 2001; Martino-Roth *et al.*, 2003); a dose-gradient with years or weeks worked and the cytogenetic end-point which remained after adjusting for smoking was found in two (Oesch *et al.*, 1994; Zhu *et al.*, 2001). These data strongly suggest that occupational exposures in painting lead to increased levels of DNA damage.

(c) Aromatic DNA adducts

In a study among 208 Korean workers, aromatic DNA adducts assessed by ^{32}P-postlabelling tended to be higher in paint users (particularly coal-tar paint users) compared with on-site controls. When the data from general painters and coal-tar painters were combined, they showed higher adduct levels than on-site controls (Lee *et al.*, 2003).

4.2.2 Genetic effects for some individual constituents of paints

(a) Benzene

See Section 4 of the *Monograph* on Benzene in this volume.

(b) Toluene

Toluene is mainly converted to benzyl alcohol and excreted as hippurate. Human data are inconclusive with regards to the genotoxicity of toluene. Studies in exposed workers are limited by concurrent exposure to other chemicals, small cohort size, and a lack of historical exposure monitoring, and it is likely that the methods are not sufficiently sensitive to detect small, but significant, manifestations of genetic toxicity (ATSDR, 2000a). In some cytogenetic studies in

occupationally exposed populations, increases in chromosomal aberrations (two studies), micronuclei (one study) and DNA strand-breaks (one study) have been reported. Genotoxicity testing in experimental systems (rats, mice and cultured mammalian cells including studies on DNA strand-breaks) has been limited and has produced mostly negative results (Chen *et al.*, 2008). DNA-adduct formation has not been detected (IARC, 1999).

Higher frequencies of micronucleated polychromatic erythrocytes (PCE) have been observed in mice following co-exposure to benzene and toluene via inhalation at lower and intermittent co-exposures, compared with mice exposed to benzene or toluene alone (Wetmore *et al.*, 2008). The authors suggested that, at the doses used in this study (50 ppm for benzene and 100 ppm for toluene), toluene could enhance benzene-induced clastogenic or aneugenic bone-marrow injury.

(c) Xylene

Genotoxicity studies on mixtures of xylenes and on the individual isomers of xylene have provided consistently negative results in a variety of *in vitro* and *in vivo* assays and test systems (bacteria, yeast, cultured mammalian cells, mice, rats, and humans). Xylenes may cause DNA fragmentation indirectly, i.e. at cytotoxic concentrations because of nucleases released from lysosomes in dying cells. There is some evidence from bacterial test systems suggesting that xylene metabolites, specifically *meta*-xylenol, *para*-xylenol, 2,4-dimethylphenol, and *ortho*-methylbenzyl alcohol, are non-mutagenic (ATSDR, 2007b).

(d) Dichloromethane

Dichloromethane is consistently mutagenic in microorganisms. Weaker and less consistent responses are seen in mammalian systems, predominantly in mice, both *in vitro* and *in vivo*. The compound induced SCE, chromosome breakage, chromosome loss and DNA single-strand breaks in human cells, while results in rodent cells were inconclusive or negative (IARC, 1999). Mechanistic studies have established a link between GST-mediated metabolism of dichloromethane and its genotoxicity and carcinogenicity in mice. The GST enzyme responsible for the metabolism of dichloromethane is expressed to a significantly greater extent in mouse tissues than in rat, hamster or human tissues. The available data suggest a plausible mechanism for the development of liver and lung tumours in mice, but not in rats exposed to dichloromethane (IARC, 1999).

(e) Trichloroethylene

Studies of structural chromosomal aberrations, aneuploidy and SCE in peripheral lymphocytes of workers exposed to TCE were inconclusive but suggested clastogenic effects (IARC, 1995; ATSDR, 1997). TCE did not induce chromosomal aberrations, dominant lethal mutations, SCE or unscheduled DNA synthesis in rodents, whereas an increased induction of micronuclei and DNA single-strand breaks or alkali-labile sites was observed. Although TCE may not be genotoxic, several of its metabolites are reactive and potentially genotoxic substances, suggesting that genotoxic effects may be a concern for workers exposed to trichloroethylene (ATSDR, 1997; Lash *et al.*, 2000b; Tabrez & Ahmad, 2009). Several isomers of 1,2-dichlorovinyl-cysteine, a product of TCE metabolism in the kidney, are mutagenic in the *in vitro* Ames assay. These products have been identified in the urine of workers exposed to TCE.

(f) Cadmium and chromium

The genotoxic effects of cadmium and chromium are described in Section 4 of the *Monograph* on these two metals in *IARC Monograph* Volume 100C (IARC, 2012).

(g) Inorganic lead

Equivocal results have been published with respect to the mutagenicity of water-soluble lead compounds in mammalian cells in culture; in most classical test systems, effects were weak or restricted to toxic doses. In cultures of various mammalian cells and in lead-exposed animals, lead acetate, lead chromate and lead nitrate induced DNA strand-breaks. Chromosomal aberrations and micronuclei have been shown consistently in mammalian cells in culture, in experimental animals (in bone-marrow cells of lead-exposed animals) and in several cases also in humans occupationally exposed to lead. In some studies, these effects were correlated with blood-lead concentrations. However, with respect to epidemiological studies, confounding exposures cannot be ruled out (IARC, 2006).

Two mechanisms may underlie lead-induced genotoxicity, namely a disruption of pro-oxidant/antioxidant balance, at least in part through interaction with the sulfhydryl groups of key enzymes, and as a result of interference with DNA-repair systems. There is little evidence that lead interacts directly with DNA at blood-lead concentrations normally encountered. The involvement of reactive oxygen species (ROS) in lead-induced genotoxicity has been shown at different experimental levels. Molecular mechanisms may be enhanced lipid peroxidation, inhibition of antioxidant defence systems, catalysis of Fenton-type reactions and the inhibition of aminolevulinic acid dehydratase. The latter reaction leads to the accumulation of the haeme precursor aminolevulinic acid, with the subsequent generation of ROS and induction of oxidative DNA damage (IARC, 2006).

Lead interacts with proteins, including those involved in DNA repair. Lead has been shown to inhibit the apurinic/apyrimidinic endonuclease (APE1) at low concentrations (in the micromolar range) in cultured AA8 cells, leading to accumulation of a-purinic sites and to an increase in methylmethane sulfonate-induced mutagenicity (McNeill *et al.*, 2007). This latter mechanism may be responsible for enhancing the genotoxicity of other agents. Furthermore, lead interferes with the repair of DNA double-strand breaks via interaction with the stress-response pathway induced by the ATM (ataxia-telangiectasia mutated) protein (Gastaldo *et al.*, 2007). Low concentrations of lead stimulate cell growth via mobilization of free intracellular Ca^{2+} and activation of protein kinase C (PKC), which triggers a signal-transduction cascade leading to stimulation of DNA synthesis (IARC, 2006).

(h) Styrene

Data from studies in experimental systems (*in vitro* and *in vivo*) and from studies in humans indicate that exposure to styrene can result in the formation of DNA adducts. However, mice, but not rats, develop lung tumours after exposure to styrene, even though both species form DNA adducts, also in organs other than the lung. Circulating styrene 7,8-oxide – the active metabolite of styrene – may also play a role. Since the concentration of styrene in blood is two orders of magnitude higher in the rat than in the mouse, the lung tumours in mice probably develop as a result of in situ formation of styrene 7,8-oxide, which causes cytotoxicity, or increased cell proliferation, or DNA-adduct formation. It is likely that the proposed mechanism involving conversion of styrene to styrene 7,8-oxide in mouse Clara cells is not operative in human lungs to a biologically significant extent. However, based on the observations in human workers regarding styrene 7,8-oxide in blood, and DNA adducts and chromosomal damage in lymphocytes, it cannot be excluded that this and other mechanisms are important for organs other than the lung (IARC, 2002).

(i) PAHs

Genotoxic effects of PAHs are described in *IARC Monograph* Volume 92 (IARC, 2010d) and the *Monograph* on benzene in this volume.

After metabolic activation, PAH mixtures are genotoxic in humans and individual PAHs are genotoxic in experimental systems. In the complex mixtures to which humans are exposed, some of the genotoxic effects of PAHs can be ascribed to benzo[*a*]pyrene and are described in Volume 96 (IARC, 2010d) and in the *Monograph* on Benzene in this volume.

(j) Aromatic amines and azo dyes

The genotoxic effects of aromatic amines and azo dyes such as 4-aminobiphenyl, benzidine, benzidine-based dyes and 2-naphthylamine, are described in *IARC Monograph* Volume 99 (IARC, 2010c), and in the *Monographs* on these specific substances elsewhere in this Volume.

4.2.3 Indirect effects potentially related to genotoxicity

(a) Haematological and immunological effects

Haematological changes were observed in several studies of painters. These included reduced levels of total white blood cells, T-cells and natural killer cells (Moszczyński *et al.*, 1996; Rothman *et al.*, 1997; Kim *et al.*, 1999). Furthermore, an increased prevalence of leukopenia, anaemia and granulocytopenia was observed among painters. Immunological changes were also reported in several studies. These effects included specific immunoglobulin (G and E) responses to hexamethylene diisocyanate – an aliphatic diisocyanate used in the manufacture of paints and surface coating, which can induce asthma (Grammer *et al.*, 1988; Cartier *et al.*, 1989; Baur *et al.*, 1996; Tee *et al.*, 1998; Redlich *et al.*, 2001; Pronk *et al.*, 2007) and increased proliferation of lymphocytes after *in vitro* stimulation with this substance (Redlich *et al.*, 2001; IARC, 2010a).

4.3 Susceptible populations

Several studies have addressed the interplay between genetic factors, biological and clinical endpoints and were reviewed in *IARC Monograph* Volume 98 (IARC, 2010a). In one study considering bladder cancer as an endpoint, the slow acetylation status (*N*-acetyltransferase 2 phenotype) was over-represented in painters (n = 16) with bladder cancer (88%) compared with their healthy colleagues (65%) (n = 26) (Golka *et al.*, 2001). The effects of the *NAT2* polymorphism are also described for arylamines in Volume 99 (IARC, 2010c).

Few studies have addressed the effect of genetic polymorphism on biological endpoints. In one study no significant associations were detected between any of the biomarker responses (chromosomal aberrations, SCE, micronuclei) and either the *GSTM1* or *GSTT1* genotype. However, the small size of the study (25 car painters and 37 unexposed controls) does not allow definite conclusions to be made on the relationship between genetic polymorphisms and biomarkers (Testa *et al.*, 2005).

In another study, among 181 painters using coal-tar paints (n = 111) or general paints (n = 70) and 27 on-site controls, no gene–environment interactions between *GSTM1* (all workers, 51% *GSTM1*-null) or *GSTT1* (all workers, 54% *GSTT1*-null) and aromatic DNA-adduct formation was found among any of the groups exposed (Lee *et al.*, 2003).

Only one recent study has addressed the interplay between genetic polymorphisms and biological endpoints. In this study the effect of polymorphisms in genes involved in metabolism of xenobiotics (*CYP2E1*, *GSTM1*) and in DNA repair ($XRCC1^{194}$ *Arg/Trp*, *Trp/Trp*, $XRCC1^{280}$ *Arg/His*, $XRCC3^{241}$ *Thr/Met*) on chromosomal aberration (CA) frequency was investigated (Hoyos-Giraldo *et al.*, 2009). A significant effect was observed of the *CYP2E1 C1/C1* genotype, which increased the CA frequency in exposed

workers. Exposed workers with the *GSTM1-null* genotype had a statistically significantly elevated CA frequency compared with controls and exposed workers with a *GSTM1*-positive genotype. Exposed workers with *XRCC1*^{194}*Arg/Trp* and *Trp/Trp* genotypes had statistically higher CA frequencies compared with those with the *XRCC1*^{194}*Arg/Arg* genotype. Also, there was an association between the *XRCC1*^{280}*Arg/Arg* and *XRCC3*^{241}*Thr/Thr* genotypes and a significant increase of CA frequency in exposed workers. The authors suggested that these wild-type genotypes may decrease the capacity to repair DNA single- and double-strand breaks and influence the formation of chromosomal aberrations (Hoyos-Giraldo *et al.*, 2009).

In most studies that measured a variety of cytogenetic end-points and markers of genotoxicity, elevated levels of genetic damage were reported in painters. Mechanistic data reviewed by ATSDR (1997, 2000a, b, 2007a, b) and by previous *IARC Monograph* evaluations on selected specific chemicals that had been or still are prevalent in exposures during painting, strongly support a role of these substances in the induction of haematopoietic malignancies (benzene, trichloroethylene), liver cancer (trichloroethylene), lung cancer (cadmium, chromium, PAHs) and bladder cancer (aromatic azo dyes).

4.4 Synthesis

The multiple genetic and cytogenetic effects observed among workers employed as painters or in the paint industry provide strong evidence in support of genotoxicity as one mechanism underlying the observed increase in cancer risk. However, due to the complexity and changing nature of the exposure mixtures and the potential interactions between exposures as a painter, other mechanisms are also likely. While it is clear that exposures to some agents in the paint industry have decreased over time, recent cytotoxicity studies and the ongoing exposures to multiple mutagens and carcinogens continue to raise concerns about cancer risks.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of occupational exposure as a painter. Occupational exposure as a painter causes mesothelioma, and cancers of the urinary bladder and lung.

Also, a positive association has been observed between maternal exposure to painting (including pre-conception and during pregnancy) and childhood leukaemia in the offspring.

No data in experimental animals relevant to exposure as a painter were available to the Working Group.

The multiple genetic and cytogenetic effects observed among workers employed as painters and the information on individual chemicals to which painters are exposed provide strong evidence to support genotoxicity as a mechanism underlying the observed increase in cancer risk. However, due to the complexity and changing nature of the exposure mixtures and the potential interactions between exposures as painters, other mechanisms are also likely. While it is clear that exposures as a painter to some agents have been reduced over time, recent genotoxicity studies and the exposure to multiple mutagens and carcinogens continue to raise concerns about cancer risks.

Occupational exposure as a painter is *carcinogenic to humans (Group 1)*.

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