CARBON BLACK

Carbon black has been considered by previous Working Groups in April 1984, March 1987 and October 1995 (IARC, 1984, 1987, 1996). Since that time, new data have become available, and these have been included in the present monograph and have been taken into consideration in the evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

The Chemical Abstract Service Registry Number for all carbon blacks is 1333–86–4.

Acetylene black

Chem. Abstr. Name: Carbon black, acetylene
IUPAC Systematic Name: Carbon black, acetylene
Synonyms: CI: 77266; CI Pigment Black 7; explosion acetylene black; explosion black
Trade names: P68, P1250, Shawinigan Acetylene Black and Ucet

Channel black

Chem. Abstr. Name: Carbon black, channel
IUPAC Systematic Name: Carbon black, channel
Synonyms: CI: 77266; CI Pigment Black 7; impingement black
Trade names: Aroflow, Arrow, Atlantic, Black Pearls, Carbolac, Carbomet, CK3, Collocarb, Conductex (Continental), Croflex, Crolac, Degussa, Dixie, Dixiecell, Dixiedensed, Elf, Excelsior, Farbruss, Fecto, Huber, Kosmink, Kosmobil, Kosmolak, Kosmos, Kosmovar, Micronex, Mogul, Monarch, Neo-Spectra, Peerless, Printex, Raven, Regent, Royal Spectra, Special Black IV & V, Spheron, Superba, Super-Carbovar, Super-Spectra, Texas, Triangle, United, Witco and Wyex

Furnace black

Chem. Abstr. Name: Carbon black, furnace
IUPAC Systematic Name: Carbon black, furnace
Synonyms: CI: 77266; CI Pigment Black 7; gas-furnace black; oil-furnace black
Trade names: Aro, Arogen, Aromex, Arovel, Arotone, Atlantic, Black Pearls, Carbodis, Collocarb, Conductex (Continex), Corax, Croflex, Dixie, Durex, Elftex, Essex, Furnal, Furnex, Gastex, Huber, Humenegro, Kosmos, Metanex, Modulex, Mogul, Molacco, Monarch, Neotex, Opal, Peerless, Pelletex, Philblack, Printex, Rebonex, Regal, Special Schwarz, Statex, Sterling, Texas, Ukarb, United and Vulcan

Lampblack

Chem. Abstr. Name: Carbon black, lamp
IUPAC Systematic Name: Carbon black, lamp
Synonyms: CI: 77266; CI Pigment Black 6
Trade names: Carbon Black BV and V, Durex, Eagle Germantown, Flamruss, Magecol, Tinolite and Torch Brand

Thermal black

Chem. Abstr. Name: Carbon black, thermal
IUPAC Systematic Name: Carbon black, thermal
Synonyms: CI: 77266; CI Pigment Black 7; therma-atomic black
Trade names: Atlantic, Cancarb, Croflex, Dixitherm, Huber, Kosmotherm, Miike 20, P-33, Sevacarb, Shell Carbon, Statex, Sterling, Thermatomic, Thermax, Thermblack and Velvetex

1.1.2 *General description*

Carbon black is a generic term for an important family of products that is used principally for the reinforcement of rubber, as a black pigment and because of its electrically conductive properties. It is an extremely fluffy fine powder with a large surface area and is composed essentially of elemental carbon. Carbon black is one of the most stable chemical products. In general, it is the most widely used nanomaterial and its aggregate dimension ranges from tens to a few hundred nanometers (nm); it imparts special properties to composites of which it is a part.

Plants for the manufacture of carbon black are strategically located worldwide to supply the rubber tyre industry, which consumes 70% of the carbon black produced. About 20% is used for other rubber products and 10% is used for a variety of non-rubber applications. World capacity in 2005 was estimated at more than 10 million tonnes (Auchter, 2005). Over 40 grades (listed in ASTM International, 2005a) are used by the rubber industry alone. Many additional grades are marketed for non-rubber applications (Voll & Kleinschmit, 2002; Wang *et al.*, 2003; ASTM International, 2005a).

Carbon black is a form of elemental carbon that is manufactured by the controlled vapour-phase pyrolysis and partial combustion of hydrocarbons. Several processes have been used to produce carbon black, including the oil-furnace, impingement (channel), lampblack, thermal (decomposition of natural gas) and acetylene (decomposition) processes. Carbon blacks are commonly referred to by the process or the source material from which they are made, e.g. furnace black, lampblack, thermal black, acetylene black and channel black. The different grades from the various processes have certain unique characteristics, but it is now possible to produce reasonable approximations of most of these grades using the oil-furnace process, by which more than 95% of the total output of carbon black is produced (Voll & Kleinschmit, 2002; Wang *et al.*, 2003).

In contrast to carbon black, soot is a material of varying and often unknown composition that is an unwanted by-product of the incomplete combustion of all types of material that contain carbon, such as waste oil, coal, paper, rubber, plastic, household waste and also some fuel oils. Soots have a small surface area of available carbon due to their large particle size and low carbon content. They typically contain large quantities of solvent-extractable materials and their ash content can be 50% or more (European Committee for Biological Effects of Carbon Black, 1982; Voll & Kleinschmit, 2002; Wang *et al.*, 2003).

Two other commercial carbonaceous products are activated carbon (including activated charcoal) and bone black. Activated carbon is a collective name for a group of porous carbons, which are manufactured either by the treatment of carbon with gases or by the carbonization of carbonaceous materials with simultaneous activation by chemical treatment. Activated carbon possesses a porous structure, usually has small amounts of chemically bonded oxygen and hydrogen and can contain up to 20% of mineral matter, which usually consists of ash or residue as a result of ignition. The nature of this mineral material depends on the raw materials used, and can consist of silica and compounds of alkali and alkaline-earth metals, for example. X-Ray investigations show that the carbon is mainly in the form of very small crystallites with a graphite-like structure (Vohler *et al.*, 1986).

Bone black is a pigment that is derived as a by-product of the manufacture of bone char, which is made by carbonizing bones and is used principally in sugar refining. Bone black is used primarily as a colourant in artists' paint and for tinting vinyl fabrics for upholstery and automotive interiors. The carbon content of bone black is usually approximately 10% (Lewis, 1988, 1993).

Soot, activated carbon and bone black, as well as other forms of carbonaceous products, are not considered in this monograph.

1.1.3 *Chemical and physical properties of the technical products*

(a) Particle size

Different types of carbon black have a wide range of primary particle sizes, large surface areas per unit mass, low contents of ash and solvent-extractable materials and

varying degrees of particle aggregation. A carbon black with a high degree of aggregation is said to have a high 'structure'. Structure is determined by the size and shape of the aggregated primary particles, the number of primary particles per aggregate and their average mass.

Carbon black is initially formed as roughly spherical primary particles, which, in most cases, rapidly form aggregates. An aggregate is a chain of primary carbon particles that are permanently fused together in a random branching structure. The aggregate may consist of a few or hundreds of spherical particles (or, as in the case of thermal black, primarily single spheres rather than chains). The chains are open structures and are used to absorb fluids and reinforce materials such as rubber. The aggregates can bind together by van der Waals forces in more loosely associated agglomerates, or they may be compressed into pellets (up to 0.5 cm) that are held together by means of binders (molasses and/or lignosulfonates) (Dannenberg *et al.*, 1992; Gardiner *et al.*, 1992a).

Two dimensions are necessary to define a carbon black aggregate. (1) *Mean diameter of the component spheres in the chain*: this is a measure of the 'thickness' of the chain, is called the primary particle size and is generally inversely proportional to the surface area of the carbon black. (2) *Extent of the branched chain aggregate*: this is called the aggregate size and is the dimension of the rigid framework that is the aggregate.

In addition to these two dimensions, there is a property or 'structure' which is the volume of space that is 'reinforced' by the aggregate—essentially, the amount of fluid it can absorb internally. A standard method of measuring this property is by the dibutyl phthalate absorption of a carbon black (in units of millilitres per 100 g).

The properties and grades of carbon black that largely determine its use are related to structure, surface area and condition. Over the years, a system for the designation of types was developed in the production and consumer industries which used the initial letters of words that describe a particular carbon black. For example, HAF stood for high-abrasion furnace black, and SRF stood for semi-reinforcing furnace black. These generic designations have largely been replaced by the technical classification system developed by the American Society for Testing and Materials (ASTM). This system, originally adopted in 1966, is primarily for rubber-grade carbon blacks and consists of a letter followed by a three-digit number. Thus, the letter N stands for normal cure of a rubber compound and the first digit following the letter designates the group number, which is determined by the average primary particle size as measured by electron microscopy. The particle range of rubber-grade carbon black is arbitrarily divided into 10 groups, as shown in Table 1.1. The third and fourth characters of this system are numbers that are assigned arbitrarily. For example, HAF black has ASTM number N330 (ASTM International, 2005a).

More than 40 grades of carbon black are currently in use in the rubber industry and all contribute to the physical properties of the finished rubber product, such as tensile strength and resistance to abrasion. Almost as many specialty grades (some of which are re-brands of the standard rubber-grade carbon blacks) are used in the paint, plastics, ink

and other such industries. In these applications, particle size and surface characteristics contribute to tinting strength and blackness.

Table 1.2 presents a summary of surface area and primary particle size, aggregate diameter and agglomerate size for different types of carbon black.

Table 1.1. Particle range of rubber-grade carbon blacks

Group number	Typical average primary particle size (nm)	Average surface area (m^2/g)
0	0–10	>150
1	11–19	121–150
2	20–25	100–120
3	26–30	70–99
4	31–39	50–69
5	40–48	40–49
6	49–60	33–39
7	61–100	21–32
8	101–200	11–20
9	201–500	0–10

From Auchter (2005)

Table 1.2. Summary information on particle size

Carbon black	Surface area (m^2/g)	Approximate diameter of primary particle size (nm)	Diameter of aggregate (nm)	Size of agglomerate
Oil-furnace	12–240	10–400	50–400	Large (<2 mm)
Thermal	6–15	120–500	400–600	Large (<2 mm)
Impingement (channel)		10–30	50–200	Large (<2 mm)
Lampblack	15–25	60–200	300–600	Large (<2 mm)
Acetylene black	15–70	30–50	350–400	Pelletizes poorly

Compiled by the Working Group from Kuhlbusch *et al.* (2004); Kirk-Othmer (2005)

(b) Production processes, raw materials and uses

Table 1.3 lists some of the major types of carbon black that are available, together with data on production process, raw materials and major use properties in the compounding of elastomers. Within each of the groups listed, several commercial modifications have been made; for example, one producer alone lists five different grades of intermediate superabrasion furnace carbon black, including low structure, low modulus, high structure and others (Auchter, 2005). Table 1.4 provides the ASTM

designations for furnace blacks used in rubber, three typical measures of surface area (iodine adsorption, nitrogen absorption and statistical thickness) and one measure of the degree of aggregation (dibutyl-phthalate absorption). Table 1.5 provides similar information for furnace blacks used in inks, paints and plastics.

Table 1.3. Grades, production processes, selected properties and uses of carbon black

Type	Designation		Production process and/or feedstock	Average primary particle diameter (nm)	Iodine absorption number[a] (g/kg)	Primary rubber processing properties and use
	Acronym	ASTM				
Superabrasion furnace black	SAF	N110	Oil furnace	17	145	High reinforcement; used in special and off-road tyre products for which high abrasion resistance is required.
Intermediate superabrasion furnace black	ISAF	N220	Oil furnace	21	121	High reinforcement and tear strength, good processing; used in passenger, off-road and special tyres for which good abrasion resistance is required.
High-abrasion furnace black	HAF	N330	Oil furnace	31	82	Medium-high reinforcement, low modulus, high elongation, good flex, tear and fatigue resistance; used in tyre tread, carcass and sidewall compounds, motor mounts, weather-stripping and bicycle tyres
Fast-extruding furnace black	FF	N550	Oil furnace	53	43	Medium-high reinforcement, high modulus and hardness, low die swell and smooth extrusion; used in tyre inner liners, carcass and sidewall compounds and hose and other extruded goods
General-purpose furnace black	GPF	N660	Oil furnace	63	36	Medium reinforcement and modulus, good flex and fatigue resistance, low heat build-up; used in tyre carcass, inner liners and sidewalls, sealing rings, cable jackets, hose and extruded goods
Semi-reinforcing furnace black	SRF	N762	Oil furnace	110	27	Medium reinforcement, high elongation and resilience, low compression set; used in mechanical goods, footwear, inner tubes and floor mats
Medium thermal black	MT	N990	Natural gas	320	9	Low reinforcement, low modulus, hardness, hysteresis and tensile strength, high elongation and loading capacity; used in wire insulation and jackets, mechanical goods, footwear, belts, hose, gaskets, O-rings and tyre inner liners

From Auchter (2005) [from Dannenberg (1978); Lyon & Burgess (1985)]

[a] Used as a measure of surface area, which is an indication of reinforcement ability

Table 1.4. Typical properties of rubber-grade carbon blacks

ASTM Classification	Iodine adsorption (g/kg)	NSA (m^2/g)	STSA (m^2/g)	DBPA (mL/100 g)
N110	145	127	115	113
N115	160	137	124	113
N120	122	126	113	114
N121	121	122	114	132
N125	117	122	121	104
N134	142	143	137	127
N135	151	141	–	135
S212	–	120	107	85
N219	118	–	–	78
N220	121	114	106	114
N231	121	111	107	92
N234	120	119	112	125
N293	145	122	111	100
N299	108	104	97	124
S315	–	89	86	79
N326	82	78	76	72
N330	82	78	75	102
N335	92	85	85	110
N339	90	91	88	120
N343	92	96	92	130
N347	90	85	83	124
N351	68	71	70	120
N356	92	91	87	154
N358	84	80	78	150
N375	90	93	91	114
N539	43	39	38	111
N550	43	40	39	121
N582	100	80	–	180
N630	36	32	32	78
N642	36	39	–	64
N650	36	36	35	122
N660	36	35	34	90
N683	35	36	34	133
N754	24	25	24	58
N762	27	29	28	65
N765	31	34	32	115
N772	30	32	30	65
N774	29	30	29	72
N787	30	32	32	80
N907	–	9	9	34
N908	–	9	9	34
N990	–	8	8	43
N991	–	8	8	35

From ASTM International (2005a)
NSA, nitrogen surface area; STSA, statistical thickness surface area; DBPA, dibutyl phthalate absorption

Table 1.5. Typical properties of furnace blacks used in inks, paints, paper and plastics

Furnace black	Surface area[a] (m^2/g)	Primary particle size (nm)	DBPA (mL/100 g)		Bulk density (g/L)		Volatile content (%)
			Fluffy	Pellets	Fluffy	Pellets	
Normal furnace grades							
High colour	250–300	14–15	70–75	60–65	50–300	400–550	1.2–2.0
Medium colour	150–220	16–24	47–122	46–117	130–300	390–550	1.0–1.5
Regular colour	45–140	20–37	42–125	42–124	176–420	350–600	0.9–1.5
Low colour	24–45	41–75	71	64–120	256	352–512	0.6–0.9
Surface oxidized grades							
High colour	400–600	10–20	121	105	–	–	8.0–9.5
Medium colour (long flow)	100–138	23–24	49–60	55	240–360	530	3.5–5.0
Medium colour (medium flow)	96–110	25	49–72	70	225–360	480	2.5–3.5
Low colour	30–40	50–56	48–93	–	260–500	–	3.5

From Dannenberg *et al*. (1992)
DBPA, dibutyl-phthalate absorption
[a] Calculated by the Brunauer, Emmett and Teller (BET) procedures

Furnace black can be produced with a wide range of properties. Thermal black typically has the largest particle size and smallest surface area of the carbon blacks, with spherical particles, a low degree of aggregation and low oxygen content. Lampblack is characterized by a high degree of aggregation of mid-size particles and small surface area. Acetylene black is typically very pure (carbon content, ~99.7%) with an extremely high degree of aggregation and is the most crystalline or graphitic of the carbon blacks. Characteristics of channel black include small particle size and a high level of surface oxidation (Dannenberg *et al.*, 1992; Wang *et al.*, 2003).

1.1.4 *Extractable impurities in carbon black*

Because of their source materials, the methods of their production and their large surface areas and surface characteristics, commercial carbon blacks typically contain varying quantities of adsorbed by-products from the production process, particularly aromatic compounds. Several methods have been developed and used to extract and characterize these adsorbed chemicals (see Section 1.1.5(*b*)). The classes of chemical most commonly identified in these extracts are polycyclic aromatic hydrocarbons

(PAHs), nitro derivatives of PAHs (nitro-PAHs) and PAHs that contain sulfur. Examples of these three classes of chemical identified in carbon black extracts are given in Table 1.6.

Table 1.6. Some compounds identified in carbon black extracts

Polycyclic aromatic hydrocarbons (PAHs) (see also IARC, 1984, 2010)	Fluorene
Acenaphthene	Indeno[1,2,3-*cd*]pyrene
Acenaphthylene	Naphthalene
Anthanthrene	Perylene
Anthracene	Phenanthrene
Benz[*a*]acenaphthylene	Pyrene
Benz[*a*]anthracene	*Nitro derivatives of PAHs* (nitro PAHs) (see also IARC, 1987)
Benzo[*b*]fluoranthene	1,3-Dinitropyrene
Benzo[*ghi*]fluoranthene	1,6-Dinitropyrene
Benzo[*j*]fluoranthene	1,8-Dinitropyrene
Benzo[*k*]fluoranthene	9-Nitroanthracene
Benzo[*a*]pyrene	3-Nitro-9-fluorenone
Benzo[*e*]pyrene	1-Nitronaphthalene
Benzo[*ghi*]perylene	1-Nitropyrene
Chrysene	1,3,6-Trinitropyrene
Coronene	*PAHs that contain sulfur*
4*H*-Cyclopenta[*def*]phenanthrene	Benzo[*def*]dibenzothiophene
Cyclopenta[*cd*]pyrene	Dibenzothiophene
Dibenz[*ah*]anthracene	Phenanthro[4,5-*bcd*]thiophene
Fluoranthene	Triphenyleno[4,5-*bcd*]thiophene

Modified from IARC (1996)

The specific chemicals detected in carbon black extracts and their relative quantities vary widely from sample to sample. Extraction method, type and grade of carbon black and post-extraction treatments all appear to be factors that affect the type and quantity of impurities obtained, and substantial batch-to-batch variation is typical.

Benzo[*ghi*]perylene, coronene, cyclopenta[*cd*]pyrene, fluoranthene and pyrene are among the PAHs frequently found at the highest levels in carbon black extracts. For example, in a study of five types of furnace black used in tyre manufacture, extraction with hot benzene after 250 hours yielded means of 252–1417 mg extract/kg carbon black. The quantities of various PAHs found in the extracts were as follows (mg/kg): anthanthrene, < 0.5–108; benzacridine derivative, < 0.5; benzo[*def*]dibenzothiophene and benzo[*e*]acenaphthylene, < 0.5; benzofluoranthenes (total), < 0.5–17; benzo[*ghi*]fluoranthene, 20–161; benzo[*ghi*]perylene, 23–336; benzopyrenes (total), 2–40; cyclopenta[*cd*]pyrene, < 0.5–264; coronene and isomer, 13–366; dimethylcyclopentapyrene and/or dimethylbenzofluoranthene, 2–57; fluoranthene, 10–100; indeno[1,2,3-*cd*]pyrene, 1–59; phenanthrene and/or anthracene, < 0.5–5; and pyrene, 46–432 (Locati *et al.*, 1979). The results of two similar studies that used benzene

to extract adsorbates from several oil-furnace blacks and one thermal black are shown in Table 1.7 (Taylor *et al.*, 1980; Zoccolillo *et al.*, 1984).

Table 1.7. Concentrations of total extractable adsorbate and benzo[*a*]pyrene in the benzene extracts of 10 carbon blacks

ASTM designation[a]	Surface area (m^2/g)	Total extract (mg/kg) (no. of samples)	Concentration of benzo[*a*]pyrene (mg/kg) (no. of samples)
N220	118	250 (2)	0.29 (4)
N234	128	630 (2)	1.08 (5)
N326	80	225 (1)	0.18 (1)
N339	90	510 (4)	1.46 (2)
N347	90	343 (1)	0.50 (1)
N351	70	780 (3)	5.47 (5)
N375	101	1020 (5)	3.81 (2)
N550	42	610 (1)	0.14 (1)
N660	36	653 (6)	4.80 (6)
N990[b]	10	8020 (1)	35.00 (1)

From Taylor *et al*. (1980); Zoccolillo *et al.* (1984)
[a] For American Society for Testing and Materials designations of types, see Tables 1.3 and 1.4.
[b] N990 is a thermal black.

PAH fractions from six different batches of the same furnace black (ASTM N660) were analysed and ranged from 200 to 736 mg/kg; benzo[*a*]pyrene concentrations ranged from 1.2 to 9.7 mg/kg in benzene extracts (Zoccolillo *et al.*, 1984).

Seven types of carbon black used in tyre production in Poland (domestic: JAS-220, JAS-330, JAS-530; imported: HAF-N-326, HAF-N-330, SRF-N-762 and Dure × –0) were analysed. Toluene-soluble extractable compounds, including PAHs, were determined by a gravimetric method and benzo[*a*]pyrene by high-performance liquid chromatography (HPLC) with a spectrometric detector. Toluene-soluble compounds amounted to 0.12–0.25% (by weight). Benzo[*a*]pyrene, at a range of 1.44–3.07 ppm [mg/kg], was detected in five of the seven carbon blacks examined (Rogaczewska *et al.*, 1989).

Agurell and Löfroth (1993) studied the variation in impurities of a furnace carbon black (ASTM N330) manufactured in Sweden over a 3-year period. The PAHs that were determined in benzene extracts and their ranges of concentration (mg/kg carbon black) were: phenanthrene, 0.9–15; fluoranthene, 4.5–72; pyrene, 26–240; benzo[*ghi*]fluoranthene, 7.2–72; cyclopenta[*cd*]pyrene, 6.6–188; chrysene, 0.1–1.3; benzo[*b*]fluoranthene, benzo[*j*]fluoranthene and benzo[*k*]fluoranthene, 0.4–18; benzo[*e*]pyrene, 0.9–19; benzo[*a*]pyrene, 0.9–28; perylene, 0.1–3.5; indeno[1,2,3-*cd*]pyrene, 2–43; benzo[*ghi*]perylene, 14–169; and coronene, 14–169.

Somewhat higher total levels of PAHs were found in extracts of thermal blacks. A 24-hour benzene extract of an ASTM N990-type thermal black yielded approximately 4000 mg extract/kg carbon black. Individual PAHs (mg/kg) included: benzo[*ghi*]perylene (1217), coronene (800), pyrene (603), anthanthrene (299), fluoranthene (197), benzo[*a*]pyrene (186) and benzo[*e*]pyrene (145) (De Wiest, 1980). The total level of PAHs in the benzene extract of another sample of ASTM N990 thermal black was 2140 mg/kg, which included 35 mg/kg benzo[*a*]pyrene (Zoccolillo *et al.*, 1984).

Typical and specified PAH contents were compared for three samples of thermal black and two of furnace black. Levels of benzo[*a*]pyrene ranged from 0.03 to 0.2 ppm in the thermal black samples and up to 0.001 ppm in the furnace blacks; levels of total PAHs ranged from 1.5 to 9.2 ppm in the thermal black samples and from 0.01 to 0.26 ppm in the furnace black samples (Cabot Corporation, 2005a).

Nitro PAHs were identified in extracts of some samples of channel black and furnace black that had been subjected to oxidative treatment with nitric acid. Discovery of these by-products in a photocopy toner in the late 1970s led to modifications of the oxidative process; these changes have reportedly eliminated the presence of nitro PAHs in commercial furnace blacks that have been produced since 1980 (Fitch *et al.*, 1978; Fitch & Smith, 1979; Rosenkranz *et al.*, 1980; Sanders, 1981; Ramdahl *et al.*, 1982; Butler *et al.*, 1983).

Several oxidized PAHs (e.g. ketones, quinones, anhydrides and carboxylic acids) were also identified in samples of carbon black that had undergone oxidative treatment (Fitch *et al.*, 1978; Fitch & Smith, 1979; Rivin & Smith, 1982), and one study detected 3-nitro-9-fluorenone in a nitric acid-treated carbon black that was used to make carbon ink in China (Jin *et al.*, 1987).

Carbon black that is made from high-sulfur feedstocks frequently contains detectable quantities of extractable aromatic compounds that contain sulfur such as benzothiophene derivatives (Lee & Hites, 1976; Nishioka *et al.*, 1986).

Trace amounts of a variety of inorganic elements (e.g. calcium, copper, iron, manganese, potassium, lead, arsenic, chromium, selenium and zinc) have also been identified in some analyses of samples of carbon black (Collyer, 1975; Sokhi *et al.*, 1990; Cabot Corporation, 2005b).

1.1.5 *Analysis*

This section briefly reviews methods for industrial hygiene measurements in workplaces where carbon black is manufactured or used, methods to detect the presence of carbon black in various matrices and methods used to isolate and analyse surface contaminants of carbon black (see Section 1.1.4).

(a) Industrial hygiene assessment

Exposure to particulates in occupational environments is generally determined gravimetrically. The behaviour of carbon black in air and its deposition in the respiratory

tract on inhalation are important for human exposure, and are determined by the aerodynamic diameter of the particles. The aerodynamic diameter can be measured by impactors and is dependent on the geometric diameter, density of the material and shape of the aggregates. Most commonly, the size distribution of airborne particles is expressed as its mass median aerodynamic diameter (MMAD) and the geometric standard deviation. Several dust fractions are often identified as 'total' dust, inhalable dust and respirable dust.

Inhalable dust is approximately equivalent to the fraction of airborne material that enters the nose and mouth during breathing and is therefore available for deposition anywhere in the respiratory tract (International Organization for Standardization, 1995; Health and Safety Executive, 2000). The inhalable fraction depends on the prevailing movement of air around the exposed person and on whether breathing is by the nose or mouth. It is, however, possible to define target specifications for sampling instruments which approximate the inhalable fraction; these target specifications are provided by the International Organization for Standardization (1995). In the United Kingdom, the standard sampling devices for measuring inhalable dust are the multiorifice sampler, the Institute of Occupational Medicine (IOM) sampler and the conical inhalable sampler (cis) (Health and Safety Executive, 2000).

Respirable dust is approximately equivalent to the fraction of the airborne material that penetrates the gas-exchange region of the lung. The respirable fraction varies for different individuals; however, it is possible to define a target specification for sampling instruments that approximates the respirable fraction for the average person (International Organization for Standardization, 1995). Respirable dust is generally collected using a cyclone pre-selector (Health and Safety Executive, 2000)

The term 'total' dust refers to the total particulate as represented (in North America at least) by the fraction that is collected by a closed-face three-piece plastic sampling cassette that holds a 37-mm filter (Eller, 1994; Occupational Safety and Health Administration, undated). The term 'total' dust is not equivalent to all airborne dust; in fact, measurements of inhalable dust using the IOM sampling head are 1.0–2.5 times higher than 'total' dust levels that are measured by a closed-face 37-mm filter cassette, depending on the aerodynamic diameter of the particle (Werner *et al.*, 1996).

Methods for the measurement of elemental carbon exist but have not been widely used in the carbon black manufacturing industry (e.g. Eller, 1994; Occupational Safety and Health Administration, undated). These are relatively complicated and expensive, but could be applied to environments in which mixed dust exposures exist, e.g. in tyre manufacture.

Recently, several studies have attempted to collect data on the size distribution of airborne particulates at carbon black manufacturing sites (Wake *et al.*, 2002; Kuhlbusch *et al.*, 2004;). This can be achieved by using a scanning mobility particle sizer (SMPS) linked to a condensation particle counter. The SMPS fractionates the particles that are in the size range of 15–734 nm through their electrical mobility. Kuhlbusch *et al.* (2004) also used an aerodynamic particle sizer to identify and characterize airborne particles with

an aerodynamic diameter in the range of 0.5–15 μm by drawing the aerosol through a nozzle that accelerates the particles. The velocity of the particles is dependent upon their aerodynamic diameter (Kuhlbusch *et al.*, 2004).

The bioavailability of the PAHs adsorbed onto the surface of carbon black has been assessed by quantifying the concentration of the major adsorbed PAH, pyrene, using its urinary metabolite, 1-hydroxypyrene. The urine was adjusted to pH 5.0 and incubated with 50 μL β-glucuronidase/aryl sulfatase for 4 hours at 37 °C. After extraction and washing, the hydrolysed urine was injected into an HPLC unit with a fluorescence detector. The limit of detection was approximately 0.075 nmol/L [16 ng/L] (Gardiner *et al.*, 1992b). Similar methods have been reported more recently (Tsai *et al.*, 2002a).

(b) Carbon black in various matrices

Several organizations have published standard methods for the determination of carbon black in rubber (International Organization of Standardization, 1992; ASTM International, 2000 [D2663–95a]; Standards Australia International Ltd, 2001; ASTM International, 2003 [D6370–99], 2005b [D3192–05]). Standard methods for determining carbon black in polyolefin pipes and fittings are also available (International Organization for Standardization, 1986; ASTM International, 2001 [D4218–96]; Japanese Standards Association, 2003).

ASTM International (2004a) [D3849–04] has also published a method for the morphological characterization of carbon black primary aggregates by transmission electron microscopy to derive the mean particle and aggregate size of carbon black in the dry (as manufactured) state or in products. ASTM International (2004b) [D6602–03b] also has a method for distinguishing ASTM-type carbon black, in the N100 to N900 series, from other environmental particulates.

(c) Adsorbates on carbon blacks

Several methods have been reported for the extraction and analysis of adsorbates on carbon black. Soxhlet extraction with various organic solvents has been the primary method used to remove adsorbed chemicals from samples of carbon black, but vacuum sublimation or extraction combined with sonification have also been used (Zoccolillo *et al.*, 1984). The efficiency of Soxhlet extraction depends on extraction time and solvent, the type of carbon black, the relationship between weight of sample/volume of solvent and the amount of extractable material. Some solvents can react with the surface groups of carbon black and form artefacts during the extraction (Fitch *et al.*, 1978).

Taylor *et al.* (1980) examined the efficiency of three solvents (24-hour Soxhlet) as measured by extractability of benzo[*a*]pyrene from five furnace blacks. They found that toluene and benzene had quite similar efficiencies, but that cyclohexane could not remove more than 10% of the benzene-extractable benzo[*a*]pyrene from any of the furnace blacks. Toluene was, however, clearly the best extractant when the adsorbate content of the carbon black was low (less than 1 mg/kg).

Analytical methods used to determine the components of carbon black extracts produced by Soxhlet extraction with various solvents have been summarized (Jacob & Grimmer, 1979). Common methods include gas chromatography with packed and capillary columns and HPLC with spectrophotometric and spectrofluorometric detection.

Zoccolillo *et al.* (1984) reported the determination of PAHs in carbon black by Soxhlet extraction with benzene, purification by silica gel thin-layer chromatography and analysis by gas chromatography and/or HPLC.

Jin *et al.* (1987) described a method for the analysis of nitroarenes in carbon black which involved Soxhlet extraction of the sample with organic solvents (the use of chlorobenzene resulted in the highest overall yield), pre-separation by column chromatography on silica gel and separation and determination by reverse-phase HPLC with ultraviolet detection.

Several national and international organizations have published standard methods for the determination of total solvent-extractable material in carbon black and related products (International Organization for Standardization, 1988; Standards Australia International Ltd/Standards New Zealand, 2003; ASTM International, 2004c [D4527–99], ASTM International, 2005c [D305–84]). All methods involve Soxhlet extraction of the product with an appropriate solvent (acetone or toluene) and gravimetric determination of the extract residue after removal of the solvent.

1.2 Production and use

Carbon black is produced by the partial oxidation or thermal decomposition of hydrocarbon gases or liquids. Several processes have evolved over the years, yielding a variety of products that differ in particle size, structure, purity and method of manufacture, including furnace black, thermal black, lampblack, acetylene black and channel black. Furnace black is by far the predominant form of carbon black in commerce, and accounts for over 95% of total world production of carbon black. Thermal black is far less important and only minor quantities of the other three blacks are used in highly specialized applications. Approximately 70% the world consumption of carbon black is for the production of tyres and tyre products for automobiles and other vehicles. Approximately 20% is used in other rubber products such as hose, belting, mechanical and moulded goods, footwear and other uses, and the remainder (nearly 10%) is used in plastics, printing ink, paint, paper and miscellaneous applications (Auchter, 2005).

1.2.1 *Production*

(a) Processes

Carbon black was first produced many centuries ago for use as a pigment in inks and lacquers by a simple lampblack process. The channel black process was developed in the nineteenth century when large quantities of natural gas became available, but worldwide use of carbon black was still less than 1000 tonnes. Following the discovery of the

usefulness of carbon black in the reinforcement of rubber at the beginning of the twentieth century, production increased rapidly and a gas-furnace process was introduced in the 1920s. In the 1940s, oil supplanted gas as a feedstock in the production of furnace black and, following the end of the Second World War, carbon black manufacture was established in many industrialized countries (Dannenberg *et al.*, 1992).

(i) *Furnace black*

The oil-furnace process generates > 95% of all carbon black produced in the world. It was developed in 1943 and rapidly displaced previous gas-based technologies because of its higher yields and the broader range of carbon blacks that could be produced. It also captures particulates effectively and has greatly reduced their release into the environment around carbon black plants. The oil-furnace process is based on the partial combustion of residual aromatic oils. Because residual oils are widely available and are easily transported, the process can be carried out with little geographical limitation, which has led to the construction of carbon black plants all over the world. Plants are typically located in areas of tyre and rubber goods manufacture. Because carbon black has a relatively low density, it is far less expensive to transport feedstock than to transport the carbon black (Wang *et al.*, 2003).

The basic process consists of atomizing preheated oil in a combustion gas stream that is formed by burning fuel in preheated air. Some of the atomized feedstock is combusted with excess oxidant in the combustion gas. Temperatures in the region of carbon black formation range from 1400 to > 1800 °C. The gases that contain carbon black are quenched by spraying water into the stream as it passes through a heat exchanger and into a bag filter. The bag filter separates the unagglomerated carbon black from the by-product tail gas, which comprises mainly nitrogen and water vapour. The fluffy black from the bag filter is mixed with water to form wet granules that are dried in a rotary dryer and bagged or pelleted (Wang *et al.*, 2003).

Preferred feedstocks for the oil-furnace process are heavy fuel oils such as catalytic cracker residue (after removal of residual catalyst), ethylene cracker residues and distilled heavy coal-tar fractions. Other specifications of importance are absence of solid materials, moderate-to-low sulfur content and low alkali metal content (Wang *et al.*, 2003).

(ii) *Thermal black*

Thermal black is made by the thermal decomposition of natural gas, coke-oven gas or liquid hydrocarbons in the absence of air or flames. Its economic production requires inexpensive natural gas. Today, it is among the most expensive of the carbon blacks that are regularly used in rubber goods. Because of its unique physical properties, it is used in some rubber and plastics applications such as O-rings and seals, hose, tyre inner liners, V-belts, other mechanical goods and in cross-linked polyethylene for electrical cables (Wang *et al.*, 2003).

The thermal black process, which dates from 1922, is cyclic and uses two refractory-lined cylindrical furnaces or generators. While one generator is heated to about 1300 °C

with a burning mixture of air and hydrogen off-gas, the other pre-heated generator is fed with natural gas which 'cracks' to form carbon black and hydrogen. The effluent gas, which comprises approximately 90% hydrogen, carries the carbon black to a quench tower where water sprays lower its temperature before it enters the bag filter. The carbon black collected from the filters is screened, hammer-milled and then bagged or pelleted (Wang *et al.*, 2003).

(iii) *Lampblack*

The lampblack process is the oldest and most primitive carbon black process that is still being carried out. The ancient Egyptians and Chinese employed techniques similar to modern methods that collect the lampblack by deposition on cool surfaces. Basically, the process consists of burning various liquid or molten raw materials in large, open, shallow pans under brick-lined flue enclosures with a restricted air supply. The smoke from the burning pans passes through low-velocity settling chambers from which the carbon black is cleared by motor-driven ploughs. In more modern installations, the carbon black is separated by cyclones and filters. Lampblacks have similar properties to the small-surface area oil-furnace blacks. Production is small, and is mostly carried out in Europe. The main use of lampblack is in paints, as a tinting pigment in which a blue tone is desired and in some special applications in the rubber industry (Wang *et al.*, 2003).

(iv) *Acetylene black*

The high carbon content of acetylene (92%) and its exothermic decomposition to carbon and hydrogen make it an attractive raw material for conversion to carbon black. Acetylene black is made by a continuous decomposition process at atmospheric pressure and 800–1000 °C. Acetylene is fed into reactors where, at temperatures above 800 °C, the exothermic reaction is self-sustaining and requires cooling by water to maintain a constant reaction temperature. The carbon black-laden hydrogen stream is then cooled followed by separation of the carbon from the hydrogen tail gas. Acetylene black is very fluffy with a bulk density of only 19 kg/m^3, is difficult to compact and resists pelletization. Commercial grades are compressed to various bulk densities of up to 200 kg/m^3. The unique features of acetylene black result in high electrical and thermal conductivity, low moisture adsorption and high liquid absorption (Wang *et al.*, 2003).

(v) *Channel black*

Between the First and the Second World Wars, the channel black process produced most of the carbon black used worldwide for rubber and pigment applications. The last channel black plant in the USA was closed in 1976. The demise of channel black was caused by environmental problems, cost, smoke pollution and the rapid development of oil-furnace process grades that were equal or superior to channel black products, particularly for use in synthetic rubber tyres (Wang *et al.*, 2003).

The name channel black derived from the steel channel irons used to collect carbon black deposited by small flames of natural gas that impinged on their surface iron channels. Today, coal-tar fractions are used as raw material in addition to natural gas and,

in modern installations, channels have been replaced by water-cooled rollers. The carbon black is scraped off the rollers, and the off-gases from the steel box-enclosed rollers are passed through bag filters where additional carbon black is collected. The oils used in this process must be vapourized and conveyed to the large number of small burners by means of a combustible carrier gas, such as coke-oven gas. The yield of rubber-grade carbon black is 60% and that of high-quality colour grades is 10–30%. The characteristics of carbon blacks from roller process impingement are basically similar to those of channel blacks. The grades of smaller particle size are used as colour (pigment) carbon blacks and the larger (~30 nm) grade is used in rubber (Wang *et al.*, 2003).

(b) Capacity, production and consumption of carbon black

Carbon black is produced worldwide. Table 1.8 presents world capacity for carbon black production.

The consumption of carbon black in western Europe over the past decade rose to 1509 thousand tonnes in 2000 but has steadily declined since then to 1397 thousand tonnes in 2004. Production capacities were sharply reduced during this time of lower demand, from 1455 thousand tonnes in 2000 to 1273 thousand tonnes in 2004 (see Table 1.9) (Auchter, 2005).

Trends in production of carbon black in central and eastern European countries over a similar time period are presented in Table 1.10.

As in western Europe, consumption (and also production and capacity) of carbon black in the USA peaked in 2000. Table 1.11 provides an overview of carbon black supply and demand in the USA since 1971. There are currently five producers of furnace black in the USA, one of which also makes thermal black. In addition, two manufacture bone black and another produces lampblack (Auchter, 2005).

There are eight producers of carbon black in Japan; the seven producers of furnace black represent 97% of total capacity and one company produces acetylene black. Japanese supply of and demand for carbon black since 1991 are summarized in Table 1.12.

Annual capacity of producers of carbon black in other countries in Asia and the East (as of January 2005) was estimated to be 3.25 million tonnes, including Australia (87 000 tonnes), China (1 381 000 tonnes), India (584 000 tonnes), Indonesia (135 000 tonnes), Malaysia (100 000 tonnes), the Philippines (1000 tonnes), Republic of Korea (620 000 tonnes), Singapore (12 000 tonnes), Taiwan, China (110 000 tonnes) and Thailand (220 000 tonnes) (Auchter, 2005).

1.2.2 *Use*

The primary use of carbon black is in rubber products, particularly in tyres, but also in many other automotive and non-automotive rubber applications. Carbon black also is used in paint, plastics, paper, inks, ceramics and other minor applications. Consumption patterns in the USA, western Europe and Japan in 2004 are summarized in Table 1.13.

Table 1.8. World capacity for carbon black production (as at 1 January 2005)

Region	Million tonnes	Percentage of total
North America[a]	2.3	25
South America	0.5	6
Western Europe	1.3	14
Eastern Europe	1.4	16
Japan	0.8	9
Other Asia[b]	3.3	26
Africa and Middle East	0.4	4
Total	10.0	100

From Auchter (2005)
[a] Canada, Mexico and the USA
[b] Australia, China, India, Indonesia, Malaysia, the Philippines, Republic of Korea, Singapore and Thailand

Table 1.9. Western European production capacity for carbon black (as at 1 January 2005)

Country	No. of plants	Thousand tonnes	Percentage
Belgium	1	6	<1
France	4	264	21
Germany	4	322	25
Italy	3	221	17
Netherlands	2	155	12
Portugal	1	35	3
Spain	1	60	5
Sweden	1	40	3
United Kingdom	2	170	13
Total	19	1273	100

From Auchter (2005)

Table 1.10. Central and eastern European production of carbon black (thousand tonnes)

Year	Croatia	Czech Republic	Hungary	Poland	Romania	Russia	Other[a]	Total
1994	22	41	42	26	19	350	40	540
1997	24	53	50	25	21	316	25	514
2000	21	65	50	24	13	425	23	621
2002	20	80	50	26	16	529	26	747
2004	25	95	50	19	18	670	20	897

From Auchter (2005)
[a] Mainly Slovakia and the Ukraine

Table 1.11. Capacity, production and consumption of carbon black in the USA (thousand tonnes)[a]

Year	No. of operating plants	Capacity	Production	Consumption
1971	42	1820	1380	1295
1981	35	1575	1285	1200
1991	21	1538	1216	1195
1994	21	1635	1501	1505
1997	21	1889	1592	1592
2000	21	2020	1642	1670
2004	18	1847	1617	1592

From Auchter (2005)
[a] Includes furnace black, thermal black, acetylene black, bone black and lampblack

Table 1.12. Japanese capacity, production and consumption of carbon black (thousand tonnes)

Year	Capacity	Production	Consumption
1991	788	793	796
1994	785	704	714
1997	845	776	828
2000	787	767	828
2004	751	804	872

From Auchter (2005)

Table 1.13. Consumption patterns of carbon black in 2004 (thousand tonnes)

Use	USA	Western Europe	Japan
Automotive use			
Tyres, tubes and tread	1098	936	655
Belts, hoses and miscellaneous	159		
Other rubber products (industrial, molded and extruded goods)	145	335	170
Non-rubber use (paint, plastics, paper, ink, ceramics and other)	191	126	47
Total	1593	1397	872

From Auchter (2005)

Carbon black is used to reinforce rubber—that is, to increase the resistance of rubber to abrasion, tear, fatigue and flexing. It also improves the tensile strength and processing characteristics of many elastomers (natural and synthetic). Consumption of carbon black worldwide is highly dependent on the rubber industry, which typically accounts for 89–91% of total consumption (Auchter, 2005).

The major use for carbon black in elastomers is in tyre manufacture (automobile, truck, bus, agricultural, aircraft and industrial), retread rubber and inner tubes. Carbon black typically comprises 20–40% of the tyre by weight. Other automotive applications of carbon black include its use in elastomers for wire and cable, belts, hoses, O-rings, insulation stripping, shock and motor mounts and other such products. Carbon black is used in elastomers in applications other than automotive, including hoses, conveyor belts, roofing, covers for wire and cable, coated fabrics, gaskets, packaging, gloves, footwear, floor mats, tape, hard rubber products, pontoons and toys (Auchter, 2005).

Plastics are the largest non-elastomer use for carbon black. In addition to use as a colourant, carbon black is frequently used as an effective stabilizer of ultraviolet light, an additive for controlling electrical conductivity or a strength-imparting filler.

The printing ink industry consumes almost one-third of the special industrial (non-rubber) carbon blacks produced in the USA. The grade and concentration used depend on the type and quality of the ink and are selected for factors such as the required degree of colour, gloss, tone, viscosity, tack and rheological properties. Carbon black content of inks ranges from 5 to 22%.

Carbon black is used as a colourant for tinting and pigmentation in all types of paints and coatings. Relatively small quantities are added to some industrial formulations (e.g. primers and floor finishes) to impart electrical conductivity.

The production of carbon paper is the principal use of carbon black in the paper industry. Other uses are in photograph albums, leatherboard, wrapping and bag papers, in backing paper for photographic film and in highly conductive and electrosensitive papers.

Miscellaneous other applications of carbon black are in dry-cell batteries, photocopy toners and magnetic tapes (Auchter, 2005).

1.3 Occurrence

1.3.1 *Natural occurrence*

Carbon black does not occur as a natural product.

1.3.2 *Occupational exposure*

Human exposure is primarily to the aggregate and agglomerate forms of carbon black.

A large amount of data on exposure to carbon black is available from surveys conducted in the carbon black manufacturing industry in Europe and the USA. Much less is known on exposure to carbon black in downstream user industries, most notably the rubber industries. In these industries, carbon black is often only one of many substances being used and its specific measurement has rarely been taken. Measurements of occupational exposure to particulates are generally taken using non-specific dust sampling methods, as described in Section 1.1.5(*a*). For the carbon black manufacturing industry, the assumption can be made that carbon black particles are predominantly measured by these sampling devices (Kuhlbusch *et al.*, 2004). Other important issues in a review of occupational exposure to carbon black are the physical and chemical characteristics of the particles. Generally, very little is known about the levels of ultrafine carbon black in manufacturing and downstream user industries.

The National Occupational Exposure Survey conducted in the USA by the National Institute for Occupational Safety and Health (1995) between 1981 and 1983 indicated that about 1 729 000 employees were potentially exposed to carbon black. [The estimate is based on a survey of companies and did not involve measurements of actual exposure, and might, for many workers, involve very low levels and/or incidental exposure to carbon black.]

No data were available on exposure to carbon black in the non-automotive rubber, paint, printing or printing ink (i.e. ‘user’) industries. Operators in user industries who handle fluffy or pelleted carbon black during rubber, paint and ink production are expected to have significantly lower exposures to carbon black than workers in carbon black production. Other workers in user industries who handle it occasionally have little opportunity for exposure. End-users of these products (rubber, ink or paint) are unlikely to be exposed to airborne carbon black particles, which are bound within the product matrix.

(a) Manufacturing industries

The results of two large-scale multiphase industry-wide exposure assessment surveys in Europe and the USA are summarized below, followed by a review of results from smaller and often older studies. In the European study, exposures to inhalable and respirable dust were measured. Levels of exposure to carbon black in the carbon black manufacturing industry in the USA have been expressed as 'total' or respirable dust and, more recently, as inhalable dust. A study by Kerr *et al.* (2002) investigated the relationship between inhalable dust (using the IOM sampling head) and 'total' dust (using 37-mm closed cassettes) and found a ratio of 2.97 (inhalable:total) which can be used to convert 'total exposure' into inhalable dust exposure, as performed by Harber *et al.* (2003) for the data from the USA.

(i) *Major surveys conducted in Europe*

A large study of the respiratory health effects of exposure to carbon black dust was carried out in the European carbon black manufacturing industry (Gardiner *et al.*, 1993, 2001; van Tongeren *et al.*, 2002). As part of this study, a large quantity of exposure data was collected during three surveys (survey I, 1987–89; survey II, 1991–92; and survey III, 1994–95) in 18 factories in seven countries across western Europe (France, Germany, Italy, the Netherlands, Spain, Sweden, United Kingdom) (Gardiner *et al.*, 1992a, 1996; van Tongeren, 2000; van Tongeren *et al.*, 2000). Both respirable and inhalable dust fractions were measured, and a total of 8015 inhalable and 7404 respirable measurements were collected from a large proportion of the workforce. Tables 1.14 and 1.15 present the results of exposure measurements of inhalable and respirable dust by occupational category, respectively.

The highest exposure levels were observed for warehousemen, who are responsible for the packing and shipment of carbon black, and the site crew, who are responsible for cleaning any carbon black spillages. The arithmetic mean exposure to inhalable dust for the warehousemen was reduced from 3.4 mg/m^3 in the first survey to 1.7 mg/m^3 in the second and 1.5 mg/m^3 in the third survey. Similar declining trends were observed for other occupational categories (van Tongeren, 2000; van Tongeren *et al.*, 2000).

van Tongeren (2000) calculated the probability that the long-term mean exposure of a worker's to inhalable dust is in excess of the occupational exposure limit of 3.5 mg/m^3 and found that, for warehousemen, this probability declined from 42% in the first survey to 9% in the second and to only 4% in the third survey. For the site crew, these probabilities were 21%, 10% and 10%, respectively. Personal exposure levels varied significantly across the various factories, even within the same job category.

As the mortality studies in Europe were carried out in the United Kingdom and Germany, the levels of exposure to inhalable dust for the packers (warehousemen) in factories in these countries have been presented in Table 1.16. The results suggest that there is considerable variation in exposure between the factories. For example, in the first survey (1987–89), exposure to inhalable dust varied from 0.1 mg/m^3 in one German factory to 6 mg/m^3 in another German factory. The exposure levels for the warehouseman

Table 1.14. Exposure measurements of inhalable dust (mg/m^3) by job category and survey in the European carbon black manufacturing industry

Job category	Survey I (1987–89)					Survey II (1991–92)					Survey III (1994–95)				
	No.	AM	GM	GSD	Range	No.	AM	GM	GSD	Range	No.	AM	GM	GSD	Range
Administrative staff	313	0.26	0.16	2.63	0.02–3.55	516	0.27	0.15	3.00	0.02–7.46	571	0.24	0.11	3.10	0.02–7.35
Laboratory staff/ process control room operator	192	0.60	0.32	2.91	0.02–10.15	514	0.37	0.23	2.82	0.02–4.58	491	0.32	0.18	2.95	0.02–4.88
Instrument mechanic/ electrician	111	1.37	0.54	3.62	0.02–26.83	437	0.63	0.37	2.99	0.02–8.61	284	0.49	0.28	2.99	0.02–11.31
Process foreman/ furnace operator	169	0.91	0.49	3.11	0.02–10.29	491	0.57	0.30	3.38	0.02–9.49	489	0.53	0.28	3.31	0.02–8.07
Fitter/welder	139	1.66	1.01	2.81	0.02–19.63	358	1.08	0.62	3.27	0.02–8.75	420	0.87	0.49	3.15	0.02–9.39
Process/conveyor operator	205	1.67	0.71	3.58	0.02–26.51	532	0.93	0.52	3.17	0.02–16.92	411	0.66	0.36	3.14	0.02–14.36
Warehouseman	155	3.35	1.69	3.65	0.02–35.44	455	1.68	0.88	3.44	0.02–19.95	428	1.52	0.84	2.98	0.02–37.28
Site crew	32	3.72	1.24	4.62	0.13–18.25	151	1.33	0.60	3.57	0.02–18.07	151	1.17	0.51	3.97	0.02–12.53
Total[a]	1316	1.30	0.48	3.96	0.02–35.44	3454	0.79	0.37	3.60	0.02–19.95	3245	0.67	0.29	3.68	0.02–37.28

Adapted from van Tongeren (2000)

AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation; No., number of measurements

[a] Summary of results of all measurements (not mean of means)

Table 1.15. Exposure measurements of respirable (mg/m^3)dust by job category and survey in the European carbon black manufacturing industry

Job category	Survey I (1987–89)					Survey II (1991–92)					Survey III (1994–95)				
	No.	AM	GM	GSD	Range	No.	AM	GM	GSD	Range	No.	AM	GM	GSD	Range
Administrative staff	299	0.24	0.14	2.28	0.02–9.31	497	0.19	0.11	2.74	0.02–5.28	525	0.17	0.08	2.88	0.02–4.32
Laboratory staff/process control room operator	185	0.22	0.16	2.20	0.02–2.47	497	0.20	0.13	2.56	0.02–3.65	522	0.18	0.10	2.78	0.02–2.91
Instrument mechanic/ electrician	118	0.33	0.20	2.51	0.02–6.54	302	0.37	0.17	2.89	0.02–24.65	314	0.21	0.12	2.61	0.02–2.49
Process foreman/furnace operator	153	0.31	0.21	2.36	0.02–4.81	406	0.34	0.19	2.80	0.02–4.16	470	0.22	0.12	2.96	0.02–3.68
Fitter/welder	144	0.42	0.29	2.42	0.02–4.11	294	0.39	0.21	2.95	0.02–7.71	361	0.28	0.15	2.92	0.02–3.55
Process/conveyor operator	200	0.54	0.24	2.83	0.02–16.69	389	0.35	0.19	3.04	0.02–3.35	396	0.34	0.17	3.16	0.02–4.41
Warehouseman	161	0.82	0.44	2.90	0.02–12.00	394	0.69	0.34	3.02	0.02–18.99	394	0.54	0.28	3.18	0.02–6.23
Site crew	37	0.66	0.29	3.42	0.02–7.41	171	0.55	0.26	3.03	0.02–20.70	175	0.49	0.18	4.00	0.02–6.60
Total[a]	1297	0.40	0.21	2.69	0.02–16.69	2950	0.36	0.18	2.46	0.02–24.65	3157	0.28	0.13	3.17	0.02–6.60

Adapted from van Tongeren (2000)
AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation; No., number of measurements
[a] Summary of results of all measurements (not mean of means)

Table 1.16. Exposure of warehousemen to inhalable dust (mg/m^3) in factories the United Kingdom and Germany

Country	Factory	1987–89				1991–92				1993–95			
		No.	AM	GM	GSD	No.	AM	GM	GSD	No.	AM	GM	GSD
United Kingdom	1	10	3.50	1.71	3.91	30	2.68	1.51	3.83	53	3.47	1.77	3.4
	2	14	3.26	1.62	4.03	31	1.24	0.8	2.64	38	0.66	0.46	2.75
Germany	6	11	2.76	1.47	5.04	43	1.78	1.04	3.57	44	2.71	1.29	3.37
	7	4	0.11	0.06	3.94	11	0.36	0.2	4				
	8	4	0.62	0.47	2.29	14	0.84	0.59	2.98				
	9	11	6.02	3.31	3.51	34	2.17	1.71	1.95	20	1.44	1.10	2.42
	10	6	1.94	1.75	1.66	50	2.13	0.84	3.82	62	1.01	0.65	3.08

Adapted from van Tongeren (2000)
AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation; No., number of measurements

in this German factory fell over time to 1.44 mg/m^3 in 1993–95. Exposure in factories in the United Kingdom was between 3 and 3.5 mg/m^3 in 1987–89; however, while the exposure among the warehousemen in one factory declined to approximately 0.7 mg/m^3 in 1993–95, exposure in the other factory remained relatively stable.

(ii) *Major surveys in the USA*

Five industry-wide exposure surveys were conducted in the USA (Harber *et al.*, 2003) in 1979 (Smith & Musch, 1982), 1982–83 (Musch & Smith, 1990), 1987 (Musch & Smith, 1990), 1993–95 (Muranko *et al.*, 2001) and 2000–01 (unpublished).

In the first survey, a total of 1951 personal samples (1564 'total' dust, 387 respirable dust) were collected from 24 carbon black production facilities in the USA (Smith & Musch, 1982). A summary of the results are provided in Table 1.17. Workers who were involved in filling and stacking bags of carbon black (material handling) had the highest mean exposures to 'total' dust of up to 2.2 mg/m^3. Samples were not taken from all employment areas in every factory and the numbers of samples taken differed from area to area.

Table 1.17. Average dust exposure by employment area in carbon black production facilities in the USA (1979–80)

Area of employment	'Total' dust			Respirable dust		
	No. of plants	No. of samples	GM (mg/m^3)	No. of plants	No. of samples	GM (mg/m^3)
Administration	8	72	0.01	2	28	0.00
Laboratory	17	133	0.04	10	35	0.01
Production	22	480	0.44	14	111	0.13
Maintenance	19	386	0.59	11	89	0.12
Material handling	20	493	1.45	13	124	0.35

From Smith & Musch (1982)
GM, geometric mean

The particulate sampling survey of 1979–80 (Smith & Musch, 1982) was conducted again in 1980–82 and in 1987 (Musch & Smith, 1990). The number of participating companies decreased from seven to six and the number of plants decreased from 24 to 17. In 1980–82, 973 'total' dust samples were taken; the number fell to 577 in 1987. The data are summarized in Table 1.18. A drop of approximately 50% in exposure was evident in maintenance and material-handling sectors of the factories. Of the job categories in the maintenance sector, the following reductions were seen between the second and third surveys: utility, 0.89 down to 0.55 mg/m^3; inplant, 0.79 down to 0.52 mg/m^3; shop, 1.00 down to 0.07 mg/m^3; instrument, 0.47 down to 0.17 mg/m^3; and foreman, 0.35 down to 0.18 mg/m^3. Of the job categories in the material-handling sector, the following

reductions were seen between the second and third surveys: stack and bag, 1.92 down to 0.77 mg/m^3; bagger, 2.67 down to 0.85 mg/m^3; bulk loader, 2.07 down to 0.82 mg/m^3; stacker, 1.15 down to 0.70 mg/m^3; fork-lift truck driver, 0.53 down to 0.34 mg/m^3; and foreman, 0.18 down to 0.02 mg/m^3.

Table 1.18. Average exposure to 'total' dust by employment area in carbon black production facilities in the USA in 1980–82 and 1987

Area of employment	1980–82		1987	
	No. of samples	GM (mg/m^3)	No. of samples	GM (mg/m^3)
Administration	4	0.06	2	0.02
Laboratory	85	0.51	23	0.20
Production	273	0.45	164	0.45
Maintenance	363	0.71	181	0.36
Material handling	248	1.63	207	0.71

From Musch & Smith (1990)
GM, geometric mean

A later industry-wide survey was carried out between 1993 and 1995, during which period 1004 'total' and 1056 respirable dust measurements were collected from 21 plants from seven companies (Muranko *et al.*, 2001). The results of these measurements are summarized in Table 1.19. Results indicated that exposure had declined since the previous studies. Highest exposure levels to 'total' dust were observed for material handling; respirable dust levels were much lower. Results from 680 matched pairs of respirable and 'total' samples found a mean ratio of 0.37 (respirable:'total').

A survey was carried out in 2000–01 to measure exposure to inhalable and respirable dust in 22 plants from seven different carbon black manufacturing companies. No further details were available, although a summary of exposure to inhalable dust only by job category from this survey has been published (Harber *et al.*, 2003) (Table 1.20).

Using the conversion factor provided by Kerr *et al.* (2002), the results from the 'total' dust measurements were converted into inhalable dust (Harber *et al.*, 2003). Table 1.20 shows the estimated levels of exposure to inhalable dust by job category and sampling survey. In the early surveys, only geometric means (GMs) were reported. The levels of exposure to inhalable dust (GM) during the handling of materials declined from 4.31 mg/m^3 and 4.84 mg/m^3 in the first and second surveys to 2.11 mg/m^3, 1.13 mg/m^3 and 1.57 mg/m^3 in the third, fourth and fifth surveys, respectively. Levels of exposure in other job categories were lower in all of the surveys, although the arithmetic mean exposure in production in 1987 was higher than that in materials handling (7.70 mg/m^3 versus 6.40 mg/m^3).

Table 1.19. Levels of exposure to 'total' and respirable dust (mg/m^3) in the carbon black manufacturing industry in the USA, 1993–95

	No. of samples	AM	GM	GSD	Range	% >OEL
'Total'						
Administration	0					
Laboratory	144	0.30	0.14	3.55	0.01–2.59	0.5
Production	321	0.41	0.14	4.38	0.01–13.25	1.5
Maintenance	289	0.50	0.22	3.66	0.01–9.66	1.6
Material Handling	250	1.16	0.38	4.51	0.01–12.05	6.9
All	1004	0.59	0.20	4.31	0.01–13.25	2.6
Respirable						
Administration	0					
Laboratory	146	0.08	0.05	2.94	0.01–0.80	–
Production	321	0.11	0.05	3.36	0.01–2.62	–
Maintenance	323	0.14	0.07	3.35	0.01–1.41	–
Material Handling	266	0.23	0.11	3.38	0.01–2.31	–
All	1056	0.15	0.07	3.45	0.01–2.62	–

From Muranko *et al*. (2001)
AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation; OEL, observed effect level

(iii) *Other studies*

Kollo (1960) took 160 measurements in a Russian channel black plant where airborne dust levels ranged from 44 to 407 mg/m^3 in the factory area, from 25.3 to 278.6 mg/m^3 in the working aisles, from 9.3 to 972 mg/m^3 in the pelleting area and from 26.7 to 208.6 mg/m^3 in the packing area.

Komarova (1965) measured exposure to carbon black in the packaging departments of two Russian factories that manufactured lampblack and furnace black. The number of measurements was not specified, but the ranges were 166–1000 mg/m^3 (lampblack) and 60–78 mg/m^3 (furnace black). Slepicka *et al.* (1970) found exposures ranging from 8.4 to 29.0 mg/m^3 in two Czechoslovakian channel black factories between 1960 and 1968, although neither the number of samples nor their location were reported.

A survey in a Russian furnace black factory found a range of concentrations of 90–196 mg/m^3 [number of samples unspecified] (Spodin, 1973). The lowest and highest average concentrations recorded by another Russian factory were 1.53 ± 0.4 mg/m^3 for workers by the hatches of the electrostatic filter and 34.5 ± 8.9 mg/m^3 for workers involved in cleaning the production areas; in total, 109 samples were taken. It was noted that throughout the 1960s and 1970s, workers who packed carbon black were exposed to

Table 1.20. Exposure to inhalable dust (measured or converted from 'total' dust; mg/m^3) by job category and survey in the carbon black manufacturing industry in the USA

	1979–80			1980–82			1987			1993–95			2000–01		
	No.	AM	GM	No.	AM	GM	No.	AM	GM	No.	AM	GM	No.	AM	GM
Administration	72	NA	0.03	4	NA	0.18	2	0.53	0.06	0	–	–	125	0.35	0.18
Laboratory	133	NA	0.12	85	NA	1.51	23	3.15	0.59	144	0.89	0.59	103	0.86	0.44
Production	480	NA	1.31	273	NA	1.34	164	7.70	1.34	321	1.22	0.42	273	1.18	0.47
Maintenance	386	NA	1.75	363	NA	2.11	181	3.62	1.07	289	1.49	0.65	257	1.34	0.66
Materials handling	493	NA	4.31	248	NA	4.84	207	6.40	2.11	250	3.45	1.13	247	2.70	1.57

From Harber *et al*. (2003)
AM, arithmetic mean; GM, geometric mean; NA, not available; No., number of measurements
For 1979, 1983, 1987 and 1995 'total' dust levels were converted to inhalable dust levels based on a 2.97:1.0 ratio for inhalable: 'total'.
The estimated GM for laboratory in 1995 appears to be incorrect when compared with the original data.

two to seven times the maximal permissible concentration (10 mg/m^3 in 1975) for 60–70% of their working shifts (Troitskaya *et al.*, 1975, 1980).

In a mortality study conducted in the United Kingdom (Hodgson & Jones, 1985), a limited amount of exposure data had been collected by Her Majesty's Factory Inspectorate in 1976. Personal samples were taken from 47 people in five carbon black factories; 24 (51%) of the samples were > 3.5 mg/m^3. The highest exposure recorded for routine work was 79 mg/m^3, but workers engaged in filter-bag replacement may have been exposed to even higher levels, although exposure measurements were not reported.

In a small study to determine the bioavailability of adsorbed PAHs, Gardiner *et al.* (1992b) measured exposure to inhalable dust for five individuals who packed carbon black into 25-kg bags over a 1-week period. Personal mean dust exposures were 1.53, 5.30, 9.56, 9.99 and 13.21 mg/m^3.

Szozda (1994) reported some exposure levels based on measurements in three Polish carbon black manufacturing plants. Concentrations of total dust varied from < 10 mg/m^3 to 28.51 mg/m^3, although levels of up to 81.26 mg/m^3 were found in the packing department. Levels of carbon black in the same facilities were reported to range between 0.62 mg/m^3 and 60.61 mg/m^3, although levels in the packing department could reach up to 73.34 mg/m^3 with incidental levels of 675.5 mg/m^3. [No method for the measurement of total dust and carbon black was provided, and it is not clear what is meant by the various ranges in exposure. The result does, however, suggest that the exposure levels in these Polish carbon black manufacturing plants are higher than those in the USA and western Europe.]

(iv) *International comparison and trends over time*

It is feasible that levels of exposure to carbon black differ between workers who are employed only in the furnace process and those who are employed in other production processes (either exclusively or in addition to the furnace process). Unfortunately, the data from studies in western Europe and the USA do not allow analyses by process, and hence no objective information is available to confirm this.

A comparison of exposure surveys in Europe and the USA (Tables 1.14 and 1.20) that were carried out between the late 1980s and mid-1990s suggest that, at least for levels of inhalable dust, exposure was somewhat higher in the USA than in western Europe. For example, the overall arithmetic exposure to inhalable dust for the warehouseman in the western European study varied from 3.35 mg/m^3 in 1987–89 to 1.52 mg/m^3 in 1993–95 compared with 6.40 mg/m^3 (1987) and 3.45 mg/m^3 (1994–95) for materials handling in the study in the USA. In contrast, levels of exposure to respirable dust in the USA were lower than those in western European factories (Tables 1.15 and 1.19). These apparently contradictory results may indicate that the conversion factor (2.97) used in the studies to convert 'total' to inhalable dust levels in the USA may have been too high.

Werner *et al.* (1996) also compared the inhalable and 'total' dust fractions and observed lower inhalable:'total' dust ratios. It is possible that the application of one conversion factor for all exposure levels in every part of the process and each factory may

lead to erroneous results, as the inhalable:'total' dust ratio depends on particle size, which probably varies between factories and stages in the process. In addition, in the European study, only the filters were analysed gravimetrically rather than the whole IOM cassette, as is standard practice. This was due to external contamination of the cassettes, and could have resulted in an underestimation of the European levels by a factor of up to 20% (Gardiner *et al.*, 1992a,c).

The available data on exposure in the carbon black manufacturing industry suggest that levels have been declining since the 1960s and 1970s. Van Tongeren *et al.* (2000) analysed the data from the European carbon black manufacturing industry and found statistically significant reductions in inhalable dust exposure levels between the first (1987–89) and third (1994–95) survey, ranging from approximately a 30% reduction (GM) for the administrative staff to nearly a 60% reduction for the warehousemen and site crew. In the USA, exposure levels in warehouse operations decreased by more than 50% (GM) between 1979 and 1987 and by an additional 25% (GM) between 1987 and 2000, while significant declines occurred between 1987 and 2000 in production (AM, 85%; GM, 65%) and maintenance (AM, 63%; GM, 38%) (Harber *et al.*, 2003).

A retrospective exposure assessment was carried out for the two carbon black producing factories in the United Kingdom, which was used for the mortality study of the carbon black workers (Sorahan *et al.*, 2001). The retrospective exposure estimates were based on information provided by the companies, including exposure data, production rates and process changes. Levels of exposure to inhalable dust in the 1950s were estimated to be approximately 20 mg/m^3 for warehousemen and 30 mg/m^3 for cleaning staff (non-office). [The Working Group noted that these estimates were predominantly based on estimated effects of changes in production or control measures rather than on quantitative data, and should therefore be interpreted with caution.]

It is probable that the reduction in exposure is caused mainly by changes in the process, technological improvements, increases in the proportion of the product that is bulk loaded (by trucks and trains), hygiene and cleaning regimes, and legislative enforcement (Harber *et al.*, 2003). [Some of the decline in exposure may also have been the result of outsourcing heavily exposed tasks to other companies or contractors. Even when they had worked at the carbon black manufacturing facilities for long periods of time, contractors were not generally included in the exposure studies.]

(v) *Particle size distribution*

Little is known about the size distribution of airborne particles in the carbon black manufacturing industry. Measurements of respirable and inhalable dust have been carried out in the studies in Europe and the USA. In the European study, the respirable dust fraction of the inhalable dust ranged between 0.31 and 0.46; however, in the study in the USA, the respirable dust fraction appeared to be much lower: 0.17 in 2001 and 0.09 in 1993–95 (based on estimated levels of inhalable dust).

Two studies investigated the levels of ultrafine particles at carbon black manufacting sites (Wake *et al.*, 2002; Kuhlbusch *et al.*, 2004).

Kuhlbusch *et al.* (2004) took measurements in the packing areas of three carbon black manufacturing facilities using an SMPS and an aerodynamic particle sizer. Particle number concentrations were determined for three classes of size which correspond to three particle modes: nucleation mode (10–100 nm), accumulation mode (200–700 nm) and coarse mode (1–10 μm). Comparable results were obtained from the three plants and showed two particle modes. During bag filling, the particle number concentrations increased for particles > 400 nm aerodynamic diameter with modes of around 1 μm and > 8 μm. Ultrafine particle emissions (< 100 nm aerodynamic diameter) detected in the bag-filling areas could be attributed to forklifts running either on propane or diesel. Another source of ultrafine particles could be butane gas heaters in one of the plants.

The study by Wake *et al.* (2002) used an SMPS to estimate the total number of particles with a diameter between 16.5 and 805 nm inside (bagging) and outside a carbon manufacturing facility. The particle count in the bagging plant was much lower than that measured outside, which was probably due to particles emitted from road vehicles. Compared with other processes, the levels were similar to those found during bagging activities in nickel powder production, titanium dioxide production and plasma coating, but much lower than those found in a steel foundry and near a welding or plastic welding process.

(vi) *Exposure to PAHs*

The retention of particles in the lungs may influence the bioavailability of adsorbed materials. As the retention of particles increases, the potential for adsorbed PAHs to be eluted and absorbed may also increase.

In a study of five nonsmoking warehouse packers in a carbon black (furnace black) manufacturing plant, daily average exposures to dust were measured by air sampling, and urinary excretion of 1-hydroxypyrene (derived from pyrene) was measured in post-shift urine samples for five consecutive days during one work week. The mean ambient dust concentrations over the five days ranged from 1.5 to 13 mg/m^3. Excretion of 1-hydroxypyrene ranged from 0.10 to 0.48 μmol/mol creatinine. A regression model showed a statistically significant relationship between weekly mean concentration of airborne dust and excretion of 1-hydroxypyrene (when assuming zero excretion of 1-hydroxypyrene with zero measured dust exposure). Urinary excretion of 1-hydroxypyrene was statistically significantly lower on Monday than on other days; the authors concluded that this was affected by exposure to dust, and that the pyrene on the dust was bioavailable (Gardiner *et al.*, 1992b). [The Working Group noted that the pyrene content of the carbon black was not measured; the airborne sampling method and particle size distribution were not described. Rather than performing regression analyses based on the mean exposures of individuals for the week, it may be more informative to use the daily values of individuals in a mixed model that accounts for correlation within each of the individual values. Also, using a lag could be informative to account for the time between dust inhalation, pyrene metabolism and 1-hydroxypyrene elimination.]

Levels of particle-bound and gaseous PAHs were determined in a carbon black manufacturing plant in southern Taiwan, China (China) from personal and stationary measurements (Tsai *et al.*, 2002a,b). Dermal exposure was also determined in a small number of workers. Results for gaseous and particle-bound PAHs are shown in Table 1.21 and suggest that levels of total particle-bound and gaseous-phase PAHs were approximately equal. These are somewhat in contrast to the results from stationary measurements in eight production areas in the same carbon black plant (Table 1.22), which showed that less than 3% of total PAHs were particle-bound in all areas except for the packing area, where 31% of the total PAHs was particle-bound (Tsai *et al.*, 2002b).

From the same factory in Taiwan, China (China), urinary samples were obtained from eight pelleting workers and 22 packers on day 1 pre-shift, day 1 post-shift and day 5 post-shift to determine urinary levels of 1-hydroxypyrene (Tsai *et al.*, 2002a). Levels of urinary 1-hydroxypyrene increased over time and the highest levels were observed for the post-shift samples on day 5 (Table 1.23). Separate linear regression models were developed for the pelletizers and the packers to determine the association between levels of airborne (gaseous and particle-bound) and dermal PAHs and urinary 1-hydroxypyrene. The study suggests that urinary 1-hydroxypyrene levels on post-shift day 5 could be a suitable indicator for internal doses of PAHs.

Kuhlbusch *et al.* (2004) reported concentrations of organic, elemental and total carbon in bagging facilities at three plants and showed that elemental carbon accounted for 81–92% of total particle mass on the filters.

Table 1.21. Levels of gaseous and particle-bound total PAHs (ng/m^3) from personal measurements in a carbon black manufacturing plant in Taiwan (China)

	No.	Gaseous-phase		Particle-bound	
		Total PAHs	Range	Total PAHs	Range
Pelleting workers	8	1400	556–4120	1200	386–3670
Packers	22	1320	476–4420	1610	471–4810

Adapted from Tsai *et al.* (2002a)
PAH, polycyclic aromatic hydrocarbon

Table 1.22. Levels of gaseous, particle-bound and total PAHs in eight production areas in a carbon black manufacturing plant in Taiwan (China)

	TSM (mg/m^3)	Total ($\mu g/m^3$)	Particle-bound ($\mu g/m^3$)	Gaseous-phase ($\mu g/m^3$)	% Particle-bound
Unloading of feedstock	0.06	7.88	0.02	7.86	0.25
Furnace	0.09	3.22	0.01	3.21	0.3
Filtering/micro-pulverisation	0.07	1.65	0.02	1.63	1.1
Pelletizing	0.23	1.86	0.07	1.79	3.7
Packaging	2.04	1.99	0.61	1.38	30.8
Office/outside	0.12	0.37	0.00	0.37	0
Office/inside	0.08	1.45	0.01	1.44	0.7
Boundary	0.05	0.33	0.00	0.33	0

Adapted from Tsai *et al*. (2002b)
PAH, polycyclic aromatic hydrocarbon; TSM, total suspended matter

Table 1.23. Levels of urinary 1-hydroxypyrene (μg/g creatinine) of pelleting workers and packers at day 1 pre-shift, day 1 post-shift and day 5 post-shift

	Day 1 pre-shift		Day 1 post-shift		Day 5 post-shift	
	AM	Range	AM	Range	AM	Range
Pelleting	1.00	0.85–1.19	1.67	1.00–2.68	4.24	1.01–9.84
Packaging	0.976	0.68–1.19	2.22	0.95–4.20	4.97	2.19–12.7

Adapted from Tsai *et al*. (2002a)
AM, arithmetic mean

(b) User industries

Information on exposure to carbon black in user industries is not often available; when data are obtainable, they refer to non-specific dust measurements. In the industries, exposure to carbon black is relative to exposure to a complex mixture of particulates. Although results from particulate measurements in these industries may indicate an upper limit of exposure, it was not felt to be informative to review all of the available data on exposures in user industries. This section provides examples of exposure to dust in user industries, but is by no means a comprehensive summary of the available data and must be analysed with caution.

Between July 1972 and January 1977, the Occupational Safety and Health Administration (1977) conducted 85 workplace investigations in the USA to determine compliance with the occupational exposure limit for carbon black of both manufacturers

and users. Approximately 20% of the workplaces inspected were in violation of the exposure limit of 3.5 mg/m^3, and about 60% of these involved exposures that were one to two times higher than the limit.

Several Health Hazard Evaluations have been conducted by the National Institute of Occupational Safety and Health in facilities in the USA that either produced or used carbon black (Belanger & Elesh, 1979; Hollett, 1980; Salisbury, 1980; Boiano & Donohue, 1981). In general, these measurements were below 3.5 mg/m^3, although the studies involved a limited number of samples and a limited number of days over which the measurements were taken.

In the rubber industry, employees are exposed to carbon black mainly in the compounding and Banbury mixing areas. It was reported that the median levels of airborne dust (in which carbon black was one component) in 14 tyre and tube manufacturing plants in the USA were 1.7 mg/m^3 in compounding area samples (individual plant means ranged up to 3.9 mg/m^3) and 1.3 mg/m^3 in the Banbury mixing-area samples (for which the highest plant mean was 4.2 mg/m^3). The values of personal samples were 3.1 mg/m^3 in the compounding area (highest plant mean, 5.0 mg/m^3) and 1.9 mg/m^3 in the Banbury area (highest plant mean, 5.8 mg/m^3) (Williams *et al.*, 1980). A study by the National Institute for Occupational Safety and Health (Heitbrink & McKinnery, 1986) evaluated the effect of control measures at Banbury mixers and the mills beneath the mixers in tyre factories and found lower exposures than those found by Williams *et al.* (1980). The geometric means of exposures of mixer operators at five factories ranged from 0.08 to 1.54 mg/m^3 and those of milling operators at three factories ranged from 0.20 to 1.22 mg/m^3.

Results from studies carried out in the rubber manufacturing industry in Europe in the 1990s are presented in Table 1.24. Two studies were carried out in the Dutch rubber manufacturing industry in the mid- to late 1990s (Meijer *et al.*, 1998; Vermeulen *et al.*, 2000). Vermeulen *et al.* (2000) reported that, since the late 1980s, exposure levels for inhalable particulate in the Dutch rubber manufacturing industry had declined by 5.7% each year. In 1988, the reported mean exposure to inhalable dust (not specifically carbon black) was 5.4 mg/m^3 during compounding/mixing, 2.2 mg/m^3 during pre-treatment and 41.0 mg/m^3 during moulding (Kromhout *et al.*, 1994). The mean exposure in the weighing and mixing areas in five rubber companies in the Netherlands was 2.2 mg/m^3 in 1997 (Vermeulen, personal communication).

Meijer *et al.* (1998) reported dust levels in a manufacturer of rubber conveyor belts. The mean personal level of inhalable dust was 9.4 mg/m^3 during compounding/mixing and 1.1 mg/m^3 during calendering.

Dost *et al.* (2000) published data obtained from occupational hygiene surveys carried out by rubber manufacturers in the United Kingdom. Mean dust exposure in the weighing, mixing and milling parts of the process were 2.3 mg/m^3 in rubber goods manufacture and 2.2 mg/m^3 in rubber tyre manufacture.

Table 1.24. Personal measurements of general dust in rubber manufacturing industry

Country	Industry	Year	Department	N_F	N_S	Dust	GM (mg/m^3)	GSD	Range (mg/m^3)
Netherlands[a]	Rubber conveyor belt	1988–1991	Compounding/ mixing	1	10	Inhalable	8.2	1.9	NS
			Calendering	1	23	Inhalable	0.6	2.6	NS
United Kingdom[b]	Rubber goods	1995–97	Weighing, mixing and milling	NS	82	NS	NS	NS	0.02–18.6
	New tyres		Weighing, mixing and milling	NS	22	NS	NS	NS	0.1–9.6
Netherlands[c]	Rubber goods and tyres	1997	Mixing and weighing	5	61	Inhalable	1.0	2.9	0.2–30.3

[a] From Meijer *et al.* (1998)
[b] From Dost *et al.* (2000)
[c] From Vermeulen (personal communication)
GM, geometric mean; GSD, geometric standard deviation; N_F, number of factories in the survey; NR, not reported; N_S, number of samples

Carbon black is used in the production of toners for photocopying machines, during which charging agents and carbon black are mixed to form a resin. This material is then cooled and granulated to a fine powder. As a result, all carbon black is fixed within the matrix of the plastic polymer. All manufacturers supply toner in sealed plastic cartridges. A brief report from the Health and Safety Executive (undated) described occupational dust exposure in a toner production factory. Personal exposures to inhalable dust ranged from 0.01 to 3.95 mg/m^3 (n = 60) expressed as 6–8-hour time-weighted averages (TWA). [Assuming 15% of this dust is carbon black, this gives the range of exposure of 0.001–0.6 mg/m^3 carbon black.] (Health and Safety Executive, 2004)

In a toner cartridge-recycling site, total dust concentration in various places on the site measured in 1996 ranged from 0.03 to 1.06 mg/m^3 (Health and Safety Executive, 2004).

1.3.3 *Ambient air*

In 1978, it was estimated that 1240 tonnes of carbon black were emitted during carbon black manufacture in the USA (Rawlings & Hughes, 1979). Table 1.25 summarizes typical particulate emissions of carbon black into the air during various stages of its manufacture by the oil-furnace process before 1979. The particulate matter was reported to comprise carbon black (McBath, 1979).

Rivin and Smith (1982) reviewed the literature on emissions of carbon black into the atmosphere during its manufacture. Modern carbon black plants generally employ bag filters to reduce emissions; discharge from a bag filter in good condition during this process (under normal conditions) reportedly contains less than 50 mg/m^3 carbon black (wet basis), a concentration that is not visible (Johnson & Eberline, 1978).

Table 1.25. Typical particulate emissions during the manufacture of carbon black by the oil-furnace process

Source	Range (kg/tonne)	Average (kg/tonne)
Main process vent (uncontrolled)	0.1–5	3.27
Flare	1.2–1.5	1.35
Carbon monoxide boiler and incinerator	–	1.04
Dryer vent		
Uncontrolled	0.05–0.40	0.23
Bag filter	0.01–0.40	0.12
Scrubber	0.01–0.70	0.36
Pneumatic system vent		
Bag filter	0.06–0.70	0.29
Vacuum clean-up system vent		
Bag filter	0.01–0.05	0.03
Fugitive emissions	–	0.10
Solid waste incinerator (where used)	–	0.12

From McBath (1979)

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for carbon black in several countries are presented in Table 1.26.

Table 1.26. Occupational exposure standards and guidelines for carbon black

Country or region	Concentration (mg/m^3)	Interpretation	Carcinogenicity
Australia	3	TWA	
Belgium	3.6	TWA	
Brazil	3.5	TWA	
China	4 (T)	TWA	
	8	STEL	
Canada			
British Columbia	3.5	TWA	
	7	STEL	
Quebec	3.5	TWA	
Czech Republic	2	TWA	
Denmark	3.5	TWA	K
Finland	3.5	TWA	
	7	STEL	
France	3.5	TWA	
Germany		MAK	3B
Hong Kong	3.5	TWA	A4
Ireland	3.7	TWA	
	7	STEL	
Italy	3.5	TWA	
Japan	1 (R)	TWA; class 2 dust, containing <10% free silica	2B
	4 (T)	TWA; class 2 dust, containing <10% free silica	
Malaysia	3.5	TWA	
Mexico	3.5	TWA	A4
	7	STEL	
Netherlands	3.5	TWA	
New Zealand	3	TWA	
Norway	3.5	TWA	
Poland	4 (TI)	TWA; value applies to technical soot containing not more than 35 mg benzo[*a*]pyrene per kg of soot	
Republic of Korea	3.5	TWA	
Russia	4.0	TWA	

Table 1.26 (contd)

Country or region	Concentration (mg/m^3)	Interpretation	Carcinogenicity
South Africa	3.5	TWA	
	7	STEL	
Spain	3.5	TWA	
Sweden	3 (T)	TWA	
United Kingdom	3.5 (I)	TWA	
	7	STEL	
USA			
ACGIH (TLV)	3.5	TWA	A4
NIOSH (REL)	3.5	10-h TWA	
OSHA (PEL)	3.5	TWA	Ca

From Direktoratet for Arbejdstilsynet (2002); International Carbon Black Association (2004); ACGIH® Worldwide (2005); Deutsche Forschungsgemeinschaft (2005); Health and Safety Executive (2005); INRS (2005); Työsuojelusäädöksiä (2005)
A4, not classifiable as a human carcinogen; 2B, possibly carcinogenic to humans; 3B, substances for which in-vitro tests or animal studies have yielded evidence of carcinogenic effects that is not sufficient for classification of the substance in one of the other categories; Ca, carcinogen; I, inhalable dust; K, included in the list of substances considered carcinogenic; MAK, maximum concentration in the workplace; PEL, permissible exposure limit; R, respirable dust; REL, recommended exposure limit; STEL, short-term exposure limit; T, total dust; TI, total inhalable; TLV, threshold limit value; TWA, 8-h time-weighted average (unless otherwise specified)

The National Institute of Occupational Safety and Health (1995) considers 'carbon black' to be a material that consists of more than 80% of elemental carbon, in the form of near-spherical colloidal particles and coalesced particle aggregates of colloidal size, that is obtained by the partial combustion or thermal decomposition of hydrocarbons. In the USA, their recommended exposure limit (10-hour TWA) for carbon black is 3.5 mg/m^3. Since some PAHs may be formed during the manufacture of carbon black and may become adsorbed on it, the recommended exposure limit (10-hour TWA) for carbon black in the presence of PAHs is 0.1 mg PAHs/m^3 measured as the cyclohexane-extractable fraction.

The US Food and Drug Administration (2003) has listed two types of carbon black for use as a food contact colourant for polymers in the USA: (1) carbon black manufactured by the channel process or prepared by the impingement process from stripped natural gas; and (2) high-purity furnace black containing total PAHs that should not exceed 0.5 ppm and benzo[*a*]pyrene that should not exceed 5.0 ppb. The high-purity furnace blacks may be used at levels not to exceed 2.5% by weight of the polymer.

1.5 References

ACGIH® Worldwide (2005). *2005 Documentation of the TLVs® and BEIs® with Other Worldwide Occupational Exposure Values*, Cincinnati, OH [CD-ROM].

Agurell E, Löfroth G (1993). Impurity variations in a carbon black: characterization by the Ames *Salmonella* mutagenicity assay and polycyclic aromatic hydrocarbon analysis. *Environ Toxicol Chem*, 12:219–223.

ASTM International (2000). *Standard Test Methods for Carbon Black—Dispersion in Rubber* (Standard No. D2663–95a), Philadelphia, PA, American Society for Testing and Materials.

ASTM International (2001). *Standard Test Method for Determinants of Carbon Black Content in Polyethylene Compounds by the Muffle-furnace Technique* (Standard No. D4218–96), Philadelphia, PA, American Society for Testing and Materials.

ASTM International (2003). *Standard Test Method for Rubber—Compositional Analysis for Thermogranimetry (TGA)* (Standard No. D6370–99), Philadelphia, PA, American Society for Testing and Materials.

ASTM International (2004a). *Standard Test Method for Carbon Black. Morphological Characterization of Carbon Black Using Electron Microscopy* (Standard No. D3849–04), Philadelphia, PA, American Society for Testing and Materials.

ASTM International (2004b). *Standard Practice for Sampling and Testing of Possible Carbon Black Fugitive Emissions or Other Environmental Particulate, or Both* (Standard No. D6602–036), Philadelphia, PA, American Society for Testing and Materials.

ASTM International (2004c). *Standard Classification System for Carbon Blacks Used in Rubber Products* (Standard No. D4527–99), Philadelphia, PA, American Society for Testing and Materials.

ASTM International (2005a). *Standard Classification System for Carbon Blacks Used in Rubber Products* (Standard No. D1765–05a), Philadelphia, PA, American Society for Testing and Materials.

ASTM International (2005b). *Standard Classification System for Carbon Blacks. Evaluation in Natural Rubber* (Standard No. D3192–05), Philadelphia, PA, American Society for Testing and Materials.

ASTM International (2005c). *Standard Test Methods for Carbon Black Used in Rubber Products* (Standard No. D305–84), Philadelphia, PA, American Society for Testing and Materials.

Auchter JF (2005). *Chemical Economics Handbook: Carbon Black*, Menlo Park, CA, SRI Consulting.

Belanger PL, Elesh E (1979). *Health Hazard Evaluation and Technical Assistance HHE 78–72–618, Kentile Floors, Inc., South Plainfield, New Jersey*, Cincinnati, OH, National Institute for Occupational Safety and Health.

Boiano JM, Donohue MT (1981). *Health Hazard Evaluation HHE 80–203–960, Phillips Chemical Company, Toledo, Ohio*, Cincinnati, OH, National Institute for Occupational Safety and Health.

Butler MA, Evans DL, Giammarise AT *et al.* (1983). Application of the *Salmonella* mutagenicity assay to carbon blacks and toners. In: Cooke MW, Dennis AJ, eds, *Polycyclic Aromatic Hydrocarbons, 7th International Symposium*, Columbus, OH, Battelle Press, pp. 225–232.

Cabot Corporation (2005a). Cabot's High Purity Furnace Blacks: The Right Choice for Quality, Environmental Responsibility, and Purity! Billerica, MA.

Cabot Corporation (2005b). Cabot Carbon Blacks Typical Metal Analysis (ppm), Billerica, MA.

Collyer HJ (1975). Carbon black and ecology. In: Ayer FA, ed, *Environmental Aspects of Chemical Use in Rubber Processing Operations, March 1975, Akron, OH* (EPA-560/1–75–002; PB244 172), Washington DC, Environmental Protection Agency, pp. 130–136.

Dannenberg EM (1978). *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd Ed, Vol. 4, New York, John Wiley & Sons, pp. 658.

Dannenberg EM, Paquin L, Gwinnell H (1992). Carbon black. In: Kroschwitz JI, Howe-Grant M, eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th Ed, Vol.4, New York, John Wiley & Sons, pp.631–666.

De Wiest F (1980). [Experimental study of the blood elution process of the polycyclic aromatic hydrocarbons adsorbed on carbon. I. Physicochemistry of the particles]. *J Pharm Belg*, 35:253–265. PMID:7441474

Deutsche Forschungsgemeinschaft (2005). *List of MAK and BAT Values 2005* (Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Report No. 41), Weinheim, WILEY-VCH GmbH & Co., pp. 36, 136.

Direktoratet for Arbeidstilsynet (2002). *WEA-Guide 2002—Limit Values for Substances and Materials*, Copenhagen.

Dost AA, Redman D, Cox G (2000). Exposure to rubber fume and rubber process dust in the general rubber goods, tyre manufacturing and retread industries. *Ann Occup Hyg*, 44:329–342. PMID:10930497

Eller PM, ed (1994). *Carbon Black—Method 5000*. *NIOSH Manual of Analytical Methods*, 4th Ed, (DHHS (NIOSH) Publ. No. 94–113), Washington, DC, Government Printing Office.

European Committee for Biological Effects of Carbon Black (1982). *A comparative Study of Soot and Carbon Black* (Bulletin No. 2, January), Boston, MA, Cabot Corp.

Fitch WL, Everhart ET, Smith DH (1978). Characterization of carbon black adsorbates and artifacts formed during extraction. *Anal Chem*, 50:2122–2126. doi:10.1021/ac50036a043.

Fitch WL, Smith DH (1979). Analysis of adsorption properties and adsorbed species on commercial polymeric carbons. *Environ Sci Technol*, 13:341–346. doi:10.1021/es60151a008.

Food and Drug Administration (2003). Colorants for polymers [21CFR178.3297]. *Code Fed Regul*, Title 21, Vol. 3, Subpart D, Section 178.3297 (electronic version).

Gardiner K, Calvert IA, van Tongeren MJA, Harrington JM (1996). Occupational exposure to carbon black in its manufacture: data from 1987 to 1992. *Ann Occup Hyg*, 40:65–77. PMID:9054303

Gardiner K, Hale KA, Calvert IA *et al.* (1992b). The suitability of the urinary metabolite 1-hydroxypyrene as an index of poly nuclear aromatic hydrocarbon bioavailability from workers exposed to carbon black. *Ann Occup Hyg*, 36:681–688. doi:10.1093/annhyg/36.6.681. PMID:1471819

Gardiner K, Trethowan NW, Harrington JM *et al.* (1993). Respiratory health effects of carbon black: a survey of European carbon black workers. *Br J Ind Med*, 50:1082–1096. PMID:8280639

Gardiner K, Trethowan WN, Harrington JM *et al.* (1992a). Occupational exposure to carbon black in its manufacture. *Ann Occup Hyg*, 36:477–496. doi:10.1093/annhyg/36.5.477. PMID:1444068

Gardiner K, Trethowan WN, Harrington JM *et al.* (1992c). Occupational exposure to carbon monoxide and sulphur dioxide during the manufacture of carbon black. *Ann Occup Hyg*, 36:363–372.doi:10.1093/annhyg/36.4.363. PMID:1444064

Gardiner K, van Tongeren M, Harrington M (2001). Respiratory health effects from exposure to carbon black: results of the phase 2 and 3 cross sectional studies in the European carbon black manufacturing industry. *Occup Environ Med*, 58:496–503. doi:10.1136/oem.58.8.496. PMID:11452043

Harber P, Muranko H, Shvartsblat S *et al.* (2003). A triangulation approach to historical exposure assessment for the carbon black industry. *J Occup Environ Med*, 45:131–143.doi:10.1097/01.jom.0000052956.59271.bd. PMID:12625229

Health and Safety Executive (2005). *EH40/2005 Workplace Exposure Limits Containing the List of Workplace Exposure Limits for Use with the Control of Substances to Health Regulations 2002 (as amended),* London, Her Majesty's Stationery Office, p. 12.

Health and Safety Executive (2000). *General Methods for the Gravimetric Determination of Respirable and Inhalable Dust* (MDHS 14/3), London.

Health and Safety Executive (2004). *Nanoparticles: an Occupational Hygiene Review* (Institute of Occupational Medicine – Research Report 274), London.

Health and Safety Executive (undated)

Heitbrink WA, McKinnery WN Jr (1986). Control of air contaminants at mixers and mills used in tire manufacturing. *Am Ind Hyg Assoc J*, 47:312–321. PMID:3739900

Hodgson JT, Jones RD (1985). A mortality study of carbon black workers employed at five United Kingdom factories between 1947 and 1980. *Arch Environ Health*, 40:261–268. PMID:4062360

Hollett BA (1980). *Health Hazard Evaluation Determination Report HHEE 78–7–66, Kawecki Berylco Industries, Inc., Boyerton, Pennsylvania*, Cincinnati, OH, National Institute for Occupational Safety and Health.

IARC (1984). Polynuclear aromatic hydrocarbons, Part 2, Carbon blacks, mineral oils (lubricant base oils and derived products) and some nitroarenes. *IARC Monogr Eval Carcinog Risk Chem Hum*, 33:1–222. PMID:6590450

IARC (1987). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7:1–440. PMID:3482203

IARC (1996). Printing processes and printing inks, carbon black and some nitro compounds. *IARC Monogr Eval Carcinog Risks Hum*, 65:1–578.

IARC (2010). Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. *IARC Monogr Eval Carcinog Risks Hum*, 92:1–853.

INRS (2005). [Limit Values of Occupational Exposure to Chemical Agents in France], Paris, Institut National de Recherche et de Sécurité.

International Carbon Black Association (2004). *Carbon Black User's Guide—Safety, Health and Environmental Information.*

International Organization for Standardization (1986). *Polyolefin Pipes and Fittings—Determination of Carbon Black Content by Calcination and Pyrolysis—Test Method and Basic Specification* (ISO 6964:1986(E)), Geneva.

International Organization for Standardization (1988). *Rubber Compounding Ingredients—Carbon Black—Determination of Solvent Extractable Material* (ISO 6209:1988(E)), Geneva.

International Organization for Standardization (1992). *Rubber Compounding Ingredients—Carbon Black—Method of Evaluation in Styrene–Butadiene Rubbers* (ISO 3257:1992(E)), Geneva.

International Organization for Standardization (ISO) (1995). Measurement of Inhalable and Respirable Dust, Geneva.

Jacob J, Grimmer G (1979). Extraction and enrichment of polycyclic aromatic hydrocarbons (PAH) from environmental matter. In: Egan H, Castegnaro M, Bogovski PR, Kunte H, & Walker EA, eds, *Environmental Carcinogens. Selected Methods of Analysis,* Vol. 3, *Analysis of Polycyclic Aromatic Hydrocarbons in Environmental Samples* (IARC Scientific Publications No. 29), Lyon, IARC, pp. 79–89.

Japanese Standards Association (2003). *Method for the Assessment of the Degree of Pigment or Carbon Black Dispersion in Polyolefin Pipes, Fittings and Compounds* (JIS-K-6812:2003), Tokyo.

Jin Z-L, Dong S-P, Xu W-B *et al.* (1987). Analysis of mutagenic nitroarenes in carbon black by high-performance liquid chromatography. *J Chromatogr*, 386:185–190. doi:10.1016/S0021-9673(01)94595-9. PMID:3558602

Johnson PH, Eberline CR (1978). Carbon black, furnace black. In: McKetta JJ, Cunningham WA, eds, *Encyclopedia of Chemical Processing and Design*, Vol. 6, New York, Marcel Dekker, pp. 228–231, 236–237, 246–252, 255–257.

Kerr SM, Muranko HJ, Vincent JH (2002). Personal sampling for inhalable aerosol exposures of carbon black manufacturing industry workers. *Appl Occup Environ Hyg*, 17:681–692. doi:10.1080/10473220290096177. PMID:12363209

Kirk-Othmer (2005). Encyclopedia of Chemical Technology, 5th Ed. New York, John Wiley & Sons.

Kollo RM (1960). [A health evaluation of working conditions in a channel black plant] *Trud Leningrads Sanit Gig Med Inst*, 62:128–131.

Komarova LT (1965). [The effect of air pollution on the morbidity and health of workers in carbon black production] *Nauchn. Trud. Omsk. Med Int*, 61:115–121.

Kromhout H, Swuste P, Boleij JSM (1994). Empirical modelling of chemical exposure in the rubber-manufacturing industry. *Ann Occup Hyg*, 38:3–22. doi:10.1093/annhyg/38.1.3. PMID:8161092

Kuhlbusch TA, Neumann S, Fissan H (2004). Number size distribution, mass concentration, and particle composition of PM1, PM2.5, and PM10 in bag filling areas of carbon black production. *J Occup Environ Hyg*, 1:660–671. doi:10.1080/15459620490502242. PMID:15631057

Lee ML, Hites RA (1976). Characterization of sulfur-containing polycyclic aromatic compounds in carbon blacks. *Anal Chem*, 48:1890–1893. doi:10.1021/ac50007a020. PMID:970643

Lewis PA (1988). Carbon black. In: Lewis PA, ed., *Pigment Handbook*, Vol. I, *Properties and Economics*, 2nd Ed, New York, John Wiley & Sons, pp.743–758.

Lewis RJ Sr (1993). *Hawley's Condensed Chemical Dictionary*, 12th Ed., New York, Van Nostrand Reinhold Co., p. 160.

Locati G, Fantuzzi A, Consonni G *et al.* (1979). Identification of polycyclic aromatic hydrocarbons in carbon black with reference to cancerogenic risk in tire production. *Am Ind Hyg Assoc J*, 40:644–652. PMID:484489

Lyon F, Burgess K (1985). *Encyclopedia of Polymer Science and Engineering*, 2nd Ed., Vol. 2, New York, John Wiley & Sons, pp. 623–640.

McBath A (1979). Carbon black. In: *Compilation of Air Pollutant Emission Factors*, 3rd Ed., Suppl. 9 (EPA Report AP-42; PB81–244097), Research Triangle Park, NC, Office of Air Quality Planning and Standards, Environmental Protection Agency, pp. 49–56.

Meijer E, Heederik D, Kromhout H (1998). Pulmonary effects of inhaled dust and fumes: exposure–response study in rubber workers. *Am J Ind Med*, 33:16–23. doi:10.1002/(SICI)1097-0274(199801)33:1<16::AID-AJIM3>3.0.CO;2-U. PMID:9408525

Muranko HJ, Hethmon TA, Smith RG (2001). 'Total' and respirable dust exposures in the US carbon black manufacturing industry. *Am Ind Hyg Assoc J*, 62:57–64.

Musch DC, Smith RG (1990). Characterising occupational exposure to carbon black: Results from three particulate sampling studies. In: *Proceedings of Annual Meeting of the American Industrial Hygiene Association, St Louis, MO, June 1989*, Ann Arbor, MI, University of Michigan.

National Institute for Occupational Safety and Health (1995) *Criteria for a Recommended Standard: Occupational Exposure to Respirable Coal Mine Dust* (DHHS (NIOSH) Publication No. 95106). Cincinnati, Ohio. Available at: http://www.cdc.gov/niosh/95-106.html

Nishioka M, Chang H-C, Lee ML (1986). Structural characteristics of polycyclic aromatic hydrocarbon isomers in coal tars and combustion products. *Environ Sci Technol*, 20:1023–1027. doi:10.1021/es00152a010.

Occupational Safety and Health Administration (undated)

Occupational Safety and Health Administration (OSHA) (1977) Test for hazardous substance 527 (carbon black) from OSHA Inception through January 1977, Washington DC.

Ramdahl T, Kveseth K, Becher G (1982). Analysis of nitrated polycyclic aromatic hydrocarbons by glass capillary gas chromatography using different detectors. *J High Resolut Chromatogr*, 5:19–26. doi:10.1002/jhrc.1240050104.

Rawlings GD, Hughes TW (1979). Emission inventory data for acrylonitrile, phtalic anhydride, carbon black, synthetic ammonia, and ammonium nitrate. In: Frederick ER, ed, *Proceedings of the Specialty Conference of Emission Factors and Inventories, Anaheim, CA, November 1978*, Pittsburgh, PA, Air Pollution Control Association, pp. 173–183.

Rivin D, Smith RG (1982). Environmental health aspects of carbon black. *Rubber Chem Technol*, 55:707–761.

Rogaczewska T, Ligocka D, Nowicka K (1989). Hygienic characteristics of carbon black used in tyre production. *Pol J Occup Med*, 2:367–375. PMID:2489438

Rosenkranz HS, McCoy EC, Sanders DR *et al.* (1980). Nitropyrenes: isolation, identification, and reduction of mutagenic impurities in carbon black and toners. *Science*, 209:1039–1043. doi:10.1126/science.6996095. PMID:6996095

Salisbury S (1980). *Health Hazard Evaluation HHE 79–075–784, St. Clair Rubber Co., Marysville, Michigan*, Cincinnati, OH, National Institute for Occupational Safety and Health.

Sanders DR (1981). Nitropyrenes: the isolation of trace mutagenic impurities from the toluene extract of an after treated carbon black. In: Cooke M, Dennis AJ, eds, *Chemical Analysis and Biological Fate: Polycyclic Aromatic Hydrocarbons, 5th International Symposium*, Columbus, OH, Battelle Press, pp. 145–158.

Slepicka J, Eisler L, Mirejowsky P, Simecek R (1970). [Pulmonary changes in workers long-term exposed to soot production]. *Prac Lek*, 22:276–281.

Smith RG, Musch DC (1982). Occupational exposure to carbon black: a particulate sampling study. *Am Ind Hyg Assoc J*, 43:925–930. PMID:7158607

Sokhi RS, Gray C, Gardiner K, Earwaker LG (1990). PIXE (particle-induced X-ray emission) analysis of carbon black for elemental impurities. *Nucl Instrum Methods Phys Res*, B49:414–417.

Sorahan T, Hamilton L, van Tongeren M *et al.* (2001). A cohort mortality study of U.K. carbon black workers, 1951–1996. *Am J Ind Med*, 39:158–170. doi:10.1002/1097-0274(200102)39:2<158::AID-AJIM1003>3.0.CO;2-L. PMID:11170158

Spodin YN (1973). [Preventive sanitary inspection of the Kremenchug carbon black plant]. *Gig Trud*, 9:22–26.

Standards Australia International Ltd (2001). *Methods of Test for Elastomers. Method 17: Determination of Carbon Black Content of Vulcanized Rubber—Pyrolytic and Chemical and Degradation Methods* (AS 1683.17–2001), Sydney.

Standards Australia International Ltd/Standards New Zealand (2003). *Methods of Test for Plastics Pipes and Fittings. Method 27: Determination of Toluene Extract of Carbon Black* (AS/NZS 1462.27:2003), Sydney/Wellington.

Szozda R (1994). [Condition of the respiratory system in workers involved in carbon black production]. *Med Pr*, 45:57–61. PMID:8170378

Taylor GT, Redington TE, Bailey MJ *et al.* (1980). Solvent extracts of carbon black–Determination of total extractables and analysis for benzo(alpha)pyrene. *Am Ind Hyg Assoc J*, 41:819–825. PMID:7457372

Troitskaya NA, Velichkovsky BT, Bikmullina SK *et al.* (1975). [Substantiation of the maximum permissible concentration of industrial carbon black in the air of workrooms]. *Gig Tr Prof Zabol*, 17:32–36.

Troitskaya NA, Velichkovsky BT, Kogan FM, O'Kuz'minukh AI (1980). [On carcinogenic hazards in the carbon black industry]. *Vopr. Oncol.*, 26:63–67.

Tsai PJ, Shieh HY, Lee WJ *et al.* (2002a). Urinary 1-hydroxypyrene as a biomarker of internal dose of polycyclic aromatic hydrocarbons in carbon black workers. *Ann Occup Hyg*, 46:229–235.doi:10.1093/annhyg/mef017. PMID:12074032

Tsai PJ, Shieh HY, Lee WJ, Lai SO (2002b). Characterization of PAHs in the atmosphere of carbon black manufacturing workplaces. *J Hazard Mater*, 91:25–42. doi:10.1016/S0304-3894(01)00384-3. PMID:11900904

Työsuojelusäädöksiä (2005). *HTP-Arvot 2005*, *Sosiaali- Ja Terveysministeriö, Kemian työsuojeluneuvottelukunta*, Tampere, Kirjapaino Öhrling, p. 19.

van Tongeren MJ, Gardiner K, Rossiter CE *et al.* (2002). Longitudinal analyses of chest radiographs from the European Carbon Black Respiratory Morbidity Study. *Eur Respir J*, 20:417–425. doi:10.1183/09031936.02.00224502. PMID:12212976

van Tongeren MJA (2000). *Occupational Exposure to Carbon Black Dust in the European Carbon Black Manufacturing Industry and its Respiratory Health Effects*, PhD Thesis, University of Birmingham.

van Tongeren MJA, Kromhout H, Gardiner K (2000). Trends in levels of inhalable dust exposure, exceedance and overexposure in the European carbon black manufacturing industry. *Ann Occup Hyg*, 44:271–280. PMID:10831731

Vermeulen R, de Hartog J, Swuste P, Kromhout H (2000). Trends in exposure to inhalable particulate and dermal contamination in the rubber manufacturing industry: effectiveness of control measures implemented over a nine-year period. *Ann Occup Hyg*, 44:343–354. PMID:10930498

Vohler O, von Sturm F, Wege E *et al.* (1986). Carbon. In: Gerhartz W, Yamamoto YS, Campbell FT, Pfefferkorn R, Rounsaville JF, eds, *Ullmann's Encyclopedia of Industrial Chemistry*, 5th rev. Ed., Vol. A5, New York, NY, VCH Publishers, pp. 124–163.

Voll M, Kleinschmit P (2002). Carbon. In: *Ullmann's Encyclopedia of Industrial Chemistry*, New York, Wiley-VCH Verlag GmbH & Co.

Wake D, Mark D, Northage C (2002). Ultrafine aerosols in the workplace. *Ann Occup Hyg*, 46 Suppl. 1;235–238.

Wang MJ, Gray CA, Reznek SA *et al.* (2003). Carbon black. In: *Kirk-Othmer Encyclopedia of Chemical Technology*, New York, John Wiley & Sons, Vol 4, p 761–803.

Werner MA, Spear TM, Vincent JH (1996). Investigation into the impact of introducing workplace aerosol standards based on the inhalable fraction. *Analyst*, 121:1207–1214. doi:10.1039/an9962101207. PMID:8831279

Williams TM, Harris RL, Arp EW *et al.* (1980). Worker exposure to chemical agents in the manufacture of rubber tires and tubes: particulates. *Am Ind Hyg Assoc J*, 41:204–211. PMID:7395731

Zoccolillo L, Liberti A, Coccioli F, Ronchetti M (1984). Routine determination of polycyclic aromatic hydrocarbons in carbon black by chromatographic techniques. *J Chromatogr*, 288:347–355. doi:10.1016/S0021-9673(01)93711-2. PMID:6736145

2. Studies of Cancer in Humans

Industrial exposure to carbon black has occurred in the carbon black production industry and in several user industries, including the rubber, paint and printing industries. The risks for cancer associated with these three exposure circumstances have been evaluated previously (IARC, 1982, 1989, 1996).

The Working Group considered that the epidemiological evidence concerning the risk for cancer in user industries where there has been no attempt to identify which of the workers may have been exposed to carbon black carries little weight in the present evaluation. Consequently, in this monograph, attention was restricted to those studies that explicitly attempted to identify workers who had been exposed to carbon black. Studies based on carbon black production workers and some studies of workers in user industries satisfied this criterion.

From the point of view of exposure patterns, the greatest potential for elucidating the carcinogenicity of carbon black would seem to be in the carbon black production industry. A further advantage of studies among producers is the fact that, in this industry, carbon black was the dominant exposure in the industrial environment, whereas workers in other industries were often exposed to complex mixtures of substances, of which carbon black may in some circumstances have been a relatively minor component.

2.1 Industry-based studies

Table 2.1 summarizes industry-based studies including cohort analyses and nested case–control analyses of workers exposed to carbon black.

2.1.1 *Carbon black production*

The occurrence of cancer among employees at carbon black production facilities in the USA has been followed for different periods since 1935 and was initially described in five reports (Ingalls, 1950; Ingalls & Risquez-Iribarren, 1961; Robertson & Ingalls, 1980, 1989; Robertson & Inman, 1996) that were reviewed previously (IARC, 1996). Because of some limitations of these studies and because they have been superseded by newer, more complete studies of carbon black workers in the USA, they are not reviewed again here.

A historical cohort study was carried out among carbon black production workers in the United Kingdom (Hodgson & Jones, 1985), the results of which have been evaluated previously (IARC, 1996). Since that time, a new follow-up has been conducted that supersedes the earlier report (Sorahan *et al*., 2001). The later study collected information on a total of 2086 employees who had worked between 1947 and 1974 in any of five major carbon black production factories in the United Kingdom. The precise inclusion

Table 2.1. Industry-based studies of cancer and exposure to carbon black

Reference, location	Study population	Exposure assessment	Disease/ cancer site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment factors/ Comments
Carbon black production							
Sorahan *et al*. (2001), United Kingdom	Male employees in 5 carbon black production plants; manual workers with ≥12 months service; employed between 1947 and 1974 (*n*=1147); mortality follow-up from 1951 to 1996	Exposure assessment using worker records, experts, measurements and job-exposure matrices	All causes	Employed ≥12 months	372	1.13 (1.02–1.25)	Adjusted for age; only last job title was available; smoking histories unknown; reference: external/United Kingdom
			All cancer		137	1.42 (1.19–1.68)	
			Oesophagus		6	1.62 (0.59–3.52)	
			Stomach		8	1.0 (0.43–1.98)	
			Bladder		6	1.73 (0.64–3.77)	
			Lung and Bronchus		61	1.73 (1.32–2.22)	
				Cumulative exposure (mg/m^3.y)			Reference: low exposure (<20 mg/m^3.y)
			Lung	Medium–low (20–49)	11	0.78 (0.36–1.69)	
				Medium–high (50–99)	17	1.85 (0.93–3.68)	
				High (≥100)	20	1.32 (0.68–2.58)	
				p for trend		0.16	

Table 2.1 (contd)

Reference, location	Study population	Exposure assessment	Disease/ cancer site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment factors/ Comments
Dell *et al*. (2006), USA	Employees of 18 carbon black production facilities in several states; employed >1 year since 1930s; inception cohort (*n*=5011); mortality follow-up from inception to 2003	Worked in industry	All causes	All	1326	0.74 (0.70–0.78)	Adjusted for age, sex, race; many workers with missing information on sex and race and therefore excluded from the analysis; reference: external/state
			All cancers		330	0.83 (0.74–0.92)	
			All digestive		78	0.81 (0.65–1.02)	
			Oesophagus		11	1.15 (0.64–2.09)	
			Urinary organs and bladder		8	0.93 (0.47–1.87)	
			Lung		138	0.97 (0.82–1.15)	
			Lung	10–19 years	26	1.09 (0.74–1.59)	
				≥20 years	25	0.67 (0.45–0.99)	
Wellmann *et al.* (2006), North-Rhine Westphalia, Germany	Male blue-collar workers in a German carbon black production plant; employed for ≥1 year between 1960 and 1998 and alive in 1976 (*n*=1535); mortality follow-up in local population registries from 1976 to 1998	Exposure assessment using worker records and experts	All causes	All workers	332	1.20 (1.08–1.34)	Adjusted for age; reference: external/North-Rhine Westphalia rates
			Oesophagus		3	1.2 (0.25–3.54)	
			Stomach		5	0.76 (0.25–1.77)	
			Bladder		1	0.4 (0.0–2.1)	
			Lung		50	2.18 (1.61–2.87)	
			Lung	*Carbon black index*			Age, tobacco smoking; limited information on smoking for 77% of cohort; reference: low
				Medium–low	14	1.53 (0.66–3.65)	
				Medium–high	15	1.13 (0.49–2.60)	
				High	2	0.4 (0.09–1.86)	
Büchte *et al.* (2006); Morfeld *et al.* (2006a,b) Germany	Re-analyses of data from Wellmann *et al.* (2006) study	Various variations on original data	Lung	*All workers* Different variables of exposure an linear models	30–50	No trend	Adjusted for age, tobacco smoking; many statistical models; almost all showed no effect of carbon black; re-estimation of SMR after apportioning biases due to reference population, smoking and previous exposure
				Re-estimation of SMR		1.2–1.5	Adjusted for age, tobacco smoking, prior exposures

Table 2.1 (contd)

Reference, location	Study population	Exposure assessment	Disease/ cancer site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment factors/ Comments
Carbon black user industries							
Blum *et al*. (1979), USA	Nested case–control study within a cohort of rubber workers active or retired in 1964; cases were deaths due to stomach cancer, 1964–73; 100 cases and 400 matched controls	Experts assessed exposure of each worker to carbon black and three other substances	Stomach			**Odds ratio (90% CI)**	Adjusted for age, race, sex, duration of employment in company; reference: unexposed to carbon black
				Moderate or high exposure			
				Company A	21	1.49 (0.84–2.66)	
				Company B	33	1.74 (1.02–2.97)	
Bourguet *et al*. (1987), Ohio, USA	Nested case–control study of workers within rubber industry active in 1964 or earlier; cases ascertained in local hospitals (*n*=65); four controls matched to each case on company, year of employment, year of birth (*n*=254).	Intensity of exposure to carbon black and expert assessment	Skin	Low	14	0.7 (NG)	Adjusted for company, year of employment, year of birth, rubber stock, extender and lubricating oils, solvents; reference: unexposed to carbon black
				Medium	14	1.2 (NG)	
				High	8	0.7 (NG)	

Table 2.1 (contd)

Reference, location	Study population	Exposure assessment	Disease/ cancer site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment factors/ Comments
Blair *et al.* (1990), USA	White male employees at 10 plants with exposure to formaldehyde (*n*=20 714)	Expert assessment of exposure to many chemicals, including carbon black	Lung	Ever	20	1.3 [0.8–2.0]	Adjusted for age; reference: external/USA
				≥20 years	6	2.4 [0.9–5.2]	
Straif *et al.* (2000), Germany	Blue-collar workers in 5 German rubber companies employed after 1950 and alive in 1981 (*n*=8933); mortality follow-up, 1981–1991	Estimates of exposure to nitrosamines, asbestos, talc and carbon black by intensive exposure assessment using worker records, experts and measurements		*Exposed*			
			Stomach	>1 year	12	1.8 (0.9–3.4)	Adjusted for age
						1.2 (0.5–3.0)	Adjusted for age, nitrosamines, asbestos, talc
				>10 years	11	3.3 (1.6–6.5)	Adjusted for age
						1.5 (0.5–4.6)	Adjusted for age, nitrosamines, asbestos, talc
			Lung	>1 year	38	1.5 (1.0–2.2)	Adjusted for age
						1.1 (0.7–1.9)	Adjusted for age, nitrosamines, asbestos, talc
				>10 years	24	1.5 (0.9–2.4)	Adjusted for age
						1.1 (0.6–2.2)	Adjusted for age, nitrosamines, asbestos, talc
			Larynx	>1 year	4	5.3 (1.3–21.4)	Adjusted for age Reference: unexposed to carbon black

Table 2.1 (contd)

Reference, location	Study population	Exposure assessment	Disease/ cancer site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment factors/ Comments
Puntoni *et al*. (2004), Genoa, Italy	Dockyard workers who transported bags containing carbon black employed 1933–79 (*n*=2101); cancer incidence ascertained in Genoa cancer registry; followed-up 1986–96	Categorization by task and era		*Exposure*		**SIR (95% CI)**	Adjusted for age; poorly documented exposure; reference: external/City of Genoa incidence rates; overlaps with Puntoni *et al.* (2001).
			All cancers	Ever	208	0.95 (0.83–1.09)	
				High	60	0.94 (0.72–1.22)	
			Oesophagus	Ever	4	1.62 (0.44–4.15)	
				High	0	0 (0–4.24)	
			Stomach	Ever	3	0.29 (0.06–0.85)	
				High	1	0.33 (0.01–1.84)	
			Larynx	Ever	14	1.54 (0.84–2.58)	
				High	4	1.53 (0.42–3.93)	
			Lung	Ever	53	1.08 (0.81–1.41)	
				High	15	1.03 (0.58–1.70)	
			Bladder	Ever	32	1.30 (0.89–1.84)	
				High	14	1.97 (1.08–3.30)	
			Mesothelioma	Ever	7	7.5 (3.02–15.47)	
				High	1	3.87 (0.10–21.54)	
			Melanoma	Ever	8	2.88 (1.25–5.68)	
				High	1	1.5 (0.04–8.40)	

CI, confidence interval; NG, not given; SIR, standardized incidence ratio; SMR, standardized mortality ratio

criteria differed from company to company, depending on the availability of historical company records. For three companies, the cohort included all workers hired between 1947 and 1974, while the two others were unable to include workers who left employment before the late 1960s. The subjects who were identified were traced via national vital statistics registers from 1951 onwards or from the date they entered the cohort. The mortality follow-up ended on 31 December 1996, unless truncated by death or emigration. A total of 27 550 person–years of observation were included in the mortality follow-up. Overall, 26% of the study subjects were known to have died during the period of observation. In the entire cohort, a significant excess of mortality was observed compared with national rates standardized mortality ratio [SMR], 1.14; 95% confidence interval [CI], 1.05–1.24; based on 578 deaths). This excess was especially high (SMR, 1.36; 95% CI, 1.15–1.60; based on 145 deaths) among male manual workers with less than 12 months of employment. An even higher excess risk was observed in the entire cohort for mortality from lung cancer (SMR, 1.61; 95% CI, 1.29–2.00; based on 85 deaths), although, in the case of lung cancer, there was little difference in SMRs between male manual workers with less than 12 months and those with longer employment. The authors contended that there was little evidence of a 'healthy worker effect' bias and also that workers with less than 12 months of employment comprised a subgroup whose mortality experience was unlikely to be linked to employment in carbon black facilities. They therefore focused on a subgroup of 1147 male manual workers with over 12 months of employment in the industry for whom a highly significant SMR for lung cancer of 1.73 (95% CI, 1.32–2.22; based on 61 deaths) was observed. For cancer at most other sites, fewer than five cases were observed. For no other site did the lower bound of the 95% CI exceed 0.75. When using local area rates instead of national rates as a reference, the SMRs for total mortality and for mortality from lung cancer were slightly higher. When SMRs for lung cancer were assessed separately for each factory, two factories had particularly high SMRs, one had a slightly elevated SMR and two had too few subjects to provide informative SMR estimates. Results were ambiguous when SMRs for lung cancer were estimated by time since first employment or by job title. [While no data were available on tobacco smoking habits in this population, the fact that mortality from non-malignant respiratory disease was not elevated provides indirect evidence that, in this study, smoking habits did not differ greatly from those of the general population.]

To understand better the reasons for the excess risk for lung cancer in this cohort, Sorahan *et al*. (2001) carried out an internal study in which an intensive effort was made to estimate the exposure of study subjects to carbon black. Information on work history was collected for each worker, including the dates of starting and cessation of employment and last job title. In some factories, additional information was available. The three smallest factories had closed down by the late 1970s. The two factories that were still operating were visited by the investigators and available information relating to personal and static exposure, rate and capacity of production, purchase records and process equipment was collected for the study period. This information was complemented with data obtained through interviews of long-standing employees, and

detailed histories of the two sites were prepared. Using a combination of sources, including a database of measurements of carbon black taken during the period 1987–95 at 19 European plants among which were two of the factories from this study, and anecdotal reports on the nature of earlier conditions, a job–exposure matrix for exposure to inhalable dust was constructed, demarcated in 5- or 10-year periods. The job–exposure matrix used 12 broad job categories as the job axis. Each of the 120 job titles abstracted from employment records was allocated to one of these 12 broader job categories. Individual work history data were linked to the job–exposure matrix to produce individual estimates of cumulative exposure to carbon black, as a time-dependent variable. For internal analyses, attention was focused on lung cancer and non-malignant diseases of the respiratory system in male manual workers employed for 12 months or more. Poisson regression models included the following variables: attained age, calendar period, year of starting employment, period from first employment, employment status (still employed/left employment), factory and estimated cumulative exposure to carbon black. Variables were treated as categorical. Cumulative exposure to carbon black was categorized in the following groups in units of mg/m^3–year: <20, 20–49, 50–99 and ≥100. The results were expressed as relative risks compared with the lowest exposure group. For all causes of death other than lung cancer, there was no indication that workers with high exposure to carbon black were at excess risk compared with workers with low exposure. For lung cancer, however, the results were more ambiguous. In a statistical model that adjusted only for age, the relative risk in the two highest exposure subgroups was 1.85 (95% CI, 0.93–3.68; based on 17 deaths) and 1.32 (95% CI, 0.68–2.58; based on 20 deaths), respectively, and the *p*-value for trend was 0.16. When a multitude of other covariates was included in the models, the relative risk estimates in these two subgroups dropped to 1.57 (95% CI, 0.74–3.34) and 0.89 (95% CI, 0.40–2.01), respectively. [The Working Group noted that the inclusion of all the covariates, including the factory variable and date of hire, may have constituted overadjustment and regarded the estimates adjusted for age as more informative for the carcinogenicity of carbon black.] When analyses were run that discounted the previous 20 years of exposure, no excess risk for lung cancer due to carbon black was revealed. The authors reported some results by duration of exposure, both among all workers and among the two factories in which an excess risk was found. Among all workers, there was a suggestion of higher risk with increasing duration of employment; in the subgroup of workers in high-risk factories, there was no such suggestion. [The Working Group noted that the interpretation of this study is uncertain. It is possible that a combination of confounding factors—including smoking, previous occupations, social class and regional effects unrelated to tobacco smoking habits—produced the high SMRs, but there is little evidence to support this possibility. It is also possible that internal analyses were compromised by limitations in the estimation of cumulative exposure to carbon black. These include possible errors in dates of employment, lack of information on all jobs held in the factories, lack of documentary information in three of five plants, quite recent measurements and errors in creating a job–exposure matrix from a limited and possibly unrepresentative set of

measurements. The combination of these problems could have led to exposure misclassification to such a degree as to attenuate and distort any true dose–response relations.]

Dell *et al*. (2006) undertook an investigation that aimed to include all workers employed in the carbon black industry in the USA. Workers from 20 plants located throughout the USA were enumerated, including many of those who were studied by Robertson and Ingalls (1980, 1989) and Robertson and Inman (1996). The analysis of mortality was restricted to 18 facilities in which it was possible to identify a date of inception from which all newly employed workers could be enumerated. Only 5011 workers who began employment after these dates of inception and who had at least 1 year of service in a job that probably involved exposure to carbon black were included. Mortality was followed up from 1 year after employment to 2003 or until death through social security files and the National Death Index. Gender was unavailable for 17% of the cohort and race was unavailable for 51%. State rates (age-, sex- and race-adjusted) were used to compute expected values, with various ad-hoc adjustments for the missing information on gender and race. Cause of death was unavailable for 76 cases. The SMR for lung cancer, but not for other causes, was adjusted for missing information on cause of death. Compared with the state rates, the mortality rates among the cohort were not elevated for all causes (SMR, 0.74; 95% CI, 0.70–0.78; based on 1326 deaths), for all cancers (SMR, 0.83; 95% CI, 0.74–0.92; based on 330 deaths), for lung cancer (SMR, 0.97; 95% CI, 0.82–1.15; based on 138 deaths) or for oesophageal cancer (SMR, 1.15; 95% CI, 0.64–2.09; based on 11 deaths), nor were there excess risks among workers with more than 10 years of service. The SMRs for lung cancer were well below 1.00 for workers who had 20 years of employment and increased to the null value at about 30 years after first employment. [The Working Group noted that the SMR for lung cancer during the 20 years following first employment in the industry was unusually low.]

Wellmann *et al*. (2006) carried out a study of the mortality of workers in a large and long-standing carbon black manufacturing plant in Germany, where information on work histories and smoking habits of the employees was available. The cohort was enumerated from entry and exit books from the plant and from personnel charts. A total of 2053 blue-collar workers at the carbon black plant who had been employed continuously for at least 1 year between 1 January 1960 and 31 December 1998 were eligible. The vital status of all employees was ascertained from the local population registries of the latest place of residence. The causes of death of the deceased cohort members were determined from death certificates archived in community health departments and from the respective State Institutes of Statistics. Among all 2053 eligible workers, 1535 were men of German nationality and known to be alive on 1 January 1976. The main analyses were restricted to this cohort, for whom vital status and ascertainment of cause of death were virtually complete. Analyses of cause-specific mortality were restricted to the observation period 1976–98, for which retrospective assessment of cause of death in North-Rhine Westphalia was feasible and follow-up was reasonably complete. SMRs were calculated in relation to rates in the (West) German population and in North-Rhine Westphalia. Compared with

the (West) German population, mortality from all causes was elevated (SMR, 1.20; 95% CI, 1.08–1.34; based on 332 deaths). This was accounted for mainly by excesses in heart diseases (SMR, 1.26), chronic obstructive pulmonary disease (SMR, 1.58) and lung cancer (SMR, 2.18; 95% CI, 1.61–2.87; based on 50 deaths). No mortality from cancer at other sites was in excess, although the numbers were small, with less than seven expected cases for each of the other sites. When North-Rhine Westphalia rates were used, the risk for lung cancer was lower but still elevated (SMR, 1.83; 95% CI, 1.36–2.41; based on 50 deaths). When the cohort was further restricted to workers who started working in this company after 1960 (i.e. eliminating the subcohort of survivors who had started earlier), the SMR was even higher (SMR, 2.89; 95% CI, 2.06–3.94; based on 40 deaths). Data on individual cigarette smoking habits were collected from paper charts of the plant occupational health service. Completeness of information on smoking status increased over time and was reasonably complete after the early 1970s. Overall, information on smoking habits was available for 77% of the cohort. For these men, there was at least one document that described smoking habits reported by the physician and sometimes included information on previous smoking habits. Most frequently, a current smoker was asked for current cigarette consumption only, whereas previous smoking habits were most frequently documented for former smokers. Analyses of risk for lung cancer by smoking category indicated that the smoking variables were valid to some degree, but probably entailed some misclassification. The prevalence of smoking in the reference population increased with age, from 51.6% in the group aged 20–29 years to 75.7% in the group aged ≥79 years. The prevalence of smoking of their contemporaries was slightly higher: 55.1% for the youngest age group and between 80.8% and 89.4% in the older age groups.

To elucidate further the possible role of carbon black as a risk factor, Wellmann *et al*. (2006) performed a detailed exposure assessment by examining personnel charts to reconstruct detailed job histories. Cohort members were then categorized according to their employment for at least 1 year in different departments, such as lampblack, gas black or furnace black production. A semiquantitative scoring system to assign exposure to carbon black to job histories, depending on workplace, occupation and calendar time, was developed in collaboration with experts from the plant who were familiar with historical working conditions. The reconstruction of complete job histories including department, work area and job tasks was successful in 73% of male Germans still alive on 1 January 1976. For most other cohort members, information on work area at least was available. Internal comparisons were made using Poisson regression to assess risk for lung cancer as a function of exposure to carbon black, with adjustment for age and tobacco smoking status. Mortality from lung cancer showed no clear relation with increasing categories of average exposure or several indices of exposure to carbon black. For instance, among workers first employed after 1960, the relative risks in four subgroups with increasing average exposure to carbon black, after adjustment for smoking, were 1.00 (based on nine deaths), 1.53 (95% CI, 0.66–3.55; based on 14 deaths), 1.13 (95% CI, 0.49–2.60; based on 15 deaths) and 0.40 (95% CI, 0.09–1.86; based on two deaths).

The cohort of German carbon black workers has been the subject of two sets of re-analysis and a nested case–control study. Morfeld *et al*. (2006a) carried out an extensive series of re-analyses of the internal comparisons based on Cox regression models in contrast to the Poisson regression models used by Wellmann *et al*. (2006). They conducted 6080 analyses by crossing, in a factorial fashion, the following design parameters: study population (total cohort, total cohort with information on tobacco smoking, cohort at inception, cohort at inception with information on tobacco smoking); alternative methods for handling missing data in the job–exposure matrix that was used for exposure assessment (four different versions); a variable for exposure to carbon black (cumulative or a three-variable version with duration, average intensity and current exposure); duration of employment in selected departments; lag periods (0, 5, 10, 15 or 20 years); and various covariates (including date of birth, age or date of employment, active smoker, former smoker). The Cox regression model enabled the exposure variable to be taken into account in a time-related fashion. These variables were modelled as continuous linear variables. [If there had been a non-linear dose–response relationship and depending on the nature of the non-linearity, it may have been missed in these analyses.] A large majority of the analyses showed no trend of increasing risk for lung cancer with increasing exposure to carbon black. Indeed, most linear trends were not positive. An anomalous result for tobacco smoking (former smokers seemed to have a lower risk than nonsmokers) was explained by errors in smoking data for several cases. A positive trend was seen with duration of work in one department (lampblack) in the cohort at inception but not among other workers.

To investigate the reasons for a possible excess SMR for lung cancer in the cohort of German carbon black workers, Büchte *et al*. (2006) carried out a nested case–control study based on the cases identified by Wellmann *et al*. (2006). For each of the 50 cases, two controls were selected from the cohort using incidence density sampling and were matched on date of birth. Supplementary information on smoking history and history of employment before joining the carbon black industry was collected for each subject. Two distinct approaches—one based on a job–exposure matrix and one based on expert opinion—were used to infer exposure to asbestos, quartz, PAHs, nickel and chromium(VI) in previous jobs. In addition, information on exposure in the carbon black plant to asbestos and feedstock oil was collected. For exposure to carbon black, four different criteria were used to define the case–control database: all subjects; all subjects with information on smoking; subjects limited to those employed from 1960 onwards; and subjects limited to those employed from 1960 onwards and who had information on smoking. Further analyses were carried out with a lag period that varied from 0 to 20 years in 5-year increments. Indicator variables of whether the subject had participated in or had been a prisoner of war during the Second World War were also included. Mean cumulative exposure to carbon black was lower among cases than among controls. In most statistical analyses, the odds ratios for carbon black and lung cancer were well below 1.0, often significantly so. There was little relationship between other exposures at the carbon black plant (asbestos, feedstock oil) and risk for lung cancer. However, there were

strong relationships between exposures in previous jobs and risk. Using quartz as a marker, since the exposures were highly correlated, the odds ratios for quartz and lung cancer were greater than 5.0 and were highly significant. In many analyses, a significant protective effect of having participated in the Second World War was also observed, which the authors interpreted as evidence of a 'healthy survivor' phenomenon. [The Working Group noted that the lack of a positive association for carbon black is compatible with the results of the internal analysis of Wellmann *et al*. (2006) and that of Morfeld *et al*. (2006a). The Working Group was perplexed by the extraordinarily high odds ratios associated with exposures that were incurred before the workers entered the carbon black industry. The magnitude of these effects is difficult to reconcile with the known effects of such agents. Equally perplexing was the apparent protective effect of having participated in the Second World War.]

Morfeld *et al*. (2006b) addressed the SMR results using the external reference that was reported by Wellmann *et al*. (2006). In particular, they explored whether the reported high SMRs for lung cancer could be due to choice of an inappropriate national reference population or to inadequate control for the confounding effects of tobacco smoking or other occupational exposures outside the plant. The effect of different reference populations was evaluated by using national (West) German rates, rates for the State of North-Rhine Westphalia and rates for the City of Cologne. The authors used information from Büchte *et al*. (2006) and the methods of Axelson and Steenland (1988) to infer to what extent previous exposures may have contributed to the SMR in the cohort, and estimated that the bias to the SMR was at least 25%. The impact of confounding by tobacco smoking on the SMR was estimated by means of plant and regional data and the same methods of Axelson and Steenland (1988), and was found to have created a possible bias of at least 25%. In total, the net effect of these biases plus consideration of possible misclassification of eligibility for three subjects may have led to an approximate halving of the SMR from 2.2–3.0 to around 1.2–1.5. [The Working Group noted that the methods were complex and the results were difficult to interpret. It is not clear whether adjustment for prior exposure is justified given the possible overestimation of the effect of such exposures.]

A general excess risk for cancer was reported in workers in one carbon black production plant in the former USSR (Troitskaia *et al*., 1980). [The Working Group noted that neither absolute figures nor the method of calculating observed to expected ratios were given.]

2.1.2 *Carbon black user industries*

Following the finding of an excess risk for stomach cancer in a cohort of rubber workers in the USA, Blum *et al*. (1979) carried out a nested case–control study of stomach cancer. Cases were defined as deaths from stomach cancer (100 in total) from 1964 to 1973 in two rubber companies. Four controls were matched to each case on age, sex and company. [The criteria for selecting controls were not clear.] Using recorded job

history of each worker, the investigators and a group of environmental hygienists assessed potential exposure in each job to the following substances: polycyclic hydrocarbons, nitrosamines, carbon black and detackifiers, which were mainly talc. While not statistically significant, there was a positive association between exposure to carbon black and stomach cancer (Company A: odds ratio, 1.49; 90% CI, 0.84–2.66); based on 21 cases; Company B: odds ratio, 1.74; 90% CI, 1.02–2.97 based on 33 cases). There was some indication that the most highly exposed workers experienced the highest risk.

A nested case–control study was conducted in the tyre and rubber manufacturing industry in the USA to examine the association of squamous-cell carcinoma of the skin with rubber manufacturing materials that were presumed to be contaminated by PAHs (Bourguet *et al*., 1987). Cases of skin cancer were identified from the records of four hospitals located in Akron, OH, and these were cross-checked against a list of past and present employees of two local rubber companies who had been enumerated in 1964 for historical cohort studies conducted previously in this industry. Sixty-five cases of squamous-cell skin cancer in white men were thereby ascertained in this cohort. [The case ascertainment system may not have identified all cases in the cohort.] Controls were selected from remaining cohort members and were matched to cases on company, year of birth and year of employment, and were required to have been employed in the industry until date of diagnosis or date of leaving the industry of the corresponding case. A total of 254 matched controls were identified, with approximately four matched controls selected for each case. Two industrial hygienists assessed the exposure of each study subject to five substances: carbon black, extender oils, lubricating oils, rubber solvents and rubber stocks. Conditional logistic regression analyses were carried out with all five substances included in the models, and each one was categorized into three exposure subgroups reflecting concentration and frequency of exposure. For carbon black, the odds ratios in the low-, medium- and high-exposure subgroups were 0.7, 1.2 and 0.7, respectively, indicating the lack of an exposure–response relationship. There was also no evidence for a trend by duration of exposure.

A historical cohort of 26 561 workers employed in 10 facilities was assembled to evaluate risks for cancer associated with exposure to formaldehyde (Blair *et al*. 1990); 20 714 white men were included in the analysis. The plants were drawn from a variety of industries in which exposure to formaldehyde can be substantial and were located throughout the USA. The project was characterized by a very extensive assessment of exposure to formaldehyde. About 85% of the workers were thought to have been exposed to formaldehyde at levels above 0.1 ppm [0.123 mg/m^3]. To assess possible confounding and modification of effect due to other occupational substances, an assessment was made of the exposure of each worker to several other substances, one of which was carbon black. The exposure status of subjects was inferred from their recorded work histories that were linked to estimates of exposure in different jobs in these plants. The latter estimates were derived by industrial hygienists who carried out site visits, discussed exposure conditions with workers and plant managers and consulted available hygiene monitoring data. Although this study was not designed primarily to assess risk in relation to exposure

to carbon black, the data could be used for that purpose, and, in one report that focused primarily on exposure to formaldehyde and the risk for lung cancer, results were presented that showed the associations between each of the other substances studied and lung cancer. Expected numbers of deaths were computed using national rates. For all levels and durations of exposure to carbon black combined, there was a slight excess risk for lung cancer (SMR, 1.3 [95% CI, 0.8–2.0]; 20 observed cases). Based on 142 observed cases, the SMR for formaldehyde was 1.4 [95% CI, 1.2–1.6] for ≥20 years after first exposure. There was no clear trend by duration of exposure and the pattern of results was similar when restricted to 20 years or more since first exposure. [The Working Group noted that the description of the methods of exposure assessment and analysis for carbon black was limited. It was not clear whether all workers exposed to carbon black were also exposed to formaldehyde.]

A series of investigations was conducted to assess risks for cancer in the German rubber industry (Weiland *et al*., 1996; Straif *et al*., 1998; Weiland *et al*., 1998; Straif *et al*., 1999). While the initial series of reports addressed risks in the industry as a whole and in selected work areas, one report entailed an attempt to link cancer occurrence to selected occupational exposures, one of which was carbon black (Straif *et al*., 2000). The cohort in which this analysis was conducted comprised 8933 male German rubber workers, and included all male German blue-collar workers in five study plants who were employed during or after 1950 and who were alive and actively employed or retired on 1 January 1981. Follow-up of individual cohort members began on 1 January 1981, but not before completion of 1 year of employment, and ended at the age of 85 years, at death or at the end of the follow-up period (31 December 1991). Cohort members were identified through the computerized files of the health insurance companies and the personnel files of the rubber plants. At the start of follow-up, the cohort of 8933 workers included 6875 actively employed and 2058 retirees. Health insurance data, personnel files and population registries of the participating plants were used to determine the vital status of cohort members at the end of the observation period. Overall ascertainment of vital status for the cohort was nearly complete (99.7%). For all cohort members who were reported to have died, information from the population registry was used to request a copy of the death certificate from the respective community health department. Death certificates were successfully obtained for 2631 (96.8%) of the decedents. In comparison with the general population of western Germany, mortality from all causes was slightly elevated in the cohort of men (SMR, 1.03; 95% CI, 0.98–1.09; based on 1521 deaths). This increased mortality was concentrated among the subcohort of retirees (SMR, 1.13; 95% CI, 1.08–1.18; based on 1992 deaths), whereas the active employees showed a slightly lower SMR of 0.95 (95% CI, 0.89–1.03; based on 727 deaths) for all causes. SMRs for cancers of the stomach, larynx and lung were increased among the total cohort.

To explore further the risks related to specific exposures in this industry, the investigators (Straif *et al*., 2000) estimated the exposure of each cohort member to selected substances, namely nitrosamines, asbestos, talc and carbon black. Individual work histories within the rubber companies were reconstructed using routinely

documented and archived cost centre codes. Complete individual work histories (date of employment, work history within the rubber industry and date of termination) were available for 98.9% of the cohort members from the start of their employment. Since environmental monitoring of the compounds of interest was not performed before 1979, it was necessary to make retrospective semiquantitative estimates of exposure. In cooperation with industrial hygienists from the rubber plants involved and other experts, a scheme for exposure categorization was developed. Exposure to carbon black was rated in a dichotomous fashion (exposed versus unexposed). Complete exposure assessment was available for approximately 95% of the cohort members. Approximately one in every three cohort members was exposed to medium or high levels of asbestos and talc, and almost 20% were exposed to carbon black. In analyses that included one exposure variable at a time, mortality from stomach cancer was increased among workers with exposures to asbestos, talc and carbon black. Depending on the cut-off points used to define low- and high-exposure subgroups, the hazard rate ratio for the effect of carbon black on stomach cancer was between 1.8 (95% CI, 0.9–3.4; based on 12 deaths) and 3.3 (95% CI, 1.6–6.5; based on 11 deaths; >10 years of exposure). However, when asbestos, talc (potentially contaminated with asbestos) and nitrosamines were entered into the model, the hazard rate ratio for carbon black fell to the range of 1.2 (95% CI, 0.5–3.0) to 1.5 (95% CI, 0.5–4.6; >10 years of exposure). [Acknowledgement that the fully adjusted model is more appropriate implies acceptance that talc and/or asbestos are true risk factors for stomach cancer. Until and if such a hypothesis is accepted, the Working Group was inclined to view the significant odds ratios between carbon black and stomach cancer as meaningful.] In parallel analyses of lung cancer, a similar pattern was seen. In analyses in which carbon black was the only exposure variable, the hazard rate ratios were around 1.5 (95% CI, 1.0–2.2; based on 38 deaths) and 1.5 (95% CI, 0.9–2.4; based on 24 deaths; >10 years of exposure), depending on exposure categorization. When the other occupational exposures (nitrosamines, asbestos, talc) were included in the model, the estimates for carbon black dropped to 1.1 (95% CI, 0.7–1.9) and 1.1 (95% CI, 0.6–2.2; >10 years of exposure). [The Working Group considered that it is possible that the carbon black-associated risks for lung cancer may have been confounded by exposure to asbestos.] Analyses of laryngeal cancer were limited by small numbers. In models that used one exposure at a time, carbon black showed a hazard rate ratio of 5.3 (95% CI, 1.3–21.4; based on four deaths). There were also excess risks noted in relation to exposure to talc and asbestos. [While cigarette smoking is a plausible confounder in analyses that use comparisons with external reference populations, this is a much less probable explanation for any associations found in these internal analyses that compared one group of rubber industry workers with another. In addition, the exposure assessment for carbon black was rather crude.]

Puntoni *et al*. (2001, 2004) reported on cancer risks among a cohort of Italian dockyard workers with presumed exposure to carbon black. Between 1947 and 1957, longshoremen in the port of Genoa unloaded between 8000 and 12 000 tonnes of carbon black per year; the bags were often carried on workers' shoulders and thereby produced

considerable exposure to dust. Subsequently, the quantity of carbon black unloaded at the port decreased substantially. The cohort of workers comprised all dock workers employed at three dockyard companies between 1933 and 1979. A total of 2286 male workers were included and were categorized *a priori* into subgroups with varying exposures to carbon black. Longshoremen who unloaded carbon black pallets by forklift trucks and cranes were thought to have low or moderate exposure, depending on the frequency of the task. Men who carried carbon black in paper sacks on their shoulders had high exposure. The vital status of each man was ascertained from the demographic registry of his place of residence until 31 December 1996. Cancer frequency was established by record linkage with the Genoa cancer registry for the period 1986–96 (the interval for which data were available). Individuals who emigrated (n=16) or died (n=169) before 1986, i.e. the starting date of follow-up, were excluded from the analysis. Thus 858, 709 and 534 dockyard workers with low, moderate and high exposure to carbon black, respectively, were eligible for statistical analysis. Expected values were calculated using the population of the City of Genoa. Standardized incidence ratios (SIRs) that used the low-exposure group as reference provided an internal comparison of risk. In the entire study group, 208 cancers occurred during the follow-up period (SIR, 0.95; 95% CI, 0.83–1.09). SIRs were significantly increased for pleural mesotheliomas (SIR, 7.51; 95% CI, 3.02–15.47; based on seven cases) and melanoma (SIR, 2.88; 95% CI, 1.25–5.68; based on eight cases). Less markedly increased SIRs were detected for cancer of the larynx (SIR, 1.54; 95% CI, 0.84–2.58; based on 14 cases) and urinary bladder (SIR, 1.30; 95% CI, 0.89–1.84; based on 32 cases). The incidence of lung cancer was not increased (SIR, 1.08; 95% CI, 0.81–1.41; based on 53 cases). No indication of excess risk for cancer of the stomach (SIR, 0.29; 95% CI, 0.06–0.85; based on three cases), skin cancer other than melanoma (SIR, 0.66; 95% CI, 0.36–1.10; based on 14 cases) or cancer of the kidney (SIR, 0.67; 95% CI, 0.22–1.57; based on five cases) was observed. In the subcohort of highly exposed workers, the only statistically significant excess risk was for cancer of the urinary bladder (SIR, 1.97; 95% CI, 1.08–3.30; based on 14 cases). No cancer at other sites, including pleural mesothelioma and melanoma, showed an increased incidence in this subcohort. [The absence of any measurements in this industry during the time of exposure (1947–57) detracts from the ability to link carbon black to the risk estimates. In addition, the narrow period of cancer observation (1986–96) further detracts since cancer occurrence outside this period was ignored. The excess risks observed for mesothelioma and melanoma can be attributed to exposures other than carbon black.]

2.2 Community-based case–control studies

Table 2.2 summarizes community-based case–control studies that examined risks for cancer in workers exposed to carbon black. Of the four reports described, three are drawn from the same population (Siemiatycki, 1991; Parent *et al*., 1996, 2000).

Steineck *et al*. (1990) examined the relationship between urothelial cancer and various occupational exposures in a population-based case–control study in Sweden. The

Table 2.2. Community-based case–control studies of cancer and exposure to carbon black

Reference, study location	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Cancer site	No. of cases/controls	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders
Steineck *et al*. (1990), Stockholm, Sweden	Male incident cases during 1985–87; 80% response rate	Population controls; frequency-matched on sex and year of birth	Self-reported job history reviewed by experts	Ever exposed to carbon black	Urothelium	254/287	14	2.0 (0.8–4.9)	Year of birth, smoking
Siemiatycki (1991), Montréal, Canada	Male incident cases from 1979 to 1985; 82% response rate	Cancer controls; not matched	Self-reported job history reviewed by experts	Ever exposed to carbon black	Oesophagus Stomach Lung Urinary bladder Kidney Skin melanoma	99/2546 251/2379 857/1360 484/1879 177/2481 103/2525	11 9 52 26 14 2	2.2 (1.2–3.9) 0.8 (0.4–1.3) 1.6 (1.1–2.2) 1.2 (0.8–1.8) 1.9 (1.1–3.0) 0.4 (0.1–1.4)	Age, SES, ethnicity, smoking; 90% CI
Parent *et al*. (1996), Montréal, Canada	Male incident cases from 1979 to 1985; 82% response rate	Cancer controls; population controls, age-stratified	Self-reported job history reviewed by experts	'High' exposure to carbon black	Lung	857/1360 cancer 857/533 pop.	18 18	2.17 (0.95–4.91) 1.52 (0.58–3.97)	Age, ethnicity, SES, proxy/self-respondent, alcohol, asbestos, chromium, tobacco smoking
Parent *et al*. (2000), Montréal, Canada	Male incident cases from 1979 to 1985; 82% response rate	Population controls plus a random sample of cancer controls	Self-reported job history reviewed by experts	Any 'Substantial'	Oesophagus	99/533 pop. 99/533 cancer	11 2	2.1 (1.0–4.3) 5.7 (0.9–36)	Age, ethnicity, education, birthplace, proxy/self-respondent, alcohol, ß-carotene index, smoking

CI, confidence interval; pop., population; SES, socioeconomic status

study was based on men who were born between 1911 and 1945 and who lived in the county of Stockholm for all or part of the observation period of September 1985 to November 1987. Incident cases of urothelial cancer and/or squamous-cell carcinoma in the lower urinary tract were identified from the regional cancer registry and urological departments (*n*=320). Controls (*n*=363) were selected by stratified random sampling (by gender and year of birth) during the observation period from a computerized register that covered 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, one of which was carbon black. The adjusted odds ratio among men who were classified as having been exposed to carbon black was 2.0 (95% CI, 0.8–4.9; based on 14 cases), but they could also have been exposed to other substances, such as printing inks.

A population-based case–control study of cancer among male residents of Montréal, Canada, aged 35–70 years, included histologically confirmed cases of cancer at 11 major sites that were newly diagnosed between 1979 and 1985 (Siemiatycki, 1991). With a response rate of 82%, 3730 cancer patients were successfully interviewed. For each cancer site analysed, two control groups were used, which gave rise to two separate sets of analyses and results: one control group was selected from among cases of cancer at the other sites studied (cancer controls; see Table 2.2) and another group consisted of 533 age-stratified population controls from the general population (response rate, 72%). The interview was designed to obtain detailed lifetime job histories and information on potential confounders. Each job was reviewed by industrial hygienists who translated jobs into occupational exposures, using a checklist of 293 common occupational substances. Five per cent of the entire study population had been exposed to carbon black at some time (i.e. lifetime exposure prevalence). Among the main occupations in which exposure to carbon black was attributed in this study were painters (26%), printing industry workers (17%), motor vehicle mechanics (8%) and occupations in rubber and plastics products (6%) (Parent *et al*., 1996). The results presented (Siemiatycki, 1991) were based mainly in comparison with the cancer control group. For the following cancer sites, there was no indication of a significant excess risk in relation to any exposure to carbon black, after adjustment for age, ethnic group, social class and tobacco smoking (number of exposed cases; odds ratio): stomach (*n*=9; 0.8), colon (*n*=17; 0.7), rectum (*n*=10; 0.7), pancreas (*n*=3; 0.7), prostate (*n*=25; 1.2), urinary bladder (*n*=26; 1.2), skin melanoma (*n*=2; 0.4) and non-Hodgkin lymphoma (*n*=9; 0.9). For the following sites there was an indication of excess risk: oesophagus (odds ratio, 2.2; 90% CI, 1.2–3.9; 11 exposed cases), kidney (odds ratio, 1.9; 90% CI, 1.1–3.0; 14 exposed cases) and lung (odds ratio, 1.6; 90% CI, 1.1–2.3; 52 exposed cases).

To investigate further the possible link between carbon black and lung cancer, an additional analysis of the Montréal data set was carried out (Parent *et al*., 1996). A synthetic exposure index was created that was composed of the indices deduced for each exposed subject (concentration, frequency, confidence in the attribution of exposure,

duration) and was used to designate a lower and a higher cumulative exposure subgroup. Logistic regression analyses were carried out and were adjusted for the same covariates as those used in the analyses of Siemiatycki (1991), as well as for two recognized lung carcinogens—asbestos and chromium compounds. Using cancer controls, the odds ratios for lower and higher exposure were 1.08 (95% CI, 0.66–1.76) and 2.17 (95% CI, 0.95–4.91), respectively; using population controls, the odds ratios for lower and higher exposure were 0.87 (95% CI, 0.48–1.60) and 1.52 (95% CI, 0.58–3.97), respectively. The excess among highly exposed workers was most pronounced for small-cell tumours of the lung. Based on seven cases, the odds ratio was 5.05 (95% CI, 1.72–14.87) using cancer controls and 4.82 (95% CI, 1.36–17.02) using population controls.

To investigate occupational risk factors for oesophageal cancer in the Montréal study, a separate analysis was conducted that focused on this site only (Parent *et al*., 2000). There were 99 cases of oesophageal cancer, of which 63 were squamous-cell carcinoma. The following variables were entered into the regression models as possible confounders: age (in years), respondent status (self, proxy), education (three levels), birthplace (seven categories), alcohol consumption (three categories), an index of β-carotene intake (three levels) and two tobacco smoking variables (natural logarithm of the number of cigarette–years and smoking patterns: never smokers, former smokers for at least 11 years, former smokers for 3–10 years, former smokers for 2 years or less and current smokers). A separate model was carried out for each of 30 occupational substances, one of which was carbon black. Workers exposed to carbon black at any level had an excess incidence of oesophageal cancer (odds ratio, 2.1; 95% CI, 1.0–4.3; based on 11 cases) and in particular squamous-cell cancer (odds ratio, 3.4; 95% CI, 1.5–7.7; based on 10 cases) when using population-based controls as a comparison group. When other occupational variables were included in a model with carbon black, the results for the latter were not materially affected.

2.3 References

Axelson O, Steenland K (1988). Indirect methods of assessing the effects of tobacco use in occupational studies. *Am J Ind Med*, 13:105–118 doi:10.1002/ajim.4700130107. PMID:3344750

Blair A, Stewart PA, Hoover RN (1990). Mortality from lung cancer among workers employed in formaldehyde industries. *Am J Ind Med*, 17:683–699 doi:10.1002/ajim.4700170604. PMID:2343874

Blum S, Arp EW Jr, Smith AH, Tyroler HA (1979). Stomach cancer among rubber workers: an epidemiologic investigation. In: Lemen R, Dement JM, ed, *Dusts and Disease: Proceedings of the Conference on Occupational Exposures to Fibrous and Particulate Dust and Their Extension into the Environment.*, Park Forest South, IL, Pathotox Publisher, pp. 325–334.

Bourguet CC, Checkoway H, Hulka BS (1987). A case-control study of skin cancer in the tire and rubber manufacturing industry. *Am J Ind Med*, 11:461–473 doi:10.1002/ajim.4700110409. PMID:3578299

Büchte SF, Morfeld P, Wellmann J *et al.*; International Carbon Black Association (2006). Lung cancer mortality and carbon black exposure: a nested case–control study at a German carbon black production plant. *J Occup Environ Med*, 48:1242–1252. PMID:17159641 doi:10.1097/01.jom.0000215710.17519.cd

Dell LD, Mundt KA, Luippold RS *et al.*; International Carbon Black Association (2006). A cohort mortality study of employees in the U.S. carbon black industry. *J Occup Environ Med*, 48:1219–1229 doi:10.1097/01.jom.0000218701.62658.a2. PMID:17159639

Hodgson JT, Jones RD (1985). A mortality study of carbon black workers employed at five United Kingdom factories between 1947 and 1980. *Arch Environ Health*, 40:261–268. PMID:4062360

IARC (1982). The rubber industry. *IARC Monogr Eval Carcinog Risk Chem Hum*, 28:1–486. PMID:6957378

IARC(1989). Diesel and gasoline engine exhausts and some nitroarenes. *IARC Monogr Eval Carcinog Risks Hum*, 46:1–458. PMID:2483415

IARC (1996). Printing processes and printing inks, carbon black and some nitro compounds. *IARC Monogr Eval Carcinog Risks Hum*, 65:1–578.

Ingalls TH (1950). Incidence of cancer in the carbon black industry. *Arch Ind Hyg Occup Med*, 1:662–676. PMID:15433509

Ingalls TH, Risquez-Iribarren R (1961). Periodic search for cancer in the carbon black industry. *Arch Environ Health*, 2:429–433. PMID:13717667

Morfeld P, Büchte SF, Wellmann J *et al.* (2006a). Lung cancer mortality and carbon black exposure: Cox regression analysis of a cohort from a German carbon black production plant. *J Occup Environ Med*, 48:1230–1241. PMID:17159640 doi:10.1097/01.jom.0000215282.23531.b9

Morfeld P, Büchte SF, McCunney RJ, Piekarski C; International Carbon Black Association (2006b). Lung cancer mortality and carbon black exposure: uncertainties of SMR analyses in a cohort study at a German carbon black production plant. *J Occup Environ Med*, 48:1253–1264. PMID:17159642 doi:10.1097/01.jom.0000215344.77132.99

Parent ME, Siemiatycki J, Fritschi L (2000). Workplace exposures and oesophageal cancer. *Occup Environ Med*, 57:325–334 doi:10.1136/oem.57.5.325. PMID:10769298

Parent ME, Siemiatycki J, Renaud G (1996). Case–control study of exposure to carbon black in the occupational setting and risk of lung cancer. *Am J Ind Med*, 30:285–292 doi:10.1002/(SICI)1097-0274(199609)30:3<285::AID-AJIM6>3.0.CO;2-Y. PMID:8876796

Puntoni R, Ceppi M, Gennaro V *et al.* (2004). Occupational exposure to carbon black and risk of cancer. *Cancer Causes Control*, 15:511–516 doi:10.1023/B:CACO.0000036446.29787.94. PMID:15286471

Puntoni R, Ceppi M, Reggiardo G, Merlo F (2001). Occupational exposure to carbon black and risk of bladder cancer. *Lancet*, 358:562 doi:10.1016/S0140-6736(01)05717-8. PMID:11520532

Robertson JM, Ingalls TH (1980). A mortality study of carbon black workers in the United States from 1935 to 1974. *Arch Environ Health*, 35:181–186. PMID:7387198

Robertson JM, Ingalls TH (1989). A case–control study of circulatory, malignant, and respiratory morbidity in carbon black workers in the United States. *Am Ind Hyg Assoc J*, 50:510–515. PMID:2801500

Robertson JM, Inman KJ (1996). Mortality in carbon black workers in the United States. *J Occup Environ Med*, 38:569–570. PMID:8794954 doi:10.1097/00043764-199606000-00006

Siemiatycki J, ed (1991) *Risk Factors for Cancer in the Workplace,* CRC Press, Boca Raton, FL.

Sorahan T, Hamilton L, van Tongeren M *et al.* (2001). A cohort mortality study of U.K. carbon black workers, 1951–1996. *Am J Ind Med*, 39:158–170 doi:10.1002/1097-0274(200102)39:2<158::AID-AJIM1003>3.0.CO;2-L. PMID:11170158

Steineck G, Plato N, Gerhardsson M *et al.* (1990). Increased risk of urothelial cancer in Stockholm during 1985–87 after exposure to benzene and exhausts. *Int J Cancer*, 45:1012–1017 doi:10.1002/ijc.2910450605. PMID:1693598

Straif K, Chambless L, Weiland SK *et al.* (1999). Occupational risk factors for mortality from stomach and lung cancer among rubber workers: an analysis using internal controls and refined exposure assessment. *Int J Epidemiol*, 28:1037–1043 doi:10.1093/ije/28.6.1037. PMID:10661645

Straif K, Keil U, Taeger D *et al.* (2000). Exposure to nitrosamines, carbon black, asbestos, and talc and mortality from stomach, lung, and laryngeal cancer in a cohort of rubber workers. *Am J Epidemiol*, 152:297–306 doi:10.1093/aje/152.4.297. PMID:10968374

Straif K, Weiland SK, Werner B *et al.* (1998). Workplace risk factors for cancer in the German rubber industry: Part 2. Mortality from non-respiratory cancers. *Occup Environ Med*, 55:325–332 doi:10.1136/oem.55.5.325. PMID:9764110

Troitskaia NA, Velichkovskiĭ BT, Kogan FM, Kuz'minykh AI (1980). [Carcinogenic hazard in the manufacture of technical-grade carbon]. *Vopr Onkol*, 26:63–67 (in Russian). PMID:7355600

Weiland SK, Mundt KA, Keil U *et al.* (1996). Cancer mortality among workers in the German rubber industry: 1981–91. *Occup Environ Med*, 53:289–298 doi:10.1136/oem.53.5.289. PMID:8673175

Weiland SK, Straif K, Chambless L *et al.* (1998). Workplace risk factors for cancer in the German rubber industry: Part 1. Mortality from respiratory cancers. *Occup Environ Med*, 55:317–324 doi:10.1136/oem.55.5.317. PMID:9764109

Wellmann J, Weiland SK, Neiteler G *et al.* (2006). Cancer mortality in German carbon black workers 1976–98. *Occup Environ Med*, 63:513–521 doi:10.1136/oem.2006.026526. PMID:16497850

3. Studies of Cancer in Experimental Animals

The studies described below investigated the potential carcinogenicity of carbon black, solvent-extracted carbon black and the materials extracted from carbon black (carbon black extracts). However, individual materials extracted from various carbon blacks are not within the scope of this monograph. Some of these individual components (e.g. nitroaromatic compounds) have been evaluated previously (IARC, 1989, 1996).

Several early studies compared the carcinogenicity of carbon black or carbon black extracts administered orally or by dermal or subcutaneous application. The carbon black used in some of these studies may no longer be commercially available. More recent studies examined the carcinogenicity of inhalation exposure to or intratracheal administration of carbon black or solvent-extracted carbon black. Many of these were part of large studies carried out to investigate the carcinogenicity of diesel exhaust (see also IARC, 1989).

The Working Group identified an issue that relates to the interpretation of several studies on the inhalation and intratracheal instillation of carbon black. A lesion that is frequently seen in treated rats has been described variously as 'proliferating squamous cyst', 'proliferative keratinizing cyst', 'proliferating squamous epithelioma', 'benign cystic keratinizing squamous-cell tumour' or 'cystic keratinizing squamous-cell (CKSC) tumour'. Many authors have included this lesion in tumour counts, but the neoplastic nature of this lesion has been debated (Kittel *et al*., 1993; Carlton, 1994; Dungworth *et al*., 1994; Mauderly *et al*., 1994; Boorman & Seely, 1995; Rittinghausen *et al*., 1997; Rittinghausen & Kaspareit, 1998); its relationship to pulmonary neoplasia is uncertain. Therefore, where possible, the Working Group has listed incidences of this lesion separately from those of other pulmonary neoplasms.

3.1 Oral administration

3.1.1 *Mouse*

After two weeks of acclimatization, two groups of 31 and 28 female weanling CF_1 mice were fed 0 (controls) or 2.05 g/kg diet furnace carbon black (ASTM N375) for two years. At necropsy, all tissues were examined for gross pathology. Only tissues that had macroscopically visible lesions were examined histologically. Survival at two years was similar in treated mice (84%) and in controls (71%). No increase in tumour incidence was observed (treated mice: colon tumours, 3%; lung tumours, 23%; controls: colon tumours, 0%; lung tumours, 21%) (Pence & Buddingh, 1985). [The Working Group noted the incomplete histopathological examination.]

3.1.2 *Rat*

After two weeks of acclimatization, two groups of 29 female weanling Sprague-Dawley rats were fed 0 (controls) or 2.05 g/kg diet furnace carbon black (ASTM N375). At necropsy, all tissues were examined for gross pathology. Only tissues that had macroscopically visible lesions were examined histologically. Survival at two years was similar in controls (45%) and treated animals (38%). No increase in tumour incidence was observed (treated rats: colon tumours, 3%; kidney tumours, 3%; mammary tumours, 24%; controls: colon tumours, 3%; kidney tumours, 3%; mammary tumours, 28%) (Pence & Buddingh, 1985). [The Working Group noted the incomplete histopathological examination.]

3.2 Inhalation exposure

3.2.1 *Mouse*

Groups of 80 female Crl: NMRI BR mice, seven weeks of age, were exposed to high-purity furnace carbon black (Printex 90; primary particle size, 14 nm; specific surface area, 227±18.8 m^2/g; MMAD of particles in the exposure chambers, 0.64 μm). The extractable organic mass of the carbon black was 0.04%; the content of benzo[*a*]pyrene was 0.6 pg/mg and that of 1-nitropyrene was <0.5 ng/mg particle mass. The animals were exposed in whole-body exposure chambers for 18 hours per day on 5 days per week to 7.4 mg/m^3 carbon black for 4 months followed by 12.2 mg/m^3 for 9.5 months. After exposure, the mice were kept in clean air for further 9.5 months. A control group was exposed to clean air throughout the study. Histopathology was performed on the nasal and paranasal cavities, larynx, trachea and lung. After 11 months and up to 17 months, body weights were significantly lower (5–7%) in the carbon black-exposed mice compared with controls. During the last months, no difference in body weight was observed between the groups. After 13.5 months, mortality was 20% in the carbon black-exposed mice and 10% in controls; 50% mortality was reached after 19 months in the carbon black-exposed group and after 20 months in the control group. In exposed mice, the lung particle burden was 0.8, 2.3 and 7.4 mg carbon black per lung after 3, 6 and 12 months, respectively; at 12 months, this corresponded to a lung particle burden of 37 mg/g clean-air control lung (wet weight of control lung, 0.2 g). Tumours were only observed in the lung, but no statistical difference was observed between experimental and control animals; 11.3% (9/80) of carbon black-exposed mice had adenomas and 10% (8/80) had adenocarcinomas compared with 25% (20/80) and 15.4% (12/80) of controls, respectively (Heinrich *et al*., 1995).

3.2.2 *Rat*

Two groups of 72 female Wistar rats, seven weeks of age, were exposed by inhalation for 17 hours per day on 5 days per week to 6 mg/m^3 furnace carbon black (Printex 90;

0.04% extractable mass of organics; benzo[*a*]pyrene content, 0.6 pg/mg carbon black; 1-nitropyrene content, <0.5 pg/mg carbon black; primary particle size, 15 nm; MMAD of particles in the exposure chamber, 1.1 μm; specific surface area, 230 m^2/g). One of these groups was exposed for 43 weeks and kept for an additional 86 weeks in clean air and the other group was exposed for 86 weeks and housed in clean air for an additional 43 weeks. Two clean-air control groups of 72 animals were kept for 129 weeks. The respiratory tract of all animals was examined histopathologically. No tumour was observed in the clean-air controls. The 43-week exposure group had a lung tumour rate of 18% [13/72] (two bronchiolar/alveolar adenomas, seven benign CKSC tumours, four bronchiolar/alveolar adenocarcinomas and one squamous-cell carcinoma). The 86-week exposure group had a lung tumour rate of 8% [6/72] (one bronchiolar/alveolar adenoma, four benign CKSC tumours and one squamous-cell carcinoma). In addition to the six tumours, six other rats in the latter group developed lung lesions that were borderline between non-neoplastic and neoplastic (described as marked hyperplasia or marked squamous-cell proliferation). [The difference in the tumour rates of the two exposed groups was not statistically significant] (Dungworth *et al*., 1994; Heinrich *et al*., 1994).

A group of 100 female Wistar rats, seven weeks of age, was exposed to high-purity furnace carbon black (Printex 90; particle size 14 nm; specific surface area, 227±18.8 m^2/g; MMAD of particles in the exposure chamber, 0.64 μm). The extractable organic mass of the furnace black was 0.04%; the content of benzo[*a*]pyrene was 0.6 pg/mg and that of 1-nitropyrene was <0.5 ng/mg particle mass. Rats were exposed in whole-body exposure chambers for 18 hours per day on 5 days per week to 7.4 mg/m^3 carbon black for 4 months followed by 12.2 mg/m^3 for 20 months. After exposure, the rats were kept in clean air for further 6 months. Controls (*n*=220) were exposed to clean air throughout the study. Eight groups of 9–21 rats (interim sacrifice groups) were also exposed to carbon black or clean air for 6, 12, 18 or 24 months. Histopathology was performed on the nasal and paranasal cavities, larynx, trachea and lung. Mortality in the carbon black-exposed group was 56% after 24 months of exposure and 92% after 30 months. In the clean air group, mortality was 42% after 24 months and 85% after 30 months. Compared with the controls, the mean lifespan of the treated rats was significantly reduced. Mean body weights were significantly lower from day 300 to the end of exposure (carbon black-exposed, 325 g; control, 417 g). The lung burden of carbon black at 24 months was 43.9±4.3 mg per lung (equivalent to 31.3 mg/g clean-air control lung) and 6.7 mg per animal in the lung-associated lymph nodes (determined after 22 months of exposure). The incidence of benign and malignant lung tumours was increased in the treated groups after 30 months. The numbers of rats with lung tumours are summarized in Table 3.1 (Dungworth *et al*., 1994; Heinrich *et al*., 1995).

Three groups of 135–136 female and 138–139 male Fischer 344/N specific pathogen-free rats, 7–9 weeks of age, were exposed in whole-body exposure chambers to 0, 2.5 or 6.5 mg/m^3 furnace carbon black (Elfte × –12) for 16 hours per day on 5 days per week for up to 24 months. The carbon black aerosol was produced by an air-jet dust generator and was diluted with filtered air. The size distribution of carbon black particles in the chamber

Table 3.1. Lung-tumour incidence in female rats exposed to carbon black by inhalation

Exposure period	Carbon black-exposed (average concentration of carbon black, 11.6 mg/m^3)	Clean-air control
Interim sacrifice groups		
6 months	0/20	0/21
12 months	0/18	0/21
18 months	0/16	0/18
24 months	1/9[a]	0/10
Thirty-month study		
	20/100[a]	1/217[b]
	13/100[b]	
	4/100[c]	
	13/100[d]	
No. of animals with tumours[e]	39/100	1/217
	28/100[f]	

From Heinrich *et al*. (1995)
[a] Benign cystic keratinizing squamous-cell tumours
[b] Adenomas
[c] Squamous-cell carcinomas
[d] Adenocarcinomas
[e] Some animals had two lung tumours
[f] Excluding 11 animals that had only benign cystic keratinizing squamous-cell tumours

was bimodal: 67% of the particles were in the large-size mode (MMAD, 2.0 μm) and 33% in the small-size mode (mass median diffusion diameter, 0.1 μm). The level of extractable organic material was 0.04–0.29% (mean value during the course of exposure, 0.12%). Observations were made throughout lifespan for the majority of rats in each group (i.e. for approximately 100 males and 100 females per experimental group in total) for which body weight, survival and carcinogenicity were evaluated. Three males and three females were killed after 3, 6, 12, 18 or 23 months of exposure. After exposure for 24 months, surviving rats were kept in clean air until mortality reached 90% when the experiment was terminated. The high-dose exposure to carbon black significantly (P<0.05) reduced the median lifespan of both females and males. Survival was also significantly reduced in low-dose males. A significant reduction in the body weights of female and male rats exposed to the high dose of carbon black first occurred on days 309 and 449, respectively. This effect was seen only after day 509 of exposure for both males and females in the low-dose group. After about 22 months, the mean reduction in body weight was 16% for high-dose females and 14% for high-dose males; these figures were below 10% in low-dose animals. The exposure caused progressive, dose-related accumulation of carbon black particles in the lungs. After 23 months, the mean lung burden reached 12.4 mg/g in low-dose males, 13.9 mg/g in low-dose females, 20.2 mg/g in high-dose males and 30.0 mg/g in high-dose females. Full necropsies were performed on all animals and lungs and suspected lung tumours were examined microscopically. The incidence of the various types of lung tumour is shown in Table 3.2.

Table 3.2. Numbers of Fischer 344/N rats with lung neoplasms and numbers and types of lung neoplasm observed after exposure to 2.5 or 6.5 mg/m^3 carbon black for up to 24 months

Type of tumour	Control			Carbon black					
				2.5 mg/m^3			6.5 mg/m^3		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
No. of animals examined[a]	114	118	232	116	115	231	114	115	229
Adenoma									
No. of neoplasms	0	1	1	2	1	3	17	0	17
No. of rats with neoplasms	0	1	1	2	1	3	13	0	13
Adenocarcinoma									
No. of neoplasms	0	1	1	6	1	7	23	1	24
No. of rats with neoplasms	0	1	1	6	1	7	20	1	21
Squamous-cell carcinoma									
No. of neoplasms	0	1	1	0	0	0	1	2	3
No. of rats with neoplasms	0	1	1	0	0	0	1	2	3
Adenosquamous carcinoma									
No. of neoplasms	0	0	0	0	0	0	1	1	2
No. of rats with neoplasms	0	0	0	0	0	0	1	1	2
Malignant tumour not otherwise specified[b]									
No. of neoplasms	0	0	0	1	0	1	0	0	0
No. of rats with neoplasms	0	0	0	1	0	1	0	0	0

From Mauderly *et al*. (1994); Nikula *et al*. (1995)

[a] Including all rats that underwent gross necropsy and microscopic examination of the lung whether the rats died spontaneously, were euthanized or were killed

[b] This tumour was of a mixed mesenchymal and epithelial type

Statistical comparisons were performed using logistic regression modelling. The incidence of adenomas and adenocarcinomas was significantly increased in females, particularly at the high-dose level. There was no significant increase in the incidence of lung tumours in males. The percentages of male and female rats with lung tumours are given in Table 3.3. Exposure-related squamous cysts in the lung were classified as non-neoplastic lesions. In animals that died later than 18 months after the start of the exposure, squamous cysts (one or more per animal) were observed in 0/86 male controls, 1/73 low-dose males and 4/74 high-dose males and in 0/91 control females, 8/90 low-dose females and 13/87 high-dose females (Mauderly *et al*., 1994; Nikula *et al*., 1995).

Table 3.3. Numbers and percentages of Fischer 344/N rats examined for lung neoplasms that had one or more neoplasm following exposure to 2.5 or 6.5 mg/m^3 carbon black for up to 24 months[a]

Group	Sex	No. of rats at risk for neoplasms[b]	Rats with malignant neoplasms		Rats with malignant or benign neoplasms	
			No.	Percentage	No.	Percentage
Control	Female	105	0	0	0	0
	Male	109	2	1.8	3	2.8
	Combined	214	2	0.9	3	1.4
Carbon black						
2.5 mg/m^3	Female	107	7	6.5	8	7.5
	Male	106	1	0.9	2	1.9
	Combined	213	8	3.8	10	4.7
6.5 mg/m^3	Female	105	21	20.0	28	26.7
	Male	106	4	3.8	4	3.8
	Combined	211	25	11.8	32	15.2

From Mauderly *et al*. (1994); Nikula *et al*. (1995)

[a] Each rat with one or more neoplasm was counted only once in each neoplasm category.

[b] Values include all rats examined by gross necropsy and microscopy except those killed at 3, 6 and 12 months. The first lung neoplasm was observed between 12 and 18 months of exposure; thus all rats that died spontaneously or were euthanized in moribund condition plus those killed at 18 months or later were considered to be at risk for lung neoplasms. The total number of rats examined, including those killed at 3, 6 and 12 months, is listed in Table 3.2.

3.2.3 *Hamster*

Thirty-one male golden hamsters [age unspecified] were exposed by inhalation to fine furnace carbon black at various concentrations and for various periods. Six were exposed to 2.98–3.20 mg/ft^3 [~110 mg/m^3] for 53 days, eight to 2.98–3.20 mg/ft^3 [~110 mg/m^3] for 172 days and 17 to 1.55–1.65 mg/ft^3 for 236 days [~57 mg/m^3]. The experiment was terminated from one to 10 days following the end of exposure. No tumours were observed in the larynx or trachea (Snow, 1970).

3.3 Intratracheal administration

Rat

A group of 37 female Wistar rats, 15 weeks of age, was instilled intratracheally with 3 mg/rat furnace carbon black (Printex 90; specific surface area, 270 m^2/g) suspended in 0.9% saline once a week for 15 weeks. A control group of 39 female rats was instilled with 0.4 mL 0.9% saline once a week for 15 weeks. The animals died spontaneously, or were killed when moribund or after 131 weeks. More than 50% of rats in the treated and control groups survived to 100 weeks. The lungs were removed and evaluated microscopically. No primary lung tumour was found in the control group. In the treated animals, 65% [24/37] of the rats had primary lung tumours: three had adenomas, six had adenocarcinomas, one had an adenocarcinoma and a CKSC tumour, four had CKSC tumours, one had a CKSC tumour and an adenoma, three had squamous-cell carcinomas and six rats had squamous-cell carcinomas and additional lung tumours (one adenoma, one adenocarcinoma, three adenocarcinomas and CKSC tumours and one CKSC tumour) (Pott & Roller, 1994; Pott *et al*., 1994).

Groups of 48 female Wistar rats, 7 weeks of age, were treated by intratracheal instillation once a week for 16–17 weeks with approximately 1 mg of one of two types of extracted carbon black (Printex 90 furnace black or Lampblack 101; total particle dose, 15 mg/rat). A control group of 47 rats was treated with the vehicle (0.9% sodium chloride and 0.25% Tween 80 solution). Although the amount of organic material that could be extracted from the two carbon blacks was small (<0.1%), the particles were re-extracted with heated toluene for 4 hours before use. The specific surface areas (extracted) and primary particle sizes of Printex 90 and Lampblack 101 were 270 m^2/g and 14 nm, and 22 m^2/g and 95 nm, respectively. Satellite groups of two to four animals were used to determine the lung particle load 1 day after the last treatment. Both groups showed a lung particle load of 11 mg/lung (8.1 mg/g clean-air control lung). Fifty per cent of the animals in both groups were alive at 18 months. After 27 months, the respiratory tract of all treated animals (that died spontaneously or were killed) was investigated histopathologically. In the Printex 90-treated rats, 10/48 (21%) had lung tumours (P<0.001, Fisher's exact test; nine benign CKSC tumours, one bronchiolar/alveolar adenoma and four bronchiolar/alveolar carcinomas). In the Lampblack 101-treated animals, 4/48 rats (8%) had benign CKSC tumours. No lung tumour was observed in the 47 vehicle-treated controls (Heinrich, 1994; Dasenbrock *et al*., 1996). [The Working Group noted that the two types of carbon black investigated induced different tumour incidences, which was due probably to differences in particle size and surface areas.]

Groups of 21–48 female Wistar rats, 8–9 weeks of age, received intratracheal instillations at weekly intervals of one of two carbon blacks—Lampblack 101 (Degussa; mean particle size, 0.095 μm; density, 1.85 g/mL; specific surface area, 18.4 m^2/g) and furnace black (Printex 90; mean particle size, 0.014 μm; [density not specified]; specific surface area, 337 m^2/g) as described in Table 3.4. The dusts had been suspended by ultrasonification in 0.4 mL 0.9% phosphate buffered saline solution and 0.5% Tween 80®

Table 3.4. Dose schedules and incidence of lung tumours in female SPF Wistar rats administered carbon black by intratracheal instillation

Dust, size class	Dose instilled	Rats at start/at risk[a]	50% survival (weeks)[b]	Benign lung tumours (%)[c]	Malignant lung tumours (%)[c]	Total lung tumours (%)[c]	Metastases of other tumours to the lung (%)
Lampblack 101	5×6 mg[d]	48/45	106	33.3	26.7	60.0	15.6
	10×6 mg[e]	48/46	104	26.1	37.0	63.0	10.9
	20×6 mg[f]	48/47	108	NH	NH	70.2[g]	NH
Furnace black (Printex 90)	5×1.5 mg[h]	48/46	110	30.4	37.0	67.4	13.0
	5×3 mg[i,j]	21/18	112	22.2	66.7	88.9	11.1
	5×3 mg[j]	27/27	107	22.2	55.5	77.8	22.2
	5×3 mg	48/45		22.2	60.0	82.2	17.8
	5×6 mg	48/48	108	14.6	68.6	83.3	10.4
	10×6 mg	48/47	100	NH	NH	72.3[g]	NH
No treatment	–	48/46	124	2.2	0.0	2.2	4.3

From Pott & Roller (2005)
NH, no histopathology performed
[a] Number of rats examined that survived at least 26 weeks after first instillation
[b] Period after first instillation during which 50% of the animals died excluding rats that died immediately after anaesthesia
[c] Primary lung tumour types diagnosed as benign: adenoma and epithelioma; or malignant: adenocarcinoma and squamous-cell carcinoma; lungs with one or more malignant tumour may also have had benign tumours.
[d–f,h,i] One additional instillation by error. The dust volume of this instillation is included in the calculation of the total volume instilled.
[d] Plus 1×2.5 mg diesel soot
[e] Plus 1×3 mg diesel soot
[f] Plus 1×6 mg diesel soot
[g] Macroscopic examination
[h] Plus 1×3 mg ultrafine hydrophilic titanium dioxide
[i] Plus 1×6 mg ultrafine hydrophilic titanium dioxide
[j] These two subgroups were combined for further statistical calculations. The large difference in tumour response may be due to an inhomogeneous suspension administered to small numbers of rats per subgroup and not caused by the additional instillation of the relatively small volume of titanium dioxide (about 20% of the dose of the first subgroup).

was added to improve the homogeneity of the suspensions. A control group of 48 rats was maintained untreated. Rats were inspected for mortality and clinical signs of morbidity twice per weekday and once a day at weekends. The experiment was terminated after 30 months unless rats were killed when moribund or diagnosed with a growing subcutaneous tumour. After death of the animals and before necropsy of the thoracic and abdominal cavity, lungs were insufflated via the trachea *in situ* with 6% neutral buffered formalin. In particular, the surface of the lung was inspected and lesions were recorded.

The lungs were fixed and embedded in paraffin and sections were strained with haematoxylin–eosin. All tissues suspected of having tumours that were taken from other sites were examined for histopathological lesions, especially for primary tumours that metastasized to the lung. The lung tumour incidence in each group is summarized in Table 3.4. Statistically significant increases in benign and/or malignant lung tumours were observed with both types of carbon black (Pott & Roller, 2005).

3.4 Dermal application

Mouse

Three groups of 12, eight and eight Swiss mice [age and sex not specified] received weekly dermal applications on the clipped dorsal skin of one of three different types of furnace carbon black (Crude 'Kosmos' 40, 33 and 20) suspended in acetone [dose of carbon black not specified] containing 0.5% croton oil. A negative-control group of 20 animals was treated with acetone that contained 0.5% croton oil and a positive-control group of 15 animals was treated with a solution of 1% benzo[*a*]pyrene in acetone that contained 0.5% croton oil. The experiment lasted for 315 days. The site of application was investigated histologically. Two skin papillomas and no carcinomas were detected in the eight 'Kosmos' 33 carbon black-treated animals; no tumours were observed in the two other treated groups or the negative controls. The positive-control group had a tumour incidence of 73%: all tumours were described as squamous-cell carcinomas (von Haam & Mallette, 1952).

In the same study, 14 groups of Swiss mice received weekly dermal applications of 14 different concentrated extracts of carbon black [dose not specified] suspended in acetone that contained 0.5% croton oil. At the end of the experiment at 315 days, six mice with squamous-cell carcinoma with or without additional papillomas were found in four of the 14 groups treated with extracts. Seven mice with papillomas only were found in four other extract-treated groups (von Haam & Mallette, 1952). [The Working Group noted that the types of carbon black used for the extraction and extraction procedure were not given.]

In a series of experiments, a total of 240 CFW white and C3H brown mice [sex unspecified], 6–10 weeks of age, received thrice-weekly dermal applications of three types of carbon black (channel black, thermal black and furnace black) suspended in cottonseed oil, mineral oil or in carboxymethyl cellulose in water on the shaved back for 12–18 months. There was no increased incidence of skin tumours. In the same study, 32 groups of male CFW and C3H mice [number and age of the animals unspecified] received applications of furnace or thermal carbon black extracts (obtained by hot benzene extraction for 48 hours) from eight different carbon blacks for up to 12 months. All but one of the extracts were reported to show moderate to strong carcinogenicity (tumour incidence, 33–85%) [tumour type unspecified]. In an untreated control group of 943 CFW and C3H mice, 13 animals developed malignant neoplasms (six of the skin, six

of the liver and one of the spleen [no further details on the histology]) (Nau *et al*., 1958). [The Working Group noted several deficiencies in these experiments, namely the use of 1% benzene as a vehicle for some extracts and the limited reporting.]

3.5 Subcutaneous administration

3.5.1 *Mouse*

Ten groups of 50 male and female C57BL mice, 5–5.5 months of age, received subcutaneous administrations of 300 mg furnace carbon black (surface area, 15 m^2/g; average particle diameter, ~80 nm) that contained 0.09 mg benzo[*a*]pyrene and six other PAHs, either suspended in l mL tricaprylin or as a pellet, 300 mg channel carbon black (surface area, 380 m^2/g; average particle diameter, ~17 nm) from which no aromatic hydrocarbons were detected after extraction with benzene ('non-benzo[*a*]pyrene-extractable') either in 1.5 mL tricaprylin or as a pellet, 300 mg channel carbon black plus 0.09 mg benzo[*a*]pyrene either in tricaprylin or as a pellet, the benzene extract from 300 mg furnace carbon black in l mL tricaprylin, the remaining residue from 300 mg furnace carbon black after benzene extraction in l mL tricaprylin, 300 mg furnace carbon black treated for 3 hours with hot chromic acid and suspended in l mL tricaprylin, or 600 mg of an equal mixture of furnace and channel carbon blacks in 1.5 mL tricaprylin. Two further groups of 50 mice received injections of 1 mL tricaprylin (vehicle controls) or 0.09 mg benzo[*a*]pyrene in l mL tricaprylin (positive controls). The experiment was terminated 20 months after injection of the test materials. All suspected tumours found macroscopically were examined microscopically. Tumour incidence was calculated as a percentage and was based on the number of animals alive 5 months after the start of the study, which was the time at which the first deaths from tumours occurred (see Table 3.5). A high incidence of subcutaneous sarcoma (18/46) was observed in mice that received furnace black with extractable benzo[*a*]pyrene administered in tricaprylin, in those that received carbon black extract from furnace carbon black that contained benzo[*a*]pyrene (22/45) and in positive controls (39/41). In the other groups, few or no sarcomas were observed (Steiner, 1954).

In a series of experiments, groups of 10–20 male C3H brown or CFW white mice (total number, 344), 8–10 weeks of age, received a total dose of 17–300 mg of different carbon blacks suspended in cooking oil, tricaprylin or carboxymethyl cellulose in water as one or two subcutaneous injections and were observed for 20 months. The authors reported an 8–13% tumour index in three groups that received subcutaneous injections of carbon black (two furnace blacks and one thermal black) in cooking oil. [The Working Group noted that tumour index was defined by the authors as the percentage of tumours that occurred in animals excluding those found dead of unknown causes and that the tumours were described as 'subcutaneous mixed tumours'.] Groups of 10–30 male C3H and CFW mice, 8–10 weeks of age, also received one or two subcutaneous injections of benzene extracts of several different furnace, channel and thermal carbon blacks in

cooking oil (total dose, 0.01–6.5 mg). In 31/36 groups, tumour (mainly subcutaneous) indices of 15–100% were reported, and 22 of these had an index of >50%. No subcutaneous tumour was observed in the five other groups. Finally, four groups of 19–20 male C3H mice received as one or two subcutaneous injections 0.5–1.0 mL cooking oil that had been incubated with a furnace carbon black for 1–6 months then centrifuged to remove the carbon black; the subcutaneous tumour indices were 17, 67, 81 and 92%. Four control groups of 20–31 C3H mice were injected with 0.5–1.0 mL tricaprylin or cooking oil, and the tumour indices ranged from 0 to 5%. Of a total of 943 untreated CFW and C3H controls, six animals were reported to have malignant skin neoplasms, one [six were reported in Nau *et al*. (1958)] a malignant liver neoplasm and one a malignant spleen neoplasm [no further details on the histology] (Nau *et al*., 1960). [The Working Group noted deficiencies in experimental design and reporting in the above experiments; in particular, difficulty was experienced in interpreting the data that were presented in tabular form.]

Table 3.5. Carcinogenicity of two furnace and channel carbon blacks injected subcutaneously into C57BL mice

Materials tested	Sarcomas/ survivors at 5 months	Tumour incidence (%)	Average of death time (days)
Benzo[*a*]pyrene-containing furnace black[a], tricaprylin	18/46	39.1	363
Benzo[*a*]pyrene-containing furnace black[a], pellets	2/47	4.3	411
Non-benzo[*a*]pyrene-extractable channel black, tricaprylin	0/48	0.0	–
Non-benzo[*a*]pyrene-extractable channel black, pellets	1/47	2.1	524
Non-benzo[*a*]pyrene-extractable channel black plus benzo[*a*]pyrene, tricaprylin	0/43	0.0	–
Non-benzo[*a*]pyrene-extractable channel black plus benzo[*a*]pyrene, pellets	0/48	0.0	–
Benzene extract of benzo[*a*]pyrene-containing furnace black, tricaprylin	22/45	48.9	295
Furnace black[a] residue, tricaprylin	1/37	2.7	405
Benzo[*a*]pyrene-containing furnace black[a] treated with chromic acid, tricaprylin	0/47	0.0	–
Benzo[*a*]pyrene-containing furnace black[a] plus non-benzo[*a*]pyrene-extractable channel black, tricaprylin	0/41	0.0	–
Tricaprylin, 1.0 mL	0/43	0.0	–
Benzo[*a*]pyrene (0.09 mg), tricaprylin	39/41	95.1	233

From Steiner (1954)

[a] Furnace black from which benzo[*a*]pyrene and six other PAHs could be extracted with benzene.

3.6 Intraperitoneal administration

Rat

A group of 36 female Wistar rats [age unspecified] received intraperitoneal injections of 20 mg furnace carbon black 'Corax L' suspended in saline once a week for 4 weeks. Fifty per cent of the rats lived longer than 119 weeks and, after 132 weeks, 20% of the animals were still alive. One of 35 animals examined histopathologically at the end of the experiment had a sarcoma in the abdominal cavity (tumours of the uterus were excluded) (Pott *et al*., 1991). [The Working Group noted the low sensitivity of this assay to detect the carcinogenesis of exposure to non-fibrous particles.]

3.7 Combined administration with known carcinogens

3.7.1 *Mouse*

After two weeks of acclimatization, a group of 30 female weanling CF_1 mice was fed 2.05 g/kg diet furnace carbon black (ASTM N375) for 52 weeks and another group of 33 mice received a diet that contained no furnace black. Both groups received six weekly intraperitoneal injections of 20 mg/kg body weight (bw) 1,2-dimethylhydrazine at the start of the study. Survival was similar between treated and control animals. Carbon black did not enhance the incidence of colonic tumours induced by 1,2-dimethylhydrazine (Pence & Buddingh, 1985).

3.7.2 *Rat*

After two weeks of acclimatization, a group of 44 female weanling Sprague-Dawley rats was fed 2.05 g/kg diet furnace carbon black (ASTM N375) for 52 weeks and another group of 45 rats received a diet that contained no furnace black. Both groups received 16 weekly intraperitoneal injections of 10 mg/kg bw 1,2-dimethylhydrazine at the start of the experiment. Survival was similar between treated and control animals. Carbon black did not enhance the incidence of colonic tumours induced by 1,2-dimethylhydrazine (Pence & Buddingh, 1985).

Groups of 72 female Wistar rats, seven weeks of age, were exposed by inhalation to 2.6 mg/m^3 of a PAH-rich hard coal-tar pitch condensation aerosol (T/P aerosol; no carbon particles; benzo[*a*]pyrene content, 50 μg/m^3; MMAD, 0.5 μm) or to mixtures of 2 or 6 mg/m^3 furnace carbon black (Printex 90; see section 3.2.1 for further details) plus 2.6 mg/m^3 T/P aerosol for 17 hours per day on 5 days per week for 43 weeks followed by clean air for 86 weeks or for 86 weeks followed by clean air for 43 weeks. The T/P aerosol condensed onto the surface of the carbon black particles. The experiment was terminated at experimental week 129. When exposed for 43 weeks, lung tumour rates in the groups exposed to both T/P aerosol and carbon black showed an approximately twofold higher increase compared with the group exposed to T/P aerosol only (89/96 and

72/92 versus 39/97). There was no difference in lung tumour rates between the three groups exposed for 86 weeks (Heinrich *et al*., 1994).

3.7.3 *Hamster*

Three groups of Syrian golden hamsters [initial numbers, sex and age unspecified] received 40 weekly intratracheal instillations of carbon black [not further specified] (total dose, 60 mg/animal) in 0.1 mL saline solution containing 0.5% Tween 80 plus benzo[*a*]pyrene (total dose, 3, 9 or 9 mg) as a suspension in saline solution. Before preparing the suspension, benzo[*a*]pyrene was dissolved in acetone and adsorbed on carbon black to give small benzo[*a*]pyrene crystals. Two other groups of hamsters were treated with total doses of 3 or 9 mg benzo[*a*]pyrene without carbon black. Between 40 and 43 hamsters per group were examined histopathologically at the end of the experiment. The incidence of malignant and benign tumours of the larynx, trachea and lung was reported. The authors stated that carbon black did not enhance the carcinogenic effect of benzo[*a*]pyrene (Pott & Stöber, 1983). [The Working Group noted the inadequate reporting of many experimental details in relation to mortality and duration of the study.]

3.8 References

Boorman GA, Seely JC (1995). The lack of an ovarian effect of lifetime talc exposure in F344/N rats and B6C3F1 mice. *Regul Toxicol Pharmacol*, 21:242–243. doi:10.1006/rtph.1995.1035. PMID:7644712

Carlton WW (1994). "Proliferative keratin cyst", a lesion in the lungs of rats following chronic exposure to para-aramid fibrils. *Fundam Appl Toxicol*, 23:304–307. doi:10.1006/faat.1994.1108. PMID:7526997

Dasenbrock C, Peters L, Creutzenberg O, Heinrich U (1996). The carcinogenic potency of carbon particles with and without PAH after repeated intratracheal administration in the rat. *Toxicol Lett*, 88:15–21 doi:10.1016/0378-4274(96)03712-5. PMID:8920711

Dungworth DL, Mohr U, Heinrich U *et al.* (1994). Pathologic effects of inhaled particles in rat lungs: associations between inflammatory and neoplastic processes. In: Mohr U, Dungworth DL, Mauderly JL, Oberdörster G, eds, *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract*, Washington DC, ILSI Press, pp. 75–98.

Heinrich U (1994). Carcinogenic effect of solid particles. In: Mohr U, Dungworth DL, Mauderly JL, Oberdörster G, eds, *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract,* Washington DC, ILSI Press, pp. 57–73.

Heinrich U, Fuhst R, Rittinghausen R *et al.* (1995). Chronic inhalation exposure of wistar rats and two different strains of mice to diesel exhaust, carbon black and titanium dioxide. *Inhal Toxicol*, 7:533–556. doi:10.3109/08958379509015211.

Heinrich U, Peters L, Creutzenberg O *et al.* (1994) Inhalation exposure of rats to tar/pitch condensation aerosol or carbon black alone or in combination with irritant gases. In: Mohr U, Dungworth DL, Mauderly JL, Oberdörster G, eds, *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract*, Washington DC, ILSI Press, pp. 433–441.

IARC (1989). Diesel and gasoline engine exhausts and some nitroarenes. *IARC Monogr Eval Carcinog Risks Hum*, 46:1–458. PMID:2483415

IARC (1996). Printing processes and printing inks, carbon black and some nitro compounds. *IARC Monogr Eval Carcinog Risks Hum*, 65:1–578.

Kittel B, Ernst H, Dungworth DL *et al.* (1993). Morphological comparison between benign keratinizing cystic squamous cell tumours of the lung and squamous lesions of the skin in rats. *Exp Toxicol Pathol*, 45:257–267. PMID:7508775

Mauderly JL, Snipes MB, Barr EB *et al.* (1994) *Pulmonary Toxicity of Inhaled Diesel Exhaust and Carbon Black in Chronically Exposed Rats. Part I: Neoplastic and Nonneoplastic Lesions* (HEI Research Report Number 68), Cambridge, MA, Health Effects Institute.

Nau CA, Neal J, Stembridge VA (1958). A study of the physiological effects of carbon black. II. Skin contact. *AMA Arch Ind Health*, 18:511–520. PMID:13593888

Nau CA, Neal J, Stembridge VA (1960). A study of the physiological effects of carbon black. III. Adsorption and elution potentials; subcutaneous injections. *Arch Environ Health*, 1:512–533. PMID:13727963

Nikula KJ, Snipes MB, Barr EB *et al.* (1995). Comparative pulmonary toxicities and carcinogenicities of chronically inhaled diesel exhaust and carbon black in F344 rats. *Fundam Appl Toxicol*, 25:80–94 doi:10.1006/faat.1995.1042. PMID:7541380

Pence BC, Buddingh F (1985). The effect of carbon black ingestion on 1,2-dimethylhydrazine-induced colon carcinogenesis in rats and mice. *Toxicol Lett*, 25:273–277 doi:10.1016/0378-4274(85)90207-3. PMID:4012805

Pott F, Dungworth DL, Heinrich U *et al.* (1994). Lung tumours in rats after intratracheal instillation of dusts. *Ann Occup Hyg*, 38 Suppl. 1;357–363.

Pott F, Roller M (1994). Relevance of nonphysiological exposure routes for carcinogenicity studies of solid particles. In: Mohr U, Dungworth D, Mauderly JL, Oberdörster G, eds, *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract*, Washington DC, ILSI Press, pp. 109–125.

Pott F, Roller M (2005). Carcinogenicity study with nineteen granular dusts in rats. *Eur J Oncol*, 10:249–281.

Pott F, Roller M, Rippe RM *et al.* (1991). Tumours by the intraperitoneal and intrapleural routes and their significance for the classification of mineral fibers. In: Brown RC and Hoskins JA and Johnson NF, *Mechanism in fibre Carcinogenesis*, New York, Plenum Press, pp. 547–565.

Pott F, Stöber W (1983). Carcinogenicity of airborne combustion products observed in subcutaneous tissue and lungs of laboratory rodents. *Environ Health Perspect*, 47:293–303 doi:10.2307/3429517. PMID:6186480

Rittinghausen S, Kaspareit J (1998). Spontaneous cystic keratinizing epithelioma in the lung of a Sprague-Dawley rat. *Toxicol Pathol*, 26:298–300 doi:10.1177/019262339802600218. PMID:9547872

Rittinghausen S, Mohr U, Dungworth DL (1997). Pulmonary cystic keratinizing squamous cell lesions of rats after inhalation/instillation of different particles. *Exp Toxicol Pathol*, 49:433–446. PMID:9495643

Snow JB Jr (1970). Carbon black inhalation into the larynx and trachea. *Laryngoscope*, 80:267–287 doi:10.1288/00005537-197002000-00012. PMID:5416460

Steiner PE (1954). The conditional biological activity of the carcinogens in carbon blacks, and its elimination. *Cancer Res*, 14:103–110. PMID:13126943

von Haam E, Mallette FS (1952). Studies on the toxicity and skin effects of compounds used in the rubber and plastics industries. III. Carcinogenicity of carbon black extracts. *A M A Arch Ind Hyg Occup Med*, 6:237–242. PMID:14952048

4. Mechanistic and Other Relevant Data

In this section, the general principles of inhalation, deposition, clearance and retention of poorly soluble particles that have low toxicity are discussed. This information is also relevant to the Monographs on titanium dioxide and talc in this Volume.

4.1 Particle deposition, retention and clearance

4.1.1 *Humans*

(a) Poorly soluble particles: general introduction

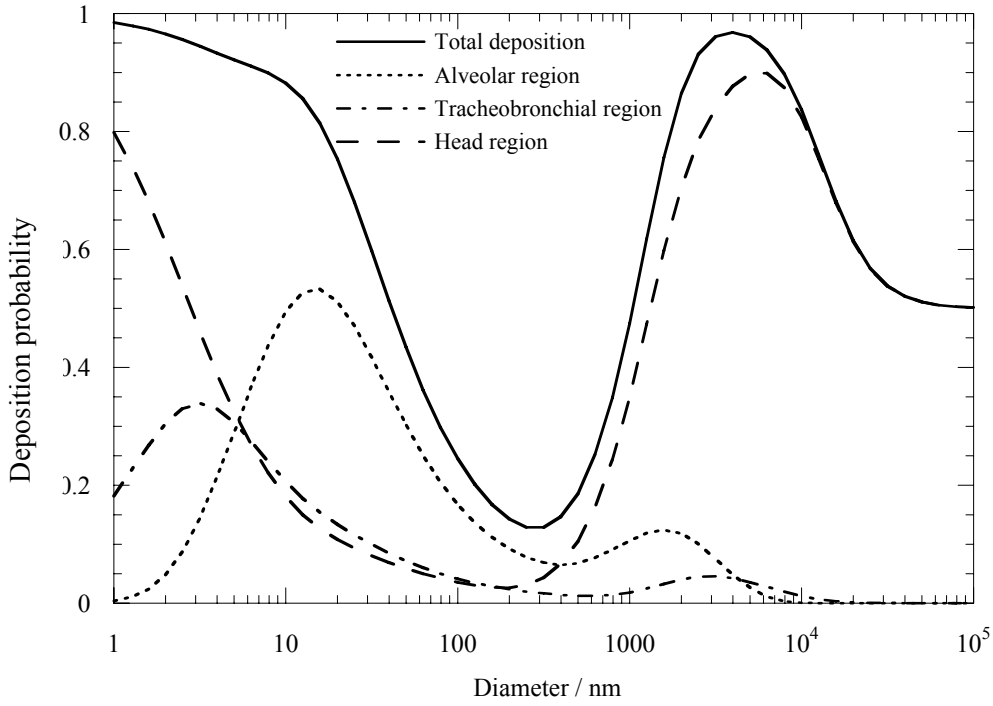
Few studies are available in humans on the kinetics of clearance and retention of the specific inhaled particles that are discussed in this volume (i.e. carbon black, titanium dioxide and talc). However, for any particles, the probability of their deposition within a given region of the respiratory tract depends on their characteristics and the physical factors that influence their transport in the airstream (e.g. air velocity and airway structure; ICRP, 1994). Deposition by mechanisms of sedimentation and impaction depends on the aerodynamic diameter, while deposition by diffusion depends on the thermodynamic diameter of the particles (ICRP 1994; Environmental Protection Agency, 2004).

Several terms have been adopted in the measurement of aerosols and estimation of the probability of particle deposition in the human respiratory tract (ICRP, 1994; International Standards Organization, 1995; ACGIH®worldwide, 2005). The term 'respirable' refers to particles that can deposit in the alveolar (gas exchange) region of the lungs. Within this monograph, respirable size fractions are defined as ultrafine (< 0.1 μm diameter of primary particle), fine (0.1–2.5 μm) and coarse (> 2.5–10 μm) particles. 'Thoracic' refers to particles that can deposit in the lung airways, while 'inhalable' refers to particles that can deposit anywhere in the respiratory tract. It is recognized that primary ultrafine particles generally exist as aggregates that have a greater surface area than larger primary particles.

A detailed discussion of particle dosimetry in the human respiratory tract can be found elsewhere (Oberdörster, 1988; ICRP, 1994; NCRP, 1997; Environmental Protection Agency, 2004; Bennett & Brown, 2005; Brown *et al*., 2005; Martonen *et al*., 2005). In brief, inhaled particles may be either exhaled or deposited in the extrathoracic, tracheobronchial or pulmonary airways. The deposition of particles in the respiratory tract depends primarily on inhaled particle size, the route of breathing (i.e. through the nose and/or mouth) and the breathing pattern (e.g. volume and frequency). Particles close to 0.3 μm in diameter have minimal mobility, i.e. they are sufficiently large that their diffusive mobility is minimal, yet small enough that their sedimentation and impaction are

also minimal. As a consequence, particles in this size range also have minimal deposition in the lung (Fig. 4.1). In general, the deposition fraction of most particle sizes (< 3–4 μm aerodynamic diameter) in humans is greater in the alveolar region than in the tracheobronchial airways. The deposition fraction for particles > 3–4 μm and < 0.01 μm in the alveolar region decreases due to their removal from the extrathoracic (particularly during nasal breathing) and tracheobronchial airways (Fig. 4.1). Of particular relevance to occupational exposures, particles that carry a charge due to the method of their generation (e.g. titanium dioxide) may have increased deposition efficiency in the lungs.

Figure 4.1. Probability of particle deposition in the human respiratory tract by region, according to the ICRP (1994) model. The average deposition has been modelled for an adult breathing through the nose at 25 L/min (light exercise), assuming nasal breathing of spherical particles with a density of 1 g/cm^3



From Maynard & Kuempel (2005)

Particles are frequently aggregates or agglomerates of smaller primary particles. The aerodynamic and thermodynamic properties of these aggregates (rather than the primary particles) affect their behaviour in the air and the probability of their deposition in the respiratory tract. Once deposited, properties such as the size and surface area of both aggregates and primary particles can potentially affect clearance kinetics.

Particle retention in the respiratory tract is determined by the balance between the rate of deposition and the rate of clearance. Particles that deposit in the tracheobronchial region are cleared by mucociliary clearance, which is relatively rapid (retention half-times of approximately 24–48 hours) (IARC, 1996), although some portion of the particles that deposit in the airways is cleared more slowly than expected (Stahlhofen *et al*., 1995). For particles that deposit in the alveolar region, the primary mechanism of clearance is by alveolar macrophage phagocytosis, migration to terminal bronchioles and the 'mucociliary escalator', through which particles are eventually swallowed or expectorated (Oberdörster, 1988). Particles that deposit in the alveolar region are associated with the slow clearance phase (retention half-times of months to years in humans) (Bailey *et al*., 1985; IARC, 1996). In a study of coal miners, little or no clearance of particles was observed (by magnetopneumography) one year after their retirement from the mine (Freedman & Robinson, 1988; Freedman *et al*., 1988). Translocation of particles to the interstitial region increases particle retention time in the lungs (ICRP, 1994). Some fraction of particles that deposit in the alveolar region may also be translocated to the lung-associated lymph nodes. This may occur by transepithelial migration of alveolar macrophages following phagocytosis of the particle or by translocation of free particles to the interstitium, where they may be phagocytosed by interstitial macrophages. Inflammation may alter mucociliary clearance, phagocytosis by alveolar macrophages and the uptake and transport of particles to and through the respiratory epithelium.

Particle deposition and clearance vary among individuals for several reasons, e.g. because of age, gender, smoking status and health status. Pre-existing lung diseases or conditions such as asthma or chronic obstructive pulmonary disease can influence the efficiency and pattern of deposition within the respiratory tract. Deposition also depends on the level of activity and breathing patterns. Deposition and retention determine the initial and retained particle dose to each region and may therefore influence the risk for developing diseases specific to those regions of the respiratory tract.

In summary, the pattern of deposition of particles depends on the particle diameter (aerodynamic or thermodynamic) and on the anatomical and physiological characteristics of the host. The deposition fraction for particles such as carbon black and titanium dioxide within the respiratory tract may vary depending on the size of the agglomerates and influences the dose to a given region of the respiratory tract. Pre-existing lung diseases or conditions can also influence deposition patterns.

(b) Deposition and retention of inhaled carbon black particles in the human respiratory tract

Several studies describe the deposition and retention of carbon black in the respiratory tract of exposed workers, as well as the health effects of these exposures, which are discussed in Section 4.2.

Although no quantitative data are available, studies of tissues from workers in carbon black factories have shown that widespread deposits of large amounts of carbon black are retained in the lungs (Rosmanith *et al*., 1969; Beck *et al*., 1985).

Lung diseases or conditions (either pre-existing or particle-related) may influence the deposition and retention of particles, e.g. by altering the size, structure and airflow patterns of the airways and by potentially affecting mechanisms of lung clearance. In a recent study of healthy humans who inhaled ultrafine carbon particles (count median diameter (CMD), 0.025 μm; geometric standard deviation (GSD), 1.6), bronchoconstriction may have caused the observed mild dysfunction of the small airways (increased airways resistance, seen as reduced maximal mid-expiratory flow rate [forced expiratory flow ($FEF_{25–75\%}$)]) (Pietropaoli *et al*., 2004). The exposures were relatively low (single 2-hour exposures to 50 μg/m^3, an ambient concentration that is found near major roads) and the individuals were healthy (no pre-existing lung disease). Bronchoconstriction was offered as the most probable mechanism, in part because pulmonary inflammation (as assessed by sputum), which would have been another possible explanation, was not observed. Reduced alveolar gas exchange (measured as reduced carbon monoxide diffusing capacity) was also observed, which was attributed to vasoconstriction. No adverse effects were observed in normal or asthmatic individuals who received single, 2-hour exposures to 10 μg/m^3 ultrafine carbon; the effects observed in the group exposed to 50 μg/m^3 were reversible. Particle deposition was not evaluated in this part of the study. In the same study, the deposition fraction of ultrafine carbon particles was measured in the respiratory tract in healthy and asthmatic subjects at rest and during exercise (Daigle *et al*., 2003; Chalupa *et al*., 2004; Frampton *et al*., 2004). The CMD of the ultrafine carbon aerosol was 0.025 μm (GSD, 1.6) (Pietropaoli *et al*., 2004), and 96% of the particles were elemental carbon (Frampton *et al*., 2004). The deposition fraction of the ultrafine particles in the respiratory tract was measured as the difference in the inspired and expired particle concentrations divided by the inspired concentration (using either mass or number concentration) (Frampton *et al*., 2004). [The Working Group noted that there may be methodological problems in relation to deposition measurements in the above series of studies as commented on by Kim and Jaques (2004).]

Compared with healthy individuals, asthmatics had an approximately 50% higher total deposition fraction of ultrafine carbon particles in the respiratory tract as either total number or mass deposited (Chalupa *et al*., 2004; Frampton *et al*., 2004). In a separate study, Brown *et al*. (2002) reported greater deposition of ultrafine particles in individuals who had obstructive lung disease.

Particle diameter influences deposition, even within the ultrafine particle size range. Daigle *et al*. (2003) and Frampton *et al*. (2004) reported the total ultrafine deposition fraction as particle mass or number, by the midpoint diameter of particle sizes from 7.5 to 75 nm. Within that particle size range, the deposition fraction increased with decreasing particle size, either at rest or with exercise, and among healthy or asthmatic individuals. For example, the deposition fraction for particles with median sizes of 65 nm and 8.7 nm increased from 0.63 to 0.74, respectively, in healthy subjects. During exercise, the deposition fraction increased from 0.84 to 0.94 for the same particle sizes and study group (Frampton *et al*., 2004).

Jaques and Kim (2000) and Kim and Jaques (2004) reported that the total deposition fraction of ultrafine aerosols in humans increased with decreasing particle size (from median diameter of 100 nm to 40 nm). The deposition fraction of particles increased to a similar extent with increases in either tidal volume or respiratory period. During exercise, tidal volume increased and residence time decreased relative to measurements taken at rest. These findings are in contrast to those of Daigle *et al*. (2003). Kim and Jaques (2004) noted that the methodology used by Daigle *et al*. (2003) may cause measurements of exhaled particle concentrations to be variable and erroneous. Furthermore, they asserted that the unusually high deposition values obtained by Daigle *et al*. (2003) were due to an improper sampling of exhaled aerosols. Although the deposition fraction of the particles decreases during exercice on a breath-by-breath basis, the total amount of particle deposition increases with exercise due to an increase in respiratory rate.

Observed and predicted deposition fractions were compared in a study of the total respiratory tract deposition of ultrafine carbon particles. In resting individuals, the observed fractions were found to be similar to those predicted by three deposition models (ICRP, 1994; NCRP, 1997; CIIT & RIVM, 2000 [the 1999 multiple path particle deposition model version from CIIT is cited, but not referenced]; Frampton *et al*., 2004). However, for exercising individuals, the total deposition fractions were higher than those predicted by the models (Frampton *et al*., 2004). This underprediction increased as the particle size increased from 10 to 100 nm; for 26-nm particles, the predicted deposition fraction was 22% lower than that measured in exercising individuals (Frampton *et al*., 2004). Among elderly subjects, the total deposition fraction observed was similar to that predicted from the ICRP (1994) model (although the model slightly overpredicted the deposition fraction of particles smaller than 0.04 or 0.05 μm, and slightly underpredicted the deposition fraction for particles larger than approximately 0.08 μm) (Kim & Jaques, 2005).

Gender was not found to affect the deposition fraction significantly in the Frampton *et al*. (2004) study in the two groups that had sufficient numbers to address this variable. In contrast, Jaques and Kim (2000) reported a greater total deposition fraction in women compared with men with the same breathing pattern, particularly for the smaller ultrafine particles (40 nm), although inter-subject variability was similar.

(c) Extrapulmonary translocation of carbon particles in humans

The translocation of coal dust particles of respirable size [specific size not noted] from the respiratory tract to other tissue sites has been observed in coal miners. Black pigment observed in the liver and spleen was associated with years in mining and severity of coal workers' pneumoconiosis (LeFevre *et al*., 1982). To reach the liver and spleen, the particles would have had to enter the blood circulation. It is not clear whether this was due to particles being cleared by the mucociliary clearance, being swallowed and entering the gastrointestinal tract and then being taken up in the blood, or whether the particles were able to pass through damaged epithelial and endothelial cells into the blood, as could occur under conditions of disease.

Several studies have been published on the clearance of agglomeration mode carbon particles (^{99m}Technetium-labelled carbon particles < 100 nm in diameter [Technegas]; Nemmar *et al*., 2002). The primary particles that compose Technegas are in the range of 5–20 nm (Lemb *et al*., 1993; Lloyd *et al*., 1995). However, before inhalation, these primary particles coagulate into aggregates that have a median diameter in the range of 100 nm to 160 nm (Lemb *et al*., 1993; Lloyd *et al*., 1995; Roth *et al*., 1997). Pulmonary retention of Technegas 45 minute after inhalation was reported by Roth *et al*. (1997) to be 95% and by Isawa *et al*. (1991) to be 98%. According to Brown *et al*. (2002), pulmonary retention 45 minute after inhalation must on average have been less than 67% in the study of Nemmar *et al*. (2002), although these data were not reported. In view of the sharp contrast in the findings of Nemmar *et al*. (2002) and those of others, Brown *et al*. (2002) contended that the results of Nemmar *et al*. (2002) were consistent with the clearance of pertechnetate, but not with that of insoluble ultrafine particles. Mills *et al*. (2006) specifically investigated this supposition. Six hours after inhalation of Technegas, 95.6% of the particles remained in the lungs, and no accumulation of radioactivity was detected in the liver or spleen. In contrast to Nemmar *et al*. (2002), Mills *et al*. (2006) found that ultrafine carbon particles do not pass directly from the lungs into the systemic circulation.

(d) Excretion of particle-adsorbed substances

The retention of particles in the lungs may influence the bioavailability of adsorbed materials. As the retention of particles increases, the potential for adsorbed PAHs to be eluted and absorbed may also increase.

In a study of five nonsmoking warehouse packers in a carbon black (furnace black) manufacturing plant, daily average dust exposures were measured by air sampling, and urinary excretion of 1-hydroxypyrene (derived from pyrene) was measured in post-shift urine samples for five consecutive days during one work week. The mean ambient dust concentrations over the five days ranged from 1.5 to 13 mg/m^3. Excretion of 1-hydroxypyrene ranged from 0.10 to 0.48 μmol/mol creatinine. A regression model showed a statistically significant relationship between weekly mean concentration of airborne dust and 1-hydroxypyrene excretion when the intercept was forced through zero—i.e. assuming zero 1-hydroxypyrene excretion with zero measured dust exposure—but not when the intercept was unconstrained—i.e. allowing for some level of 1-hydroxypyrene at zero measured dust concentration, such as from diet, as noted by the authors, or possibly from previous dust exposures. The urinary excretion was statistically significantly lower on Monday than on other days. The authors concluded that urinary excretion was affected by exposure to dust, and that the pyrene on the dust was bioavailable (Gardiner *et al*., 1992a). [The Working Group noted that the pyrene content of the carbon black was not measured. The airborne sampling method and particle size distribution were not described. Rather than performing the regression analyses based on the mean exposures of individuals for the week, it may be more informative to use the daily values in a mixed model that accounts for correlation within the values of each

individual. Also, the use of a lag could be informative to account for the time between inhalation of dust, metabolism of pyrene and elimination of 1-hydroxypyrene.]

Thirty carbon black workers (eight of whom were involved in wet pelleting and 22 in packaging) were evaluated for their levels of exposure to PAHs. Urine samples were collected on day 1 pre-shift, day 1 post-shift and day 5 post-shift and tested for 1-hydroxypyrene. The inhalable particle-bound PAHs, gaseous PAHs and dermal exposure to PAHs were measured concomitantly. The sampling train contained a filter cassette to collect particles and determine particle-bound PAHs and a sorbent tube to measure gaseous PAHs. Exposure to pyrene was statistically significantly correlated with exposure to PAHs. The results of a multiple linear regression analysis showed no correlations on post-shift day 1, but the values for exposure of the packaging workers to gaseous PAHs and inhalable particle-bound PAHs and dermal exposure to particle-bound PAHs were significantly correlated on post-shift day 5 (Tsai *et al*., 2002).

4.1.2 *Experimental systems*

(a) Rodent respiratory tract

As in humans and other species, the deposition of particles in the rodent respiratory tract depends on particle characteristics, airflow properties and airway structure. Rats are the most frequently used animals in experimental studies of inhaled particles, and some aspects of the rat respiratory tract that influence the kinetics of particle deposition therein include breathing pattern (nose or mouth), level of activity (resting or exercise) and lung structure (head airways and tracheobronchial branching pattern) (Miller, 2000). Rats are obligatory nose breathers, while humans breathe both through the nose and the mouth, the extent of which varies among individuals and also depends on level of activity (with exertion, the proportion of breathing through the mouth generally increases). Rats have more extensive airways in the nasal region; therefore, particle deposition in this region is greater in rats than in humans. The size of particles that are inhalable (capable of entering respiratory tract) differs between rats and humans (Ménache *et al*., 1995). The airway branching system is symmetric (bi- or tripodal) in humans and asymmetric (monopodal) in rats, which influences the site of deposition (airway impaction tends to be greater in the human tracheobronchial region), and, unlike humans, rats do not have respiratory bronchioles. These factors influence the kinetics of particle deposition in the respiratory tract (Ménache *et al*., 1996).

Once particles are deposited, their removal or retention are based on mechanisms of biological clearance. As for humans, particles in the tracheobronchial region of rats are cleared by the mucociliary pathway and by macrophages in the alveolar region. Particles that enter the interstitium may also enter the lymph and blood circulation. Differences in these physical and physiological factors can result in differences in the clearance rates among species. While tracheobronchial clearance is relatively rapid in both rats and humans (half-times of the order of hours to days), the normal alveolar clearance rate in rats is approximately 10 times faster than that in humans (Snipes, 1989).

Studies in rodents (primarily rats and mice) have shown that the long-term retention of particles is greater than would be predicted from rodent studies that used lower concentrations or durations of exposure. This increase in particle retention has been attributed to the excessive particle loading in alveolar macrophages and impairment of the clearance they mediate (Morrow, 1988; ILSI Risk Science Institute Workshop Participants, 2000). At sufficiently high doses, impaired clearance persists, especially in rat lungs (Bermudez *et al*., 2002, 2004; Elder *et al*., 2005). Muhle *et al*. (1990a) reported impaired alveolar clearance in rats that began at a retained particle mass dose of ~0.5 mg/rat lung and had essentially ceased at ~10 mg/rat lung (fine particles of unit density). In overloaded lungs, particles can translocate more readily to the lung interstitial and lymph nodes, and the fraction that migrates to the lymph nodes increases as the particle size decreases (Bellmann *et al*., 1989).

Lung responses to overloading in rats include increased lung weight, chronic inflammation, fibrosis and lung tumours (Muhle *et al*., 1991). Overloading was originally defined in terms of particle mass or volume dose (Morrow, 1988). However, Morrow (1992) noted that volumetric overloading did not explain the greater retention of ultrafine particles than that expected for a given mass or volume particle dose. Tran *et al*. (1999, 2000) developed a biomathematical exposure–dose–response model in which overloading in rats was based on particle surface area dose and provided a better fit to the experimental data evaluated. Ultrafine carbon black particles may be retained in the lungs to a greater extent than larger respirable particles because they escape alveolar macrophage phagocytosis (Renwick *et al*., 2001, 2004) and enter the lung interstitium (Ferin *et al*., 1992, 1994).

Overloading, as originally defined, refers only to poorly soluble, fine-sized particles of low toxicity. Other factors can also cause impaired clearance, increased particle retention and lung responses similar to those observed in overloading. These factors include cytotoxicity, such as generation of reactive oxygen species on the particle surface (e.g. crystalline silica) (Vallyathan *et al*., 1988), or escape from uptake by alveolar macrophages and entrance into the lung interstitium, as observed for ultrafine particles (Ferin *et al*., 1992, 1994; Renwick *et al*., 2001, 2004). Cytotoxic and ultrafine particles result in impaired clearance at mass doses that are much lower than those associated with classical overload (Muhle *et al*., 1990a; Bellmann *et al*., 1991; Morrow, 1992).

Several reviews, most of which focus on particle toxicity and carcinogenicity, have also described the retention kinetics of particles (including carbon black) after their deposition in the lungs of experimental animals (Morrow, 1988; Snipes, 1989; Kreyling, 1990; Morrow, 1992; Muhle *et al*., 1994; Oberdörster, 1995).

Several studies that are summarized in Table 4.1 evaluated the clearance and retention of different carbon black materials after deposition into the lung following intratracheal instillation into and inhalation by mice and rats. Bowden and Adamson (1984) instilled a

Table 4.1. Kinetics of carbon black (CB) in experimental animals

Particle type	Particle diameter and surface area	Species (age and sex)	Route of exposure and dose/exposure concentration	Duration of study	Findings	Comments	Reference
Colloidal carbon	30 nm	Swiss mouse	Intratracheal instillation; 4 mg	6 months	Most CB cleared via MC escalator; some transepithelial passage, very low lymphatic clearance; heavily laden AM remained for months in lung	No quantitative results; findings based on qualitative histological data	Bowden & Adamson (1984)
^{7}Be-labelled carbon particles (Elftex 8; furnace black)	0.01–1 μm (primary 27 nm)	Swiss mouse (4 weeks and 18 months; female)	Gavage; 7 mg	14 days	^{7}Be activity was mainly confined to the gastrointestinal tract; retained dose at 14 days: young, 3.3×10^{-5}%; old, 8.4×10^{-5}%; some activity in non-intestinal tissue	Very small fraction of CB may penetrate via Peyer's patches.	LeFevre & Joel (1986)
RCF-7 (furnace black)	0.22 μm MMAD (primary 37 nm)	Fischer 344 rat	Inhalation, 20 h/day, 7 days/ week; 6.6 mg/m^3	1–11 weeks followed by ^{14}C-diesel exposure for 45 min + 1 year of observation	Linear increase in CB lung burden with duration of exposure; lung burden ~30 mg; increased CB and ^{14}C-diesel pulmonary half-life with increasing lung burden	Retention $t_{½}$ was estimated from a two-phase lung retention model with a sequestration term.	Lee *et al*. (1987)
Elftex 12 (furnace black)	0.24 μm MMAD	Fischer 344 rat	Inhalation, 20 h/day, 7 days/ week; 7 mg/m^3	1, 3, 6 weeks exposure, followed by up to 1 year of observation	Lung burdens: 1.1, 3.5, 5.9 mg CB; 1-year retention: 8, 46, 61%; LN burden: 1, 21, 27% of initial CB lung burden; doubling of normal half-life of ~50 days occurred at CB lung burden of ~0.8 mg.	Authors propose AM sequestration model to explain retarded CB clearance at higher CB burden.	Strom *et al*. (1989)

Table 4.1 (contd)

Particle type	Particle diameter and surface area	Species (age and sex)	Route of exposure and dose/exposure concentration	Duration of study	Findings	Comments	Reference
Printex 90 (furnace black)	0.64 μm MMAD (primary 14 nm)	Wistar rat	Inhalation 95 h/week; 7.4 mg/m^3	4.5 months	Retained CB: 13.7 mg; $t_{½}$ of ^{85}Sr-labelled test particles: 472 days; prolonged half-life of various dusts detectable at rat lung burden of ~0.5 mg; complete impairment of clearance at ~10 mg	Quantitative relationship observed is similar to that of other low-toxicity low-solubility particles.	Creutzenberg *et al*. (1990); Muhle *et al*. (1990a)
Printex 90 (furnace black)	0.64 μm MMAD	Wistar rat (female)	Inhalation 19 h/day, 5 days/week; 12 mg/m^3	24 months for CB; 3, 12, 18 months for $^{59}Fe_2O_3$ and ^{85}Sr-poly-styrene particles	CB lung burden: 50.2 mg; CB half-life, 550 days; $^{59}Fe_2O_3$ half-life, 244–591 days; ^{85}Sr half-life, 472 days at 3 months then back to normal half-life of 50–60 days	No data provided to demonstrate lower alveolar deposition of ^{85}Sr particles at high lung burdens.	Creutzenberg *et al*. (1990); Muhle *et al*. (1990b, 1994)
Elftex 12 (furnace black)	2–2.4 μm MMAD (large mode) 0.02–0.1 μm DED (small mode, mass, 10–30%)	Fischer 344 rat	Inhalation; 3.5 mg/m^3, 13 mg/m^3 98 mg/m^3	16 h/day, 7 days/week; 6 h/day, 5 days/week; 4 h/day, 1 day/week; 12 weeks exposure + 24 weeks post-exposure	Pulmonary retention half-life similar for different exposure rates; average half-life ~520 days (95% CI, 350–950)		Henderson *et al.* (1992)

Table 4.1 (contd)

Particle type	Particle diameter and surface area	Species (age and sex)	Route of exposure and dose/exposure concentration	Duration of study	Findings	Comments	Reference
Elftex 12 (furnace black)	2 μm MMAD (large mode) 0.1 μm MMDD (small mode, 33%) 43 m^2/g	Fischer 344/N rat	2.5 mg/m^3, 6.5 mg/m^3	16 h/day, 5 days/week, 24 months	Double exponential clearance; slow phase, no clearance in CB-exposed group compared with half-life in controls of 113–135 days		Mauderly (1994)
Printex 90 (furnace black)	0.64 μm MMAD 227 m^2/g	Wistar rat, NMRI mouse	11.6 mg/m^3 (average)	18 h/day, 5 days/week, 24 months (rat) + 6 months post-exposure or 13.5 months (mouse) + 9.5 months post-exposure	CB accumulation kinetics test particle clearance; CB accumulation in rat and mouse lung similar (at 1 year of exposure)		Heinrich *et al*. (1995)

Table 4.1 (contd)

Particle type	Particle diameter and surface area	Species (age and sex)	Route of exposure and dose/exposure concentration	Duration of study	Findings	Comments	Reference
Carbon	40 nm	Swiss mouse (male, 25 g)	Intratracheal instillation; 2 mg (following bleomycin) Controls: carbon only; bleomycin only	Bleomycin (0.15 units) to induce lung injury, followed by carbon either 3 days or 4 weeks later. Killed 16 weeks after carbon exposure.	Carbon-only: most particles phagocytosed; some particles seen in interstitium and IM; increasing particles in LN by 16 weeks; carbon 3 days after bleomycin: large amount of carbon in fibrotic regions at 16 weeks; significantly higher insoluble residue; carbon 4 weeks after bleomycin: particle deposition in less damaged regions; particle retention similar to carbon only	Some quantitative results of carbon retention, as the retained insoluble residue at 16 weeks; detailed histology in Adamson & Hedgecock (1995); quantitative results of inflammatory cells in BAL, cell proliferation and fibrosis in Adamson & Prieditis (1995).	Adamson & Hedgecock (1995); Adamson & Prieditis (1995)

Table 4.1 (contd)

Particle type	Particle diameter and surface area	Species (age and sex)	Route of exposure and dose/exposure concentration	Duration of study	Findings	Comments	Reference
9000-type xerographic toner: 90% styrene/n-buthyl-metha-crylate, 10% furnace-type carbon black	MMAD 4.0 µm, GSD 1.5	SPF Fischer 344 rat (6 weeks; female)	Inhalation; 0, 10 and 40 mg/m^3 (respirable concentrations: ~3 and 14 mg/m^3)	6 h/day, 5 days/week, for 3 months; histology at 3 months (end of exposure) and at 18 months; retention half-life measured using: $^{59}Fe_2O_3$, ^{51}Cr-polystyrene, ^{85}Sr-polystyrene (MMAD of 0.3, 0.7, 3.5 µm, respectively).	At 10 mg/m^3: 0.4 mg lung burden; retention half-life: 277 days; slight retardation of alveolar clearance with partial recovery 6 months after end of exposure; At 40 mg/m^3: 3.0 mg lung burden; retention half-life: 2845 days; clearance retardation without reversal; AM (in BAL) without particles increased from 25% at the end of exposure to 85% after 15 months of observation, but AM did not remove the inhaled tracer particles; more migration to LN of smaller tracer particles	Low percentage of carbon black in toner but kinetics may be relevant to carbon black (thermal black) with similar particle size	Bellmann *et al*. (1989, 1992)

Table 4.1 (contd)

Particle type	Particle diameter and surface area	Species (age and sex)	Route of exposure and dose/exposure concentration	Duration of study	Findings	Comments	Reference
Carbon black (Printex-90 and Sterling V)	Printex-90 (HSCb): 14 nm primary particle; MMAD 1.2–2.4 µm (GSD 2.0–3.1); 300 m^2/g. Sterling V (LSCb): 70 nm primary particle; MMAD 0.6–0.9 µm (GSD 3.0–3.7); 37 m^2/g	Fischer 344 rats, $B6C3F_1$ mice and 276 F1B Syrian golden hamsters (5 weeks; female)	Inhalation; Printex-90: 0, 1, 7, 50 mg/m^3 (rats, mice, hamsters); Sterling V: 50 mg/m^3 (rats only).	6 h/day, 5 days/week, for 13 weeks; particle retention and effects measured at end of exposure and at 3 and 11 months post-exposure; retention also measured after 5 weeks of exposure	Similar surface area doses in rat lungs at 7 mg/m^3 HSCb, 50 mg/m^3 LSCb: ~0.3 m^2; similar mass doses at 50 mg/m^3 HSCb or LSCb: ~5.5 mg or ~8 mg, respectively; rats: prolonged particle retention in lungs at 7, 50 mg/m^3 HSCb and at 50 mg/m^3 LSCb (but post-exposure clearance was in LSCb but not at 50 mg/m^3 HSCb); mice: prolonged particle retention in lungs at 7, 50 mg/m^3 (HSCb); hamsters: prolonged retention at 50 mg/m^3 only (HSCb)	PAH content: 0.039 mg/kg (Printex-90); 8.8 mg/kg (Sterling V) (Borm *et al*. 2005)	Elder *et al*. (2005)

AM, alveolar macrophages; BAL, broncheoalveolar lavage fluid; DED, diffusion equivalent diameter; GSD, geometric standard deviation; HSCb, high surface-area carbon black; IM, interstitial macrophages; LN, lymph node; LSCb, low surface-area carbon black; MC, mucociliary; MMAD, mass median aerodynamic diameter; PAH, polycyclic aromatic hydrocarbon

very large dose (4 mg, i.e. 4% of the weight of a mouse lung) of colloidal carbon (primary particle size, 30 nm diameter) into the trachea of 60 Swiss Webster mice and followed its clearance in groups of three mice killed at intervals over a 6-month period. Most of the carbon black was cleared via the mucociliary escalator, but some transepithelial passage via type I cells also occurred. Heavily laden alveolar macrophages stayed in the lungs for the whole observation period, and there was some, although low, clearance via the lymphatic system. No quantitative results were reported.

Lee *et al*. (1987) exposed male Fischer 344 rats by inhalation to 6 mg/m^3 carbon black with a MMAD of 0.22 μm in whole-body exposure chambers for 20 hours per day on 7 days per week for 1–11 weeks (for details, see Table 4.1). Immediately following exposure to carbon black, rats were exposed by nose-only inhalation to ^{14}C-labelled diesel exhaust particulates for 45 minute and were followed for 1 year. Inhibition of lung clearance was inferred by the increased retention of radioactive diesel particles as a percentage of initial lung deposition. The percentage of retained particles increased with increasing exposures. The long-term retention half-times (estimated with a two-phase lung retention model with a sequestration term) were 57, 96 and 140 days for the 1-, 3- and 5-week exposure groups, respectively. The results at 11 weeks were not reported. The pulmonary retention of carbon black was similar to that reported for diesel exhaust by Strom *et al*. (1989).

Strom *et al*. (1989) measured the retention of carbon black (furnace black) in rat lungs and thoracic lymph nodes. Male Fischer 344 rats were exposed by inhalation (whole-body) to 7 mg/m^3 carbon black for 20 hours per day on 7 days per week for 1, 3 or 6 weeks and were followed for 1 year. Particle size was 0.07 μm CMD with a MMAD of 0.24 μm. Lung burdens of 1.1, 3.5 and 5.9 mg carbon black were achieved after 1, 3 and 6 weeks of exposure, respectively; the 1-year retention fractions were 8, 46 and 61% of the lung burden at the end of the exposure periods, respectively. At the higher doses, clearance was reduced, and the main transport of particles from the lungs was to the lung-associated lymph nodes. The proportion of carbon black transported to the thoracic lymph nodes increased with increasing exposure—1, 21 and 27% of the initial lung burden at 1, 3 and 6 weeks of exposure, respectively. The authors concluded that a carbon black lung (macrophage compartment) burden in the rat of ~0.8 mg results in a doubling of the normal retention half-time of about 50 days.

Impaired alveolar clearance and increased particle retention were also observed in an inhalation study with several particle types, including carbon black, in Wistar rats (Creutzenberg *et al*., 1990; Muhle *et al*., 1990b). The carbon black (furnace black) was Printex 90, with a primary particle size of approximately 0.014 μm and an MMAD of 0.64 μm. Female Wistar rats were exposed by inhalation (in whole-body chambers) to 7.4 ± 1.5 mg/m^3 for 19 hours per day on 5 days per week for 4.5 months. The carbon black retained in the lungs at the end of 4.5 months of exposure was 13.7 ± 2.0 mg. The retention half-time of subsequently inhaled ^{85}Sr-labelled polystyrene test particles was 472 days in these rats compared with 61 days in air controls. After the 4.5-month exposure to 7.4 mg/m^3, rats were subsequently exposed to 12 mg/m^3 for 19 hours per day

on 5 days per week for up to 24 months (Creutzenberg *et al*., 1990; Muhle *et al*., 1990a,b, 1994). Some groups were exposed for 18 months and then removed from exposure for 6 months. At 3, 6, 12, 18, 22 and 24 months of exposure, the lung and lung-associated lymph node burdens were measured. The highest carbon black lung burden was 50.2 ± 10.9 mg at 18 months, and the lymph node burden was 6.7 mg at 22 months. Interstitial fibrosis was observed in these rats at 12 and 18 months. The pulmonary retention half-times of radiolabelled tracer particles were determined at 3, 12 and 18 months of exposure, and at 18 months followed by 6 months of clean air. The retention half-time for carbon black was 550 days (95% CI, 322–1868 days) following termination of exposure. Test particle clearance of $^{59}Fe_2O_3$ (0.35 μm in diameter) was significantly prolonged with increasing duration of exposure to carbon black, with a half-time that ranged from 244 to 591 days compared with 61–96 days in air controls. In contrast, clearance of ^{85}Sr-labelled polystyrene microsphere (3.5 μm diameter) showed only prolonged retention after 3 months of exposure to carbon black with a half-time of 472 days whereas, at the 12- and 18-month exposure time-points, test particle clearance returned to control values of about 50–60 days. The authors suggested that this was due to a change in the deposition site of the larger ^{85}Sr-labelled polystyrene microspheres as a result of altered lung architecture (in response to carbon black-induced inflammation and other changes) and breathing pattern, and concluded that the retardation of clearance was detectable in rats when the retained lung burden of various dusts exceeded 0.5 mg, and that a substantial decrease in the clearance rate was observed at lung burdens exceeding 10 mg (Creutzenberg *et al*., 1990; Muhle *et al*., 1990b).

Henderson *et al*. (1992) evaluated the pulmonary retention in Fischer 344 rats of furnace black (Elftex 12) inhaled at three different dose rates such that the product of concentration × time was very similar (392 mg × h/m^3 per week). Lung burdens were 3–4 mg. The retention half-time determined over a 24-week period after exposure was not statistically significantly different among the different groups (~520 days; 95% CI, 350–950 days).

Mauderly (1994) studied the retention of tracer doses of [^{7}Be]furnace black (Elftex 12) in Fischer 344/N rats 3 and 18 months after chronic exposure to two concentrations of unlabelled carbon black (2.5 mg/m^3 and 6.5 mg/m^3). Clearance of the labelled carbon black followed a two-exponential model. The most striking difference was found in the slow-phase clearance component, which showed little or no clearance over a period of 126 days for the low- and high-dose groups compared with retention half-times of 113 and 135 days for control rats.

In a study of chronic inhalation in Wistar rats and NMRI mice exposed to furnace black (Printex 90; 11.6 mg/m^3), pulmonary particulate accumulation was measured (Heinrich *et al*., 1995). The rats were exposed for 18 hours per day on 5 days per week for 24 months; the mice were similarly exposed for 13.5 months. Both rats and mice showed similar accumulation kinetics over the exposure time; at 1 year of exposure, the normalized lung burden (mg/g of control lung) was 32 mg in rats and 37 mg in mice. In addition, rats showed significantly prolonged retention of tracer particles compared with

controls as early as 3 months after exposure, which persisted through 12 and 18 months of exposure and 3 months after the 18-month exposure (see Creutzenberg *et al*., 1990).

(b) Retention of intratracheally instilled ultrafine carbon black particles in healthy and injured lungs of mice

Using a rodent model of lung susceptibility, Adamson and Hedgecock (1995) and Adamson and Prieditis (1995) examined the particle distribution and retention of carbon black in healthy or injured (bleomycin-treated) lungs. Following treatment with bleomycin (0.15 units, by intratracheal instillation), male Swiss mice received 2 mg 40-nm carbon black in hydrolysed gel (also by intratracheal instillation) either three days or four weeks later. Groups of four mice were killed at various times up to 16 weeks after administration of the carbon black. Additional groups received carbon black only or bleomycin only. In the carbon black-only group, histological examination a few days after instillation showed that most of the carbon black was inside alveolar macrophages and polymorphonuclear leukocytes, although some particles were seen in the interstitium and interstitial macrophages (remaining for 16 weeks, when most of the alveoli were clear of inflammatory cells and particles); particles were also found in the hilar lymph nodes at 1 week, the amount of which increased by 16 weeks. In contrast, in the mice receiving carbon black 3 days after bleomycin, particles were seen to cross the denuded epithelial surface and, by 4 weeks, 'many carbon black-laden cells' were seen in the connective tissue; by 16 weeks, 'a large amount of carbon black' had been incorporated into the interstitium. In mice treated with carbon black four weeks after treatment with bleomycin, particles were again seen mostly in the air spaces (free or phagocytosed); although the alveolar surface was not denuded, cell composition was abnormal (cuboidal epithelium in fibrotic areas). The amount of carbon black retained in the lungs was assessed at 16 weeks (by digestion of the lungs in 40% potassium hydroxide). The weight of the insoluble residue at 16 weeks was statistically significantly greater (1.6 mg) in mice that received carbon black 3 days after bleomycin (when lung injury was greatest) than in mice that received either carbon black only or carbon black 4 weeks after bleomycin (~1 mg). The unexposed mice and those treated with bleomycin only had approximately 0.2 mg of insoluble residue. This study shows that the retained lung dose of carbon black can increase significantly during a condition of pulmonary inflammation and epithelial cell injury.

(c) Comparison of clearance and retention of carbon black in lungs of three rodent species

The lung retention of and response to inhaled carbon black particles (Printex 90 and Sterling V) were investigated in three rodent species: Fischer 344 rats, $B6C3F_1$ mice and 276 F1B Syrian hamsters (all females) (Elder *et al*., 2005). The Printex 90 had a primary particle size of 14 or 17 nm (both were reported), a specific surface area of 300 m^2/g and an MMAD of 1.4–2.0 μm (GSD, 2.3–2.8) for the various exposure chambers by rodent

species and exposure group. The Sterling V had a primary particle size of 70 nm, a specific surface area of 37 m^2/g and an airborne particle size of 0.8 μm MMAD (GSD, 3.2). Printex 90 was labelled as a high-surface area carbon black, while Sterling V was labelled as low-surface area carbon black. Rats were exposed to low, medium and high concentrations of Printex 90 of approximately 1, 7 and 50 mg/m^3 for each species, respectively, for 6 hours per day on 5 days per week for 13 weeks. In addition, rats only were exposed to Sterling V at a concentration of approximately 50 mg/m^3. Five or six animals were used per exposure group. The study was designed to provide the same dose, as either mass or surface area, for the two types of carbon black studied. Thus, although the mass doses were different, similar surface area doses were achieved in the rat lungs from exposure to 7 mg/m^3 Printex 90 and to 50 mg/m^3 Sterling V, i.e. approximately 0.3 m^2 (Elder *et al*., 2005). Although the surface area doses were different, similar mass doses were achieved at 50 mg/m^3 Printex 90 or Sterling V, i.e. approximately 5.5 mg or 8 mg, respectively. Particle retention in the lungs was observed to be prolonged after exposure to the mid-(7 mg/m^3) and high (50 mg/m^3) concentrations of Printex 90 in rats and mice, and also for 50 mg/m^3 Sterling V in rats. In hamsters, which had the most efficient clearance, pulmonary retention was prolonged only at the high dose.

(d) Translocation of carbon black particles from the site of deposition to other tissues

Female Swiss mice, aged 4 weeks and 18 months, were given with 7 mg ^{7}Be-labelled furnace black particles (Elftex 8) by gavage. The distribution of the isotope was determined in the animals 4 hours and 1, 2, 5 and 14 days after exposure. The authors concluded that there was uptake and distribution from the gut and that transit was more rapid in young mice. Peyer's patches (a gut-associated lymphoid tissue) of older mice took up more radiolabel than those of younger mice (LeFevre & Joel, 1986). [It was not clear from the study whether the authors verified the stable binding of the radiolabel to the particles.]

In a study of ultrafine carbon black and other particles instilled in rat lungs, Oberdörster *et al*. (1992) determined that the translocation of particles from the alveolar lumen of the lungs was dependent on particle size. Following intratracheal instillation of 0.5 mg particles of different sizes, the smaller ultrafine particles (12 and 20 nm) penetrated the alveolar epithelial cell barrier and entered the lung interstitium to a greater extent than an equal mass of larger respirable particles (> 200 nm) within 24 hours. This proportion was shown to increase with increasing particle dose as either mass or surface area.

More recent studies have shown that ultrafine carbon and other particles can translocate beyond the lungs. Oberdörster *et al*. (2002) showed that inhaled spark-generated ultrafine ^{13}C-carbon particles of approximately 25 nm in diameter were cleared rapidly from rat lungs and translocated to other organs (e.g. liver and spleen). Significant amounts of particles were found in the livers of rats in the high-exposure group (approximately fivefold higher amounts in the liver than in the lung at 24 hours).

Clearance or translocation from the lungs may also depend on the composition of the particle. For example, ultrafine iridium particles inhaled by rats for 1 hour remained in the lungs to a much greater extent and only a small proportion was cleared (< 1% in 7 days) (Kreyling *et al*. 2002). However, of the iridium particles that did translocate from the lungs, 10 times more 15-nm particles translocated than 80-nm particles. In another study in rats, inhaled ultrafine elemental silver particles were found to enter the blood circulation (Takenaka *et al*., 2001).

Inhalation of ultrafine particles may also result in translocation of particles to the brain. Ultrafine insoluble ^{13}C-carbon particles (CMD, 36 nm; GSD, 1.66) were found in the brains of Fischer 344 rats on days 1–7 following a 6-hour inhalation exposure to 160 μg/m^3 (Oberdörster *et al*., 2004). Approximately 50% of the inhaled ultrafine particles was predicted to deposit in the olfactory mucosa (assuming equal distribution) of rats and approximately 20% of that amount was found in the olfactory bulb. On day 1 after exposure, 0.35 μg/g of added ^{13}C was detected in the olfactory bulb; the amount increased on days 3 and 5 after exposure and reached 0.43 μg/g on day 7. The cerebrum and cerebellum contained significantly increased concentrations of ^{13}C on day 1, but the levels tended to decrease subsequent to exposure. The study was not designed to distinguish between the possible paths through which ^{13}C ultrafine particles could reach the brain, including crossing the blood–brain barrier (by particles that translocated into the blood following deposition anywhere in the respiratory tract) and transport of particles that deposited in the nasal olfactory mucosa along the olfactory nerve to the olfactory bulb. However, the authors concluded that the olfactory nerve pathway was the most probable explanation for the ^{13}C found in the olfactory bulb because of the significant increase in amounts in that region and the consistency with previous studies that demonstrated an olfactory nerve pathway for ultrafine particles (Bodian & Howe, 1941; De Lorenzo, 1970). Studies in non-human primates have demonstrated the translocation of 30-nm viruses and 50-nm gold particles from the nasal region to the olfactory bulb of the brain. Hunter and Dey (1998) reported another pathway through which particles may enter the central nervous system, via the trigeminal nerve, which has synaptic innervation in the nasal epithelium.

The size of individual ultrafine particles may allow their entry into cells and cellular organelles more readily than larger particles or agglomerates. In a study of concentrated particles from air pollution (including carbon particles) in human bronchial epithelial cells and mouse alveolar macrophages, the ultrafine fraction (< 100 nm) was found to penetrate the cells, localize in mitochondria and cause oxidative damage to mitochondrial membranes (Li *et al*., 2003).

(e) Kinetics of carbon black-adsorbed material

Concern had been raised that material, including carcinogenic compounds, adsorbed onto carbon black particles are retained longer in the lung upon inhalation and will subsequently lead to a greater availability of carcinogens to target cells in the lung. In particular, this would be of importance for materials such as diesel exhaust particles,

which are known to contain PAHs adsorbed onto the carbon core and which may contribute to the carcinogenic response of inhaled diesel exhaust. These studies are summarized in Table 4.2.

Pylev *et al*. (1970a,b) instilled [^{3}H]benzo[*a*]pyrene adsorbed onto furnace black particles (26–160 nm) intratracheallly into Syrian hamsters and followed retention of radioactivity for 21 days. Compared with [^{3}H]benzo[*a*]pyrene suspended in aminosol vitrum, retention of [^{3}H]benzo[*a*]pyrene was longer when adsorbed onto carbon black (Pylev *et al*., 1970b).

In another study, male Fischer 344/Crl rats were exposed by inhalation for 30 days to Elftex 12 (furnace black; primary particle size, 37 nm; surface area, 43 m^2/g) with adsorbed [7-^{14}C]benzo[*a*]pyrene (Sun *et al*., 1989) or [4,5,9,10-^{14}C]-1-nitropyrene (Wolff *et al*., 1989). A total concentration of 100 mg/m^3 was used with the addition of either 0.2, 2 or 20% benzo[*a*]pyrene or 2 mg/m^3 1-nitropyrene. The long-term retention of radioactivity from both benzo[*a*]pyrene and 1-nitropyrene was increased when adsorbed onto carbon black. For both adsorbed compounds, a biphasic clearance was found, and most radioactivity was cleared from the lungs within 1–2 days. At all time-points, 16–60 times more radioactivity was retained after treatment with the adsorbed compounds compared with administration of the pure compound. Covalent interaction of these compounds with lung macromolecules was also greater when they were co-administered with carbon black particles.

These studies demonstrate that carbon black administered to rats and hamsters either by inhalation or intratracheal instillation can act as a carrier of adsorbed material, which is subsequently cleared from the lung much more slowly than the material given alone. In another study, Buddingh *et al*. (1981) reported that benzo[*a*]pyrene was poorly eluted from carbon black *in vitro* by human plasma or by swine serum, swine lung washing or lung homogenate, which is consistent with the findings of Borm *et al*. (2005) in surfactant-containing saline solution using four different carbon blacks.

4.1.3 *Dosimetry models in humans and rodents*

Dosimetry models can be used to estimate the particle dose in a given region of the respiratory tract for any given exposure. The development, calibration and validation of these models depend on the availability of experimental data and the models can be further validated and refined as additional studies become available.

Differences in the kinetics of particle clearance and retention in rodents and humans have been taken into account, to the extent of available data, in species-specific models of particle deposition and retention. Route of breathing affects the amount and site of deposition in the respiratory tract since the efficiency of nasal deposition generally exceeds that in the oral passage (Oberdörster, 1988). In a comparison of predictions from rat and human models in the multiple path particle deposition model (CIIT & RIVM, 2002), Brown *et al.* (2005) determined that the exposure to airborne particles would

Table 4.2. Kinetics of carbon or carbon black (CB)-adsorbed compounds

Characteristics of carbon black	Adsorbed compound	Test system	Duration	End-points	Findings	Reference
Furnace black 26–160 nm	[^{3}H]BaP	Intratracheal instillation; Syrian hamster	21 days	Macrophage response and BaP retention	CB + BaP elicited more macrophages; longer BaP retention with CB than without	Pylev *et al*. (1970a,b)
Elftex 12 (furnace black) 37 nm; 43 m^2/g	^{14}[C]BaP	Inhalation; Fischer 344/N rat; 100 mg/m^3 mass with 0.2, 2 or 20% BaP; BaP alone, 2, 20 mg/m^3; intratracheal instillation of 500 µg CB±10 or 100 µg BaP	2 h exposure (nose only) + 30 days	BaP lung retention	Biphasic lung retention; long-term retention of BaP increased 16–60 times when coated onto CB; more pronounced after instillation compared with inhalation	Sun *et al*. (1989)
Elftex 12 (furnace black) 37 nm; 43 m^2/g	^{14}[C]-1-Nitropyrene	Inhalation; Fischer 344/N rat; 98 mg/m^3 CB+2 mg/m^3 nitropyrene; nitropyrene alone	2 h exposure (nose only) + 30 days	Nitropyrene lung retention	Biphasic nitropyrene retention increased when adsorbed onto CB	Wolff *et al*. (1989)

BaP, benzo[*a*]pyrene

generally need to be higher in rats to result in doses equivalent to those in human lungs, the extent of which depends on the particle characteristics and breathing patterns.

In humans, several models of particle deposition have been developed and evaluated (e.g. ICRP, 1994; NCRP, 1997; CIIT & RIVM, 2002). Studies on particle clearance and retention in human lungs have been more limited. Martonen *et al*. (2005) have provided an overview of models of human lung deposition and clearance that have been developed over the years.

Several models of particle deposition and clearance in rat lungs have been developed (e.g. Strom *et al*., 1989; Yu *et al*., 1989; Stöber *et al*., 1990; Yu & Rappaport, 1997; Stöber, 1999; Tran *et al*., 1999, 2000; CIIT & RIVM, 2002), some of which describe the rat alveolar region as a single compartment with dose-dependent clearance rate coefficients (Yu *et al*., 1989; Yu & Rappaport, 1997; CIIT & RIVM 2002), while others include additional compartments for the interstitial transport or sequestration of particles (free or phagocytosed) and dose-dependent clearance (Strom *et al*., 1989; Stöber *et al*., 1990; Stöber, 1999; Tran *et al*., 1999, 2000).

Two recent studies that compared the long-term retention kinetics of particles in rats and humans used data from coal miners in the United Kingdom and in the USA that included work histories and estimates of exposure to respirable particles and retained mass of coal and silica in the lungs and hilar lymph nodes (Kuempel, 2000; Tran & Buchanan, 2000; Kuempel *et al*., 2001). A model of lung deposition and clearance in rats was found to underpredict the retained lung burdens of particle mass in coal miners who had had lower lifetime exposures and to overpredict those of coal miners who had had high exposures. At low exposures, the rat model is a simple, first-order kinetic model that predicts effective clearance and very little particle retention in the lungs of retired miners. At high exposures, the rat model predicts impaired clearance and much higher retained burdens than those actually observed in coal miners. A human model that incorporates the concept of slow clearance (with three first-order compartments and slow-to-very slow clearance rate coefficients) (ICRP, 1994) improve the fit to the data from coal miners. However, the model structure that was required to predict adequately the retained dust burden was a higher-order model with an interstitial or sequestration compartment (Kuempel *et al*., 2001). Within this model structure, rat-based overload kinetics did not improve the fit of the data, although a lesser degree of overloading could not be ruled out. The model structure with an interstitial or sequestration compartment is consistent with the observations of little or no particle clearance from the lungs of retired miners (Freedman & Robinson, 1988) and with the retention of particles in the interstitium of human lungs (Nikula *et al*., 2001). It is also consistent with the structure of some of the animal models (Strom *et al*., 1989; Stöber *et al*., 1990; Stöber, 1999; Tran *et al*., 1999, 2000).

An area for further development in each of these mass-based models of animal and human lung dosimetry is the fate of inhaled ultrafine particles. Particle size-selective clearance is included in current models to the extent that the particle size influences the site of deposition in the respiratory tract; also, the mechanisms of biological clearance

depend on the specific region of the respiratory tract. However, experimental studies (see Section 4.1.2) have shown that the fate of inhaled ultrafine particles may differ considerably from that of larger respirable particles of the same composition, and may include translocation within lung tissues and beyond the respiratory tract.

4.2 Toxic effects

4.2.1 *Humans*

Comprehensive reviews of the toxicity of carbon black to humans are available (National Institute for Occupational Safety and Health, 1978; Rivin & Smith, 1982; IARC, 1984; Gardiner, 1995; IARC, 1996).

(a) Observations in the general population

Chest radiographic features of small opacities that are consistent with pneumoconiosis have been observed in the general population. An analysis of nine study populations reported prevalences of small opacities (International Labour Organization (ILO) grade 1/0 or greater) ranging from 0.21 to 11.7%. A meta-analysis of these data yielded a population prevalence of 5.3% (95% CI, 2.9–7.7%). The prevalence was significantly greater in Europe (11.3%; 95% CI, 10.1–12.5%) than in North America (1.6%; 95% CI, 0.6–2.6%), which could not be explained on the basis of age, gender or smoking history. There was a greater prevalence of lung opacities in men (5.5%; 95% CI, 3.4–7.6%) than in women (3.5%; 95% CI, 1.3–5.8%). The age-specific pooled prevalence was higher in the study populations with a mean age of ≥ 50 years than in those with a mean age of < 50 years in both Europe (11.7% versus 9.6%) and North America (2.3% versus 0.6%). Environmental and unaccounted occupational exposures as well as reader variability may play a role in the determination of the prevalence of small opacities in these subjects and may explain the large differences between different regions (Meyer *et al*., 1997).

(b) Respiratory effects in carbon black workers

Gärtner and Brauss (1951) first described radiological changes analogous to pneumoconiosis in 31 workers in a carbon black factory. However, these individuals had no lung function abnormality. Since that time, a series of other reports have been published on pneumoconiosis in carbon black workers.

A health survey was conducted in two German factories that produced carbon black from acetylene or from oil that was burned with light gas, respectively. Among 56 workers, 16 had been employed for more than 10 years. Two of these workers had chest X-ray changes compared with none of the 52 controls who had had radiographs taken without suspicion of lung disease (von Mai, 1966). [The selection of workers was not clear, neither were the criteria for diagnosis.]

Most studies of respiratory morbidity have methodological shortcomings or provide insufficient detail for a reliable interpretation of the results (see review by Gardiner,

1995). Nevertheless, exposure–response relationships were evident for symptoms of chronic bronchitis, small opacities on chest radiographs and several respiratory parameters (forced expiratory volume in 1 second [FEV_1], $FEF_{25–75\%}$). Studies in Germany (Küpper *et al*., 1996) and Poland (Szozda, 1994, 1996) provided evidence of a relationship between exposure to carbon black and lung function among smokers. The Polish studies also reported cases of hypertension and pneumoconiosis among carbon black workers.

Spirometry, body plethysmography and inhalation challenge tests were conducted among employees at a German carbon black production plant to assess the impact of fine carbon black dust on pulmonary function, to determine the prevalence of obstructive airway disease among the workers and to investigate whether exposure to fine dust is related to the prevalence of bronchial hyper-responsiveness. A total of 573 exposed workers (178 nonsmokers, 107 former smokers, 288 smokers) and 99 controls (46 nonsmokers, 13 former smokers, 40 smokers) participated in the study. Measurements of dust in air showed concentrations of 0.01–9.14 mg/m^3 for fine dust (9–200 nm [includes fine and ultrafine sizes]) and 1.08–19.95 mg/m^3 for total dust (mean dust concentrations, 0.58 mg/m^3 for respirable dust; 1.08 mg/m^3 for inspirable dust). Exposure to carbon black had a small but statistically significant impact on lung function in smokers ($P < 0.01$). Nevertheless, exposed smokers displayed signs of obstructive airway disease more frequently (7.3%) than exposed nonsmokers (3.9%). There was no effect of exposure to carbon black on lung function in former smokers or nonsmokers. Exposure to carbon black dust was not associated with an increased prevalence of bronchial hyper-reactivity (Küpper *et al*., 1996).

To investigate the occurrence of medical conditions related to exposure to carbon black, a large study was conducted in 18 carbon black production plants (including the German plant; Küpper *et al*., 1996) in seven European countries between mid-1987 and mid-1989. A total of 1298 respirable [SIMPEDS cyclone method] and 1317 total inhalable [Institute of Occupational Medicine head method] samples were taken and included in the study. The distributions of the TWA values were best described by a log-normal distribution and exposure was characterized by GMs and standard deviations (Gardiner *et al*., 1992b). In a subsequent study, exposure-related health effects were assessed in 3086 employees in these plants through respiratory health questionnaires, spirometry and chest radiographs. Personal monitoring was used to measure current exposure to inhalable and respirable carbon black, sulfur dioxide and carbon monoxide. The final analysis comprised 1742 employees in 15 plants (81% response rate) who provided data on respiratory symptoms and spirometry, and 1096 chest radiographs were available from 10 plants (74% response rate). In addition to the respirable (1298) and inspirable (total inhalable; 1317) dust samples mentioned above, 1301 sulfur dioxide and 1322 carbon monoxide samples were also collected. This study thus included a comprehensive assessment of current occupational exposure to carbon black dust and its associated gaseous contaminants. In respirable dust samples, the geometric mean level was 0.21 (GSD, 2.7) mg/m^3 and in total inhalable dust, the GM level was 0.57 (GSD,

4.0) mg/m^3. Associations were found between cough, sputum production, the symptoms of chronic bronchitis (mean prevalence, 10%) and indices of increasing current exposure (from 0.14 to > 0.45 mg/m^3). There was a small reduction in lung function with increasing dust exposure in both smokers and nonsmokers. Nearly 25% of the chest radiographs showed small opacities (ILO category 0/1 or greater), which were strongly associated with indices of cumulative dust exposure, after accounting for production plant and current smoking habits. The findings were consistent with a non-irritant effect of carbon black dust on the airways combined with dust retention in the lungs (Gardiner *et al*., 1993).

Chronic inflammation has also been associated with non-neoplastic lung diseases in workers with dusty jobs. Rom (1991) found a statistically significant increase in the percentage of polymorphonuclear neutrophils in the bronchoalveolar lavage (BAL) fluid of workers with respiratory impairment who had been exposed to asbestos, coal or silica (4.5% in cases versus 1.5% in controls). Elevated levels of such cells have been observed in the BAL fluid of miners with simple coal workers' pneumoconiosis (31% of total BAL cells versus 3.4% in controls; Vallyathan *et al*., 2000) and in patients with acute silicosis (a 10-fold increase over controls; Goodman *et al*., 1992; Lapp & Castranova, 1993).

The results of two additional studies (phases 2 and 3) of respiratory health of European carbon black workers showed exposure-related adverse effects of carbon black on the respiratory system, which were evident from an increase in the prevalence of cough and sputum production, and reductions in lung function, based on measurements of FEV_1, $FEF_{25–75\%}$ and the FEV_1/forced vital capacity (FVC) ratio. An increase in exposure to inhalable dust of 1 mg/m^3 was associated with an increase of 80% in the prevalence of respiratory symptoms of chronic bronchitis (odds ratio, 1.8; 95% CI, 1.3–2.6) in phase 2, but not in phase 3. The prevalence of respiratory symptoms such as cough and cough and sputum production, however, was significantly affected by an increase of 1 mg/m^3 in exposure. Working for 40 years with a mean exposure of 1 mg/m^3 (480 mg.month/m^3) was expected to increase the prevalence of cough by almost 70% (odds ratio, 1.7; 95% CI, 1.2–2.1) and that of cough and sputum production by 60% (odds ratio, 1.6; 95% CI, 1.2–2.1). Similarly, a 1-mg/m^3 increase in exposure to carbon black was associated with significant decrements in FEV_1, $FEF_{25–75\%}$ and FEV_1/FVC ratio (Gardiner *et al*., 2001).

Van Tongeren *et al*. (2002) carried out a longitudinal analysis of workers in the European carbon black manufacturing study who had provided a full-size chest radiograph in each of the three cross-sectional surveys between 1987 and 1995. All chest radiographs were read independently according to the ILO classification by three experiences readers who were blind to all factors, including the sequence in which the chest radiographs were taken. After exclusion of all workers from a factory that had a low participation rate (< 60%) in the first survey and all workers who had reported various lung injuries, operations or respiratory disease (asthma, pleurisy or pulmonary tuberculosis), data from 675 employees were available for analysis. The prevalence of small opacities with ILO category ≥ 1/0 was 13.9, 19.9 and 19.7% in the first, second and third survey, respectively. An association between cumulative exposure during the study

and progression of small opacities was observed, although only four cases of existing small opacities (≥ 1/0) in the first survey progressed to higher ILO categories. The authors concluded that exposure to carbon black was associated with the incidence of small opacities, although this effect may be reversible after cessation of exposure.

Harber *et al*. (2003) investigated whether exposure to carbon black was associated with decrements in lung function and increased prevalence of respiratory symptoms among 1755 employees from 22 North American carbon black manufacturing plants. Multiple linear regression analyses showed that cumulative exposures to 'total' and inhalable dust were both was associated with a statistically significant decrement in FEV_1 and with FVC. The slopes were –2 mL and –0.7 FEV_1/mg–year/m^3 for cumulative exposure to 'total' and inhalable dust, respectively. Cumulative exposure was also associated with an increased prevalence of chronic bronchitis in nonsmokers.

4.2.2 *Experimental systems*

(a) Inhalation exposure

The effects of subchronic inhalation of carbon black on pulmonary inflammation, expression of inflammatory cytokines and growth factors, and on lung histopathology were studied in male Fischer 344 rats exposed for 6 hours per day on 5 days per week for up to 13 weeks to 1.1, 7.1 and 52.8 mg/m^3 carbon black (Monarch 880, Cabot; diameter, 16 nm; surface area, 220 m^2/g). Effects on the lung were assessed after 6.5 and 13 weeks of exposure and after 3 and 8 months of recovery. After 13 weeks, lung burdens were 354, 1826 and 7861 μg carbon black at the three exposure concentrations, respectively. Inhalation of 1.1 mg/m^3 carbon black did not cause any of the adverse effects on the lung that were measured, but lung clearance appeared to be impaired after exposure to 7.1 and more severely so after exposure to 52.8 mg/m^3. Analysis of BAL fluid showed no effect of the lowest dose and a relative increase in the number of neutrophils after exposure to the intermediate dose that persisted. At the highest dose of carbon black, an increase in total cell number and neutrophils and a decrease in macrophages were observed. The BAL fluid concentrations of lactate dehydrogenase, β-glucuronidase and total protein were also increased at this dose. All these effects persisted until 8 months after exposure. mRNA expression of macrophage inflammatory protein 2 (MIP-2) and monocyte chemotactic protein 1 (MCP-1)—two chemotactic cytokines—was minimal in the lungs of rats in the low-dose group, but MIP-2 mRNA was clearly present at all time-points after exposure to 7.1 and 52.8 mg/m^3. MCP-1 mRNA was also increased at these doses, but this effect was persistent for up to 8 months after exposure to the high dose only. In lung tissue sections, particle-containing macrophages were seen in alveolar and alveolar duct regions after the 1.1-mg/m^3 dose. The intermediate dose produced acute inflammation (characterized by accumulation of neutrophils and macrophages within alveolar spaces), mild epithelial hyperplasia and mild interstitial fibrosis. The 52.8-mg/m^3 dose caused mainly lesions in the alveolar ducts, with pronounced epithelial hyperplasia and fibrosis. Alveolar type II cell hypertrophy and hyperplasia seen after exposure to

intermediate and high doses persisted throughout the 8-month recovery period (Driscoll *et al*., 1996).

To investigate whether the inflammatory response induced by inhaled ultrafine particles involves an increased release of systemic clotting factor, adult male Wistar rats were exposed by inhalation for 7 hours to fine or ultrafine carbon black particles. The attained total suspended particle concentrations were 1.66 mg/m^3 for ultrafine (Printex 90; diameter, 14 nm) and 1.40 mg/m^3 for fine carbon black (Huber 990; diameter, 260 nm). Particle concentration (number of particles/m^3) of the ultrafine carbon black was more than 10 times greater than that of the fine particles; the average CMDs were 114 nm for ultrafine and 268 nm for fine carbon black. Exposure to ultrafine particles caused an increase in total cell number and in the number of neutrophils in BAL fluid immediately after exposure. Both fine and ultrafine carbon black caused twofold and fourfold increases, respectively, in the number of polymorphonuclear leukocytes in BAL 16 hours after exposure. Exposure to ultrafine but not to fine carbon black particles was associated with a significant increase in the total number of blood leukocytes. Blood coagulation-related plasma, fibrinogen, factor VII and von Willebrand factor were all unaffected by exposure to particles. MIP-2 mRNA was significantly increased in BAL cells 48 hours after the end of exposure to ultrafine carbon black. The data showed a small but consistent pro-inflammatory effect of ultrafine particles that was greater than that of the same exposure (on a weight/volume basis) to fine carbon black (Gilmour *et al*., 2004).

The retention kinetics, inflammation and histopathology following exposure to carbon black were examined in female Fischer 344 rats, B6C3F$_1$ mice and F1B Syrian golden hamsters exposed to 0, 1, 7 and 50 mg/m^3 (nominal concentrations) carbon black particles (Printex 90; diameter, 14 nm; surface area, 300 m^2/g) for 6 hours per day on 5 days per week for 13 weeks. Rats were also exposed to 50 mg/m^3 (nominal) low-surface area carbon black (Sterling V; diameter, 70 nm; surface area, 37 m^2/g). Retention and effects were measured immediately after exposure and 3 and 11 months later; retention was also evaluated after 5 weeks of exposure. Significant decreases in body weight were observed only in hamsters exposed to the high dose of carbon black. Lung weights were increased in all groups exposed to this dose, but this persisted only in rats and mice up to 11 months after exposure. Lung inflammation and histopathology (lung lesions located primarily in the centriacinar regions, with the most extensive epithelial and inflammatory responses in the alveolar ducts and surrounding parenchyma) were more severe and prolonged in rats than in mice and hamsters, and were similar in rats exposed to 'surface-area equivalent' concentrations of 7 mg/m^3 Printex 90 and 50 mg/m^3 Sterling V. Hamsters had the most efficient clearance and least severe responses of the three species. The results obtained in rats suggest that the surface area of the particles is an important determinant of dose to the target tissue and subsequent effects (Elder *et al*., 2005).

(b) Intratracheal or intranasal instillation

Respiratory syncytial virus causes bronchiolitis and pneumonia in infants and may lead to the development of asthma in childhood. To determine whether exposure to

particles modulates the immune response to this virus, 8-week-old female BALB/c mice received an intratracheal instillation of 40 μg ultrafine carbon black particles (150 m^2/g) in 100 μL saline. The following day, mice were instilled with either 10^6 plaque-forming units of respiratory syncytial virus or uninfected medium. Compared with animals that received the virus alone, tumour necrosis factor-α (TNFα) protein was reduced in the BAL fluid on days 1 and 2 of infection in mice exposed to both carbon black and the virus. There was a reduction in the number of lymphocytes in the BAL fluid on day 4, and decreased levels of interferon (IFN)-γ-inducible protein lymphotactin and IFN-γ mRNAs in the lungs of mice exposed to carbon black plus virus. On days 2–4 of infection, viral titres in these mice were lower than those in animals that had received respiratory syncytial virus alone. By day 7, however, the numbers of neutrophils, expression of pro-inflammatory cytokine mRNA, TNF-α and Th2 cytokine interleukin (IL)-13 protein levels were increased in the lungs of mice exposed to carbon black plus virus, which indicated an exacerbation of infection. The data showed that pre-exposure to ultrafine particles induces an inflammatory condition that promotes Th2-type immune responses rather than the production of IFN-γ Th1, which is necessary for microbial defence (Lambert *et al*., 2003).

The ability of ultrafine and fine particles to induce inflammation, cause epithelial injury and affect alveolar macrophage clearance (phagocytosis, chemotaxis) was studied in Wistar rats instilled with 125 or 500 μg fine titanium dioxide (mean diameter, 250 nm; 6.6 m^2/g), ultrafine titanium dioxide (mean diameter, 29 nm; 49.8 m^2/g), fine carbon black (Huber 990; mean diameter, 260.2 nm; 7.9 m^2/g) or ultrafine carbon black (Printex 90; mean diameter, 14.3 nm; 253.9 m^2/g) in 0.5 mL saline. Inflammation was quantified by counting the number of neutrophils in BAL fluid. The ultrafine particles recruited more polymorphonuclear neutrophils, caused more epithelial damage and were more cytotoxic than fine particles at equal mass concentrations. Both ultrafine and fine particles significantly impaired the ability of alveolar macrophages to phagocytose fluorescent indicator beads, but only treatment with ultrafine particles enhanced the C5a-stimulated chemotactic potential of the macrophages. This study showed that ultrafine particles [of two very different materials] induced inflammation and epithelial damage to a greater extent than their larger-sized mass counterparts. In general, the effect of ultrafine carbon black was greater than that of ultrafine titanium dioxide, which suggests that there are differences in the potential hazard of different types of ultrafine particle. Epithelial injury and toxicity were associated with the inflammatory response that followed exposure to ultrafine particles. Increased sensitivity to a C5a chemotactic stimulus as a result of exposure to ultrafine particles could retain the macrophages in the lung at the site of particle deposition, and thus allow the dose to accumulate (Renwick *et al*., 2004).

To explore the role of vascular endothelial growth factor (VEGF) in the induction of alveolar capillary permeability by ultrafine particles, male ICR mice received an intratracheal instillation of 200 μg carbon black (Printex 90; diameter, 14 nm before grinding; surface area, 253.9 m^2/g). A significant and sustained increase in total proteins was observed in BAL fluid, which was maximal at 21 hours after instillation. The level of

TNFα was significantly elevated only at 4 hours, but significant increases in VEGF were seen throughout the 42-hour study period, with a peak increase at 16 hours. The results showed that ultrafine carbon black particles induce the production of VEGF, which is associated with an increase in alveolar capillary permeability. The involvement of oxidative stress in this process was supported by the observation in an in-vitro study that *N*-acetylcysteine (a scavenger of reactive oxygen species) prevents the induction of VEGF by ultrafine carbon black particles (Chang *et al*., 2005).

The kinetics of airway toxicity or inflammation and allergic sensitization to ovalbumin in response to ultrafine carbon black particles (diameter, 30–50 nm) was studied in BALB/cANNCrl mice exposed intranasally to ovalbumin (10 μg in 20 μL) alone or in combination with 2, 20 or 200 μg carbon black particles. Airway toxicity and inflammation were assessed on days 4 and 8, immune adjuvant effects were measured in the lung-draining peribronchial lymph nodes on day 8, antigen-specific immunoglobulin E (IgE) was measured on days 21 and 28 and allergic airway inflammation was studied after ovalbumin challenges on day 28. The dose of 200 μg carbon black particles, but not 20 μg or 2 μg, induced immediate airway inflammation and had immune adjuvant activity that involved enlargement of the peribronchial lymph nodes and an increased ovalbumin-specific production of Th2 cytokines IL-4, IL-5 and IL-10. Serum levels of ovalbumin-specific IgE were increased on day 21, which was indicative of systemic sensitization. This was supported by allergic airway inflammation after challenges with ovalbumin. The authors concluded that there is a correlation between early airway toxicity and adjuvant effects of carbon black particles and that local cytokine production early after exposure to these particles is predictive of airway inflammation (de Haar *et al*., 2005).

The size-specific effects of particles on pulmonary immune response, translocation to lymph nodes and expression of chemokine mRNA were studied in the lung and lymph nodes of 8-week-old male BALB/c mice exposed to ultrafine or fine carbon black particles by intratracheal instillation. In a first experiment, 25, 125 or 625 μg ultrafine carbon black particles (Printex 90; diameter, 14 nm; 300 m^2/g) were administered once a week for 4 weeks. In a second experiment with the same dose regimen, larger-sized carbon black (Flammruss 101; diameter, 95 nm; 20 m^2/g) was instilled. Total and differential cell counts and release of cytokines and chemokines were measured in BAL fluid 24 hours after the last instillation. In a third experiment, a dose of 125 μg ultrafine carbon black or larger-sized carbon black was administered according to the same schedule, and lungs and mediastinal lymph nodes were isolated 4 hours after the last instillation to measure expression of chemokine mRNA. The total cell count and differential cell counts (macrophages, lymphocytes, neutrophils) in BAL fluid increased significantly in mice exposed to the ultrafine carbon black particles in a dose-dependent manner, as did the release of IL-1β, IL-6 and TNFα. MIP-1 α/CCL-3 protein and mRNA expression were also increased in the lungs and lymph nodes of these mice. The effects seen with the 95-nm carbon black particles were weaker than those obtained with the smaller-sized particles. Particle translocation to the mediastinal lymph nodes was greater in mice given the ultrafine particles than in those that received the larger-sized carbon

black. The study showed that repeated intratracheal instillation of ultrafine carbon black particles in mice leads to pulmonary inflammation, translocation of particles to mediastinal lymph nodes and enhanced expression of chemokine mRNA in the lung and lymph nodes. These effects were stronger with ultrafine than with fine particles (Shwe *et al*., 2005).

The effects of ultrafine and fine particles on immune function in the mouse brain were investigated by the instillation of 125 μg carbon black (Printex 90; diameter, 14 nm; 300 m^2/g; or Flammruss 101; diameter, 95 nm; 20 m^2/g) into the nostrils of 8-week-old male BALB/c mice once a week for 4 weeks. Four hours after the last instillation, the olfactory bulb and hippocampus were isolated. The mRNA expression of pro-inflammatory cytokines (IL-1β and TNFα) and chemokines (MCP-1/CCL2, MIP-1α/CCL3) and monokine-induced INF-γ /CXC chemokine ligand was enhanced in the brain olfactory bulb but not in the hippocampus of mice instilled with 14-nm carbon black particles. The 95-nm particles did not show effects in either organ at the doses used (Shwe *et al.*, 2006).

Yang *et al*. (1999) tested the combined effect of particulates and organic compounds on the alveolar macrophage response to bacteria or bacterial products (such as lipopolysaccharide) and the secretion of pro-inflammatory cytokines (IL-1 and TNFα). A comparative study of the pulmonary responses to exposure to diesel exhaust particles, carbon black and silica was conducted in male Sprague-Dawley rats that were exposed to a single intratracheal dose (5 or 35 mg/kg bw) of diesel exhaust particles (NIST; MMAD, 0.5 μm), carbon black (Elftex 12 furnace black; MMAD, 0.1–0.6 μm), silica (Min-U-Sil; MMAD, < 5 μm) or saline. The alveolar macrophages isolated from the particle-exposed rats were challenged *ex vivo* with lipopolysaccharide (0.1 μg/10^6 alveolar macrophages) and cytokines were monitored. In addition, rats were exposed to a single dose of diesel exhaust particles (5 mg/kg bw) followed 3 days later by exposure to lipopolysaccharide (1 mg/kg bw) for 3 hours *in vivo*. Exposures to diesel exhaust particles, carbon black and silica resulted in polymorphonuclear neutrophil infiltration and elevated levels of albumin and lactate dehydrogenase in the BAL fluid. The alveolar macrophages from the carbon black- and silica-exposed rats showed an increased production of TNFα but not of IL-1 and did not show a decreased response to a subsequent challenge with lipopolysaccharide. Upon *ex-vivo* challenge with lipopolysaccharide, the alveolar macrophages from diesel exhaust particle-exposed rats showed a significant decrease in TNFα. The authors concluded that diesel exhaust particles, carbon black and silica all induced a pulmonary response due to particle stimulation, but only diesel exhaust particles suppressed cytokine release in alveolar macrophages in response to stimulation with lipopolysaccharide.

Nilsen *et al*. (1997) studied the adjuvant activity of diesel exhaust particles (NIST 1650; MMAD, 0.03 μm; 64 m^2/g) and carbon black (Regal 250R; MMAD, 0.035 μm; 65 m^2/g) on systemic IgE production in ovalbumin-treated mice after intranasal administration. Female Balb/cA mice were immunized four times with ovalbumin (20 μg) alone or in combination with diesel exhaust particles (25 μg) or carbon black (25 μg). One and 2 weeks later, increased responses in both the number of responding animals and

serum IgE antibody were seen in the animals treated with ovalbumin and either of the particles; the activity of diesel exhaust particles was more pronounced than that of carbon black, which indicated that the organic matter adsorbed to the diesel exhaust particles and the non-extractable carbon cores were both responsible for the observed adjuvant effect.

Al-Humadi *et al*. (2002) exposed Brown Norway rats intratracheally to saline, carbon black or diesel exhaust particles at 5 mg/kg bw followed by exposure for 30 minute to ovalbumin (90 mg/m^3) or saline 1, 8, 18 and 29 days later. Exposure to diesel exhaust particles, carbon black or ovalbumin alone did not result in abnormal levels of inflammatory cells, lactate dehydrogenase or total protein in the BAL fluid. However the combinations of ovalbumin with diesel exhaust particles or carbon black increased these markers, and also the level of IL-4 mRNA in lung tissue and serum levels of ovalbumin-specific IgG and IgE.

The effect of acute exposure to diesel exhaust particles on phase I and phase II enzymes was investigated in rat lung. Intratracheal administration of these particles enhanced cytochrome P450 (CYP) 1A1 protein levels and enzyme activity one day after exposure; enzyme levels returned to control values after five days. Carbon black particles (35 mg/ kg bw) did not induce CYP1A1 protein or enzyme activity. However, both particle types (at 5 and 35 mg/kg bw) caused a significant decrease in CYP2B1 protein and enzyme activity at day 1, which was persistent up to day 7 with 35 mg/kg bw. Similarly, both treatments significantly attenuated glutathione *S*-transferase (GST)-Pi protein on day 1 after exposure and decreased the activities of GST and catalase on days 1 and 7. The diesel exhaust particles, but not carbon black, significantly induced quinone reductase activity on day 7. The authors suggested that diesel exhaust particles may induce CYP1A1 and quinone reductase enzymes by a chemical effect, while the carbonaceous core may be involved in the attenuation of CYP2B1, GST and catalase protein levels and enzyme activities (Rengasamy *et al*., 2003).

Zhao *et al*. (2004) evaluated the change in lung metabolic enzymes in response to concentrations of 35 mg/kg bw saline, diesel exhaust particles and carbon black intratracheally instilled into rats that were then killed 1, 3 or 7 days later. Metabolically activated fractions (S9) were extracted from control and exposed rat lungs. The mutagenic activity of 2-aminoanthracene, 2-aminofluorene, 1-nitropyrene and an organic extract of diesel exhaust particles was then determined in *Salmonella typhimurium* YG1024. The S9 from the control and exposed rats showed a dose-dependent increase in mutagenic activity of all four compounds. Compared with the saline control, the S9 from the carbon black-exposed rats was a less potent inducer of mutagenicity of 2-aminoanthracene. When inhibitors of CYP1A1 (α-naphthoflavone, 1 μM/plate) or CYP2B1 (metyrapone, 10 μM/plate) were added to the reaction mixture to monitor the involvement of CYP1A1 in S9 metabolic activity in the lung, α-naphthoflavone inhibited the metabolic activation of 2-aminoanthracene induced by S9 from carbon black-exposed rats to a lesser extent than the metabolic activity induced by S9 from rats exposed to saline and diesel exhaust particles. The rats exposed to both particle types revealed a significant change in phase I and II enzymes in the lungs, including CYP1A1, CYP2B1, GST and nicotinamide

adenine dinucleotide phosphate quinone-oxidoreductase (Rengasamy *et al*., 2003). The authors suggested that, after exposure to carbon black, the reduction in the constitutive enzyme CYP2B1 in the lung may play a role in the pulmonary handling of mutagenic agents (Zhao *et al*., 2004).

(c) Other routes

The effect of ultrafine particles on the microcirculation in extrapulmonary organs was investigated in C57BL/6 mice that received intra-arterial infusions of 1×10^7 or 5×10^7 ultrafine carbon black particles (Printex 90; diameter, 14 nm; surface area, 300 m^2/g) suspended in 200 µL buffer containing 15% human albumin. Two hours after infusion, platelet– and leukocyte–endothelial cell interactions, sinusoidal perfusion, endothelial fibrin deposition and the phagocytic activity of Kupffer cells were analysed by intravital video fluorescence microscopy in the liver microvasculature. The particles induced accumulation of platelets in the hepatic microvessels, which was associated with pro-thrombotic changes on their endothelial surface. Accumulation of particles in the liver had a strong procoagulatory effect, but did not trigger an inflammatory reaction or induce microvascular or hepatocellular tissue injury (Khandoga *et al*., 2004).

The possible adjuvant effect of diesel exhaust particles (NIST; diameter, 30 nm; 64 m^2/g) and carbon black (Regal 250R; diameter, 35 nm; 60 m^2/g), which was used as a surrogate for a non-extractable core of diesel exhaust particles with a similar size and surface area, on the response to the allergen ovalbumin was studied in BALB/c mice. A footpad inoculation was followed by a popliteal lymph node assay and other immunotoxic evaluations, including the weight change of popliteal lymph nodes, cell numbers and proliferation and specific serum IgE anti-ovalbumin antibody levels. Carbon black, although less potent than diesel exhaust particles, exhibited a similar capacity to increase the local lymph node response and specific serum IgE response to ovalbumin. Both particles had a significant adjuvant effect on the local immune-mediated inflammatory response and systemic specific IgE response to allergen, which suggested that the non-extractable particle core contributed substantially to the adjuvant activity of diesel exhaust particles (Løvik *et al*., 1997).

(d) Ex-vivo and in-vitro studies

In a study on the cytotoxicity of diesel exhaust particles, their phagocytosis and the resulting immune response, carbon black particles (FR103; diameter, 95 nm) that were included as a surrogate of the carbonaceous core of the diesel exhaust particles were reported to contain 1.5% of the PAH content of the diesel exhaust particles. Human bronchial epithelial cells (16HBE14o-) and human nasal epithelial cells in primary culture were exposed to the two particle types. Treatment with carbon black particles (10 $\mu g/cm^2$ for 48 hours; concentrations were expressed per square centimeter since the particles sediment rapidly onto the culture) stimulated the release of granulocyte macrophage

colony-stimulating factor (GM–CSF) and IL-8, but to a lesser extent than diesel exhaust particles (Boland *et al*., 1999).

The expression of human leukocyte antigen-DR (HLA-DR) on the cell membrane of antigen-presenting cells is of major importance for the induction of an allergic response in the airways. Because environmental particulates may induce or enhance allergic sensitization, a study was conducted to investigate the potential of carbon black (Vulcan M; CMD, 90 nm), diesel exhaust particles and urban air particulates (0.1–1000 ng/cm^2) to induce the expression of HLA-DR in cultures of differentiated THP-1 human monocytes, which are used as a model for alveolar macrophages. The 'adjuvant' potential of the particles on IFN-γ, a known enhancer of HLA-DR, was also studied. The particles alone did not induce HLA-DR on the THP-1 cells after 48 hours of incubation. However, even at very low concentrations, carbon black (1 ng/cm^2 and above) and diesel exhaust particles (0.1 ng/cm^2 and above) interacted with IFN-γ (100 U/mL) to enhance HLA-DR expression up to 2.5-fold. This in-vitro finding suggests the existence of a mechanism by which particles exert an adjuvant activity and which may partially explain how exposure to particles can enhance allergic sensitization (Don Porto Carero *et al*., 2002).

The effects of 10, 20 or 30 μg/cm^2 ambient particulate matter, diesel exhaust particles and carbon black particles (FR103; diameter, 95 nm) on cultured human bronchial epithelial (16HBE14o-) cells were compared. No significant effects on cell viability were observed after incubation with either particle type. In contrast to ambient particulate matter and diesel exhaust particles, carbon black particles did not disturb cell growth or induce the production of peroxides or the release of GM–CSF. Carbon black particles were more actively phagocytosed than the two other particle types (Baulig *et al*., 2003a). In a subsequent study, the same carbon black particles (10, 20 or 30 μg/cm^2, equivalent to 50, 100 or 150 μg/mL) did not cause an increase in reactive oxygen species or induce the expression of CYP1A1 mRNA in 16HBE14o- cells, whereas diesel exhaust particles did (Baulig *et al*., 2003b).

In another study that compared the effects of various forms of diesel exhaust and carbon black particles (10 μg/cm^2) on 16HBE cells, the latter weakly induced the release of GM–CSF and activated nuclear factor-κB (Bonvallot *et al*., 2001).

To investigate whether reduced clearance from the lung after exposure to ultrafine particles may be due to impaired phagocytosis by alveolar macrophages, an in-vitro study was conducted with the macrophage cell line J774.2 MΦ. The cells were exposed for 8 hours to fine titanium dioxide (mean diameter, 250 nm; 6.6 m^2/g), ultrafine titanium dioxide (mean diameter, 29 nm; 49.8 m^2/g), carbon black (Huber 990; mean diameter, 260.3 nm; 7.9 m^2/g) or ultrafine carbon black (Printex 90; mean diameter, 14.3 nm; 253.9 m^2/g). The particles had no cytotoxic effects. The ability of the macrophages to phagocytose 2-μm latex beads was significantly reduced ($P < 0.001$) after exposure to 0.39 μg/mm^2 ultrafine carbon black and 0.78 μg/mm^2 of all particle types compared with the control. Furthermore, ultrafine carbon black induced a significant ($P < 0.001$) reduction in macrophage phagocytosis at a lower dose than fine carbon black (0.39 and 0.78 μg/mm^2, respectively). At all doses, exposure to ultrafine carbon black resulted in a

larger number ($P < 0.001$) of non-phagocytic macrophages compared with the other particle types. The culture medium collected after exposure of macrophages to particles had no significant effect on the phagocytic ability of naive macrophages, which suggests that cell-to-cell contact rather than a soluble factor was responsible for the defective phagocytosis. The authors concluded that slowed clearance of particles, especially ultrafine particles, can in part be attributed to a particle-mediated impairment of macrophage phagocytosis (Renwick *et al*., 2001; see also the in-vivo study by Renwick *et al*., 2004, discussed above).

Because ultrafine particles and transition metals have been postulated to be important determinants of the toxicity and potential adverse health effects of particulate air pollution, the interactions between transition metal salts and fine and ultrafine carbon black particles were studied. In all experimental systems used, the ultrafine particles were more reactive than the larger-sized particles. Incubation of ultrafine carbon black (Printex 90; diameter, 14 nm; 253.9 m^2/g) with the reactive oxygen species-sensitive probe dichlorofluorescin diacetate in a cell-free system generated significantly more reactive oxygen species than the larger-sized carbon black particles (Huber 990; 260 nm; 7.9 m^2/g). Addition of cupric sulfate, ferrous sulfate or ferric chloride further increased the generation of reactive oxygen species induced by ultrafine carbon black. In Mono Mac 6 macrophages (a human monocytic cell line), the 14-nm carbon black again produced more reactive oxygen species than the 260-nm particles, but iron salts had no additive effect. Ultrafine carbon black decreased the cellular content of glutathione (GSH) and adenosine triphosphate (ATP) in the murine macrophage cell line J774. Further reductions in GSH and ATP were seen after the addition of iron salts but only at the highest concentration tested (500 μM). A concentration-dependent increase in the production of TNFα was also observed in J774 cells after exposure to ultrafine carbon black, but this effect was not further enhanced by the addition of iron salts even at the highest concentration tested (500 μm). In the rat lung, ultrafine carbon black (125 μg) induced a significant influx of neutrophils in the BAL fluid. This inflammatory effect was enhanced by the addition of ferric chloride (100 μM), which was inactive alone. The authors concluded that ultrafine particles and metal salts interact by chemical potentiation in a cell-free system to generate reactive oxygen species. This potentiation was not observed in the presence of macrophages, probably because the iron is sequestered or chelated by the cells. In the lung, ultrafine particles and iron salts interacted synergistically in generating inflammation (Wilson *et al*., 2002).

The capacity of fine carbon black (Huber 990; diameter, 260 nm; 7.9 m^2/g) to activate serum factors that stimulate the migration of murine alveolar macrophages was compared with that of ultrafine carbon black (Printex 90; diameter, 14 nm; 254 m^2/g). Incubation of fetal bovine serum with 5 and 10 mg/mL ultrafine carbon black caused a 1.4- and 1.8-fold increase, respectively, in migration of macrophages compared with untreated serum. These effects were partially inhibited by further incubation with antioxidants (Trolox or Nacystelin). An equivalent mass of fine carbon black (10 mg/mL) did not show chemotactic activity. On an equal mass basis, ultrafine carbon black particles activated

serum factors, possibly C5a-like proteins, to a greater extent than fine carbon black particles (Barlow *et al*., 2005).

The mouse monocyte/macrophage cell line RAW264.7 was used to determine the adverse effects of exposure *in vitro* to 30 and 120 μg/mL size-fractionated urban air particles (particulate matter (PM) 2.5–10; $PM_{2.5}$) collected in the city of Rome and carbon black (Huber NG90; diameter, 200–250 nm). Urban air particles induced a significant release of arachidonic acid after a 5-hour exposure at both concentrations, while carbon black was effective only at 120 μg/mL. After 5 hours, the 120-μg/mL concentration of the two PM fractions stimulated the production of TNFα about 10-fold more strongly than carbon black particles, but the stimulation diminished after 24 hours. In contrast, carbon black-stimulated TNFα production did not show such a decrease. Production of IL-6 was enhanced by incubation with urban air particles but not with carbon black. Carbon black was consistently less effective than the urban particles (Pozzi *et al*., 2003).

Chin *et al*. (1998) evaluated the role of adsorbed mutagens, such as benzo[*a*]pyrene, on carbon black particles in cellular response and signal transduction. A cultured macrophage cell line (RAW264.7) was exposed to carbon black (N339; diameter, 0.1 μm) and benzo[*a*]pyrene-adsorbed carbon black (2 μg/mL benzo[*a*]pyrene) for up to 24 hours. The benzo[*a*]pyrene-adsorbed carbon induced time-dependent expression and release of TNFα and apoptosis in RAW cells, which were inhibited by a TNFα-neutralizing antibody. Neither carbon black nor benzo[*a*]pyrene alone induced these effects. TNFα activates mitrogen-activated protein kinase (MAPK) activity and the extracellular signal-regulated kinases p42/44 in a time-dependent manner, and treatment of RAW264.7 cells with the MAPK inhibitor PD-098059 inhibited the apoptosis and TNFα secretion induced by benzo[*a*]pyrene-adsorbed carbon black. The results indicated that adsorbed mutagens on carbonaceous particles may play a role in the induction of apoptosis and inflammatory responses, such as the release of cytokines like TNFα.

Ultrafine particles including carbon black (Printex 90, diameter, 12 nm; 300 m^2/g), elemental carbon (diameter, 90 nm; 600 m^2/g) and diesel exhaust particles (diameter, 120 nm; 108 m^2/g; 10–320 μg/mL/10^6 cells) caused a variety of cytoskeletal dysfunctions including impaired phagocytosis (approximately 50% of controls), inhibited cell proliferation and decreased cell viability in primary alveolar macrophages from dogs and a mouse alveolar macrophage cell line (J774A.1) within 24 hours of treatment with a dose of 320 μg/mL/10^6 cells (Möller *et al*., 2002).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 Animals

In a study designed to evaluate the effects of subacute exposure to inhaled benzo[*a*]pyrene (adsorbed on a carbon black carrier) on testicular steroidogenesis and epididymal function in Fischer 344 rats, one of the control groups was exposed to carbon black alone (Elftex 12; 4 hours daily for 10 days). Blood and sperm samples were collected immediately after the last exposure on day 10, and 24, 48 and 72 hours later. There were no differences in progressive sperm motility or serum testosterone concentration in the rats exposed to carbon black only compared with untreated controls. [The study showed that subacute exposure to inhaled benzo[*a*]pyrene adsorbed on carbon black affects testosterone levels and epididymal function] (Inyang *et al*., 2003).

4.4 Genetic and related effects (for details and references, see also Table 4.3)

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems*

Carbon black has been found to be negative in most assays for mutagenicity (IARC, 1996). In rats exposed by inhalation to carbon black for 12 weeks, the hypoxanthine(guanine) phosporibosyltransferase gene *(Hprt)* mutant frequency was elevated in type II cells; however, carbon black did not induce a significant increase in DNA adducts in the peripheral lung tissue of rats after two years of inhalation exposure. In another study, exposure of rats by inhalation to carbon black increased DNA adduct levels in type II cells, while K-*ras* mutations were found in one of 18 neoplasms analysed from carbon black-exposed rats. No exposure-related *p53* mutation was found.

Most in-vitro mutagenicity studies of carbon black have given negative results, including several Ames tests, mouse lymphoma assays and mouse embryo morphological cell transformation assays (IARC, 1996). Carcinogenicity studies in rats *in vivo* have led to the proposal that secondary genotoxicity of carbon black is based on an overloading mechanism that leads to the generation of reactive oxygen species from infiltrated inflammatory cells, the oxidation of DNA bases and DNA strand breaks or lipid peroxidation, the secretion of inflammatory mediators that have been independently implicated in secondary genotoxic and proliferating events that lead to tumour formation from poorly soluble dust (Driscoll *et al*., 1997; Gallagher *et al*., 2003; Gilmour *et al*., 2004; Elder *et al*., 2005). The release of inflammatory mediators or factors, such as leukotrienes, reactive oxygen species, cytokines (TNFα, IL-1, IL-8), fibronectin and transforming growth factor β, is already known to be involved in the damage of local tissue and remodelling (Borm & Driscoll, 1996). The overloading that leads to the secondary genotoxic mechanism, which involves persistent lung inflammation and injury, is dependent on the species of animal, surface coating and composition, as seen with diesel

Table 4.3. Genetic and related effects of carbon blacks or their formulations

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DNA strand breaks, isolated ΦX174 replicative form supercoiled plasmid *in vitro*	+[c]	NT	20	Dick *et al*. (2003)
Salmonella typhimurium TA100, TA1535, TA1537, TA1538, TA98, reverse mutation	–[d]	–[d]	3750	Kirwin *et al.* (1981)
Salmonella typhimurium TA100, TA98, reverse mutation	+[e]	+[e]	NR	Agurell & Löfroth (1983)
Salmonella typhimurium TA100, reverse mutation	–[f]	–[f]	50 mg/plate	Venier *et al.* (1987)
Salmonella typhimurium TA98, reverse mutation	–[g]	NT	250	Rosenkranz *et al.* (1980)
Salmonella typhimurium TA98, reverse mutation	(+)[h]	NT	500	Rosenkranz *et al.* (1980)
Salmonella typhimurium TA98, reverse mutation	+[i]	NT	5.0	Rosenkranz *et al.* (1980)
Salmonella typhimurium TA98, reverse mutation	(+)[f]	+[f]	5.0 mg/plate	Venier *et al.* (1987)
Salmonella typhimurium nitroreductase deficient strains TA98NR, TA98/1,8DNP, reverse mutation	+[e]	NT	NR	Agurell & Löfroth (1983)
Drosophila melanogaster, somatic mutation (mosaics), sex-linked recessive mutation, dominant lethal test, aneuploidy (sex-chromosome loss)	–[d]		10 000 larval feeding	Kirwin *et al.* (1981)
DNA strand breaks, Comet assay, Chinese hamster V79 cells *in vitro*	–[k]		137.9 μg/cm^2, 3 h	Zhong *et al*. (1997)
Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–[d]	–[d]	40 000	Kirwin *et al.* (1981)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–[d]	–[d]	1000	Kirwin *et al.* (1981)
Micronucleus formation, M3E3/C3 hamster epithelial cells *in vitro*	+[l]	NT	1	Riebe-Imre *et al.* (1994)
Anchorage independent growth, M3E3/C3 hamster lung epithelial cells *in vitro* (undifferentiated and differentiated small mucus granule cell stage)	+[l]	NT	100	Riebe-Imre *et al.* (1994)
Cell transformation, C3H/10T½ mouse fibroblasts *in vitro*	–[d]	NT	16 000	Kirwin *et al.* (1981)

Table 4.3 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DNA adduct formation, ^{32}P-postlabelling (PAH–DNA adducts), A549 human lung epithelial cells *in vitro*	–[m]		100 μg/cm^2	Borm *et al*. (2005)
DNA strand breaks, Comet assay, human A549 and monocytic THP-1 cells *in vitro*	?[j]		1.6	Don Porto Carero *et al*. (2001)
DNA strand breaks, Comet assay, human embryonic lung HEL 299 cells in vitro	–[k]		137.9 μg/cm^2, 3 h	Zhong *et al*. (1997)
DNA adduct formation, ^{32}P-postlabelling, (PAH–DNA adduct) Fischer 344 rats *in vivo*	–[m]		50 mg/m^3, inh, 13 wks	Borm *et al*. (2005)
DNA adduct formation, ^{32}P-postlabelling in female Wistar rat lung *in vivo*	–[n]		11.3 mg/m^3, inh, 18 h/d × 5 d/wk × 2 yr,	Gallagher *et al*. (1994)
DNA adduct formation, (8-oxo-dG), Fischer 334 rat lung *in vivo*	+[o]		50 mg/m^3, 6 h/d × 5 d/wk × 13 wk; 7 mg/m^3, 44 wk recovery	Gallagher *et al*. (2003)
Tp53, K-*Ras* mutation in pulmonary carcinomas in Fischer 344/N rats *in vivo*	–[p]		6.5 mg/m^3, 16 h/d × 5 d/wk × 24 mo	Swafford *et al.* (1995); Belinsky et al. (1997)
Gene mutation, *Hprt* locus, type II alveolar cells isolated from rats treated *in vivo*	+[q]		7.1 mg/m^3, inh, 6 h/d × 5 d/wk × 13 wk	Driscoll *et al.* (1996)

Table 4.3 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Gene mutation, *Hprt* locus, rat alveolar epithelial RLE-6TN cells exposed to BAL fluid from rats exposed *in vivo*	+[r]		100 mg/kg bw, it, 15 mo after	Driscoll *et al*. (1997)
Binding to DNA (DNA adduct) (^{32}P-postlabelling) in Fischer 344/N rat alveolar type II cells *in vivo*	+[p]		6.2 mg/m^3, inh, 16 h/d × 5 d/wk × 12 wk	Bond *et al*. (1990)

[a] +, positive; (+), weak positive; –, negative; ? inconclusive;
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw; d, day; inh, inhalation; it, intratracheal; mo, month;NR, not reported; NT, not tested; wk, week; yr, year; 8-oxo-dG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; 1,8 DNP, 1,8 dinitropyrene
[c] Ultrafine carbon black; diameter, 14 nm; surface area, 253.9/m^2/g
[d] Rubber-grade furnace black N339; surface area, 100 m^2/g; 48-h toluene extractables 0.15%; particles suspended in dimethyl sulfoxide (DMSO) (Ames test + sister chromatid exchange assay), acetone (cell transformation test) or culture media (mouse lymphoma test)
[e] Carbon blacks from various manufacturers (20 samples); Soxhlet extraction of 1-g samples with 200 mL benzene for 16 h and solvent exchange into DMSO
[f] Carbon black used for refining tanned skins (7 samples); (a) sonication of 2 g samples in 40 mL benzene for 0.5 h; (b) Soxhlet extraction of 4-g samples with 50 mL toluene for 48 h; solvent exchange into DMSO (1 g extract/mL)
[g] Black Pearls L (furnace black, manufacture of which involves a nitration-oxidation step); suspension in DMSO at 5 mg/mL for 5 h before testing
[h] Raven 5750 (furnace black, oxidative after-treated); soxhlet extraction of 10-g samples with toluene for 48 h; low-temperature concentration and solvent exchange into 1 mL DMSO
[i] Black Pearls L (furnace black, manufacture of which involves a nitration-oxidation step); Soxhlet extraction of 10 g samples with toluene for 48 h; low-temperature concentration and solvent exchange into 1 mL DMSO
[j] Vulcan M, furnace black, carbon black mean diameter, 100 nm, 8 mg/5 mL of RPMI medium
[k] Cabot NJ, 37 nm, 8 mg/mL MEM
[l] Carbon black [not otherwise characterised]; carbon black suspended in the culture medium containing undifferentiated cells for 72 h
[m] Printex-90, 300 m^2/g, Sterling V, 30–40 m^2/g; N330, 70–90 m^2/g; Lampblack 101, 20 m^2/g; suspended in Hank's balanced salt solution *in vitro*, whole-body exposure *in vivo*
[n] Printex-90 (furnace black); MMAD, 0.65 m; surface area, 270 m^2/g; carbon black in air at 2 yr mean of 11.3 mg/m^3; whole-body exposure
[o] Printex-90, 16 nm, surface area 300 m^2/g; whole-body exposure
[p] Elftex-12 (furnace black); 2 μm MMAD (large mode); 0.1 μm MMDD (small mode); surface area, 43 m^2/g; whole-body exposure
[q] Monarch 880; 16 nm; surface area, 220 m^2/g; MMAD 880 nm; whole-body exposure
[r] Monarch 900; 15 nm; surface area, 230 m^2/g, intratracheal instilltion

exhaust particles and carbon black (a surrogate for carbonaceous particles), particle size and shape, and surface area (Schins, 2002; Gallagher *et al*., 2003; Gilmour *et al*., 2004).

Male Fischer rats were exposed for 6 hours per day on 5 days per week for up to 13 weeks to 1.1, 7.1 and 52.8 mg/m^3 carbon black (Monarch 880; diameter, 16 nm; surface area, 220 m^2/g). Mutagenesis in alveolar epithelial cells was assessed after 6.5 and 13 weeks of exposure and after 3 and 8 months of recovery. *Hprt* mutation frequency was significantly increased in alveolar epithelial cells after 13 weeks of exposure to 7.1 and 52.8 mg/m^3 carbon black and after 3 and 8 months of recovery in high-dose rats. No increase in *Hprt* mutation frequency was seen in the low-dose group. The induction of mutation in alveolar epithelial cells occurred after carbon black exposures that resulted in significant inflammation and epithelial hyperplasia (see Section 4.2.2) (Driscoll *et al*., 1996).

Driscoll *et al*. (1997) investigated lung adenomas and carcinomas in female Fischer rats exposed by intratracheal instillation to poorly soluble particles (10 or 100 mg/kg bw α-quartz or carbon black; Monarch 900; diameter, 15 nm; surface area, 230 m^2/g) and the relationship between exposure to particles, inflammation and mutagenesis in alveolar type II cells. After 15 months of exposure, BAL cells were examined histopathologically. Neutrophilic inflammation was detected in the rats exposed to 10 and 100 mg/kg bw carbon black and epithelial hyperplasia was observed in the rats exposed to 100 mg/kg bw carbon black. The frequency of *Hprt* mutations was higher in alveolar epithelial type II cells of rats exposed to 100 mg/kg bw carbon black. In-vitro exposure of rat lung epithelial RLE-6TN cells to BAL cells from rats treated with 100 mg/kg bw carbon black or with 10 or 100 mg/kg bw α-quartz also increased the frequency of *Hprt* mutants, but addition of catalase to BAL cell:RLE-6TN co-cultures inhibited this increase (the effect of catalase was tested only with BAL cells from rats treated with α-quartz). The authors concluded that inhibition of the BAL cell-induced mutations by catalase implies that cell-derived oxidants play a role in this response, whereas the ability of particle-elicited macrophages and neutrophils to exert a mutagenic effect on epithelial cells *in vitro* supports a potential role for these inflammatory cells in the mutagenic effects of particle exposure *in vivo*.

Gallagher *et al*. (2003) tested the hypothesis that chronic inflammation and cell proliferation play a role in the development of tumours after long-term high-dose particle contact with lung epithelial cells. Female Fischer 344 rats were exposed to 1, 7 and 50 mg/m^3 Printex 90 carbon black (diameter, 16 nm; surface area, 300 m^2/g) and 50 mg/m^3 Sterling V carbon black (diameter, 70 nm; surface area, 37 m^2/g) for 6 hours per day on 5 days per week for 13 weeks. A significant increase in the induction 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG) was observed in the lung following the 13-week exposure to 50 mg/m^3 Printex 90 and a 44-week recovery period. However, no increase in 8-oxo-dG was observed with Sterling V carbon black after 13 weeks of exposure or during the 44-week recovery period. Since neither Sterling V (50 mg/m^3) nor Printex 90 (7 mg/m^3) induced a significant increase in 8-oxo-dG in the lung at the end of the 13-week exposure, the retained large particle mass was not correlated with adverse

effects, whereas the particle surface area was a better dose parameter for the induction of 8-oxo-dG. The authors suggested that prolonged high-dose exposure to carbon black can promote oxidative DNA damage, which is consistent with the hypothesis that inflammatory cell-derived oxidants may play a role in the pathogenesis of rat lung tumours following long-term high-dose exposure to carbon black.

Carbon black did not induce a significant increase in DNA adducts (detected as a diagonal radioactive zone to identify nitrated amine or arylamine adducts) in the peripheral lung tissue of rats after 2 years (Gallagher *et al*., 1994) or 12–13 weeks of inhalation exposure (Bond *et al*., 1990; Borm *et al*., 2005). In other inhalation studies, rats exposed to carbon black for 3 months had a significant but not dose-related increase in DNA adducts in alveolar epithelial cells (Mauderly *et al*., 1994). K-*ras* and *Tp53* mutations, which are markers of the early stages of squamous-cell carcinoma in humans, may not be related to exposure to carbon black (Swafford *et al*., 1995; Belinsky *et al*., 1997).

Carbon black that is used as a surrogate for diesel exhaust particle carbon core includes significant amounts of adsorbed organic materials that have been identified as mutagenic. Carbon black and diesel exhaust particles have already been tested in various experimental systems to compare the contribution of the chemicals adsorbed onto carbon black to mutagenesis and immunomodulation. Absorbed chemicals, such as PAHs, are very tightly bound to carbon black; however, PAHs are released from organic extracts of low-surface area particles with a high PAH content (Borm *et al*., 2005). The contrasting cellular response to exposure to diesel exhaust particles and carbon black may be due to the presence of adsorbed organic components in the former. Exposure of rats to carbon black increases TNFα production of the alveolar macrophages, while exposure to diesel exhaust particles does not, which indicates that adsorbed organic compounds, including PAHs, play a role in host susceptibility to pulmonary infection (Yang *et al*., 1999).

Additional genotoxicity assays, including a Comet assay (single-cell gel electrophoresis), gave negative results for carbon black in human embryonic lung Hel 299 fibroblasts and Chinese hamster V79 cells and positive results in T-cell THP-1 and human lung A541 cells but only at a high dose (1600 ng/mL) (Zhong *et al*., 1997; Don Porto Carero *et al*., 2001). DNA adducts were observed only for one of four carbon black samples in lung epithelial cells *in vitro* (Borm *et al*., 2005).

Timblin *et al*. (2002) studied proto-oncogene expression, proliferation and apoptosis in murine alveolar epithelial cells after exposure to ultrafine carbon black (Monarch 880) at a concentration of 10 $\mu g/cm^2$ for 24 and 48 hours. A significant increase in the number of cells in the S phase of the cell cycle was observed, which suggested early injury and subsequent unscheduled DNA synthesis that may represent compensatory cell proliferation. After 24 and 48 hours, a significant decrease in the percentage of cells in the G_2/M and an elevation of that in the subG_0/G_1 followed by a decrease in the number of cells in the G_0/G_1 were observed, which indicated apoptosis. Ribonuclease protection assays demonstrated that cells exposed to ultrafine carbon black for 8 hours had increased mRNA levels of proto-oncogenes *fos* and *jun* and apoptosis associated genes *fas* and

caspase 8. In contrast, cells exposed to the fine carbon black (Monarch 120) had a significant increase in only *fra*-1 mRNA levels, demonstrating that ultrafine carbon black stimulated changes in the expression of genes linked to both proliferative and apoptic pathways.

The effects of fine and ultrafine carbon black on rat BAL macrophages and human blood monocytes were investigated with regard to the roles of calcium and reactive oxygen species. Ultrafine carbon black (Printex 90; mean diameter, 14 nm) but not fine carbon black (Huber 900; mean diameter, 260 nm) was found to increase the resting cytosolic Ca^{2+} concentration in these cells when tested at equal mass (200 μg/mL). The calcium channel blocker, verapamil, reduced intracellular calcium concentration and activation of transcription factor AP-1 in rat alveolar macrophages after stimulation with ultrafine carbon black. A calcium antagonist and an antioxidant (Trolox and Nacystelin) also reduced ultrafine carbon black-stimulated NF-κB activation in human monocytes, as well as ultrafine carbon black-stimulated TNFα protein release in rat alveolar macrophages and human monocytes. The authors suggested that ultrafine particles may exert pro-inflammatory effects by modulating intracellular calcium concentrations, activation of transcription factors and cytokine production through a reactive oxygen species-mediated mechanism (Brown *et al*., 2004).

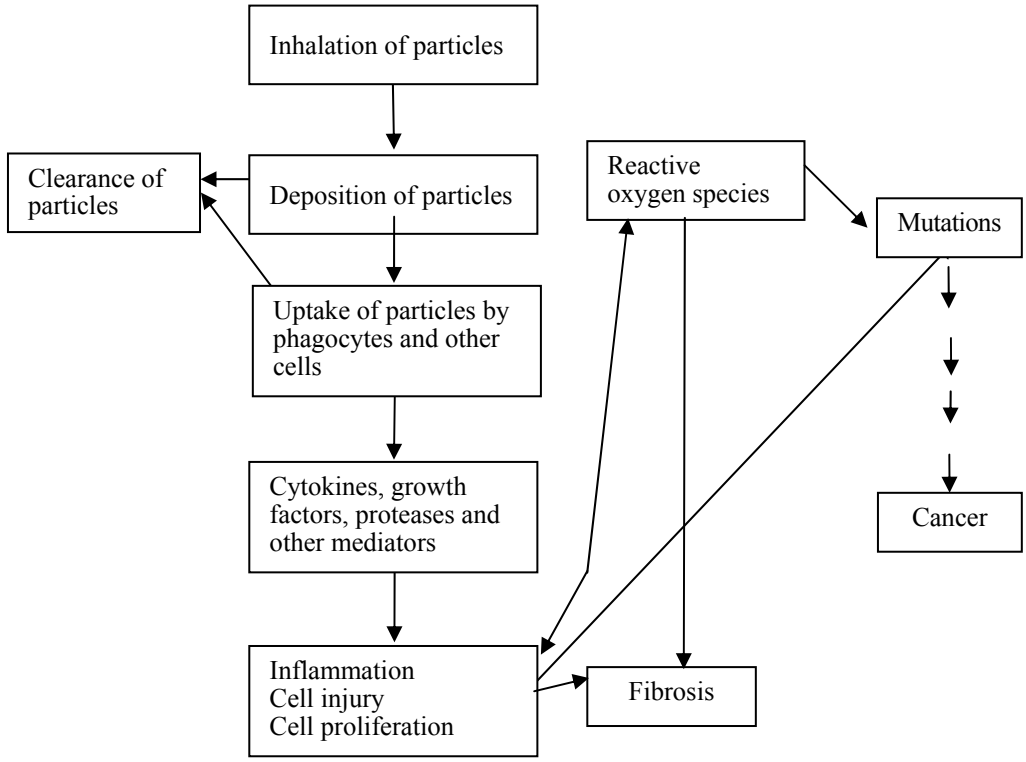
To study the effects of ultrafine particles on airway epithelial cell proliferation, normal human bronchial epithelial cells were exposed to 6.1–30.7 μg/cm^2 ultrafine (diameter, 11.2 nm; 457 m^2/g) and fine (diameter, 250 nm; 7.8 m^2/g) carbon black. Ultrafine carbon black elicited proliferation in a time- and dose-dependent manner and activated the extracellular signal-regulated kinase signalling pathway in an antioxidant- and epidermal growth factor receptor-dependent manner. Accordingly, the authors suggested that ultrafine carbon black causes oxidative stress-mediated proliferation of airway epithelium (Tamaoki *et al*., 2004).

4.5 Comparison of toxicokinetics and toxicodynamics of inhaled poorly soluble particles in animals and humans

Several studies have shown that rats, but not mice or hamsters, develop excess incidences of lung cancer after chronic inhalation of 'overloading' doses of poorly soluble particles. Several studies have discussed this phenomenon and the challenges it poses for the extrapolation of chronic effects in rats to the human situation (Morrow, 1994; Levy, 1995; Oberdörster, 1995; Watson & Valberg, 1996; ILSI Risk Science Institute Workshop Participants, 2000; Miller, 2000; Oberdörster *et al*., 2002; Rausch *et al*., 2004; Hext *et al*., 2005).

To evaluate the appropriateness of the rat as an experimental model to assess the carcinogenic hazard of poorly soluble particles in the lungs of humans, it is necessary to assess the scientific evidence that allows for comparisons among species of exposure, dose, response and mode of action. A conceptual framework is presented in Fig. 4.2.

Figure 4.2. Conceptual framework of carcinogenesis induced by poorly soluble particles in rats



The scheme represents the sequence of events and modes of action that are considered to be involved in the formation of tumours that are observed in the lungs of rats after high exposure to poorly soluble particles (see text for further details)

4.5.1 *Exposure–dose relationship*

Inhaled particles may present a hazard when they are deposited in sufficient quantities (dose) and interact with cells or tissues at responsive target sites along the respiratory tract. The relationship between exposure to particles and inhaled dose is described by the kinetics of particle deposition and clearance, and may be influenced by the retained particle dose (see Section 4.1.1.*c*). The kinetic differences in exposure–dose relationships of inhaled particles in humans and rats, including the kinetics of overloading, can be described quantitatively using lung dosimetry models (see Section 4.1.3). Inhaled and deposited particles are cleared from the normal lungs of healthy rats more rapidly than from those of humans. However, at high lung burdens, normal clearance from the rat lung can be impaired and the lung can be inundated to such a degree that, in time, clearance

effectively ceases. This phenomenon (which is termed 'overload') is observed with poorly soluble particles that are generally considered to have low toxicity (Morrow, 1988). Overload was originally described in terms of the particle dose as either a mass or volume (to take into account differences in particle density). However, ultrafine particles have been observed to cause impaired clearance at much lower mass doses than fine particles (Lee *et al*., 1985a; Heinrich *et al*., 1995; Bermudez *et al*., 2002, 2004). Dose of particle surface area was shown to be a better predictor of key indicators of rat lung overload (i.e. increased particle retention and neutrophilic inflammation) in a study that used two fine particles with different specific surface areas (titanium dioxide and barium sulfate) and compared these results with those of ultrafine titanium dioxide from another study (Oberdörster *et al*., 1994a; Tran *et al*., 2000).

Much more is known about overload in rats than in humans. Inundated or impaired alveolar macrophage-mediated clearance in rats has been postulated as a pivotal factor in the development of lung overload (Morrow, 1988). The same factors that interfere with clearance in rats may contribute to accumulation of particle mass dose in humans. Although no kinetic data are available to determine whether overload occurs in humans by processes similar to those described in rats, reduced lung clearance and retained mass lung burdens comparable with those that cause overloading in rats have been observed in coal miners (Freedman & Robinson, 1988; Freedman *et al*., 1988). Historically, the average lung burdens of particle mass in coal miners (approximately 14 g per whole lung) (Stöber *et al*., 1965; Kuempel, 2000; Tran & Buchanan, 2000) have exceeded the doses associated with overload and substantial impairment of clearance in rats (≈10 mg/lung) (Muhle *et al*., 1990a).

At sufficient concentrations and durations of exposure to inhaled fine particles, rats may accumulate greater masses of particles than the lung burdens seen in most workers. Conversely, for ultrafine particles, the retained mass doses associated with impaired clearance in rodents are similar to lung burdens that could occur in workers. For any experimental model that is used for hazard assessment in humans or to evaluate dose–response relationships, it is important to evaluate doses in experimental animals that are comparable with those that may occur in humans.

Lung clearance can also become impaired in humans and experimental animals for reasons other than overload (Morrow, 1988). For example, in humans, toxic gases and particles have been shown to impair clearance by affecting normal cilia function, mucous rehology and phagocytosis. Ultrafine particles may be cleared less effectively than larger-sized particles due to impaired phagocytosis (Renwick *et al*., 2001, 2004; Geiser *et al*., 2005).

Impaired clearance and overload are not unique to rats, but can also occur in other species although to different degrees (Bermudez *et al*., 2002, 2004; Elder *et al*., 2005). In contrast, overload has not been observed in hamsters at concentrations at which it readily appears in rats and mice, and clearance in hamsters seems to be affected to a lesser degree or recovers quickly. How human lung clearance would behave under similar circumstances is unclear but, by analogy to coal workers, chronic impairment of clearance

occurs and often persists long after exposure ceases (Freedman & Robinson, 1988; Freedman *et al*., 1988).

Rats chronically exposed to sufficiently high concentrations of poorly soluble particles experience a steady reduction in alveolar clearance rates and an accumulation of intralumenal and interstitial particles (Ferin *et al*., 1992; Oberdörster *et al*., 1994a,b; Warheit *et al*., 1997; Bermudez *et al*., 2002, 2004). In rodents, ultrafine particles translocate to the interstitium to a greater extent than fine particles (Ferin *et al*., 1992; Oberdörster *et al*., 1992, 1996; Geiser *et al*., 2005). In studies that compared the pattern of particle retention in the lungs of rats, monkeys and humans exposed to coal dust and/or diesel exhaust, a higher volume percentage of dust was observed in the alveolar lumen of rats than in the interstitium of monkeys and humans (Nikula *et al*. 1997a,b, 2001); however, no data were available to compare the actual retained doses in the specific lung regions of each species. The biological significance of the interstitial/lumenal distribution in the development of overload and the consequent toxic sequel is not clear, either within a given species or among species.

4.5.2 *Dose–response relationships*

With continued inhalation of sufficiently high concentrations of particles, rats that achieve overload may develop pulmonary fibrosis and lung tumours (Lee *et al*., 1985a,b, 1986; Warheit *et al*., 1997). Oberdörster (1996, 2002) proposed that the effects of high doses observed in rats may be associated with two thresholds: (1) a pulmonary dose that results in reduced macrophage-mediated clearance which leads to shut-down and overload and (2) a higher dose associated with overload at which normal antioxidant defences within the lung are overwhelmed and pulmonary tumours may initiate and develop.

In contrast to fine particles, much lower concentrations of ultrafine particles (e.g. 2.5, 6.5 or 11.5 mg/m^3 carbon black and ~10 mg/m^3 ultrafine titanium dioxide) were associated with impaired clearance, persistent inflammation and malignant lung tumours in chronic inhalation studies in rats (Heinrich *et al*., 1995; Nikula *et al*., 1995).

(a) Mechanistic considerations (overall mode of action)

A cascade of events that was proposed to describe the biological process that starts with some particle deposition at critical target cells or tissues within the rat lung and results in rat lung tumours includes: sustained inflammation, production of reactive oxygen species, depletion of antioxidants and/or impairment of other defence mechanisms, cell proliferation and gene mutations. These individual steps comprise an overall mode of action that can be used to compare responses of rats with those of other species including humans (see Fig. 4.2). The dose metric that best describes the dose–response relationship for poorly soluble particles in the rat lung has been examined in various studies (Driscoll *et al*., 1996; Pott & Roller, 2005; Morfeld *et al*., 2006). The

surface area, volume and size of particles have all been shown to be related to the tumour response in rats.

At particle lung burdens that are associated with impaired clearance in rats (e.g. beginning at a mass dose of ~0.5 mg/lung and completely overloaded at ~10 mg/lung for fine particles of unit density; Muhle *et al*., 1990a), a sustained and widespread cellular inflammatory response occurs. The cell population is dominated by activated and probably (under these conditions) persistent polymorphonuclear neutrophils and secretes a collection of mediators (reactive oxygen species, pro-/anti-inflammatory cytokines, proteases, cytotoxins, fibrogenic and other growth factors) that act through the pulmonary milieu on surrounding cells or tissues and surrounding structures (Castranova, 1998, 2000; Knaapen *et al*., 2004). The degree of sustained inflammation experienced by rodents (most notably rats) at high lung burdens has not been observed in humans. However, humans may experience sustained inflammation in certain disease states. One such human condition (which may be particle-stimulated—e.g. by silica—or may be cytogenic) is late-stage, interstitial pulmonary fibrosis (Daniels & Jett, 2005). Patients with interstitial pulmonary fibrosis and chronic inflammation have been reported to develop a higher incidence of lung tumours, frequently in the most inflamed areas. In addition, chronic inflammation has been associated with non-neoplastic lung diseases in workers with dusty jobs. Rom (1991) found a statistically significant increase in the percentage of polymorphonuclear neutrophils in the BAL fluid of workers with respiratory impairment who had been exposed to asbestos, coal, or silica (4.5% in cases versus 1.5% in controls). Elevated levels of polymorphonuclear neutrophils have been observed in the BAL fluid of miners with simple coal workers' pneumoconiosis (31% of total BAL cells versus 3% in controls) (Vallyathan *et al*., 2000) and in patients with acute silicosis (a 10-fold increase over controls) (Goodman *et al*., 1992; Lapp & Castranova 1993). An elevated incidence of lung cancer has been observed in some workers exposed to poorly soluble particles including crystalline silica (Rice *et al*., 2001; Attfield & Costello, 2004) and diesel exhaust particles (Stayner *et al*., 1998), although these materials may have greater inherent toxicity than other poorly soluble particles such as titanium dioxide, carbon black and talc.

The precise role of chronic inflammation in the development of cancer is uncertain, but there is considerable evidence that chronic inflammation may have a multifaceted role in this process. Activated cells in the lung are known to release various reactive intermediates, most notably those derived from oxygen. Sustained excess of oxidant activity is known to deplete antioxidant defences gradually. These defence mechanisms in the lungs of humans and rats clearly differ, in that humans are overall relatively deficient in some of them (Slade *et al*., 1985). Reactive oxygen species within cells may damage DNA directly and potentially induce mutations. Moreover, cell damage and promitotic stimuli initiated by reactive oxygen species promote cell turnover and proliferation, events that may enhance the risk for DNA replication error and/or expand a mutated or transformed cell to initiate a tumour.

The mechanism that involves inflammation and oxidative stress which lead to tumour formation is considered to be a secondary genotoxic mechanism, in contrast to a primary genotoxic mechanism in which the agent interacts directly with DNA (Knaapen *et al*., 2004).

(b) Interspecies extrapolation

There remains uncertainty with regard to identifying in detail the cascade of events that lead to rat lung cancer following inhalation of poorly soluble particles that include talc, carbon black and titanium dioxide. However, as shown in Fig. 4.2, several important steps can be identified that are supported by a substantial rodent database. An important question that needs to be addressed is the extent to which the steps outlined in Fig. 4.2 for rat lung cancer are also operative in other animal species including humans. The majority of animal studies that have evaluated the effects of poorly soluble particles on the respiratory tract have been conducted in rats; species differences such as particle inhalability, breathing conditions, respiratory tract structure and pulmonary defences need to be considered when toxicological findings from rodents are extrapolated to humans (Brown *et al*., 2005). Exposure to airborne particles would generally need to be higher in rats to result in equivalent particle doses in the human lung (Brown *et al*., 2005).

All animals species used routinely in particle toxicology and humans are susceptible to impairment of clearance of poorly soluble particles from the lungs. Impaired clearance is probably one of the first steps necessary to initiate a sequence of events that may lead to lung cancer in rats exposed to poorly soluble particles (see Fig. 4.2). However, different animal species exhibit differences in particle-induced impairment of clearance, which can result in different lung burdens (expressed as mass or surface area) following exposures to the same particle concentrations (Elder *et al*., 2005).

Similarly, pulmonary inflammation has been reported to be a consequence of exposures to poorly soluble particles in both experimental animals and humans (Driscoll *et al*., 1996; Elder *et al*., 2005; Shwe *et al*., 2005; Rom, 1991; Vallyathan *et al*., 2000). The pathophysiology of particle-induced fibrosis in humans and fibrosis and lung cancer in rats from lung overload—with lung burden being expressed as mass, volume and/or surface area for fine and ultrafine particles—involves chronic inflammation, hyperplasia and cell proliferation, altered collagen deposition and architecture.

Rats and mice, in contrast to hamsters, exhibit sustained inflammation associated with particle lung burden, but lung tumours induced by poorly soluble particles have only been observed in rats. It has been shown that rats are uniquely susceptible to poorly soluble particle-induced lung cancer relative to mice and hamsters. While some of the steps indicated in Fig. 4.2 have been demonstrated in humans exposed to poorly soluble particles, it is not known to what extent humans are susceptible to particle-induced lung cancers associated with titanium dioxide, carbon black or talc.

4.5.3 *Alternative mechanisms*

Studies of poorly soluble particles in rodents provide evidence to support the hypothesis that one mode of action involves chronic inflammation, epithelial proliferation and the generation of reactive oxygen species that lead to mutagenic event(s) proximate to cancer. Alternative mechanisms to these could be involved, although the data to support them are limited. For example, it has been shown that particles such as carbon black, titanium dioxide and talc can translocate, once deposited on the lung surface, into the lung epithelial cells which are considered to be progenitor cells for some types of tumour that are associated with the inhalation of poorly soluble particles. Poorly soluble particles may interfere with the cytoskeleton during cell division, which may lead to aneuploidy and elicit genotoxicity.

4.6 References

ACGIH®worldwide (2005). *TLVs® and BEIs® Based on Documentation of the Threshold Limit Value for Chemical Substances and Physical Agents and Biological Indices*, Cincinnati, OH, American Conference of Governmental Industrial Hygienists, Appendix C, pp. 74–77.

Adamson IYR, Hedgecock C (1995). Patterns of particle deposition and retention after instillation to mouse lung during acute injury and fibrotic repair. *Exp Lung Res*, 21:695–709. doi:10.3109/01902149509050837. PMID:8556989

Adamson IYR, Prieditis HL (1995). Response of mouse lung to carbon deposition during injury and repair. *Environ Health Perspect*, 103:72–76. doi:10.2307/3432259. PMID:7543046

Agurell E, Löfroth G (1983). Presence of various types of mutagenic impurities in carbon black detected by the Salmonella microsome assay. In: Waters MD, ed, *Short-term Bioassays in the Analysis of Complex Environmental Mixtures, III*, New York, Plenum Press, pp. 297–306.

Al-Humadi NH, Siegel PD, Lewis DM *et al.* (2002). The effect of diesel exhaust particles (DEP) and carbon black (CB) on thiol changes in pulmonary ovalbumin allergic sensitized Brown Norway rats. *Exp Lung Res*, 28:333–349. doi:10.1080/01902140290091976. PMID:12097228

Attfield MD, Costello J (2004). Quantitative exposure–response for silica dust and lung cancer in Vermont granite workers. *Am J Ind Med*, 45:129–138. doi:10.1002/ajim.10348. PMID:14748044

Bailey MR, Fry FA, James AC (1985). Long-term retention of particles in the human respiratory tract. *J Aerosol Sci*, 46:295–305. doi:10.1016/0021-8502(85)90037-0.

Barlow PG, Donaldson K, MacCallum J *et al.* (2005). Serum exposed to nanoparticle carbon black displays increased potential to induce macrophage migration. *Toxicol Lett*, 155:397–401. doi:10.1016/j.toxlet.2004.11.006. PMID:15649623

Baulig A, Sourdeval M, Meyer M *et al.* (2003a). Biological effects of atmospheric particles on human bronchial epithelial cells. Comparison with diesel exhaust particles. *Toxicol In Vitro*, 17:567–573. doi:10.1016/S0887-2333(03)00115-2. PMID:14599446

Baulig A, Garlatti M, Bonvallot V *et al.* (2003b). Involvement of reactive oxygen species in the metabolic pathways triggered by diesel exhaust particles in human airway epithelial cells. *Am J Physiol Lung Cell Mol Physiol*, 285:L671–L679. PMID:12730081

Beck B, Gohlke R, Sturm W *et al.* (1985). [Carbon black lung as an occupational disease.]. *Z Erkrank Atm Org*, 164:254–266 (in German).

Belinsky SA, Swafford DS, Finch GL *et al.* (1997). Alterations in the K-ras and p53 genes in rat lung tumors. *Environ Health Perspect*, 105 Suppl 4;901–906. doi:10.2307/3433301. PMID:9255578

Bellmann B, Muhle H, Creutzenberg O *et al.* (1989). Reversibility of clearance impairment after subchronic test toner inhalation. *Exp Pathol*, 37:234–238. PMID:2637160

Bellmann B, Muhle H, Creutzenberg O *et al.* (1991). Lung clearance and retention of toner, utilizing a tracer technique, during chronic inhalation exposure in rats. *Fundam Appl Toxicol*, 17:300–313. doi:10.1016/0272-0590(91)90220-X. PMID:1662649

Bellmann B, Muhle H, Creutzenberg O, Mermelstein R (1992). Irreversible pulmonary changes induced in rat lung by dust overload. *Environ Health Perspect*, 97:189–191. doi:10.2307/3431352. PMID:1396457

Bennett WD, Brown JS (2005). Particle dosimetry in the respiratory tract. In: Foster WM & Costa DL, eds, *Air Pollutants in the Respiratory Tract*, 2nd Ed, New York, Marcel Dekker, pp. 21–73.

Bermudez E, Mangum JB, Asgharian B *et al.* (2002). Long-term pulmonary responses of three laboratory rodent species to subchronic inhalation of pigmentary titanium dioxide particles. *Toxicol Sci*, 70:86–97. doi:10.1093/toxsci/70.1.86. PMID:12388838

Bermudez E, Mangum JB, Wong BA *et al.* (2004). Pulmonary responses of mice, rats, and hamsters to subchronic inhalation of ultrafine titanium dioxide particles. *Toxicol Sci*, 77:347–357. doi:10.1093/toxsci/kfh019. PMID:14600271

Bodian D, Howe HA (1941). The rate of progression of poliomyelitis virus in nerves. *Bull Johns Hopkins Hosp*, 69:79–85.

Boland S, Baeza-Squiban A, Fournier T *et al.* (1999). Diesel exhaust particles are taken up by human airway epithelial cells in vitro and alter cytokine production. *Am J Physiol*, 276:L604–L613. PMID:10198358

Bond JA, Johnson NF, Snipes MB, Mauderly JL (1990). DNA adduct formation in rat alveolar type II cells: cells potentially at risk for inhaled diesel exhaust. *Environ Mol Mutag*, 16:64–69. doi:10.1002/em.2850160203. PMID:2209565

Bonvallot V, Baeza-Squiban A, Baulig A *et al.* (2001). Organic compounds from diesel exhaust particles elicit a proinflammatory response in human airway epithelial cells and induce cytochrome P450 1A1 expression. *Am J Respir Cell Mol Biol*, 25:515–521. PMID:11694458

Borm PJ, Driscoll K (1996). Particles, inflammation and respiratory tract carcinogenesis. *Toxicol Lett*, 88:109–113. doi:10.1016/0378-4274(96)03725-3. PMID:8920724

Borm PJA, Cakmak G, Jermann E *et al.* (2005). Formation of PAH–DNA adducts after in vivo and vitro exposure of rats and lung cells to different commercial carbon blacks. *Toxicol Appl Pharmacol*, 205:157–167. doi:10.1016/j.taap.2004.10.020. PMID:15893543

Bowden DH, Adamson IYR (1984). Pathways of cellular efflux and particulate clearance after carbon instillation to the lung. *J Pathol*, 143:117–125. doi:10.1002/path.1711430206. PMID:6737118

Brown JS, Zeman KL, Bennett WD (2002). Ultrafine particle deposition and clearance in the healthy and obstructed lung. *Am J Respir Crit Care Med*, 166:1240–1247. doi:10.1164/rccm.200205-399OC. PMID:12403694

Brown DM, Donaldson K, Borm PJ *et al.* (2004). Calcium and ROS-mediated activation of transcription factors and TNF-alpha cytokine gene expression in macrophages exposed to ultrafine particles. *Am J Physiol Lung Cell Mol Physiol*, 286:L344–L353. doi:10.1152/ajplung.00139.2003. PMID:14555462

Brown JS, Wilson WE, Grant LD (2005). Dosimetric comparisons of particle deposition and retention in rats and humans. *Inhal Toxicol*, 17:355–385. doi:10.1080/08958370590929475. PMID:16020034

Buddingh F, Bailey MJ, Wells B, Haesemeyer J (1981). Physiological significance of benzo(alpha)pyrene adsorbed to carbon blacks: elution studies, AHH determinations. *Am Ind Hyg Assoc J*, 42:503–509. PMID:6264776

Castranova V (1998). Particulates and the airways: basic biological mechanisms of pulmonary pathogenicity. *Appl Occup Environ Hyg*, 13:613–616.

Castranova V (2000). From coal mine dust to quartz: mechanisms of pulmonary pathogenicity. *Inhal Toxicol*, 12 Suppl. 2;7–14. doi:10.1080/08958370050164842.

Chalupa DC, Morrow PE, Oberdörster G *et al.* (2004). Ultrafine particle deposition in subjects with asthma. *Environ Health Perspect*, 112:879–882. doi:10.1289/ehp.6851. PMID:15175176

Chang C-C, Chiu H-F, Wu Y-S *et al.* (2005). The induction of vascular endothelial growth factor by ultrafine carbon black contributes to the increase of alveolar-capillary permeability. *Environ Health Perspect*, 113:454–460. doi:10.1289/ehp.7457. PMID:15811836

Chin BY, Choi ME, Burdick MD *et al.* (1998). Induction of apoptosis by particulate matter: role of TNF-alpha and MAPK. *Am J Physiol*, 275:L942–L949. PMID:9815112

CIIT & RIVM (2002). *Miltiple-path Particle Deposition: A Model for Human and Rat Airway Particle Dosimetry*, Research Triangle Park, NC/? CIIT Centers for Health Research/National Institute for Public Health and the Environment, The Netherlands, Bilthoven.

Creutzenberg O, Bellmann B, Heinrich U *et al.* (1990). Clearance and retention of inhaled diesel exhaust particles, carbon black, and titanium dioxide in rats at lung overload conditions. *J Aerosol Sci*, 21 Suppl. 1;S455–S458. doi:10.1016/0021-8502(90)90279-7.

Daigle CC, Chalupa DC, Gibb FR *et al.* (2003). Ultrafine particle deposition in humans during rest and exercise. *Inhal Toxicol*, 15:539–552. doi:10.1080/08958370304468. PMID:12692730

Daniels CE, Jett JR (2005). Does interstitial lung disease predispose to lung cancer? *Curr Opin Pulm Med*, 11:431–437. doi:10.1097/01.mcp.0000170521.71497.ba. PMID:16093818

De Lorenzo ATD (1970). The olfactory neuron and the blood-brain barrier. In: *Taste and Smell in Vertebrates*. Wolstenholme GEW, Knight J, eds, (CIBA Foundation Symposium Series). London, J. & A. Churchill pp. 151–176.

Dick CA, Brown DM, Donaldson K, Stone V (2003). The role of free radicals in the toxic and inflammatory effects of four different ultrafine particle types. *Inhal Toxicol*, 15:39–52. doi:10.1080/08958370304454. PMID:12476359

Don Porto Carero A, Hoet PHM, Verschaeve L *et al.* (2001). Genotoxic effects of carbon black particles, diesel exhaust particles, and urban air particulates and their extracts on a human alveolar epithelial cell line (A549) and a human monocytic cell line (THP-1). *Environ Mol Mutag*, 37:155–163. doi:10.1002/em.1023. PMID:11246222

Don Porto Carero A, Hoet PHM, Nemery B, Schoeters G (2002). Increased HLA-DR expression after exposure of human monocytic cells to air particulates. *Clin Exp Allergy*, 32:296–300. doi:10.1046/j.1365-2222.2002.01266.x. PMID:11929496

Driscoll KE, Carter JM, Howard BW *et al.* (1996). Pulmonary inflammatory, chemokine, and mutagenic responses in rats after subchronic inhalation of carbon black. *Toxicol Appl Pharmacol*, 136:372–380. doi:10.1006/taap.1996.0045. PMID:8619246

Driscoll KE, Deyo LC, Carter JM *et al.* (1997). Effects of particle exposure and particle-elicited inflammatory cells on mutation in rat alveolar epithelial cells. *Carcinogenesis*, 18:423–430. doi:10.1093/carcin/18.2.423. PMID:9054638

Elder A, Gelein R, Finkelstein JN *et al.* (2005). Effects of subchronically inhaled carbon black in three species. I. Retention kinetics, lung inflammation, and histopathology. *Toxicol Sci*, 88:614–629. doi:10.1093/toxsci/kfi327. PMID:16177241

Environmental Protection Agency (2004). *Air Quality Criteria for Particulate Matter. Volume II* (EPA/600/P-99/002bF), Research Triangle Park, NC.

Ferin J, Oberdörster G, Penney DP (1992). Pulmonary retention of ultrafine and fine particles in rats. *Am J Respir Cell Mol Biol*, 6:535–542. PMID:1581076

Ferin J, Oberdörster G, Soderholdm SC, Gelein R (1994). The rate of dose delivery affects pulmonary interstitialization of particles in rats. *Ann Occup Hyg*, 38 Suppl. 1;289–293.

Frampton MW, Utell MJ, Zareba W *et al.* (2004). Effects of exposure to ultrafine carbon particles in healthy subjects and subjects with asthma. *Res Rep Health Eff Inst*, 126:1–47, discussion 49–63. PMID:15768531

Freedman AP, Robinson SE (1988). Noninvasive magnetopneumographic studies of lung dust retention and clearance in coal miners. In: Frantz RL & Ramani RV, eds, *Respirable Dust in the Mineral Industries: Health Effects, Characterization and Control*, University Park, PA, Penn State University Press, pp. 181–186.

Freedman AP, Robinson SE, Street MR (1988). Magnetopneumographic study of human alveolar clearance in health and disease. *Ann Occup Hyg*, 32 Suppl. 1;809–820.

Gallagher J, Heinrich U, George M *et al.* (1994). Formation of DNA adducts in rat lung following chronic inhalation of diesel emissions, carbon black and titanium dioxide particles. *Carcinogenesis*, 15:1291–1299. doi:10.1093/carcin/15.7.1291. PMID:7518360

Gallagher J, Sams R II, Inmon J *et al.* (2003). Formation of 8-oxo-7,8-dihydro-2′-deoxyguanosine in rat lung DNA following subchronic inhalation of carbon black. *Toxicol Appl Pharmacol*, 190:224–231. doi:10.1016/S0041-008X(03)00187-X. PMID:12902193

Gardiner K (1995). Effects on respiratory morbidity of occupational exposure to carbon black: a review. *Arch Environ Health*, 50:44–60. doi:10.1080/00039896.1995.9955012. PMID:7717769

Gardiner K, Hale KA, Calvert IA *et al.* (1992a). The suitability of the urinary metabolite 1-hydroxypyrene as an index of poly nuclear aromatic hydrocarbon bioavailability from workers exposed to carbon black. *Ann Occup Hyg*, 36:681–688. doi:10.1093/annhyg/36.6.681. PMID:1471819

Gardiner K, Trethowan WN, Harrington JM *et al.* (1992b). Occupational exposure to carbon black in its manufacture. *Ann Occup Hyg*, 36:477–496. doi:10.1093/annhyg/36.5.477. PMID:1444068

Gardiner K, Trethowan NW, Harrington JM *et al.* (1993). Respiratory health effects of carbon black: a survey of European carbon black workers. *Br J Ind Med*, 50:1082–1096. PMID:8280639

Gardiner K, van Tongeren M, Harrington M (2001). Respiratory health effects from exposure to carbon black: results of the phase 2 and 3 cross sectional studies in the European carbon black

manufacturing industry. *Occup Environ Med*, 58:496–503. doi:10.1136/oem.58.8.496. PMID:11452043

Gärtner H, Brauss FW (1951). [Studies on the question of carbon black lung and on the harmfulness of carbon dust part in dust of carbon factories.] *Med Welt*, 8:253–256 (in German).

Geiser M, Rothen-Rutishauser B, Kapp N *et al.* (2005). Ultrafine particles cross cellular membranes by nonphagocytic mechanisms in lungs and in cultured cells. *Environ Health Perspect*, 113:1555–1560. doi:10.1289/ehp.8006. PMID:16263511

Gilmour PS, Ziesenis A, Morrison ER *et al.* (2004). Pulmonary and systemic effects of short-term inhalation exposure to ultrafine carbon black particles. *Toxicol Appl Pharmacol*, 195:35–44. doi:10.1016/j.taap.2003.10.003. PMID:14962503

Goodman GB, Kaplan PD, Stachura I *et al.* (1992). Acute silicosis responding to corticosteroid therapy. *Chest*, 101:366–370. doi:10.1378/chest.101.2.366. PMID:1735256

de Haar C, Hassing I, Bol M *et al.* (2005). Ultrafine carbon black particles cause early airway inflammation and have adjuvant activity in a mouse allergic airway disease model. *Toxicol Sci*, 87:409–418. doi:10.1093/toxsci/kfi255. PMID:16014737

Harber P, Muranko H, Solis S *et al.* (2003). Effect of carbon black exposure on respiratory function and symptoms. *J Occup Environ Med*, 45:144–155. doi:10.1097/01.jom.0000052955.59271.66. PMID:12625230

Heinrich U, Fuhst R, Rittinghausen R *et al.* (1995). Chronic inhalation exposure of Wistar rats and two different strains of mice to diesel engine exhaust, carbon black, and titanium dioxide. *Inhal Toxicol*, 7:533–556. doi:10.3109/08958379509015211.

Henderson RF, Barr EB, Cheng YS *et al.* (1992). The effect of exposure pattern on the accumulation of particles and the response of the lung to inhaled particles. *Fundam Appl Toxicol*, 19:367–374. doi:10.1016/0272-0590(92)90175-H. PMID:1459368

Hext PM, Tomenson JA, Thompson P (2005). Titanium dioxide: inhalation toxicology and epidemiology. *Ann Occup Hyg*, 49:461–472. doi:10.1093/annhyg/mei012. PMID:15790613

Hunter DD, Dey RD (1998). Identification and neuropeptide content of trigeminal neurons innervating the rat nasal epithelium. *Neuroscience*, 83:591–599. doi:10.1016/S0306-4522(97)00324-2. PMID:9460765

IARC (1984). Polynuclear aromatic hydrocarbons, Part 2, Carbon blacks, mineral oils (lubricant base oils and derived products) and some nitroarenes. IARC Monogr Eval Carcinog Risk Chem Hum, 33:1–222. PMID:6590450

IARC (1996). Printing processes and printing inks, carbon black and some nitro compounds. *IARC Monogr Eval Carcinog Risks Hum*, 65:1–578.

ICRP (1994). *Human Respiratory Tract Model for Radiological Protection. A Report of a Task Group of the International Commission on Radiological Protection* (ICRP Publication 66), Edinburgh, Pergamon, International Commission on Radiological Protection.

ILSI Risk Science Institute Workshop Participants (2000). The relevance of the rat lung response to particle overload for human risk assessment: a workshop consensus report. *Inhal Toxicol*, 12:1–17.

Inyang F, Ramesh A, Kopsombut P *et al.* (2003). Disruption of testicular steroidogenesis and epididymal function by inhaled benzo(a)pyrene. *Reprod Toxicol*, 17:527–537. doi:10.1016/S0890-6238(03)00071-6. PMID:14555190

Isawa T, Teshima T, Anazawa Y *et al.* (1991). Technegas for inhalation lung imaging. *Nucl Med Commun*, 12:47–55. doi:10.1097/00006231-199101000-00006. PMID:1850822

International Standards Organization (1995). *Air Quality—Particle Size Fraction Definitions for Health-related Sampling* (ISO 7708:1995), Geneva.

Jaques PA, Kim CS (2000). Measurement of total lung deposition of inhaled ultrafine particles in healthy men and women. *Inhal Toxicol*, 12:715–731. doi:10.1080/08958370050085156. PMID:10880153

Khandoga A, Stampfl A, Takenaka S *et al.* (2004). Ultrafine particles exert prothrombotic but not inflammatory effects on the hepatic microcirculation in healthy mice in vivo. *Circulation*, 109:1320–1325. doi:10.1161/01.CIR.0000118524.62298.E8. PMID:15007013

Kim CS, Jaques PA (2004). Analysis of total respiratory deposition of inhaled ultrafine particles in adult subjects at various breathing patterns. *Aerosol Sci Technol*, 38:525–540. doi:10.1080/02786820490465513.

Kim CS, Jaques PA (2005). Total lung deposition of ultrafine particles in elderly subjects during controlled breathing. *Inhal Toxicol*, 17:387–399. doi:10.1080/08958370590929493. PMID:16020035

Kirwin CJ, LeBlanc JV, Thomas WC *et al.* (1981). Evaluation of the genetic activity of industrially produced carbon black. *J Toxicol Environ Health*, 7:973–989. doi:10.1080/15287398109530039. PMID:7021866

Knaapen AM, Borm PJA, Albrecht C, Schins RPF (2004). Inhaled particles and lung cancer. Part A: Mechanisms. *Int J Cancer*, 109:799–809. doi:10.1002/ijc.11708. PMID:15027112

Kreyling WG (1990). Interspecies comparison of lung clearance of 'insoluble' particles. *J Aerosol Med*, 3 Suppl. 1;S-93–S-110. doi:10.1089/jam.1990.3.Suppl_1.S-93.

Kreyling WG, Semmler M, Erbe F *et al.* (2002). Translocation of ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low. *J Toxicol Environ Health*, A65:1513–1530. PM:12396866.

Kuempel ED (2000). Comparison of human and rodent lung dosimetry models for particle clearance and retention. *Drug Chem Toxicol*, 23:203–222. doi:10.1081/DCT-100100111. PMID:10711398

Kuempel ED, O'Flaherty EJ, Stayner LT *et al.* (2001). A biomathematical model of particle clearance and retention in the lungs of coal miners. *Regul Toxicol Pharmacol*, 34:69–87. doi:10.1006/rtph.2001.1479. PMID:11502158

Küpper HU, Breitstadt R, Ulmer WT (1996). Effects on the lung function of exposure to carbon black dusts. Results of a study carried out on 677 members of staff of the DEGUSSA factory in Kalscheuren/Germany. *Int Arch Occup Environ Health*, 68:478–483. doi:10.1007/BF00377873. PMID:8891789

Lambert AL, Trasti FS, Mangum JB, Everitt JI (2003). Effect of preexposure to ultrafine carbon black on respiratory syncytial virus infection in mice. *Toxicol Sci*, 72:331–338. doi:10.1093/toxsci/kfg031. PMID:12660365

Lapp NL, Castranova V (1993). How silicosis and coal workers' pneumoconiosis develop–A cellular assessment. *Occup Med*, 8:35–56. PMID:8384379

Lee KP, Trochimowicz HJ, Reinhardt CF (1985a). Pulmonary response of rats exposed to titanium dioxide (TiO2) by inhalation for two years. *Toxicol Appl Pharmacol*, 79:179–192. doi:10.1016/0041-008X(85)90339-4. PMID:4002222

Lee KP, Trochimowicz HJ, Reinhardt CF (1985b). Transmigration of titanium dioxide (TiO2) particles in rats after inhalation exposure. *Exp Mol Pathol*, 42:331–343. doi:10.1016/0014-4800(85)90083-8. PMID:3996554

Lee KP, Henry NW III, Trochimowicz HJ, Reinhardt CF (1986). Pulmonary response to impaired lung clearance in rats following excessive TiO2 dust deposition. *Environ Res*, 41:144–167. doi:10.1016/S0013-9351(86)80177-3. PMID:3757966

Lee PS, Gorski RA, Hering WE, Chan TL (1987). Lung clearance of inhaled particles after exposure to carbon black generated from a resuspension system. *Environ Res*, 43:364–373. doi:10.1016/S0013-9351(87)80037-3. PMID:2440669

LeFevre ME, Green FHY, Joel DD, Laqueur W (1982). Frequency of black pigment in livers and spleens of coal workers: correlation with pulmonary pathology and occupational information. *Hum Pathol*, 13:1121–1126. doi:10.1016/S0046-8177(82)80250-5. PMID:6757099

LeFevre ME, Joel DD (1986). Distribution of label after intragastric administration of 7Be-labeled carbon to weanling and aged mice. Proc Soc Exp Biol Med, 182:112–119. PMID:3960856

Lemb M, Oei TH, Eifert H, Günther B (1993). Technegas: a study of particle structure, size and distribution. *Eur J Nucl Med*, 20:576–579. doi:10.1007/BF00176550. PMID:8053994

Levy LS (1995). The 'particle overload' phenomenon and human risk assessment. *Indoor Built Environ*, 4:254–262. doi:10.1177/1420326X9500400503.

Li N, Sioutas C, Cho A *et al.* (2003). Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. *Environ Health Perspect*, 111:455–460. doi:10.1289/ehp.6000. PMID:12676598

Lloyd JJ, Shields RA, Taylor CJ *et al.* (1995). Technegas and Pertechnegas particle size distribution. *Eur J Nucl Med*, 22:473–476. doi:10.1007/BF00839062. PMID:7641756

Løvik M, Høgseth A-K, Gaarder PI *et al.* (1997). Diesel exhaust particles and carbon black have adjuvant activity on the local lymph node response and systemic IgE production to ovalbumin. *Toxicology*, 121:165–178. doi:10.1016/S0300-483X(97)00075-9. PMID:9230448

von Mai O (1966). [Carbon black lungs.] *Z ges Hyg*, 12:421–425 (in German).

Martonen TB, Rosati JA, Isaacs KK (2005). Modeling deposition of inhaled particles. In: Ruzer LS, Harley NH, eds, *Aerosols Handbook: Measurement, Dosimetry, and Health Efffects*, CRC Press, Boca Raton, FL, pp. 113–155.

Mauderly JL (1994). Noncancer pulmonary effects of chronic inhalation exposure of animals to solid particles. In: Mohr U, Dungworth DL, Mauderly JL & Oberdörster G, eds, *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract*, Washington DC, ILSI Press, pp. 43–55.

Mauderly JL, Snipes MB, Barr EB *et al.* (1994). Pulmonary toxicity of inhaled diesel exhaust and carbon black in chronically exposed rats. Part I: Neoplastic and nonneoplastic lung lesions. *Res Rep Health Eff Inst*, 68:1–75, discussion 77–97. PMID:7530965

Maynard AD, Kuempel ED (2005). Airborne nanostructured particles and occupational health. *J Nanopart Res*, 7:587–614. doi:10.1007/s11051-005-6770-9.

Ménache MG, Miller FJ, Raabe OG (1995). Particle inhalability curves for humans and small laboratory animals. *Ann Occup Hyg*, 39:317–328. PMID:7793751

Ménache MG, Raabe OG, Miller FJ (1996). An empirical dosimetry model of aerodynamic particle deposition in the rat respiratory tract. *Inhal Toxicol*, 8:539–578. doi:10.3109/08958379609002572.

Meyer JD, Islam SS, Ducatman AM, McCunney RJ (1997). Prevalence of small lung opacities in populations unexposed to dusts. A literature analysis. *Chest*, 111:404–410. doi:10.1378/chest.111.2.404. PMID:9041989

Miller FJ (2000). Dosimetry of particles in laboratory animals and humans in relationship to issues surrounding lung overload and human health risk assessment: a critical review. *Inhal Toxicol*, 12:19–57. doi:10.1080/089583700196536. PMID:10715617

Mills NL, Amin N, Robinson SD *et al.* (2006). Do inhaled carbon nanoparticles translocate directly into the circulation in humans? *Am J Respir Crit Care Med*, 173:426–431. doi:10.1164/rccm.200506-865OC. PMID:16339922

Möller W, Hofer T, Ziesenis A *et al.* (2002). Ultrafine particles cause cytoskeletal dysfunctions in macrophages. *Toxicol Appl Pharmacol*, 182:197–207. doi:10.1006/taap.2002.9430. PMID:12183099

Morfeld P**,** Albrecht C**,** Drommer W**,** Borm PJA (2006). Dose–response and threshold analysis tumor prevalence after intratracheal instillation of six types of low- and high-surface-area particles in a chronic rat experiment. *Inhal Toxicol*, 18**:**215**–**225.

Morrow PE (1988). Possible mechanisms to explain dust overloading of the lungs. *Fundam Appl Toxicol*, 10:369–384. doi:10.1016/0272-0590(88)90284-9. PMID:3286345

Morrow PE (1992). Dust overloading of the lungs: update and appraisal. *Toxicol Appl Pharmacol*, 113:1–12. doi:10.1016/0041-008X(92)90002-A. PMID:1553742

Morrow PE (1994). Mechanisms and significance of 'particle overload'. In: Mohr U, Dungworth DL, Mauderly JL, Oberdörster G, eds. *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract*, Washington DC, International Life Sciences Institute Press, pp. 17–25.

Muhle H, Bellmann B, Creutzenberg O *et al.* (1990a). Dust overloading of lungs after exposure of rats to particles of low solubility: comparative studies. *J Aerosol Sci*, 21:374–377. doi:10.1016/0021-8502(90)90062-3.

Muhle H, Creutzenberg O, Bellmann B *et al.* (1990b). Dust overloading of lungs: investigations of various materials, species differences, and irreversibility of effects. *J Aerosol Med*, 3 Suppl. 1;S111–S128. doi:10.1089/jam.1990.3.Suppl_1.S-111.

Muhle H, Bellmann B, Creutzenberg O *et al.* (1991). Pulmonary response to toner upon chronic inhalation exposure in rats. *Fundam Appl Toxicol*, 17:280–299. doi:10.1016/0272-0590(91)90219-T. PMID:1662648

Muhle H, Bellmann B, Creutzenberg O (1994). Toxicokinetics of solid particles in chronic rat studies using diesel soot, carbon black, toner, titanium dioxide, and quartz. In: Mohr U, Dungworth DL, Mauderly JL, Oberdörster G, eds, *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract*, Washington DC, ILSI Press, pp. 29–41.

National Institute for Occupational Safety and Health (1978). *Criteria for a Recommended Standard for Occupational Exposure to Carbon Black* (DHEW Publication No. (NIOSH) 78–204), Washington DC, Department of Health, Education and Welfare.

NCRP (1997). *Deposition, Retention, and Dosimetry of Inhaled Radioactive Substances* (Report No. 125), Bethesda, MD, National Council on Radiation Protection and Measurements.

Nemmar A, Hoet PH, Vanquickenborne B *et al.* (2002). Passage of inhaled particles into the blood circulation in humans. *Circulation*, 105:411–414. doi:10.1161/hc0402.104118. PMID:11815420

Nikula KJ, Snipes MB, Barr EB *et al.* (1995). Comparative pulmonary toxicities and carcinogenicities of chronically inhaled diesel exhaust and carbon black in F344 rats. *Fundam Appl Toxicol*, 25:80–94. doi:10.1006/faat.1995.1042. PMID:7541380

Nikula KJ, Avila KJ, Griffith WC, Mauderly JL (1997a). Lung tissue responses and sites of particle retention differ between rats and cynomolgus monkeys exposed chronically to diesel exhaust and coal dust. *Fundam Appl Toxicol*, 37:37–53. doi:10.1006/faat.1997.2297. PMID:9193921

Nikula KJ, Avila KJ, Griffith WC, Mauderly JL (1997b). Sites of particle retention and lung tissue responses to chronically inhaled diesel exhaust and coal dust in rats and cynomolgus monkeys. *Environ Health Perspect*, 105 Suppl 5;1231–1234. doi:10.2307/3433538. PMID:9400729

Nikula KJ, Vallyathan V, Green FH, Hahn FF (2001). Influence of exposure concentration or dose on the distribution of particulate material in rat and human lungs. *Environ Health Perspect*, 109:311–318. doi:10.1289/ehp.01109311. PMID:11335177

Nilsen A, Hagemann R, Eide I (1997). The adjuvant activity of diesel exhaust particles and carbon black on systemic IgE production to ovalbumin in mice after intranasal instillation. *Toxicology*, 124:225–232. doi:10.1016/S0300-483X(97)00150-9. PMID:9482124

Oberdörster G (1988). Lung clearance of inhaled insoluble and soluble particles. *J Aerosol Med*, 1:289–330. doi:10.1089/jam.1988.1.289.

Oberdörster G (1995). Lung particle overload: implications for occupational exposures to particles. [PMID:7784625.]. *Regul Toxicol Pharmacol*, 21:123–135. doi:10.1006/rtph.1995.1017. PMID:7784625

Oberdörster G (1996). Significance of particle parameters in the evaluation of exposure–dose–response relationships of inhaled particles. *Inhal Toxicol*, 8 Suppl;73–89. PMID:11542496

Oberdörster G (2002). Toxicokinetics and effects of fibrous and nonfibrous particles. *Inhal Toxicol*, 14:29–56. doi:10.1080/089583701753338622. PMID:12122559

Oberdörster G, Ferin J, Gelein R *et al.* (1992). Role of the alveolar macrophage in lung injury: studies with ultrafine particles. *Environ Health Perspect*, 97:193–199. doi:10.2307/3431353. PMID:1396458

Oberdörster G, Ferin J, Soderholm S *et al.* (1994a). Increased pulmonary toxicity of inhaled ultrafine particles: due to lung overload alone? *Ann Occup Hyg*, 38 Suppl. 1;295–302.

Oberdörster G, Ferin J, Lehnert BE (1994b). Correlation between particle size, in vivo particle persistence, and lung injury. *Environ Health Perspect*, 102 Suppl 5;173–179. doi:10.2307/3432080. PMID:7882925

Oberdörster G, Finkelstein J, Ferin J *et al.* (1996). Ultrafine particles as a potential environmental health hazard. Studies with model particles. *Chest*, 109 Suppl;68S–69S. doi:10.1378/chest.109.3_Supplement.68S. PMID:8598163

Oberdörster G, Sharp Z, Atudorei V *et al.* (2002). Extrapulmonary translocation of ultrafine carbon particles following whole-body inhalation exposure of rats. *J Toxicol Environ Health A*, 65:1531–1543. doi:10.1080/00984100290071658. PMID:12396867

Oberdörster G, Sharp Z, Atudorei V *et al.* (2004). Translocation of inhaled ultrafine particles to the brain. *Inhal Toxicol*, 16:437–445. doi:10.1080/08958370490439597. PMID:15204759

Pietropaoli AP, Frampton MW, Hyde RW *et al.* (2004). Pulmonary function, diffusing capacity, and inflammation in healthy and asthmatic subjects exposed to ultrafine particles. *Inhal Toxicol*, 16 Suppl 1;59–72. doi:10.1080/08958370490443079. PMID:15204794

Pott F, Roller M (2005). Carcinogenicity study with nineteen granular dusts in rats. *Eur J Oncol*, 10:249–281.

Pozzi R, De Berardis B, Paoletti L, Guastadisegni C (2003). Inflammatory mediators induced by coarse (PM2.5–10) and fine (PM2.5) urban air particles in RAW 264.7 cells. *Toxicology*, 183:243–254. doi:10.1016/S0300-483X(02)00545-0. PMID:12504355

Pylev LN, Roe F, Vorvik D (1970a). [A study of macrophage reaction of the pulmonary tissue of hamsters in response to the intratracheal insufflation of tritium labelled (3H)-benz[*a*]pyrene mixed with carbon black and asbestos.] Patol Fiziol Eksp, 14:47–51 (in Russian).

Pylev LN, Roe F, Vorvik D (1970b). [Distribution and excretion of 3H-benz(alpha)pyrene from the bodies of animals following its intratracheal injection with asbestos and carbon black]. *Vopr Onkol*, 16:61–69. PMID:5419653

Rausch LJ, Bisinger EC Jr, Sharma A (2004). Carbon black should not be classified as a human carcinogen based on rodent bioassay data. *Regul Toxicol Pharmacol*, 40:28–41. doi:10.1016/j.yrtph.2004.04.004. PMID:15265604

Rengasamy A, Barger MW, Kane E *et al.* (2003). Diesel exhaust particle-induced alterations of pulmonary phase I and phase II enzymes of rats. *J Toxicol Environ Health A*, 66:153–167. doi:10.1080/15287390306403. PMID:12653020

Renwick LC, Donaldson K, Clouter A (2001). Impairment of alveolar macrophage phagocytosis by ultrafine particles. *Toxicol Appl Pharmacol*, 172:119–127. doi:10.1006/taap.2001.9128. PMID:11298498

Renwick LC, Brown D, Clouter A, Donaldson K (2004). Increased inflammation and altered macrophage chemotactic responses caused by two ultrafine particle types. *Occup Environ Med*, 61:442–447. doi:10.1136/oem.2003.008227. PMID:15090666

Rice FL, Park R, Stayner L *et al.* (2001). Crystalline silica exposure and lung cancer mortality in diatomaceous earth industry workers: a quantitative risk assessment. *Occup Environ Med*, 58:38–45. doi:10.1136/oem.58.1.38. PMID:11119633

Riebe-Imre M, Aufderheide M, Gärtner-Hübsch S *et al.* (1994). Cytotoxic and genotoxic effects of insoluble particles in vitro. In: Mohr U, Dungworth DL, Mauderly JL, Oberdörster G, eds, *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract*, Washington DC, ILSI Press, pp. 519–523.

Rivin D, Smith RG (1982). Environmental health aspects of carbon black. Rubber Chem Technol, 55:707–761.

Rom WN (1991). Relationship of inflammatory cell cytokines to disease severity in individuals with occupational inorganic dust exposure. *Am J Ind Med*, 19:15–27. doi:10.1002/ajim.4700190104. PMID:1846507

Rosenkranz HS, McCoy EC, Sanders DR *et al.* (1980). Nitropyrenes: isolation, identificaton, and reduction of mutagenic impurities in carbon black and toners. *Science*, 209:1039–1043. doi:10.1126/science.6996095. PMID:6996095

Rosmanith J, Kandus J, Holuša R (1969). [Carbon pneumoconiosis.] *Int Arch Gewerbepathol* Gewerbehyg, 25:292–298 (in German). doi:10.1007/BF00394785.

Roth C, Kreyling WG, Scheuch G *et al.* (1997). Deposition and clearance of fine particles in the human respiratory tract. *Ann Occup Hyg*, 41 Suppl. 1;503–508.

Schins RPF (2002). Mechanisms of genotoxicity of particles and fibers. *Inhal Toxicol*, 14:57–78. doi:10.1080/089583701753338631. PMID:12122560

Shwe TT, Yamamoto S, Kakeyama M *et al.* (2005). Effect of intratracheal instillation of ultrafine carbon black on proinflammatory cytokine and chemokine release and mRNA expression in

lung and lymph nodes of mice. *Toxicol Appl Pharmacol*, 209:51–61. doi:10.1016/j.taap.2005.03.014. PMID:16331831

Shwe TT, Yamamoto S, Ahmed S *et al.* (2006). Brain cytokine and chemokine mRNA expression in mice induced by intranasal instillation with ultrafine carbon black. *Toxicol Lett*, 163:153–160. doi:10.1016/j.toxlet.2005.10.006. PMID:16293374

Slade R, Stead AG, Graham JA, Hatch GE (1985). Comparison of lung antioxidant levels in humans and laboratory animals. *Am Rev Respir Dis*, 131:742–746. PMID:4003918

Snipes MB (1989). Long-term retention and clearance of particles inhaled by mammalian species. Crit Rev Toxicol, 20:175–211. doi:10.3109/10408448909017909. PMID:2692607

Stahlhofen W, Scheuch G, Bailey MR (1995). Investigations of retention of inhaled particles in the human bronchial tree. *Radiat Prot Dosimetry*, 60:311–319.

Stayner L, Dankovic D, Smith R, Steenland K (1998). Predicted lung cancer risk among miners exposed to diesel exhaust particles. *Am J Ind Med*, 34:207–219. doi:10.1002/(SICI)1097-0274(199809)34:3<207::AID-AJIM2>3.0.CO;2-S. PMID:9698989

Stöber W (1999). POCK model simulations of pulmonary quartz dust retention data in extended inhalation exposures of rats. *Inhal Toxicol*, 11:269–292. doi:10.1080/089583799197096. PMID:10380170

Stöber W, Einbrodt HJ, Klosterkötter W (1965). Quantitative studies of dust retention in animal and human lungs after chronic inhalation. In: Davies CN, ed, *Inhaled Particles and Vapours II*, Edinburgh, Pergamon Press, pp. 409–418.

Stöber W, Morrow PE, Morawietz G (1990). Alveolar retention and clearance of insoluble particles in rats simulated by a new physiology-oriented compartmental kinetics model. *Fundam Appl Toxicol*, 15:329–349. doi:10.1016/0272-0590(90)90059-S. PMID:1699830

Strom KA, Johnson JT, Chan TL (1989). Retention and clearance of inhaled submicron carbon black particles. *J Toxicol Environ Health*, 26:183–202. doi:10.1080/15287398909531244. PMID:2466129

Sun JD, Wolff RK, Maio SM, Barr EB (1989). Influence of adsorption to carbon black particles on the retention and metabolic activation of benzo[*a*]pyrene in rat lungs following inhalation exposure or intratracheal instillation. *Inhal Toxicol*, 1:1–19. doi:10.3109/08958378909145222.

Swafford DS, Nikula KJ, Mitchell CE, Belinsky SA (1995). Low frequency of alterations in p53, K-ras, and mdm2 in rat lung neoplasms induced by diesel exhaust or carbon black. *Carcinogenesis*, 16:1215–1221. doi:10.1093/carcin/16.5.1215. PMID:7539340

Szozda R (1994). The respiratory health of carbon black workers–differences between Polish, west European and American scientific reports. *J UOEH*, 16:91–95. PMID:8146503

Szozda R (1996). Pneumoconiosis in carbon black workers. J UOEH, 18:223–228. PMID:8829263

Takenaka S, Karg E, Roth C *et al.* (2001). Pulmonary and systemic distribution of inhaled ultrafine silver particles in rats. *Environ Health Perspect*, 109 Suppl 4;547–551. doi:10.2307/3454667. PMID:11544161

Tamaoki J, Isono K, Takeyama K *et al.* (2004). Ultrafine carbon black particles stimulate proliferation of human airway epithelium via EGF receptor-mediated signaling pathway. *Am J Physiol Lung Cell Mol Physiol*, 287:L1127–L1133. doi:10.1152/ajplung.00241.2004. PMID:15298855

Timblin CR, Shukla A, Berlanger I *et al.* (2002). Ultrafine airborne particles cause increases in protooncogene expression and proliferation in alveolar epithelial cells. *Toxicol Appl Pharmacol*, 179:98–104. doi:10.1006/taap.2001.9343. PMID:11884242

van Tongeren MJA, Gardiner K, Rossiter CE *et al.* (2002). Longitudinal analyses of chest radiographs from the European carbon black respiratory morbidity study. *Eur Respir J*, 20:417–425. doi:10.1183/09031936.02.00224502. PMID:12212976

Tran CL, Buchanan D (2000). *Development of a Biomathematical Lung Model to Describe the Exposure–dose Relationship for Inhaled Dust among UK Coal Miners* (IOM Report TM/00/02), Edinburgh, Institute of Occupational Medicine.

Tran CL, Jones AD, Cullen RT, Donaldson K; C. L. Tran, A. D. Jones, R. T. Cull (1999). Exploration of the mechanisms of retention and clearance of low-toxicity particles in the rat lung using a mathematical model. *Inhal Toxicol*, 11:1077–1108. doi:10.1080/089583799196600. PMID:10562698

Tran CL, Buchanan D, Cullen RT *et al.*; C. L. Tran, D. Buchanan, R. T. Cull (2000). Inhalation of poorly soluble particles. II. Influence of particle surface area on inflammation and clearance. *Inhal Toxicol*, 12:1113–1126. doi:10.1080/08958370050166796. PMID:11114784

Tsai P-J, Shieh H-Y, Lee W-J *et al.* (2002). Urinary 1-hydroxypyrene as a biomarker of internal dose of polycyclic aromatic hydrocarbons in carbon black workers. *Ann Occup Hyg*, 46:229–235. doi:10.1093/annhyg/mef017. PMID:12074032

Vallyathan V, Shi XL, Dalal NS *et al.* (1988). Generation of free radicals from freshly fractured silica dust. Potential role in acute silica-induced lung injury. *Am Rev Respir Dis*, 138:1213–1219. PMID:2849348

Vallyathan V, Goins M, Lapp LN *et al.* (2000). Changes in bronchoalveolar lavage indices associated with radiographic classification in coal miners. *Am J Respir Crit Care Med*, 162:958–965. PMID:10988113

Venier P, Tecchio G, Clonfero E, Levis AG (1987). Mutagenic activity of carbon black dyes used in the leather industry. *Mutagenesis*, 2:19–22. doi:10.1093/mutage/2.1.19. PMID:3331689

Warheit DB, Hansen JF, Yuen IS *et al.* (1997). Inhalation of high concentrations of low toxicity dusts in rats results in impaired pulmonary clearance mechanisms and persistent inflammation. *Toxicol Appl Pharmacol*, 145:10–22. doi:10.1006/taap.1997.8102. PMID:9221819

Watson AY, Valberg PA (1996). Particle-induced lung tumors in rats: evidence for species specificity in mechanisms. In: Mauderly JL, McCunney RJ, eds, *Particle Overload in the Rat Lung and Lung Cancer. Implications for Human Risk Assessment,* Washington DC, Taylor & Francis, pp. 227–257.

Wilson MR, Lightbody JH, Donaldson K *et al.* (2002). Interactions between ultrafine particles and transition metals in vivo and in vitro. *Toxicol Appl Pharmacol*, 184:172–179. doi:10.1006/taap.2002.9501. PMID:12460745

Wolff RK, Sun JD, Barr EB *et al.* (1989). Lung retention and binding of [14C]-1-nitropyrene when inhaled by F344 rats as a pure aerosol or adsorbed to carbon black particles. *J Toxicol Environ Health*, 26:309–325. doi:10.1080/15287398909531256. PMID:2926831

Yang H-M, Barger MW, Castranova V *et al.* (1999). Effects of diesel exhaust particles (DEP), carbon black, and silica on macrophage responses to lipopolysaccharide: evidence of DEP suppression of macrophage activity. *J Toxicol Environ Health* A, 58:261–278. doi:10.1080/009841099157232. PMID:10598952

Yu CP, Chen YK, Morrow PE (1989). An analysis of alveolar macrophage mobility kinetics at dust overloading of the lungs. *Fundam Appl Toxicol*, 13:452–459. doi:10.1016/0272-0590(89)90282-0. PMID:2612778

Yu RC, Rappaport SM (1997). A lung retention model based on Michaelis-Menten-like kinetics. *Environ Health Perspect*, 105:496–503. doi:10.2307/3433577. PMID:9222134

Zhao HW, Barger MW, Ma JKH *et al.* (2004). Effects of exposure to diesel exhaust particles (DEP) on pulmonary metabolic activation of mutagenic agents. *Mutat Res*, 564:103–113. PMID:15507375

Zhong B-Z, Whong W-Z, Ong T-M (1997). Detection of mineral-dust-induced DNA damage in two mammalian cell lines using the alkaline single cell gel/comet assay. *Mutat Res*, 393:181–187. PMID:9393610

5. Summary of Data Reported

5.1 Exposure data

Carbon black is a generic term for a particulate form of elemental carbon manufactured by the vapour-phase pyrolysis and partial combustion of hydrocarbons. Carbon blacks are categorized, on the basis of different production processes by which they are made, as acetylene black, channel black, furnace black, lampblack or thermal black. Acetylene, furnace and thermal blacks have been produced since the early twentieth century. Over 95% of all carbon black produced today is furnace black. Worldwide production capacity of carbon black in 2005 was approximately 10 million tonnes.

Carbon blacks are characterized by the size distribution of the primary particles and the degree of their aggregation and agglomeration. Human exposure is primarily to carbon black particles in aggregate and agglomerate forms. Average aggregate particle diameters in several commercially produced carbon blacks range from 50 to 600 nm and the more loosely associated agglomerates can reach up to many micrometers in diameter. The majority of carbon blacks currently manufactured have small quantities (< 1%) of organic compounds, including polycyclic aromatic hydrocarbons, adsorbed onto their surface.

About 90% of carbon black is used in rubber products, predominantly in tyres. Carbon black is also used as a pigment in inks, paints and coatings and in plastics.

Exposures to carbon black vary markedly between and within any production facility and over time. The highest levels of exposure are experienced by packers and site cleaners. Some studies before 1970 found that extremely high levels of exposure to carbon black could have occurred in the manufacturing industry. Exposure studies in this industry in the USA and western Europe after the late 1970s found personal geometric mean exposures to inhalable dust to be less than 5 mg/m^3. By the mid- to late 1990s the geometric mean levels of inhalable dust were below 2 mg/m^3. The geometric mean levels of respirable dust were below 0.5 mg/m^3. No data were available that would allow the characterization or quantification of exposure to ultrafine primary particles. Exposure in the user industries is difficult to assess because of the lack of data and concomitant exposure to many other particles but exposure levels are assumed to be lower, with the possible exception of workers who handle carbon black in these industries. Exposure to carbon black does not occur during the use of products in which carbon black is bound to other materials, such as rubber, printing ink or paint.

5.2 Human carcinogenicity data

The greatest potential for elucidating the carcinogenicity of carbon black is in the carbon black production industry where it has been the primary industrial exposure. Cohort studies of carbon black production workers have been conducted in Germany, the United Kingdom and the USA.

A cohort study was conducted among blue-collar workers in a long-standing, large German carbon black production plant. When mortality was compared with regional rates, there was an approximate doubling of risk for lung cancer. Exposure was assessed using full work history records from the plant and expert judgements. Further, company medical records provided some information on tobacco smoking for most of the workers. Compared with the lowest exposure group, and after adjusting for smoking, there was no indication that workers with several indices of or average exposure to carbon black had higher mortality. However, the precision of these subgroup risk estimates was low. There was no excess mortality from cancer at most other sites, including oesophagus, stomach and urinary bladder, although the numbers were small.

Another group of investigators analysed the same German cohort of carbon black workers using different methods. They confirmed that there was no exposure–response relationship within the cohort between estimated exposure to carbon black and lung cancer. After accounting for regional variations in cancer and different methods of adjustment for tobacco smoking and other exposures, the overall risk for lung cancer was slightly elevated, although the Working Group was not persuaded that all the adjustments were warranted.

The study of workers in five carbon black production facilities in the United Kingdom involved a large group with a long follow-up. When compared with national mortality rates, there was a clear excess of mortality from lung cancer. Although tobacco smoking histories were not known, there was no corresponding significant excess of other diseases known to be associated with smoking. The excess risk was manifest in two of five factories. Exposure was assessed using last job from worker records and a job–exposure matrix based on expert judgement and measurements from two of the five plants. When adjusted for age and divided into four subgroups based on cumulative exposure levels, relative risk did not increase monotonically with increasing exposure, although the two highest exposure categories showed higher relative risks than the two lowest categories. There was no significant excess risk for cancer at any other site.

A study in the USA included a large cohort of workers from 18 plants with good ascertainment of cohort members and effective mortality follow-up over a long period of time. There was no indication of excess risk for cancer at any of the sites reported. There was no indication that long-service workers had higher risks than short-service workers. For most types of cancer, including lung cancer, the numbers of deaths observed did not exceed the numbers expected on the basis of national rates. No results were provided taking into account various levels of exposure to carbon black or tobacco smoking habits.

Additional evidence is provided by studies of workers who were exposed to carbon black in some other industries.

Within a large cohort of German rubber industry workers, an attempt was made to assess exposure to carbon black. The exposure assessment was rather crude. In statistical analyses of carbon black that did not include other exposure variables as potential confounders, there were significant excess risks for cancers of the larynx, lung and stomach. When exposure to nitrosamines, asbestos and talc were considered, the excess risks were no longer statistically significant.

A cohort study was carried out among workers in the USA to assess cancer risks due to exposure to formaldehyde in 10 participating plants that were spread across several industries. To control for confounding and modification of effect by other exposures, exposures of workers to various other chemicals, including carbon black, were assessed by industrial hygienists. Overall, among carbon black-exposed workers, there was a slight non-significant excess risk for lung cancer. There was no clear trend by duration of exposure.

A study of Italian dockyard workers was based on the undocumented but reasonable premise that those who unloaded and carried bags of carbon black experienced higher exposures. Apart from mesothelioma and malignant melanoma, neither of which were probably attributable to exposure to carbon black, only one site—urinary bladder cancer—showed some evidence of a statistically significant excess. For lung cancer, stomach cancer and cancer at several other sites, there was no indication of excess risk.

In a community-based case–control study in Montréal, Canada, interviews were designed to obtain detailed lifetime job histories and information on potential confounders. Potential occupational exposures were identified for each job description; carbon black was among the exposures assessed. Few if any of the exposed subjects had worked in the manufacture of carbon black. Many workers were exposed to carbon black in bound matrices such as paint or rubber. It is probable that workers exposed to carbon black in this study were exposed to lower levels than those in other studies. There was an indication of excess risk associated with exposure to carbon black for cancers of the lung, oesophagus and kidney, but not for cancer of the stomach, urinary bladder or at other sites.

A Swedish community-based case–control study reported a non-significant increased risk for urothelial cancer for men exposed to carbon black.

Seven studies were considered to be informative for lung cancer of which three were among carbon black production workers. The Working Group considered the studies of carbon black producers in Germany, the United Kingdom and the USA, to be the most informative for assessing cancer risk. The two studies from Germany and the United Kingdom indicated an excess risk compared with external references. Confounding by tobacco smoking could not be excluded, although it was unlikely to have explained the entire excess risk. However, in both cohorts, internal analyses by level of exposure to carbon black gave equivocal but mainly null results. The study of carbon black workers in the USA suggested no excess mortality, but did not assess risk by level of exposure. In

studies that assessed risks for lung cancer among user industries, the most informative study of German rubber workers showed some indication of excess risk that disappeared when asbestos and talc were adjusted for in the analysis. Of the remaining studies, two others showed non-significant excesses (formaldehyde cohort in the USA and the Canadian community-based case–control study) and one showed no excess risk for lung cancer linked to the handling of carbon black (Italian dockworkers).

For cancers of the urinary bladder, kidney, stomach and oesophagus, isolated results indicate excess risks, but these are not sufficient to support an evaluation of human carcinogenicity. There is no evidence of an effect of carbon black for other cancer sites.

5.3 Animal carcinogenicity data

Two different carbon black products were tested by inhalation exposure in two studies in female rats and in one study in rats of each sex. Significant increases in the incidence of malignant lung tumours or of benign and malignant lung tumours combined were observed in female rats in all three studies. In addition, an increased incidence of lesions described as benign cystic keratinizing squamous-cell tumours or squamous-cell cysts was observed. In one study in female mice exposed by inhalation, carbon black did not increase the incidence of respiratory tract tumours.

In two studies of intratracheal administration to female rats using two types of carbon black and in one study using one type, an increased incidence of malignant lung tumours or of benign and malignant lung tumours combined was observed.

In several experiments of dermal application in mice that used various carbon blacks, no carcinogenic effect on the skin was observed; the dermal application of benzene extracts of several carbon blacks resulted in skin tumours.

In one study in male and female mice using the same types of carbon black by subcutaneous injection, a carbon black that contained demonstrable quantities of carcinogenic polycyclic aromatic hydrocarbons produced local sarcomas, whereas a carbon black in which no polycyclic aromatic hydrocarbon was detected did not produce such sarcomas. In several experiments in mice, solvent extracts of carbon black produced sarcomas following subcutaneous injection.

No adequate study of the carcinogenicity of carbon black administered by the oral or intraperitoneal route was available.

5.4 Mechanistic considerations and other relevant data

The deposition pattern of carbon black particles depends on the particle size (aerodynamic or thermodynamic) and on the anatomical and physiological characteristics of the host. The deposition fraction of carbon black influences the dose to a given region of the respiratory tract. Some studies described the retention of carbon black in the respiratory tract of exposed workers, as well as the health effects of these exposures. For example, lung tissues from workers in carbon black factories have been shown to contain

deposits of carbon black. Lung diseases or conditions may influence the deposition and retention of particles such as carbon black. For instance, asthmatics had a higher total deposition of ultrafine carbon particles in the respiratory tract compared with healthy individuals. The amount of carbon black deposited can also increase with increasing minute volume, for instance in individuals taking exercise or during heavy work loads. High retained mass lung burdens and decrease in lung clearance have been observed in miners.

Non-cancer respiratory effects in carbon black workers that have been reported include cough, sputum production, bronchitis, chest radiographic opacities (e.g. pneumoconiosis) and decrements in lung function.

Many studies have been conducted on the deposition and retention kinetics of inhaled carbon particles following intratracheal instillation or inhalation in rodent species. In general, all rodent species investigated displayed evidence of rapid clearance of inhaled carbon particles when exposure concentrations did not result in lung overload (impaired clearance resulting in accumulation of particles in the lung tissue). Experimental studies of ultrafine particles of carbon black have shown that rodents experience dose-dependent impairment of alveolar macrophage-mediated clearance, which occurs at lower mass doses of ultrafine particles than these of with larger particles. Overloading has been observed in rats, mice and hamsters exposed to carbon black. Hamsters appear to exhibit the most efficient clearance of carbon black particles compared with rats and mice. Adverse lung responses to inhaled carbon black (pulmonary inflammation and epithelial injury) increase significantly with the increased retained lung dose of carbon black. Fine and ultrafine carbon black particles can translocate beyond the lungs to other organs.

Several toxic effects of carbon black have been reported in rodent species. They toxic were dose-dependent and included inflammation, lung epithelial cell injury and lung lesions that were more severe and prolonged in rats than in mice and hamsters. Exposure to carbon black particles modulates the immune system. In-vitro studies showed evidence that carbon black particles can generate reactive oxygen species in cell-free systems, increase the production of tumour necrosis factor-α and activate serum factors such as complement.

The genotoxicity of carbon black has been evaluated and found to be negative in most assays for mutagenicity. In one study in rats exposed to carbon black by inhalation, the *Hprt* mutant frequency was elevated in lung epithelial cells following a 15-week exposure. A significant increase in pro-mutagenic 8-oxo-7,8-dihydro-2′-deoxyguanosine induction was observed in the lungs of rats exposed for 13 weeks to one type of carbon black. Carbon black did not induce a significant increase in DNA adducts in the peripheral lung tissue of rats after 2 years of inhalation exposure. K-*ras* mutations were found in one of 18 neoplasms analysed from carbon black-exposed rats; no exposure-related *Tp53* mutation was found. In vitro, rat lung epithelial cells exposed to bronchoalveolar lavage fluid from rats instillated with carbon black showed an increase in *Hprt* mutant frequency. Most in-vitro mutagenicity studies of carbon black have proved negative.

6. Evaluation and Rationale

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of carbon black.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of carbon black.

There is *sufficient evidence* in experimental animals for the carcinogenicity of carbon black extracts.

6.3 Overall evaluation

Carbon black is *possibly carcinogenic to humans (Group 2B)*.

6.4 Rationale

In making this evaluation the Working Group considered the human and animal evidence as well as the evidence on potential mechanisms through which carbon black may cause cancer in humans.

The human epidemiological evidence was inconsistent. Two of the three studies of carbon black production workers observed excess risk for lung cancer and other studies provided mixed evidence for an increased risk for lung and other cancers. The few studies that assessed exposure–response for lung cancer, including the two that observed excess risks compared with the general population, provided weak or inconclusive evidence of a dose–response. Overall, these results led the Working Group to conclude that there was *inadequate evidence* from epidemiological studies to assess whether carbon black causes cancer in humans.

Three studies of female rats that inhaled carbon black and three additional studies of female rats exposed intratracheally found significant increases in the incidence of malignant lung tumours, providing *sufficient evidence* that carbon black can cause cancer in animals. Solvent extracts of carbon black were used in one study of rats in which skin tumours were observed after dermal application and several studies of mice in which sarcomas were seen following subcutaneous injection, providing *sufficient evidence* that carbon black extracts can cause cancer in animals.

The Working Group considered a large body of mechanistic information. For lung cancer in rats, it was concluded that a sequence of events that starts with impaired clearance and accumulation of particles in the lung, causing inflammation, cell injury and

production of reactive oxygen species that eventually lead to mutations, was well supported by experimental evidence, although some data also supported alternative pathways. High retained mass lung burdens and decreased lung clearance have been observed in coal miners, which led the Working Group to conclude that animal cancer data obtained under conditions of impaired lung clearance are relevant to humans. There was a minority opinion in the Working Group that would support the classification of carbon black in Group 2A, and invoked the analogy with quartz particles, which are carcinogenic in the lung of rats and humans. However, based on current evidence, the Working Group considered that the degree to which all elements of the above-mentioned mechanism may operate in humans is not clear and, thus, the mechanistic information did not alter the overall evaluation of Group 2B.