CARBON BLACK

1. Exposure Data

Carbon black was considered by previous Working Groups (IARC, 1984, 1987a). New data have since become available, and these are included in the present monograph and have been taken into consideration in the evaluation.

1.1 Chemical and physical data

1.1.1 *Nomenclature*

The Chem. Abstr. Serv. Reg. No. 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; Ucet

Channel black

Chem. Abstr. Name: Carbon black, channel

IUPAC Systematic Name: Carbon black, channel

Synonym: 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; 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; 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; 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; Velvetex

1.1.2 *General description*

Carbon black is sometimes confused with soot but it is a very different material (Medalia *et al.*, 1981). Carbon black is a powdered form of elemental carbon manufactured by the controlled vapour-phase pyrolysis of hydrocarbons. Different types of carbon black have a wide range of particle sizes, high surface areas per unit mass, quite low contents of ash and toluene-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 particles, the number of primary particles per aggregate and their average mass.

The fundamental unit of a carbon black is the aggregate. This is a chain of roughly spherical 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 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 in pellets (up to 0.5 cm) held together by means of binders (molasses/lignosulfonates) (Dannenberg *et al.*, 1992; Gardiner *et al.*, 1992a).

To describe a carbon black aggregate, two dimensions are necessary:

(1) *Mean diameter of the component spheres in the chain*. This is a measure of the chain 'thickness'. This is called the primary particle size and generally is inversely proportional to the surface area of the 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 black, in units of mL/100 g.

Also of importance for human exposure is the behaviour of carbon black in air and its deposition in the respiratory tract upon inhalation. This is determined by the aerodynamic diameter of the particles. The aerodynamic diameter can be measured by impactors and is dependent upon the geometric diameter, material density and shape factor of the aggregates. Most commonly, the size distribution of airborne particles is expressed as its mass median aerodynamic diameter (MMAD) with its geometric standard deviation.

Carbon black is variously known as acetylene black, channel black, furnace black, lampblack or thermal black, depending on the specific process by which it is manufactured (see Section 1.2.1). The properties of typical types of carbon black are presented in Tables 1–6.

In contrast to carbon black, soot is a material of varying and often unknown composition, which is an unwanted by-product of the incomplete combustion of all kinds of carbon-containing materials, such as waste oil, coal, paper, rubber, plastic, garbage and also fuel oils or gasoline. Soots have a low available carbon surface area owing to their large particle size and small carbon component. They typically contain large quantities of dichloromethane- and toluene-extractable materials, and their ash content can be 50% or more (European Committee for Biological Effects of Carbon Black, 1982).

Two other commercial carbonaceous products are activated carbon and bone black. Activated carbon is a collective name for a group of porous carbons. These 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 with small amounts of chemically bonded oxygen and hydrogen, and can contain up to 20% of mineral matter, which is usually indicated as 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 by-product of the bone char industry. Bone char is made by carbonizing bones and is used principally in sugar refining. Bone black is a pigment derived from bone char, 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).

1.1.3 *Chemical and physical properties of the technical products*

All commercially available types of carbon black are insoluble in water and organic solvents, but various types differ in other chemical and physical properties. The ranges of properties of each of the four types of carbon black are summarized in Table 1. Analyses of samples of carbon black produced commercially in the United States of America and

Europe are given in Table 2, and those of the carbon black types produced in Japan are given in Table 3.

Table 1. Typical ranges of properties for four types of carbon black pigment

Property	Acetylene black	Furnace black	Lampblack	Thermal black
Average aggregate diameter (nm)	NR	80–500	NR	300–810[a]
Average primary particle diameter (nm)	35–50	17–70	50–100	150–500
Surface area[a], N, (m^2/g)	60–70	20–200	20–95[b] (17–25)[c]	6–15
Oil absorption (mL/g)	3.0–3.5	0.67–1.95	1.05–1.65	0.30–0.46
pH	5–7	5–9.5	3–7	7–8
Volatile matter (%)	0.4	0.3–2.8	0.4–9.0[c] (0.5–1.5)[d]	0.10–0.50
Hydrogen (%)	0.05–0.10	0.45–0.71	NR	0.3–0.5
Oxygen (%)	0.10–0.15	0.19–1.2	NR	0.00–0.12
Benzene extract (%)	0.1	0.01–0.18	0.00–1.4	0.02–1.7
Ash (%)	0.00	0.1–1.0	0.00–0.16	0.02–0.38
Sulfur (%)	0.02	0.05–1.5	NR	0.00–0.25
Density (g/mL)	NR	1.80	1.77[b]	NR

From Garret (1973), Weast (1981) and Hess & Herd (1993)
NR, not reported
[a] Surface area calculated by the nitrogen adsorption method
[b] Value in the United States
[c] Value in Europe (data provided by European carbon black manufacturers (IARC, 1984))

Extractable polycyclic aromatic hydrocarbons (PAHs), nitro-PAHs, and sulfur-containing aromatics from carbon black are discussed in Section 1.1.4.

Acetylene black

Acetylene black is characterized by its high purity, low oxygen content and an extremely high degree of aggregation or structure. X-Ray analysis indicates that acetylene black is the most crystalline or graphitic of the commercial blacks. The levels of ash content and benzene-extractable materials are very low, and acetylene black is not readily wetted by water, since its surface is saturated with hydrogen atoms.

Channel black

Channel black is no longer produced in the United States but, in Europe, its manufacture still continues and, in some operations, is expanding. In the past, channel black was characterized by its small particle size, low degree of aggregation or structure, relatively high content of oxygen complexes on its surface and acidic pH. Natural gas was used as the feedstock and water was not required for the quenching of the reaction,

Table 2. Analyses of samples of several carbon blacks produced commercially in the United States and Europe

Property	Acetylene		Furnace (HAF/N330)	Furnace (FEF/N550)	Lampblack		Thermal (FT/N880)	Thermal (MT/N990)
	USA	Germany			USA	Europe		
Average aggregate diameter (nm)	NR	NR	260	470	NR	NR	300	400
Average particle diameter (nm)	40	35	28	42	65	95	200	400
Surface area (BET) (m^2/g)	65	70	80	42	22	20	12	7
Toluene extract (%)	0.1	0.05[a]	0.08	NR	0.2[a]	0.1[a]	0.8	0.3
pH	4.8	7.0	7.5	NR	3.0	7.0	9.0	8.5
Volatile matter (%)	0.3	0.05	1.0	1.0	1.5	1.0	0.5	0.5
Ash (%)	0.0	0.05	0.3	0.2	0.02	0.05	0.1	0.3
Composition (%)								
Carbon	99.7	99.8	97.9	98.4	98	98	99.2	99.3
Hydrogen	0.1	0.05	0.3	0.4	0.2	0.4	0.5	0.3
Sulfur	0.02	0.005	0.6	0.7	0.8	0.6	0.01	0.01
Oxygen	0.2	0.05	0.8	0.4	0.8	0.4	0.3	0.1

From Hoechst Aktiengesellschaft (1979); Dannenberg (1978); IARC (1984); Robertson & Smith (1994)
NR, not reported; HAF, high-abrasion furnace; FEF, fast extrusion furnace; FT, fine thermal; MT, medium thermal; BET, the Brunauer, Emmett and Teller procedure for calculating surface area
[a] Benzene extract (%)

and, therefore, channel black had a very low ash content. The volatile content of channel black was about 5% but could be increased to as much as 18% by after-treatments. The surface of this channel black reportedly contained hydroxyl, carbonyl and carboxylic acid groups (Garret, 1973; Claassen, 1978).

Table 3. Typical analyses of three types of carbon black commercially available in Japan

Property	Acetylene black	Furnace black	Thermal black
Average particle diameter (nm)	40	21	90
Iodine adsorption (mg/g)[a]	105	119	26
DBPA[b] (mL/100g)	125	115	27
pH	7.5	7.7	8.5
Volatile matter (%)	0.2	1.4	0.5
Ash (%)	0.1	0.25	0.4

From IARC (1984)

[a] Iodine adsorption is reported as the milligrams of iodine adsorbed per gram of carbon black under specified conditions established by the American Society for Testing and Materials (American Society for Testing and Materials, 1995a) and has been used to approximate the surface area of carbon blacks (Johnson & Eberline, 1978)

[b] DBPA, the dibutyl phthalate absorption method, a standard procedure for measuring void volume, a characteristic related to structure

Channel black, when manufactured, was available as a dry chemical in either powder or pelleted form. Three types were available for reinforcing rubber — easy, medium and hard processing. These varied slightly in particle diameter, that with the largest particle diameter (approximately 29 nm) being known as easy-processing channel and that with the smallest (approximately 22 nm) as hard-processing channel (IARC, 1984).

The average diameters of the channel blacks used for colour and ink applications are shown in Table 4. Medium-flow channel blacks and long-flow channel blacks received an after-treatment with hot air to increase their volatile contents and thereby increase the 'flow' of the lithographic inks in which they were used.

Carbon black made in Germany by an impingement roller process from aromatic hydrocarbon-containing coal-tar residues and coke-oven gases is said to have similar properties to those of older channel black. It has an acidic pH, a volatile content of about 5%, a surface area of about 100 m^2/g and an average particle diameter of 10–30 nm (Claassen, 1978; Dannenberg *et al.*, 1992).

Furnace black

Furnace black consists of irregularly shaped aggregate structures of spherical particles. Originally produced by the gas-furnace process, it is now produced almost entirely by the oil-furnace process. Gas-furnace black was characterized by a low degree

Table 4. Average diameters of channel blacks used in colours and inks

Channel black	Symbol	Average diameter (nm)
High-colour channel	HCC	12
Medium-colour channel	MCC	16
Regular colour channel	RCC	25
Medium-flow channel	MFC	25
Long-flow channel	LFC	25

From IARC (1984)

of structure and had properties that led to a low-to-medium reinforcing performance. Oil-furnace blacks have a substantially higher degree of aggregation and structure and, consequently, furnace black is now available with a wide range of characteristics depending on the desired product performance. The quality of furnace black is controlled by variations of the raw materials, operating temperatures, atmospheric turbulence and by alteration of furnace design. A very small percentage of the total quantity of furnace blacks is subjected to after-treatment by various oxidation processes for particular applications.

Furnace black is available in several grades. Those used in rubber products have been classified by the American Society for Testing and Materials (ASTM) according to a standard four-character nomenclature system. In this system, the letter N indicates that the product gives a normal curing rate, while the letter S indicates that it reduces the rate of cure. The first digit is used to designate the typical average particle size (e.g. 1 indicates 11–19 nm and 9 indicates 201–500 nm) and the last two digits are assigned arbitrarily. The N100 series are super-abrasion furnace blacks; the N200 series are intermediate super-abrasion furnace blacks; the N300 series are high-abrasion furnace blacks; the N500 series are fast-extrusion furnace blacks; and the N700 series are semi-reinforcing furnace blacks. The N900 series are thermal blacks (American Society of Testing and Materials, 1995a).

Table 5 provides the ASTM designations for furnace blacks used in rubber, a description of their types, the symbols used to designate the types, as well as three typical measures of surface area (iodine adsorption, cetyl trimethyl ammonium bromide adsorption and nitrogen adsorption), one measure of the degree of aggregation (dibutyl phthalate absorption) and one rough measure of particle size (tinting strength). Table 6 provides similar information for furnace blacks used in inks, paints and plastics.

Lampblack

Lampblack is considered to be the forerunner of all carbon blacks. Essential and typical properties of lampblack are its high degree of aggregation or structure and low surface area. Formerly, lampblack was an oily product sold in the fluffy state or partially

Table 5. Typical properties of currently available furnace blacks for rubber[a]

ASTM designation	Type of black	Symbol	Iodine adsorption[b] (mg/g)	CTAB[c] (m^2/g)	Surface area, N_2[d] (m^2/g)	DBPA[e] (mL/100 g)	Tinting strength[f] (%)
N110	Super-abrasion furnace	SAF	145	126	143	113	124
N115	Super-abrasion furnace	SAF	160	128	143	113	123
N121	Super-abrasion furnace, high structure	SAF-HS	121	121	124	132	121
N125	Super-abrasion furnace	SAF	117	126	122	104	123
N134	Super-abrasion furnace	SAF	142	134	145	127	132
N135	Super-abrasion furnace	SAF	151	127	141	135	119
S212	Intermediate super-abrasion furnace, low structure, slow cure	–	90	119	120	85	115
N220	Intermediate super-abrasion furnace	ISAF	121	111	115	114	115
N231	Intermediate super-abrasion furnace, low modulus	ISAF-LM	121	108	111	92	117
N234	Improved intermediate super-abrasion furnace, high structure	ISAF-HS	120	119	126	125	124
N293	Conductive furnace	CF	145	114	130	100	117
N299	Intermediate super-abrasion furnace, high structure	ISAF-HS	108	104	103	124	113
S315	High-abrasion furnace, low structure, slow curing	HAF-LS-SC	60	95	91	79	–
N326	High-abrasion furnace, low structure	HAF-LS	82	83	78	72	112
N330	High-abrasion furnace	HAF	82	82	79	102	103
N335	High-abrasion furnace	HAF	92	88	85	110	110
N339	Improved high-abrasion furnace, high structure	HAF-HS	90	93	96	120	110
N343	High-abrasion furnace	HAF	92	95	97	130	114
N347	High-abrasion furnace, high structure	HAF-HS	90	87	85	124	103
N351	High-abrasion furnace, high structure	HAF-HS	68	73	71	120	100
N356	Super-processing furnace, high structure	SPF-HS	92	93	91	154	105
N358	High-abrasion furnace, high structure	HAF-HS	84	88	82	150	99
N375	Improved high-abrasion furnace, high structure	HAF-HS	90	96	93	114	115
N539	Fast-extruding furnace, low structure	FEF-LS	43	41	40	111	–
N550	Fast-extruding furnace	FEF	43	42	42	121	–
N582	Acetylene black	FEF	100	76	80	180	67
N630	General-purpose furnace, low structure	GPF-LS	36	35	34	78	–

Table 5 (contd)

ASTM designation	Type of black	Symbol	Iodine adsorption[b] (mg/g)	CTAB[c] (m^2/g)	Surface area, N_2[d] (m^2/g)	DBPA[e] (mL/100 g)	Tinting strength[f] (%)
N642	General-purpose furnace, very low structure	–	36	34	39	64	–
N650	General-purpose furnace, high structure	GPF-HS	36	38	37	122	–
N660	General-purpose furnace	GPF	36	36	35	90	–
N683	General-purpose furnace, high structure	GPF-HS	35	39	37	133	–
N754	Semi-reinforcing furnace, low structure	SRF-LS	24	29	25	58	–
N762	Semi-reinforcing furnace, low modulus	SRF-LM	27	29	28	65	–
N765	Semi-reinforcing furnace, high structure	SRF-HS	31	33	36	115	–
N772	Semi-reinforcing furnace	SRF	30	33	31	65	–
N774	Semi-reinforcing furnace, high modulus	SRF-HM	29	29	29	72	–
N787	Semi-reinforcing furnace, high modulus	SRF-HM	30	31	30	80	–
N907	Medium thermal, non-staining, free flowing	MT-NS-FF	–	–	10	34	–
N908	Medium thermal, non-staining	MT-NS	–	–	10	34	–
N990	Medium thermal, free flowing	MT-FF	0	9	9	43	–
N991	Medium thermal	MT	–	8	9	35	–

From Ford & Lyon (1973), Garret (1973), Dannenberg (1978), Smith (1982), Dannenberg *et al.* (1992) and American Society for Testing and Materials (1995a)

[a] The values given are often averages of typical values supplied by several manufacturers.

[b] ASTM standard method No. D1510

[c] CTAB, cetyl trimethyl ammonium bromide measurement of surface area; ASTM standard method No. D3765

[d] ASTM standard method No. 3037/4820, surface area calculated by the nitrogen adsorption method

[e] DBPA, dibutyl phthalate absorption; ASTM standard method No. D2414

[f] ASTM standard method No. 3265

Table 6. Typical properties of furnace blacks for inks, paints, paper and plastics

Furnace black	Surface area[a] (m^2/g)	Particle size (nm)	Aggregate size (nm)	DBPA (mL/100 g)		Bulk density (g/L)		Nigrometer index[b]	Tinting strength (%)	Volatile content (%)
				Fluffy	Pellets	Fluffy	Pellets			
Normal furnace grades										
High colour	250–300	14–15	60	70–75	60–65	50–300	400–550	65–76	117–124	1.2–2.0
Medium colour	150–220	16–24	50–160	47–122	46–117	130–300	390–550	74–78	118–124	1.0–1.5
Regular colour	45–140	20–37	60–220	42–125	42–124	176–420	350–600	84–93	73–119	0.9–1.5
Low colour	24–45	41–75	280–430	71	64–120	256	352–512	94–99	48–69	0.6–0.9
Surface oxidized grades										
High colour	400–600	10–20	–	121	105	–	–	64	100–135	8.0–9.5
Medium colour (long flow)	100–138	23–24	–	49–60	55	240–360	530	83–84	112–135	3.5–5.0
Medium colour (medium flow)	96–110	25	–	49–72	70	225–360	480	84	112–114	2.5–3.5
Low colour	30–40	50–56	–	48–93	–	260–500	–	92–100	64	3.5

From Dannenberg *et al.* (1992)
DBPA, dibutyl phthalate absorption
[a] As calculated by the Brunauer, Emmett and Teller (BET) procedures
[b] A method for measuring the diffuse reflectance from a black paste with a black tile standard. The low numbers represent the 'jettest', or most intense, black grades

compressed; however, recent grades are essentially free of residual oil and sold as a dry pigment or as a suspension in linseed oil.

The ASTM (American Society for Testing and Materials, 1995b) specifications for the dry pigment are: moisture and other volatile matter, 3.0% max.; acetone extract, 1.0% max.; ash, 0.5% max.; and coarse particles (residue on a No. 325 sieve), 0.5% max. Specifications for the paste in oil are: pigment, 25% min.; linseed oil, 75% max.; moisture and other volatile matter, 0.7% max.; and coarse particles (residue on a No. 325 sieve), 1.0% max.

Thermal black

Thermal black exhibits the largest particle size and the lowest surface area of the commercial carbon blacks. Consisting of discrete spherical particles, it also has the lowest degree of aggregation or structure, and is also characterized by low oxygen content.

Thermal blacks are available in several grades. Table 5 provides information on the ASTM classification of these products, according to the system described above for furnace black.

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. A number of methods have been developed and used to extract and characterize these adsorbed chemicals (see Section 1.1.5(*b*)). The classes of chemicals most commonly identified in these extracts are PAHs, nitro derivatives of PAHs (nitro-PAHs) and sulfur-containing PAHs. Examples of these three classes of chemicals identified in carbon black extracts are given in Table 7.

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 after-treatments all appear to be factors that affect the types and quantities of impurities obtained. However, substantial batch-to-batch variation is typical.

Among the PAHs frequently found at the highest levels in carbon black extracts are benzo[*ghi*]perylene, coronene, cyclopenta[*cd*]pyrene, fluoranthene and pyrene. For example, in a study of five types of furnace black used in tyre manufacture, extraction with hot benzene after 250 h yielded means of 252–1417 mg extract per 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

Table 7. Some compounds identified in carbon black extracts

Polycyclic aromatic hydrocarbons (PAHs) (see also IARC, 1983)
- Acenaphthylene
- Anthanthrene
- Anthracene
- Benz[*a*]acenaphthylene
- Benz[*a*]anthracene
- Benzo[*b*]fluoranthene
- Benzo[*ghi*]fluoranthene
- Benzo[*j*]fluoranthene
- Benzo[*k*]fluoranthene
- Benzo[*a*]pyrene
- Benzo[*e*]pyrene
- Benzo[*ghi*]perylene
- Chrysene
- Coronene
- 4*H*-Cyclopenta[*def*]phenanthrene
- Cyclopenta[*cd*]pyrene
- Dibenz[*a,h*]anthracene
- Fluoranthene
- Indeno[1,2,3-*cd*]pyrene
- Naphthalene
- Perylene
- Phenanthrene
- Pyrene

Nitro derivatives of PAHs (nitro-PAHs) (see also IARC, 1987b, 1989)
- 1,3-Dinitropyrene
- 1,6-Dinitropyrene
- 1,8-Dinitropyrene
- 9-Nitroanthracene
- 3-Nitro-9-fluorenone
- 1-Nitronaphthalene
- 1-Nitropyrene
- 1,3,6-Trinitropyrene

Sulfur-containing PAHs
- Benzo[*def*]dibenzothiophene
- Dibenzothiophene
- Phenanthro[4,5-*bcd*]thiophene
- Triphenyleno[4,5-*bcd*]thiophene

From Falk & Steiner (1952); Gabor *et al.* (1969); Gold (1975); Qazi & Nau (1975); Renes (1975); Wallcave *et al.* (1975); Lee & Hites (1976); Fitch *et al.* (1978); Nakajima *et al.* (1978); Fitch & Smith (1979); Locati *et al.* (1979); De Wiest (1980); Rosenkranz *et al.* (1980); Taylor *et al.* (1980); Sanders (1981); Ramdahl *et al.* (1982); Rivin & Smith (1982); Butler *et al.* (1983); Novrocik *et al.* (1983); Nishioka *et al.* (1986); Jin *et al.* (1987); Agurell & Löfroth (1993)

results of two similar studies, which used benzene to extract adsorbates from a number of oil-furnace blacks and one thermal black are shown in Table 8 (Taylor *et al.*, 1980; Zoccolillo *et al.*, 1984).

Table 8. Benzo[*a*]pyrene concentrations in the benzene extracts of 10 carbon blacks

ASTM designation[a]	Surface area (m^2/g)	Total extract (mg/kg) (no. of samples)	Benzo[*a*]pyrene concentration (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)	4.8 (6)
N990	10	8020 (1)	35.00 (1)

From Taylor *et al.* (1980) and Zoccolillo *et al.* (1984)

[a] For American Society for Testing and Materials designations of types, see Table 5

PAH fractions from six different batches of the same furnace black (ASTM designation 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 Durex-0) were analysed. The toluene-soluble extractable compounds, including PAHs, were determined by the gravimetric method, and benzo[*a*]pyrene by high-performance liquid chromatography (HPLC) with a spectrometric detector. Toluene-soluble compounds were found to amount 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 of impurities in a furnace carbon black (N330) manufactured in Sweden over a three-year period. The following PAHs were determined at the following ranges of concentration in benzene extracts (mg/kg carbon black): 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 PAH were found in extracts of thermal blacks. A 24-h benzene extract of an N990-type thermal black yielded approximately 4000 mg extract per kg carbon black. Individual PAHs included (mg/kg): 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 PAH in the benzene extract of another N990 thermal black sample was 2140 mg/kg, which included 35 mg/kg benzo[*a*]pyrene (Zoccolillo *et al.*, 1984).

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

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

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

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

1.1.5 *Analysis*

This section briefly reviews methods of analysis to detect the presence of carbon black in various matrices, as well as methods used to isolate and analyse surface contaminants (see Section 1.1.4).

(*a*) *Carbon black in various matrices*

Because of the difficulty of separating carbon black from other airborne particulates in the workplace, total dust is usually measured as a surrogate for airborne concentration of carbon black in facilities producing or using carbon black. Both personal membrane-filter and static high-volume sampling techniques are used to collect carbon black in the work environment, followed by gravimetric analysis to arrive at the total dust concentration. Free carbon has been determined by predigestion of a sample with nitric acid to destroy organic matter followed by weighing of the residue and ignition between 140 and 700 °C. The amount of free carbon is determined by the loss of weight upon ignition (United States National Institute for Occupational Safety and Health, 1978). The gravimetric method [Method 5000] of the United States National Institute for Occupational Safety and Health for determining total dust has a working range of 1.5–10 mg/m^3

for a 200-L sample of air and an estimated limit of detection of 0.03 mg/sample (Eller, 1994).

The American Society for Testing and Materials (1995a) has published similar methods for the analysis of carbon black in several natural and synthetic rubbers. It has been reported that thermogravimetric analysis is accurate for determining the carbon black content of rubbers in the range of 0.1 to 30% by weight (Charsley & Dunn, 1981).

(*b*) *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 the adsorbed chemicals from the carbon black samples, but vacuum sublimation or extraction combined with sonification have also been used (Zoccolillo *et al.*, 1984). The efficiency of the Soxhlet extraction depends on the extraction time and solvent, the type of carbon black, the relationship between sample weight/solvent volume and the amount of extractable material. Some solvents can react with the surface groups of carbon black and form artifacts during the extraction (Fitch *et al.*, 1978).

Locati *et al.* (1979) found that in five furnace blacks a Soxhlet extraction time of 150 h was necessary to remove 95% of the benzene-extractable matter and 250 h for exhaustive extraction. They also observed that the lower the relative molecular mass was, the shorter the time necessary to obtain extraction was.

Taylor *et al.* (1980) examined the solvent efficiency of three solvents (24-h Soxhlet) as measured by benzo[*a*]pyrene extractability 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).

Giammarise *et al.* (1982) found that benzene, toluene, monochlorobenzene and *ortho*-dichlorobenzene were all effective extraction solvents for nitropyrenes from an old carbon black sample with a high level of nitropyrene impurities (approximately 70 mg/kg). Monochlorobenzene was the best extractant. When a current carbon black with only traces of nitropyrene impurities (approximately 0.5 mg/kg) was extracted, monochlorobenzene removed more than 90% of the nitropyrenes within 24 h, while toluene extracted only 60% in that time.

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

Colmsjö and Östman (1988) reported a method to isolate and fingerprint some high-molecular-weight PAHs in carbon black. The PAH fraction of a carbon black extract (Soxhlet-extracted with dichloromethane) was isolated with a backflush technique and applied to an amino-bonded stationary phase for HPLC. This fraction was further separated by reverse-phase HPLC and each subfraction was analysed by low-temperature fluorescence.

Sigvardson and Birks (1984) reported that selective detection of nitro-PAHs in carbon black was achieved by Soxhlet extraction with toluene, evaporation to dryness, dissolution in dichloromethane and direct injection into the HPLC column. The nitro-PAHs were reduced online to the corresponding amino-PAHs and detected by peroxyoxalate chemiluminescence.

Jin *et al.* (1987) described a method for the analysis of nitroarenes in carbon black. The method involved the 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.

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

1.2 Production and use

1.2.1 *Production*

The early Chinese and Hindus produced carbon black for their inks and lacquers by a simple lampblack process. Lampblack supplied the needs of the pigment industry until the opening of the natural gas fields in the United States in 1872 and the establishment of the channel process. At that time, annual world consumption of carbon black was less than 1000 tonnes. Consumption increased rapidly following the discovery in 1904 of carbon black's usefulness in the reinforcement of rubber; the needs of the growing world rubber industry were met by supplies of channel black and lampblack from the United States. In 1922, the gas-furnace process was introduced in the United States (Garret, 1973). The increasing cost of natural gas led to a switch to the oil-furnace process in the early 1940s and to the final closure of channel black manufacture in the United States in 1976. Since oil feedstock is readily transported, the oil-furnace process can be located close to the user industries, and, following the end of the Second World War, carbon black manufacture was established in many industrialized countries (Dannenberg *et al.*, 1992).

Worldwide production of carbon black in 1993 was about six million tonnes (estimate based on demand for carbon black; see Table 11). Production data on carbon black in

several countries from 1987 to 1994 are presented in Table 9, and production data on carbon black by grade in the United States, western Europe and Japan in 1988 are presented in Table 10.

Table 9. Production of carbon black in several countries from 1987 to 1994 (thousand tonnes)

Country	1987	1988	1989	1990	1991	1992	1993	1994
Canada	172	181	190	178	157	161	166	167
China	290	290	320	327	334	NA	NA	NA
France	232	241	270	252	224	232	204	235
Germany	361	379	401	393	380	375	334	297
Italy	190	200	202	180	185	182	171	187
Japan	635	740	779	783	793	771	702	698
Republic of Korea	NA	NA	NA	NA	232	248	300	311
USA	1355	1324	1320	1302	1234	1370	1462	1503

From Anon. (1989, 1991a); Dannenberg *et al.* (1992); Anon. (1993); China National Chemical Information Centre (1993); Anon. (1995)
NA, not available

Table 10. Production of carbon blacks for rubber in 1988 in the United States, western Europe and Japan (thousand tonnes)

Grade	USA	Western Europe	Japan
Tread grades			
N100	35	28	37
N200	158	161	118
N300	555	528	300
Total	748 (55.2%)	717 (63.8%)	455 (61.5%)[a]
Non-tread grades			
N500	120	153	136
N600	326	137	87
N700	129	103	29
N900 (thermal)	23	–	9
Total	598 (44.1%)	393 (35.0%)	261 (35.3%)[a]
Other grades			
Acetylene	9	14	24
Total carbon black	1355	1124	740[a]

Adapted from Dannenberg *et al.* (1992)
[a] Calculated by the Working Group

Carbon black is produced by many companies in Russia, 12 companies in China, six companies each in India, Japan and the United States, three companies each in Canada, France, Italy and the Netherlands, two companies each in Australia, Brazil, Germany, the Republic of Korea, Poland, Spain, Thailand and the United Kingdom, and one company each in Chile, Colombia, the Czech Republic, Estonia, Hungary, Iran, Malaysia, Mexico, the Philippines, Portugal, Romania, South Africa, Sweden, Taiwan and Turkey (Chemical Information Services, 1994; Cabot Co., 1995).

Acetylene black

Acetylene black was first made commercially in Germany in 1928, in Canada in the 1930s, in Japan in 1942 and in the United States in 1964. It is currently estimated to comprise substantially less than 1% of total carbon black production (Dannenberg *et al.*, 1992).

The dissociation of acetylene into carbon and hydrogen was achieved as early as 1861, and the first commercial process was based on the partial combustion of acetylene (Bean, 1964). Subsequently, a process based on the explosion of an electric arc was developed in Germany. The process currently in use — continuous thermal decomposition — is covered by a series of patents going back to 1938 and was reported in 1964 to have been in commercial use for some years in continental Europe, Asia and Canada (Bean, 1964; Claassen, 1978).

In the continuous thermal decomposition process for acetylene black, the reaction is initiated by burning the acetylene feedstock with a controlled amount of air. When the reaction temperature is sufficiently high (e.g. 800 °C), the air supply is shut off, oxidation ceases and an exothermic self-sustained dissociation of acetylene to form hydrogen and acetylene black occurs at temperatures of up to 1000 °C (Dannenberg *et al.*, 1992).

Channel black

The channel process for making carbon black was first used commercially in the United States in 1872 (Garret, 1973). From the First World War to the Second World War, the channel black process accounted for most of the carbon black used worldwide for rubber and pigment applications. However, rising prices of natural gas, smoke pollution, low yield and the rapid development of the furnace-process grades of carbon black have been given as reasons for this process being abandoned in 1976 in the United States; operations still exist and are being expanded in Europe (Dannenberg, 1978; Dannenberg *et al.*, 1992).

In the channel or impingement process, small natural-gas flames were impinged on channel irons that collected the deposited carbon black (Garret, 1973). This process gave only very low yields (5%); however, in Germany, a plant making carbon black by an impingement process, sometimes called 'gas black', is reported to give yields of 60% using coal-tar residues containing naphthalene or anthracene as the carbon feedstock. In this process, the molten material is evaporated by a stream of hot coke-oven gas and heated to about 370 °C prior to reaching the burners. The flames are directed onto

revolving water-cooled pipes and the carbon black, which forms on impingement, is continuously scraped from the pipes. For the production of finer-particle black for use as pigments, the amount of oil carried by the gas is decreased and the vapours to the burner are diluted with air (Claassen, 1978).

Production of channel black in the United States reached a peak of 307 000 tonnes in 1948, but it had fallen to 132 000 tonnes by 1960 and showed a steady decline until production stopped in 1976. The quantity of carbon black made by the manufacturer in Germany using the impingement process is believed to constitute less than 1% of total world production of carbon black.

Furnace black

The gas-furnace process for making carbon black was first introduced in the United States in 1922, and the oil-furnace process in 1943 (Garret, 1973). Furnace black was first produced commercially in Japan around 1950. The gas-furnace process, which is based on the partial combustion of natural gas, was carried out using refractory-lined retorts or furnaces at a temperature of 1200–1500 °C. The process achieved only low yields of carbon black and has not been used in the United States since the 1960s (Dannenberg, 1978). In the oil-furnace process, which is now used to produce over 95% of total output of all carbon black, a heavy aromatic feedstock from a petroleum refinery or petrochemical operation is injected by atomization into a high-velocity stream of combustion gases produced by the complete burning of an auxiliary fuel (such as natural gas) with excess air. Although some of the feedstock is burned at 1200–1850 °C, most is converted to hydrogen and carbon black with high yields. Downstream, the reaction gases are cooled by spraying with water. The carbon black particles are then separated from the gases and pelletized. A very small percentage of furnace black is subjected to after-treatment by various oxidation processes, some of which have involved nitration. In the United States, about 95% of feedstocks are decant oils (clarified heavy distillates from the catalytic cracking of gas oils); European feedstock sources are 50% decant oils and 50% ethylene tars and creosote oils (Dannenberg *et al.*, 1992).

Lampblack

Lampblack was first produced commercially in the United States in the 1840s (Patterson, 1980). It is made principally by burning aromatic petroleum oils and coal-tar products, such as creosote and anthracene oils, in open, shallow pans using a restricted air supply (Smith, 1964). This is carried out at temperatures lower than those for other carbon black processes. The lampblack is separated from the gases and pelletized. Currently, only a few plants located mostly in western and eastern Europe still produce these rather coarse blacks (mean particle diameter, approximately 100 nm) which have special properties (Vohler *et al.*, 1986; Dannenberg *et al.*, 1992). Lampblack is not produced in Japan.

Lampblack is produced on a small scale; total production is believed to constitute less than 1% of total world production of carbon black.

Thermal black

In the thermal process, which dates back to 1922, a chamber filled with checkered brickwork is heated to about 1300 °C by injecting a burning mixture of gas and air. When the required temperature has been reached, the flow of burning gas is stopped and the hydrocarbon feedstock (usually gas) is injected. Contact with the hot bricks causes the feedstock to crack, forming carbon black and hydrogen. This process is run cyclically using two chambers, one being heated while the other produces carbon black. In one plant in the United Kingdom, medium thermal black is produced from oil rather than using natural gas as the raw material (Johnson & Eberline, 1978; Dannenberg *et al.*, 1992).

Total production of thermal black is estimated to be about 2% of total carbon black production of North America, western Europe and Japan.

1.2.2 *Use*

The primary use of carbon black (for example, approximately 90% in the United States) is in rubber products (see IARC, 1982), including tyres (69% in the United States), tubes, treads and other automotive products (about 10% in the United States) and other industrial rubber products (11% in the United States). Miscellaneous non-rubber uses (approximately 10%) include applications as pigments in paints, plastics, paper, inks and ceramics. These levels of use have been steady for the past 10 years (Anon., 1985, 1988, 1991b, 1994). World demand for carbon black by region is presented in Table 11. Western Europe consumes 74% in tyres and other automotive products and almost 20% in other industrial rubber products. Applications as pigments in western Europe and Japan account for 5–6% of consumption (Dannenberg *et al.*, 1992).

Table 11. World carbon black demand by region (thousand tonnes)

Region	1983	1993
North America	1387	1664
Central and South America	221	336
Western Europe	1058	1102
Eastern Europe	1022	556
Africa and the Middle East	107	147
Asia and Oceania	1139	2173
World	4934	5978

From The Freedonia Group (1994a)

Information on the quantities of carbon black used in various applications is very seldom presented in a form that provides separate data on the individual types of carbon black. However, it can be inferred that the major carbon black used is furnace black, since this is the predominant item in commerce, and that thermal black follows as a distant second place; minor quantities of the other carbon blacks are used in highly

specialized applications. Most carbon black is supplied as wet or dry pellets, but very small amounts are still shipped in bags as fluffy black.

Carbon black is an intense black pigment, but its principal industrial use today is based on its ability to reinforce natural and synthetic rubbers (for a description of the rubber manufacturing processes in which carbon blacks are used, see IARC, 1982). Addition of carbon black in quantities in the range 10–150 parts per 100 parts by weight of rubber polymer results in very marked improvements in the properties of vulcanized rubbers, particularly in terms of resistance to abrasion, tear strength, tensile strength, stiffness and hardness. Addition of carbon black also changes the properties of rubbers in the unvulcanized condition, so improving handling and shaping in the manufacture of all types of rubber products. Carbon black is particularly useful in its ability to reinforce rubber. The world rubber industry is thus dependent on the use of carbon black.

The most important product of the rubber industry is the pneumatic tyre and this represents the single largest application of carbon black. For every 100 parts by weight of rubber used in the manufacture of a tyre, there are about 60 parts by weight of carbon black. Since tyres also contain steel and textile materials, carbon black represents about 25% of the total weight of a finished pneumatic tyre. The consumption of the various grades of carbon black can be divided into 'tread grades' for tyre reinforcement and 'non-tread' grades for non-tread tyre use and other applications. In the United States, 55% of carbon black produced for rubber is for tread grades; tread-grade production is 64% in western Europe and 60% in Japan (Dannenberg *et al.*, 1992).

Many of the non-tyre applications of carbon black in rubber are also for the automotive industry — for example, in hoses, weatherstrips, sponge seals and engine mountings. Overall, about 80% of total carbon black consumption is for automotive applications.

For more than a thousand years before the discovery in 1904 of its reinforcing effect in rubber, carbon black was used as a pigment. Today, although pigments represent less than 10% of the total usage, it is used in inks, paints, lacquers, cements, paper, coatings and in plastics, where it is also used as an ultraviolet absorber.

Acetylene black

Acetylene black is used primarily for speciality applications because of its relatively high cost. Approximately 95% of worldwide use of acetylene black is in the manufacture of dry-cell batteries. Because of its ability to absorb large quantities of electrolyte, acetylene black imparts greater capacity, longer shelf-life and lower resistance to dry cells than any other filler. Its high thermal and electrical conductivity also imparts desirable properties to certain rubber and plastic products, such as thermal insulators, belt drives, cable sheathing, hoses and shoe soles (Bean, 1964; Union Carbide Corp., 1964; Claassen, 1978; Gulf Oil Chemicals Company, 1982; Vohler *et al.*, 1986).

Channel black

Channel black has been used for rubber reinforcement and as a pigment. In rubber reinforcement, it was reported to yield products with high tensile strength, high elongation and high tear resistance. With the smallest particle size, channel black gave high colour intensity when used as a pigment in paint, ink and plastics. The carbon black made by the impingement process in Germany also reportedly finds limited use in rubber reinforcement and more extensive use in pigment applications in printing inks, plastics, lacquers and coatings. High-quality oxidized black from this process is particularly useful in deep black lacquers and coatings (Claassen, 1978; Vohler *et al.*, 1986).

Furnace black

Over 95% of the carbon black in the rubber industry is produced by the furnace process (Garret, 1973), and furnace black is also used in printing inks, plastics and paints. For these different purposes, a wide variety of specially tailored grades possessing the necessary properties are available (for example, different grades are used in tyre sidewalls).

The furnace black process has the advantage of being continuous and carried out in closed reactors, which means that all parameters and inputs can be controlled. Properties of carbon black, such as surface area, particle size, structure, absorptivity, abrasion resistance, tint strength and others, can systematically be varied in the furnace black process by adjusting the operating parameters. Thus, most semi-reinforcing rubber blacks (SRF, GPF, FEF) with specific surface areas of 20–60 m^2/g, and active reinforcing blacks (HAF, SAF, ISAF) (see Table 5 for definition of these terms) with specific surface areas of 65–150 m^2/g are manufactured by this process, as are, tó an increasing extent, pigment-grade types of carbon black with much larger surface areas and smaller particle sizes (Vohler *et al.*, 1986).

The major application of furnace black in the rubber industry is in the manufacture of tyres, retread rubber and inner tubes. Other automotive uses in elastomers include belts, hose, motor mounts, O-rings and wire and cable covers. Non-automotive uses in elastomers include coated fabrics, conveyor belts, floor mats, footwear, gaskets, gloves, hard rubber products, hose, packaging, pontoons, toys and wire and cable covers.

The majority of the furnace black used in printing inks is for newspaper inks, with the remainder divided among lithographic/offset, gravure, letterpress, flexographic and other inks. Furnace black is also used as a colourant in alkyd and acrylic enamels, industrial finishes, lacquers and a variety of other paints.

Furnace black is used in plastics principally for the following purposes: as an antistatic agent, colourant, filler (sometimes to impart strength) and ultraviolet radiation stabilizer and as an additive to increase or decrease electrical conductivity. End-uses include appliances, automotive accessories, extrusion and calender coatings, film, housewares, phonograph records, pipe and conduit, and wire and cable (Dannenberg, 1978; Dannenberg *et al.*, 1992).

Lampblack

Most of the lampblacks produced currently are coarse particulates with special properties (Vohler *et al.*, 1986). They are used mainly as non-reinforcing or semi-reinforcing blacks in rubber goods. Lampblacks are used to a lesser extent as pigments for tinting and shading cosmetics, enamels, inks, lacquers, paints and plastics. Lampblack pigments are readily dispersible and have little tendency to float in paint or ink formulations (Claassen, 1978). The principal use of lampblack in the pigmentation of artists' paints is in water colours; it has a more minor role in oil colours (Levison, 1973).

The physical and electrical properties of lampblack make it useful in the production of arc carbons, brushes and resistors. Its high tinting strength and hiding power has led to its use in blackboards, cement, crayons and leather (Garret, 1973).

Thermal black

Thermal black is used principally in mechanical rubber goods with high filler content (Vohler *et al.*, 1986). Thermal black is used in non-tyre rubber when low reinforcement is required, and it is used in speciality polymers and in neoprene, nitrile and ethylene–propylene elastomers (Patterson, 1980). End-product applications include belts, footwear, gaskets, hose, mechanical goods, V-belts, O-rings and seals, tyre innerliners and wire insulation (Dannenberg, 1978).

1.3 Occurrence

1.3.1 *Natural occurrence*

Carbon black is not known to occur as natural product.

1.3.2 *Occupational exposure*

Occupational exposure by any route to carbon black has been reduced markedly in the last 30–35 years, mainly by technological improvements, increases in the proportion of the product that is bulk loaded (by trucks and trains) and legislative enforcement. Until recently, very few reliable data on occupational exposure to carbon black were available, but two major prospective cross-sectional studies in the United States and Europe (France, Germany, Italy, the Netherlands, Spain, Sweden and the United Kingdom) have characterized exposure accurately in these workforces. These data and those from the previous studies have been reviewed (Gardiner, 1995a) but a further summary of the more important data is given below.

The majority of the studies of occupational exposure do not report adequately the sampling strategies with which the data were collected. Only in one study were the measurements taken specifically for the purpose of an epidemiological study and hence used techniques such as person/day randomization. Rarely were the type (personal/-static), duration or rationale for the number of samples stated. It is possible to measure a variety of aerosol fractions, but usually respirable and total inhalable dust are measured. Respirable dust is that fraction of an aerosol with an aerodynamic diameter suitable for

penetration into the alveoli/gas exchange region of the lung (typically < 10 μm). Total inhalable dust is that fraction of an aerosol with an aerodynamic diameter suitable for inspiration into the respiratory system (typically < 100 μm). Differences in definitions of these fractions and in the methodologies by which they are measured require that inter-study comparison should be undertaken with care.

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, 25.3 to 278.6 mg/m^3 in the working aisles, 9.3 to 972 mg/m^3 in the pelletizing area and 26.7 to 208.6 mg/m^3 in the packing area.

Sands and Benitez (1961) used a static high-volume sampler to measure total dust in various areas of three factories processing rubber (one in Uruguay and two in the United States). The range in the three factories was 0.14–4.59 mg/m^3, 1.06–17.66 mg/m^3 and 1.06–38.84 mg/m^3, with the range being 1.77–38.84 mg/m^3 by the Banbury mixer loading area, 1.41–13.42 mg/m^3 during milling and 0.14–4.24 mg/m^3 in the general air of the milling rooms. It was suggested by the authors that 3.5 mg/m^3 represented a safe and achievable air standard which prompted the American Conference of Governmental Industrial Hygienists (ACGIH) to propose a threshold limit value (TLV) of 3.5 mg/m^3 in 1965, which was adopted in 1967 (American Conference of Governmental Industrial Hygienists, 1993).

Komarova (1965) measured exposure to carbon black in the packaging department of two Russian factories manufacturing 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 was quoted.

A survey found a range of concentrations of 90–196 mg/m^3 (from an unspecified number of samples) in a Russian furnace black factory (Spodin, 1973). The lowest and highest average concentrations recorded by another Russian study 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 packing carbon black were exposed to 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).

Between July 1972 and January 1977, the United States Occupational Safety and Health Administration conducted 85 workplace investigations 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 total inhalable exposure limit of 3.5 mg/m^3, and about 60% of these were one to two times above the limit (United States Occupational Safety and Health Administration, 1977).

A number of Health Hazard Evaluations have been conducted by the United States National Institute of Occupational Safety and Health in facilities either producing or using carbon black (Belanger & Elesh, 1979; Hollett, 1980; Salisbury, 1980; Boiano & Donohue, 1981). In general, these measurements were less than 3.5 mg/m^3, although

these 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 has been reported that for total dust (in which carbon black was one component) the median levels in 14 tyre and tube manufacturing plants in the United States were 1.7 mg/m^3 for the compounding area samples (individual plant means ranged up to 3.9 mg/m^3) and 1.3 mg/m^3 for the Banbury mixing-area samples (for which the highest plant mean was 4.2 mg/m^3). The values for personal samples were 3.1 mg/m^3 for the compounding area (highest plant mean, 5.0 mg/m^3) and 1.9 mg/m^3 for the Banbury area (highest plant mean, 5.8 mg/m^3) (Williams *et al.*, 1980). A United States National Institute for Occupational Safety and Health study (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 mixer operators' exposures at five factories ranged from 0.08 to 1.54 mg/m^3 and the geometric means of milling operators' exposures at three factories ranged from 0.20 to 1.22 mg/m^3.

Over a six-month period, beginning in October 1979, a total of 1951 personal samples (1564 total dust, 387 respirable dust) were collected from 24 carbon black production facilities in the United States (Smith & Musch, 1982). A summary of the results are provided in Table 12. Workers involved in filling and stacking bags of carbon black (material handling) had the highest mean total dust exposures 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. These data were subsequently used in the first cross-sectional analyses of the American respiratory morbidity study (Robertson *et al.*, 1988) and the update of the American cohort study examining circulatory, respiratory and malignant diseases (Robertson & Ingalls, 1989).

Table 12. Summary of average dust exposure by employment area in United States carbon black production facilities (1979–80)

Area of employment	Total dust			Respirable dust		
	No. of plants	No. of samples	Geometric mean (mg/m^3)	No. of plants	No. of samples	Geometric mean (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)

In a mortality study conducted in the United Kingdom (Hodgson & Jones, 1985), the authors used a limited amount of exposure data collected by Her Majesty's Factory

Inspectorate in 1976. Personal samples were taken of 47 people in five carbon black factories, 24 (51%) of these being above 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.

The United States particulate sampling survey of 1979–80 (Smith & Musch, 1982) was repeated twice, once in 1980–82 and then again 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 13. A drop of approximately 50% in exposure was evident in maintenance and material handling parts of the factories. Of the job categories in the maintenance section, the following reduction was seen between the second and third surveys: utility, 0.89 to 0.55 mg/m^3; in plant, 0.79 to 0.52 mg/m^3; shop, 1.00 to 0.07 mg/m^3; instrument, 0.47 to 0.17 mg/m^3; and foreman, 0.35 to 0.18 mg/m^3. Of the job categories in the material handling section, the following reduction was seen between the second and third surveys: stack and bag, 1.92 to 0.77 mg/m^3; bagger, 2.67 to 0.85 mg/m^3; bulk loader, 2.07 to 0.82 mg/m^3; stacker, 1.15 to 0.70 mg/m^3; fork-lift truck driver, 0.53 to 0.34 mg/m^3; and foreman, 0.18 to 0.02 mg/m^3.

Table 13. Summary of average total dust exposure by employment area in United States carbon black production facilities in 1980–82 and 1987

Area of employment	1980–82		1987	
	No. of samples	Geometric mean (mg/m^3)	No. of samples	Geometric mean (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)

The most recent and comprehensive data come from the exposure assessment element of the trans-European respiratory morbidity study (Gardiner *et al.*, 1993). The first data published from this study were from a pilot study assessing the bioavailability of the adsorbed PAHs. Five individuals packing carbon black into 25-kg bags were assessed over the period of a week; their weekly personal mean dust exposures were 1.53, 5.30, 9.56, 9.99 and 13.21 mg/m^3 (Gardiner *et al.*, 1992b).

The first cross-sectional phase of the prospective European study was conducted between 1987 and 1989 with the second extending from 1990 to 1992. A fully randomized, epidemiologically based sampling strategy was used to minimize the inherent biases of worker selection, and a statistically relevant proportion of all job categories in

all 18 plants was taken. In addition, both respirable and total inhalable dust fractions were measured. In the first phase, 1278 respirable and 1288 total inhalable dust samples were taken (Gardiner *et al.*, 1992a). The use of a unique multiplication factor derived from the variability of the phase I data (Gardiner, 1995b) means that, in phase II, significantly more samples were taken — 2941 respirable and 3433 total inhalable dust samples (Gardiner *et al.*, 1996). The respirable dust data for both phases are presented in Table 14 and the data for total inhalable dust are summarized in Table 15.

As with the data presented by Musch and Smith (1990), it is evident that in the three years between the two surveys exposure had decreased by approximately 50% (total inhalable dust, 49.9%; respirable dust, 42%) (Gardiner *et al.*, 1996).

The National Occupational Exposure Survey conducted by the United States National Institute for Occupational Safety and Health (1995) between 1981 and 1983 indicated that about 1 729 000 employees in the United States 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 these user industries who handle the fluffy or pelletized 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 have little opportunity for exposure. End users of these products (rubber, ink or paint) are not exposed to carbon black *per se*, since it is bound within the product matrix.

1.3.3 *Ambient air*

In 1978, it was estimated that 1240 tonnes of carbon black were emitted during carbon black manufacture in the United States (Rawlings & Hughes, 1979). Table 16 summarizes typical particulate carbon black emissions into the air during various stages of manufacture by the oil-furnace process prior to 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 carbon black (wet basis) at less than 50 mg/m^3, a concentration that is not visible (Johnson & Eberline, 1978).

Tyre dust, of which carbon black is a component, was estimated, in a 1969 study, to account for approximately 0.8% of the aerosol above an urban area in California. An estimated 0.2% of the particulates in the aerosol consisted of elemental carbon contributed by tyre dust (Friedlander, 1973).

Carbon black was not detected in the atmosphere around a factory in Germany where it was manufactured (Deimel & Dulson, 1980).

Table 14. Respirable dust data from phase I and II of the European respiratory morbidity study

Job title	Phase I			Phase II		
	No. of samples	Geometric mean (mg/m^3)	Maximum (mg/m^3)	No. of samples	Geometric mean (mg/m^3)	Maximum (mg/m^3)
Administrative staff (office bound, phase I)	278	0.15	1.09	302	0.09	2.07
Administrative staff (non-office bound, phase II)	–	–	–	163	0.12	1.16
Laboratory assistant	134	0.20	16.36	320	0.12	2.98
Process control room operator	44	0.18	1.33	159	0.13	5.28
Instrument mechanic	61	0.20	1.94	181	0.18	24.65
Electrician	62	0.27	7.60	134	0.15	1.59
Process foreman	79	0.21	0.94	253	0.18	3.36
Furnace operator	48	0.27	5.59	144	0.22	4.16
Fitter	107	0.35	4.77	238	0.19	3.18
Welder	41	0.27	1.10	66	0.28	7.71
Process operator	177	0.29	19.36	310	0.16	3.35
Conveyor operator	53	0.20	1.74	79	0.30	3.10
Warehouse/packer	159	0.50	13.92	408	0.35	19.00
Cleaner	35	0.32	8.60	183	0.27	20.70

From Gardiner *et al.* (1996)

Table 15. Total inhalable dust data from phase I and II of the European respiratory morbidity study

Job title	Phase I				Phase II			
	No. of samples	Geometric mean (mg/m^3)	% > 3.5 mg/m^3	Maximum (mg/m^3)	No. of samples	Geometric mean (mg/m^3)	% > 3.5 mg/m^3	Maximum (mg/m^3)
Administrative staff (office bound, phase I)	289	0.18	0.0	2.77	302	0.12	0.0	1.71
Administrative staff (non-office bound, phase II)	–	–	–	–	186	0.19	0.0	2.56
Laboratory assistant	143	0.38	2.1	9.66	326	0.24	0.0	2.44
Process control room operator	50	0.29	0.0	2.19	157	0.17	0.0	1.40
Instrument mechanic	59	0.55	8.5	22.67	257	0.40	1.6	8.61
Electrician	58	0.65	10.3	31.12	193	0.33	0.0	3.33
Process foreman	70	0.37	0.0	3.42	296	0.25	0.7	5.03
Furnace operator	56	0.54	5.4	9.21	156	0.44	1.9	9.48
Fitter	95	1.28	11.6	22.77	270	0.53	2.6	6.87
Welder	41	1.18	7.3	9.56	75	1.06	10.7	8.75
Process operator	179	0.96	16.8	30.75	420	0.44	1.4	16.92
Conveyor operator	59	0.53	5.1	4.20	127	0.64	4.7	8.97
Warehouse/packer	151	1.96	35.1	41.11	490	0.96	12.0	19.95
Cleaner	38	1.24	21.1	21.17	178	0.58	8.4	18.04

From Gardiner *et al.* (1996)

Table 16. 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)

Because the production of carbon black often involves the combustion of aromatic residual oils from petroleum refining and coal tar, the carbon black industry must also consider potential ambient air emissions of sulfur and nitrogen oxides, hydrogen sulfide, volatile hydrocarbons and carbon monoxide (The Freedonia Group, 1994b).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for carbon black are presented in Table 17. The use of carbon black from hydrocarbon sources in food contact materials is provisionally accepted by FAO (Food and Agriculture Organization of the United Nations)/WHO (World Health Organization) (United Nations Environment Programme, 1995).

The United States Food and Drug Administration (1976, 1994a) has banned the use of carbon black (prepared by the impingement or channel process) for direct use in food, drugs and cosmetics (21 CFR 81.10). The United States Food and Drug Administration (1994b) has approved the following uses of carbon black:

- Carbon black (channel process) is permitted as an indirect food additive as a component of adhesives that come in contact with food (21 CFR 175.105);
- Carbon black (channel process, prepared by the impingement process from stripped natural gas) is permitted as a colourant (21 CFR 178.3297) in resinous and polymeric coatings that come in contact with food (21 CFR 175.300) and in rubber articles intended for repeated use that come in contact with food (21 CFR 177.2600);

Table 17. Occupational exposure limits and guidelines for carbon black

Country	Year	Concentration (mg/m^3)	Interpretation
Argentina	1991	3.5	TWA
Australia	1993	3	TWA
Belgium	1993	3.5	TWA
Bulgaria[a]	1995	3.5	TWA
Canada	1991	3.5	TWA
Colombia[a]	1995	3.5	TWA
Denmark	1993	3.5	TWA
Finland	1993	3.5	TWA
		7	STEL (15 min)
France	1993	3.5	TWA
Germany	1995	None	
Jordan[a]	1995	3.5	TWA
Mexico	1991	3.5	TWA
Netherlands	1994	None	
New Zealand[a]	1995	3.5	TWA
Philippines	1993	3.5	TWA
Republic of Korea[a]	1995	3.5	TWA
Russia	1993	4	MAC
Singapore[a]	1995	3.5	TWA
Sweden	1993	3	TWA
United Kingdom	1995	3.5	TWA
		7	STEL (15-min)
USA			
ACGIH (TLV)	1995	3.5[b]	TWA
NIOSH (REL)	1994	3.5[c] (Ca)	TWA
OSHA (PEL)	1994	3.5	TWA
Viet Nam[a]	1995	3.5	TWA

From US National Institute for Occupational Safety and Health (NIOSH) (1994a,b); US Occupational Safety and Health Administration (OSHA) (1994); American Conference of Governmental Industrial Hygienists (ACGIH) (1995); Deutsche Forschungsgemeinschaft (1995); Health and Safety Executive (1995); United Nations Environment Programme (1995)

TWA, time-weighted average; STEL, short-term exposure limit; MAC, maximal allowable concentration; TLV, threshold limit value; REL, recommended exposure limit; Ca, potential occupational carcinogen; PEL, permissible exposure limit

[a] Follows ACGIH TLVs

[b] Substance identified by other sources as a suspected or confirmed human carcinogen

[c] In the presence of polynuclear aromatic hydrocarbons (PAHs), the limit for PAHs is 0.1 mg/m^3 TWA, determined as cyclohexane-extractable fraction

- Carbon black (channel process) is permitted as a component of polysulfide polymer-polyepoxy resins that come in contact with dry food (21 CFR 177.1650);
- Carbon black (channel process or furnace combustion process) is permitted as an optional adjuvant substance: in perfluorocarbon-cured elastomers that come in contact with non-acid food (pH above 5.0) at concentrations not to exceed 15 parts per 100 parts of the terpolymer (21 CFR 177.2400) and in phenolic resins in molded articles that come in contact with non-acid food (pH above 5.0) (21 CFR 177.2410).

Because of the possibility that traces of oil feedstocks can appear in the wastes, the United States Environmental Protection Agency (1994a) has banned the discharge of process waste-water pollutants into navigable waters by carbon black manufacturers utilizing any of the following processes: furnace, thermal, channel, or lamp. The United States Environmental Protection Agency (1994b) has exempted carbon black from the requirement of a tolerance when used as a colourant/pigment in animal tags (40 CFR 180.1001).

2. Studies of Cancer in Humans

Industrial exposure to carbon black has occurred in the carbon black production industry and in a number of user industries, including the rubber, paint and printing industries. The cancer risks associated with these three exposure circumstances have been evaluated within the *IARC Monographs* programme (see IARC, 1982, 1989b; see also this volume).

The Working Group felt that epidemiological evidence concerning cancer risk 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 carbon black-exposed workers. Some 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. Also, it appears that concentration of exposure was substantially higher in the past in the carbon black production workers than in the user industries. 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 user industries were often exposed to complex mixtures of substances, of which carbon black may have been a relatively minor component. Potential confounding of results by concomitant occupational exposures is therefore a significant, potential problem in studies among users. The potential for such confounding bias is greatest when the study population is concentrated in an industry in which there is a single, dominant exposure (or a small number of dominant exposures) other than carbon black. To the extent that the study population includes many different types of carbon black users, each with distinct

profiles of concomitant exposures, the likelihood of a strong confounding effect would be diluted. From this point of view, the relative risk estimates due to carbon black exposure derived from studies that include a variety of carbon black user industries provide less opportunity for confounding bias than do studies in a user industry in which most workers have the same profile of concomitant exposures.

2.1 Industry-based studies

Table 18 summarizes cohort studies and Table 19 case–control studies of workers exposed to carbon black.

2.1.1 *Studies in the carbon black production industry*

The cancer occurrence among employees at carbon black production facilities in the United States has been followed for different periods since 1935 and is described in five reports (Ingalls, 1950; Ingalls & Risquez-Iribarren, 1961; Robertson & Ingalls, 1980, 1989; Robertson & Inman, 1996).

Mortality results from the first two reports were subsumed by Robertson and Ingalls (1980), which represents the most complete report on the mortality experience of workers employed by any of four major carbon black manufacturing companies, with production plants located in Texas, Oklahoma and Louisiana, United States (Ingalls, 1950). Eligible study subjects were male employees aged 15 years and over with 12 months or more service during the years 1935–74 at any of the carbon black plants. Between 1950 and 1975, the average number of active workers in all participating companies was about 1250 per year. In the early years, there were equal numbers of workers in the two major processes — channel black production and furnace black production; by 1960, channel black production was dwindling and most workers were involved in the furnace black plants. The mortality experience of the cohort was traced via insurance company records. This company provided death benefit insurance to participating members of the cohort between 1935 and 1974. Over the entire period, there was a total of 34 739 person-years of observation in the mortality follow-up. [It is not stated how many distinct individuals were in the study.] Only 2% of these person-years at risk were in the age group 65 and over. Expected numbers of deaths were calculated from state vital statistics (death rates for white men at five-year intervals starting in 1937 applied to annual employee censuses by age, in five-year groups). There were 29 observed cancer deaths (standardized mortality ratio (SMR) [0.7 (95% confidence interval [CI], 0.5–1.0)]) (Table 18). There were six observed deaths due to cancers of the digestive organs and the peritoneum (SMR [0.6; 95% CI, 0.2–1.4]). There were 13 observed deaths due to cancers of the respiratory system (SMR [0.9; 95% CI, 0.5–1.5]). For all malignancies combined, there was no evidence of increasing mortality with increasing years of service, no significant excess cancers in any of the eight five-year periods and no trend in relative risk of cancer over time.

In a short communication, Robertson and Inman (1996) made a preliminary report of an extension of the follow-up of this cohort. Cohort members from two of the original four companies and those from an additional company were traced for an additional

Table 18. Cohort studies among workers exposed to carbon black

Reference location	Study subjects	Period of follow-up	Occupation/exposure	Cancer site/ cause of death	No. obs.	RR	95% CI	Comments
Robertson & Ingalls (1980) Southern USA	Male employees of US carbon black producers	1935–74	Employees with carbon black exposure (34 729 person-years)	All causes	190	[0.8]		Age- and race-adjusted comparison with state populations. No smoking information
				All cancers	29	[0.7]	[0.5–1.0]	
				Gastrointestinal	6	[0.6]	[0.2–1.4]	
				Respiratory	13	[0.9]	[0.5–1.5]	
			Subset with ≥ 20 years service	All cancers	15	[0.8]		Few person-years over age 65
Hodgson & Jones (1985) United Kingdom	Male employees of 5 United Kingdom carbon black producers	1947–80	Employees with carbon black exposure (19 266 person-years)	All causes	129	0.8	[0.7–1.0]	Age-adjusted comparison with local populations. No smoking information. Few person-years over age 65
				All cancers	42	1.0	[0.7–1.3]	
				Lung	25	1.5	[1.0–2.2]	
				Urinary bladder	3	2.5	[0.5–7.3]	
Blair *et al.* (1990) USA	Male employees at plants with formaldehyde exposure	Not given	Subset with carbon black exposure	Lung	20	1.3	[0.8–2.0]	Age-adjusted comparison with US population. No smoking information
			≥ 20 years duration	Lung	6	2.4	[0.9–5.2]	
			≥ 20 years latency	Lung	11	1.4	[0.7–2.5]	
Robertson & Inman (1996) Southern USA	Male employees of US carbon black producers	1935–94	Employees with carbon black exposure (55 784 person-years)	All causes	377	0.7	0.6–0.8	Age- and race-adjusted comparison with state populations. No smoking information. Short communication. Incompletely documented. This cohort largely overlaps with that of Robertson & Ingalls (1980).
				All cancers	79	0.7	0.6–0.9	
				Gastrointestinal	12	0.5	0.3–0.8	
				Respiratory	34	0.8	0.6–1.1	

RR, relative risk estimates — all SMRs (standardized mortality ratios)

Table 19. Case–control studies of workers exposed to carbon black

Reference location	Study base	Cases	Controls	Exposure	Cancer site	No. of exposed cases/ controls	RR	95% CI	Comments
Robertson & Ingalls (1989) USA	Male employees of carbon black producers active in 1980	Previously diagnosed with skin cancer (n = 24)	One matched for age and one matched for age and duration of employment (n = 48)	Cumulative exposure index for carbon black	Skin	24/NG	0.9	0.3–3.2	Prevalent cases may well be unrepresentative. Not clear how exposure was dichotomized.
Bourguet *et al.* (1987) USA	Male employees of rubber manufacturing industry active in 1964 or earlier	Subsequently diagnosed with skin cancer in local hospitals (n = 65)	Four matched to each case on company, year of birth, year of hire (n = 254)	Intensity of exposure to carbon black:	Skin				'Intensity of exposure' reflected concentration and frequency of exposure. The findings did not indicate any exposure–response relationship nor any trend by duration of exposure.
				Low		14/47	0.7	NG	
				Medium		14/49	1.2	NG	
				High		8/48	0.7	NG	
Steineck *et al.* (1990) Sweden	Male general population of Stockholm	Urothelial cancers 1985–87 (n = 254)	Population control frequency matched on sex and year of birth (n = 287)	Ever exposed to carbon black including printing inks	Urothelial	14/9	2.0	0.8–4.9	Adjusted for year of birth and smoking
Siemiatycki (1991) Canada	Male general population of Montréal	Incident cases from 1979 to 1985, with any of 19 types of cancer	Cancer controls, not matched	Ever exposed to carbon black (i.e. 'any' exposure)					Adjusted for age, social class, ethnicity and smoking
		Oesophagus (99)	2546		Oesophagus	11/NG	2.2	[1.1–4.4]	
		Stomach (251)	2397		Stomach	9/NG	0.8	[0.4–1.4]	
		Colon (497)	2056		Colon	17/NG	0.7	[0.5–1.1]	
		Rectum (257)	1299		Rectum	10/NG	0.7	[0.4–1.3]	
		Pancreas (116)	2454		Pancreas	3/NG	0.7	[0.2–2.2]	
		Lung (857)	1360		Lung	52/NG	1.6	[1.1–2.3]	
		Prostate (449)	1550		Prostate	25/NG	1.2	[0.7–1.9]	
		Urinary bladder (484)	1879		Urinary bladder	26/NG	1.2	[0.7–1.9]	
		Kidney (177)	2481		Kidney	14/NG	1.9	[1.1–3.3]	
		Skin melanoma (103)	2525		Skin melanoma	2/NG	0.4	[0.1–1.8]	
		Non-Hodgkin's lymphoma (215)	2357		Non-Hodgkin's lymphoma	9/NG	0.9	[0.5–1.8]	

Table 19 (contd)

Reference location	Study base	Cases	Controls	Exposure	Cancer site	No. of exposed cases/ controls	RR	95% CI	Comments
Parent *et al.* (1996) Canada	Male general population of Montréal	As in Siemyatycki (1991) lung (n = 857)	Cancer control (n = 1360)	Higher exposure to carbon black	All lung cancers		2.2	1.0–4.9	Adjusted for age, social class, ethnicity, smoking, asbestos and chromium compounds. 'Higher' exposure reflects concentration, frequency, confidence in attribution and duration of exposure.
					Oat-cell carcinomas		5.1	1.7–14.9	
					Squamous-cell carcinomas		0.8	0.2–2.8	
					Adenocarcinomas		2.1	0.5–8.2	
			Population control (n = 533)		All lung cancers		1.5	0.6–4.0	
					Oat-cell carcinomas		4.8	1.4–17.0	
					Squamous-cell carcinomas		0.4	0.1–1.6	
					Adenocarcinomas		1.8	0.4–7.7	

RR, relative risk — all ORs (odds ratios); NG, not given

20 years to 1994, bringing the total person-years of observation up to 54 784. [Of these, 7% were in age groups over 65.] Expected numbers of deaths were based on white male, age-, calendar year- and state-specific death rates. The overall SMR was 0.7 and the SMR for all cancers was 0.7 (95% CI, 0.6–0.9) (Table 18). The SMR for respiratory cancer, based on 34 observed cases, was 0.8 (95% CI, 0.6–1.1).

[The Working Group noted that the system used for ascertainment of vital status, based on records of the insurance company, may well have led to under-ascertainment of deaths in this cohort of workers. Such under-reporting might not lead to bias in estimates of risk if departures from the company were unrelated to mortality risk and if the person-years of observation have been appropriately adjusted for 'loss to view'. The published reports do not provide sufficient detail to reassure the Working Group that these problems have been given adequate consideration. The fairly low overall SMR of 0.7 lends some weight to the hypothesis of a systematic downward bias.]

Information on cancer morbidity was presented in the first, second and fourth reports from this group. The incidence of cancer for the earlier periods (1944–49 and 1949–57) was ascertained from annual examinations and insurance claims (Ingalls, 1950; Ingalls & Risquez-Iribarren, 1961). These cancer incidences were compared with the cancer incidence reported from New York State in 1950 and with that of workers in the carbon black industry whose jobs did not involve exposure to carbon black. Among carbon black workers, only a handful of cases of cancer were ascertained (three in the first report and six in the second); of these nine cases in the 'exposed' cohort, five were skin cancers of which two were melanomas. There were three more skin cancers in the presumed 'unexposed' cohort, of which two were melanomas. Based on the absence of an excess of observed over expected deaths in the entire cohort and the absence of any apparent difference between the 'exposed' and 'unexposed' subcohorts, the authors concluded that there was no evidence of excess cancer incidence. [The Working Group noted that the data presented in the two early reports are obscure as to case-ascertainment procedures and the definition of comparison groups, which are based on very small numbers.]

The fourth report from this group described a study examining morbidity among the same cohort of carbon black industry workers in the United States (Robertson & Ingalls, 1989). The study base consisted of workers aged 15 and over employed in 1980 on site at any of seven carbon black producers. A nested case–control design was used (see Table 19). A case was defined as a member of the study population who had filed a health insurance claim with a physician's diagnosis of either a malignant neoplasm, a disease of the circulatory system or a disease of the respiratory system. For each case, two controls were selected from the workers in the study base who had none of these diagnoses, one matched for age alone and one matched for age and duration of employment. Exposure to carbon black was estimated by attributing to each job the exposure levels found in a previous hygiene survey of jobs and combining it with duration of employment to produce a cumulative exposure index. In total, 36 cases of malignant neoplasm were ascertained, of which 24 were skin cancers (12 basal-cell and 12 squamous-cell), three were lung cancers and the remainder were spread among other sites. The odds ratio for all cancers was 1.1 (95% CI, 0.4–2.7) and that for skin cancers was 0.9 (95% CI, 0.3–3.2).

[The Working Group noted that the use of a study base of workers active at a single point in time led to small numbers. Further, the distribution of cancer sites among prevalent cases would not reflect the site distribution of incident cases; for example, cancers with long survival (e.g. skin cancer) would be over-represented and cancers with short survival (e.g. lung cancer) would be under-represented. The exposure contrast used to compute the odds ratio was unclear.]

A historical cohort study was carried out among carbon black production workers in the United Kingdom (Hodgson & Jones, 1985). Data were collected on 1422 male manual workers with at least one year of service between 1947 and 1974 in any of five major carbon black production factories. For three of the companies, the investigators believed that they had compiled virtually complete rosters of all eligible workers; for the other two, they did not have available those workers who had left the industry before the late 1960s. The subjects identified were traced via national vital statistics registers. For the three 'completely enumerated' subcohorts, the follow-up period began one year after initial exposure to carbon black (i.e. after beginning employment) and for the two 'incompletely enumerated' subcohorts, the follow-up period began after the late 1960s. For members of all subcohorts, the follow-up ended on 31 December 1980, unless truncated by death or emigration. There were a total of 19 266 person-years of observation in the mortality follow-up, of which only 4% were in the age group over 65 years. Overall, 9% of the study subjects were known to have died during the period of observation. Irrespective of whether the comparison was with national mortality rates or with regionally specific mortality rates, there was a deficit in this cohort of deaths from all causes (of approximately 15%) (this was made up mainly of deficits of circulatory and non-malignant respiratory deaths). For specific cancer sites, there was a deficit of deaths from stomach cancer (0 observed, 4.1 expected), parity in deaths from colorectal cancer (3 observed, 4.0 expected), an excess of deaths from urinary bladder cancer (3 observed, 1.3 expected) and most notably an excess of deaths from respiratory cancer (SMR, 1.5 [95% CI, 1.0–2.3]; 25 observed cases) (Table 18). [The deficit of deaths from all causes was probably due largely to the 'healthy worker effect' but also partly to a survivor bias in the two 'incompletely enumerated' factories as those inception subcohorts included workers who had remained (i.e. survived) in the industry for up to 20 years.] The excess of deaths from lung cancer was most evident in one of the five factories (10 observed, 4.8 expected), although there were slight excesses in the other four factories combined as well (15 observed, 11.7 expected). [The Working Group noted that this factory was one that had incomplete early data, but it is unlikely that this could have biased the results in the observed direction.] Industrial hygiene measurements had been taken in 1976 in the various factories. About one-half of all personal samples were above the benchmark TLV for carbon black of 3.5 mg/m^3. There was no indication that the factory with the greatest excess risk had higher exposure levels than the other factories. On the contrary, the measured levels were somewhat lower on average, although they were based on small numbers of measurements. A nested case–control study was carried out, comparing the cases of lung cancer with controls chosen from the unaffected members of the cohort, matched for factory and date of birth. The duration of employment did not differ between cases and controls. [The Working Group noted that the report contained too little infor-

mation on this study to evaluate the findings adequately.] While no data were presented on smoking habits in this population, the authors refer to an early study in this industry in which smoking habits were not found to have differed greatly from those of the general population.

A general excess risk of cancer was reported in workers in one carbon black producing plant in the former USSR (Troitskaya *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 *Studies in carbon black user industries*

A nested case–control study was conducted in the tyre and rubber manufacturing industry to examine the association of squamous-cell carcinoma of the skin with rubber manufacturing materials 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, United States, 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 authors acknowledge that their 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 hire, and were required to have been employed in the industry until the corresponding case's date of diagnosis or date of leaving the industry. A total of 254 matched controls were identified, with approximately four matched controls selected for each case. Two experienced industrial hygienists assessed each study subject's exposure 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 categorized into three exposure subgroups reflecting concentration and frequency of exposure. For carbon black, the odds ratios in these three exposure subgroups were 0.7, 1.2 and 0.7, respectively, indicating the lack of an exposure–response relationship (see Table 19). There was also no evidence for any trend by duration of exposure.

A historical cohort of 26 561 workers employed in 10 facilities was assembled to evaluate cancer risks associated with exposure to formaldehyde (see IARC, 1995) (Blair *et al.* 1990). The plants were drawn from a variety of industries in which exposure to formaldehyde can be substantial and were located across the United States. 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]. In order to assess possible confounding and modification of effect due to other occupational substances, an assessment was made of each worker's exposure to a number of other substances, one of which was carbon black. The exposure status of subjects was inferred from their recorded work histories, 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 carbon black exposure, the data could be used for that purpose, and, in one report focusing primarily on exposure to formaldehyde and lung cancer risk, results were presented showing the associations between each of the other substances collected 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) (Table 18). 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 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.]

2.2 Community-based case–control studies

In a Swedish case–control study of urothelial cancer during 1985–87 (Steineck *et al.*, 1990), described in the monograph on printing trades and printing inks in this volume, p. 76, the odds ratio for men having been exposed to carbon black was 2.0 (95% CI, 0.8–4.9; 14 cases), adjusted for year of birth and for smoking (Table 19). However, some of these workers had been exposed to printing inks and other substances.

A population-based case–control study of cancer among male residents of Montréal, Canada, aged 35–70, included histologically confirmed cases of cancer at 11 major sites, newly diagnosed between 1979 and 1985, in 19 major hospitals (Siemiatycki, 1991). With a response rate of 82%, 3730 cancer patients were successfully interviewed. For each site of cancer analysed, two control groups were used, giving 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 19) and the other 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 a trained team of chemists and industrial hygienists who translated jobs into occupational exposures, using a checklist of 293 common occupational substances. Cumulative exposure indices were created for each substance, on the basis of duration, concentration, frequency and the degree of certainty in the exposure assessment itself, and these were analysed at two levels: 'any' and 'substantial' exposure; the latter is a subset of 'any'. Five percent 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 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 presentation of published results was based mainly on the cancer control group. For the following cancer sites, there was no indication of excess risk in relation to any exposure to carbon black, after adjustment for age, ethnic group, social class and smoking (number of exposed

cases; odds ratio): stomach (9; 0.8), colon (17; 0.7), rectum (10; 0.7), pancreas (3; 0.7), prostate (25; 1.2), urinary bladder (26; 1.2), skin melanoma (2; 0.4) and non-Hodgkin's lymphoma (9; 0.9). For the following sites there was indication of excess risk (number of exposed cases; odds ratio [95% CI]): oesophagus (11; 2.2 [1.1–4.4]), kidney (14; 1.9 [1.1–3.3]) and lung (52; 1.6 [1.1–2.3]).

To investigate further the possible link between carbon black and lung cancer, an additional analysis of the Montréal data set was carried out. A synthetic exposure index was created, composed of the indices deduced for each exposed subject (concentration, frequency, confidence in the attribution of exposure, duration), and this index was used to designate a lower and a higher cumulative exposure subgroup. Logistic regression analyses were carried out, adjusting for the same covariates as in the above analyses, as well as for two recognized lung carcinogens, asbestos and chromium compounds. Using cancer controls, the odds ratios for lower and higher exposure were 1.1 (95% CI, 0.7–1.8) and 2.2 (95% CI, 1.0–4.9); using population controls, the odds ratios for lower and higher exposure were 0.9 (95% CI, 0.5–1.6) and 1.5 (95% CI, 0.6–4.0), respectively. The excess among highly exposed workers was most pronounced for oat-cell tumours of the lung: odds ratios, 5.1 (95% CI, 1.7–14.9) using cancer controls and 4.8 (95% CI, 1.4–17.0) using population controls (Table 19) (Parent *et al.*, 1996).

3. Studies of Cancer in Experimental Animals

The studies described in the following sections include those investigating the potential carcinogenicity of carbon black, solvent-extracted carbon black and the materials extracted from carbon black (carbon black extracts). However, a detailed review of individual materials extracted from various carbon blacks is not part of this monograph. Some of these individual components (e.g. nitroaromatic compounds) have been evaluated in previous monographs (IARC, 1989a).

Several early studies compared the carcinogenicity of carbon black or carbon black extracts when administered orally or by skin or subcutaneous application. More recent studies have examined the carcinogenicity of inhaled or intratracheally administered carbon black or solvent-extracted carbon black. Many of these studies were part of large studies carried out to investigate the carcinogenicity of diesel exhaust (see also IARC, 1989c).

The Working Group also considered some issues relating to the interpretation of several of the inhalation and intratracheal instillation studies of carbon black. A lesion frequently seen in treated rats has been described variously as 'proliferating squamous cyst', 'proliferative keratin cyst', 'proliferating squamous epithelioma', 'benign cystic keratinizing squamous-cell tumour' or 'cystic keratinizing squamous-cell (CKSC) tumour'. Various authors have included this lesion in tumour counts, but the neoplastic nature of this lesion has been debated (Vainio *et al.*, 1992; Carlton, 1994; Dungworth *et al.*, 1994; Mauderly *et al.*, 1994); 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.

The Working Group considered reports by von Haam and Mallette (1952), von Haam *et al.* (1958), Nau *et al.* (1958a, 1960, 1962), Shabad *et al.* (1972) and Davis *et al.* (1975) in their evaluation, but, because of deficiencies in detail of design, performance and/or reporting, did not use this information in reaching its conclusion.

3.1 Oral administration

3.1.1 *Mouse*

After two weeks of acclimatization, two groups of 31 and 28 female weanling CF1 mice received a diet for two years that did or did not (controls) include furnace black (ASTM N-375; 2.05 g/kg diet). At necropsy, all tissues were examined for gross pathology. Only tissues with macroscopically diagnosed alterations were examined histologically. Survival at two years was similar in treated mice (84%) and in controls (71%). No increase in tumour incidence was observed (Pence & Buddingh, 1985). [The Working Group noted the small numbers of animals and the incomplete histopathological examination.]

3.1.2 *Rat*

After two weeks of acclimatization, two groups of 29 female weanling Sprague-Dawley rats received a diet for two years that did or did not (controls) include furnace black (ASTM N-375; 2.05 g/kg diet). At necropsy, all tissues were examined for gross pathology. Only tissues with macroscopically diagnosed lesions were examined histologically. Survival at two years was similar in controls (38%) and treated animals (45%). No increase in tumour incidence was observed (Pence & Buddingh, 1985). [The Working Group noted the small numbers of animals and the incomplete histopathological examination.]

3.2 Inhalation

3.2.1 *Mouse*

Groups of 80 female Crl: NMRI BR mice, seven weeks old, were exposed to high purity furnace 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. For 18 h per day on five days per week, the animals were exposed in whole-body exposure chambers to 7.4 mg/m^3 carbon black for four months followed by 12.2 mg/m^3 for 9.5 months. After exposure, the mice were kept in clean air for another 9.5 months. A control group was exposed to clean air throughout. 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 group compared with the control group. During the last months, no difference between the groups was observed. After 13.5 months, mortality was 20% in the carbon black-exposed group and

10% in the control group; 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 three, six and 12 months, respectively; and, at 12 months, this corresponded to a lung particle burden of 37 mg/g clean air control lung. Among tissues examined, tumours were only observed in the lung. However, no statistical difference was observed between experimental and control animals: carbon black-exposed mice, 11.3% [9/80] adenomas and 10% [8/80] adenocarcinomas; controls, 25% [20/80] adenomas and 15.4% [12/80] adenocarcinomas (Heinrich *et al.*, 1995).

3.2.2 *Rat*

Two groups of 72 female Wistar Crl:(WI)BR rats, seven weeks old, were exposed by inhalation for 17 h per day on five days per week to 6 mg/m^3 furnace black (Printex 90; 0.04% extractable mass of organics (content of benzo[*a*]pyrene, 0.6 pg/mg and that of 1-nitropyrene, < 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 group 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 were kept for 129 weeks. The respiratory tract of all animals was examined histopathologically. The 43-week exposure group had a lung tumour rate of 18% [13/72] (2 bronchiolar/alveolar adenomas, 7 benign CKSC tumours, 4 bronchiolar/-alveolar adenocarcinomas and 1 squamous-cell carcinoma). The 86-week exposure group had a lung tumour rate of only 8% [6/72] (1 bronchiolar/alveolar adenoma, 4 benign CKSC tumours and 1 squamous-cell carcinoma). In addition to the six tumours of the latter group, six rats showed lung lesions in the borderline between non-neoplastic and neoplastic (described as marked hyperplasia or marked squamous-cell proliferation). [The difference in the tumour rates of the two exposure groups was not statistically significant.] No tumour was observed in the clean air controls (Heinrich *et al.*, 1994).

A group of 100 female Wistar Crl:(WI)BR rats, seven weeks old, was exposed to high purity furnace black (Printex 90; particle size 14 nm; specific surface area, 227 ± 18.8 m^2/g; MMD 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 for 18 h per day on five days per week in whole-body exposure chambers to 7.4 mg/m^3 carbon black for four months followed by 12.2 mg/m^3 for 20 months (average 11.6 mg/m^3). After exposure, the rats were kept in clean air for another six months. Controls were exposed to clean air throughout. Additional groups of 9–20 rats were also exposed to carbon black and were killed at six, 12, 18 and 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 to the controls, the mean lifespan of the treated rats was significantly reduced (Kaplan-Meier method using the SAS-lifetest programme). 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/lung [equivalent to 31.3 mg/g clean air control lung] and 6.7 mg/animal in the lung-associated lymph nodes (determined after 22 months of exposure). Benign and malignant lung tumours were increased in the treated groups. The numbers of rats with lung tumours are summarized in Table 20 (Heinrich *et al.*, 1995).

Table 20. Number of female rats with lung tumours after carbon black exposure

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

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

Groups of 135–136 female and 138–139 male Fischer 344/N specific pathogen-free rats, seven to nine weeks old, were exposed to 0, 2.5 or 6.5 mg/m^3 furnace black (Elftex-12) for 16 h per day on five days per week for up to 24 months in whole-body exposure chambers. The carbon black aerosol was produced by an air jet dust generator and was diluted with filtered air. The carbon black particle size distribution in the chamber was bimodal with 67% in the large-size mode (MMAD, 2.0 μm) and 33% in the small-size mode (MMAD, 0.1 μm). The level of extractable organic material was 0.04–0.29% (mean value during the course of exposure was 0.12%). Observations throughout the complete lifespan were made for the majority of rats in each group (that is, for approximately 100 males and 100 females in total). From these data, body weight, survival and carcinogenicity were evaluated. After exposure for 24 months, surviving rats were kept in clean air until mortality reached 90%. Three female and three male rats selected randomly from each group were killed after three, six, 12, 18 or 23 months for multiple evaluations, including particle burden and histopathology. The high-dose exposure to

carbon black reduced the median lifespan of both females and males significantly. The survival of males was also significantly reduced by the low-dose exposure to carbon black (Kaplan-Meier method for determining survival curves; statistical method, log-rank test of Harrington and Flemming). A significant reduction in the body weights of female and male rats exposed to the high-dose carbon black first occurred on days 309 and 449, respectively. For the low-dose exposure to carbon black, this effect was seen only after day 509 of exposure for both males and females. After about 22 months of exposure to the high-dose carbon black, the mean reduction in body-weight was 16% for females and 14% for males. For the low-dose exposure to carbon black, these figures were below 10%. 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 of clean air control lung in low-dose males, 13.9 mg/g of clean air control lung in low-dose females, 20.2 mg/g of clean air control lung in high-dose males and 30 mg/g of clean air control lung in high-dose females. Full necropsies were performed on all animals and lungs and suspected lung tumours were examined microscopically. The incidences of the various types of lung tumours are shown in Table 21. Statistical comparisons were performed using logistic regression modelling. The incidences of adenomas and adeno-carcinomas were significantly increased in females, particularly at the high-dose level. The percentages of male and female rats with lung tumours are given in Table 22. Exposure-related squamous cysts in the lung were classified as non-neoplastic lesions. In animals dying later than 18 months after the start of the exposure, squamous cysts (1 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, 8/90 and 13/87 control, low-dose and high-dose females, respectively (Mauderly *et al.*, 1994; Nikula *et al.*, 1995).

3.3 Intratracheal administration

Rat

A group of 37 female Wistar rats, 15 weeks old, was instilled intratracheally under CO_2 anaesthesia with furnace black (Printex 90) of a high specific surface area (270 m^2/g). The carbon black was suspended in 0.9% sodium chloride using ultrasonication and 3 mg/rat were instilled 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 at the latest. More than 50% of rats in the treated and control groups survived to 100 weeks. The respiratory tract was evaluated microscopically. No primary lung tumour was found in the control group. In the treated animals, 65% [24] of the rats had primary lung tumours — three rats had adenomas, six rats had adenocarcinomas and one additional rat had an adenocarcinoma and a CKSC tumour, four rats had CKSC tumours and one additional rat had a CKSC tumour and an adenoma, three rats had squamous-cell carcinomas and six rats had squamous-cell carcinomas and additional lung tumours (1 adenoma, 1 adenocarcinoma, 3 adenocarcinomas and CKSC tumours, 1 CKSC tumour) (Pott & Roller, 1994; Pott *et al.*, 1994).

Table 21. Numbers of different types of lung neoplasms observed and numbers of rats with each type of neoplasm[a]

Type of tumour	Control			Low-dose carbon black (2.5 mg/m^3)			High-dose carbon black (6.5 mg/m^3)		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
No. of animals examined[b]	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[c]									
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 Mauderley *et al.* (1994)

[a] Several rats had multiple types of tumours or multiple tumours of a single type or both; thus, these rats (or their tumours) are counted more than once in this table

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

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

Table 22. Summary of numbers and percentages of rats examined for lung neoplasms that had one or more neoplasms[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
Low-dose 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
High-dose carbon black (6.5 mg/m^3)	Female	105	21	20	28	26.7
	Male	106	4	3.8	4	3.8
	Combined	211	25	11.8	32	15.2

From Mauderly *et al.* (1994)

[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 rats killed at three, six 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 three, six and 12 months, is listed in Table 21.

Groups of 48 female Wistar Crl:(WI)BR rats, seven weeks of age, were treated by intratracheal injection once a week for 16–17 weeks with approximately 1 mg of two types of extracted carbon black (furnace Black Printex 90 or Lampblack 101). Resultant total particle doses were 15 mg/animal. A control group of 47 rats was treated with the vehicle (0.9% sodium chloride + 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 h before they were used in this experiment. The specific surface areas (extracted) and primary particle sizes of Printex 90 and Lamp Black 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 one day after the last treatment. Both groups showed a lung particle load of 11 mg [8.1 mg/g of clean air control lung]. Fifty percent of the animals in both groups were alive at 18 months. After an experimental time of 27 months, the respiratory tract of the 48 treated animals per group was investigated histopathologically. In the Printex 90 carbon black-treated rats, 10 had lung tumours ($p < 0.001$, Fisher's exact test) (9 benign (CK) squamous-cell tumours, 1 bronchiolar/alveolar adenoma and 4 bronchiolar/-alveolar carcinomas). In the lampblack-treated animals, four rats had benign (CK) squamous-cell tumours. No lung tumour was observed in the 47 vehicle-treated controls (Heinrich, 1994; Dasenbrock *et al.*, 1996).

3.4 Skin application

Mouse: In a series of experiments by Nau *et al.* (1958b), groups of CFW white and C3H brown mice [sex unspecified], six to 10 weeks old, received thrice-weekly skin applications by brush of 10% or 20% carbon black (of several types) suspended in cottonseed oil or mineral oil (oil suspension) or in 1% carboxymethyl cellulose (water suspension). Tests were also carried out with 20% extracted carbon black or benzene extracts of various carbon blacks. The types of carbon black were said to be representative of materials used at that time (see Table 23).

A total of 240 CFW white and C3H brown mice [sex unspecified], six to ten weeks old, received thrice-weekly skin applications by brush of 10% or 20% of three carbon blacks (product No. 5, furnace black; product No. 8, thermal black; and product No. 13, channel black; see Table 23), which contained 0–1% benzene-extractable material and were suspended in cottonseed, mineral oil or 1% carboxymethyl cellulose. These were applied on the shaved back of the mice for 12–18 months (estimated total dose, 3.6–12.8 g/mouse). No skin tumour was reported, but five tumours occurred in other organs in channel black-painted mice. Another 130 animals received treatment with a benzene-extracted carbon black (product No. 5, furnace black; see Table 23) (estimated total dose, 6.3–23.4 g/mouse); no skin tumour was observed, but two lymphosarcomas were reported (Nau *et al.*, 1958b).

Groups of male C3H and CFW mice [numbers and age unspecified] received thrice-weekly skin applications of carbon black extracts obtained by hot benzene extraction from eight different carbon blacks for up to 12 months. All but one of the extracts was reported to show moderate to strong carcinogenicity for the skin (see Table 24). Groups of positive controls (162 mice) received thrice-weekly skin applications of 3-methylcholanthrene (estimated total dose, 7–24 mg/mouse) or benzo[*a*]pyrene (26–27 mg/mouse) in water, oil or benzene (32 mg/mouse) for six to 18 months. [The Working Group noted several deficiencies in these experiments, namely inadequacies in experimental design with the use of 1% benzene as a vehicle for some extracts, and the limited reporting.] (Nau *et al.*, 1958b).

3.5 Subcutaneous and/or intramuscular administration

Mouse: Groups of 50 male and female C57Bl mice, 5–5.5 months of age, received subcutaneous injections of the following: 300 mg of a furnace black (surface area, 15 m^2/g; average particle diameter of about 80 nm) containing 300 mg/kg (ppm) benzo[*a*]pyrene, either suspended in 1 ml tricaprylin or as a pellet; 300 mg of a channel black (surface area, 380 m^2/g; average particle diameter of about 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 black plus 0.09 mg benzo[*a*]pyrene either in tricaprylin or as a pellet; benzene extract from 300 mg furnace black in 1 mL tricaprylin; the extracted carbon black from the 300 mg furnace black after benzene extraction in 1 mL tricaprylin; 300 mg furnace black treated for 3 h with hot chromic acid and suspended in 1 mL tricaprylin; and 600 mg of a mixture of

Table 23. Types and properties of carbon blacks used in Nau *et al.* studies

Product No.	Supplier No.	Type	Parent material	Iodine surface area, average[a] (m^2/g)	Benzene extract, average (%)	pH, average	Volatile, average (%)	Grade of black
2	1	Oil furnace	Oil residue	52.7	0.374	9.09	3.53	HAF
1	1	Oil furnace	Oil residue	184.5	0.15	8.86	3.17	CF
9	2	Gas furnace	Gas	21.5	0.06	9.69	0.70	HMF
10	2	Furnace	Gas-oil	28.4	0.07	8.85	1.42	FEF or MAF
11	2	Furnace	Gas-oil	61.7	0.05	9.22	1.29	HAF
12	2	Furnace	Gas-oil	99.3	0.05	9.02	2.34	ISAF
3	3	Oil furnace	Oils	76.0	0.053	9.58	4.51	HAF
4	3	Oil furnace	Oils	35.5	0.125	9.53	2.05	FEF
13	4	Channel	Gas	108.0	0.00	4.99	5.08	MPC
14	4	Channel special	Gas	126.0	0.02	9.00	2.50	STC
5	5	Oil furnace	Oils	35.5	0.17	9.08	1.96	FEF
8	5	Thermal combustion	Gas	11.5	1.04	7.47	1.04	MT
6	5	Oil furnace	Heavy aromatic tar plus natural gas	67.7	0.246	9.70	2.46	HAF
7	5	Gas furnace	Gas	21.7	0.118	9.83	0.69	SRF
15	5	Oil furnace	Oil	62.4	0.26	6.72	3.01	HAF
16	5	Gas furnace	Gas	111.0	0.08	5.81	5.15	Ink black

HAF, high-abrasion furnace; CF, conducting furnace; HMF, high modules furnace; FEF, fast-extruding furnace; MAF, medium-abrasion furnace; ISAF, intermediate super-abrasion furnace; MPC, medium-processing channel; STC, special thermal channel; MT, medium thermal; SRF, semi-reinforcing furnace

[a]Iodine surface area levels are lower than nitrogen surface area levels.

Table 24. Induction of skin tumours with various carbon black extracts in mice treated for at least 12 months

Type of material used[a]	Total dose of benzene extract (mg)	Final tumour index[b] (%)
High-abrasion furnace black		
Product No. 2	12.7	0
	45.0	15.0
	51.4	16.0
	201.7	82.0
Product No. 3	12.6	0
	20.0	0
	24.3	0
	147.4	33.0
Product No. 6	12.6	0
	16.5	0
	32.5	24.0
	36.5	52.0
	170.0	85.0
Fast-extruding furnace black		
Product No. 4	10.8	0
	21.8	7.0
	26.6	9.0
	135.0	44.0
Product No. 5	27.0	33.0
	32.9	25.0
	129.0	25.0
	201.0	74.0
Semi-reinforcing furnace black		
Product No. 7	6.3	0
	7.9	14.0
	8.9	0
	15.4	0
	18.0	0
	24.0	0
	132.6	73.0
Conducting furnace black		
Product No. 1	17.9	0
	21.5	0
	136.6	0
Medium thermal black		
Product No. 8	117.1	85.0

From Nau *et al.* (1958b)

[a] See also Table 23

[b] Defined by the authors as the percentage of animals, not dying from other cases, developing skin tumours during the treatment period

furnace black and channel black in 1.5 mL tricaprylin. Further groups of 50 mice received injections of 1.0 mL tricaprylin (vehicle controls) or 0.09 mg benzo[*a*]pyrene per mouse in 1 mL tricaprylin (positive controls). The experiment was terminated at 20 months after injection of the test materials. All questionable tumours found post-mortem were examined microscopically. Tumour incidence was calculated as a percentage and was based on the number of animals alive five months after the start of the study, which was the time at which the first deaths from tumours occurred. In nine of the 12 groups (treated and controls), few or no sarcomas were induced and 70% of the animals were still alive 12 months after the start of the experiment; in the other three, 52–66% of the mice were still alive at this time. In animals treated with the carbon black containing benzo[*a*]pyrene (a furnace black), a significantly increased incidence of subcutaneous sarcomas (a few of which metastasized) was observed when compared with tricaprylin controls. The incidence of subcutaneous sarcomas induced by the injection of test materials and the 'average fatal time' (i.e. time to death from subcutaneous sarcoma) are summarized in Table 25. High incidences of sarcoma (18/46) were observed in mice receiving furnace black with extractable benzo[*a*]pyrene administered in tricaprylin, in those receiving the carbon black extract from furnace black containing benzo[*a*]pyrene (22/45) and in positive controls (39/41). It should be noted that administration of furnace black containing benzo[*a*]pyrene in pellet form in the absence of tricaprylin induced an incidence of sarcomas of only 2/47 and that of non-benzo[*a*]pyrene-extractable channel black in pellet form induced an incidence of only 1/47. Extracted furnace black, that is furnace black following benzene treatment, induced one sarcoma in 37 animals; no subcutaneous sarcoma developed in any of the other groups. It was found that mixing non-benzo[*a*]pyrene-extractable carbon black with benzo[*a*]pyrene-extractable carbon black (furnace and channel blacks) resulted in a loss of carcinogenicity of the latter (Steiner, 1954).

A series of 21 groups of 10–20 male or female C3H brown or CFW white mice (total number, 344), eight to 10 weeks old, received a total dose of 17–300 mg of different carbon blacks suspended in cooking oil, tricaprylin or 1% 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 receiving subcutaneous injections of carbon black (product Nos 4, 7 and 8 (two furnace blacks and one thermal black); see Table 23) in cooking oil. The tumour index was defined by the author as the percentage of tumours occurring in 'animals excluding those found dead of causes unknown'. The tumours were described as 'subcutaneous mixed tumours' (Nau *et al.*, 1960).

Three groups of 20 C3H, 20 C3H and CFW or 10 C3H male and female mice received two subcutaneous injections of an extracted furnace black (product No. 5; see Table 23) (after extraction in hot benzene for 24 h) (total dose, 0.14–150 mg) in cooking oil or in 1% carboxymethyl cellulose in water and were observed for 20 months. No tumour occurred at the injection site among 19 mice killed at the end of the experiment or in animals dying during the course of the experiment (Nau *et al.*, 1960).

Table 25. Carcinogenicity of carbon blacks

Materials tested	Tumours/ survivors at 5 months	Tumour yield (%)	Average fatal 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 can be extracted with benzene

Groups of 10–30 male and female C3H and CFW mice, eight to 10 weeks old, received one or two subcutaneous injections of benzene extracts of different carbon blacks in cooking oil (total dose, 0.01–6.5 mg) (product Nos 1–10 and 15–17; see Table 23). In 31/36 groups, tumour indices of 15–100% were reported, 22 of which had an index of ≥ 50%. No subcutaneous tumour was observed in five groups. Further groups given subcutaneous injections of 0.2–3.25 mg benzene extracts of carbon black (product No. 5; see Table 23) in 1% carboxymethyl cellulose in water or methanol extracts of carbon blacks (product Nos. 1, 5–7; see Table 23) in water were reported to have a nil tumour index. Similar groups of 9–20 C3H mice received one subcutaneous injection of 0.1 or two subcutaneous injections of 0.2 mg extracted material readsorbed onto carbon black (product No. 5; see Table 23) in cooking oil or in carboxymethyl cellulose in water; a nil tumour index was again reported. Further groups of 19–20 C3H mice received as one or two subcutaneous injections 0.5–1.0 mL of cooking oil, which had been incubated with carbon black (product No. 5; see Table 23) for one to six months then centrifuged to remove the carbon black; the subcutaneous tumour index in these animals was 17–92% (Nau *et al.*, 1960).

As a positive control, 14 groups of 10–20 CFW and/or C3H mice, eight to 10 weeks of age, received as one or two subcutaneous injections 0.002–1.0 mg 3-methylcholanthrene (MCA) in cooking oil; the reported tumour indices ranged from 25–100%. When four groups of 20 C3H mice received as one or two subcutaneous injections 0.05–

0.25 mg MCA in carboxymethyl cellulose in water, reported tumour indices ranged from 12 to 95%, whereas a nil tumour index was reported for five groups of 12 female C3H mice receiving one subcutaneous injection of 0.002-0.01 mg MCA in carboxymethyl cellulose in water. Eleven further groups of 15–21 male and female C3H mice received single subcutaneous injections of 0.01–0.2 mg MCA adsorbed onto different carbon blacks (product Nos 1, 5–7, 13 and 18; see Table 23) in cooking oil. For three of these groups (product Nos 1, 13 and 7), the reported tumour indices were 5, 5 and 7%, respectively; for the other products, the tumour index was nil. When four groups of 10–22 C3H mice received the same amount of MCA adsorbed onto carbon blacks (product Nos 5 and 14; see Table 23) in carboxymethyl cellulose in water, the reported tumour index was nil. Two groups of 20 C3H mice injected with 0.1 mg benzo[*a*]pyrene alone or adsorbed onto carbon black (product No. 5; see Table 23) in carboxymethyl cellulose in water were reported to have tumour indices of 56 and 0%, respectively. Four 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 were reported to have malignant skin neoplasms, one a malignant neoplasm of the liver and one a malignant neoplasm of the spleen. [No detail as to the histology of these tumours was available.] No animal developed a subcutaneous sarcoma (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 presented in tabular form.]

3.6 Intraperitoneal administration

Rat: A group of 36 female Wistar rats was injected intraperitoneally once per week for four weeks with 20 mg furnace black 'Corax L' suspended in 2 ml saline [1.2% volatiles; toluene extract, < 0.1%; primary particle size, 23 nm; surface area, 150 m^2/g]. Fifty percent of the rats lived longer than 119 weeks, and after 132 weeks 20% of the animals were still alive. One out of 35 animals examined histopathologically at the end of the experiment had a sarcoma in the abdominal cavity (tumours of the uterus were excluded). Other groups treated in the same way with total doses of 80 mg diesel soot (no local tumour in 34 rats), 20 mg titanium dioxide (0/47), 250 mg non-fibrous silicon carbide (1/22), 250 mg activated carbon (1/25), 160 mg magnetite (2/34) or 160 mg iron (III) oxide (0/33) did not show an increased tumour incidence either. Fibrous dust administered in the same way induced significantly increased incidences of mesotheliomas/sarcomas in the abdominal cavity with total doses sometimes as low as 1–2 mg; for example, 13/21 rats injected intraperitoneally with 1.25 mg fibrous silicon carbide developed mesotheliomas/sarcomas (Pott *et al.*, 1991). [The Working Group noted the apparent low power of this assay to detect carcinogenesis arising from exposure to non-fibrous particles.]

3.7 Combined administration with known carcinogens

3.7.1 *Mouse*

After two weeks of acclimatization, two groups of 30 and 33 female weanling CF1 mice received a diet for 52 weeks that did or did not (controls) include furnace black (ASTM N-375, 2.05 g/kg diet). Both groups of mice received six weekly intraperitoneal injections of 20 mg/kg bw 1,2-dimethylhydrazine at the start of the study. At necropsy, all tissues were examined for gross pathology. Only tissues with macroscopically diagnosed lesions were examined histologically. Survival was similar in 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, two groups of 44 and 45 female weanling Sprague-Dawley rats received a diet for 52 weeks that did or did not (controls) include furnace black (ASTM N-375, 2.05 g/kg diet). Both groups of rats received 16 weekly intraperitoneal injections of 10 mg/kg bw 1,2-dimethylhydrazine at the start of the experiment. At necropsy, all tissues were examined for gross pathology. Only tissues with macroscopically diagnosed lesions were examined histologically. Carbon black did not enhance the incidence of colonic tumours induced by 1,2-dimethyl-hydrazine (Pence & Buddingh, 1985).

Two groups of 72 female Crl:(WI)BR rats, seven weeks old, were exposed by inhalation for 17 h per day on five days per week to a PAH-rich hard coal-tar pitch condensation aerosol (T/P aerosol) that contained no carbon particles. The exposure concentration of 2.6 mg/m^3 T/P aerosol contained 50 μg/m^3 benzo[*a*]pyrene among other PAHs. The MMAD of this aerosol was 0.5 μm. Four other groups of 72 female rats each were exposed to two mixtures of furnace black (Printex 90) and T/P vapour resulting in benzo[*a*]pyrene concentrations in these exposure atmospheres of 50 μg/m^3. Two of these four groups were exposed to the T/P aerosol containing 2 mg/m^3 carbon black and the other two groups were exposed to the T/P aerosol containing 6 mg/m^3 carbon black. The T/P vapour condensed onto the surface of the carbon black particles. One group of each of the three exposure atmospheres was exposed for 43 weeks and kept in clean air for 86 weeks. The other was exposed for 86 weeks and kept in clean air for 43 weeks. The two control groups of 72 rats each were kept in clean air for 129 weeks. No lung tumour was observed in clean air groups. Comparing the three 43-week exposure groups, the lung tumour rates of the groups combining T/P aerosol with carbon black showed an approximately two-fold higher increase compared to the groups exposed to T/P aerosol only. There was no difference in the lung tumour rates between the three exposure groups exposed for 86 weeks (Heinrich *et al.*, 1994).

3.7.3 *Hamster*

Syrian golden hamsters from the TNO/Holland breeding farm [sex unspecified] were treated intratracheally with a total dose of 60 mg/animal carbon black [not further

specified] together with 3 and 9 mg benzo[*a*]pyrene. Benzo[*a*]pyrene was dissolved in acetone with the carbon black added to obtain smaller benzo[*a*]pyrene particles and to provide condensation of benzo[*a*]pyrene on carbon black after acetone vaporization. Two other groups of hamsters were treated with 3 and 9 mg benzo[*a*]pyrene without carbon black. The total dose was administered by 40 instillations once per week in 0.1 mL saline solution containing 0.5% Tween 80. Between 40 and 43 hamsters per group were examined histopathologically at the end of the experiment. Malignant and benign tumour incidences in the larynx, trachea and lung were 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.]

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Studies of lung tissue from workers in carbon black factories have shown widespread deposits of large amounts of carbon black (Rosmanith *et al.*, 1969; Beck *et al.*, 1985). [No quantification of data were given.]

Five nonsmoking warehouse packers in a furnace black manufacturing plant were examined for exposure to dust, the level of which was assessed by air sampling and from the urinary excretion of 1-hydroxypyrene (derived from pyrene) in post-shift urine for five consecutive days during one work week. The average dust concentrations over the five days ranged from 1.53 to 13.21 mg/m^3. The average urinary excretion of 1-hydroxypyrene was 0.103–0.475 μmol/mol creatinine. The urinary excretion was lower on Mondays than on the other days. The authors concluded that urinary excretion was affected by dust exposure, and that the pyrene on the dust was bioavailable (Gardiner *et al.*, 1992b). [The Working Group noted the pyrene content of the carbon black was not measured.]

4.1.2 *Experimental systems*

(*a*) *Kinetics*

Several review articles, mostly focusing on particulate 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).

A number of studies, summarized in Tables 26–33, using intratracheal instillation and inhalation in mice and rats evaluated the retention kinetics of different carbon black materials after deposition into the lung. Bowden and Adamson (1984) instilled 4 mg of

colloidal carbon (primary particle size, 30 nm diameter) into the trachea of Swiss mice and followed its clearance in groups of three mice killed at intervals over a six-month period. They reported that most of the carbon black was cleared via the mucociliary escalator, but some transepithelial passage via type I cells occurred as well. Heavily laden alveolar macrophages stayed in the lung for the whole observation period and there was some, although low, clearance via the lymphatic system. No quantitation of the results was reported.

Several groups evaluated the retention kinetics of inhaled carbon black in the lungs of rats. Lee *et al.* (1987) and Strom *et al.* (1989) used two different furnace blacks (RCF [regular colour furnace]-7 and Elftex 12), which were inhaled in whole-body exposure chambers for 20 h per day on seven days a week for one to 11 weeks (for details, see Table 26). The MMADs were 0.22 and 0.24 μm, respectively. Both studies found a significantly prolonged retention half-life with increasing lung burdens. Lee *et al.* (1987) determined the retention kinetics of subsequently administered ^{14}C-diesel particles and found that pulmonary half-life ($t_{½}$) increased with increasing lung burden. Strom *et al.* (1989) determined carbon black lung burdens and lymph nodal burdens of carbon black. Lung burdens of 1.1, 3.5 and 5.9 mg carbon black were achieved after one, three and six weeks' exposure, respectively; the one-year retention fractions were 8, 46 and 61% of the lung burden at the end of the exposure periods, respectively. Additionally, carbon black was retained in the regional thoracic lymph nodes at 1, 21 and 27% of the initial lung burden, respectively. The authors concluded from their results 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.

Muhle *et al.* (1990) confirmed these results in an inhalation study using Wistar rats. These inhaled furnace black (Printex 90) of a particle size of 0.64 μm MMAD. The inhalation was for 95 h per week at a concentration of 7.4 ± 1.5 mg/m^3 for a total of 4.5 months. The retained carbon black at the end of exposure amounted to 13.7 ± 2.0 mg. The retention $t_{½}$ of subsequently inhaled ^{85}Sr-labelled polystyrene test particles was 472 days in these rats compared with 61 days in air controls. The carbon black data fitted well into the retention kinetic data obtained with other low-toxicity, low-solubility particles and the authors concluded that a rat lung burden of ~0.5 mg of such particles, including carbon black, resulted in a prolongation of retention half-time. This quantitative relationship is similar to that observed with other particulate materials.

Another study by the same group (Creutzenberg *et al.*, 1990; Muhle *et al.*, 1994) used the same carbon black material (Printex 90); in a whole-body exposure system, female Wistar rats inhaled an average exposure concentration of 7.5 mg/m^3 for up to four months, then 12 mg/m^3 for 19 h per day on five days a week for up to 24 months. At three, six, 12, 18 and 24 months of exposure, the retention of carbon black was determined as well as the influence of exposure to carbon black on the alveolar macrophage-mediated clearance function in the lung. The carbon black lung burden reached a level of 50.2 ± 10.9 mg at 18 months and the respective retention $t_{½}$ for carbon black was determined to be 550 days (95% CI, 322–1868 days) following termination of exposure. Test particle clearance of $^{59}Fe_2O_3$ (0.35 μm diameter) was significantly prolonged with increasing carbon black exposure duration, with $t_{½}$ ranging

Table 26. Kinetics of carbon black 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 37 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 observation	Linear increase of CB lung burden with exposure duration; lung burden ~30 mg; increased CB and ^{14}C-diesel pulmonary $t_{½}$ with increasing lung burden	Methodology for determining $t_{½}$ is not described adequately	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 observation	Lung burdens: 1.1, 3.5, 5.9 mg CB; 1-year retention: 8, 46, 61%; LN burden: 1, 21, 27% of initial lung CB; doubling of normal $t_{½}$ of ~50 days occurs 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)
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 $t_{½}$ at rat lung burden of ~0.5 mg	Quantitative relationship observed is similar to those of other low-toxicity low-solubility particles	Muhle *et al.* (1990)

Table 26 (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	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-polystyrene particles	CB lung burden: 50.2 mg; CB $t_{1/2}$, 550 days; $^{59}Fe_2O_3$ $t_{1/2}$, 244–591 days; ^{85}Sr $t_{1/2}$, 472 days at 3 months then back to normal $t_{1/2}$ of 50–60 days	No data are provided to demonstrate lower alveolar deposition of ^{85}Sr particles at high lung burdens	Creutzenberg *et al.* (1990); Muhle *et al.* (1994)
Elftex 12 (furnace black)	2–2.4 μm MMAD (large mode) 0.02–0.1 μm DED (small mode, 10–30%)	Fischer 344 rat	Inhalation 3.5 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 $t_{1/2}$ not different for different exposure rates; average $t_{1/2}$ ~520 days (95% CI, 350-950)		Henderson *et al.* (1992)
Elftex 12 (furnace black)	20 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 to $t_{1/2}$ in controls of 113–135 days		Mauderly *et al.* (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 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)

CB, carbon black; MC, mucociliary; LN, lymph node; AM, alveolar macrophages; MMAD, mass median aerodynamic diameter; $t_{1/2}$, retention half-life; DED, diffusion equivalent diameter

from 244 to 591 days, compared with 61–96 days in air controls. In contrast, ^{85}Sr-labelled polystyrene microsphere (3.5 μm diameter) clearance showed only a prolonged retention half-time after three months of exposure to carbon black with a retention $t_{½}$ of 472 days, whereas at the 12- and 18-month exposure time points, the test particle clearance returned to control values of about 50–60 days. The authors explained this by a change in the deposition site of the larger ^{85}Sr-labelled polystyrene microspheres due to altered lung architecture (in response to carbon black-induced inflammation and other changes) and breathing pattern. [The Working Group noted that this seems to be a reasonable explanation, especially in view of the increase in lung weight due to inflammatory responses after the heavy exposure to carbon black particles of 1.7-fold and six-fold at three and 12 months, respectively. However, no data were provided to illustrate the lower alveolar deposition of ^{85}Sr-labelled test particles.]

In a study of chronic inhalation in Wistar rats and NMRI mice exposed to furnace black (Printex 90; 11.6 mg/m^3), the pulmonary particulate accumulation was measured (Heinrich *et al.*, 1995). The rats were exposed for 24 months and the mice for 13.5 months. Both rats and mice showed similar accumulation kinetics over the exposure time; at one year of exposure, the normalized lung burden (mg/g of control lung) was 32 mg (rats) and 37 mg (mice). In addition, rats showed significantly prolonged retention of tracer particles compared to controls as early as at three months of exposure and which persisted through 12 and 18 months of exposure and until three months after the 18 months' exposure (see Creutzenberg *et al.*, 1990).

A study by Henderson *et al.* (1992) evaluated the pulmonary retention 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 ranged between 3 and 4 mg. The retention $t_{½}$ determined over a 24-week post-exposure period was not statistically significant between the different groups and was reported as ~520 days with a 95% CI of 350–950 days.

Mauderley *et al.* (1994) studied the retention of tracer doses of [^{7}Be]-furnace black (Elftex 12) in rats at three and 18 months of 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 with about 50% of it cleared in control animals with retention $t_{½s}$ of 14 and 19 days and in the exposed rats between 14 and 40% cleared with retention $t_{½s}$ ranging between four and 10 days. The most striking differences were found in the slow-phase clearance components, which showed little or no clearance over a time period of 126 days for the low- and high-dose groups compared to retention $t_{½s}$ of 113 and 135 days for control rats.

In an attempt to determine the translocation of carbon black particles after gastric administration, LeFevre and Joel (1986) gavaged four-week-old and 18-month-old female Swiss mice with 7 mg ^{7}Be-labelled furnace black particles (Elftex 8). They then determined the isotope distribution at 4 h and one, two, five and 14 days later; they concluded from their findings that there is uptake and distribution from the gut and that transit is more rapid in young mice. Peyer's patches of older mice take up more carbon than those of younger mice.

Overall, these studies demonstrate that exposures to carbon black that achieve lung burdens exceeding about 0.5–1 mg/g rat lung result in significant prolongation of the retention $t_{½}$ of carbon black in the lung and, moreover, affect the clearance function of alveolar macrophages for other particulate material. This is in agreement with the concept of particle lung overload (see review, Morrow 1988), which is defined as a significant impairment of the alveolar macrophage-mediated particle clearance function due to high loading of alveolar macrophages with low-toxicity, low-solubility particles. The only study comparing the kinetics of inhaled carbon black in rats and mice found that the pulmonary accumulation was similar in both species leading to a condition of particle overload. There are no kinetic data on sex differences in rats or differences in other species.

(*b*) *Kinetics of carbon black adsorbed material*

Concern had been raised in the past that material, including carcinogenic compounds, adsorbed onto carbon black particles will be 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 a carbon core and which have been thought to contribute to a carcinogenic response of inhaled diesel exhaust. The studies considered are summarized in Table 27.

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

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

These three studies demonstrate that carbon black administered to rat and hamster lung either by inhalation or instillation can act as a carrier of adsorbed material which subsequently is cleared much more slowly than the compound given without carbon black adsorption.

Table 27. Kinetics and effects of carbon black adsorbed compounds

Carbon black characteristics	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 to inhalation; covalent interactions of BaP with lung macromolecules increased when administered as CB coating	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 to CB; nitropyrene covalently bound to macromolecules was 10-fold greater at 30 days when inhaled adsorbed compared to nitropyrene alone	Wolff *et al.* (1989)

BaP, benzo[*a*]pyrene; CB, carbon black

4.1.3 *Comparison between animals and humans*

Although carbon black has been identified in humans, no quantitative data are available on retention of carbon black in humans. However, based on studies with other highly insoluble particulate materials, it can be assumed that the normal retention $t_{½}$ in humans is longer than that measured in rats by a factor of approximately 10. Thus, Bailey *et al.* (1985) found that retention $t_{½s}$ of inhaled monodisperse 1 and 4 μm diameter fused aluminosilicate particles in humans ranged from ~200–700 days, depending on the time after exposure, with an average of ~500 days for most of the particles to be cleared, in comparison to rat data (Muhle *et al.*, 1990) which demonstrate a retention $t_{½}$ of 61–96 days. This presumes that the retention kinetics of different particles of low solubility and low toxicity are the same, as has been demonstrated in rats. Normal pulmonary retention $t_{½s}$ for low-solubility, low-toxicity particles in mice have been reported as ~55 days (Kreyling, 1990).

Heavy exposure to carbon black in occupational settings may lead to high carbon black burdens in the human lung. In analogy to the rat, if this lung burden exceeds ~0.5 mg/g lung, it would be expected that the normal retention half-life may be prolonged. Indeed, there is some evidence showing that occupations leading to heavy particulate loads of the lung (e.g. coal mining) show a prolonged clearance of the dust from the alveolar space (Stober *et al.*, 1965; Freedman & Robinson, 1988; Freedman *et al.*, 1988)

4.2 Toxic effects

4.2.1 *Humans*

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

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

In 56 workers in two German carbon black factories (one produced carbon black from oil that was burned with lightgas, the other from acetylene), two (both belonging to the 16 workers who had an exposure time exceeding 10 years) had chest X-ray changes, compared to none among 52 controls (who had had radiographs taken without suspicion of lung disease) (Mai, 1966). [The selection of workers is not clear, neither are the criteria for diagnosis.]

In a study by Valic *et al.* (1975), respiratory function was measured in a group of 35 carbon black workers (average age, 38.8 years) and 35 controls matched for age, body weight and smoking habits examined in 1964 and again in 1971. Measurements of carbon black concentrations in the work environment showed that the respirable concentration (mean, < 1 μm) was 7.2 mg/m^3 in 1964 and 7.9 mg/m^3 in 1971. By 1971,

the average duration of exposure was 12.9 years and was more than 10 years for 26/35 workers. In 1971, carbon black workers who smoked exhibited a reduced forced vital capacity and a reduced forced expiratory volume compared with smoking controls. For carbon black workers who did not smoke, there was no significant difference compared with nonsmoking controls. However, for both smoking and nonsmoking carbon black workers, the annual declines in these parameters were three- to four fold greater than expected. Radiological lung changes, characterized by slight interstitial fibrosis, were found in 17.1% of the workers. These lung changes progressed between 1964 and 1971. [The selection of exposed and unexposed populations is unclear.]

In a study on carbon black (furnace) workers, Cocarla *et al.* (1976) found that 29 (20.3%) of 143 workers exposed for a mean of 19 years had pneumoconiosis, often accompanied by generalized or local emphysema and disturbances of lung perfusion. In the same subpopulation, an increase in levels of serum immunoglobulin (Ig)A and a decrease in IgM were observed. Measurements of air levels of carbon black were not reported.

In 125 carbon black-exposed workers in dry-cell battery and tyre manufacture (mean exposure time of about five years), a reduction in pulmonary function and an increase in respiratory symptoms were observed in comparison to 145 controls (healthy non-industrially exposed men with a [sic] history of respiratory disease). The largest reduction in lung function was observed in the group that had exposure to the highest mean dust level (31 mg/m^3) at the dry-cell battery factory. The most common respiratory symptoms were cough with phlegm (28 and 22% in the battery and tyre factories, respectively). Radiographs were reported to show no abnormality (Oleru *et al.*, 1983). [Only a fraction of all workers was examined; the selection criteria are not clear. No adjustment was made for smoking; however, only 12.8% of workers in the study group were smokers.]

In a Czech factory producing carbon black from anthracene, out of 12 workers exposed for $\geq$ 15 years, one had chest radiographical findings consistent with pneumoconiosis. One additional worker, who had been exposed for 27 years and who had no symptoms of respiratory disease or lung function disturbances, had fine, diffuse changes in the chest radiogram; an open lung biopsy was taken from this worker. There was heavy pigmentation of the lung surface. Histological examination revealed heavy deposits of carbon black particles and slight, mainly reticular fibrosis with associated emphysema (Rosmanith *et al.*, 1969). [No information on exposure levels; selection of the workers for examination is not clear, neither are the smoking habits.]

Beck *et al.* (1985) studied X-radiographs of various thicknesses of carbon black deposits. They concluded that radiographical changes in workers were due to tissue reaction rather than to simple deposition. Further, the authors examined lung tissue from two subjects [smoking not defined] with radiographical changes and found fibrous tissue and emphysema around the carbon deposits. On the other hand, a biopsy from a worker with generalized nodulation did not reveal fibrosis (Slepicka *et al.*, 1970).

In a study of 83 currently exposed carbon black workers (at least two years' exposure) and 144 controls, the current workers had statistically significantly higher prevalences

than the controls of the following: chronic bronchitis (60% versus 19%), 'obstructive disturbance of ventilation' at spirometric examination (24% versus 6%) and nonspecific bronchial hyper-reactivity on histamine test (28% versus 3%). In a total of 83 currently and 46 formerly exposed workers, 2.3% (average exposure time, 23.3 years) displayed findings in chest radiograms suggesting pneumoconiosis and an additional 6.9% had slighter changes. Data on dust exposure were not given (Kandt, 1985). [The type of carbon black factory and the selection of workers and controls are not well described.]

In 3027 carbon black workers (92.3% men, 7.7% women) employed in 19 plants (mean employment time, 10.9 years), slight associations were found between prevalences of chronic cough and sputum production and dust exposure, as assessed from job titles in nonsmokers (39–49% in different exposure intensity categories). In smokers, there was no association. There were no data on dust levels. Further, spirometry indicated minor exposure-associated reductions in the forced vital capacity and forced expiratory volume. Moreover, routine chest radiographs, taken during the previous two years, of 935 of the workers from 11 of the 19 plants where they could be obtained revealed six cases of a simple type of pneumoconiosis [smoking status not stated], all belonging to the group of 396 workers who had been employed for more than 10 years (Crosbie, 1986). [A large proportion of the radiographs was taken by the mass miniature technique, which is not optimal for detection of minor changes.]

In a multicentre European study, a population of 1742 employees (92% men, 8% women in the original study base) in 15 carbon black factories were examined (mean duration of employment 14.2 years). [Most of them were identical to those studied earlier by Crosbie (1986).] In a total of 1317 samples of total inhalable dust, the geometric mean level was 0.57 (geometric standard deviation, 4.0) mg/m^3 and in 1298 respirable dust samples the geometric mean level was 0.21 (2.7) mg/m^3. Associations were found between frequencies of cough, sputum and symptoms of chronic bronchitis (mean prevalence, 10%) and current exposure. Forced vital capacity and forced expiratory volume showed slight decreases with increasing dust exposure in both smokers and nonsmokers. Chest radiographs could only be taken in 10 of the 15 plants, and they were taken for 1096 workers. Of these, 24.4% showed small opacities (International Labour Organization category 0/1 or greater), with a strong association with rising cumulated exposure (five categories). Preliminary analyses indicated associations between radiographical findings and lung function (Gardiner *et al.*, 1993).

In 913 employees of six carbon black producers, there was no consistent association between forced vital capacity or forced expiratory volume (fractions of predicted values) and cumulative dust exposure (range < 50–≥ 200 mg/m^3 $\times$ months), when age and smoking habits were taken into consideration. Information on exposure was obtained from measurements made one year earlier in 24 plants [relation to the population studied for health effects unclear]. Some 1500 total dust samples obtained by personal monitoring showed geometric mean time-weighted average levels ranging from 0 to 2.0 mg/m^3, with 76% below 1.0 mg/m^3 (Robertson *et al.*, 1988). [Because of the lack of occupational histories from several of the factories, there was a major loss of workers (804) from the original study base (1717), and this might have affected the outcome. The Working Group noted that the spirometry values had already been standardized by

comparison with referents to calculate their predicted percentage before being used again in the age-specific two-way analysis of variance.]

Three years later, 697 (76%) of these workers were retested. The total group showed small, statistically nonsignificant increases in forced vital capacity and forced expiratory volume. The author states that the most likely explanation for those findings is the variability of lung function testing (Robertson, 1996).

In a cross-sectional study, chest radiograms were taken for 507 predominantly male workers in a German carbon black factory. The average duration of employment was given as approximately 25 years. Of the radiograms, 75.5% were classified as International Labour Organization (ILO) category 0/0, 13.0% as 0/1, 8.9% as 1/0, 2.4% as 1/1 and 0.2% as 2/1. The authors ascribed the findings in the latter two categories to two cases of silicosis unrelated to exposure to carbon black and to prevalent smoking (70% smokers or ex-smokers) (Küpper *et al.*, 1994a,b).

In the same factory, lung function (body plethysmography, including measurements after inhalation of a single concentration of methacholine) was investigated in 578 carbon black-exposed and 99 unexposed workers. The fine dust concentration was 0.01–9.14 mg/m^3 (total dust, 1.08–19.95 mg/m^3). The duration of exposure was not stated, but the average 'dust-years' (dust exposure times duration of exposure) were 11.3 in nonsmokers, 21.5 in ex-smokers and 16.3 in smokers. In multiple linear regression analysis (allowing for age), exposure to carbon black had a significant effect on deterioration of lung function in the nonsmoking group only. Thus, there was a significant decrease in airway resistance (which, however, was dependent on two extreme values) and expiratory flow. However, in the smokers'group, pathological findings (as compared to expected values in reference populations) in airway resistance were more frequent among the carbon black-exposed workers than in the unexposed controls. There was no significant association between bronchial hyper-reactivity and exposure to carbon black (Küpper *et al.*, 1996).

In a case–control study of employees of seven carbon black producers in the United States, workers who had submitted medical insurance claims with diagnoses of selected diseases of the respiratory and circulatory systems were individually matched for age and year of service with undiseased co-workers. Individual cumulative total dust exposures for cases and controls were estimated. Cases with a disease of the respiratory system (27 pairs) had a nonsignificantly higher cumulative total dust exposure than did the controls; cases with diseases of the circulatory system (48 pairs) had significantly lower cumulative total dust exposure than the controls (Robertson & Ingalls, 1989).

Among other effects of exposure to carbon black (lampblack), dermatological lesions, such as the presence of carbon black 'tattoos' on hands and forearms, as well as follicular blackheads containing carbon black on uncovered skin surfaces, have been reported (Capusan & Mauksch, 1969). A brownish discoloration of the conjunctiva has occurred after long-term use of eye-liner containing carbon black, with accumulation of pigment in the tissues (Sugar & Kobernick, 1966; Haddad & Zehetbauer, 1980).

In a study of 58 current and 35 former male workers (at least two years of exposure) in a carbon black factory (channel black) and 60 controls, the currently exposed workers

had a significantly higher prevalence of nasal complaints (including hyposmia) than either former workers or controls. Moreover, rhinoscopy revealed mucosal findings in 27% of the currently exposed workers versus only 9% of the controls. However, X-rays of the paranasal sinuses and cytology of nasal secretions did not reveal differences. The total dust concentration ranged from 9.0 to 13.35 mg/m^3 in the machine room and from 4.4 to 8.2 mg/m^3 in the operators' room (Kandt & Biendara, 1985).

4.2.2 *Experimental systems*

(*a*) *Inhalation studies*

A number of inhalation studies discussed in the following paragraphs are summarized in Table 28.

An early study by Snow (1970) showed that inhalation of thermal black with a particle diameter of ~0.15–0.2 μm and a surface area of between 10 and 15 m^2/g resulted in oedema of the laryngeal folds in Syrian hamsters exposed for 6 h per day on five days per week for a total of 53 and 172 days to a concentration of 105 mg/m^3 and for 236 days to a concentration of 56 mg/m^3 (see Table 28). Evaluation was limited to the larynx and trachea and consequently no effects on the lower respiratory tract were reported.

In another early study by Rhoades (1972), Long-Evans rats were exposed to gas channel black with a mass median diameter of 2.2 μm at a concentration of 4 mg/m^3 continuously for 16 days. The focus here was on the surfactant system, and findings of alveolar thickening and atelectasis were reported but no further effect related to surfactant. [The Working Group noted the lack of detail in the reporting of lung damage.]

Nau *et al.* (1976) exposed rhesus monkeys, Syrian hamsters and guinea-pigs to thermal black at a concentration of 53 mg/m^3 for 6 h per day on six days per week; the rodents were exposed for a total of 236 days and the monkeys for three years. No significant change in the lung was found in guinea-pigs despite the high concentration and long duration of exposure and no finding was given for the hamster lung. In monkeys, particles were adsorbed in regional lymph nodes and a moderate to severe emphysematous response with massive particle accumulation was observed in the lung. The investigators also reported right hypertrophy of the ventricular septum and, to a degree, of the left ventricle in the exposed monkeys. [The reporting of the findings was inadequate and no determination of the lung dose was made.]

Fenters *et al.* (1979) exposed CD-1 mice to a concentration of 1.5 mg/m^3 (0.3 μm MMAD) Sterling MT CT-6729 medium thermal black by inhalation for 3 h per day on five days per week for a total of four, 12 and 20 weeks. A challenge with virus and bacteria was included and it was found that there was decreased resistance to these infections, as seen by a reduced bactericidal capacity in the lung. They also observed morphological changes in the conducting airways and alveoli by scanning electron microscopy. [Alterations in immune responses using a plaque-forming assay were inconsistent, and no lung dose was reported.]

Wright (1986) found no increased type II cell proliferation after exposure of Fischer 344 rats to a concentration of 6.1 mg/m^3 of an unspecified carbon black (MMAD, 0.22 μm) for 20 h per day on seven days a week for 14 days [no lung burden data given].

Table 28. Non-neoplastic effects of carbon black in inhalation studies in experimental animals

Particle type	Particle diameter and surface area	Species (age and sex)	Exposure concentration	Duration of study	End-points	Findings	Comments	Reference
Thermal black	0.15–0.2 μm, 10–15 m^2/g	Syrian hamster	~56 mg/m^3 ~105 mg/m^3	6 h/day, 5 days/week, 53 and 172 days (high), 236 days (low)	Histology of larynx and trachea	Oedema of laryngeal folds; retention of tracheal and subglottic glands of amorphous eosinophilic material; no morphological changes	Study limited to larynx and trachea	Snow (1970)
Gas channel black	2.2 μm MMD	Long-Evans rats	4 mg/m^3	16 days (continuous)	Surfactant properties	Alveolar thickening, atelectasis; no surfactant effects	No lung dose; poor reporting of lung damage	Rhoades (1972)
Thermal black		Rhesus monkey, C3H mouse, hamster, guinea-pig	53 mg/m^3	6 h/day, 6 days/week, 236 days (rodents), 3 years (monkey)	Histology of lung and heart; pulmonary function (monkey)	Monkey: particles in the lymph; moderate to severe emphysematous lesions; massive particle accumulation; ventricular hypertrophy; guinea-pig: no significant lung changes	Inadequate reporting of findings; high concentration	Nau *et al.* (1976)
Sterling MT CT-6729 (medium thermal black)	0.3 μm MMAD	CD-1 mouse	1.5 mg/m^3	3 h/day, 5 days/week, 4, 12, 20 weeks	Immune response; infectivity challenge (virus and bacteria)	Decreased resistance to infection; bactericidal capacity in lung reduced; SEM changes in conducting airways and alveoli	Changes in immune response were inconsistent (plaque-forming assay); no lung dose reported	Fenters *et al.* (1979)
Carbon black [unspecified]	0.22 μm MMAD	Fischer 344 rat	6.1 mg/m^3	20 h/day, 7 days/week up to 14 days	Cell proliferation	Type II cell proliferation increased after diesel exhaust or NO_2 but not after CB	Lung burden not determined	Wright (1986)

Table 28 (contd)

Particle type	Particle diameter and surface area	Species (age and sex)	Exposure concentration	Duration of study	End-points	Findings	Comments	Reference
Elftex 12 (furnace black)	2.0 μm MMAD (large mode) 0.02–0.12 μm MMDD (small mode) 43 m^2/g	Fischer 344 rat (14–15 weeks; male)	10 mg/m^3	7 h/day, 5 days/week, 12 weeks	Lung inflammation, histology	12% PMN in BAL; 2.2 mg CB lung burden; macrophage aggregates engorged with CB in terminal bronchioles and alveolar ducts; type II cell hyperplasia	Effects of CB and concurrently tested diesel exhaust were very similar	Wolff *et al.* (1990)
Elftex 12 (furnace black)	2–2.4 μm MMAD (large mode) 0.02–0.12 μm DED (small mode, 10–30%)	Fischer 344/N rat (11–15 weeks; female)	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	BAL analysis and histopathology at different exposure rates and constant $c \times t$	Lung burden 3–4 mg; cellular (PMN) and biochemical (protein, LDH, β-glucuronidase) parameters significantly increased at all exposure rates to same degree; slight thickening of alveolar septa with hypertrophic epithelial cells; increased lung weights	Exposure rate does not influence toxic effects of inhaled CB	Henderson *et al.* (1992)
Printex 90 (furnace black) (± pyrolyzed pitch ± irritant gases)	0.64 μm MMAD 227 m^2/g	Wistar rat	6 mg/m^3	18 h/day, 5 days/week 10 months + 20 months post-exposure	Histology/ morphology	Squamous metaplasia; squamous differentiation of type II cells as precursor stages of squamous metaplasia in rats	Results specific to exposure to CB only not reported; pitch-related effects and BaP + CB cannot be distinguished	Nolte *et al.* (1993)

Table 28 (contd)

Particle type	Particle diameter and surface area	Species (age and sex)	Exposure concentration	Duration of study	End-points	Findings	Comments	Reference
Printex 90 (furnace black) (± pyro-lyzed pitch)	0.64 µm MMAD 227 m^2/g	Wistar rat	6 mg/m^3	18 h/day, 5 days/week, 10 months + 20 months post-exposure	Histopatho-logy; focus on hyperplasia and metaplasia	Hyperplastic bronchiolar epithelium, metaplasia, inflammation, alveolar histiocytosis, alveolar lipoproteinosis	Focus is on cellular changes rather than CB specific effects; no clear distinction was made between effects of CB and pitch	Nolte *et al.* (1994)
Regal GR (furnace black) (96.9% carbon)	2.4 µm MMAD, 88 m^2/g	Swiss mouse (5 weeks; female)	10 mg/m^3	4 h/day, 4 days + 7 days observation	Infectivity model, bacterial and viral challange the day following exposure	No effect of CB alone on integrity of lung defences against bacterial and viral challenge; no pulmonary inflammation by BAL; co-exposure to 2.5 ppm acrolein impaired all defences	Short exposure duration; no lung burden data	Jakab (1993)
Regal GR (furnace black)	2.4 µm MMAD, 88 m^2/g	Swiss mouse (5 weeks; female)	10 mg/m^3	4 h, 24 h post-exposure	BAL analysis and AM phagocytosis	No change from controls; co-exposure to 1.5 ppm O_3 showed significant inflammation and suppression of phagocytosis	Exposure duration short	Jakab & Hemenway (1994)

Table 28 (contd)

Particle type	Particle diameter and surface area	Species (age and sex)	Exposure concentration	Duration of study	End-points	Findings	Comments	Reference
Elftex 12 (furnace black)	2.0 μm MMAD (large mode) 0.1 μm MMDD (small mode) (33%) 43 m^2/g	Fischer 344/N rat (male and female)	2.5 mg/m^3 6.5 mg/m^3	16 h/day, 5 days/week, 24 months	Histo-pathology; particle clearance; BAL parameters	Reduction in body weight; lung burden 21.0 and 38.5 mg CB; LN accumulation; dose-related increase in lung weight; BAL parameters (PMN, protein, LDH, β-glucuronidase); histology: chronic active inflammation, bronchiolar/alveolar metaplasia, alveolar proteinosis, septal and focal fibrosis, alveolar hyperplasia, squamous cysts; impaired clearance of ^7Be CB particles at 3 and 18 months; accumulation of fluorescent microspheres in macrophage aggregates; female rats show greater response than males	Results nearly identical to those of studies performed concurrently using diesel exhaust	Mauderly *et al.* (1994); Nikula *et al.* (1995)
Printex 90 (furnace black)	0.64 μm MMAD 227 m^2/g	Wistar rat (female)	6 mg/m^3	17 h/day, 5 days/week, 10 months + 20 months post-exposure or 20 months + 10 months post-exposure	Histo-pathology; hyperplasia; metaplasia	Inflammation: bronchiolar/alveolar hyperplasia, alveolar histiocytosis, lipoproteinosis; squamous metaplasia (probably from type II cells)		Dungworth *et al.* (1994)
			11.3 mg/m^3	18 h-day, 5 days/ week, 24 months + 6 months post-exposure				

Table 28 (contd)

Particle type	Particle diameter and surface area	Species (age and sex)	Exposure concentration	Duration of study	End-points	Findings	Comments	Reference
Monarch 880 (furnace black)	0.88 μm MMAD (16 nm primary particle) 220 m^2/g	Fischer 344 rat	1.1, 7.1, 52.8 mg/m^3	6 h/day, 5 days/week, for 13 weeks exposure; 3 months and 8 months post-exposure	BAL parameters; cell proliferation; histopathology; dosimetry	Lung burdens, 0.35, 1.8 and 7.8 mg; no change in any parameter at lowest concentration; dose-related increase at middle and high dose in cellular and biochemical lavage parameters; dose-related increase in alveolar cell proliferation		Driscoll *et al.* (1996)
Printex 90 (furnace black)	0.64 μm MMAD 227 m^2/g	Wistar rat (female) NMRI mouse (female)	11.6 mg/m^3 (average)	*Rats*: 18 h/day, 5 days/week, 24 months + 6 months post-exposure	Histopathology; lung clearance; dosimetry	*Rats*: body weights decreased, lung weight increased; lung burden, 44 mg; LN, 6.7 mg; impaired lung clearance; BAL: cellular and biochemical parameters increased; moderate to high-grade bronchiolar/alveolar hyperplasia; slight to moderate interstitial fibrosis	Responses were very similar in both species compared to concurrently run diesel exhaust and ultrafine titanium dioxide	Heinrich *et al.* (1995)
				Mice: 18 h/day, 5 days/week 13.5 months + 9.5 months post-exposure		*Mice*: body weights decreased, lung weights increased; lung burden, 7.4 mg (37 mg/g control lung, similar to rat)		

MMD, mass median diameter; MMAD, mass median aerodynamic diameter; SEM, scanning electron microscopic; CB, carbon black; MMDD, mass median diffusion diameter; PMN, polymorphonuclear neutrophils; BAL, bronchoalveolar; c × t, concentration × time; LDH, lactate dehydrogenase; BaP, benzo[*a*]pyrene; AM, alveolar macrophages; LN, lymph node

More detailed characterizations of pulmonary responses to carbon black were reported by Wolff *et al.* (1990) and Henderson *et al.* (1992). Elftex 12 (furnace black) was aerosolized to give a large and small mode particle size distribution with a MMAD of 2 μm and mass median diffusive diameter (MMDD) of 0.02–0.12 μm. In the study by Wolff *et al.* (1990) an exposure concentration of 10 mg/m^3 was delivered to 14–15-week-old male Fischer 344/N rats for 7 h per day on five days per week for a total of 12 weeks. At a carbon black lung burden of 2.2 mg, it was found that 12% of the lavageable cells consisted of polymorphonuclear neutrophils. Aggregates of macrophages engorged with carbon black were found in the terminal bronchioles and alveolar ducts, and type II cell hyperplasia was also observed. Concurrently tested diesel exhaust particles showed very similar effects.

In the study by Henderson *et al.* (1992), the aim was to expose the rats to a different dose rate such that the product of concentration × time was very similar. Thus, 11–15-week-old female Fischer 344/N rats were exposed to concentrations of 3.5 mg/m^3 for 16 h per day on seven days a week, 13 mg/m^3 for 6 h per day on five days a week and 98 mg/m^3 for 4 h on one day per week. Each exposure lasted for a total period of 12 weeks, followed by a 24-week post-exposure period. Resulting lung burdens ranged between 3 and 4 mg. In spite of the different exposure rates, the cellular and biochemical parameters of bronchoalveolar lavage fluid increased to the same degree. In all exposure groups, a slight thickening of alveolar septa with hypertrophic epithelial cells was found and lung weights were significantly increased. The authors concluded that the exposure rate over this range does not influence resulting toxic effects of inhaled carbon black in the lungs.

Histological and morphological end-points were evaluated in a study by Nolte *et al.* (1993, 1994) following inhalation of Printex 90 (furnace black) by Wistar rats with or without the addition of pyrolyzed pitch and irritant gases such as nitrogen dioxide. The exposure concentration was 6 mg/m^3 for 18 h per day on five days per week for a total of 10 months with a 20-month post-exposure observation period. Findings were squamous metaplasia and squamous differentiation of type II cells, which was considered to be a precursor stage of the squamous metaplasia in this rat model of particle inhalation. However, it was difficult to differentiate the results due to exposure to carbon black only from those of changes induced by the combination of carbon black and pitch. [The Working Group noted the poor reporting of exposure concentration, exposure details and results specific to carbon black.]

Jakab (1993) determined the influence of carbon black inhalation on the resistance of mice to a bacterial and viral challenge one day after exposure. Five-week-old female Swiss mice were exposed to 10 mg/m^3 Regal GR (furnace black) (particle size, 2.4 ± 2.75 μm MMAD) for 4 h per day for a total of four days followed by a seven-day observation period. Carbon black alone had no effect on the integrity of lung defences against the bacterial and viral challenges and no pulmonary inflammatory response was detected in parameters of bronchoalveolar lavage fluid. In contrast, co-exposure to 2.5 ppm [5.7 mg/m^3] acrolein resulted in an impairment of the measured lung defence parameters (total and differential cell counts and albumin levels). This change in biological effect was not observed with acrolein alone. [The Working Group noted the rela-

tively short duration of exposure to carbon black by inhalation. No lung burden data were reported.]

In an effort to determine the effect of exposure to carbon black in combination with ozone on alveolar macrophage phagocytosis, Jakab and Hemenway (1994) exposed five-week-old female Swiss mice to 10 mg/m^3 Regal GR (furnace black) (MMAD, 2.4 ± 2.75 μm) for 4 h. Analysis of bronchoalveolar lavage fluid 24 h later showed that there was no change in comparison to controls in animals exposed to carbon black only, and alveolar macrophage phagocytosis was not affected. Exposure to ozone alone caused significant changes in these parameters. [The Working Group noted that the exposure duration was rather short to see a significant effect of carbon black on the end-points studied.]

A detailed study comparing exposures to carbon black and diesel exhaust particles was reported by Mauderly *et al.* (1994) and Nikula *et al.* (1995). Male and female Fischer 344 rats were exposed to 2.5 mg/m^3 and 6.5 mg/m^3 Elftex 12 (furnace black) for 16 h per day on five days per week for a total of 24 months. Three males and three females each were sacrificed at three, six, 12, 18 and 23 months of exposure for evaluation of lung burden and lymph node burdens, histopathology, bronchoalveolar parameters and clearance of test particles. Particle size measurements resulted in a bimodal distribution with 2.0 μm MMAD for the large fraction, measured by a cascade impactor, and 0.1 μm MMDD for the small fraction, measured by parallel-flow diffusion battery (33%). Results showed a reduction in body weight at a final lung burden of 21.0 and 38.5 mg carbon black in the two exposure groups. Significant accumulation of carbon black with time occurred in the lymph nodes, and there was a dose-related increase in lung weight. Polymorphonuclear neutrophils and biochemical (protein, lactate dehydrogenase, β-glucuronidase) parameters of bronchoalveolar lavage fluid showed significant dose-dependent increases. Table 29 lists the occurrence of these and other non-neoplastic lung lesions found in the carbon black-exposed rats before and after 18 months of exposure. For most of the end-points examined, no significant difference in severity or incidence was observed between female and male rats. However, chronic active inflammation, alveolar proteinosis and bronchiolar/alveolar metaplasia occurred consistently with greater incidences and somewhat greater severity in females compared to males. Alveolar hyperplasia and squamous cysts were also found. Even at the low-exposure level, alveolar epithelial hyperplasia was observed in 4/6 rats after three months and 6/6 rats after six months of exposure. Bronchiolar/alveolar metaplasia was first observed in the high-dose group after 12 months of exposure (2/6 rats) and was present in 18/18 rats of this group and 22/24 rats of the low-dose group killed after either 23 months of exposure or after an additional six weeks without exposure. A total of 12 rats with squamous cysts were observed, 10 of which were in the group kept the additional six weeks without exposure. None of 19 squamous cysts increased in size after implantation into athymic mice, compared with 1/2 squamous-cell carcinomas and 2/8 lung adenocarcinomas. When ^{7}Be carbon black particles were administered at three and 18 months of exposure, significant retardation of their respective lung clearance was observed which increased with duration of exposure. Moreover, inhalation of fluorescent-labelled microspheres at three and 18 months of exposure caused significant

Table 29. Percentages (and severity scores) of rats dying, euthanized or sacrificed that had non-neoplastic lung lesions during a two-year exposure to carbon black (CB)[a,b]

Lesion	Female rats						Male rats					
	Control		Low CB (2.5 mg/m^3)		High CB (6 mg/m^3)		Control		Low CB (2.5 mg/m^3)		High CB (6 mg/m^3)	
	< 18 months	> 18 months	< 18 months	> 18 months	< 18 months	> 18 months	< 18 months	> 18 months	< 18 months	> 18 months	< 18 months	> 18 months
Alveolar macrophage hyperplasia	0 (0–0)	4 (0–1)	100 (1–3)	100 (2–4)	96 (0–4)	100 (3–4)	30 (0–2)	0 (0–0)	100 (1–3)	100 (1–3)	100 (2–4)	100 (2–4)
Alveolar epithelial hyperplasia	0 (0–0)	9 (0–2)	90 (0–3)	100 (1–4)	93 (0–4)	100 (2–4)	9 (0–0)	2 (0–2)	98 (0–4)	100 (1–3)	100 (1–4)	100 (1–4)
Chronic active inflammation	0 (0–0)	5 (0–1)	24 (0–2)	34 (0–2)	37 (0–3)	63 (0–2)	0 (0–0)	1 (0–3)	9 (0–2)	14 (0–2)	20 (0–2)	34 (0–3)
Septal fibrosis	0 (0–0)	2 (0–1)	52 (0–3)	96 (0–3)	78 (0–3)	100 (1–4)	3 (0–1)	1 (0–1)	61 (0–3)	92 (0–3)	75 (0–4)	99 (0–4)
Alveolar proteinosis	0 (0–0)	1 (0–2)	29 (0–2)	66 (0–3)	52 (0–3)	97 (0–4)	0 (0–0)	0 (0–0)	2 (0–1)	15 (0–1)	25 (0–2)	66 (0–4)
Focal fibrosis with epithelial hyperplasia	0 (0–0)	0 (0–0)	0 (0–0)	17 (0–4)	7 (0–2)	31 (0–3)	0 (0–0)	0 (0–0)	0 (0–0)	6 (0–2)	2 (0–2)	25 (0–3)
Squamous metaplasia	0 (0–0)	0 (0–0)	0 (0–0)	6 (0–2)	0 (0–0)	24 (0–3)	0 (0–0)	0 (0–0)	2 (0–1)	1 (0–1)	2 (0–3)	3 (0–2)
Number of rats	23	91	21	95	27	87	32	86	44	71	44	71

From Nikula *et al.* (1995)

[a] Animals dying, euthanized or sacrificed before and after 18 months of exposure were pooled

[b] Severity scores range from 1 to 4, with 4 being the most severe effect/lesion

sequestration of these particles in aggregated alveolar macrophages in the alveolar space as well as in the pulmonary interstitium, and this increased with exposure time and exposure concentration. Thus, at 18 months of exposure, both the low-dose and high-dose carbon black-exposed groups exhibited ~50% of the fluorescent microspheres in aggregated macrophages in the alveolar parenchyma. All of these results were nearly identical to those of comparison groups exposed concurrently to the same concentration of diesel exhaust.

A number of studies performed at the Fraunhofer Institute (Hannover, Germany) focused on histopathological events after exposure to carbon black, as well as inflammatory responses and parameters of lung clearance. The carbon black material used was Printex 90 (furnace black) with a surface area of 227 m^2/g; the aerosolized particles had an MMAD of 0.64 μm. Heinrich *et al.* (1995) reported results in female Wistar rats and female NMRI mice exposed to an average concentration of 11.6 ± 1.9 mg/m^3 Printex 90 for 18 h per day on five days per week for a total of 24 months (in rats) with an additional six-month post-exposure period, or 13.5 months (in mice) with an additional 9.5-month post-exposure time. Findings included decreased body weight and progressively increasing lung weight in rats, first measured at three months, with a lung burden (not contributing to lung weight) of 44 mg carbon black per lung at the 24-month time point. Carbon black (6.7 mg) was found in the lung-associated lymph nodes, and impaired lung clearance of test particles was found during this study (see Muhle *et al.*, 1994). Significant increases in cellular and biochemical parameters of lung lavage were also observed. Histologically, moderate to high-grade bronchiolar/alveolar hyperplasia and slight to moderate interstitial fibrosis were observed in addition to significant findings of lung tumours which are reported in the previous section.

In mice, there was also a decrease in body weight and an increase in lung weight at a lung burden of 7.4 mg at 12 months of exposure. This lung burden, when normalized to a control lung, corresponded to 37 mg carbon black/g control lung which was similar to the normalized rat lung burden of carbon black of 32 mg/g control lung. No detailed description of nonneoplastic histological changes in the lungs of mice was provided, although there was elevated mortality during exposure in this and, more so, in other groups so that the planned 18-month exposure duration had to be shortened to 13.5 months. Overall, responses found in rats and mice exposed to carbon black were very similar to the responses in the respective groups of animals concurrently exposed to diesel exhaust or ultrafine titanium dioxide particles (Heinrich *et al.*, 1995).

Dungworth *et al.* (1994) gave a more detailed description of effects induced in female Wistar rats by inhalation of 6 mg/m^3 carbon black for 17 h per day on five days a week for 10 months with a subsequent 20-month post-exposure period (72 rats) or inhalation for 20 months with a subsequent 10-month post-exposure period (72 rats). Another group (100 rats) was exposed to 11.3 mg/m^3 for 18 h per day on five days a week for a total of 24 months with up to a six-month post-exposure period. Findings were chronic active inflammation, including bronchiolar/alveolar hyperplasia, alveolar histiocytosis, lipoproteinosis and squamous metaplasia (probably originating from type II cells).

Nolte *et al.* (1994) also reported results after exposure of Wistar rats to 6 mg/m^3 of this same material for 18 h per day on five days a week for a total of 10 months with an additional 20-month post-exposure period. As in the study described previously (Nolte *et al.*, 1993), a clear distinction in their reporting was not drawn between those effects found in animals exposed to carbon black only and those found in animals that were co-exposed to carbon black and pyrolyzed pitch — the focus of this study was on cellular changes and cell dynamics. Thus, they reported hyperplastic bronchiolar epithelium and metaplasia as well as inflammatory responses including alveolar histiocytosis and alveolar lipoproteinosis.

A subchronic inhalation study with Monarch 880 (furnace black) was performed in Fischer 344 rats exposed to 1.1, 7.1 and 52.8 mg/m^3 for 6 h per day on five days a week for a total of 13 weeks with an eight-month post-exposure period (Driscoll *et al.*, 1996). The MMAD of the carbon black aerosol was 0.88 μm and the primary particle size was 16 nm with a specific surface area of 220 m^2/g. Lung burdens at the end of exposure were 0.35, 1.8 and 7.8 mg, respectively; there was continued accumulation of carbon black in the tracheobronchial lymph nodes during the post-exposure period in the mid- and high-dose groups only. Inflammatory cellular and biochemical parameters of lung lavage (total and differential cell counts; protein and lysosomal and cytoplasmic enzymes) and cell proliferative responses as well as histopathological evaluation showed no change in the low-exposure group as compared to controls at any time point. The groups exposed to the higher concentrations had dose-related increases in cellular and biochemical broncho-alveolar parameters as well as in alveolar cell proliferative responses at the end of exposure which remained elevated throughout the post-exposure period in the highest exposure group. Cellular inflammatory parameters also remained elevated during post-exposure in the mid-exposure group whereas lavage protein and enzyme levels returned to control values. Table 30 summarizes the findings of non-neoplastic end-points determined in this study at the end of the subchronic exposure and up to eight months post-exposure.

In summary, these studies show that once a certain lung burden has been achieved, inhalation of carbon black in rats results in significant inflammatory responses in the lung. The reported inflammatory pulmonary responses may be mechanistically related to subsequent fibrotic as well as neoplastic effects observed in long-term chronic inhalation studies at high-exposure concentrations. The effects of carbon black appear to be more severe in rats than in mice, based on the single mouse study. In addition, female rats seemed to respond with higher incidence and greater severity than males with respect to chronic, active inflammation, alveolar proteinosis and bronchiolar/alveolar metaplasia.

(*b*) *Instillation studies*

A number of studies evaluating non-neoplastic effects of carbon black were performed by intratracheal instillation (see Table 31). Bowden and Adamson in a number of studies from 1978 through 1982 evaluated cellular responses in mice, specifically focusing on the kinetics of macrophages and polymorphonuclear neutrophils. They used India ink (Pelikan Co.) in most of their studies which has a primary particle diameter of

Table 30. Three-month multi-exposure inhalation study of carbon black in rats

End-point	Exposure concentration (mg/m^3)		
	1.1	7.1	52.8
Continued post-exposure accumulation in lymph nodes	–	+	+
No. of AM increased:			
End of exposure	–	+	+
Post-exposure	–	–	+
No. of PMN increased:			
End of exposure	–	+	+
Post-exposure	–	+	+
Cell proliferation:			
End of exposure	–	+	+
Post-exposure	–	–	(+)
Fibrotic response	–	(+)	+

Compiled from Driscoll *et al.* (1996)
–, no response; +, marked response; (+), mild response; AM, alveolar macrophages; PMN, polymorphonuclear macrophages

30–40 nm and was instilled mostly at doses of 4 mg into Swiss mice [sex not always specified]. Subsequent evaluation showed that there was generally a biphasic macrophage response in which the first phase occurred without mitotic activity whereas the second phase showed mitosis of primarily interstitial macrophages. There was also a high initial response in terms of elicitation of polymorphonuclear neutrophils, which reached twice the number of alveolar macrophages (Adamson & Bowden, 1978; Bowden & Adamson, 1978). They also observed that this very high dose and extremely high dose rate (4 mg instilled) resulted in rapid migration of blood monocytes to pulmonary alveoli and rapid production of monocytes in the bone marrow (Adamson & Bowden, 1980). In a study with male Swiss mice using doses as low as 0.1 mg and as high as 8 mg (dose–response study), these authors observed (Adamson & Bowden, 1981) that the number of alveolar macrophages elicited was correlated to the dose delivered and that this response was very similar to that to other different types of particles administered. In further studies (Adamson & Bowden, 1982a), they confirmed that the responses are not unique to carbon black but also occur after different particles, including latex, are instilled into the mouse. Further, they showed that chemotactic factors are elicited in the alveolar space and detectable in bronchoalveolar lavage fluid. They further determined the importance of the macrophage to elicit the initial response; when whole-body irradiated mice were instilled with carbon black, a limited macrophage response occurred which was followed by proliferation of interstitial macrophages still present in the lungs of these irradiated mice (Adamson & Bowden, 1982b; Bowden & Adamson, 1982).

Table 31. Non-neoplastic effects of carbon black by instillation studies in experimental animals

Particle type	Particle diameter and surface area	Species (age and sex)	Dose	Observation period	End-points	Findings	Comments	Reference
India ink (Pelikan Co.)	30–40 nm	Swiss mouse	4 mg	Up to 28 days	Macrophage proliferation and CB transport in lung	Biphasic macrophage response; first phase without mitotic activity; second-phase mitosis of interstitial macrophages; initial large PMN increase in BAL (twice AM numbers); some CB particles crossed epithelium to reach peribronchial and perivascular sites	Very high dose and dose rate	Adamson & Bowden (1978); Bowden & Adamson (1978)
India ink (Pelikan Co.)	30–40 nm	Swiss mouse	4 mg	Up to 7 weeks	Macrophage and blood monocyte response	Rapid migration of blood monocytes to pulmonary alveoli and rapid production of monocytes in bone marrow after CB dosing	Very high dose and dose rate	Adamson & Bowden (1980)
India ink	30 nm	Swiss mouse (male)	0.1, 1, 2, 4, 8 mg	Up to 14 days	Macrophage response	Confirming findings (Adamson & Bowden (1978); number of AM elicited is related to dose delivered; lowest dose showed very little response	Focus of study was on macrophage kinetics after different particle types	Adamson & Bowden (1981)
Colloidal carbon	30 nm	Swiss mouse	4 mg (donor)[a] BAL supernatant (recipient)[a]	2 days Up to 14 days	PMN and macrophage response	Chemotactic factors in BAL after CB cause PMN and AM influx	Similar response also after latex particles, not unique to CB	Adamson & Bowden (1982a)
Colloidal carbon	30 nm	Swiss mouse	4 mg, whole-body irradiated and controls	Up to 20 weeks	Macrophage response after monocyte depletion	Limited initial macrophage response after monocyte depletion, followed by interstitial macrophage proliferation; increased translocation of CB to interstitium in depleted mice with decreased AM output	Response not specific to CB; importance of AM for containment of particles in alveolar space	Adamson & Bowden. (1982b); Bowden & Adamson (1982)

Table 31 (contd)

Particle type	Particle diameter and surface area	Species (age and sex)	Dose	Observation period	End-points	Findings	Comments	Reference
Furnace black Regal 660	~20 nm	Fischer 344 rat (male)	0.5 mg	24 h	BAL response, interstitial passage	Inflammatory response (PMN and protein in BAL) is correlated with particle surface area; CB passage to interstitium is less than for ultrafine TiO_2; interstitial access can influence alveolar inflammation	Surface area correlation applies to both ultrafine and larger-sized TiO_2 particles	Oberdörster *et al.* (1992)

CB, carbon black; PMN, polymorphonuclear macrophages; BAL, bronchoalveolar lavage; AM, alveolar macrophages; TiO_2, titanium dioxide
[a]4 mg carbon black instilled into donor mice, from which supernatant of BAL was obtained and administered to recipient mice

Macrophage depletion also resulted in an increased translocation of administered carbon black to interstitial sites. Overall, the studies of these investigators confirmed the importance of the alveolar macrophage in pulmonary defences to particles including carbon black. Both the alveolar macrophage and the interstitial macrophage systems are of importance in this response as part of the pulmonary defence system against particles.

Oberdörster *et al.* (1992) administered 0.5 mg furnace black (Regal 660) with a primary particle size of ~20 nm to male Fischer 344 rats by intratracheal instillation. In addition, other particle types (ultrafine and larger-sized titanium dioxide) were administered at different dose levels, and the bronchoalveolar lavage response and interstitial access of particles was determined 24 h later. They found that the inflammatory response as measured by lavaged polymorphonuclear macrophages and lavage protein was correlated best with the particle surface area of different particle types of titanium dioxide; the inflammatory response induced by carbon black also fitted the same regression. Interstitial access of ultrafine titanium dioxide particles was greater than that for carbon black, with higher doses resulting in a diminished inflammatory response in the alveolar space (larger polymorphonuclear macrophage) and a shift of the inflammation towards the interstitium.

In a study of the effects of benzo[*a*]pyrene on rat lung, Davis *et al.* (1975) dosed intratracheally groups of 18 female Wistar rats, 12–16 weeks of age at the beginning of the experiment, with 0.5, 1.0 or 2.0 mg benzo[*a*]pyrene with or without 0.5 mg carbon black on 18 occasions at biweekly intervals. One group received carbon black alone and one received no treatment. Group mean survival times ranged from 73 to 109 weeks. At autopsy, all rats given carbon black had black deposits in their lungs, mainly in alveolar macrophages. These animals also showed significantly more severe columnar and cuboidal metaplasia of the alveolar epithelium, whereas rats receiving benzo[*a*]pyrene alone showed no increased severity of metaplasia. However, squamous metaplasia of the alveolar epithelium was increased in rats receiving carbon black alone as well as carbon black with benzo[*a*]pyrene.

Overall, these results from intratracheal instillation studies with carbon black show that high acute doses of carbon black elicit a significant pulmonary inflammatory response which is possibly related to the large specific surface area of the particles.

(*c*) *Ex-vivo and in-vitro studies*

A number of studies have been performed with carbon black using either in-vivo exposure to the particulate compound with subsequent isolation of cells and specific in-vitro investigations or primary in-vitro exposure of cell systems to evaluate effects. These studies are summarized in Table 32.

Miller and Zarkower (1974) exposed Balb/c mice by inhalation to 5.4 mg/m^3 carbon black [unspecified] with a mass median diameter of 1.8 µm continuously for seven to 28 days. The aim was to investigate effects on the immune system. After exposure, spleen and lung lymph node T and B cell lymphocytes were isolated and an in-vitro lymphocyte assay, including a transformation test, was performed. They reported significant changes in the responsiveness to mitogens of both B and T lymphocytes as well as changes in

Table 32. In-vitro toxicity studies of carbon black

Particle type	Particle diameter and surface area	Test system	Dose/exposure concentration	Findings	Comments	Reference
Not specified	1.8 µm	Balb/c mouse: inhalation exposure; isolation of spleen and lung lymph node T and B cells; in-vitro transformation of lymphocyte and migration of macrophage	5.4 mg/m^3, 7–28 days continuously	Significant changes in responsiveness to both B- and T-lymphocyte-specific mitogens; changes in lymphocyte populations	Lung dose not determined; altered immune response, possibly due to high CB lung burden and inflammation	Miller & Zarkower (1974)
Fisher carbon black (thermal black)	25 µm 31 m^2/g	Effect of adsorption of BaP; uptake into 1 ml of rat liver microsomes	16.7 mg CB + 5 µg BaP; 30 min incubation	BaP was not released from CB and there was no uptake into microsomes, in contrast to other particles (Fe_2O_3, SiO_2, asbestos)	Relevancy of test system (high doses) is questionable	Lakowicz & Bevan (1979, 1980)
Fisher carbon black (thermal black)	25 µm 31 m^2/g	Effect of adsorption of BaP on particles for uptake rate into model membranes	16.7 mg CB + 5 µg BaP; 30 min incubation	BaP was not released from CB, no uptake into membranes in contrast to BaP adsorbed on other particles	Relevancy of test system (high doses) is questionable	Lakowicz *et al.* (1980)
3 Oil furnace blacks	96, 168, 220 nm 128, 101, 70 m^2/g	In-vitro elution of BaP from CB using plasma, serum, lung lavage fluid; in-vivo feeding study with CB in mice to study AHH induction	*In-vitro*: 5–20 g CB with biological medium, 24 h *In-vivo*: 0.08, 2 and 20 g/kg diet, 30–180 days	Less than 0.005% of adsorbed BaP can be eluted by biological media; in-vivo feeding at high dose does not induce AHH in mouse lung or liver	Results are in contrast to other in-vivo bioavailability studies of BaP; test system may not be relevant	Buddingh *et al.* (1981)
4 Oil furnace blacks	96, 168, 175, 220 nm 128, 101, 90, 70 m^2/g	Elution of adsorbed BaP from CB into phospholipid vesicles	100 µg CB	Elution of BaP from CB depends on amount of BaP present; rate and extent of elution is lowered with less adsorbed BaP	Study aims at bioavailability of PAH adsorbed onto CB particles; high-dose study not relevant for *in vivo*	Bevan & Worrell (1985)

Table 32 (contd)

Particle type	Particle diameter and surface area	Test system	Dose/exposure concentration	Findings	Comments	Reference
4 Oil furnace blacks	96, 168, 175, 220 nm 128, 101, 90, 70 m^2/g	Elution of adsorbed BaP from CB into phospholipid vesicles from rat lung homogenate and simulated lung fluid	Up to 200 mg CB	0.2–0.6% of BaP can be eluted; more elution from low surface area CB and high BaP content	Very low elution *in vitro* using biological systems	Bevan & Yonda (1985)
Regal 660 (furnace black)	10 m^2/g	In-vitro activation of rat serum with particles to determine chemotactic activity for AM	5–25 mg CB/ml serum; 10% serum for AM chemotaxis	CB has highest activity for different particles (SiO_2, asbestos, PVC, TiO_2) to activate serum chemotactic factors	High doses	Oberdörster *et al.* (1989)
2 Oil furnace carbon blacks (N339 & Black Pearl 2000)	Not given. Surface area of N 339 is 15-fold less than that of Black Pearl 2000	Phagocytosis assay with AM from Wistar rats; CB adsorbed with polar and semi-polar compounds	1.5 ml of 0.04 mg/ml suspension for 2×10^5 AM, 45 min	AM phagocytosis of CB + adsorbate suppressed only for low surface CB; Fc-receptor mediated phagocytosis of sheep red blood cells was impaired after previous uptake only of low surface area CB + adsorbate	Surface properties are important for fate of particle-pollutant complexes	Jakab *et al.* (1990)

CB, carbon black; BaP, benzo[*a*]pyrene; AHH, arylhydrocarbon hydroxylase; PAH, polycyclic aromatic hydrocarbons; AM, alveolar macrophage

lymphocyte populations. Spleen lymphocytes of carbon black-exposed mice also exhibited significantly enhanced ratios of transformation after sensitization of the mice with tuberculosis antigen.

Lakowicz and Bevan (1979, 1980) and Lakowicz *et al.* (1980) investigated the effect of adsorption of benzo[*a*]pyrene onto Fisher carbon black (thermal black) (25 μm particle size) on uptake into either rat liver microsomes or into model membranes. 5 μg benzo[*a*]pyrene had been adsorbed onto 16.7 mg carbon black which was incubated with model systems for 30 min. Release of benzo[*a*]pyrene from the carbon black was not detected, and no uptake into liver microsomes or model membranes occurred. This is in contrast to the enhanced uptake of benzo[*a*]pyrene absorbed onto certain other particles (haematite, silica and asbestos) that were also tested by these authors.

Additional studies were performed to evaluate the in-vitro elution of benzo[*a*]pyrene from carbon black using either plasma, serum or lung lavage fluid from rats, phospholipid vesicles, or phospholipid vesicles, rat lung homogenates and simulated lung fluids (Buddingh *et al.*, 1981; Bevan & Worrell, 1985; Bevan & Yonda, 1985). These studies are listed in Table 32 and show that very little of the benzo[*a*]pyrene adsorbed onto carbon black particles can be eluted by biological media. The eluted amount depends on the total amount of benzo[*a*]pyrene present on the carbon black. Together with their in-vitro studies, Buddingh *et al.* (1981) also reported results of a feeding study with carbon black in mice designed to examine the induction of arylhydrocarbon hydroxylase in the lung and liver; they did not find induction of this enzyme even at the highest dose level of 20 g/kg of diet carbon black for up to 180 days.

Oberdörster *et al.* (1989) investigated activation of chemotactic serum factor *in vitro* by furnace black (Regal 660) and compared it to other particle types such as titanium dioxide, polyvinyl chloride (PVC), asbestos and silicon dioxide. They found that, on a mass basis, carbon black showed the greatest ability to induce chemotactic factors for alveolar macrophages in rat serum. The authors suggested that surface area may play an important role in the inducibility of such factors, since titanium dioxide, with a very low surface area, showed the lowest response.

Jakab *et al.* (1990) studied alveolar macrophage phagocytosis of two different oil furnace carbon blacks with high and low surface areas and with adsorbed polar and semi-polar compounds. The carbon blacks (1.5 ml of a 0.04 mg/ml suspension) were incubated with 2×10^5 alveolar macrophages from Wistar rats for 45 min. For the low surface area carbon black particles only, they observed depressed alveolar macrophage phagocytosis of the carbon black and the adsorbates as well as for sheep red blood cells that had previously been incubated with the carbon black–adsorbate complex. The authors suggested that surface properties are important parameters to determine the fate of particle–pollutant complexes in the lung.

No firm conclusions about the in-vitro toxicity or effects on cell systems can be drawn from these limited in-vitro studies reported in the literature. With respect to elution of adsorbed benzo[*a*]pyrene, it appears that desorption from carbon black particles occurs at a very low rate and to a very low degree. However, in-vivo studies

(see section 4.1.2(*b*)) have demonstrated clearly that adsorbed material can be eluted readily.

(*d*) *Other studies*

A number of studies have been performed with carbon black that may not be directly relevant for an evaluation of carcinogenicity — the route of exposure was in most cases rather unusual. These studies consist of experiments of intracardiac, intravenous, intrabladder-wall and intraventricular (central nervous system) injections of carbon black into experimental animals. The material used was mostly India ink (Pelikan Co.) and the major conclusion from these studies is that systemically administered carbon black particles can be trapped in the pulmonary circulation and be transported to pulmonary interstitial sites and alveolar macrophages. This is a suggested route of elimination of foreign bodies from the systemic circulation according to the authors (Blau & Veall, 1967; Vales *et al.*, 1967; Bertheussen & Nissen, 1976; Bertheussen *et al.*, 1978 (see Table 33)).

4.3 Reproductive and developmental effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see also Table 34 and Appendices 1 and 2)

The activity of carbon black particles and of their corresponding solvent extracts in short-term assays must be considered separately. When carbon black particles are tested, results may be influenced by such experimental conditions as the presence of serum, the concentration of dimethyl sulfoxide or other solvents, or the duration of exposure. In addition, these assays may underestimate in-vivo exposure owing to the short duration of the experiments. Conversely, the amount of chemicals eluted by solvent extracts of carbon blacks may be greater than that which would be eluted by biological fluids (Buddingh *et al.*, 1981). Additionally, the nature of the solvent and the temperature and duration of the Soxhlet extraction influence the final biological response (Sanders, 1981; Giammarise *et al.*, 1982; Butler *et al.*, 1983).

Several different carbon blacks have been assayed in short-term tests. These include a rubber-grade furnace black (N339), a nitric acid after-treated black (Black Pearls), a third carbon black of unspecified type, and several unspecified carbon black pastes. In addition, extracts of three of the above and 20 other carbon black samples have been tested. The data are summarized in Table 34.

Table 33. Other studies of carbon black related to non-neoplastic end-points

Particle type	Particle diameter and surface area	Test system	Dose	Findings	Comments	Reference
India ink (Pelikan) (+ 4.3% fish glue, 1% phenol)	20–50 nm	Guinea-pig: intracardiac injection (animals turned slaty grey for a few min); study of thymus uptake	0.1–0.15 ml/100 g bw of 10% suspension	CB found in macrophages throughout thymus. Foreign bodies can reach thymus	Not relevant for CB toxicity	Blau & Veall (1967)
Not given	16 and 70 nm	Intravenous injection into rabbits; reaction of pulmonary vessels	5 mg, up to 13 weeks follow-up	Formation of emboli in pulmonary vessels; endothelial hyperplasia; passage of CB to alveolar space and elimination	Not relevant for CB toxicity	Vales *et al.* (1967)
India ink (Pelikan)	Not given	Injection into urinary bladder wall of rat; sacrifice after 1–24 h	0.1–0.2 ml of 25% suspension	CB found in AM at 24 h, suggesting pulmonary excretion of foreign bodies	Not relevant for CB toxicity	Bertheussen & Nissen (1976)
India ink (Pelikan)	Not given	Injection into ventricular system of Wistar rat	3 : 1 mixture of saline : CB	CB found in macrophages in alveolar septae of lung as elimination pathway	Not relevant for CB toxicity	Bertheussen *et al.* (1978)

CB, carbon black; AM, alveolar macrophages

Table 34. 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		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–[c]	–[c]	3750	Kirwin *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+[d]	+[d]	NR	Agurell & Löfroth (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–[e]	–[e]	50	Venier *et al.* (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–[c]	–[c]	3750	Kirwin *et al.* (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–[c]	–[c]	3750	Kirwin *et al.* (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–[c]	–[c]	3750	Kirwin *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–[f]	0	250	Rosenkranz *et al.* (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	(+)[g]	0	500	Rosenkranz *et al.* (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+[h]	0	5.0	Rosenkranz *et al.* (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–[c]	–[c]	3750	Kirwin *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+[d]	+[d]	NR	Agurell & Löfroth (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	(+)[e]	+[e]	2.5	Venier *et al.* (1987)
SAS, *Salmonella typhimurium* TA98NR, reverse mutation	+[d]	0	NR	Agurell & Löfroth (1983)
SAS, *Salmonella typhimurium* TA98/1,8DNP, reverse mutation	+[d]	0	NR	Agurell & Löfroth (1983)
DMM, *Drosophila melanogaster*, somatic mutation (mosaics)	–[c]		10 000 larval feeding	Kirwin *et al.* (1981)

Table 34 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DMX, *Drosophila melanogaster*, sex-linked recessive mutation	–[c]		10 000 larval feeding	Kirwin *et al.* (1981)
DML, *Drosophila melanogaster*, dominant lethal test	–[c]		10 000 larval feeding	Kirwin *et al.* (1981)
DMN, *Drosophila melanogaster*, aneuploidy (sex-chromosome loss)	–[c]		10 000 larval feeding	Kirwin *et al.* (1981)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–[c]	–[c]	40 000	Kirwin *et al.* (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–[c]	–[c]	1000	Kirwin *et al.* (1981)
MIA, Micronucleus induction, M3E3/C3 hamster epithelial cells *in vitro*	+[i]	0	1	Riebe-Imre *et al.* (1995)
TCM, Cell transformation, C3H/10T½ mouse fibroblasts *in vitro*	–[c]	0	16 000	Kirwin *et al.* (1981)
TCL, Anchorage independent growth, M3E3/C3 hamster epithelial cells *in vitro* (undifferentiated and small mucus granule cell stage)	+[j]	0	100	Riebe-Imre *et al.* (1995)
GVA, *p53*, K-*ras* in pulmonary carcinomas in F344/N rats	–[k]		3.5 inh 16 h/d × 5 d/wk × 24 mo	Swafford *et al.* (1995)
GVA, *hprt* Mutation analysis in type II alveolar cells isolated from rats after exposure	+[l]		1.5 inh. 6 h/d × 5 d/wk × 13 wk	Driscoll *et al.* (1995)
BVD, Binding to DNA (^{32}P-postlabelling) in F344/N rat alveolar type II cells *in vivo*	+[k]		3.5 inh 16 h/d × 5 d/wk × 12 wk	Bond *et al.* (1990)

Table 34 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
BVD, Binding to DNA (^{32}P-postlabelling) in Wistar rat lung *in vivo*	–[m]		7.3 inh 18 h/d × 5 d/wk × 2 yr	Gallagher *et al.* (1994)

[a] +, positive; (+), weak positive; –, negative; 0 not tested; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose. In-vitro tests, μg/mL; in-vivo tests, mg/kg bw; NR, dose not reported; MMAD, mass median aerodynamic diameter; MMDD, mass median diffusion diameter

[c] Rubber-grade furnace black N339, surface area 100 m^2/g, 48-h toluene extractables 0.15%; particles suspended in DMSO (Ames test + SCE assay), acetone (cell transformation test) or culture media (mouse lymphoma test).

[d] 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

[e] 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).

[f] 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.

[g] Raven 5750 (furnace black, oxidative aftertreated). Soxhlet extraction of 10-g samples with toluene for 48 h. Low-temperature concentration and solvent exchange into 1 mL DMSO.

[h] 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.

[i] Carbon black [not otherwise characterised]; carbon black suspended in the culture medium containing undifferentiated cells for 72 h.

[j] Carbon black [not otherwise characterised]; carbon black suspended in the culture medium containing undifferentiated or differentiated cells for 72 h.

[k] Elftex-12 (furnace black); 2 μm MMAD (large mode); 0.1 μm MMDD (small mode); surface area, 43 m^2/g. Whole-body exposure

[l] Monarch 880 (furnace black); 0.8 μm MMAD (16 nm primary particle); surface area, 220 m^2/g. Whole-body exposure

[m] 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

In an extensive study, Kirwin *et al.* (1981) tested a rubber-grade furnace black (N339; surface area, 100 m^2/g; toluene extractables (48-h), 0.15 wt%) in the following five short-term assays:

(1) Mutagenicity in *Salmonella typhimurium*: no mutagenic activity was observed in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 or TA100 at concentrations of carbon black of up to 7.5 mg/plate in the presence or absence of an Aroclor-induced rat-liver homogenate supernatant fraction (S9); cellular toxicity (TA100) was assessed and viable count was reduced by 27% at 7497 µg/plate of carbon black. [It was not reported whether, or for how long, the carbon black particles were suspended in dimethyl sulfoxide (DMSO) prior to testing.]

(2) Sister chromatid exchange in Chinese hamster ovary cells: the carbon black was suspended in DMSO at 100 mg/mL [time and temperature unspecified] and then diluted in culture medium to give a final concentration range of 0.00032–1 mg/mL; cells were exposed for 2 h both in the presence and absence of S9; very small increases in the frequency of sister chromatid exchange as compared to the control value with and without S9 were observed for several concentrations, but these were not dose related.

(3) L5178Y $tk^{+/-}$ mouse lymphoma mutagenicity assay: cells were exposed for 4 h [time extended for an unspecified time owing to difficulty in separating carbon black from cells] to concentrations of carbon black of 10–40 mg/mL in the absence of S9 and of 5–15 mg/mL in the presence of S9; cell survival was < 1% at the highest concentration; no mutagenicity was observed.

(4) C3H/10T½ CL8 mouse embryo morphological cell transformation assay: carbon black suspended in acetone was tested at four concentrations ranging from 2–16 mg/mL; no transformed focus was observed.

(5) Genetic activity in *Drosophila melanogaster*: larvae were fed diets containing 1% carbon black until pupation; flies were scored for mosaics, Y-chromosome loss, chromosomal aberrations and dominant lethal and sex-linked lethal mutations; no genetic effect was observed.

A nitric acid-treated furnace black (Black Pearls; surface area, 115 m^2/g; toluene extractables (48-h), 0.3 wt%) (Sanders, 1981) was tested for mutagenicity in *S. typhimurium*. Particles were first suspended in DMSO for 5 h and an aliquot containing 500 µg carbon black was then tested in strain TA98. No mutagenic activity was observed (Rosenkranz *et al.*, 1980).

An aliquot of a 48-h Soxhlet toluene extract (solvent exchanged into DMSO) equivalent to 10 µg of the above carbon black was, however, mutagenic in the same strain. This carbon black contained nitrated pyrenes at a level of 67 mg/kg (Sanders, 1981). More recent production lots of this grade of carbon black had a 200-fold reduction in nitrated pyrene content; extracts had a mutagenicity that was reduced by the same order of magnitude (Rosenkranz *et al.*, 1980; Agurell & Löfroth, 1983; Butler *et al.*, 1983).

Benzene or acetone extracts of 20 commercial carbon blacks were tested in the *Salmonella* mutagenicity assay. Of the 20 extracts (some of which required activation

with rat-liver S9), 15 were mutagenic to strains TA98 and/or TA100 and five were inactive (Agurell & Löfroth, 1983).

Venier *et al.* (1987) tested the mutagenicity in *S. typhimurium* strains TA98 and TA100 of seven carbon black pastes that are used as commercial leather dyes. Samples were assayed for mutagenicity either directly or after extraction with benzene. The compounds that were tested were in the form of thick pastes and the carbon black content ranged from 5 to 8%. In all compounds but one, carbon black was dispersed in 10–15% casein solution in water containing small amounts of sulfonated castor oil and cresols. Different extraction procedures were used for the pastes. No mutagenicity was observed either directly or after sonication with benzene in any of the carbon black samples tested. After a 48-h extraction of carbon blacks with boiling toluene, four carbon black samples were mutagenic in strain TA98 in the presence of S9. The activity ranged from 1.3 to 9.7 induced revertants/mg equivalent of extract. A weak direct mutagenic activity in strain TA98 was shown by one extract. The presence of PAHs in the toluene extracts was reported by the authors to explain the mutagenicity of only one carbon black sample. Low or undetectable levels of PAHs were found in other mutagenic extracts.

Two studies analysed the extent to which exposure of rats to carbon black induced DNA adducts in lung tissue (Bond *et al.*, 1990; Gallagher *et al.*, 1994). Both studies employed the ^{32}P-postlabelling assay to measure DNA adducts.

Gallagher *et al.* (1994) exposed female Wistar rats (Crl:(WI)BR) to furnace black (Printex 90) particles. The carbon black exposure was 7.5 mg/m^3 for the first four months and 12 mg/m^3 for the last 20 months. Exposures were for 18 h per day on five days a week for two years using whole-body exposure chambers. The carbon black surface area was 270 m^2/g. The MMAD of the carbon black particles for the exposures was 0.65 μm. The extractable organic matter, as determined by solvent extraction with dichloromethane, was 0.039%. After two years of exposure, animals were killed and the distal tip of the peripheral left lung lobe was removed for analysis of DNA adducts using the nuclease P1 or butanol extraction versions of the ^{32}P-postlabelling assay. ^{32}P-Postlabelling analysis detected one major radiolabelled spot that was referred to as adduct 1. DNA adduct levels for adduct 1 after two years of exposure to carbon black were about 9 adducts/10^9 bases and about 17 for the filtered-air controls. Adduct 1 was found to increase in an age-related fashion and was presumed by the authors to be a ^{32}P-labelled I-compound. Adduct levels were determined for the diagonal radioactive zone; however, no significant elevation in adduct levels in this zone was observed in lung DNA isolated from the carbon black-exposed animals.,

Bond *et al.* (1990) exposed male and female Fischer 344/N rats to filtered air or carbon black (6.2 mg/m^3) for 12 weeks. The carbon black was Elftex-12 (furnace black) of which 59% of the mass had a 1.9 μm MMAD and 41% of the mass had a 0.10 μm geometric mean diameter and surface area characteristics similar to those of eluted diesel soot but negligible amounts of extractable organic chemicals and no measurable mutagenic activity. Rats were exposed for 16 h per day on five days a week for 12 weeks. DNA adducts in alveolar type II cells were assessed at the end of the exposure. The authors report the presence of several adducts as assessed by the nuclease P1 version of

the ^{32}P-postlabelling assay. The level of carbon black-induced adducts was significantly elevated above that seen in controls. Total levels of DNA adducts in type II cells from control and carbon black-exposed rats were approximately 5 and 25 adducts/10^9 bases, respectively. The authors could not determine whether exposure to carbon black induced an increase in the level of adducts already present in cells from sham-exposed rats or if carbon black induced the formation of new adducts with chromatographic characteristics of I-spots.

Riebe-Imre *et al.* (1994) assessed the ability of carbon black particles [the Working Group was aware that this was Printex 90 (furnace black)] to induce cytotoxicity, cell transformation and micronuclei formation in a fetal Syrian hamster lung epithelial cell line. The cytotoxicity of the carbon black particles was negligible. Carbon black particles induced in-vitro transformation in small mucus granule cell-differentiated M3E3/C3 cells and in undifferentiated M3E3/C3 cells. Carbon black particles showed a much weaker activity in undifferentiated cells compared to differentiated cells. They also reported cytoskeletal changes. Concentrations of carbon black used in the transformation studies ranged from 100 to 300 μg/mL. Peak responses in the differentiated cells occurred at 200 μg/mL and were approximately four-fold over those of controls. In the undifferentiated cells, peak concentrations were observed at 300 μg/mL and were approximately eight-fold over those of controls. A dose-related increase was observed in the frequency of micronuclei over the dose range 0.1–2.0 μg/mL. However, maximal responses were only approximately 50% greater than the control frequency of about 4.5%; there was no indication of variation, and the possibility of different responses at higher doses (that were tolerated in the cell transformation test) were not reported.

Swafford *et al.* (1995) analysed pulmonary carcinomas from rats exposed to diesel exhaust, furnace black (Elftex 12) and air for alterations in K-*ras* and *p53* to determine if mutations were similar. Details of the exposure conditions are described in Nikula *et al.* (1995). Briefly, male and female Fischer 344/N rats (seven to nine weeks of age) were exposed for 16 h per day on five days per week for 24 months to diesel exhaust or carbon black at concentrations of 2.44 and 6.33 mg/m^3 for diesel exhaust and 2.46 and 6.55 mg/m^3 for carbon black. Controls were exposed to air only. The number of carcinomas analysed were 28 for diesel exhaust, 18 for carbon black and five for air only. K-*ras* exon 1 mutations were found in two neoplasms, one each from diesel exhaust and carbon black exposure groups. No mutations in the K-*ras* gene were observed in lung neoplasms from control rats. Immunohistochemical staining revealed evidence of *p53* inactivation in 2/4 squamous-cell carcinomas and adenocarcinomas from carbon black-exposed rats. *p53* Mutational analyses revealed the presence of one mutation in a diesel exhaust-induced squamous-cell carcinoma. This mutation was reported by the authors to be a silent mutation. [The Working Group noted that it is not clear whether the only (silent) mutation was in a diesel exhaust or carbon black-exposed rat.]

A subchronic inhalation study with Monarch 880 (furnace black) was performed in Fischer 344 rats exposed to 1.1, 7.1 and 52.8 mg/m^3 for 6 h per day on five days a week for a total of 13 weeks with an eight-month post-exposure period (Driscoll *et al.*, 1996). The MMAD of the carbon black aerosol was 0.88 μm and the primary particle size was 16 nm with a specific surface area of 220 m^2/g. The rat alveolar type II cell isolation and

the *hprt* clonal selection assay were used. Mutant frequencies ranged from 8.2 to 5.2 mutants/10^6 epithelial cells in the air control animals. Exposure to 52.8 mg/m^3 carbon black resulted in *hprt* mutant frequencies which were 4.3-, 3.2- and 2.7-fold greater than the air control group, immediately, three and eight months after exposure, respectively. A significant increase in the frequency of *hprt* mutants was detected immediately after 13 weeks of exposure to 7.1 mg/m^3 carbon black but not after three or eight months of recovery. No significant changes in the *hprt* mutant frequency were observed for alveolar epithelial cells from rats exposed to 1.1 mg/m^3 carbon black. This mutagenic response occurred at exposures that also resulted in significant pulmonary inflammation, epithelial hyperplasia and fibrosis.

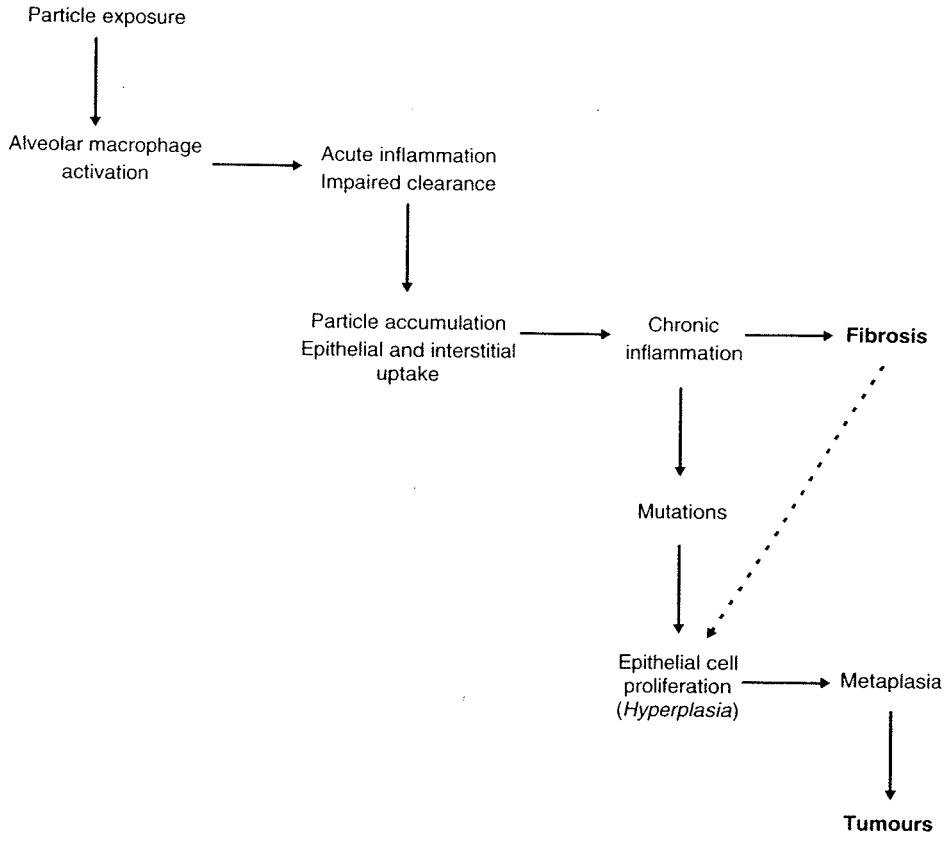
4.5 Mechanistic considerations related to carcinogenicity

Figure 1 describes a hypothesized mechanistic model for effects of particle exposure in the lung. More specifically, the model, derived from inhalation studies in rats, pertains to exposure to low-toxicity low-solubility particles. This topic has also been discussed at a recent symposium (Mauderly & McCunney, 1996). Phagocytosis of such particles by alveolar macrophages leads to activation by alveolar macrophage and the subsequent release of inflammatory cytokines, growth factors, chemokines, enzymes and reactive oxygen species. This in turn recruits polymorphonucleocytes from the circulatory system into the alveolar space, thus amplifying the inflammatory response including the release of additional reactive oxygen species. This inflammatory response is dependent on the dose of deposited and phagocytized particles. Particularly, impairment of alveolar macrophage-mediated particle clearance due to lung particle overload results in further particle accumulation and amplifies this process, leading to chronic inflammation, including fibrotic changes. The continuous release of reactive oxygen species can result in increased mutation frequencies in specific target cells, which become manifest during increased cell proliferative responses. Subsequent responses include metaplastic changes, which finally result in tumour formation.

This specific mechanism involving reactive oxygen species is based on studies by Driscoll *et al.* (1996), which showed that carbon black in rats led in a dose-dependent manner to increased mutation frequency of the type II cells in those cases where significantly increased numbers of inflammatory cells were present. Earlier studies by Driscoll (1996) have shown that co-incubation of rat lung epithelial cells with inflammatory polymorphonucleocytes also resulted in increased mutation frequencies and that this response could be significantly decreased in the presence of antioxidants. Thus, oxidative damage to DNA due to released reactive oxygen species from inflammatory cells appears to be a plausible mechanism underlying the particle-induced rat tumour response. In further support of this hypothesis are the studies of Bond *et al.* (1990) who reported elevated levels of DNA damage in alveolar type II cells of rats exposed to concentrations of carbon black known to induce an inflammatory response.

An alternative mechanism relates to physical phenomena due to particles taken up by target cells. As pointed out in Figure 1, high pulmonary particle burdens result in

Figure 1. Mechanistic chain of events for pulmonary effects of low-toxicity, low-solubility particles assumed to be operative in rats



Adapted from Oberdörster (1995)

increased uptake by epithelial cells and access of particles into the pulmonary interstitium. A study by Riebe-Imre *et al.* (1994) reported that a fetal Syrian hamster lung epithelial cell line, when incubated with different doses of carbon black, showed increased transformation, particularly when these cells were already differentiated. Carbon black also induced a dose-dependent enhancement of micronucleus formation in these cells, mostly due to clastogenic effects. Since these effects were observed in an epithelial cell line derived from hamsters after in-vitro exposures, the relevance to the in-vivo situation needs to be addressed. Particle-induced lung tumours have not been observed in hamsters, and target cells in the only species that shows particle-induced tumours (the rat) are most likely of alveolar origin, including the type II cells. This mechanistic hypothesis, based on physically induced DNA alterations, may be less plausible and relevant than the one of particle-induced oxidative damage.

The particle-associated rat lung tumours (e.g. diesel exhaust) cannot be extrapolated to mice or hamsters; these species do not, at comparable lung burdens of particles, develop lung tumours. For carbon black specifically, this species difference has been demonstrated between rats and mice. Several inhalation studies with low-solubility, low-toxicity particles, one of them with carbon black, have shown that no lung tumour was

induced in mice at exposure concentrations and lung burden that exceeded the capacity of the lung to clear the particles and induced significant toxicity.

A central question is whether the toxic and defensive mechanisms suggested to operate in rats also operate in humans. Very little is known about the relationship between overload and lung cancer risk in humans, although it may be assumed that this overload-related mechanism could occur in humans exposed to sufficient levels (or doses). Limited indirect inferences regarding this issue may be derived from the available epidemiological studies of workers exposed to carbonaceous particles. The epidemiological studies of carbon black workers are not very informative in this regard. It is interesting to note that studies of coal miners have generally failed to detect an increased risk for lung cancer (Merchant *et al.*, 1986; Harrington & Levy, 1994). This evidence has been interpreted by some scientists as suggesting that a lung overload-related mechanism does not induce cancer in humans. However, there are other plausible interpretations for these observations that should be considered. It is difficult, as with nearly all epidemiological studies, to rule out that limitations in sample size, bias and other study design issues might explain these negative findings. The Working Group considered that the fact that coal miners are not permitted to smoke while working may have introduced a negative confounding bias for lung cancer in these studies. This bias is consistent with the observation of a deficit in lung cancer risk in these studies. Furthermore, it is important to consider the surface area characteristics of the inhaled low-toxicity, low-solubility particle (including coal dust) and its impact on dose.

Lung particle burden in the lungs of these workers by mass were on average ~15 mg/g lung. However, although pulmonary particle accumulation by mass is very high in coal miners, particle mass may not be the most relevant dose parameter for a correlation with specific long-term effects. It has been suggested, based on results of a number of studies, that surface area of retained particles may be a better parameter for correlation with pulmonary inflammation and neoplastic events. Thus, it may well be that coal miners, in spite of the high mass loading of particles in the lungs, did not reach a sufficient surface area of the retained particles. Also in rats, it has been found in some studies that lung particle mass burdens in this range, and even higher, did not result in increased tumour incidences. For example, chronic studies in rats with toner particles and pigment-grade titanium dioxide at exposure concentrations of 16 mg/m^3 and 50 mg/m^3, respectively, resulted in typical findings of particle overload (e.g. impaired particle clearance at lung burdens of ~12 and 60 mg/g lung, respectively) but with less inflammatory response and without induction of lung tumours. When these pulmonary mass particle burdens are expressed in terms of their surface area, the retained dose (by particle surface area) is lower than the dose (by surface area) observed to induce lung tumours in rats in other studies.

Epidemiological studies of diesel-exposed workers may also contribute something to this issue. A recent review of the epidemiological literature in this area concluded that these studies suggest a small-to-moderate increase in lung cancer risk, and that these findings do not appear to be fully explicable by confounding or other sources of bias (Cohen & Higgins, 1995). These studies are pertinent because it has been suggested, based on the recent experimental studies of rats exposed to high concentrations of diesel

exhaust and carbon black (Nikula *et al.*, 1994; Heinrich *et al.*, 1995), that the increased risk for lung cancer associated with diesel exhaust in rats might be explained by the carbonaceous core rather than the organic fraction of diesel soot. Workers in these studies were generally exposed to diesel exhaust levels below 200 $\mu g/m^3$, which is below the level at which overload of the lung in humans is believed to occur (Cohen & Higgins, 1995). These findings might be interpreted as suggesting either that lung overload occurs at lower levels than expected among humans, or that an overload-related mechanism may play the dominant role only at the high-exposure levels used in experimental studies.

In addition to these dose considerations, it is also of importance to consider differences in specific defence mechanisms between rats, mice and humans. The Working Group is not aware of studies which have evaluated specific pulmonary defences, including antioxidant levels, in humans under particle load conditions; such data, in contrast, are available for rats and mice. Thus, whether humans respond to chronic inhalation of particles, including carbon black, more like a rat or more like a mouse cannot be decided at present. It should be emphasized that the dose plays a most important role in the chain of mechanistic events outlined in Figure 1.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Carbon black is a powdered form of elemental carbon manufactured by the vapour-phase pyrolysis of hydrocarbon mixtures, such as heavy petroleum distillates and residual oils, coal-tar products, natural gas and acetylene. Worldwide production of carbon black in 1993 was approximately 6 million tonnes.

Carbon blacks are categorized as acetylene black, channel black, furnace black, lampblack or thermal black, according to the process by which they are manufactured. Lampblack is the oldest type of carbon black, having been used as a pigment for centuries. Channel black, produced from natural gas, was introduced in the late nineteenth century and was the major carbon black used worldwide in the early twentieth century for rubber and pigment applications; with the exception of a special product made in Germany, it is no longer produced. Acetylene, furnace and thermal blacks have been produced since the early twentieth century. Over 90% of all carbon black produced today is furnace black.

The primary use of carbon black is in rubber products, mainly tyres and other automotive products, but also in many other rubber products such as hoses, gaskets and coated fabrics. Much smaller amounts of carbon black are used in inks and paints, in plastics and in the manufacture of dry-cell batteries.

Types of carbon black are characterized by the size distribution of the primary particles, the degree of their aggregation and agglomeration and the various chemicals adsorbed onto the surfaces. Average primary particle diameters in several commercially produced carbon blacks range from 10 to 400 nm, while average aggregate diameters

range from 100 to 800 nm. Typical classes of chemicals adsorbed onto the carbon black surface are polycyclic aromatic hydrocarbons (PAHs), nitro derivatives of PAHs and sulfur-containing PAHs. Examples of PAHs extracted most frequently from carbon black using a variety of extraction methods (e.g. prolonged Soxhlet extraction with benzene or toluene) include benzopyrenes, benzo[*ghi*]perylene, coronene, fluoranthene and pyrene.

Exposures to carbon black vary markedly within any production facility. The highest levels of exposure are experienced by those who interact with the process the most, including fitters/welders, warehouse packers and site cleaners. Exposures can vary greatly among factories and regionally.

Several studies in the 1960s found very high levels of exposure, even up to 1000 mg/m^3 in furnace, lamp- and channel black plants. Later studies in some countries have found lower levels, although many of these were in excess of the existant occupational exposure limits. In the late 1980s and early 1990s, more extensive studies in western Europe and the United States have found (geometric mean) personal exposure to total inhalable carbon black to be on average less than 1 mg/m^3. Even lower exposures may occur among some workers in industries using carbon black, such as rubber, printing ink and paint manufacture, and exposures to carbon black in the use of rubber, printing ink or paint are negligible.

5.2 Human carcinogenicity data

The greatest potential for elucidating the carcinogenicity of carbon black is in the carbon black production industry where carbon black has been the prime industrial exposure and where exposure levels have been high. Cohort studies of carbon black production workers have been conducted in the United States and in the United Kingdom. Interpretation of the study in the United States is hampered by problems of uncertainty in the completeness of the cohort and in the definition and completeness of follow-up. The study in the United Kingdom also had some problems in completeness of the cohort, but the follow-up was probably complete. In both cohorts, fewer observed than expected deaths due to all causes occurred and, in the study in the United States, this may in part have been attributable to under-ascertainment of deaths or to inflation of person-years of follow-up. The study in the United States found no excess mortality due to any type of cancer when compared to state vital statistics rates; in fact there were deficits for some types of cancer. The study in the United Kingdom found an excess of respiratory cancer deaths (standardized mortality ratio, 1.5; 95% confidence interval, 1.0–2.2).

A nested case–control study within the United States cohort was hampered by very small numbers and problems of interpretation. Most cases were of non-melanoma skin cancer. Neither for all cancers combined nor for skin cancers alone was there evidence that cases had higher cumulative exposure to carbon black than controls.

A cohort study was carried out among workers in the United States to assess cancer risks due to exposure to formaldehyde. Ten participating plants were spread across several industries in which workers may have experienced exposure to formaldehyde. To control for confounding and modification of effect by other exposures, workers'

exposures to various other chemicals, including carbon black, were assessed by industrial hygienists. For all assessed levels and durations of exposure to carbon black combined, there was a slight nonsignificant excess of lung cancer. There was no clear trend by duration of exposure. Carbon black-exposed workers in this cohort may also have been exposed to formaldehyde and other substances.

Another industry-based study was a nested case–control study conducted in the tyre and rubber manufacturing industry to examine the association of squamous-cell carcinoma of the skin with rubber manufacturing materials. For each study subject, industrial hygienists assessed exposure to five substances, including carbon black, based on evaluations of each subject's job history. The results of this study indicated no effect of carbon black on skin cancer.

In a community-based case–control study in Canada, interviews were designed to obtain detailed lifetime job histories and information on potential confounders. Potential occupational exposures were identified for each job description, and among the exposures assessed was carbon black. In this study population, potential exposure to carbon black occurred in some individuals in user industries, notably among painters and in the printing and rubber industries. For the following cancer sites, there was no indication of excess risk in relation to carbon black: stomach, colon, rectum, pancreas, prostate, urinary bladder, skin melanoma and non-Hodgkin's lymphoma. For the following sites there was indication of excess risk: oesophagus, kidney and lung. The lung cancer excess was particularly concentrated among oat-cell cancers.

A Swedish case–control study reported a nonstatistically significantly increased risk for urothelial cancer for men exposed to carbon black.

In assessing all the available data, there is no evidence of an effect of carbon black for most cancer sites. For cancers of the urinary bladder, kidney and oesophagus, isolated results indicate excess risks, but these are not sufficient to support an evaluation of human carcinogenicity.

Two studies were informative for non-melanoma skin cancer (a nested case–control study among the United States carbon black production cohort and a nested case–control study among rubber workers); neither demonstrated any excess risk for skin cancer due to carbon black.

Of the studies listed above, four were considered informative for lung cancer. Of those, two indicated excess risk among carbon black-exposed workers at borderline statistical significance (the carbon black production cohort in the United Kingdom and the Canadian community-based study), one indicated excess risk but was not significant (the United States formaldehyde cohort) and the other indicated no excess (the United States carbon black production cohort).

Each of the available studies has limitations for the specific purpose of assessing the carcinogenicity of carbon black. The Working Group considered the study of carbon black producers in the United Kingdom to be the most informative for this purpose. That study indicated an excess risk of borderline significance. Confounding by smoking could not be excluded, although some information was presented indicating that it was unlikely. The formaldehyde cohort study indicated a slight excess of lung cancer among

the subgroup exposed to carbon black, but this could easily have been due to chance or confounding by formaldehyde or other occupational substances. The community-based study in Montréal of exposure in a variety of user industries showed an elevated risk in the subgroup categorized as having high exposure to carbon black; the result was of borderline statistical significance using a cancer series control group and not significant using a population control group. It is not clear which control group provides the most valid estimates. Even the high-exposure subgroup of this study was unlikely to have experienced exposure levels of the same order of magnitude as did workers in the carbon black production industry. Although the United States carbon black worker study, which was negative, was large, its methodological limitations detracted from its value. The Working Group therefore considered the whole body of evidence rather weak and the results conflicting.

5.3 Animal carcinogenicity data

No adequate study of the carcinogenicity of carbon black administered by the oral route was available.

In one study in female mice by inhalation exposure, carbon black did not increase the incidence of respiratory tract tumours.

Two different carbon black products were tested in two inhalation studies in female rats and in one study using rats of each sex. Significant increases in the incidence of malignant lung tumours and the incidence of benign and malignant lung tumours combined were observed in female rats in all three studies. In addition, increased incidences of lesions described as benign cystic keratinizing squamous-cell tumours or squamous cysts were observed.

In two studies in female rats by intratracheal administration, using one type of carbon black, both extracted and non-extracted material increased the incidence of benign and malignant lung tumours. In one of the studies, a different type of extracted carbon black with a larger primary particle size increased the incidence of lesions described as benign cystic keratinizing squamous-cell tumours.

In several skin-painting studies in mice using various carbon blacks, no carcinogenic effect on the skin was observed; the painting of several carbon black extracts (benzene extracts) resulted in skin tumours.

In a series of studies in male and female mice by subcutaneous injection, a carbon black containing demonstrable quantities of carcinogenic PAHs produced local sarcomas, whereas a carbon black from which no PAH was detected did not produce such sarcomas. In several studies in mice, solvent extracts of carbon black produced sarcomas following subcutaneous injection.

5.4 Other relevant data

Upon inhalation exposure of humans to carbon black, these particles are deposited in the lung. The exposure may cause slight radiological changes. The prevalence of radiological findings has varied considerably among different studies, probably because

of varying radiological techniques and possibly also due to different exposure circumstances and possible concomitant exposures to other compounds. Further, workers may develop chronic bronchitis and a slight reduction in lung function. These findings may be interpreted mainly as a slight nonspecific irritant effect of heavy dust exposure. On the other hand, some data indicate a fibrous tissue reaction in the area surrounding the carbon deposits in the lung parenchyma.

Studies on the pulmonary retention of inhaled carbon blacks in rats and mice have shown that these particles behave very similarly to other low-solubility, low-toxicity particles. Carbon black displayed normal retention characteristics in rats at lung burdens not exceeding a certain level which is approximately in the range of 0.5–1 mg/g of lung. At higher lung burdens, a prolonged clearance is found. Impaired particle clearance due to high loading of carbon black in experiments with rats results in increased accumulation of particles. Subsequent inflammatory responses occur which develop into chronic active inflammation. Increased collagen deposition from proliferating fibroblasts, increased epithelial cell proliferation and metaplasia have been found at high lung burdens of carbon black. It appears that the high specific surface area of most carbon blacks may be an important parameter in the induction of inflammatory and subsequent other responses in the lung. One study with carbon black in rats confirmed findings with other particles that females are more sensitive than males.

Most assays for mutagenicity are negative for carbon black. In rats exposed to carbon black by inhalation, *hprt* mutant frequency was elevated in type II cells following a 12-week exposure. Carbon black did not induce a significant increase in DNA adducts in 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. K-*ras* mutations were found in one out of 18 neoplasms analysed from a carbon black-exposed rat. No exposure-related *p53* mutation was found.

Some mechanistic considerations on particle-induced lung neoplasms are presented.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of carbon black.

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.

Overall evaluation

Carbon black is *possibly carcinogenic to humans (Group 2B).*

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

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