para-ARAMID FIBRILS

1. Exposure Data

1.1 Chemical and physical data

The term 'aramid fibre' refers to a manufactured fibre in which the fibre-forming substance is a long-chain synthetic polyamide with at least 85% of the amide linkages attached directly to two aromatic rings (Preston, 1978; Yang, 1993). '*para*-Aramid fibres' are those in which the amide linkages are in the para (1,4) positions on the aromatic rings. *para*-Aramid fibres of poly(*para*-phenyleneterephthalamide) have been available commercially as Kevlar® from DuPont, United States, since 1972 (Yang, 1993) and as Twaron® from Akzo, the Netherlands, since 1986. Other *para*-aramid fibres from different copolymers are also available commercially (Mera & Takata, 1989), but no data on the biological effects of these copolymers were available to the Working Group.

para-Aramid fibrils are smaller-diameter sub-fibres that can be released from *para*-aramid fibres during some processing operations (Cherrie *et al.*, 1995).

meta-Aramid fibres are also produced commercially but are not considered in this monograph.

1.1.1 *Nomenclature*

There are at least three Chemical Abstracts Registry Numbers in current use for poly(*para*-phenyleneterephthalamide) and its manufactured fibres.

Chem. Abstr. Serv. Reg. No.: 24938-64-5

Chem. Abstr. Name: Poly(imino-1,4-phenyleneiminocarbonyl-1,4-phenylenecarbonyl)

Deleted CAS Nos: 93120-87-7; 119398-94-6; 131537-80-9; 132613-81-1

Synonyms: Aramica; poly(imino-*para*-phenyleneiminocarbonyl-*para*-phenylenecarbonyl); poly(imino-*para*-phenyleneiminoterephthaloyl); poly(1,4-phenylene terephthalamide); poly(*para*-phenylene terephthalamide); poly(*para*-phenylenediamine-terephthalic acid amide); PPTA

Chem. Abstr. Serv. Reg. No.: 25035-37-4

Chem. Abstr. Name: 1,4-Benzenedicarboxylic acid, polymer with 1,4-benzenediamine

Synonyms: 1,4-Benzenediamine-terephthalic acid copolymer; *para*-phenylenediamine, polyamide with terephthalic acid; *para*-phenylenediamine-terephthalic acid copolymer; poly(*para*-phenylene terephthalamide); PPD-T

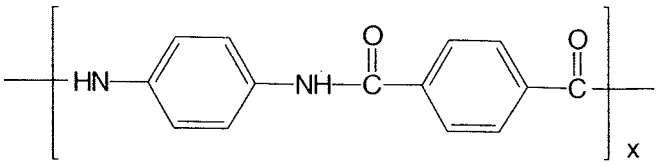
Chem. Abstr. Serv. Reg. No.: 26125–61–1

Chem. Abstr. Name: 1,4-Benzenedicarbonyl dichloride, polymer with 1,4-benzenediamine

Synonyms: *para*-Phenylenediamine-terephthalic acid chloride copolymer; *para*-phenylenediamine-terephthaloyl chloride copolymer; poly(*para*-phenylene terephthalamide)

1.1.2 *Structure of typical fibre and fibril*

General structural formula (poly(*para*-phenylene terephthalamide)):



Molecular formula: $(C_{14}H_{10}N_2O_2)_x$

Typical polymer molecular mass: *c.* 20 000 (Yang, 1993)

1.1.3 *Chemical and physical properties*

Some physical properties of *para*-aramid fibres are given in **Table 1**.

Table 1. Physical properties of some *para*-aramid fibres[a]

Property	Kevlar® 29	Kevlar® 49	Kevlar® 149	Twaron® (regular)	Twaron® (high modulus)	Technora® (PPTA co-polymer)
Density (g/cm^3)	1.44	1.45	1.48	1.44	1.45	1.39
Tensile strength (Gpa)	2.8	2.8	2.4	2.8	2.8	3.4
Tensile modulus (Gpa)	58	120	165	80	125	73
Elongation at break (%)	4.0	2.5	1.3	3.3	2.0	4.6
Flammability (LOI)[b]	29	29	29	29	29	25
Heat resistance at 200 °C (%)	75	75	–	90	90	75
Acid resistance (%)	10	10	–	–	–	89
Moisture regain (%)	7	4	1	7	3.5	2

[a] From Mera & Takata (1989); Teijin (1989, 1993) for Technora

[b] LOI, limiting oxygen index

Generally, *para*-aramid fibres have medium to very high tensile strength, medium to low elongation at break and moderate to very high tensile modulus. The strength to weight ratio of *para*-aramid is high; on a weight-for-weight basis, it is five times as strong as steel, 10 times as strong as aluminium and up to three times as strong as E-glass. The volume resistivities and dielectric strengths of these fibres are also high, even at elevated temperatures. Aramid fibres are heat resistant, with mechanical properties being retained at temperatures of up to 300–350 °C; aramids will not melt. Nor will aramid fibres support combustion without additional heat input; carbonization is not

appreciable under 400 °C. However, overheating or laser cutting of *para*-aramid fabrics and *para*-aramid reinforced laminates may generate some toxic off-gases. Whole aramid fibres are generally resistant to chemicals, with the exception of strong mineral acids and bases (to which the Technora® copolymer is highly resistant) (Preston, 1978; Hanson, 1980; Galli, 1981; Brown & Power, 1982; Chiao & Chiao, 1982; Mera & Takata, 1989; World Health Organization, 1993; Yang, 1993).

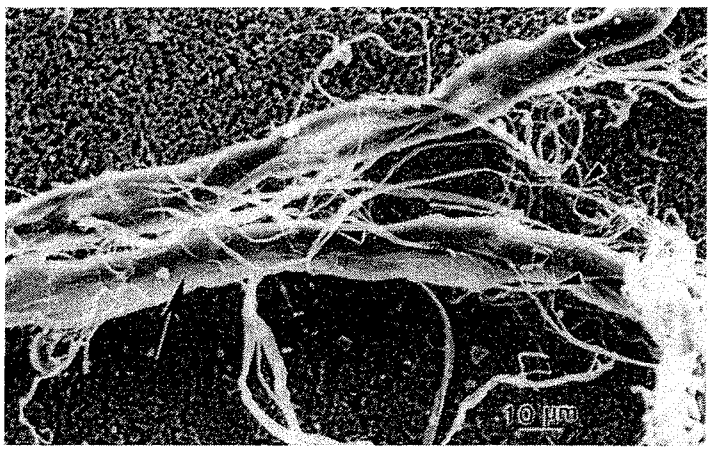
1.1.4 *Technical products*

Kevlar® *para*-aramid fibre was first introduced to the high-temperature fibre market as Fiber B continuous filament yarn in 1972. A high modulus version of Fiber B was later introduced as PRD-49 fibre. These code names were later replaced by Kevlar® 29 and Kevlar® 49, respectively, after commercialization. Similar types were subsequently marketed by Akzo (later Akzo Nobel) under the trade name of Twaron®. Several other *para*-aramid filament yarns have since been introduced, differing mainly in elongation and modulus characteristics (Mera & Takata, 1989; Yang, 1993).

para-Aramid continuous filaments are supplied as such, but also serve as feedstocks for the manufacture of other product types, such as staple (fibre lengths, 38–100 mm), short-cut (length, 6–12 mm) and pulp (milled or ground short fibres; average particle lengths, 0.4–4 mm) (World Health Organization, 1993; Yang, 1993).

Figure 1 illustrates the typical *para*-aramid fibre with associated fibrils. Continuous filament, staple and short-cut fibres are typically 12–15 μm in diameter. During processing, operations that are abrasive peel a few fibrils of < 1 μm diameter off the surface. *para*-Aramid pulp, on the other hand, is a highly fibrillated product. Pulp has many fine, curled, ribbon-like fibrils attached to the surface of the short core fibre; it is these fibrils (within the respirable size range) that can break off the fibre and become airborne during manufacture and use. The branched and entangled fibrils in the pulp have a high aspect ratio (> 100 : 1) and a surface area of 8–10 m^2/g, which is approximately 40 times that of the standard filament (World Health Organization, 1993; Yang, 1993; Cherrie *et al.*, 1995; Minty *et al.*, 1995).

Figure 1. Scanning electron micrograph of *para*-aramid fibres (large arrow) and attached fibrils (small arrowheads)



It is reported (Mera & Takata, 1989) that the *para*-aramid Technora®, a copolymer of terephthalic acid with *para*-phenylenediamine and 3,4′-oxydiphenylenediamine (ECETOC, 1996), is less prone to fibril formation, perhaps because of the greater flexibility of its copolymer chain and looser crystal structure.

para-Aramid filament and staple may be supplied as yarn and fabrics or incorporated in composites. Pulp may also be supplied as a pre-mix with fillers and/or elastomers (Yang, 1993).

1.1.5 *Analysis*

Sampling and analytical methods for organic fibres include the measurement of total airborne or respirable mass concentration and the determination of airborne fibre counts by phase contrast optical microscopy (PCOM). Sampling methods used for organic fibres are similar to those used for inorganic fibres, such as asbestos or man-made mineral fibres. These methods typically involve drawing a measured volume of air through a filter mounted in a holder that is located in the breathing zone of the subject. For the measurement of mass concentrations, either poly(vinyl chloride) or glass fibre filters are normally used. These filters are stabilized in air and weighed against control filters, both before and after sampling, to permit correction of weight changes caused by varying humidity. For the assessment of fibre number concentrations, cellulose ester membrane filters are usually used. This filter can be made optically transparent with one of several clearing agents (e.g. triacetin, acetone or ethylene glycol monomethyl ether) and the fibres on random areas of the filter can then be counted and classified using PCOM (World Health Organization, 1985, 1993; Eller, 1994a).

Although the basic methods for the determination of total airborne mass and fibre number concentrations are similar in most countries, specific reference methods for the determination of organic fibres have not been developed (World Health Organization, 1993). There are differences in the sampling and fibre-counting procedures, the filter sizes and types and the clearing agents and microscope types used by various investigators. These differences, combined with subjective errors in sampling and counting, all contribute to variations in results.

In a study to validate sampling and analytical methods for airborne *para*-aramid fibrils, Cherrie *et al.* (1995) reported that the potential problems noted above can be avoided by a combination of PCOM and fluorescence microscopy with appropriate sample handling techniques to minimize electrostatic charge.

The improved resolution of electron microscopy and the identification capacity of transmission electron microscopy, selected area electron diffraction and energy dispersive X-ray analysis, make these methods useful for the more complete characterization of small-diameter fibres (World Health Organization, 1993; Eller, 1994b). However, due to the cost, the time of sample preparation and analysis and the relative unavailability of instrumentation, these methods have so far rarely been used for analyses of organic fibres (Cherrie *et al.*, 1995).

1.2 Production and use

1.2.1 *Production*

para-Aramid fibres are produced by a two-step process — polymer production followed by spinning. The first step is the low-temperature-solution polymerization of di-acid chlorides (e.g. terephthaloyl chloride) and diamines (e.g. *para*-phenylenediamine) in amide solvents. Polar solvlents such as *N*-methylpyrrolidone and dimethylacetamide are used as polymerization solvents; formerly, hexamethylphosphoramide was used. The *para*-aramid polymer is neutralized and then isolated from the polymerization solution. Next, a 'spinning solution' is created by redissolving the polymer in concentrated sulfuric acid. This liquid crystalline solution is extruded through a spinneret, and the acid is extracted and neutralized; the result is a highly oriented fibre (Mera & Takata, 1989; World Health Organization, 1993; Yang, 1993).

meta-Aramid fibres, such as Dupont's Nomex® (poly(*meta*-phenyleneisophthalamide)), are made by similar methods. However, *meta*-aramid fibres do not have the highly-oriented crystalline structure that gives *para*-aramid fibres their strength and unique physical properties (Preston, 1978; Mera & Takata, 1989).

para-Aramid fibre has been sold commercially since 1972 (Yang, 1993). The production capacity in 1978 was reported to be approximately 6800 tonnes (Galli, 1981). More recently, the combined production capacity in United States, the Netherlands and Germany was estimated at 25 thousand tonnes (Hodgson, 1989); however, plants in the Netherlands, Northern Ireland and Japan have been expanded or brought on line since then, increasing worldwide capacity to nearly 40 thousand tonnes (World Health Organization, 1993; Akzo Nobel, 1996).

1.2.2 *Use*

para-Aramid fibres are used principally in advanced composite materials to improve strength, stiffness, durability, dielectric properties or heat resistance. Since the fibre improves these properties without adding much weight, it is used principally in the aerospace industry, for military purposes and in sports equipment (World Health Organization, 1993).

para-Aramid fibres are used as a reinforcing fibre for composites, thermoplastics, tyres and mechanical rubber goods. They are used in limited amounts as an overlay on metals and in cement or concrete. Woven fabrics of *para*-aramid are used in all-weather clothing, parachutes, ropes and cables, ballistic body armour and hard armour. *para*-Aramid pulp is used as an asbestos substitute in automotive friction products (e.g. brake pads and linings), gaskets, thixotropic sealants and adhesives (Mera & Takata, 1989; Yang, 1993).

1.3 Occurrence and exposure

1.3.1 *Natural occurrence*

para-Aramid fibres are not known to occur as a natural product.

1.3.2 *Occupational exposure*

Verwijst (1990) described exposure monitoring during *para*-aramid fibre and pulp manufacturing and during laboratory operations using a light microscope. Personal air concentrations ranged from 0.01 to 0.1 fibril/mL, with the highest values being for pulping. A relatively high exposure (0.9 fibril/mL) was also noted during water-jet cutting of composites, but only if the water was recycled and contained high concentrations of fibrils.

Since the initiation of Kevlar® *para*-aramid fibre production (in about 1971), employee exposures and air levels in United States manufacturing plants have been measured by the same PCOM techniques used for asbestos (PCAM 239 before about 1982 and NIOSH 7400 'A' (Eller, 1994b) more recently; i.e. fibres > 5 μm in length and length: diameter ratio > 3 : 1) (Merriman, 1992). For continuous filament yarn handling, exposures are extremely low (0.02 fibre/mL maximum) (Reinhardt, 1980). Cutting of staple and floc fibre produced levels of 0.2 fibre/mL or less with a single peak measurement of 0.4 fibre/mL. Pulp drying and packaging operations led to maximum concentrations of 0.09 fibre/mL.

Merriman (1992) monitored airborne *para*-aramid fibre concentrations using PCOM in brake pad production, gasket and composite fabrication and staple yarn spinning processes (see **Table 2**). In brake pad manufacturing (in which dry *para*-aramid pulp is mixed with powdered fillers and resin, pressed, cured, ground and drilled), no exposures exceeded 0.19 fibre/mL. Average personal exposures were less than 0.1 fibre/mL. In gasket sheet and gasket manufacturing (where *para*-aramid pulp is mixed with fillers and solvated rubber cement, rolled into sheets and die-cut into smaller pieces that may be finished by sanding the edges), a total of 62 personal and area samples in four plants gave no personal exposures greater than 0.15 fibre/mL and no area concentrations greater than 0.27 fibre/mL. Mean exposures were less than 0.1 fibre/mL for all operations.

Machining of *para*-aramid fabric-reinforced organic matrix composites also produced very low exposures; most were less than 0.1 fibre/mL, although one exposure reached 0.25 fibre/mL during trimming. Although operator exposure during water-jet cutting was only 0.03 fibre/mL, the cutting sludge in a single sample was highly enriched with respirable fibrils and much higher levels (2.9 fibres/mL) were found in area samples taken close to the floor (Merriman, 1992).

In contrast, Merriman (1992) found that significant *para*-aramid fibril exposure levels occurred in staple fibre carding and its subsequent processing into yarn. Carding is highly abrasive and the fibrils produced are entrained in the high air flows created by the spinning cylinders. Monitoring of operators in six yarn-spinning mills (67 personal samples) gave average exposures ranging from 0.18 to 0.55 fibre/mL, with one operation reaching a maximum of 2.03 fibres/mL.

Kauffer *et al.* (1990) characterized airborne fibre concentrations and size distributions during the machining of carbon fibre- and aramid-based composites in industry and the laboratory. Concentrations were typically well below 1 fibre/mL, as determined by optical microscopy; scanning electron revealed mean lengths to be 1.9–4.3 μm, and mean

length : diameter ratios to be 4.4 : 1–8.8 : 1. The authors concluded that most of the respirable material consisted of resin debris.

Table 2. Airborne fibre concentrations in workplaces handling *para*-aramid fibre pulp[a]

Manufacturing industry	Operations	No. of personal samples	Mean (fibre/mL)	Maximum (fibre/mL)
Brake pads	Mixing	20	0.07	0.15
	Preforming	17	0.08	0.19
	Grinding/drilling	8	0.04	0.08
	Finishing/inspecting	3	0.05	0.11
Gaskets	Mixing	30	0.05	0.15
	Calendering	1	–	0.02
	Grinding/sanding	5[b]	[0.08][b]	0.27[c]
	Cutting	15[b]	0.02	0.07[c]
Composite	Sanding/trimming	NG	[0.08][b]	0.25
	Water-jet cutting	NG	0.03	2.91[c]
Staple yarn	Grinding	5	0.18	0.28
	Carding	16	0.39	0.79
	Drawing	4	0.32	0.87
	Roving	6	0.33	0.72
	Spinning	15	0.18	0.57
	Twisting/winding	13	0.55	2.03
	Finishing	2	0.30	0.48
	Weaving	6	0.35	0.58

[a] From Merriman (1992)
[b] Area and personal samples
[c] Maximum individual area sample
[ ], calculated by the Working Group; NG, not given

In a series of studies in *para*-aramid fibre and textile production facilities in Germany, concentrations of respirable particles (length, ≥ 5 μm; diameter ≤ 3 μm; length : diameter ratio ≥ 3 : 1) averaged 0.02 to 0.14 fibres/mL (Bahners *et al.*, 1994).

More recently, Cherrie *et al.* (1995) measured exposures to airborne fibrils among *para*-aramid process workers in the United Kingdom. Eleven manufacturing sites were selected as representative of the spectrum of *para*-aramid uses in industry (processors of continuous filament yarn, users of pulp, users of staple and processors of resin-impregnated cloth making composites). Activities at these sites included yarn spinning, weaving, production of gaskets and friction material, production and machining of thermoset composites and manufacturing of sporting goods. Personal sampling was performed in accordance with the methods outlined in the HSE Method No. 59 (Health and Safety Executive, 1989), with minor modifications to exclude electrostatic effects. Samples were counted by PCOM and sized with scanning electron microscopy; respirable *para*-aramid fibres [fibrils] were identified separately by means of fluorescence

microscopy. The results of 63 personal exposure measurements to respirable fibres [fibrils] are summarized in **Table 3**. The exposure, expressed as the geometric mean (GM) of the 8-h time-weighted average (TWA) for each job class ranged from 0.005 to 0.4 fibril/mL. The ranges of the geometric means of the *para*-aramid fibre lengths and diameters for these job classes were 2.3–13.8 μm and 0.31–1.29 μm, respectively. The authors noted that the relatively low exposures could be attributable to the efficient ventilation systems in use in the sites examined.

Table 3. Respirable fibre [fibril] concentrations of *para*-aramid by production category and job class[a]

Form of *para*-aramid	Job	No.	GM	GSD
Filament yarn	Stretch breaking	4	0.019	1.1
	Blender	2	0.049	1.3
	Winding or braiding	4	0.006	1.4
		1	0.005	
	Quality control	1	0.020	
	Stores	1	0.005	
	Weaving	4	0.029	2.2
	Labourer	1	0.140	
Pulp	Mixer/weigher	1	0.180	
		1	0.040	
		4	0.054	5.5
	Calender or press	3	0.023	1.3
		5	0.052	2.0
		5	0.011	1.4
Staple fibres	Carding or spinning	3	0.036	1.2
		3	0.033	1.7
	Winding or braiding	1	0.400	
		1	0.050	
	Separator	1	0.200	
	Blending	1	0.090	
Cloth	Lay-up and trim	4	0.021	1.9
		4	0.005	1.0
	Drill or grinding	4	0.032	1.2
		3	0.020	1.0
	Plaster room	1	0.020	

[a] From Cherrie *et al.* (1995)
GM, geometric mean concentration (fibre/mL) of 8-h time-weighted average; GSD, geometric standard deviation

Busch *et al.* (1989) studied the particle and gaseous emissions that occur during the laser cutting of aramid fibre-reinforced epoxy plastics. The mass-median aerodynamic diameter (MMAD) of particles generated was 0.21 μm, but neither the concentration of dust nor the fibre content of the dust were reported. Gas chromatography/mass spectrometry analyses of samples on charcoal and silica tubes demonstrated the following

release of gases per gram of material pyrolized during cutting: 5.4 mg benzene, 2.7 mg toluene, 0.45 mg phenylacetylene, 1.4 mg benzonitrile, 1.0 mg styrene, 0.55 mg ethylbenzene, 0.15 mg *meta*- and *para*-xylene, 0.04 mg *ortho*-xylene, 0.28 mg indene, 0.16 mg benzofuran, 0.15 mg naphthalene and 0.73 mg phenol.

Moss and Seitz (1990) conducted limited personal exposure monitoring during the laser cutting of *para*-aramid-reinforced epoxy matrix. Transmission electron microscopy analysis of an air sample collected within a few feet of the cutting operation revealed few fibres (0.15–0.25 μm in diameter and < 10 μm in length). In addition to fibre measurements, hydrogen cyanide concentrations in the cutting room area ranged from 0.03 to 0.08 mg/m^3 with a TWA of 0.05 mg/m^3. Carbon monoxide concentrations ranged from 10 to 35 ppm and nitrogen oxides (nitric oxide and nitrogen dioxide) concentrations were < 0.5 to 5 ppm.

1.4 Regulations and guidelines

Guidelines and standards for occupational exposures to *para*-aramid fibres are being developed. In the United Kingdom, the occupational exposure standard for *para*-aramid fibres is 0.5 fibre/mL respirable dust (8-h time-weighted average) (Minty *et al.*, 1995). In France, the occupational exposure limit (VME [mean exposition value] or [time-weighted] average exposure) for *para*-aramid fibres is currently 1.5 respirable fibres/mL and will become 1.0 fibre/mL in 1997 (Ministère du Travail et des Affaires Sociales, 1996). In the Netherlands, a MAK (maximal workplace concentration) value of 2.5 fibrils/mL is a recommended interim occupational exposure limit (Dutch Expert Committee for Occupational Standards, 1990). In the United States, occupational exposures to *para*-aramid fibres are currently regulated by United States Occupational Safety Health Administration (1995) with the inert or nuisance dust standard (15.0 mg/m^3 total dust and 5.0 mg/m^3 respirable fibres as the permissible exposure limits), although DuPont has recommended an 8-h TWA exposure limit of 2.0 fibres/mL for Kevlar® (Yang, 1993).

In Germany, there is no MAK (maximal workplace concentration) value for *para*-aramid (fibrous dust), which is classified as a III A2 carcinogen (a substance shown to be clearly carcinogenic only in animal studies but under conditions indicative of carcinogenic potential at the workplace) (Deutsche Forschungsgemeinschaft, 1996).

In the province of Québec, Canada, an exposure limit standard for *para*-aramid fibres of 1 fibre/mL (respirable dust) has been introduced in 1994 (Anon., 1995).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Inhalation exposure

Rat: Four groups of 100 male and 100 female weanling Sprague-Dawley-derived (Crl:CD (SD) BR) rats were exposed to atmospheres containing 0, 2.5, 25 or 100 *para*-aramid fibrils/mL for 6 h a day, five days a week for two years by whole-body exposure. A further group of rats was exposed to 400 *para*-aramid fibrils/mL but, due to excessive premature mortality of the rats, the exposures were terminated after 12 months; the surviving animals were maintained for the next 12 months. The *para*-aramid fibrils used in these experiments were prepared from a batch of commercial pulp with a particularly high fibril content. Fibrils were separated from the pulp matrix by high-pressure air impingement. At all exposure concentrations, the atmospheres contained mainly respirable fibrils (mass median diameter, < 2 μm) and more than 70% of the mass was of respirable size; about 18% of the fibrils were shorter than 5 μm. The fibre counts at the various concentrations corresponded to 0, 0.08, 0.32, 0.63 and 2.23 mg/m^3. There were interim kills of 10 males and 10 females per group of rats at three, six and 12 months. The surviving animals were killed after two years. All rats were subjected to extensive gross and microscopic examination. The authors did not present the interim results extensively; only brief reference was made to the 12-month period for the 400-fibrils/mL group. Lung weights were significantly increased in the two higher-dose groups compared to controls. However, no clinical signs or excess mortality were observed in rats exposed from 2.5 to 100 fibrils/mL. At 400 fibrils/mL, 29 male rats and 14 female rats died due to obliterative bronchiolitis during the 12-month exposure period. After the two years' exposure, rats that had received 2.5 fibrils/mL had a normal alveolar architecture, with a few 'dust-laden' macrophages in the alveolar airspaces. At exposure concentrations of 25 fibrils/mL, however, fibrils had been retained in the respiratory bronchioles and alveolar duct region, especially in the alveolar duct bifurcations. In these rats, alveolar bronchiolization was present, as was slight type II pneumocyte hyperplasia; some alveolar ducts and alveoli were thickened with microgranulomas and slight fibrosis (see **Table 4**). The rats exposed to 100 *para*-aramid fibrils/mL had a more severe response than those exposed to 25 fibrils/mL; this response included the following: dense deposition of inhaled fibrils, accumulation of dust cells, foamy macrophage response, type II pneumocyte hyperplasia, granulomatous tissue response and alveolar bronchiolization (**Table 4**). Examination of alveolar ducts and adjoining alveoli revealed a patchy thickening due to the fibrous organization of the intra-alveolar exudate and granulomatous tissue response. Of the female rats exposed at this concentration, 4/69 had developed cystic lesions, which were referred to by the authors as 'cystic keratinizing squamous-cell carcinomas', while 6/69 had squamous metaplasias [the overlap between these two groups was not stated]; these lesions, which developed within 18–24 months of exposure, were found in either the lower right or left lobe, and appeared to be derived from metaplastic squamous cells in areas of alveolar bronchiolization. Bronchiolo-alveolar adenomas were reported in 3/69 females; the incidence was 1/68 in males (see

Table 4. Main pulmonary lesions in rats exposed to *para*-aramid fibrils for two years

Sex	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Fibre concentration (fibrils/mL)	0	0	2.5	2.5	25	25	100	100	400	400
Number in group	69	68	69	64	67	65	68	69	36	56
Pulmonary lesions										
Dust cell (macrophage) response	0	0	1[a]	0	65[a]	63[a]	67[c]	68[c]	32[c]	54[c]
Foamy macrophage response	7	4	2	3	21	20	47	65	18	51
Hyperplasia, type II pneumocyte	0	0	1[a]	0	65[b]	63[b]	67[c]	68[c]	32[c]	54[c]
Fibrosis, collagenized, dust deposition	0	0	0	0	67[a]	57[a]	67[b]	65[b]	35[b]	54[b]
Bronchiolarization, alveoli	0	0	0	1	37	51	48	68	16	52
Granuloma, cholesterol	3	2	1	1	1	2	2	12	1	25
Emphysema, centriacinar, dust deposition	0	0	0	0	0	0	0	0	32	39
Squamous metaplasia, alveoli, focal	0	0	0	0	0	0	0	6	0	1
Adenoma, bronchiolo-alveolar	1	0	1	0	1	0	1	3	2	2
Squamous-cell carcinoma, cystic, keratinized	0	0	0	0	0	0	0	4	1	6
Revised version of the squamous-cell carcinoma, cystic, keratinized[d]										
Pulmonary keratin cyst	0	0	0	0	0	0	0	4	0	6
Keratinizing squamous-cell carcinoma	0	0	0	0	0	0	0	0	1	0

Modified from Lee *et al.* (1988)
[a] Very slight
[b] Slight
[c] Moderate
[d] From Brockmann *et al.* (1995); Frame *et al.* (1996)

Table 4). As mentioned above, the authors did not report the pulmonary lesions observed immediately following a year's exposure to 400 *para*-aramid fibrils/mL, but stated that they were 'significantly decreased' following the recovery year; the authors also stated that fibre lengths 'appeared significantly shorter'. Nevertheless, cystic keratinizing squamous-cell carcinomas were reported in 6/56 female rats exposed at 400 fibrils/mL; the incidence in males was 1/36. In addition, squamous metaplasia was found in 1/56 females. In 2/56 females and 2/36 males, a bronchiolo-alveolar adenoma was reported (see **Table 4**). Almost all animals showed slight fibrosis and 70–90% had some emphysema. At 25 fibrils/mL, and above, some macrophages with inclusions (mostly < 1 μm long), were found in bronchus-associated lymphoid tissue, resulting from 'transmigration' of intrapulmonary fibrils; there was no evidence for transmigration to the pleura. This lesion was characterized as a benign tumour; however, the authors designated it as a 'cystic keratinizing squamous-cell carcinoma' (CKSCC). At the time there was no clear definition of a benign squamous lung tumour (Mohr *et al.*, 1990; Dungworth *et al.*, 1992). To distinguish between squamous metaplasia and CKSCC microscopically was extremely difficult since the lung tumours were differentiated and were devoid of either tumour metastasis or obvious tumour invasion to the adjacent tissue. Also, as there was no evidence of malignancy on the basis of biological behaviour and morphological characteristics, the reported CKSCC could be interpreted as a benign neoplastic lesion (Lee *et al.*, 1988).

Since the publication of Lee *et al.* (1988), considerable discussion has taken place concerning the nature of the CKSCC (see **Table 5**). A panel of pathologists agreed that these cystic lesions found in the *para*-aramid fibre-exposed rats should be referred to as 'proliferative keratin cysts'. These lesions were lined by well-differentiated stratified epithelium with a central keratin mass and were not considered by the majority of the panel to be neoplastic in nature nor to be of relevance to carcinoma development (Carlton, 1994). In 1995, a pathology workshop on keratinous lesions in the rat lung, organized by the Deutsche Forschungsgemeinschaft, reached agreement on the criteria for the classification of cystic lesions (see **Table 5**) (Boorman *et al.*, 1996).

Subsequently, the lesions from the *para*-aramid inhalation study were re-evaluated according to these new criteria (Brockmann *et al.*, 1995; Frame *et al.*, 1996, 1997). This re-evaluation fully confirmed the conclusions as reported by Carlton (1994) (see also **Table 4**).

3.2 Intraperitoneal administration

Rat: A group of 31 female Wistar rats, five weeks old, was given three weekly intraperitoneal injections of 2, 4 and 4 mg/animal *para*-aramid fibrils (total dose, 10 mg/animal) in saline. The test material was prepared by ultrasonic treatment only. In animals killed 2.5 years after treatment, a combined sarcoma/mesothelioma incidence of 4/31 test animals and 2/32 vehicle controls was found. The median life span of the *para*-aramid-treated group was 121 weeks. In a further experiment, an attempt was made to get finer fibrils and better suspension by drying, milling and ultrasonic treatment.

Table 5. Status of the *para*-aramid-induced cystic keratinizing lesions

Findings	Reference
Lesions characterized as cystic keratinizing squamous-cell carcinoma (CKSCC); found primarily in the lungs of female rats. Derived from metaplastic squamous cells in areas of alveolar bronchiolization. Described as a unique type of benign lung tumour, experimentally induced and not spontaneously observed in humans or other animals. Relevance for human risk assessment questionable.	Lee *et al.* (1988)
International panel of 13 pathologists convened to obtain consensus on the most proper morphological classification of CKSCC. Consensus reached for the diagnostic term 'proliferative keratin cyst'. These lesions lined by a well-differentiated stratified squamous epithelium with a central keratin mass. All participants agreed that the cystic keratinizing lesions were not malignant neoplasms. The majority (10/13) was of the opinion that the lesions were not neoplasms. A minority (3/13) considered the lesions to be benign tumours.	Carlton (1994); Levy (1994)
Approximately 700 cases of keratinizing lung lesions in rats observed in six carcinogenicity studies on various materials including carbon black, diesel exhaust and titanium dioxide were investigated by light microscopy to clarify nomenclature and classification of these lesions. Structure of keratinizing squamous lung lesions were compared with cystic squamous lesions in the skin of rats. Concluded that the reviewed cystic lung lesions are true neoplasms and that the growth pattern is inconsistent with a simple cyst.	Kittel *et al.* (1993)
International workshop of toxicological pathologists reviewed cystic keratinizing lesions of the rat lung. These lesions develop in response to the chronic inhalation of diverse particulate materials. A group of pathologists analysed slides from all available studies. The workshop reached a consensus as to classification of these unique pulmonary tissue responses and offers diagnostic criteria for application. This classification scheme was offered as diagnostic criteria. The four stages for proliferative squamous lesions of the rat lung were: (1) squamous metaplasia (2) pulmonary keratin cyst (3) cystic keratinizing epithelioma (4) squamous-cell carcinoma (a) keratinizing (b) non- or poorly keratinizing These cystic keratinizing lung lesions appear to be unique to rats, and it was concluded by the panel that if the only evidence of tumorigenicity is the presence of cystic keratinizing epitheliomas, then it may not have relevance for human safety evaluation.	Brockmann *et al.* (1995); Boorman *et al.* (1996)

Table 5 (contd)

Findings	Reference
The squamous cystic keratin lesions from the *para*-aramid two-year inhalation study of Lee *et al.* (1988) were re-evaluated by four pathologists (three participants of the panel) according to the criteria obtained at the international workshop above. Using the criteria established by the panel, unanimous agreement was reached for a diagnosis of pulmonary keratin cyst for 9 of 10 cystic keratinizing squamous lesions produced in female rats. The one remaining cystic squamous lesion was more difficult to classify; one pathologist considered the lesion to be a cystic keratinizing epithelioma, and three considered it to be a pulmonary keratin cyst. The squamous lung lesion that occurred in one male rat was diagnosed unanimously as squamous-cell carcinoma. The authors concluded that the keratin lesions are probably not relevant for human risk assessment of pulmonary cancer.	Brockmann *et al.* (1995); Frame *et al.* (1996)

A group of 53 female Wistar rats, eight weeks of age, received five weekly injections of 5 mg/animal of this *para*-aramid sample in saline (total dose, 20 mg). The median fibre length was 4.9 μm, the median fibre diameter was 0.48 μm, and the number of *para*-aramid fibrils administered was 1260×10^6. The treated animals had a median life span of 106 weeks, and the number of animals with sarcomas/mesotheliomas was 3/53. In a control group, 2/102 tumours were reported (Pott *et al.*, 1987; 1989). [The Working Group noted that the authors observed aggregation of the *para*-aramid fibrils when in suspension in water.]

A single intraperitoneal injection of 25 mg/animal *para*-aramid fibrils in aqueous Tween 80 was given to groups of 20 male and 20 female Sprague-Dawley rats [age unspecified]. Controls received injections of water. The fibrils had been obtained by 'water fractionation' of commercial-grade *para*-aramid pulp, but no fibre dimensions were stated. At the end of two years, no animals showed mesotheliomas at either site of injection. In a similar experiment in which 1, 5 and 10 mg *para*-aramid fibrils were injected intraperitoneally in 20 male and 20 female Sprague Dawley rats, no peritoneal mesotheliomas were observed by 76 weeks after injection (Maltoni & Minardi, 1989).

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

4.1 Deposition, distribution, persistence and biodegradability

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

Kinetics

A number of studies, some of which are summarized in **Table 6**, have used inhalation in rats and hamsters to evaluate the retention kinetics of *para*-aramid fibrils after deposition in the lung.

Groups of male Sprague-Dawley rats were exposed through whole body to *para*-aramid fibrils at concentrations of up to 18 mg/m^3 for 6 h per day, five days per week, for two weeks. Groups of five of these rats were killed and examined at intervals up to six months. Fibrils accumulated mainly at the bifurcation of the alveolar ducts and adjoining alveoli, with only a few fibrils being deposited in the peripheral alveoli (Lee *et al.*, 1983).

Warheit *et al.* (1994) evaluated fibre deposition and clearance patterns to test the biopersistence of an inhaled organic fibre and an inorganic fibre in the lungs of exposed rats. Male Crl:CD BR rats were exposed for five days to aerosols of *para*-aramid fibrils (877–1344 fibrils/mL; 9–11 mg/m^3; also referenced in Warheit *et al.*, 1992) or wollastonite fibres (835 fibres/mL; 114 mg/m^3). The lungs of exposed rats were digested to quantify dose, fibre dimensional changes over time and clearance kinetics. The results showed that inhaled wollastonite fibres were cleared rapidly with a retention half-time of less than one week. In contrast, *para*-aramid showed a transient increase in the numbers of retained fibrils at one week after exposure, with rapid clearance of fibres thereafter, and a retention half-time of 30 days. Over the six months after exposure to inhaled *para*-aramid fibrils, these investigators detected a progressive decrease in the mean length of the fibrils from 12.5 to 7.5 μm (mean diameter declined from 0.33 to 0.23 μm). The percentages of fibres > 15 μm in length decreased from 30% immediately after exposure to 5% after six months; the percentage of fibres in the 4–7 μm range increased from 25 to 55% during the same period. Warheit *et al.* (1994) concluded that both inhaled *para*-aramid and wollastonite fibres have low durability in the lungs of exposed rats.

As a component of the two-year inhalation study of Lee *et al.* (1988), Kelly *et al.* (1993) investigated the deposition and clearance of lung-deposited *para*-aramid fibrils. Fibrils recovered from lung tissue in exposed CD rats were counted and measured by PCOM. The mean dimensions of inhaled *para*-aramid fibrils were 12 μm in length and < 0.3 μm in diameter. After two years of continuous exposure at 2.5, 25 or 100 fibrils/mL, or one year of exposure plus one year recovery at 400 fibrils/mL; mean fibril lengths approached 4 μm. The time required for fibrils to be reduced to < 5 μm in the lung was markedly less at lower exposure concentrations.

Searl (1997) carried out a study to assess the relative biopersistence of respirable *para*-aramid fibrils, UICC chrysotile B and Code 100/475 fibreglass in rat lungs. The biopersistence of all three test fibres was measured by quantifying the changes in retained lung burden over time following 10-day inhalation exposures at the same target concentrations (700 fibres/mL) for each fibre type. The lung-burden analyses for all three fibre types showed large reductions in the numbers and volumes of retained fibres during the 16 months following exposure. Most of this reduction in lung fibre burden occurred during the first three months following exposure, but the pattern of clearance of different size classes varied with fibre type. The *para*-aramid data showed rapid clearance of the

Table 6. Studies on the biodegradability of *para*-aramid fibrils

Study design	Species	Relevant findings	General conclusions	Reference
1-week inhalation exposure; fibre concentration 613–1344 fibrils/mL	Rat	Transient increase in retained fibrils; fibre lengths decreased from 12.5 to 7.5 μm during 6 months after exposure.	Results indicated the biodegradation (i.e. one fibre breaking into two) of the inhaled *para*-aramid fibrils.	Warheit *et al.* (1992)
3-week, 1- and 2-year inhalation exposure; fibre concentrations 2.5, 25 100 and 400 fibrils/mL	Rat	Lung fibre accumulation rate/exposure was similar for three highest concentrations and was threefold higher than at 2.5 fibrils/mL; mean lengths of inhaled fibrils decreased from 12 to 4 μm.	Inhaled *para*-aramid fibrils have low durability; fibril shortening mechanism may limit residence time in the lungs of exposed workers.	Kelly *et al.* (1993)
2-week inhalation exposure; *para*-aramid fibril concentrations 419 and 772 fibrils/mL; UICC chrysotile B fibre concentrations 458 and 782 fibres/mL	Rat	Median length of *para*-aramid fibrils recovered from lung tissue decreased from 8.6 to 3.7 μm over a 6-month post-exposure period; median length of UICC chrysotile B fibres increased from 3.4 to 11.0 μm over a 3-month post-exposure period.	Reduction in the median length of *para*-aramid fibrils; clearance of short but little or no clearance of long UICC chrysotile B fibres; *para*-aramid fibrils are biodegradable; long UICC chrysotile B fibres are biopersistent.	Warheit *et al.* (1996a)
2-week inhalation exposure to *para*-aramid, UICC chrysotile B, and Code 100/475 fibreglass; fibre concentration 700 fibrils/-mL; follow-up through 16 months	Rat	Rapid clearance of long *para*-aramid fibrils during first months combined with initial increase in the numbers of recovered shorter fibrils; similar clearance pattern for Code 100/475 fibreglass; rapid reduction of retained short UICC chrysotile B fibres, longer UICC chrysotile B fibres cleared very slowly.	*para*-Aramid data consistent with disintegration of *para*-aramid into shorter fibrils; durability of long (> 15 μm) UICC chrysotile B fibres much greater than that of long *para*-aramid or Code 100/475 fibreglass	Searl (1996)
2-week inhalation exposure to *para*-aramid fibrils; fibril concentrations 358 and 659 fibrils/mL; post-exposure period three months	Syrian hamster	Clearance studies showed an early increase in the numbers of recovered fibrils, corresponding to a shortening of the lengths; mean lengths of recovered *para*-aramid fibrils were reduced from 11 to 6 μm at one and three months post-exposure.	Inhaled *para*-aramid fibrils biodegrade in the lungs of exposed hamsters; these data are consistent with those in rats of Warheit *et al.* (1995).	Warheit *et al.* (1996b)

Table 6 (contd)

Study design	Species	Relevant findings	General conclusions	Reference
Implantation of *para*-aramid fibres (Coverall cord) subcutaneously in 42 rats	Rat	One month post-implant a foreign body giant cell reaction occurred; the *para*-aramid implant was degraded and *para*-aramid material was observed in phagocytic cells.	*para*-Aramid fibres are unacceptable as implant material for anterior cruciate ligament replacement, due to the biodegradability of the fibre in the body.	Jerusalem *et al.* (1990)
Implantation of *para*-aramid fibres as substitute for the anterior cruciate ligament in the knee of 51 Merinoland sheep	Sheep	Similar giant cell reaction; indications of biodegradation of the aramid material was more obvious relative to the subcutaneous experiment.		
Implantation of *para*-aramid fibre (Kevlar 29) tested for prosthesis performance in sheep; *para*-aramid implanted in a tubular configuration in 40 sheep; evaluated 3–12 months post-exposure	Sheep	Failure of the implant led to the understanding that the *para*-aramid fibre had degraded in this animal study; no mechanisms of degradation were determined.	Significant stabilization of the knee joint and in-growth of tissue were impaired by a significant degradation of the *para*-aramid fibres.	Dauner *et al.* (1990)
Study of the biodegradability of *para*-aramid fibres (Kevlar 49) in human plasma; bundles of fibres incubated at room temperature in fresh human plasma for 6–26 weeks; evaluated by scanning electron microscopy	Human	Human plasma had no effect upon the surface characteristics of *para*-aramid fibres.	*para*-Aramid fibres are not biodegradable in human plasma.	Wening & Lorke (1992)

longest fibrils during the first month following exposure, combined with an initial increase in the numbers of shorter fibrils. This is consistent with the idea that *para*-aramid fibrils break into successively shorter fragments that can be cleared more readily by macrophages. The Code 100/475 fibreglass data also showed rapid clearance of the longest fibres combined with an increase in the numbers of very short fibres, which is consistent with the removal of long fibres through breakage. In contrast, the UICC chrysotile B data showed a more rapid reduction in the numbers of retained short fibres than of long fibres, which is consistent with preferential clearance of short fibres by macrophages and minimal transverse breakage of fibres. The biopersistence of all three fibre types, in terms of total lung burden retained over 16 months, was similar; however, the durability of long (> 15 μm) UICC chrysotile B fibres was substantially greater than that of long fibres of *para*-aramid or the Code 100/475 fibreglass. The clearance of the three fibre types could not be adequately described by the first order kinetic model, which is often applied in studies of lung clearance (Muhle *et al.*, 1990).

Warheit *et al.* (1995) compared the effects of inhaled UICC chrysotile B and *para*-aramid fibrils in rats exposed for two weeks to size-separated *para*-aramid fibrils or UICC chrysotile B fibres at target concentrations of 400 and 750 fibres/mL. Following exposure, the post-exposure recovery time periods used for evaluation were as follows: immediately after two-week exposure; five days post-exposure; and one, three, six and 12 months post-exposure. Attempts were made to size-separate the UICC chrysotile B fibres for inhalation testing in order to increase the mean lengths of the fibre preparation. The final mean aerosol concentrations were 458 and 782 fibres/mL for the low-concentration and high-concentration UICC chrysotile B groups and 419 and 772 fibrils/mL for the low-concentration and high-concentration *para*-aramid-exposed groups. Although the fibre aerosol concentrations were similar for the two fibre types, the lungs of animals exposed to *para*-aramid fibrils retained a greater dose (two- to threefold) of long fibres in comparison to UICC chrysotile B-exposed rats. In addition, count median lengths of fibres recovered from the lungs of *para*-aramid-exposed rats were 8.6 μm but only 3.5 μm in the UICC chrysotile B-exposed animals. Fibre clearance studies demonstrated that the *para*-aramid fibrils were initially cleared at a slower rate and this was consistent with a reduction in mean fibre lengths (indicating biodegradation, i.e. one fibre breaking into two fibres). Subsequently, the fibres were cleared more rapidly. Fibre biopersistence/durability results demonstrated that the long UICC chrysotile B fibres were essentially retained or cleared at a slow rate. In contrast, *para*-aramid fibrils were shown to have low biodurability in the lungs of exposed animals. In this regard, median lengths of UICC chrysotile B fibres recovered from exposed lung tissue increased over time, while median lengths of *para*-aramid fibrils decreased over time (Warheit *et al.*, 1995, 1996a). The proliferative effects and enhanced biodurability of UICC chrysotile B, which has been associated with the induction of chronic disease, did not occur with *para*-aramid fibrils.

Warheit *et al.* (1996b) performed a multifunctional study to compare the pulmonary effects of inhaled *para*-aramid fibril exposure in male Syrian golden hamsters to those previously measured in similarly exposed rats. Male Syrian golden hamsters were exposed whole-body to aerosols of size-separated *para*-aramid fibrils for two weeks at

target fibre concentrations of 350 and 700 fibrils/mL. Following completion of exposures, the lungs of fibre-exposed hamsters and controls were evaluated at several post-exposure time periods, including immediately after (i.e. time zero), as well as 10 days and one and three months after exposure. Actual mean aerosol fibre concentrations over the two-week exposure period were measured as 358 and 659 fibrils/mL. At time zero, the authors measured the mean lung burden of the high-dose hamster group to be 1.4×10^6 fibrils/lung. The mean number of retained *para*-aramid fibrils decreased from 1.4×10^6 to 5.0×10^5 during the three-months post-exposure. These investigators also carried out biopersistence/fibril dimensional studies in the hamsters through the three-months post-exposure which demonstrated the breakage of inhaled *para*-aramid fibrils: the mean length of fibrils recovered from hamster lungs immediately after a two-week exposure (i.e. time zero) was 10.4 μm; at one-month post-exposure, mean fibril length was 6.3 μm; at three-months post-exposure, mean fibril length had decreased further to 6.1 μm. These reductions in the lengths of retained fibrils over time signifies a shortening of the retained fibrils, which is consistent with the results of earlier studies in *para*-aramid-exposed rats, in which the mean and median lengths of retained fibrils were progressively reduced with increasing residence time in the lungs of exposed animals.

4.2 Toxic effects

4.2.1 *Humans*

Reinhardt (1980) reported in brief the results of patch testing to assess skin irritancy and sensitization using human volunteers. In these studies, which involved more than 100 individuals, there was no skin sensitization but some minimal skin irritation following dermal contact with *para*-aramid or *meta*-aramid fabrics. [The Working Group noted that preparation of the fibres was not described.]

Workers exposed to *para*-aramid fibres and sulfur dioxide were studied for pulmonary function effects. In the baseline study, spirometry (forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1)) and diffusing capacity in exposed workers were compared with a reference group involved in polyester fibre processing; no significant differences in diffusing capacity were detected. Follow-up results one year later demonstrated no significant differences in diffusing capacity between the two groups (Pal *et al.*, 1990).

4.2.2 *Experimental systems*

(*a*) *Inhalation studies*

In a study also described in Section 4.1.2, rats were exposed to a range of *para*-aramid fibril concentrations for two weeks. Rats killed at various periods after exposure at the lowest level (up to 26 fibrils/mL) showed a macrophage response only. At the highest exposure levels (280 fibrils/mL and above), the investigators noted granulomatous lesions with fibrotic thickening at the alveolar duct bifurcations. Six months after exposure, a nearly complete recovery of the granulomatous lesions and a marked

reduction of the fibrotic lesions were found. The fibres appeared to be quickly fragmented and reduced in size (Lee *et al.*, 1983).

Lee *et al.* (1988) carried out a chronic inhalation study using groups of 100 male and female Crl:CD (SD) BR rats (for full description, see Section 3.1). After two years' *para*-aramid exposure at the lowest exposure level (2.5 fibrils/mL), rats were found to have a normal alveolar architecture of the lungs, with a few dust-laden macrophages in the alveolar air spaces; this was considered to be the NOAEL (no observed acceptable effect level). At 25 and 100 fibrils/mL, a dose-related increase in lung weight was noted, as were a dust cell response, slight type II pneumocyte hyperplasia, alveolar bronchiolization and a negligible amount of collagenized fibrosis in the alveolar duct region. In addition, at 100 fibrils/mL, proliferative keratin cysts were observed in four females (6%) but no male rats (see **Table 5** for the discussion concerning this lesion). Female rats also had more prominent foamy alveolar macrophages, cholesterol granulomas and alveolar bronchiolization. A group of rats was also exposed to *para*-aramid at 400 fibrils/mL. However, owing to excessive numbers of rat deaths, this exposure was terminated at 12 months and the animals were followed for an additional year. Twenty-nine male and 14 female rats died owing to obliterative bronchiolitis, which resulted from the dense accumulation of inhaled *para*-aramid fibrils in the ridges of alveolar duct bifurcations after exposure at this level for one year. The animals that survived both the year of exposure at 400 fibrils/mL and the year of follow-up had markedly reduced lung dust content, average fibre lengths and pulmonary lesions. However, rats in this experimental group did show slight centriacinar emphysema and minimal fibrosis in the alveolar duct region; one male rat (3%) developed a carcinoma and six female rats (11%) developed proliferative keratin cysts (see **Tables 4** and **5**).

To assess the potential of squamous cystic lesions for progression to malignancy, Mauderly *et al.* (1994) carried out a study in which primary lung neoplasms and squamous cysts from rats exposed to carbon black or diesel exhaust were removed and implanted into athymic (nude) mice. Six out of 18 adenocarcinomas and three out of five squamous-cell carcinomas were successfully transplanted and grew in the nude mice. In contrast, none of the 26 squamous cysts (19 from carbon black- and seven from diesel exhaust-exposed rats) were successfully transplanted into the athymic mice (**Table 7**). These results provided evidence that the autonomous growth behaviour of the squamous cysts is fundamentally different from the two other neoplasms tested.

Groups of 24 male Crl:CD BR rats were exposed to *para*-aramid fibrils by nose only for 6 h per day for three or five days at concentrations ranging from 600 to 1300 fibrils/mL (gravimetric concentrations ranging from 2 to 13 mg/m^3). Four rats per group were evaluated subsequently at 0, 24, 72 and 96 h, one week, and one, three or six months after exposure. Five-day exposures elicited a transient granulocytic inflammatory response with an influx of neutrophils into alveolar regions and concomitant increases in bronchoalveolar lavage (BAL) fluid levels of alkaline phosphatase, lactate dehydrogenase (LDH) and protein. These latter increases returned to control levels within one week and one month of exposure. Increased pulmonary cell labelling was detected in terminal bronchiolar cells immediately after exposure but this had also returned to control values one week later. Histopathological examination of the lungs of these *para*-

aramid-exposed animals revealed only minor effects, characterized by the presence of fibre-containing alveolar macrophages situated primarily at the junctions of terminal bronchioles and alveolar ducts (Warheit *et al.*, 1992).

Table 7. Growth of rat-derived lung tumours and squamous cysts transplanted into nude mice

Lesion type	Number implanted	Transplant success (%)
Adenocarcinoma	18	33
Squamous-cell carcinoma	5	60
Squamous cysts	25	0

From Warheit (1995) [data obtained from Mauderly *et al.* (1994)]

In inhalation experiments in rats, Warheit *et al.* (1995, 1996a) compared the effects of size-selected UICC chrysotile B asbestos fibres with size-selected *para*-aramid fibrils at similar fibre concentrations (400 and 750 fibres/mL). Following two weeks of exposure, the following post-exposure recovery time periods were used for evaluation: immediately after the two-week exposure, and at five days and one, three, six and 12 months post-exposure. The major endpoints of this study were (i) pulmonary 5-bromo-2′-deoxy-uridine (BrdU) cell proliferation evaluations and biochemical assessments of BAL fluids; (ii) morphometry and histopathology of the proximal alveolar regions; and (iii) durability/dimensional analysis of fibres recovered from the lungs of exposed animals. The final mean aerosol concentrations were 458 and 782 fibres/mL for the UICC chrysotile B exposure groups and 419 and 772 fibrils/mL for the *para*-aramid-exposed groups. Examination of the biochemical and cellular BAL fluid data revealed that a two-week exposure to either *para*-aramid or UICC chrysotile B produced a transient pulmonary inflammatory response in the rats. The histopathological and morphometric studies demonstrated that both *para*-aramid and UICC chrysotile B fibres produced a minimal to mild inflammatory response, which led to thickening of alveolar duct bifurcations. These effects peaked at one month after exposure and had essentially reversed by six and 12 months after exposure. Warheit *et al.* (1995, 1996a) did, however, find differences in the responses to these two fibre types. Inhalation of UICC chrysotile B fibres produced substantial increases in cellular proliferation of terminal bronchiolar, proximal alveolar, visceral pleural/subpleural and mesothelial cells, and many of these effects were sustained through to three months after exposure, suggesting that UICC chrysotile B produces a potent proliferative response in the airways, lung parenchyma and subpleural/pleural regions. In contrast, exposure to the higher dose of *para*-aramid fibrils produced a transient increase in terminal bronchiolar and visceral pleural/subpleural cell labelling immediately after exposure with no further significant increases at any later time.

In a similar experiment to that described above, male Syrian golden hamsters were exposed to aerosols of size-separated *para*-aramid fibrils for two weeks at intended fibre concentrations of 350 and 700 fibrils/mL. Following completion of these whole-body exposures, the lungs of fibre-exposed hamsters and controls were evaluated at several time periods after exposure, including immediately after (i.e. time zero), as well as at 10 days and one and three months after exposure. The major endpoints of this study were assessments of (i) fibre deposition and clearance (see Section 4.1.2); (ii) the biopersistence of inhaled fibrils; (iii) cellular proliferation of terminal bronchiolar, pulmonary parenchymal and subpleural surfaces; (iv) BAL fluid parameters; and (v) lung histopathology. The final mean aerosol fibre concentrations over the two-week exposure period were 358 and 659 fibres/mL. BAL studies demonstrated a transient influx of neutrophils that persisted through to one month after exposure. Lavage biomarkers such as LDH and protein were not significantly different from controls. Histopathological analysis revealed minor lesions characterized by increased numbers of alveolar macrophages (with or without fibrils) admixed with lesser numbers of neutrophils and some cellular debris. The lesions were similar for most high- and low-dose animals. As is typical for dust/fibre inhalation studies, lesions were most prominent in alveolar duct regions. The results of cell proliferation studies of *para*-aramid-exposed hamsters and controls demonstrated a small but transient increase in immunostaining of terminal bronchiolar cells relative to controls but this was not statistically significant. In addition, labelling indices of cells in the pulmonary parenchyma and subpleural regions were not significantly different from unexposed controls (Warheit *et al.*, 1996b). The transient nature of this response is similar to the cell labelling data reported in rats exposed to *para*-aramid for two weeks by Warheit *et al.* (1995, 1996a).

(*b*) *Intratracheal instillation*

Reinhardt (1980) described briefly a study of intratracheal administration of *para*-aramid dust in rats, but it is unclear whether fibre dust or unspun, non-fibre-shaped polymer dust was used. A 21-month follow-up of an unknown number of rats showed an early, non-specific inflammatory reaction, subsiding within a week, followed by foreign-body granuloma development with negligible collagen formation. All tissue reactions subsided over time.

(*c*) *Intraperitoneal administration*

Brinkmann and Müller (1989) described the following stages of events following weekly intraperitoneal injections of 5 mg *para*-aramid fibres [fibre size distribution or sample preparation methods not specified] suspended in 1 mL physiological saline for four weeks in eight-week-old Wistar rats. At 28 months after the first injection, the rats were sacrificed and the greater omentum with pancreas and adhering lymph nodes were removed and examined histologically by light and scanning electron microscopy. In an initial stage, multinucleated giant cells, phagocytosis of the *para*-aramid fibres and an inflammatory reaction were observed. In a second stage, granulomas with central necrosis developed, indicating the cytotoxic nature of the fibres. A third stage was characterized by 'mesenchymal activation with capsular structures of collagenous fibres

as well as a slight mesothelial fibrosis'. Finally, the reactive granulomatous changes in the greater omentum of the rats were accompanied by proliferative mesothelial changes. The authors noted that the reaction to *para*-aramid fibres following intraperitoneal administration resembled the well-studied reaction to similar injections of glass or asbestos fibres. It was also noted that, as in the case of mineral fibres, fragments of *para*-aramid fibres were transported through lymphatic pathways and stored in lymph nodes where they caused inflammatory reactions. [The Working Group noted that these observations were based on two rats from the study of Pott *et al.* (1989).]

(*d*) *In-vitro studies*

Dunnigan *et al.* (1984) demonstrated that *para*-aramid fibres (90% ≤ 5 μm in length and ≤ 0.25 μm in diameter; average length and diameter, 2.72 and 0.138 μm, respectively) were cytotoxic to pulmonary alveolar macrophages obtained from adult male Long-Evans black-hooded rats. This was shown by analysis of the release of LDH, lysosomal enzymes, β-galactosidase and ATP (adenosine triphosphate) content (incubation time, 18 h). The cytotoxic response in freshly harvested and cultured cells was considered to be similar to or greater than that for UICC chrysotile B. However, it should be noted that these fibres would not be included in fibres counts in the occupational setting, determined according to WHO criteria (World Health Organization, 1985).

Franz *et al.* (1984) compared *para*-aramid fibres of undefined lengths with UICC crocidolite and found a comparable degree of cytotoxicity, as measured by LDH and β-galactosidase release and ATP content in guinea-pig alveolar macrophages.

Warheit *et al.* (1992) carried out macrophage functional studies *in vitro* on rat cells recovered by pulmonary lavage following five-day exposures to inhaled *para*-aramid fibrils at 950 or 1300 fibrils/mL. The percentages of activated macrophages recovered from fibril-exposed rats were not significantly different from controls at any post-exposure period. Similarly, the in-vitro phagocytic and chemotactic capacities of macrophages recovered from *para*-aramid-exposed rats were not significantly different from macrophages recovered by lavage from controls.

Kelly *et al.* (1993) carried out in-vitro fibril durability studies to determine whether proteolytic enzyme attack could account for the reduction in fibril length over time as measured in the lungs of exposed rats. The in-vitro durability of *para*-aramid fibrils was investigated in saline and in a series of proteolytic enzyme preparations, including collagenase, pancreatin, papain and trypsin. The results showed that fibrils exposed to all of these enzyme solutions for three months at 37 °C appeared to be shorter than the saline-exposed fibrils. However, the decrease was statistically significant only for the pancreatin preparation.

Marsh *et al.* (1994) compared the in-vitro effects of *para*-aramid fibrils (size-separated from pulp by density sedimentation) with those of reference samples of UICC crocidolite and UICC chrysotile B. No negative controls were used in this study. The mean lengths and diameters of the *para*-aramid sample were 6.0 μm and 0.4 μm, respectively. The mean lengths and diameters of the UICC crocidolite and UICC chrysotile B samples were 3.14 and 0.13 μm and 3.21 and 0.06 μm, respectively. Both hamster

tracheal epithelial cells and RL90 fibroblasts, plated at 5×10^4 cells/well, were incubated separately with fibrils at dust concentrations ranging from 1 to 20 μg/cm^2 ($1–100 \times 10^6$ fibrils). The major endpoints were colony-forming efficiency, a tritiated ^{3}H-thymidine incorporation assay and the ornithine decarboxylase assay. The results of cytotoxicity tests indicated that *para*-aramid was as toxic to hamster tracheal epithelial and RL90 cells as were UICC crocidolite and UICC chrysotile B on both an equal mass basis and equal fibre number basis. In hamster tracheal epithelial cells, *para*-aramid caused a statistically significant increase in ^{3}H-thymidine incorporation and colony-forming efficiency and produced a dose-dependent induction of ornithine decarboxylase enzyme activity. Proliferative effects related to asbestos or *para*-aramid exposures were not observed in RL90 fibroblasts.

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 on the genetic effects of *para*-aramid fibrils in humans.

4.4.2 *Experimental systems* (see also **Table 8** and Appendices 1, 2 and 3)

The mutagenicity of *para*-aramid fibrils was tested in *Salmonella typhimurium*. Neither ethanol or chloroform extracts of fibrils nor direct application of fibres at 14 mg/mL induced mutations in this bacterium, even in the presence of aroclor-induced rat liver S9 preparation. The dose of *para*-aramid used was not cytotoxic. Mutation at the *hprt* locus was assessed in Chinese hamster V79 fibroblasts. The two following doses of *para*-aramid fibrils were tested: 42.5 mg/mL after incubation in culture medium for seven days at 37 °C; and 120 mg/mL after incubation in dimethyl sulfoxide for seven days at 37 °C. Neither preparation was toxic or induced 8-azaguanine-resistant colonies. The effect of fibres added directly to cultures was not tested (Wening *et al.*, 1989; 1995).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

para-Aramid fibres are long-chain synthetic polyamides, most commonly poly(*para*-phenyleneterephthalamide), and have been produced commercially since the early 1970s. The combination of high strength, high temperature resistance and light weight make these fibres useful in the reinforcement of composite materials for the aerospace and sports equipment industries, in woven fabrics used in protective apparel and in automotive brake pads and gaskets.

During abrasive processing operations, small-diameter respirable fibrils can be released into the air. Highest occupational exposures to *para*-aramid fibrils have been measured in the processing of shorter (staple) fibres in yarn.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

para-Aramid fibrils were tested for carcinogenicity in one study in rats by inhalation exposure. An increased incidence of cystic keratinizing squamous-cell carcinomas was reported. However, subsequent re-examinations and evaluation of these lesions revealed a diagnosis of pulmonary keratinizing cysts. The biological significance of these lesions is unclear. *para*-Aramid fibrils were also tested in two experiments in rats by intraperitoneal injection. No intra-abdominal tumours were observed.

5.4 Other relevant data

Inhalation exposure to *para*-aramid fibrils in rats for two years produced minimal pulmonary fibrosis. Chronic inhalation studies demonstrate that inhaled *para*-aramid fibrils are biodegradable in the lungs of rats. Similarly, two-week inhalation studies in rats and hamsters demonstrate transient pulmonary inflammatory and cell proliferative responses and biodegradability of inhaled fibrils in the lungs of exposed animals. *para*-Aramid fibrils demonstrate some cytotoxic activity to cells under in-vitro conditions.

para-Aramid fibril extracts were not mutagenic to *Salmonella typhimurium* or to Chinese hamster V79 fibroblasts.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of *para*-aramid fibrils.

There is *inadequate evidence* in experimental animals for the carcinogenicity of *para*-aramid fibrils.

Overall evaluation

para-Aramid fibrils *cannot be classified as to their carcinogenicity to humans (Group 3).*

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

Table 8. Genetic and related effects of *para*-aramid fibrils

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	NT	NG	Wening *et al.* (1989)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	14 000	Wening *et al.* (1995)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	NT	NG	Wening *et al.* (1989)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	–	14 000	Wening *et al.* (1995)
SA4, *Salmonella typhimurium* TA104, reverse mutation	–	NT	NG	Wening *et al.* (1989)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	NT	NG	Wening *et al.* (1989)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	14 000	Wening *et al.* (1995)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	NT	NG	Wening *et al.* (1989)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	14 000	Wening *et al.* (1995)
SA8, *Salmonella typhimurium* TA538, reverse mutation	–	NT	NG	Wening *et al.* (1989)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	NT	NG	Wening *et al.* (1989)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	14 000	Wening *et al.* (1995)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	NT	NG	Wening *et al.* (1989)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	14 000	Wening *et al.* (1995)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus	–	NT	120 000	Wening *et al.* (1995)

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

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; NG, not given

6. References

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