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Toxicology of Man-Made Organic Fibres

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Table of Abbreviations

AED	Aerodynamic Equivalent Diameter
AM	Alveolar Macrophage
AP	Alkaline Phosphatase
ATP	Adenosine Triphosphate
BAL	Bronchoalveolar Lavage
β -Gal	Beta-Galactosidase
BrdU	5-Bromo-2-deoxyuridine
CHO	Chinese Hamster Ovary Cells
CKSCC	Cystic Keratinizing Squamous Cell Carcinomas
DNA	Deoxyribonucleic acid
FEV_1	Forced Expiratory Volume (1 sec)
FGF	Fibroblast Growth Factor
FVC	Forced Vital Capacity
GSD	Geometric Standard Deviation
IgE IgG	Immunoglobulin E Immunoglobulin G
IL	Interleukin
ip	Intraperitoneal
LDH	Lactate Dehydrogenase
MMAD	Mean Mass Aerodynamic Diameter
MMOF	Man-Made Organic Fibres
MMVF	Man-Made Vitreous Fibres
NMRD	Non-Malignant Respiratory Disease
NOF	Natural Organic Fibres
OR	Odds Ratio
OSHA	Occupational Safety and Health Administration

Table of Abbreviations	
PAH(s)	Polycyclic Aromatic Hydrocarbon(s)
PAN	Polyacrylonitrile
PCOM	Phase Contrast Optical Microscope
PDGF	Platelet Derived Growth Factor
PKC	Proliferative Keratin Cyst(s)
PMR	Proportional Mortality Ratio
PVA	Poly(vinylalcohol)
RFP	Respirable-sized Fibre-shaped Particulate(s)
RNA	Ribonucleid Acid
SEM	Scanning Electron Microscope
SEM/EDX	Scanning Electron Microscope/Energy Dispersive X-ray
SMR	Standardized Mortality Ratio
SHE	Syrian Hamster Embryo
TGF	Transforming Growth Factor
TNF	Tumour Necrosis Factor
UICC B	Specific collection (B) of fibre samples maintained by UICC (Union Internationale contre le Cancer)
WHO	World Health Organisation
µm	Micro Meter

SUMMARY

The established relationship between inhalation of asbestos fibres of respirable size and disease has led to a belief that all similarly sized and shaped particles of other materials are equally dangerous to human health. Organic fibres, man-made or natural, produce small numbers of respirable fibre-shaped particulates.

This report briefly describes the nature of man-made organic fibres and the release of respirable fibre-shaped particulates, reviews the available data on occupational exposure, health effects and the toxicology of man-made organic fibres, compares organic and mineral fibres and indicates data gaps and areas of research which could contribute most to risk assessment.

Little is known about the generation of respirable fibre-shaped particulates during production, use and disposal of man-made organic fibres but available data on industrial exposure indicate that the exposure potential is low, typically between 0.01 and 0.1 fibres/cm^3 for commodity fibres and below 0.5 fibres/cm^3 for *p*-aramids.

Much is known about the health hazards of natural organic fibres, but none of this is related or has been ascribed to fibre-shaped respirable-sized particulates. Two case reports suggest a relationship between respirable particles derived from man-made organic fibres and respiratory disease but any relationship with fibre shape is uncertain in these cases. The health effects described were different from those induced by exposure to asbestos. The few epidemiological studies on health risks from occupational exposures in the man-made organic fibre industry are inadequate to exclude or to establish a human health risk from exposure to respirable fibre-shaped particulates from man-made organic fibres.

Man-made organic fibres differ from natural and man-made mineral fibres in several characteristics that determine toxicity, e.g. chemical composition, surface structure, physical characteristics of respirable fibre-shaped particulates and biodegradability.

The limited toxicological database indicates that the biological activity of respirable fibre-shaped particles derived from man-made organic fibres and from natural and man-made mineral materials are quantitatively and qualitatively different.

Future research should focus primarily on man-made organic fibres with more than a trivial exposure potential. Toxicological test systems, currently in use for screening and/or classification of fibres, need to

be re-evaluated for their relevance to man-made organic fibres before test results can be extrapolated to any hazard. A combination of tests for cytotoxicity and genotoxicity with acute inhalation, subchronic inhalation and bio-degradability studies will provide useful information. Epidemiological studies are unlikely to contribute significantly to future risk assessments, because of the apparent impossibility to establish significant differences in exposure levels and/or finding non-exposed controls; exposure in industry being of the same magnitude as in the general population.

1. INTRODUCTION

Synthetic or man-made organic fibres (MMOF) have been produced for more than 4 decades and semi-synthetic organic fibres for even longer. Some chemicals used in their production may cause occupational disease, the fibres and dust originating from them have received scant attention. The toxicity of fibres, especially asbestos, has drawn attention to the possible health hazards of respirable fibre-shaped particulates (RFP) in general. Only two reports indicate a possible human health hazard from synthetic organic fibres (see section 3). In contrast, the production and use of natural organic fibres (NOF) has always been associated with considerable respiratory disease. Most of this relates to toxic or allergenic proteins and other substances of vegetable, bacterial or fungal origin. Yet, despite the considerable dustiness of textile processing, especially in the early days of industrialisation, a relationship between lung malignancies and organic RFP has never been identified.

It has long been known that exposure to asbestos is related to the development of cancer in man (Merewether, 1949; Doll, 1955; Wagner *et al*, 1960) and an enormous body of corroborative epidemiological evidence has been collected, which confirms a causal relationship. In addition, the many factors involved in the carcinogenicity and fibrogenic activity of fibrous material have been studied.

The importance of fibre dimensions (Stanton *et al*, 1981) to fibre toxicity is well proven and quantifiable. Fibre durability is clearly also an important factor, but less well quantified. Factors like surface and physico-chemical properties show less correlation with toxicity. Although several toxicological methods are useful for comparing the hazards of fibres, they have not been or cannot be validated as indicators of human hazard or risk; this distinction is often not fully understood (See section 4.3).

As a result, an impression has been created that every fibre-shaped particle small enough to reach the lung poses a threat to man, unless proven otherwise. While the debate on the possible health effects of MMOF continues, both NOF and MMOF are coming under consideration (MAK, 1993). So far only *p*-aramid fibres have been comprehensively tested and evaluated. Initial studies on several other fibres have recently been published (Rosenbruch *et al*, 1992) and others may have to follow, especially on pulp (ground fibres) and fibres that result in occupational exposure to respirable fragments during production processes or normal use.

This report considers the need for a tiered approach to the toxicity testing of MMOF, recognising that such testing is not the first step in the risk assessment of MMOF. Earlier steps, especially exposure assessment, are currently being studied by others (Bahners *et al*, 1994) and will be mentioned only briefly in this document.

2. DEFINITIONS AND NOMENCLATURE, COMPOSITION, PROPERTIES, PRODUCTION, LIFE CYCLE

A fibre is one of the thread-like filaments which form a textile or other materials; fibres have a small diameter in relation to their length.

Of particular interest to toxicologists are fibres which are microscopically small and have a length-to diameter ratio greater than 3; these include many particulates that are curled, branched or otherwise irregularly shaped.

A "fibril" is a small fibre or a subdivision of a fibre. For example an asbestos fibre can split longitudinally to form a group of fibrils of the same length but of much smaller diameter.

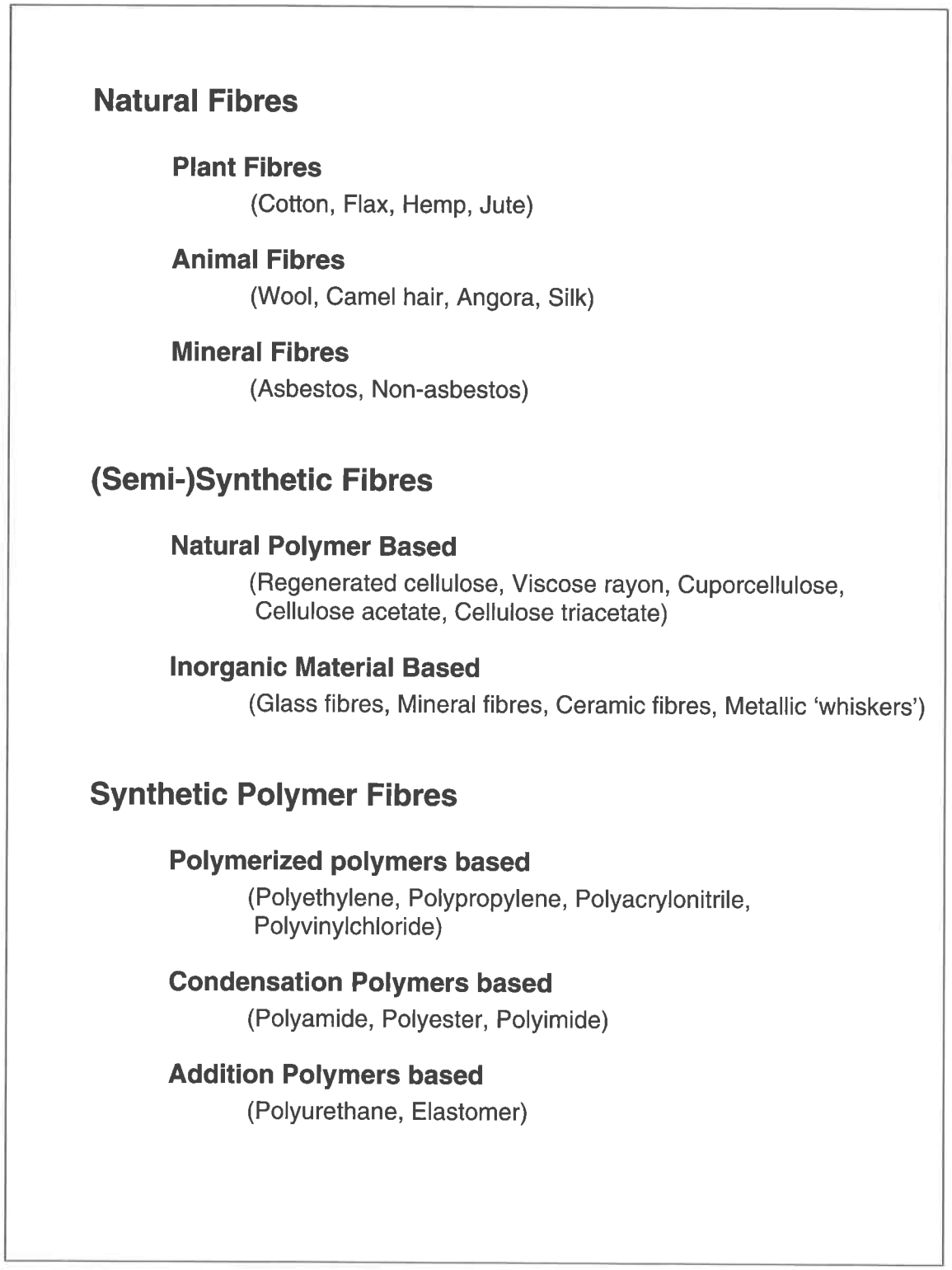
In this document the term "Respirable-sized Fibre-shaped Particulate" (RFP) is used when referring to those fibres of interest to toxicologists as defined above. The word "fibre" is reserved to cover its original meaning. However, when referring to or quoting from the existing literature it is sometimes necessary to use the original terminology, i.e "fibers" or "fibres" instead of RFP.

For the purpose of this report, man-made organic fibres (MMOF) are continuous lengths (filament) or filament cut into shorter sizes (staple fibre), produced from fully synthetic or semi-synthetic polymers. An overview of different types of fibrous materials is given in figure 1.

Some MMOF have been used in surgery and the tissue reactions after implantation have been described in various publications. The fate of inhaled MMOF particles is, however, largely unknown. It is even uncertain which MMOF generate appreciable numbers of RFP and, if so, at which stage of their life cycle. In the case of *p*-aramids, low levels of RFP have been measured in the work environment (see section 2.5.2). For most of the other materials, only recently a few monitoring results have been reported. However, there are indications that respirable fragments of synthetic polymers may be found in the lungs of individuals working in the clothing industry (Cortez Pimentel, 1975; Hillerdal *et al*, 1990).

The following paragraphs indicate the physical and chemical factors that should be taken into account in the risk assessment of RFP from MMOFs. For more extensive reading see Hall (1975), Chapman (1974), McIntyre and Denton (1986), v. Krevelen (1990), v. Falckai (1981) and Ullmann (1992).

Figure1: Sources of fibrous material



2.1 NOMENCLATURE

In the broad sense, "respirable" means "capable of being carried by breath into the respiratory system". For a particle, this capability is largely determined by its aerodynamic resistance. This is generally expressed in terms of "aerodynamic equivalent diameter" (AED), sometimes referred to as mass median aerodynamic diameter (MMAD), determined by comparing the sedimentation velocity of the particle in air to that of spherical particles of known diameters and a density of 1.0 g/cm^3. As a rough guide, particles with an AED up to 100 μm can enter the upper parts of the respiratory system (the nose and throat); particles with an AED of less than 5 μm may be carried into the lower parts of the system including gas exchange areas of the lung in humans (ISO 7708, 1995). It should be noted that the physical dimensions may be much larger than the AED.

In occupational hygiene and inhalation toxicology, the word "total dust" is generally used to indicate the total concentration of dust particles of AED up to 50 μm. The term "respirable" denotes the concentration of dust particles with an AED of 5 μm and less.

For RFP, the AED is largely determined by the diameter of the fibres rather than their length. RFP having an AED greater than 12 μm for humans and 6 μm for rodents are generally considered to be nonrespirable, i.e, large numbers are not likely to reach the gas exchange regions of the lung, (respiratory bronchioles and alveoli) (Schlesinger, 1985). Fibres with physical diameters less than or equal to 3 μm are considered respirable, even with lengths as great as 100-200 μm (Timbrell, 1965, 1983).

For regulatory purposes, "respirable fibres" (i.e. RFP) have been defined in most countries as befitting the description (with minor variations):

Length > 5μm, Diameter <3μm, Length/Diameter > 3

In this regulatory definition, the relation between dimensions and toxicity is taken into account, but it should be realised that it is based upon convenience rather than on a scientifically proven sharp demarcation.

2.2 COMPOSITION

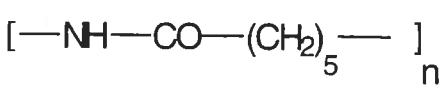
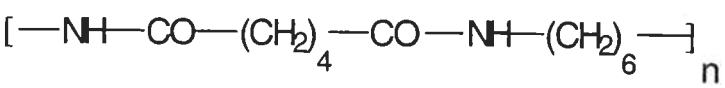
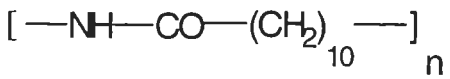
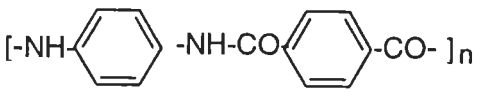
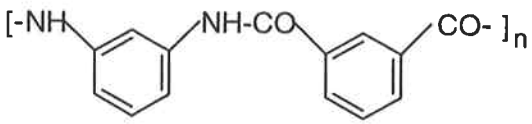
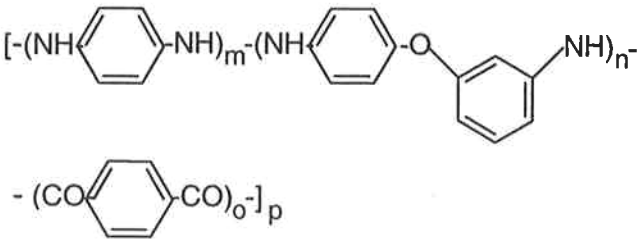
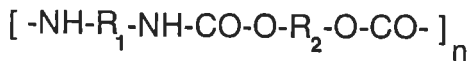
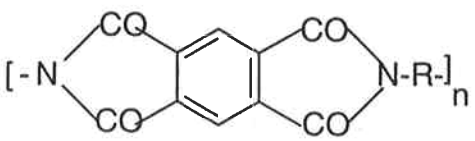
Synthetic polymers and semi-synthetic polymers have been created in nearly endless variations and modifications and many have been used to produce MMOFs. Table 1 (pages 8 and 9) lists some of the major types of fibre-forming materials.

Table 1: Some Polymers for Synthetic Fibres *

POLYMER TYPE	REPEATING UNIT	TRADE NAME
	Polyolefin	
Polyethylene	$[\text{-}CH_2\text{-}CH_2\text{-}]_n$	Trofil Spectra
Polypropylene	$[\text{-}CH(CH_3)\text{-}CH_2\text{-}]_n$	Herculon
	Polyvinyl	
Polyacrylonitril	$[\text{-}CH(CN)\text{-}CH_2\text{-}]_n$	Dralon
Polyvinylchloride	$[\text{-}CH(Cl)\text{-}CH_2\text{-}]_n$	Fibravyl Leavil
Polyvinylalcohol	$[\text{-}CH(OH)\text{-}CH_2\text{-}]_n$	Kuralon
	Polyester	
Polyethyleneterephthalate	$[-O-CO-C_6H_4-CO-O-(CH_2)_2-]_n$	Trevira Diolen
Polybutyleneterephthalate	$[-O-CO-C_6H_4-CO-O-(CH_2)_4-]_n$	

* Several of the 'trade names' are also 'registered trade marks'

Table 1 (cont.): Some Polymers for Synthetic Fibres

POLYMER TYPE	REPEATING UNIT	TRADE NAME
Aliphatic Polyamide		
PA6		Perlon
PA6.6		Nylon (Generic name)
PA11		Rilsan
Fully Aromatic Polyamide		
Poly(p-phenylene-terephthalamide)		Kevlar Twaron
Poly(m-phenylene-isophthalamide)		Nomex
Copoly(p-phenylene-diphenylethertere-phthalamide)		Technora
Others		
Elastane		Lycra Dorlastan
Polyimide		

It should be recognised that generic names like "nylon" or "acrylics" indicate groups of polymeric materials with similar chemical compositions and chemical links between monomers and that various members of a group may have very different physical and chemical properties.

Semi-synthetic fibres based on cellulose differ from natural cellulose fibres in structure, molecular weight of the (reconstituted) cellulose polymer and in functional endgroups attached to the cellulose molecules.

Synthetic polymers may be composed of a single monomer or several monomers. Polymers may be pure or co-polymerised with other polymers; bicomponent fibres may be composed of several elements, each from a different polymer, in a skin-and-core or a back-to-back configuration.

Carbon fibres form a group on their own. They are produced by controlled pyrolysis of extruded pitch, synthetic yarn or semisynthetic yarn. Their composition is over 99% pure carbon, and the physical and chemical properties are totally different from MMOF.

To add to the diversity, synthetic polymers will contain traces of monomers, short-chain polymers, catalysts and all kinds of additives. The production method may leave traces of solvents or thermal degradation products in the fibres and the spun fibres may be given an appropriate chemical finish to aid spinning or improve comfort when used in clothing-related textile. Dyeing and delustering materials may also be applied as soluble or insoluble pigments (see section 2.6.5).

The surface characteristics of MMOF are complex and can be influenced by the chemistry of the base polymer and monomers as well as the spinning process and post-spinning treatment, surface treatment with spinning preparations, finishes, dyeing and delustering materials as well as residual mono- and oligomers, metal traces and/or catalyst residues. Spinning preparations and finishes are applied in small quantities to the surfaces of the intact fibre and some are used on speciality but not commodity fibres. Thus the amount remaining on the surface may be negligible on some MMOF-RFP, but considerable on others.

Depending on the chemistry of the base polymer and co-polymers, the surface can present acid, basic or amphoteric properties and be hydrophillic or hydrophobic. Polyacrylonitrile for example may react like an acid, while polyamide is basic, and wool contains both cationic and anionic groups and is amphoteric. All functional groups are converted into salts during dyeing processes.
Double bonds in the aliphatic chain and aromatic rings may also be accessible to chemical reactions. As most MMOF have a distinct skin-and-core structure, it is conceivable that torn-off RFPs have surfaces with properties different from those of the base material.

Although the physico-chemical and the toxicological properties of these additive materials may be well-known, the possible additive or synergistic effects when present on the surface or leached from inhaled RFP has not been studied.

Table 2 lists examples of substances added to the polymers during the production of MMOF. The list is not exhaustive but includes the most widely used materials.

Table 2: Additives (incl. trace element they may contain)

Lubricants	Vegetable oil Mineral Oil Synthetic liniments (polyethylene or polypropyleneoxides)
Emulgators and/or tensides	Sulfonated fatty acid glycerides Fatty acids Polyethyleneoxide adducts Quaternary ammonium compounds Others
Antistatic agents	Cationic, anionic and non-ionogenic compounds
Bactericides	Of any type, e.g. quaternary hydroxyalkyl ammonium salts
Antioxidants, light inhibitors, aging inhibitors	Sterically hindered phenols, e.g. Substituted tert-butyl or di-tert-butylphenols; polymer amines or acid amides with sterically hindered N-substituents
Flame retardants	Phosphonates, chlorides
Coatings	Polysiloxanes (on polyurethanes) Epoxy resins Proprietary formulations
Pigments	May contain Cu, Co, Ni, Ti (as TiO2)
catalyst residues	Alkali metals (in acrylics) Sb, Ge, Mn, Mg, Zn, Co, Ni, Ti (in polyeters)

2.3 STRUCTURE

Chemical composition is not the only or the most important factor governing the physical and chemical properties of polymers and fibres made from them. Degree of polymerisation, orientation of the molecules, degree of crystallinity, cross-linking between molecules etc. are of great influence and can be readily manipulated. For example: polyethylene fibres, which are melt-spun from a low-density polymer have little strength and stretch enormously prior to breaking. Gel-spun high-density polyethylene, which is chemically identical, is a true high-performance fibre with extreme strength and little or no elongation before breaking (so-called high modulus fibre). Although it is likely that a high degree of crystallinity and longitudinal orientation will increase the tendency to generate RFP, this remains to be demonstrated.
Some polymers form microfibrils composed of alternating amorphous layers and crystalline blocks. The amorphous layers may be important in chemical (and enzymatic) breakdown as they are more vulnerable to chemical attack than the crystalline regions. In *p*-aramid and other polymers with more rigid, rod-like macromolecules, a radially oriented "pleated sheet" structure is microscopically visible. Apparently the areas between the blocks that make up the "pleated sheets", although not amorphous, are also more vulnerable to physico-chemical attack. Finally, a clear skin-and-core structure has been observed and this may have consequences for the physical properties of sheared-off fragments (Northolt *et al*, 1992).

2.4 PHYSICAL PROPERTIES

The flexibility of a RFP may have an important influence on the pulmonary deposition pattern and in the pathophysiological processes (Pott, 1977) For most synthetics, data on physical properties of RFP are lacking. The properties and mechanical analysis of *p*-aramid RFP show that they are likely to deform more easily than glass or asbestos RFP (Knoff, 1993). They also show so-called "kink bands" (areas of compressive yield) which makes them vulnerable to physico-chemical attack (Kelly *et al*, 1993). An important observation in this respect was made by Bahners *et al* (1994), showing that tensile strength and modulus (fibre stiffness) of polyamide decreases considerably after a 60-day incubation in saline.

2.5 DIMENSIONS

2.5.1 Filament

Synthetic filaments are spun in continuous lengths, with diameters ranging from greater than 500 μm (e.g. monofilament fishing-line) to 1 μm (ultrafine polypropylene) (ICF, 1986). Typically, however, the diameter

of a filament ranges between 10 and 20 μm. So far it is largely unknown if and how the factors mentioned later in section 2.5 and 2.6 influence the formation and/or size of RFP.

2.5.2 Respirable-sized Fibre-shaped Particulates (RFP)

Marijnissen *et al* (1989) described a method for preparing nylon RFP with precisely defined dimensions (length = 16.4 μm, relative standard deviation 22%, diameter = 0.94 μm, relative standard deviation 21%). The RFP are cut with a microtome from spun fibres of uniform diameter. This material may be different from RFP of the same material created by stress or shearing forces (see section 2.4).

p-Aramid RFP have been described by several authors (Lee *et al*, 1988b, Verwijst, 1990, Cherrie *et al*, 1994). Typically they are curly, ribbon-shaped and branched, with a strong tendency to form non-respirable-sized agglomerates. There is evidence, that the physico-chemical properties (e.g. solubility, dye-ability) of these RFP and the spun fibre are different (see section 2.3).

p-Aramid RFP, artificially generated for inhalation toxicity test purposes[3] , had lengths up to 100 microns (mode 10-20 micron) and diameters less than 1 μm (Lee *et al,* 1988b). However, the tangling and branching of the fibrils led to the formation of agglomerates with a MMAD between 2.5 and 10 μm, and a mean diameter of 3.6 μm (Warheit *et al*, 1992). It should be stressed that these RFP are different both in appearance and in distribution of dimensions, from those found in commercial pulp (Schins *et al*, 1993) and those collected at various workplaces (Davies, 1995).

Free *p*-aramid RFP, counted by the WHO (1985) method for asbestos, were found in the atmosphere of a *p*-aramid production facility at low concentrations; actual dimensions of the particles were not specified (Verwijst, 1990).

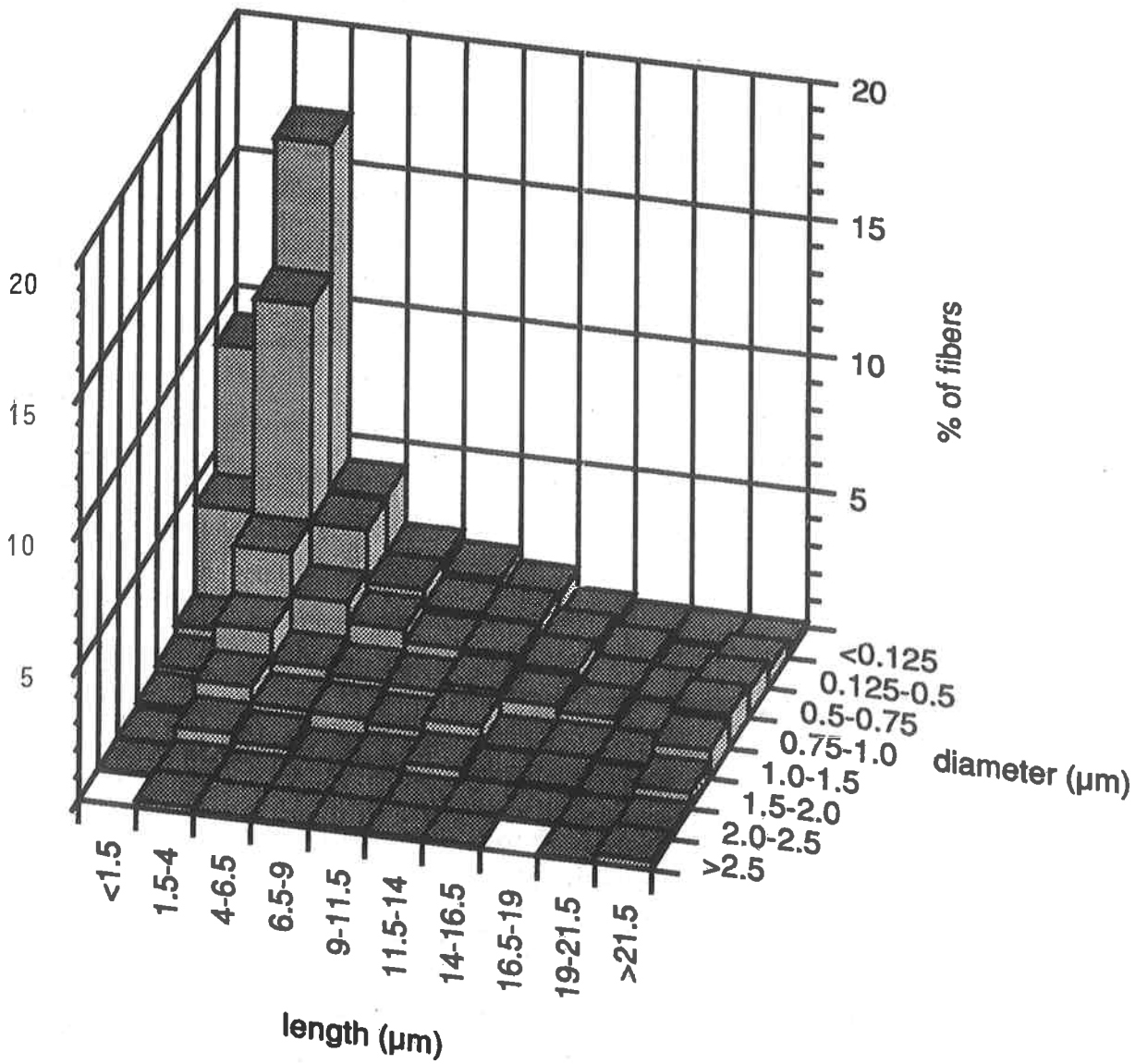
p-Aramid RFP isolated from a standard industrial pulp were measured by Schins *et al* (1993). Figure 2 shows the length/diameter relations and distribution.

Cherrie *et al*, (1994) determined *p*-aramid RFP in the atmosphere of industrial workplaces using *p*-aramid by phase-contrast optical microscope (PCOM) and asbestos counting rules; geometric mean concentrations ranged between 0.005 and 0.4 fibres/cm^3. Measurement with the scanning electron microscope (SEM) showed geometric mean lengths ranging from 13.3 μm (geometric standard deviation

[3] Note: all inhalation studies with *p*-aramid described in this review used material from the same specially prepared *p*-aramid ultrafine fibre batch described by Lee (1988b).

(GSD) 1.7) to 2.3 µm (GSD 2.3), and geometric mean diameters of 0.31 µm (GSD 1.6) to 1.01 µm (GSD 1.9). Statistically significant differences in RFP dimensions were observed between the three different types of processed material, i.e. filament, staple and pulp.

Figure 2 Length and Size Distribution of *p*-aramid RFP Obtained in Standardised Fashion from Commercially Available Pulp (from: Schins *et al*, 1993)



Filament-derived *p*-aramid RFP were generally short, flattened and curly with very few branches; the staple-derived RFP were relatively long, straight and thick with more short branches, and the pulp-derived RFP generally in-between. In these and other morphological aspects, such as shape and splitting, the workplace samples were all different from the material used in inhalation chamber exposures (Davies, 1995).

Hesterberg *et al*, (1992) used artificially generated and size-selected polypropylene RFP in inhalation toxicity testing. The fibres had a geometric mean length of 30.3 ± 2.6 μm and geometric mean diameter of 1.6 ± 0.6 μm. It is not known if RFP of similar dimensions are found in polypropylene processing.

Nord (1974) found dust levels ranging from 0.2 to 3.1 mg/m^3 in the men's clothing industry, where cotton and blends of cotton and synthetics are used. Some RFP were identified, but the fraction of the collected dust that was either respirable or fibre-shaped was unknown. The diameters of the fibre-shaped particulates collected on the filters ranged from 2 to 20 μm.

Tiesler and Schittger, (1992) found large amounts of cellulose RFP in the processing of shredded paper insulation material. These RFP were described as being longer than 5 μm, with diameters smaller than 3 μm, and with length/diameter ratios in excess of 3. However, this material is different in nature from the natural or semisynthetic cellulosic fibres processed in the textile industry.

Holt *et al,* (1972, as in cited Jones *et al*, 1982) attempted to generate RFP from carbon fibre with a hammer mill capable of generating up to 6000 f/ml RFP from chrysotile. Ninety-nine percent of the airborne particles were nonfibrous, and only few of the fibrous particles were of a respirable size (described as 1.0-2.5 μm diameter and < 10 μm length).

2.5.3 Identification, counting and sizing of RFP from MMOF

The major problem in studying RFP-related health problems is identification of RFP arising from MMOF. In the workplace, mixed fibre exposures are the rule rather than the exception. MMOFs from which RFP are derived are chemically similar in that they are composed chiefly of carbon and hydrogen. A large number of MMOF contains oxygen and a high proportion contains nitrogen. A smaller number of MMOF contains chlorine. Thus chemical identification would prove to be difficult. Sophisticated techniques which might identify relatively small amounts of synthetic fibres, such as secondary mass spectroscopy and X-ray photoelectron spectroscopy, are highly surface-sensitive and therefore likely to measure surface contaminants rather than the base material. A promising development for the identification of individual fibres in air samples or biological material is a modified SEM/EDX method, using "fingerprints"

(characteristic spectra) of reference materials (Tulke *et al*, 1995, in press). Optical fluorescence microscopy methods have been used to identify *p*-aramid RFP, but other organic fibres and the sampling filters may also show some degree of fluorescence (Cherrie *et al*, 1994).

A second problem relates to the applicability of the rules generally followed for counting RFP. Due to a tendency to branch, curl and clump, it is often difficult to decide if what is seen microscopically is a free RFP, a firmly attached branch or part of a clump. Establishing the dimensions of particles (sizing) may be equally difficult. RFP from MMOF show marked dimensional variations in contrast to the much more regular shape of e.g. amphibole asbestos (Bahners *et al*, 1994).

2.6 LIFE CYCLE

2.6.1 Filament Spinning

In the synthetic fibre industry, "spinning" denotes the process used to turn a polymer into a fibre. However, this term is also used to indicate the process of turning multiple short fibres (staple) into a yarn. In this Technical Report, "filament spinning" is used to indicate the former.

Several processes are used for filament spinning:

- "Wet spinning": a solution of the polymer is pumped through a spinneret (plate with many small-diameter holes) into another solution where coagulation or precipitation leads to the formation of filaments (cellulosics, some acrylics). One variation on this process is spinning into an airgap prior to the bath (*p*-aramids).

- "Dry spinning": a solution of the polymer is pumped through a spinneret into a hot-air chamber, where the solvent evaporates.

- "Melt spinning": the molten polymer is pumped through a spinneret and quickly cooled.

- "Gel spinning": a modification of the wet spinning technique to produce extended molecular chain crystallisation (leading to very high modulus).

- "Split-film": processes involving melt- or wet spinning of wide film that is split lengthwise, generating coarse flat fibres.

2.6.2 Stretching (or Drawing)

Filaments are nearly always stretched, either directly after filament spinning or in a secondary process after being wound on a reel. Stretching greatly increases the degree of molecular orientation and of crystallinity in the filaments, leading to increased strength and higher modulus. These properties may influence the tendency to generate RFP.

2.6.3 Texturising

Synthetic fibres are sometimes deformed in order to give the final yarn more bulk or stretch properties. Stuffer-boxes, meshed gears, fluted rollers and sophisticated twisting and tangling techniques are all used to induce deformation of the hot filaments, followed by cooling before release. Differential shrinking in bicomponent filaments is also used to create spiral or wavy deformation. The processes themselves do not generate much dust, because the polymers are hot and therefore malleable, but the resulting permanent deformation of the fibre may increase the tendency to generate RFP.

2.6.4 Staple Fibre

Filament is often cut or stretch-broken into short lengths and then spun into yarn, mainly to increase the bulk of the yarn. The staple is delivered in compressed bales. In order to use the staple it has to be "opened" (loosened-up) and "carded" (oriented length-wise). These processes can be dusty, presumably because the dust generated earlier in the cutting process is liberated here. In exposure monitoring, the highest concentrations of *p*-aramid RFP (up to 2 RFP/ml short-term peak concentrations) were measured near the carding operations (DuPont de Nemours, internal data).

2.6.5 Further Processing

Filaments are usually twisted, although untwisted yarn may be used in so-called non-wovens, e.g. needle felt, glue-bonded or heat-bonded fabrics. Spun staple yarn and twisted filament are used in weaving, knitting, cording, etc. These are dry processes with a potential for dust formation, although the yarn is always protected by lubricants. Fabrics thus formed are subjected to a whole range of further treatments, e.g. dyeing, filling, shrinking, etc. These generally are wet processes unlikely to produce dust. Production of garments and other products involves cutting and stitching, both are potentially dust-forming processes.

2.6.6 Uses

MMOF have widespread uses and are found, for example in clothing, upholstery and carpets. Industrial uses include non-wovens (e.g. for roofing and geotextiles), ropes, cables, formation of composites (e.g. tyres and belts with polyester, high-tech epoxy composites with *p*-aramid), filtration and insulation.
It is not known to what degree regular wear leads to the formation of RFP, although very small amounts (0.01 to 0.1 fibres/cm^3) of RFP were found in the hot and moist uprising air currents around a normally dressed person (Bahners *et al*, 1994)

2.6.7 Recycling

Prior to the introduction of MMOF, cellulose-based fabrics were recycled into high-quality paper and woollens were reprocessed into new garments. Due to the impossibility of separating the synthetics from the natural materials these practices have largely vanished.
However, large-scale collections of old garments are still common. Re-useable items are manually selected, the remainder being mainly tipped or burned. A small fraction is shredded and recycled into low-grade applications, e.g. cardboard, flannels and felts (Maetschke *et al*, 1994). These processes are said to be extremely dusty, but no exposure data are available.

2.7 OCCUPATIONAL EXPOSURE DATA

2.7.1 *p*-Aramids

Cherrie *et al*, (1994) measured exposures to airborne fibres amongst processors of *p*-aramids. Sites were selected as representative of the whole spectrum of *p*-aramid uses in industry, such as 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 for the Determination of Hazardous Substances Nº 59, with minor modifications to exclude electrostatic effects (HSE,1989). Samples were counted by PCOM and sized with SEM, and *p*-aramid RFP were separately identified by means of fluorescence microscopy. The exposure, expressed as the geometric mean (GM) of the 8-hr time-weighted average (TWA) for each job class, was in general very low, ranging from 0.005 to 0.4 fibres/cm^3. The authors considered that exposures would be higher without the sophisticated ventilation systems currently in use in the sites examined.

Reports on the generation of RFP during tooling of composites are at first sight contradictory. Studies in the Dutch and French aerospace industry (Verwijst, 1990; Doppler *et al*, 1990) indicate that tooling nearly

always generates matrix particles of non-respirable size with fibres attached. However, the Fraunhofer Institute (Bush *et al*, 1991) reported that "several millions of respirable fibrils were generated per meter cut edge during routing operations". The contradiction is at least partly explained by the "worst-case" approach in the Fraunhofer study, the different monitoring techniques and the fact that "several millions of respirable fibrils", more or less evenly distributed throughout several cubic meters of air surrounding a router is equivalent to "a few fibres/cm^3" (Cherrie *et al*, 1994).

High pressure waterjet cutting of *p*-aramid reinforced composites generates RFP, although aggregated within water droplets. Medium-sized droplets in the spray may carry hundreds of RFP for several meters (Verwijst, 1990). Some high-modulus fibres are ground into pulp for use as fibre reinforcing in brake linings and gaskets. A small percentage of RFP is present in such pulp, made of *p*-aramid fibres (Schins *et al*, 1993). Contrary to the situation with asbestos, this does not seem to pose an exposure hazard to garage personnel repairing brakes, as *p*-aramid fibres carbonize at the high temperatures that are generated when brakes are used (Grünthaler and Weisser, 1985).

2.7.2 Carbon Fibre

Jones *et al* (1982) described the exposure in a production unit and in a laboratory handling composites. Mean total dust concentrations were 0.16 mg/m^3 and 0.36 mg/m^3 respectively, with mean "respirable" (non-fibrous dia. < 7μm; no reasons given for this non-standard cut-off point) dust levels being 0.16 mg/m^3 and 0.09 mg/m^3. Based upon microscopic examination, it was stated that no fibre-shaped inhalable carbon particles were present, because nearly all carbon fibre particles retained their original diameter of > 7μm.

Mazumder *et al* (1982) found "significant quantities of carbon-fiber aerosol in the 0.1-10 μm MMAD range" as the result of cutting and grinding virgin carbon fibres and carbon fibre-reinforced composites, but without any quantitative specification.

The low exposure potential of carbon fibre was confirmed by data from NASA regarding aircraft crash and fire conditions, where burning composites generated a range of 0 to 0.14 RFP/cm^3, with diameters < 3.5 μm and lengths > 5 μm (Zumwalde and Harmison, 1980).

2.7.3 Other MMOF and NOF

Many papers address the dust problem in the natural fibre industry. However, none have been found that describe RFP concentrations, the standard being respirable dust on a weight per volume basis. Therefore, this chapter is limited to data concerning MMOF.

Drews and Hatcher (1983) measured dust levels in textile mills. Generally they were well below 1 mg/m^3 as measured with a vertical elutriator. Most of the dust was cellulosic (cotton) and only minor amounts were polyester. Dimensions of the dust particulates were not given so the percentage of RFP is not known. The amount of dust released from polyester was about one quarter of that released by cotton, calculated from the yarn weights. Interestingly, in factories with well-engineered ventilation systems and consequently low total dust levels the relative contribution of polyester was higher. This is possibly due to preferential removal of the low-density cellulosic particles.

Abdel-Kader *et al*, (1987) reported that dust concentrations were "far below the OSHA standards" in textile mills (range 0.069-0.396 mg/m^3); the single mill that used only polyester had dust levels comparable to those in the cotton and cotton/synthetics processing mills. Again, no data on RFP were available.

Tiesler and Schittger (1992) reported concentrations of cellulose RFP up to 57.3 x 10^6/m^3 in the processing of shredded paper insulation material, counting all RFP with a diameter of 3 µm or less and lengths of 5 µm or more. The air fraction with diameters of 1 µm or less contained a RFP concentration of 12.4 x 10^6/m^3. However, the nature of material is different from the natural or semisynthetic cellulosic fibres processed in the MMOF industry.

The first reports from a comprehensive exposure study in the German textile industry, indicate that in the processing of several types of MMOF (single and mixed) RFP concentrations were typically between 0.01 and 0.1 fibres/cm^3. Air was sampled at fixed positions around yarn-spinning, twisting and felting machinery using the Verband Deutscher Industrie (VDI)-methods for asbestos and a modified "Gravicon" sampler (not specified). Counting was by PCOM and SEM. The levels found in the room air were similar to those found in the air surrounding a dressed person, suggesting that industrial exposure and exposure of the general population are similar. However, more detailed reports are awaited, as the initial report is mainly describing the technical difficulties of sampling MMOF-RFP (Bahners *et al*, 1994).

2.8 CONCLUSIONS

MMOF and RFP derived from MMOF differ from the RFP from mineral fibres in nearly every physical and chemical aspect (with the exception of length and diameter ranges that are by definition the same for all RFP), and in nearly all aspects of their life cycle. The occupational exposure levels for MMOF-derived RFP appear to be low (typically far below 0.5 fibres/cm^3), although this awaits confirmation from more comprehensive studies.

3. HUMAN HEALTH EFFECTS

3.1 CASE STUDIES

Cortez Pimentel *et al* (1975) described seven workers in the synthetic fibre industry with varying degrees of bronchopulmonary disease. Biopsies showed focal septal thickening, interstitial fibrosis and granulomatous lesions in which foreign material was found which was probably acrylic, polyester and/or nylon. The clinical symptoms were of extrinsic allergic alveolitis in most cases, but there was no immunological evidence for this diagnosis. The authors produced similar lesions by exposing guinea pigs to Nylon and Orlon dust by inhalation and concluded that an unidentified immunological factor caused pulmonary disease after exposure to MMOF dust. The possible causative, additive or synergistic effects of additives (described in section 2.2) and the possibility of so-called "humidifier disease" caused by the factory environment were not considered. Quantitative exposure data were not available and it is not stated whether the material found in the biopsies and in the lungs of the experimental animals was fibre-shaped.

Hillerdal *et al* (1990) described three patients who had been employed for decades in cutting and measuring acrylic and polyester cloth, and imitation leather (presumably polyurethane). Pulmonary biopsies showed diffuse pulmonary fibrosis, and granulomas around foreign bodies presumed (but not proven) to be particles from synthetic fibres. Exposure data and dimensions of the particles were not available.

These are the only case studies found in the literature.

3.2 MORBIDITY STUDIES

Sigsgaard *et al* (1992) studied pulmonary function parameters and serum IgE, IgG and α_1-antitrypsin levels in cotton, wool and MMOF mill workers. In these mills, exposure to dust, endotoxins and microbial spores was measured. Total dust and respirable dust levels were comparable in the three mills, but there were virtually no measurable levels of endotoxins or spores in the MMOF mill. The cotton and wool mill workers had significant reductions in FEV_1 and FVC when compared to the MMOF mill workers over the course of the work shift (mainly related to endotoxin exposure).

In a review of the incidence of byssinosis and other diseases among textile workers, Kilburn (1983) concluded that synthetic fibres can produce mild ventilatory impairment and can cause granulomas and

fibrosis with varied symptoms. This conclusion was based solely on the paper of Cortez Pimentel *et al*, (1975).

Valic and Zuskun (1977) described a much lower incidence of ventilatory impairment among polyacrylonitrile workers than among workers previously exposed to hemp or cotton. However, the exposure data were expressed in terms of weight, not fibre number. The comparison, based on exposure to fibre dust, may be inappropriate, because ventilatory impairment from natural organic fibres is probably due to spores and microbiological toxins, which are absent from synthetic fibres.

English abstracts from Russian sources mention skin and mucosal membrane disorders as well as bronchitis in workers allegedly exposed to fine carbon fibre dust with diameters of 2 μm and below. There was, however, considerable co-exposure from acetic acid, acrylonitrile, carbon monoxide, propene, propanone and hydrogen cyanide, "sometimes at levels exceeding permissible concentrations" (Fedyakina, 1982, Troitskaya *et al*, 1985).

3.3 MORTALITY STUDIES

In the natural organic fibre (cotton, wool, silk, flax etc.) industry, byssinosis has been associated with the presence of water soluble aminoglycosides on unwashed cotton, flax and hemp. In the wool and silk industry, pulmonary allergy is the major health hazard, especially in atopic individuals (Montgomery, 1982). A link between RFP and disease has not been established in these industries. It is noteworthy that mesotheliomas have never been reported from the NOF industry, and chronic exposure to cotton dust even seems to reduce the risk of lung cancer risks (Hodgson and Jones, 1990).

Several studies describe mortality patterns among textile workers, but in general these are concerned with the consequences of exposures to chemicals in the synthetic fibre industry, such as dyestuffs and solvents, rather than exposure to RFP. Some examples:

Working in the polypropylene fibre manufacturing industry was alleged to be associated with an increased risk of colon carcinoma, but this could not be confirmed in later updates (Goldberg and Theriault, 1994a,b). Allegedly increased risks for pancreatic cancer due to methylene chloride exposure in the manufacture of cellulose triacetate, could not be confirmed (Lanes *et al*, 1990).

Exposure to acrylonitrile (and dimethylamide) was not related to mortality from tumours of the colon and intestine (Mastrangelo G *et al*, 1993), nor to mortality from lung cancer (Chen *et al*, 1987).

Bladder cancer was identified in a census study as a probable occupational risk for workers in the English and Welsh textile dyeing industry (Dolin, 1992), and a case-control study in Spain detected an odds ratio (OR) of 4.41 for workers involved in textile dyeing or printing (Gonzales *et al*, 1988). However, an

increased risk for bladder cancer among textile workers was not apparent in similar studies involving English and Welsh female textile workers (Roman *et al*, 1985). In other record linkage studies increased risks for thyroid cancer, liver cancer, prostate cancer and colon cancer among "textile workers" and for cervical cancer among "female textile workers" respectively were identified (Carstensen *et al,* 1990, Saurez *et al*, 1989, Hoar and Blair, 1984, Delzell and Grufferman, 1983). (This type of studies is in general of value for hypothesis building only, mainly because the (last) occupational or (last) job title bears little or no relation to past exposures) .
Siemiatycki *et al,* (1986) found a weak association between the incidence of colorectal and bladder cancer and (undefined) exposure to synthetic fibre (relative risk 1.5 and 1.8 respectively). However, the proportional mortality ratio (PMR) is not high, the number of cases small and the job definitions too unspecific to exclude the influence of other exposures.

Hours *et al*, (1989) described a follow-up mortality study on a cohort in a nylon/polyester factory in Lyon, France. A slight increase in overall cancer mortality (SMR 115.1, 95% CI 98-134) lung cancer mortality (SMR 139.6, 95% CI 102-188) and possibly bladder cancer mortality (SMR 203, 95% CI 82-421) was found. However, no distinction was made between workers at the polymerisation stage (with multiple chemical exposures) and those at the textile departments with possible exposure to RFP, and relevant exposure data are not provided.
O'Brien and Decoufle (1988) described an elevated risk of mortality from testicular cancer and lymphocytic leukaemia in the Georgia (USA) carpet and textile industry (PMR 2.9 and 3.2 respectively). A previously reported increase of the incidence of leukaemia in a Yorkshire (UK) carpet facility was reported to be due to an overall increase in the entire local population of which the origin is unknown (Cartwright *et al*, 1987).

Exposure to RFP has never been studied as a separate risk factor in the synthetic fibre industry, and only a few studies have been identified in which RFP-exposure might have been an important factor. Dubrow and Gute (1988) found an increased PMR for non-malignant respiratory diseases (NMRD) among textile workers in Rhode Island. This was as expected for cotton workers, but there was also a surprisingly high PMR for NMRD in workers exposed to "silk and synthetics" only. The authors indicated probable biases and confounding factors which, together with the small number of workers studied, undermine the conclusion that their observations can be related to MMOF exposure. Exposure data were not available.

Zappa *et al,* (1993) found a strong association between lung cancer and work on the reprocessing of wool derived from used clothes and rags. The overall OR was 1.45 (95% CI 1.0-2.1), whereas rag sorters and weavers had an OR of 2.2 and 1.7 (95% CI 1.3-3.7 and 1.1-2.7) respectively. A time-based analysis suggests that asbestos, blended into wool, and mineral oil, used in weaving, might be partly, but not

completely, responsible as these factors were not present in all of the factories. There were no data on exposure to RFP.

3.4 CONCLUSIONS

Case studies as well as morbidity and mortality studies involving MMOF have been reviewed. The available studies are insufficient, either by design or by lack of data, to exclude or establish a health risk from exposure to RFP from MMOF. Two case reports link disease in humans to MMOF inhalation. The described pulmonary effects are clearly distinct from those seen after asbestos exposures. The morbidity and mortality studies failed to provide any evidence, mainly because RFP measurements were not made in any of the studies.

4. TOXICOLOGICAL EFFECTS

4.1 FIBRE TOXICITY STUDIES

4.1.1 Role of Studies

To gain an understanding of models and the findings from them, it is necessary to consider these systems in general terms and to review findings on asbestos and man-made vitreous fibres (MMVF).

Two types of studies can be distinguished:

- *in vitro* durability studies:
  Durability *in vivo* involves at least two factors: mechanical fragmentation into smaller fibres and chemical solubility in biological fluids. Inhaled fibres are in contact with extracellular fluid, at approximately pH 7, and intracellular or lysosomal fluid, at approximately pH 5; thus solubility at each pH is relevant to biopersistence.
  Both static and flow-through systems have been used to determine *in vitro* fibre solubility (Law *et al*, 1990). Additional studies are needed to determine whether *in vitro* solubility rates correlate with the durability and biopersistence of fibres in the lung *in vivo*. There are indications that solubility in systems is less applicable to the durability of MMOF since intracellular enzymatic attack might be involved in their degradation *in vivo* (Horauer,1960; Williams, 1979). In addition to chemical solubility, a test that estimates the mechanical fragmentation potential of a fibre may be useful as a means of predicting biopersistence.

- *In vitro* toxicological studies: Cell culture systems have been valuable tools in fibre toxicology for mechanistic studies and have been proposed for fibre toxicity screening.

Short-term *in vitro* assays have several advantages, including

- speedy performance of studies, usually 1 to 2 weeks,
- the low expense compared to inhalation studies,
- the ability to control several variables in the cell culture environment (e.g., culture conditions, homogeneous populations of cells, fibre dose), and
- the ability to evaluate critical changes in gene activation (oncogenes) or inactivation (cancer-suppressor genes) using molecular biology techniques.

In vitro toxicology studies have contributed to the evolution of a model of the mechanisms of fibre-induced pathogenesis (i.e., lung inflammation, fibrogenesis and oncogenesis).
The studies fall into three categories:

- cytotoxicity,
- inflammation and fibrogenesis, and
- genotoxicity (model of oncogenesis).

Cytotoxic effects that have been examined include cell membrane disruption, inhibition of cell proliferation, and inhibition of colony formation. Genotoxic effects include micronucleus induction, chromosomal changes (aneuploidy, clastogenesis, anaphase abnormalities), gene mutation and colony transformation. Early studies quantified fibre-induced cell death and genotoxic events. More recently, the focus has shifted to the study of subcellular and molecular events including DNA and RNA transfection and oncogene activation, as well as the biochemical interactions of immunogenic and other cell types.

There are several interpretative problems associated with *in vitro* studies of fibre toxicity. Any RFP-related chromosomal or DNA changes observed in a study may be cell- or tissue-specific and not necessarily relevant to different pulmonary cell types exposed under physiological conditions. Most *in vitro* systems are unicellular and single cell-RFP interactions cannot duplicate events in a multicellular system like the lung. Moreover, many cell types used in these studies may not be relevant to cells of the respiratory tract. In addition no assessments of RFP deposition, translocation, clearance, or biopersistence can be made using *in vitro* culture systems. All these factors limit considerably the predictive value of studies for assessment of fibre toxicity to mammals.

Hesterberg (1988) has suggested a battery of short-term tests as a way to overcome some of these limitations. Such a battery should combine several cell culture systems with other types of tests, such as fibre solubility tests and short-term animal inhalation studies. However, no such battery has so far been found fit for screening purposes.

An important limiting factor is the lack of a true negative control, i.e. a fibre that does not have similar cytotoxic properties to asbestos and other mineral fibres. Hart *et al* (1994) have shown that for several inorganic materials with clear-cut differences in *in vivo* toxicity, there was similar toxicity for CHO cells, which correlated only with RFP length. If this holds true in other *in vitro* tests, then systems would not provide a valid model for predicting fibre toxicity *in vivo*.

4.1.2 Solubility Tests with MMOF

p-Aramid fibres, carbon fibres and chrysotile were kept for 8 weeks in a static Gamble solution and for two weeks in a flow-through system. Whereas chrysotile split into many fibrils the two other fibres were virtually untouched (Förster, 1984).

p-Aramid fibres and polyester fibres were incubated in physiological sodium chloride solution with and without lysosomal enzymes at pH 5, 6 and 7.2. Polyester quickly broke down at pH 5 in the presence of enzymes, but *p*-aramid was unaffected (Mieschental *et al*, 1987).

The solubility of various natural and synthetic fibres in Gamble's solution was determined by atomic absorption spectrometry. Carbon and aramid fibres were practically insoluble and there was no evidence of alteration to the surface when examined by SEM/EDX (Larsen, 1989).

Several materials, including three MMOF compositions (polypropylene, polyethylene, and polycarbonate), were compared for solubility in Gamble's solution at pH 7.6. After 180 days in a flow-through system, there was virtually no dissolution, no significant change in surface area, only slight weight gain (ranging from 0.08 to 0.5%) and no visible surface change. This was in contrast to results obtained with several MMVFs (Law *et al*, 1990).

Incubation in human plasma for up to 26 weeks had no effect on the diameter or surface morphology of the *p*-aramid fibres (Wening and Lorke, 1992).

Kelly *et al,* (1993) found a reduction in mean length of *p*-aramid RFP after three months exposure to pancreatin in a flow-through system.

4.1.3 Cell Culture Studies of MMOF

Carbon Fibres

Martin et al (1989) established the degree of cytotoxicity of five graphite fibre composite materials machined by various operations (characterized by Boatman *et al*, (1988) in rabbit alveolar macrophages by examination of trypan blue exclusion, release of (radioactive) ^{51}Cr and phagocytosis as measured by light microscopy. However, it was not clear in the report whether the materials were fibrous, particulate or both, and matrix material was present in addition to graphite.

In studies conducted by Styles and Wilson (1973), unspecified carbon dust was not considered cytotoxic to rat alveolar and peritoneal macrophages. Less than 2% of peritoneal macrophages and 5% of alveolar macrophages were killed following phagocytosis of carbon dust with particle diameters of 2-15 μm.

p-Aramid fibres

p-Aramid RFP, (90% ≤ 5 μm in length by 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, as shown by determination of leakage of cytoplasmic LDH, lysosomal enzymes, ß-Gal actosidase and ATP-content (incubation time 18 hours). The cytotoxic response in freshly harvested and cultured cells was considered to be similar to or greater than that for UICC B Canadian chrysotile (Dunnigan *et al*, 1984). However, these fibres would not be included in fibre counts in the occupational setting, determined according to WHO criteria (WHO, 1985).

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

Wening *et al*, (1989) briefly reported that p-aramid fibres were not mutagenic in Ames-tests with the Salmonella strains TA 97, TA 98, TA 100, TA 102, TA 104, TA 1535, TA 1537, and TA 1538. They were also not cytotoxic in CHO cells. Fibers, ethanol extracts and chloroform extracts were all tested. However, the dimensions of the tested fibers are not given. In fact there is no indication that the RFP in p-aramid RFP were tested.

Polyester fibres

A study of the cytotoxic activity of polyester RFP gave a negative result as measured by LDH release from guinea-pig alveolar macrophages but this might have been due to the large amount of non-fibrous dust in the sample and the tendency of the fibre-shaped particles to clump together (Ehrhart *et al*, 1982).

Polyolefin fibres

In studies conducted by Styles and Wilson (1973), polyethylene and polypropylene were considered to be among the least toxic of a number of dusts tested for cytotoxic activity in rat alveolar and peritoneal macrophages. It is not clear whether this material was fibrous, particulate, or both.

The toxicity of size-separated RFP fibres was examined in CHO-K1 cells (Hart and Hesterberg, unpublished data). These were the same as the RFP used in the inhalation study reported by Hesterberg *et al.* (1992) (see section 4.2.3). Since polypropylene RFP float on water, suspensions of RFP and cells were agitated for 7 to 8 hours in an incubator. Polypropylene RFP were less potent than MMVF-RFP in inhibiting cell proliferation and colony formation and fewer polypropylene RFP were taken up by the cells. The investigators caution, however, that in this test system, the cell-RFP contacts could have been less for polypropylene than for MMVF because the extremely buoyant nature of the polypropylene resulted in these RFP riding on the surface of the suspension, while the MMVF-RFP and cells tend to mingle together within the suspension. Size-selected polycarbonate RFP, which are slightly more dense than water, were also tested for toxicity towards CHO cells (Hart et al, 1993) Similarly-sized MMVF (L 22 ± 17 µm, D 1.4 ± 0.9 µm) or polycarbonate RFP (L 23 ± 17 µm, D 1.4 ± 1.2 µm) were incubated with adherent CHO cultures for 2-3 days. Both fibre types were observed to settle on the cell layer. However, very few polycarbonate RFP were taken up by the cells in contrast to the large number of intracellular MMVF-RFP. The inhibition of CHO cell proliferation by polycarbonate was negligible while similar concentrations of MMVF (RFP/cm^2 of culture) reduced cell numbers to 50% of negative control cultures.

4.2 INHALATION TESTS WITH MMOF

4.2.1 Role of Inhalation Studies

Inhalation tests have some obvious advantages over other test systems: the route of exposure is the same as in humans and exposure is directed to the intact pulmonary system including all natural defence, metabolic and exacerbation mechanisms. In rats, the incidence of fibrosis, lung cancer and mesothelioma after exposure to asbestos is comparable to those in humans (Warheit and Hartsky, 1994(b)). Disadvantages of animal inhalation studies include species differences in respiratory anatomy and function, species-specific pathology both in control animals and in treated animals (in the latter especially as the result of "overloading"), and relatively low sensitivity. The value of the approach for fibre toxicity screening is limited because it is time-consuming, expensive and cannot elucidate the details of cellular and molecular events. In addition it may prove to be extremely difficult to generate sufficient amounts of RFP from MMOF. Despite these limitations, a WHO consultation concluded that inhalation studies are currently the best available laboratory model for assessing the human health risks of fibre exposure (WHO,1992).

Subchronic and chronic inhalation tests are used to study health effects and dose-effect relations. More recently short-term inhalation studies with extended follow-up periods have been employed to study biodegradability, cellular reactions, proliferative reactions, repair and clearance mechanisms (Warheit, 1995). When studying biopersistence of MMOF-RFP in this fashion, the digestion of the lung tissue as

required for RFP counting and sizing may pose a particular problem. The methods normally used for mineral RFP, such as low-temperature plasma ashing or digestion with strong acids or bases may easily destroy most man-made or natural organic RFP. Enzyme digestion methods may solve this problem (IOM, 1993).

4.2.2 Short-term Inhalation Studies

p-Aramid fibres

Rats killed at various periods after a two-week exposure to a range of *p*-aramid RFP concentrations showed only a macrophage response at the lowest level (up to 26 fibres/cm^3) and granulomatous lesions at the alveolar duct bifurcations with fibrotic thickening at the higher levels (280 fibres/cm^3 and above). At 6 months post-exposure, nearly complete recovery of the granulomatous lesions and marked reduction of the fibrotic lesions was found. The fibres appeared to be quickly fragmented and reduced in size (Lee *et al*, 1983).

Groups of 24 male Crl:CDBR rats were exposed nose-only to ultrafine p-aramid fibrils for 6 h/d for 3 or 5 days at concentrations of 600 to 1300 fibres/cm^3 (gravimetric concentrations of 2 to 13 mg/m^3). Groups of 4 rats/group were examined at 0, 24, 72, 96 h, 1 wk and 1, 3, or 6 months postexposure (Warheit *et al*, 1992). Five day exposures elicited a transient granulocytic inflammatory response with an influx of neutrophils into alveolar regions and concomitant increases in AP, LDH and protein levels in bronchoalveolar lavage (BAL) fluid , which returned to control levels between one week and one month postexposure. Increased pulmonary cell labelling (BrdU) occurred in terminal bronchiolar cells immediately after exposure but returned to control values one week later. Histopathological examination of the lungs revealed only the presence of fibre-containing alveolar macrophages, primarily at the junctions of terminal bronchioles and alveolar ducts. Fibre clearance studies demonstrated a transient increase in the numbers of retained fibrils after one week postexposure, with rapid clearance of fibres thereafter. The transient increase in the number of fibres could be due to transverse cleaving of the fibres, since their average lengths continued to decrease over time. A progressive decrease in mean lengths (12.5 μm to 7.5 μm) and diameters (0.33 μm to 0.24 μm) occurred over a six month period postexposure. More importantly, the number of longer (i.e. > 5 μm) fibres showed a sharp decrease, beginning after one week, declining to 4% of the original values after 24 weeks. The number of short fibres (i.e. < 5 μm) was stable up to 12 weeks, and then also dropped sharply. These data show that the longer and potentially more hazardous fibres are quickly broken into shorter fragments. The generation of short fragments keeps up with the clearance as long as there are sufficient long fibres present. These data indicate that p-aramid fibrils have limited durability in the lungs of exposed rats.

Preliminary data from an independent study, that compared the biodegradability of p-aramid, size-selected chrysotile and code 100/475 glass, confirm the above findings (IOM, 1995). The investigators

previously reported considerable difficulties in the digestion of lung tissue without digesting the organic fibrous material.

In another study, size-selected chrysotile asbestos was compared to *p*-aramid RFP of similar dimensions, under exposure conditions as described above. The initial pulmonary cellular reaction, studied by ultrastructural morphometry of the alveolar ridges was similar for both fibre types and reversible within 6 months. In contrast, BrdU labelling showed a weak and transient reaction of epithelial cells with *p*-aramid, whereas chrysotile caused sustained significant increases compared to controls in both epithelial and mesothelial cell proliferation (Warheit, 1994 (d)).

Carbon fibres

Holt and Horne, (1978) exposed guinea-pigs to chopped carbon fibre dust for 104 hours at concentrations up to 20 mg/m^3. Ninety nine percent of the airborne particles were non-fibrous and about 1.0 μm in diameter, and only few of the airborne fibres were of respirable dimensions (reported as 1.0-2.5 μm diameter and > 10 μm length). The animals were sacrificed at intervals ranging from 1 to 144 days after cessation of exposure. Histologically, only small increases in macrophage numbers, containing mostly non-fibrous carbon particles were seen. A few fibre-shaped particles were found extracellularly.

4.2.3 Subchronic Inhalation Studies with MMOF

Polyolefin fibres

Groups of 22 male Fischer 344 rats were exposed nose-only 6 hrs/day, 5 days/week for 90 days to filtered air containing 0, 12, 20, or 46 polypropylene fibres/cm^3 (0, 15, 30, or 60 mg/m^3), size-selected to have an average diameter of 1.6 μm and an average length of 20 μm. There were no statistically significant changes in body or lung weight or excess mortality in exposed animals when compared to the control. Selected animals were examined at 30 and 90 days during the study and 30 days postexposure. At all times, there were dose- and duration-dependent changes in the lungs, characterized by increased cellularity and early bronchiolitis but no deposition of collagen. The changes appeared to be reversible at the lower doses 30 days postexposure. There was a strong association between the administered concentration, the time of exposure and lung fibre burden (Hesterberg *et al*, 1992).

Carbon fibres

Owen et al, (1986) reported that carbon fibre particles were phagocytosed by macrophages, but that no local inflammatory reaction or fibrosis occurred in male Sprague Dawley rats after 4, 8, 12 and 16 weeks

of exposure to 20 mg/m^3 of carbon fibre dust, including 16 weeks plus 32 weeks recovery. However, the diameter (7 μm) of the material used was much larger than the range of concern for RFP.

Groups of male Crl:CDBR rats were exposed nose-only to aerosols of respirable-sized carbon fibres, pitch-based or polyacrylonitrile (PAN)-based, at target concentrations of 50 or 100 mg/m^3 for periods ranging from 1 to 5 days (6 h/d) and examined at 0, 24, and 72 h, 10 d, 1 and 3 months postexposure. A 5-d exposure to 47 or 106 mg/m^3 (47 or 62 fibres/cm^3, pitch-based carbon fibres) produced a dose-dependent inflammatory response in the lungs, manifested by increased numbers of lavaged neutrophils and significant increases in LDH, protein and AP in bronchoalveolar fluids shortly after exposure, which were reversible within 10 days. Results from BrdU labelling studies in rats exposed for 5 days demonstrated an increased turnover of lung parenchymal cells 10 days or 1 month after exposure which did not correlate with the measured inflammation in bronchoalveolar lavage fluids; no increases in turnover of terminal bronchiolar cells were found at any time. Pigment-laden alveolar macrophages, as well as minimal Type II epithelial cell hyperplasia were observed, primarily at the junctions of the terminal bronchioles and alveolar ducts (Warheit, 1994a).

Others

Cortez Pimentel *et al*, (1975) exposed 28 guinea-pigs to manually pulverized nylon and 10 guinea- pigs to polyacrylonitrile dust for nearly one year. Eighteen nylon-exposed and 10 polyacrylonitrile-exposed animals were histologically examined either at terminal sacrifice or after interim deaths (6 animals). Macroscopically visible nodules surrounded by small areas of emphysema were found in in 14 and 10 animals respectively. The lesions were described as intraseptal granulomas consisting of oedema, reticular fibres and granulomatous cellular proliferations made up of histocytes and fibroblasts. All lesions contained microscopically visible birefringent material. No mention was made of other pathological lesions, e.g. fibrosis. Unfortunately, no respirable dust concentrations or particle dimensions were given.

4.2.4 Chronic Inhalation Studies with MMOF

Determinants of fibre toxicity after chronic inhalation

Recent studies on insulation wools and refractory ceramic fibres (Hesterberg *et al,* 1993a) have strongly indicated that internal dose and dimension of fibres are not sufficient to explain the differences in toxicity of different types of fibres. The importance of other fibre characteristics, such as chemical composition, surface charge, and biologic persistence is now well recognized (McClellan *et al*, 1992; Hesterberg *et al*, 1991a; Morgan and Holmes, 1984; Bellman *et al*, 1987).

p-Aramid fibres

Groups of 100 male and female Crl:CD(SD)BR rats were exposed to ultrafine p-aramid fibrils, separated from the p-aramid pulp matrix by high pressure air impingement, at concentrations of 0, 2.5, 25, and 100 fibres/cm^3 (0, 0.8, 0.31, and 0.63 mg/m^3) 5 d/wk for two years (Lee *et al*, 1988b). An additional group of 100 animals was exposed on the same schedule to 400 fibres/cm^3 (2.23 mg/m^3) but owing to toxicity, exposure was terminated at 12 months and the animals were followed for an additional year. There were interim sacrifices of 10 males and 10 females per group at 3, 6, and 12 months. At 2.5 fibres/cm^3, the alveolar architecture of the lungs was normal with a few dust-laden macrophages in the alveolar airspaces. This was considered to be the NOAEL. At 25 and 100 fibres/cm^3, there was a dose-related increase in lung weight, a dust cell response, slight Type II pneumocyte hyperplasia, alveolar bronchiolarization and a negligible amount of collagenized fibrosis in the alveolar duct region. In addition, at 100 fibres/cm^3, proliferative keratin cysts (PKC)[2] were observed in four female (6%) but not in male rats. Exposed female rats also had more prominent foamy alveolar macrophages, cholesterol granulomas and alveolar bronchiolarization than the exposed male rats. In the 400 fibres/cm^3 groups, 29 male and 14 female rats died within the first year with obliterative bronchiolitis resulting from dense accumulation of inhaled p-aramid fibres in the ridges of alveolar duct bifurcations. In animals surviving one year postexposure, the lung dust content, average fibre length and the severity of pulmonary lesions in

[2] Initially, these lesions were termed "cystic keratinizing squamous cell carcinomas". The exact nature of these lesions has been questioned and an expert panel of pathologists re-examined all the proliferative lesions in the lungs of p-aramid treated rats. The consensus of the expert pathologists was that these lesions were not malignant and a diagnosis of "proliferative keratin cyst" was more appropriate (Carlton, 1994). In 1995, a "Pathology Workshop on keratinous lesions in the rat lung", organized by the Deutsche Forschungsgemeinschaft studied the slides from 13 different studies with different materials, and reached agreement on the criteria for classification of the keratinous lesions. They agreed on diagnosic criteria for:

1. simple metaplasia (transition of alveolar epithelium into squamous epithelium)
2. pulmonary keratinous cysts (thin-walled hollow lesions filled with keratin (horn-like substance) without signs of autonomous growth)
3. cystic keratinizing epitheliomas (as above, but with signs of benign peripheral autonomous growth)
4. squamous cell carcinomas, of which two types are acknowledged: a) the keratinizing type, which may or may not arise from the wall of an epithelioma, b) the non- or poorly-keratinizing type, which occurs independent.

These lesions appear to be unique for the rat lung; even epitheliomas occur only at a late stage, and they do not necessarily (or often) progress to squamous cell carcinomas; thus, it should not be considered as a precancerous lesion. The chairman of this panel expressed as his personal opinion that a malignant degeneration would be more substance-dependent than time-dependent.
The panel expressed their opinion that, as long as lung pathology was limited to the epitheliomas, they had probably little relevance for humans (Wagner, 1995).
Subsequently, the lesions from the p-aramid inhalation study were re-evaluated according to these new criteria (Brockmann *et al*, 1995). This re-evaluation fully confirmed the conclusions as reported by Carlton (1994).

surviving rats were markedly reduced, but there was slight centriacinar emphysema and minimal fibrosis in the alveolar duct region. One male rat (1/36; 3%) developed a squamous cell carcinoma and six female rats (6/56; 11%) developed PKCs. There was also a small increase in the number of bronchioalveolar adenomas, but these lesions appeared to be unrelated to the PKC and PKC-associated lesions.

This study has been critized for having been terminated too early for an eventual development of the PKCs into malignancies. A chance degeneration of a small percentage of these lesions can of course never be excluded, but the observed nature of the existing lesions does not support such speculation.

The deposition of p-aramid fibres and their clearance from the lung were investigated. Fibres recovered from lung tissue in exposed CD rats were counted and measured by phase contrast microscopy. The mean initial dimensions of inhaled p-aramid fibres were 12 μm length and <0.3 μm diameter. After 2 years of continuous exposure at 2.5, 25, or 100 fibres/cm^3, or 1 year exposure plus 1 year recovery at 400 fibres/cm^3, the mean length of fibres approached 4 μm. The time required for fibre length to be reduced to <5 μm in the lung was markedly less at lower exposure concentrations. The authors concluded that p-aramid fibres are less durable in the lungs of rats and humans than could be expected from the physical and chemical properties of the original fibre material (Kelly *et al*, 1993).

4.3 INSTILLATION AND INJECTION TESTS

4.3.1 Role of Instillation/Injection Tests

Intraperitoneal and intrapleural injections in rats of RFP dispersions easily produce a high incidence of mesotheliomas. They have been extensively employed to establish the influence of RFP dimensions on carcinogenicity (Stanton *et al,* 1981, Pott *et al,* 1980). Intracavitary models have been advocated as relatively cheap and highly sensitive tests to predict the carcinogenicity of fibres. However, the route of administration bypasses all natural defenses, and the single dose (or few repeated doses) early in life is also unphysiological. There is considerable concern that intracavitary models may give false positive results, even for the prediction of mesothelioma risk, and there is no agreement over the predictive value for lung cancer. The WHO consultation (WHO, 1992) concluded that the intraperitoneal model cannot be used for quantitative risk assessment or for comparing relative hazards of different fibres.

Intratracheal instillation is sometimes regarded as a relatively easy and cheap alternative to inhalation studies. However, the bolus administration often leads to uneven distribution of RFP over the lung and localized overloading effects.

4.3.2 Intraperitoneal Tests

p-Aramid fibres

In studies by Pott *et al,* (1987), 5 week old female Wistar rats were administered 10 mg p-aramid fibres prepared by ultrasonic treatment in 3 weekly intraperitoneal injections of 2,4 and 4 mg. In animals sacrificed 2.5 years after treatment, there was a combined sarcoma/mesothelioma incidence of 12.9% in test animals and 6.3% in controls. In an additional study in which there was an attempt to obtain finer fibres and better suspension by drying, milling and ultrasonic treatment, 20 mg p-aramid in saline was injected intraperitoneally into 8 week old Wistar rats in 5 injections of 4 mg weekly. At 28 months after injection, the percentage of animals bearing sarcomas/mesotheliomas was 5.8%. In a subsequent report by Pott *et al*, (1989), in which both the fibre size distribution (90% of fibres had diameter of <0.76 μm and 10% had a length >12 μm, 40% between 12 and 4,9 μm and 50% <4,9 μm) and number of fibres were characterized, there was no significant increase in the number of peritoneal tumours relative to saline controls. There were tumours in 3 of 53 (5.7%) female Wistar rats compared to 2 of 102 (2%) in the controls at 130 weeks following intraperitoneal administration of 4 weekly doses of 5 mg of milled bulk p-aramid (total dose, 20 mg). The number of p-aramid fibres administered was 1260×10^6. Administration of a smaller total dose of UICC B chrysotile (0.25 mg; 202×10^6 fibres), produced a tumour incidence of 68%.

In a study in which 25 mg of p-aramid fibres were administered intraperitoneally to Sprague-Dawley rats (20 of each sex), there were no peritoneal mesotheliomas at termination (104 weeks) (Maltoni and Minardi, 1989). In an additional study by the same investigators, there were no peritoneal mesotheliomas at 76 weeks in similarly sized groups of rats of the same strain following intraperitoneal administration of 1, 5, or 10 mg p-aramid fibres (Maltoni and Minardi, 1989).

In an earlier study (Davis, 1987), doses of 0.25, 2.5, or 25 mg of p-aramid pulp violently desegregated by a turreted tissue homogenizer were administered by single intraperitoneal injection in phosphate buffered saline to three groups of 3 month old male AF/Han strain rats of 48, 32 and 32 animals respectively. The cellular reaction to injected p-aramid was considered to be vigorous, with development of large cellular granulomas. Two out of 32 animals in the 25 mg dose group, developed peritoneal mesotheliomas and although this was not a significant increase, it was concluded that the p-aramid preparation possessed a low but definitive carcinogenic potential when administered intraperitoneally.

Polyolefin fibres

Wistar rats received intraperitoneal injections of 10 mg of polypropylene fibres in saline starting at 8 weeks of age, once a week for 5 wk (total = 50 mg). At 28 months after injection, 4% of the animals had tumours; 2 of 102 (2.5%) rats injected intraperitoneally with saline had malignant tumours in the abdominal cavity. No significant increase in peritoneal tumours was observed (Pott *et al*, 1987, 1989).

Carbon fibres

The one study on intraperitoneal injection of "carbon dust" cannot be interpreted as far as RFP are concerned since it could not be ascertained whether the material was fibrous or particulate or both (Styles and Wilson, 1973).

Others

Rosenbruch *et al*, (1992) found fibre aggregation and foreign body reactions, but no significant increase in abdominal tumours, after intraperitoneal administration of cellulose, PAN and PVA fibres in rats. The PAN was milled to a median diameter and length of 2.5 and 34 μm respectively. The PVA could not be prepared in this fashion and was retained at its original median diameter of 16 μm and microtome-cut to a median length of 90 μm. The size of the cellulose fibres was not stated but described as non-respirable aggregates. These aggregates and the PVA fibres which were non-respirable and outside the range believed to present a carcinogenic hazard, induced a slight increased (statistically non-significant) number of mesotheliomas, whereas the PAN did not.

4.3.3 Intratracheal Instillation

Carbon fibres

Fedyakina (1984) found an initial inflammatory reaction, moderate cytotoxicity and a moderate fibrogenicity of dust from carbon fibres derived from polyacrylonitrile and hydrated cellulose.

Troitskaya *et al*, (1984; abstract only) stated that dust from polyacrylonitrile-derived carbon fibres was several-fold less fibrogenic than chrysotile.

Intratracheal instillation in rats of dust particles derived from machining different types of carbon (and glass) fibre containing composites led to moderate inflammatory and fibrogenic reactions, depending on the type of carbon fibre (Luchtel *et al*, 1989).

However, there is no information available on the RFP content of the material in any of these studies.

p-Aramid fibres

Reinhardt (1980) briefly described a study of intratracheal administration of *p*-aramid polymer 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 decreased over time.

Polyolefin fibres

According to IPCS (1993), the only intratracheal study with polyolefins was inadequate for evaluation.

4.4 CONCLUSIONS

Currently used solubility studies are inappropriate for most MMOF. studies with cell cultures are extremely useful for mechanistic work, but are not yet suitable for screening purposes, mainly because the finding of length-dependent cytotoxicity and the lack of a negative fibre control. The number of *in-vitro* studies with MMOF-RFP is limited and does not allow any conclusions.

In vivo intracavitary studies (intraperitoneal, intrapleural) are considered by some researchers as good indicators of a carcinogenic hazard, but their significance for human risk assessment is disputed. Their applicability for MMOF is doubtful. The few intraperitoneal studies done with p-aramid RFP gave ambiguous results.

Intratracheal studies suffer from several shortcomings due to the non-physiological dosing method. Intratracheal studies have not been done with MMO-RFP.

Inhalation studies are considered to be most appropriate for hazard identification despite objections related to cost, sensitivity and interspecies differences. The results of inhalation studies with MMOF-RFP indicate considerable differences in biological behaviour, compared to mineral RFP.

5. MECHANISMS OF TOXICITY

Virtually all of the information currently available regarding the mechanisms of fibre toxicity have been derived from the experience with asbestos and man-made mineral fibres, more correctly called man-made vitreous fibres (MMVF). Whether the toxic activity and the mechanisms of toxicity of organic RFP are similar or identical to those of inorganic RFP, remains to be determined. However, due to the differences in chemistry and physico-chemical characteristics between the two general fibre-types, it is quite likely that significant differences will be found.

In the absence of adequate data on the toxicity and the mechanisms of toxicity of organic RFP, the following discussion is limited to mechanisms known to be applicable to asbestos and/or MMVF (with the exception of biodegradability of *p*-aramids). These mechanisms may or may not be applicable to RFP of MMOFs.

5.1 RFP DIMENSIONS

It is widely accepted that RFP dimensions are an important factor in influencing the pathogenesis of asbestos- and MMVF-related lung disease. This was first established in studies of carcinogenesis using the intrapleural and peritoneal injection routes (Pott *et al*, 1980; Stanton *et al*, 1981).

Wright and Kuschner (1977) reported that intratracheal instillation of "long" samples of size-separated MMVFs and asbestos produced pulmonary fibrosis, while shorter samples produced no significant effects. The finding that, in a one-year inhalation study, rats developed lung tumours and fibrosis after exposure to long (>20 μm) but not short (<5 μm) amosite and chrysotile RFP supports these conclusions (Davis and Jones, 1988). In addition, toxicological studies suggest that inhalation of silicon carbide fibrils and whiskers could pose a serious health risk (Birchall *et al*, 1988; Bogoroch and Luck, 1988, Lapin *et al*, 1991) while non-fibrous silicon carbide particulates appeared to have few adverse effects on the lungs of exposed animals and silicon carbide dust was considered to be a nuisance dust (ACGIH, 1988).

RFP from MMOF, as distinct from those from MMVF, can be quite irregular in their dimensions and have a strong tendency to aggregate, both in air and in liquid. Differentiation, sizing and counting is therefore sometimes impossible.

5.2 FIBRE DEPOSITION AND TRANSLOCATION

5.2.1 Deposition

Fibre inhalation and deposition are the initial events that can lead to fibre-related lung disease. Fibre size and geometry (specifically aerodynamic diameter) are the major determinants of fibre distribution within the lung. Fibres having an AED greater than 12 μm for humans and 6 μm for rodents are generally considered to be nonrespirable, i.e, large numbers are not likely to reach the gas exchange regions of the lung, (respiratory bronchioles and alveoli) (Schlesinger, 1985). Fibres with physical diameters less than or equal to 3 μm are considered respirable, even with lengths as great as 100-200 μm (Timbrell, 1965, 1983). Fibre deposition occurs mainly by impaction, sedimentation and interception. Little is known about the possible role of electrostatic precipitation and diffusion in fibre deposition (Lippmann, 1988). Impaction and sedimentation are governed by the AED of fibres. Impaction is favoured by a high flow velocity and occurs in the larger airways. In contrast, sedimentation is favoured by low flow velocity, long residence time and small airway size. The likelihood of interception increases with fibre length (Timbrell, 1965). The early pathogenesis of fibre-induced lung diseases is probably determined to a large extent by the initial pattern of fibre deposition in the pulmonary tree. It is generally considered that, in humans, the larger bronchial airway bifurcations are the preferred sites of particle deposition and it is here that bronchial cancer is often found (Lippmann, 1988). Little is known about the deposition sites at the alveolar level in humans. However, it has been demonstrated that inhaled fibres and particulates small enough to pass through the conducting airways of rodents, deposit primarily at alveolar duct bifurcations, perhaps as a consequence of air flow characteristics (Brody and Roe, 1983; Warheit and Hartsky, 1990). Alveolar deposition has been shown to decrease rapidly with increasing fibre length and aerodynamic diameter; this is in conformity with the increase in the proportion of tracheobronchial deposition with increasing fibre lengths (Morgan *et al*, 1980; Morgan and Holmes, 1984).

5.2.2 Translocation

Translocation refers to the movement of intact fibres after their initial deposition. Fibres may translocate to foci at the respiratory bronchioles, onto the ciliated epithelium at the terminal bronchioles, or into and through the epithelium to interstitial storage sites, along lymphatic drainage pathways or to the pleura. Fibres can also migrate from the initial deposition sites to the lung periphery and to other tissues distant from the lungs. The pathways and processes involved in most of these translocations are poorly understood.

5.3 FIBRE BIOPERSISTENCE/BIODEGRADABILITY

Fibre biopersistence can be defined as the period of fibre retention in the lung or in other tissues. Biopersistence may be influenced by the number of fibres present, their dimensions, surface characteristics, chemical composition, surface area and other factors. Differences in any of these could alter fibre toxicity. Biodegradability refers to the breakdown and/or dissolution of fibres within the lung or other tissues; mechanical, chemical and/or enzymatic factors may be involved (Muhle *et al*, 1991). Fibres can be eliminated from the lung by clearance involving macrophage uptake and transport to the mucociliary escalator or by dissolution. *In vivo* lung instillation experiments have demonstrated that short segments of MMVF are more readily removed from the lungs by macrophages and mucociliary clearance than are longer fibres (Morgan and Holmes, 1984).

The biopersistence of a fibre in the lung is dependent upon the site and rate of deposition, as well as rates of translocation, clearance, dissolution and biomodification of the fibre in the lung. *In vivo* dissolution of glass fibres has been shown to depend on fibre dimension and composition.

Long asbestos fibres are selectively retained in the lungs of exposed rats. Chrysotile fibres progressively split into thinner fibrils, whereas crocidolite does not show reduction in diameter (Roggli and Brody, 1984). These findings have been confirmed by Bellmann *et al* (1986, 1987), in a two-year intratracheal instillation/fibre clearance study. Muhle *et al*, (1991) confirmed these findings for crocidolite in an intratracheal installation study in which he also found clearance halftimes of around 11 days for wollastonite and 38 to 238 days for a range of glass samples.

The results of these studies suggest that long and biopersistent fibres, e.g. amosite, crocidolite and, to a lesser extent, chrysotile, are the ones which have a tendency to produce severe pulmonary effects.

p-Aramid RFP quickly break into shorter fragments (<5 µm), which are then slowly removed from the lung (Warheit *et al*, 1992). This process is considerably slower after high exposures than after low exposures (Kelly *et al*, 1993). This may indicate that the breakdown process is macrophage-mediated, as this is slowed down in overload situations (See section 5.5).

Polyolefin RFP showed a marked relationship between occurrence of segmentation and partial transverse breaks on the one hand, and exposure duration, concentration and length of post exposure period on the other. The duration of the study (max. 90 days exposure, 30 days recovery) (Hesterberg, 1992) may have been too short to demonstrate the fragmentation that was found 180 days after subcutaneous injection (Waitzova *et al*, 1986).

5.4 SURFACE CHEMISTRY

Several aspects of surface chemistry have been implicated as contributing to mineral fibre toxicity, including the presence of atoms or ions with unsaturated valences or impaired charges (especially on fresh surfaces), polar surfaces, electrical vacancies, exposed cations and anions, and the presence of transition metals that participate in redox-reactions and the formation of active oxygen species (Fubini, 1993). Some of these factors are obviously not applicable to MMOF and this may well be one of the crucial differences between them and mineral fibres.

The surface characteristics of MMOF are complex and related to the usage of the end product and may differ considerably (see 2.2). Most MMOF have a distinct skin and cove structure which may result in differences between the Form-off RFP and the base material.

5.5 PARTICLE OVERLOAD

The term "particle overload" was introduced to describe the situation in which particles (including RFP) accumulate in the lungs of experimental animals. Under such circumstances the particle half-time in the lung increases substantially (and may exceed the life of the animal), resulting in lung burdens far in excess of expectations based upon low-dose experiments. Under such circumstances, effects are seen that, to a large extent, are species-specific but not specific for the tested materials.

Particle overload has been documented following long-term inhalation of excessively high concentrations of nuisance dusts, e.g., TiO_2, carbon black or toner particles. Morrow (1988) has summarized the findings of several studies performed in rats that involved the deposition of high burdens of particles; common observations include abnormal dust accumulation, chronic pulmonary inflammation, increased lung weights, epithelial cell proliferation, hyperplasia and metaplasia, pulmonary fibrosis and the development of cystic lesions or epithelial tumours.

Evidence increasingly points to a disturbance in the transmigration of particle-containing alveolar macrophages from the alveoli up the conducting airways as the underlying cause of the diminution in lung clearance rate. There is evidence that progressive immobilisation of the rat macrophages is related to the total volume of phagocytozed particles (Oberdörster *et al*, 1992).

With RFP, the alveolar clearance diminishes at much lower particle counts and total phagocytised volume than with non-fibrous particles of the same material (Muhle, personal communication).

The importance of this phenomenon is that the effects on the lungs observed at overload concentrations are not relevant to lower exposure levels and may be considered non-specific. Therefore they are not necessarily relevant to the assessment of risks to humans exposed to the concentrations of particles or fibres found in home or workplace, where overload does not occur.

5.6 INTERSPECIES, INTERSTRAIN AND GENDER DIFFERENCES

5.6.1 General Species Differences

Rodent species are commonly used in particle or fibre inhalation toxicity studies designed to simulate human exposures and to evaluate lung responses to inhaled dusts. However, important anatomical and physiological differences exist between common experimental animals and humans that may influence particle or fibre deposition and corresponding lung clearance responses.

Anatomical differences

Human lungs have a symmetrical dichotomous airway branching pattern that favours concentrated deposition of dusts and fibres on branch points or bifurcations; rodents exhibit a highly asymmetric, monopodial branching pattern that should reduce the tendency for concentrated areas of deposition. The distal airways of human lungs contain several generations of nonrespiratory bronchioles and three generations each of respiratory bronchioles and alveolar ducts. In contrast, respiratory bronchioles are poorly developed in guinea pigs and hamsters and are generally absent in mice and rats (Warheit 1989 (a)). As a consequence, fibres tend to deposit on alveolar duct bifurcations in rodents, whereas in humans they concentrate on the final respiratory duct bifurcation (Brody and Roe, 1983). Moreover, it has been shown that the development of early asbestos-induced lesions occurs at sites of initial fibre deposition (Warheit *et al*, 1984, Brody *et al*, 1984).

Another possibly important difference between humans and rodents is that rodents are obligate nasal breathers, whereas humans may favour oral breathing while speaking or during exercise, thus permitting enhanced particle penetration to the lungs (Warheit, 1989).

Particle deposition

There are marked differences between species with respect to particle deposition, e.g. the maximum size of inhaled particles in rodents is somewhat smaller than in humans, as is the size of the particles deposited in the alveoli (Schlesinger, 1985). Most of these differences are due to the above mentioned

anatomical and respiratory differences, which also lead to differences between humans and rodents in preferential deposition sites for RFP (Craighead *et al*, 1982).

The retention of particles in the various points of the respiratory tract does not vary very much between species, although as body weight increases, the dose per unit bodyweight decreases (Palm *et al*, 1956, MacMahon *et al*, 1977, Raabe *et al*, 1977). However, the guinea-pig shows markedly lower alveolar deposition in comparison to other rodents (Warheit and Hartsky, 1989, Warheit and Hartsky, 1990).

Particle clearance

A variety of mechanisms are associated with the removal of particles from the respiratory tract:

- clearance by the tracheobronchial mucociliary escalator or nasal mucus flow to the throat and expectoration or swallowing. Transport from the deeper lung regions towards the tracheobronchial mucociliary escalator is a slow, macrophage-mediated process that may be less effective by an order of magnitude in humans and large animal species than in rodents (Kreyling,1990);

- some particles may translocate to the interstititum and/or lymphatics. The size of particles, their solubility and locus of deposition influence their solution rate and interaction with lung fluids; interspecies differences have not been studied;

- phagocytosis by macrophages. Inflammatory responses, mediated by macrophages and other leucocytes may influence the acute and final degree of damage. It has been demonstrated that there are large differences between rodent species in macrophage response to chemotactic factors and phagocytic activity (Warheit *et al* 1988, Warheit, 1989). This corresponds to clear interspecies differences *in vivo* with regard to alveolar macrophage activity and phagocytosis, and to interspecies differences in the cellular inflammatory responses (Warheit *et al,* 1994b). Which species best simulates the human response remains to be determined.

5.6.2 Species Differences in Incidences of Lung Tumours and Mesotheliomas

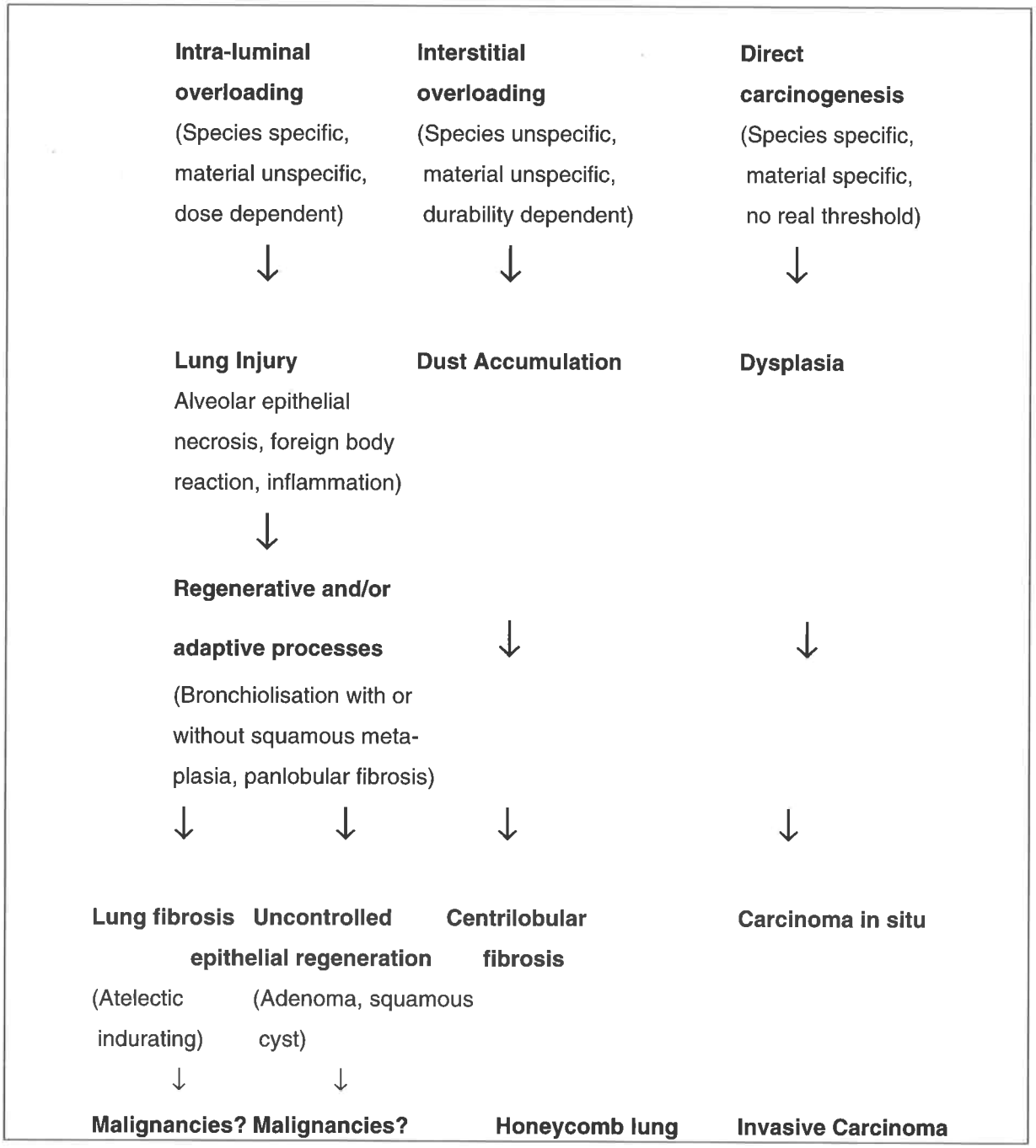
Rats readily develop lung tumours or keratin cysts in response to chronic inhalation of certain materials, but mice and hamsters are much more resistant (Heinrich *et al,* 1986; Mauderly *et al*, 1987). Schultz (in press) described various processes in the rat lung leading to fibrosis and tumour formation, and indicated which are species-specific (Figure 3).

Hamsters are relatively resistant to the formation of lung tumours but appear to be more sensitive than rats to the development of mesotheliomas (Lee *et al*, 1981, Hesterberg *et al*, 1991a, 1991b). Davis *et al*

(1986, 1988), and Wagner *et al* (1974, 1985) have conducted studies which demonstrate the lung tumorigenic and mesotheliogenic responses of rats to inhaled asbestos or erionite.

To summarize these studies, clear interspecies differences have been demonstrated in lung tumour and mesothelioma development in animals chronically exposed to particles or fibres by inhalation. Rats appear to be a reasonable model for assessing lung tumorigenic and mesotheliogenic responses in humans in that chronically exposed rats develop tumour types most of which have been also observed in humans (e.g. adenomas and carcinomas). Proliferative keratin cysts (PKC) do not occur in humans and they may be a response to excessive dust concentrations that is unique to the rat. Interpretation of lung tumour responses in chronically-exposed mice are difficult because of the high incidences of spontaneous tumours in most strains. Hamsters appear to be resistant to the development of lung tumours but are extremely sensitive to the induction of mesotheliomas following exposures to certain fibre-types. Because chronic fibre inhalation studies have been conducted in hamsters with few appropriate reference materials, it is difficult to determine whether the hamster is a relevant model for humans.

Figure 3: Pathogenesis in the rat lung



5.6.3 Strain Variations

Strain variations have not been demonstrated with RFP so far. This subject may need attention in the future, because differences in pulmonary responses between rat strains have been demonstrated in

Sprague-Dawley (CD) derived and Fisher 344 rats, exposed to non-fibrous silica particulates. The available data suggest a quantitative rather than qualitative difference in the pulmonary responses of CD and F344 rats, at least to crystalline silica (Gavett *et al*, 1992, Warheit and Hartsky, 1994).

5.6.4 Gender-Related Differences in Incidence of Tumours and Keratin Cysts

In many studies, female rats have developed a higher incidence of lung tumours than their male counterparts. This was demonstrated with antimony trioxide (Groth *et al,* 1986), volcanic ash (Wehner *et al,* 1986) and talc (NTP, 1992). However, it should be noted that the incidence of pulmonary fibrosis was not different in female and male rats, and that chronic inhalation studies on other particulate substances have shown an equivalent incidence of lung tumours in exposed male and female rats e.g., diesel exhaust particles (Mauderly *et al*, 1987).

Cystic keratinizing squamous cell lesions were also found predominantly in female rats in chronic inhalation studies with TiO_2 (Lee *et al*, 1986a) and with *p*-aramid RFP (Lee *et al*, 1988).

In summary, gender may not be a predisposing factor to the development of particle-induced pulmonary fibrosis following chronic inhalation exposure. The data reviewed here support the contention that chronically-exposed female rats have a higher incidence than males of pulmonary tumours or keratin cysts. It has been suggested that this may merely be due to the greater longevity of female rats. While both male and female rats should be evaluated in future chronic inhalation studies on particles or fibres, the consequences for human risk assessment are still uncertain.

5.7 INFLAMMATION AND FIBROGENESIS

Inhalation of fibres can cause an inflammatory response characterized by cell injury, increased lung epithelial permeability and an influx of inflammatory cells (neutrophils, monocytes, and lymphocytes). An association exists between inflammation and the development of pulmonary fibrosis. The conclusion has been reached earlier that inflammation and the release of inflammatory mediators are necessary, but not always sufficient, for the development of fibrosis (Crouch, 1990). Whether inflammation is a prerequisite for the development of fibre-induced pulmonary fibrosis has not been studied in sufficient detail.

The role of oxygen radicals in asbestos-induced inflammation and pulmonary fibrosis has recently been investigated by chronic administration of antioxidants to asbestos-exposed rats (Mossman *et al*, 1990). The results support a possible role of oxygen radicals in asbestos-induced lung injury.

Growth factors have been implicated in several studies of the progression of fibre-induced pulmonary fibrosis and described in numerous reviews. Briefly, it has been shown that competence factors, such as platelet-derived growth factor (PDGF) and fibronectin, as well as progression factors such as interleukin (IL-1) and insulin-like growth factor (IGF), play critical roles in the progression of cells through the cell cycle. Competence factors allow cells to respond to other growth factors (progression factors) which initiate DNA synthesis and mitosis. Alveolar macrophages synthesize and secrete at least six different growth factors for fibroblasts, including IL-1, tumour necrosis factor-a (TNF-α), IL-6, fibroblast growth factor (FGF), PDGF, and transforming growth factor-ß (TGF-ß) (Kovacs 1991).

Asbestos fibres were shown to stimulate production of a PDGF homologue by alveolar macrophages which is mitogenic for rat lung fibroblasts (Kumar *et al*, 1988). PDGF is the classical competence factor for fibroblasts (Goldstein and Fine, 1986). In addition, AM-derived PDGF is chemotactic for fibroblasts (Osornio-Vargas *et al*, 1991). Lavaged cells are also capable of releasing progression factors for fibroblasts (Rom *et al*, 1988; Lemaire *et al*, 1986). This release coincides with the development of histopathological changes. Progression of fibrotic lung disease depends on production of connective proteins as well as increased mesenchymal cell proliferation. The TGF, which is secreted by alveolar macrophages and induces fibroblast proliferation, was also shown to increase elastin production by neonatal lung fibroblasts (McGowan and McNamer, 1990).

5.8 MECHANISMS OF MINERAL FIBRE CARCINOGENESIS

A working model for the mechanism of RFP pathogenicity has recently been described by Hesterberg (1993b).

The basis of this model is phagocytosis of RFP by macrophages; short RFP are then removed via the mucociliary elevator, biodegradable RFP are broken down and removed in a similar fashion[5] . Long, biopersistent RFP are only partly phagocytosed, and some of the subsequent events could initiate or promote tumorigenesis:

- The macrophage, that is unable to degrade or remove the long RFP, continues to release mediators, and when eventually killed, releases its toxic lysosomal contents, mediators and RFP, thus starting a new cycle of injury and repair (Rom *et al*, 1991).

[5] The breakdown of long RFP into smaller fragments could easily lead to a substantial localized increase in the number of small fibres, which could then lead to the overload phenomena as described for non-fibrous particulates. This hypothesis might explain the findings in the paramid inhalation study of Lee *et al* (1988).

- Cell proliferation in the lung (Brody *et al*, 1989) could result from compensatory replacement of cells killed by fibres or from stimulatory mediators released by phagocytic cells. Elevated cell proliferation increases the opportunities for errors to occur in DNA replication which might lead to oncogenic transformation. Increased rates of cell proliferation could also limit the efficiency of the cells to repair DNA damage induced by other chemical or physical mutagens, and could be one explanation for the co-carcinogenic effect of asbestos and cigarette smoking observed in man.

- A decrease might occur in the surveillance and killer cell activity of the overtaxed immune system engaged in attacking the nondegradable fibres. This process in turn could result in a failure to detect and destroy transformed cells.

Carcinogenesis could also result from direct fibre-induced changes in genetic material, including clastogenesis and alterations in chromosome number. For example, asbestos was shown to result in neoplastic transformation in cultured SHE cells (Hesterberg and Barrett, 1984), rat mesothelial cells (Jaurand *et al*, 1991) and human mesothelial cells (Lechner *et al*, 1985). According to this hypothesis long, durable fibres, which cannot be cleared from the lung, are ingested by cells and accumulate in the perinuclear region.

- DNA damage may be induced in both resting and dividing cells by reactive oxidants (OH-radicals and others) formed on the fibre surface (Pezerat *et al*, 1989) or by clastogenic factors produced by the host cell. Alternatively or additionally, reactive oxidants such as superoxide and nitric oxide may be released by other cells involved in the inflammatory process (Mossman *et al*, 1989; Oshima and Bartsch, 1994).

- In the dividing cell, ingested fibres could mechanically or chemically disrupt the microtubules of the mitotic spindle, causing abnormal migration of the chromosomes during anaphase.

- Chromosomes could also be broken or prevented from migrating by becoming adsorbed onto the fibre surface.

Different mechanisms may apply to different target tissues within the whole animal. For example, inflammatory mediators and fibrosis may enhance the genesis of epithelial tumours of the lung airways, whereas direct genotoxic mechanisms may apply to mesothelial tumours originating in the pleura.

The majority of the epithelial cells lining the airways might not be vulnerable to the direct genotoxic effects of fibres because these cells appear to be programmed to differentiate terminally.

Although the basal epithelial layer capable of transformation may be not directly accessible, fibres could be brought into contact by translocation or mechanical penetration.

5.9 CONCLUSIONS

Dimensions and biopersistence are critical, but are not the only factors in the development of pulmonary disease due to inhaled mineral RFP. The direct chain of events leading to fibrosis and cancer after exposure to mineral RFP has not been fully described. Many factors have been identified that may greatly modify the final outcome; some are material-specific, others species (and/or gender) specific.

For MMOF-RFP there are even less data with regard to mechanisms of toxicity. Differences between males and females have been observed in rats exposed to RFP derived from p-aramid. It remains to be established which of the factors summarized above (and to what extent are applicable to MMOF-RFP, as well as to what extent animal data apply to the human hazard assessment.

6. FINAL CONCLUSIONS AND FUTURE PERSPECTIVES

6.1 FINAL CONCLUSIONS

1. Both experimental and environmental monitoring data indicate that most if not all MMOF have a limited tendency to form RFP. Preliminary exposure data indicate that although minute amounts of MMOF-RFP can be found everywhere in the indoor environment, the concentrations are so low that this should not cause serious concern.

2. There are insufficient epidemiological data to indicate that MMOF-derived RFP constitute a health risk to humans. The paucity of morbidity reports after more than 40 years of large-scale production indicate that there is no reason for immediate concern. If the presently available exposure data are correct, prospective epidemiological research among synthetic fibre workers is unlikely ever to correlate any observations to MMOF-derived RFP exposure unambiguously, because the current industrial exposure appears to be no higher than background levels. Retrospective research is hardly feasible in this respect, because no quantitative historical exposure data are available.

3. The available toxicology data suggest that the hazard, if any, of MMOF-RFP, is different both qualitatively and quantitatively from that of mineral fibres.
   Differences between MMOF and mineral fibres include solubility, vulnerability to enzymatic attack, chemical composition, surface chemistry; electrostatic charging and shape of RFP. Consequently the behaviour in biological systems is likely to be totally different, as has already been demonstrated with e.g. intraperitoneal and inhalation tests with *p*-aramid RFP. Indeed, all toxicological test systems, currently used for screening and/or classification of mineral RFP would need validation and evaluation of their relevance for MMOF-RFP, before any extrapolation of test results could be made.

4. Should toxicity testing be deemed necessary, the huge number of different MMOFs would necessitate the use of a tiered approach to toxicity testing. Unfortunately, use of an *in vitro* test screening battery is not yet feasible. Currently, the most sensible approach would be to use a combination of *in vitro* tests for cytotoxicity and genotoxicity together with acute inhalation, subchronic inhalation and bio-degradability studies.

5. To avoid waste of valuable resources, it seems reasonable and justified to await further confirmation of the exposure data, and to limit further research on toxic hazards to those fibres which prove to have a more than trivial exposure potential.

6. Finally, the data currently available are insufficient to justify the classification of MMOF for carcinogenicity or to justify the establishment of a specific OEL, other than by the existing regulations on nuisance dust (perhaps with the exception of the well-studied p-aramids, although there is considerable debate over the interpretation of the available data).

6.2 FUTURE PERSPECTIVES

As can be judged from the "Final Conclusions", there seems to be no urgent need to address the toxicology of MMOF-RFP. However, if regulatory pressure so requires, the following topics should be addressed:

1. There is a need to extend the database on the exposure potential of MMOF. Concurrently, there is a need to validate monitoring techniques and counting methods, in view of the differences in physical behaviour and morphology, as compared to mineral of MMVF-derived RFP.

2. If and when toxicity testing is considered, methods will have to be developed to generate sufficient numbers of RFP from various MMOF. Physical and chemical properties of these RFP must be similar to those found in the environment to which man is exposed. The influence of surface additives and trace elements needs consideration.

3. There is a need for morbidity and mortality studies in the MMOF-industry to confirm (or not) the absence of relevant health risks. In view of the combined effects of smoking and mineral fibres, special attention must be given to smoking in such studies. As noted above, however, such studies are unlikely to be of great help in the risk assessment of MMOF-derived RFP because of the lack of adequate control populations.

4. More information is needed with respect to surface activity, the role of surface chemistry, the influence of chemical composition and to study differences between artificially prepared RFP and "naturally" occurring RFP in the working and living environment. studies are well suited for this type of research. Before *in vitro* tests can be used for screening purposes, a fibre negative dust must be found. Biodegradable synthetic fibres may be useful in this respect.

5. More insights in the mechanisms of toxicity of RFP, the role of lung overload and biodegradability is required in order to compare the MMOF-derived RFP with mineral RFP with known toxicity. Short-term inhalation studies with extended follow-up periods (as described in 4.2.2) are suited for this type

of research. For the biodegradability issue, solutions will have to found for the digestion of lung tissue without digesting the organic RFP as well. Enzymatic digestion may be a solution (IOM, 1993).

DOCUMENTATION

The Task Force consulted and used selected references from textbooks, reviews the proceedings of conferences and workshops in which one or more of the Members participated, and computerized database searches. Additional references were taken from the literature as mentioned above, or from the personal knowledge of the authors. All published and unpublished documents cited in this document are available to interested readers.

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Database searches were performed using DIMDI (Köln, Germany) for acces.
The following databases were combined (in brackets the start date of the time period covered by these databases, the end-date being dependent on the dates of the various searches):
TOXBIO (01.01.1973)
TOXCAS (01.01.1965)
TOXLINE (01.01.1965)
IPA (01.01.1970)
EMBASE (01.01.74)
MEDLINE (01.01.66)

Searches were done by creating a profile using the keywords "fibre ?" or "fiber ?" or "textile". References on morbidity and mortality were found by adding the keyword "human", "occupational", "mortality, "morbidity" or "epidemiology" to the profile. Toxicological references were found by adding the keyword "toxi?" or "canc?" or "carc?" to the profile. studies were found by adding "" or "cell culture" to the profile. Dedicated searches were done using the keywords "aramid?" and "carbon fib?". References found in this manner were manually selected on the basis of the contents, as judged by the abstract, and the selected original papers were obtained.

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