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# Toxicology of Man-Made Organic Fibres (MMOF)

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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<br>IgG | Immunoglobulin E<br>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**

## Natural Fibres

**Plant Fibres**
(Cotton, Flax, Hemp, Jute)

**Animal Fibres**
(Wool, Camel hair, Angora, Silk)

**Mineral Fibres**
(Asbestos, Non-asbestos)

## (Semi-)Synthetic Fibres

**Natural Polymer Based**
(Regenerated cellulose, Viscose rayon, Cuporcellulose, Cellulose acetate, Cellulose triacetate)

**Inorganic Material Based**
(Glass fibres, Mineral fibres, Ceramic fibres, Metallic 'whiskers')

## Synthetic Polymer Fibres

**Polymerized polymers based**
(Polyethylene, Polypropylene, Polyacrylonitrile, Polyvinylchloride)

**Condensation Polymers based**
(Polyamide, Polyester, Polyimide)

**Addition Polymers based**
(Polyurethane, Elastomer)

## 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):

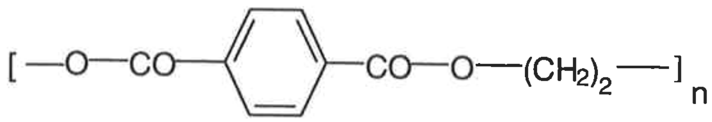
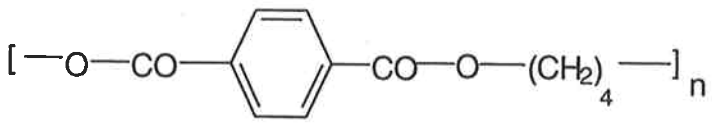
$$\text{Length} > 5\mu m,\ \text{Diameter} < 3\mu m,\ \text{Length/Diameter} > 3$$

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

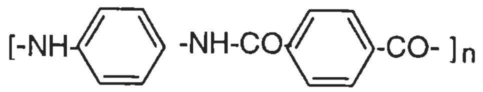
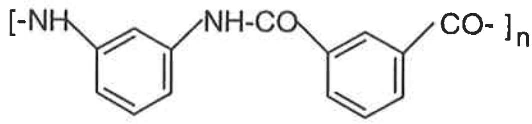
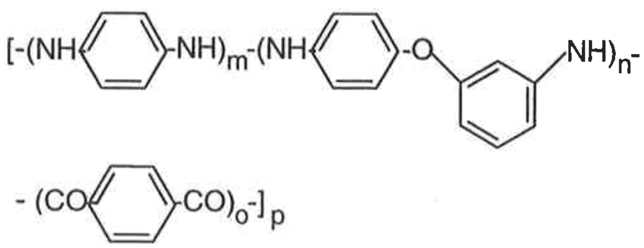
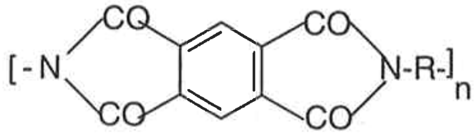
Synthetic polymers and semi-synthetic polymers have been created in nearly endless variations and modifications and many have been used to produce MMOFs. Table 1 (pages 8 and 9) lists some of the major types of fibre-forming materials.

**Table 1: Some Polymers for Synthetic Fibres ***

| POLYMER TYPE | REPEATING UNIT | TRADE NAME |
|---|---|---|
| | **Polyolefin** | |
| **Polyethylene** | $[-CH_2-CH_2-]_n$ | Trofil<br>Spectra |
| **Polypropylene** | $[-CH(CH_3)-CH_2-]_n$ | Herculon |
| | **Polyvinyl** | |
| **Polyacrylonitril** | $[-CH(CN)-CH_2-]_n$ | Dralon |
| **Polyvinylchloride** | $[-CH(Cl)-CH_2-]_n$ | Fibravyl<br>Leavil |
| **Polyvinylalcohol** | $[-CH(OH)-CH_2-]_n$ | Kuralon |
| | **Polyester** | |
| **Polyethyleneterephthalate** |  | Trevira<br>Diolen |
| **Polybutyleneterephthalate** |  | |

* 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** | $[-NH-CO-(CH_2)_5-]_n$ | Perlon |
| **PA6.6** | $[-NH-CO-(CH_2)_4-CO-NH-(CH_2)_6-]_n$ | Nylon (Generic name) |
| **PA11** | $[-NH-CO-(CH_2)_{10}-]_n$ | Rilsan |
| **Fully Aromatic Polyamide** | | |
| **Poly(p-phenylene-terephthalamide)** |   | Kevlar Twaron |
| **Poly(m-phenylene-isophthalamide)** |   | Nomex |
| **Copoly(p-phenylene-diphenylethertere-phthalamide)** |   | Technora |
| **Others** | | |
| **Elastane** | $[-NH-R_1-NH-CO-O-R_2-O-CO-]_n$ | Lycra Dorlastan |
| **Polyimide** |   | |