WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS
ON THE
EVALUATION OF CARCINOGENIC RISK
OF CHEMICALS TO MAN

Asbestos

VOLUME 14

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER
LYON
1977

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EVALUATION OF THE CARCINOGENIC RISK

OF CHEMICALS TO MAN:

Asbestos

Volume 14

This publication represents the views of an
IARC Working Group on the
Evaluation of the Carcinogenic Risk of Chemicals to Man
which met in Lyon,
14-17 December 1976

IARC WORKING GROUP ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN: ASBESTOS

Lyon, 14-17 December 1976

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Note to the reader

Every effort is made to present the monographs as accurately as possible without unduly delaying their publication. Nevertheless, mistakes have occurred and are still likely to occur. In the interest of all users of these monographs, readers are requested to communicate any errors observed to the Unit of Chemical Carcinogenesis of the International Agency for Research on Cancer, Lyon, France, in order that these can be included in corrigenda which will appear in subsequent volumes.

Since the monographs are not intended to be a review of the literature and contain only data considered relevant by the Working Group, it is not possible for the reader to determine whether a certain study was considered or not. However, research workers who are aware of important published data that may change the evaluation are requested to make them available to the above-mentioned address, in order that they can be considered for a possible re-evaluation by a future Working Group.

CONTENTS

INTRODUCTION

For a general introduction to the IARC programme on the Evaluation of the Carcinogenic Risk of Chemicals to Man, the reader is referred to the preamble given in other recent volumes of the IARC monographs, which describes the working procedures and criteria adopted by such Working Groups.

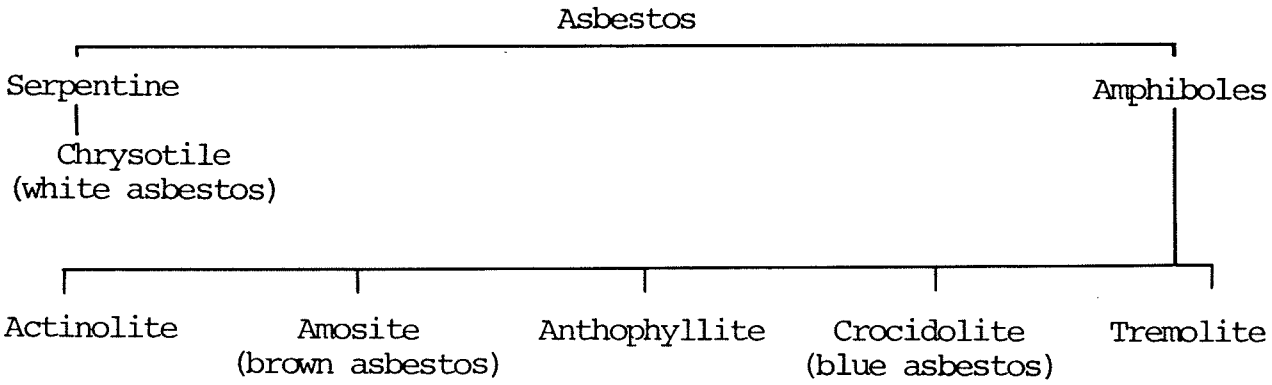
In this volume several changes in the usual layout of the monographs have been made; namely, data which concern asbestosis and the occurrence of asbestos fibres in human tissues, which would normally have been considered in section 3.2, 'Other relevant biological data', have been considered in separate sections after the epidemiological studies. Section 4, 'Comments on Data Reported and Evaluation', is given in a unified form, without separating animal from human data.

ASBESTOS

Asbestos was previously evaluated in October 1972 (IARC, 1973). Since that time new published data became available which were considered by a Working Group especially convened in 1975. The present Working Group has made a final evaluation of all available data published or accepted for publication up to December 1976.

1. Chemical and Physical Data

Asbestos is the generic name used for a group of naturally occurring mineral silicate fibres of the serpentine and amphibole series. Government agencies in various countries, and industrial groups, currently characterize six fibrous silicates as 'asbestos' (Speil & Leineweber, 1969; US Department of Labor, 1975): the fibrous serpentine mineral chrysotile and the fibrous amphiboles actinolite, amosite, anthophyllite, crocidolite and tremolite.



Current usage of the term asbestos is restricted to these specific silicates, although there are many minerals with fibrous crystal habits that occur naturally. These latter mineral species, however, either do not possess such properties traditionally ascribed to asbestos as, for instance, heat stability, thermal and electrical insulation, the ability to be woven, stability in acids or alkalis, or do not occur in sufficient concentrations for exploitation. The original definition of the word asbestos is derived from the Greek, 'incombustible'.

1.1 Synonyms and trade names

Chem. Abstr. Reg. Serial No.:	1332-21-4	Asbestos fibre
		Asbestos
	12001-29-5	Chrysotile
		Serpentine; 7-45 asbestos;
		Avibest C; Cassiar AK;
		Calidria RG 144;
		Calidria RG 600
	17068-78-9	Anthophyllite
		Azbolen asbestos
		Ferroanthophyllite
	13768-00-8	Actinolite
	12172-73-5	Amosite
		Mysorite
	12001-28-4	Crocidolite
	14567-73-8	Tremolite
		Silicic acid, calcium magnesium salt (8:4)

1.2 Chemical and physical characteristics

(a) Chrysotile

(i) Atomic structure: On the basis of powder diffraction and single crystal X-ray crystallographic studies and transmission electron microscopic and selected area electron diffraction investigations, chrysotile has been shown to be a curled sheet silicate, spiralled as a helix around a central capillary (Clifton *et al.*, 1966; Huggins & Shell, 1965; Jagodzinski & Kunze, 1954a,b; Kalousec & Muttart, 1957; Pundsack, 1956; Whittaker, 1963a; Yada, 1967; Zussman *et al.*, 1957).

Chrysotile is the fibrous member of the serpentine mineral group, possessing a rolled trioctahedral clay structure; it is the magnesium analogue of kaolinite (Deer *et al.*, 1962). Half of chrysotile sheet silicate is composed of planar-linked silica tetrahedra in a pseudo-hexagonal arrangement. Here, all three oxygens at the base of the tetrahedra are shared in a common plane. All unshared apical oxygens in this

sheet 'point' in a single direction, above the plane, towards an adjoining 'brucite' layer, which is composed of magnesium ions coordinated octahedrally with oxygen and hydroxyl groups. Two of the three apical oxygens in the tetrahedral sheet replace hydroxyl groups to form the brucite layer. The complete, single chrysotile structure consists of a 1:1 sheet structure of silica and brucite, joined by shared tetrahedral apices. The distance between adjacent composite sheets is in the order of 7.3 nm, with symmetry element repeat every two sheets, or 14.6 nm. The dimensions of the brucite sheet (5.4 nm x 9.3 nm) and the silica tetrahedral sheet (5.0 nm x 8.7 nm) indicate that these basic units are structurally mismatched. There are several mechanisms by which the sheets may 'change' in size so that they will 'fit' over each other: (1) the bonds may stretch to fit, producing a misshapen molecular arrangement; (2) smaller ions may enter the octahedral brucite group, or larger ions may enter the tetrahedral silica group, thereby decreasing or increasing the respective sheet sizes; or (3) the structure may be warped, with the larger brucite sheet curling over the smaller 'tridymite' sheet. The latter mechanism (3) appears to be the dominant method of structural accommodation for chrysotile, although the presence of trace metals and marked disorder along specific crystallographic directions suggest that other factors account for some of such accommodation.

The curvature of chrysotile, its misshapen bond angles and resultant charge distribution produce a structure that may be considered to be unstable. A comparison of the stability of the different serpentine mineral forms (Nagy & Bates, 1952) clearly demonstrates this.

The charge on the surface of chrysotile in an aqueous medium is controlled by the hydroxyl groups surrounding the magnesium ion. Because of the adsorption of hydrogen ions at the surface, a net positive charge is produced (Speil & Leineweber, 1969). The surface is commonly hydrophilic, so that particles of chrysotile form a stable suspension in water (Pundsack, 1956, 1961).

(ii) Chrysotile crystal polytypes: Curving of chrysotile most commonly occurs around the a axis, i.e., the hollow fibre tube axis parallels crystallographic a, forming a girdle of c axes. The structure

of chrysotile is complicated by the different ways in which the composite sheets are stacked. If adjacent sheets are stacked so that magnesium hydroxyl groups are offset in the same direction and successive sheets have the same brucite configuration, the resulting symmetry belongs to the monoclinic system, and the mineral species is termed 'clinochrysotile'. However, stacking of sheets may reverse so that the net displacement is effectively cancelled. This results in an orthorhombic symmetry. This mineral species is called '*ortho*-chrysotile'. Another species of fibre, '*para*-chrysotile', is characterized on the basis of its tubular development parallel to the *b* crystallographic axis. This variety occurs only rarely.

Some investigators indicate that electron diffraction patterns of chrysotile fibres yield fibre patterns of both *ortho*- and clinochrysotiles; i.e., natural chrysotiles are commonly mixtures of polytypes. However, single fibrils appear to be of either one structural type or the other, and single individual fibrils with mixed characteristics have not been observed (Zussman *et al.*, 1957).

(iii) Fibrils and fibres: Electron micrographs show that single chrysotile fibrils are hollow tubes (Clifton *et al.*, 1966; Langer & Pooley, 1973; Langer *et al.*, 1974; Maser *et al.*, 1960; Yada, 1967). Some of these micrographs suggest that there are channels between individual fibrils as well as internal capillaries. The internal capillaries of chrysotile have been studies and their dimensional characteristics recorded: these range from 20-130 nm (Badollet, 1948; Langer & Pooley, 1973; Langer *et al.*, 1974; Maser *et al.*, 1960; Pundsack, 1961; Whittaker, 1963a; Yada, 1967, 1971). Outer fibril dimensions of up to 600 nm (usually 200-300 nm) in width have been reported (Whittaker, 1963a). Some authors have suggested that chrysotile fibril dimensions are different in different geological localities, e.g., Canadian fibrils tend to be larger than South African varieties. Fibril growth appears to be related to the process of crystallization and to both the chemical and physical environment (Bates, 1959; Bates *et al.*, 1950; Jagodzinski & Kunze, 1954a,b; Kalousec & Muttart, 1957). A more recent paper (Yada, 1967) has demonstrated that within a single mineral

specimen the capillary and fibril widths may vary significantly, and the presence of chrysotile fibrils without the central capillary has been demonstrated. Chrysotile fibrils may develop as both 'cone-in-cone' concentric cylinders and as progressive rolled sheet helices spiralling around a central capillary.

(iv) Chemistry

Major oxides: The ideal crystal chemical formula for chrysotile is : $X_6\ (Si_4O_{10})(OH,O,F,Cl)_8$. X represents octahedrally coordinated cations of the brucite layer. Magnesium most commonly occupies this position up to the available 6.00 sites, although iron, nickel and manganese may be present at up to several tenths of a percent (Table 1). The Si position represents the tetrahedrally coordinated cation of the silica layer and is almost entirely filled by silicon to the hypothetical 4.00 site vacancy. Rarely, aluminium may be present in the structure; the hydroxyl group may in rare instances be replaced by oxygen, fluorine or chlorine. All substitutions are related to original rock type, provenance and conditions of growth.

The chemical composition of chrysotile is uniform in comparison to that of the amphibole asbestos minerals. A comparison of the empirical composition of chrysotile with that of naturally occurring fibres indicates that the latter tend to be 'dirty': some trace oxides are always present. The high Fe^{2+} and Fe^{3+} contents usually result from contamination by magnetite, which is a ubiquitous accompanying mineral phase when the serpentinized rock is an ultramafic type. Calcium oxide reflects serpentine deposits originating from a silicified dolomite.

Minor and trace elements in chrysotile: Ni, Cr and Co have been identified in trace amounts within chrysotile deposits derived from ultramafic (serpentine) bodies (Table 1). Iron is also ubiquitous. Occasionally, other trace metals are observed, but their presence tends to reflect that of trace mineral phases associated with the fibre. For example, high iron content in Canadian fibres may reflect the presence of both ferrian nemalite and/or magnetite (Liebling & Langer, 1972). The substitution of nickel and iron for magnesium in chrysotile is

Table 1

Chemical composition of chrysotile (%)

Oxide	On basis of $Mg_6Si_4O_{10}(OH)_8$	Canadian (avg.) (Gaze, 1965)	Shabani, So.Afr. (avg.) (Harington, 1965)	Chrysotile (avg.)[a]
SiO_2	43.35	40.3	39.15	41.8-42.0
Al_2O_3		0.7	2.15	0.1- 0.5
Fe_2O_3		1.5	1.18	0.2- 1.3
FeO		1.0	1.33	0.1- 1.6
MgO	43.66	42.4	40.32	41.8-42.8
CaO		0.2	1.09	0 - 0.1
Na_2O			0.09	0 - trace
K_2O			0.15	0 - 0.1
SO_3				0 - 0.1
CO_2		0.2	0.41	0 - trace
$+H_2O$	12.99	13.7	13.09	13.6-14.0
	100.00	100.0	98.96	

Common trace metals detected:

chromium (follows MgFe) - up to 1000 µg/g fibre
cobalt (follows Fe) - up to 1000 µg/g fibre
nickel (follows Mg) - up to 5000 µg/g fibre

[a] Aboutville, N.Y. (Kalousec & Muttart, 1957); Danville, Quebec (Pundsack, 1956; Pundsack & Reimschussel, 1956); Transvaal, South Africa (Brindley & Zussman, 1957); Gila, Arizona (Nagy & Faust, 1956)

commonplace in deposits derived from ultramafic rock types (Langer *et al.*, 1972a,b; Morgan & Holmes, 1970; Morgan *et al.*, 1975). Such deposits provide the bulk of chrysotile fibre to the world market.

(v) Impurities

Common mineral impurities associated with chrysotile: There are a large number of rock types which may be presursors of, or associated with, serpentine bodies. These include dunite, dolomite, gabbro, hornblendite (amphibolite), norite, peridotite, picrites and pyroxenite (Deer *et al.*, 1962; Johansen, 1937). Alteration of these rocks to serpentine, accompanied by the formation of lizardite, antigorite and chrysotile, may also include the survival of pre-existing mineral phases. Rock-forming minerals such as olivine and pyroxene may survive the alteration process and contaminate the final mineral fibre. Occasionally, nemalite, tremolite, anthophyllite and a number of other fibrous mineral phases may be associated with the serpentine body. Ore minerals, e.g., niccolite (nickel arsenide), cobaltite (cobalt arsenide sulphide), arsenopyrite (iron sulphide arsenide), chromite (chromium oxide) or magnetite (iron oxide) may often be present in quantities sufficient to form exploitable mineral deposits. Geological literature is replete with reports of the association of such ore deposits with a serpentinized host rock. Therefore, chemical and mineralogical data may suggest not only elemental substitutions within the chrysotile structure but more commonly associated trace mineral phases as well.

Chrysotile fibre that has originated from serpentinized dolomites is often contaminated with the carbonate mineral, calcite (Deer *et al.*, 1962; Diller, 1919; Huggins & Shell, 1965). As with the chrysotile fibre originating from ultramafic rock types, the number of associated contaminant phases in carbonate rocks is high. Several papers have listed common minerals and metals associated with chrysotile (e.g., Diller, 1919). Common analytical techniques, generally X-ray diffraction, have been used to demonstrate these various mineral associations (Badollet & Gantt, 1965). As in the case of trace metal analysis, trace mineral phases closely follow geological rock type.

The quantities of trace mineral impurities in chrysotile appear to range considerably (Speil & Leineweber, 1969). When present, their particle sizes tend to be extremely small, in the order of a few hundred microns and less (Badollet & Edgerton, 1961). Chrysotiles derived from serpentized dolomites tend to have calcite intergrowths of a size similar to that of magnetite.

Occasionally, the chrysotile fibril itself may contain quantities of amorphous material that is of chrysotile composition but not necessarily of the same molecular proportions. For example, it has been noted that the progressive leaching of chrysotile with distilled water may yield what appears to be the mineral phase *alpha*-sepiolite (Hargreaves & Taylor, 1946).

Hydrocarbon traces : Adsorption of hydrocarbons onto the chrysotile surface has been documented (Harington, 1965; Harington & Roe, 1965). Natural organic contamination is far less common in chrysotile than in crocidolite and amosite, but contamination during industrial fabrication is apparently more widespread than previously thought. Storage of fibre in various containers is one such source of hydrocarbon contamination (Commins & Gibbs, 1969).

Impurities added during preparation: Occasionally, impurities such as nickel-steel fragments are added to the product during the processing of chrysotile asbestos. These are apparently the result of abrasion of machinery by the mineral impurities. The amounts of such steel particles are generally small (Ayer & Lynch, 1967; Badollet, 1952). Hammer milling may increase considerably the nickel, chromium, cobalt and iron content (Badollet & Edgerton, 1961).

(vi) Harsh and soft chrysotiles : It has been recognized on the basis of field observation that the serpentine mineral chrysotile occurs naturally with a range of physical properties. There appear to be differences in the relative flexibility of chrysotile fibres derived from different geological localities; these have been termed 'harsh' and 'soft' fibres (Speil & Leineweber, 1969).

The relative flexibility and 'feel' of the fibre bundle has been used to distinguish between these types (Dana & Ford, 1957). Although the terms 'harsh' and 'soft' have been applied to certain fibre types to suggest extreme characteristics, fibres generally occur as gradations between these mineral end-types (Badollet, 1948). Occasionally, fibre bundles are observed that do not flex readily, that possess characteristics of harsh fibre types, but that are not truly harsh. These tend to be fibre bundles of chrysotile intergrown intimately with mineral impurities. For example, Canadian fibre tends to possess intergrowths of magnetite and nemalite parallel to the fibre axis. Although these fibres appear to be harsh in the hand specimen, removal of the fibres from the mineral matrix produces a soft flexible mineral species. A summary of recognized properties of these fibre types is given in Table 2.

The nature of the fibre bundle and the mechanical ease of reducing such fibres to individual fibrils are directly related to the relative degree of harshness or softness. Soft fibres tend to break open easily, producing a large surface area, which permits leaching of magnesium from the exposed fibre surfaces, increasing solution conductivity (Table 2). The relative degree of fibril disorientation may be measured by variations in selected area electron diffraction patterns (Langer *et al.*, 1974).

(vii) Other properties: The chemical stability of chrysotile is limited. When it is in contact with dilute acids or even with solutions at pH of less than 10.8, magnesium tends to be removed from the fibre surface (Hargreaves & Taylor, 1946). On a comparative basis, the stability of chrysotile is generally much less than that of the other serpentine minerals (Nagy & Bates, 1952). Magnesium loss *in vivo* has been demonstrated by both electron microprobe analysis of fibres in tissues and by studies of neutron-activated fibres released in laboratory animals (Langer *et al.*, 1972a,b: Morgan & Holmes, 1970; Morgan *et al.*, 1975). Chemical degradation is accompanied by physical degradation as well (Jaurand *et al.*, 1976).

Table 2

Characteristics of soft and harsh chrysotile

Property	Soft fibre	Harsh fibre	Reference
FIBRE BUNDLE			
Feel	Smooth, silky	Harsh, splintery	Badollet, 1948
Tenacity (flexibility)	Flexible, may be bent to > 90° without rupture	Stiff, ruptures at < 90°	Badollet, 1948
Size reduction (length)	Poor, resists fibre axis break	Good, easily broken across fibre axis	Badollet, 1948
Fibrilization of bundle	Excellent to good, easily opened	Poor, tends to remain in tight bundles	Badollet, 1948
Surface area (equal amount of materials identically size-reduced)	Average Canadian sample: 23 m^2/g; some as high as 30 m^2/g	Average harsh : 11 m^2/g; some as low as 4 m^2/g	Badollet & Streib, 1955
INDIVIDUAL FIBRILS			
Appearance under electron microscope	Fibrous, thin filaments moderately translucent	Lath-like, electron-dense bundles	Badollet, 1952; Bates, 1958; Zussman *et al.*, 1957
Individual fibrils	Empty to partially-filled capillary	Filled capillaries	Zussman *et al.*, 1957
Electron diffraction pattern	Arced reflections, disordered inter-fibril relationships	Single round or streaked reflections, ordered inter-fibril relationships	Badollet, 1952; Zussman *et al.*, 1957
PHYSICAL PROPERTIES (BULK SAMPLE)			
Porosity	High	Low	Badollet, 1948;
Filter rates	Slow	Fast	Badollet, 1948 Badollet & Streib, 1955
Filtrate clarity	Clear	Cloudy	Badollet, 1948
Conductivity (2.9% suspension)	Average Arizona soft: 22.2 $ohms^{-1}cm^{-1}$ ($x10^5$)	Average Arizona harsh: 11.9 $ohms^{-1}cm^{-1}$ ($x10^5$)	Pundsack & Reimschussel, 1956
Mg leach (% NaCl equivalent)	0.27	0.10	Pundsack & Reimschussel, 1956
CHEMICAL PROPERTIES (BULK SAMPLE)			
Structural water (dry weight)	12.5-14.5%	11.0-12.5%	Badollet & Streib, 1955
CaO content	Trace to nil (Arizona soft)	Trace to minor oxide (Arizona harsh)	Diller, 1919; Pundsack & Reimschussel, 1956
Al_2O_3 content	Trace to minor oxide (Arizona soft)	Trace to nil (Arizona harsh)	Diller, 1919

The physical stability of chrysotile is also limited. Chrysotile appears to lose its crystalline character when its size is reduced beyond a certain range. This can be observed after chrysotile is ball-milled for periods of more than 60 seconds (Langer *et al.*, 1977). These structural changes can be followed by means of X-ray diffraction and infra-red spectrographic and other techniques. Mechanical energy first breaks the physically weak chemical bonds; chrysotile is initially disrupted along the stacking direction, as indicated by a loss of the (*h*0*l*) reflections (Brindley & Zussman, 1957).

This is of particular importance in terms of interpreting biological data in which animal experimentation is carried out using materials which have been ball-milled for size reduction. It has been shown that ball-milling results in decreased haemolytic activity and in the activation of free radicals on chrysotile surfaces (Langer *et al.*, 1977).

A range in the densities of natural chrysotile fibres has been observed: values for Arizona chrysotiles, derived from serpentized dolomites, have been reported to be between 2.19 and 2.25 g/ml (Huggins & Shell, 1965); the density of chrysotile from Canada has been shown to be approximately 2.56 g/ml (Kalousec & Muttart, 1957; Pundsack, 1956). These reported ranges in density of chrysotile have been attributed both to mineral impurities and to the presence of magnesium silicate material that 'stuffs' the central capillaries and fibril interstices in the fibre bundle.

Chrysotile has also been shown to possess paramagnetic properties, which can be used to produce alignment of fibres for counting and sizing (Timbrell, 1975).

(viii) The wide geological distribution of serpentine rocks; chrysotile as a contaminant: Chrysotile asbestos is mined as a non-metallic ore; however, the mineral itself is far more widespread than previously thought. For example, serpentine belts are associated with nearly every major mountain chain axis around the world (Hess, 1955), and serpentine is a common host rock for some ore deposits (Bateman, 1959). It has been shown that naturally occurring serpentine

consists of mixtures of chrysotile and of antigorite (Nagy & Faust, 1956) and the platy phase lizardite (Brindley & Zussman, 1957). Therefore, exposure to chrysotile may come from a variety of rock types in which chrysotile itself is not being mined as such. A number of fibrous minerals may be interdispersed with or associated with chrysotile, for example, amphibole asbestos varieties (Table 3) (Langer *et al.*, 1971; Pooley, 1976).

Table 3

Synonyms for serpentine-like rocks, alteration products and minerals that may contain or be associated with chrysotile

Rocks	Minerals (Faust & Fahey, 1962)	
serpentine	antigorite	meerschaum
vermiculite	antillite	metaxite
talc	aquacreptite	neolite
	baltimorite	ophicalcite
	bastite	picrolite
	bowenite	picrosmine
	dermatite	porcellophite
	deweylite	pyknotrope
	hydrophite	retinalite
	jenkinsite	schweizerite
	lizardite	termophyllite
	marmolite	williamsite

(b) Amphibole asbestos minerals

The amphibole asbestos minerals are each as complex as chrysotile. The following descriptions are offered as an outline, and a table is provided for direct comparison of the different mineral species (Table 4).

(i) Atomic structure: The amphibole minerals are structurally inosilicates, double-chains, cross-linked with bridging cations. The structure is formed by co-planar sharing of two of three oxygens at the base of the silica tetrahedra, which extends as a single chain along an infinite axis. The double chain is completed by the third oxygen, which is shared between two tetrahedra of opposite, facing chains. These units form the asbestos fibre axis (Deer *et al.*, 1967; Ernst, 1968; Whittaker, 1960, 1963b).

Table 4

Amphibole minerals directly or possibly related to asbestos

Asbestos type	Asbestiform-related mineral
actinolite-tremolite	ferroactinolite garnierite hexagonite richterite tirodite
anthophyllite	ferroanthophyllite ferrogedrite gedrite
crocidolite	crossite glaucophane magnesioriebeckite riebeckite
amosite	cummingtonite grunerite kupfferite montasite

The different amphibole asbestos fibres possess this basic structure, with small modifications brought about by chemical variation. Cation substitutions within the amphibole structure modify interplanar spacings and the stacking angle of chain units, referred to as the *beta* angle. This angle forms the inclined plane of monoclinic structures. Unit cell dimensions and *beta* angles are obtainable from any number of reference sources (Deer *et al.*, 1967; Whittaker, 1960, 1963b). A review of such properties, e.g., space group symmetry, is given in Table 5.

(ii) Chemistry: The complexity of the amphibole asbestos minerals can be illustrated by a brief and general description of amphibole crystal chemistry. There are several general chemical structural formulae used for all amphibole minerals: $(WXY)_{7-8}\ (Z_4O_{11})_2\ (O,OH,F)_2$ (Mason, 1958) or, more frequently, $W_{0-1}\ X_2\ Y_5\ (Si_4O_{11})_2\ (O,OH,F)_2$ (Ernst, 1968). The cations WXY correspond to the structural sites A, M_1, M_2, M_3 and M_4. Some confusion generally arises from the description of the chemistry of

Table 5

Mineral relationships and common substitutions of the amphibole asbestos types

Asbestos fibre	Related mineral system	General chemical formula	Crystal system & space group	Cation in M4 site	Common cation substitution and resulting mineral
anthophyllite	anthophyllite-gedrite	$(FeMg_6)Si_8O_{22}(OH)_2$	orthorhombic Pnma	Mg±Fe	Mg ⇌ Fe ferroanthophyllite (Mg,Fe)Si ⇌ Al,Al gedrite (Mg,Si) ⇌ (Al,Al) gedrite (Mg,Si) ⇌ (Fe,Al) ferrogedrite
amosite	grunerite-cummingtonite	$(Fe_6Mg)Si_8O_{22}(OH)_2$	monoclinic C2/M	Fe±Mg	Fe ⇌ Mg magnesio-grunerite cummingtonite Fe ⇌ Mn mangano-grunerite mangano-cummingtonite
actinolite-tremolite	actinolite-tremolite	$Ca_2(MgFe_6)Si_8O_{22}(OH)_2$ $Ca_2(Mg_6Fe)Si_8O_{22}(OH)_2$	monoclinic C2/M monoclinic C2/M	Ca Ca	Fe ⇌ Mg complete gradation: ferroactinolite-tremolite Fe ⇌ Mn tirodite
crocidolite	riebeckite-glaucophane	$Na(Fe_2^{3+}Fe_3^{2+})Si_8O_{22}(OH)_2$	monoclinic C2/M	Na	Fe^{3+} ⇌ Al Fe^{2+} ⇌ Mg complete gradation: riebeckite-glaucophone

crystals in terms of structural accommodations of cations. The interchanged notation for structural and chemical symbols would be expressed as : $(A)_{0-1}$ $(M_4\ M_4)$ $(M_1\ M_1\ M_2\ M_2\ M_3)$ $(Si_4O_{11})_2$ $(O,OH,F)_2$. Therefore, chemistry and structure are interdependent and related to factors such as cation size and valence (Table 6).

Basically, the amphibole minerals consist of chain structures, with nine structural sites that may accommodate cations. Any change in ratios of these different cations would change the mineral species. However, for the different asbestos types, there appears to be limited substitution in terms of chemical species and of their locations in the structure (Table 5).

Anthophyllite: Anthophyllite is considered to be an orthorhombic magnesium-iron amphibole with possible aluminium substitution. This mineral species forms a partial solid solution with the mineral gedrite, an aluminium-rich fibre of similar properties (Table 5).

Amosite: Amosite is an exploited variety of grunerite. As part of the grunerite-cummingtonite solid solution series, amosite tends to occur with more iron than magnesium in its structure. Manganese substitution may occur in concentrations of up to 4% by oxide weight (Table 5).

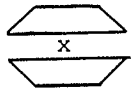
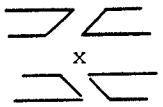
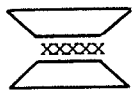
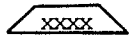
Actinolite and tremolite: Actinolite and tremolite appear to form a solid solution series, representing end-members of that mineral group (Deer *et al.*, 1967). Both mineral species possess calcium in the M_4 structural site, with complete iron-magnesium gradations in the M_1 through M_3 valence sites. Occasionally, manganese substitutes for iron (Table 5).

Crocidolite: Crocidolite is the exploited form of the rock-forming amphibole mineral riebeckite. Riebeckite may change chemically with replacement of Fe^{2+} for magnesium and Fe^{3+} for aluminium (Table 5). For example, magnesio-riebeckite is mined as crocidolite in Bolivia (Speil & Leineweber, 1969).

The chemical contents of the amphibole asbestos types are given in Table 7.

Table 6

Chemical and structural notations for the amphiboles

Cation site	Structural notation[a]	Cation coordination	Number of site cations in unit cell	Change of cation	Location in structure	Common elements
W	A[b]	10 - 12 FCN	1	+ to ++	back of 2 opposed chains 	Na, X, Li Ca
X	M4	6 - 8 FCN	2	+ to ++	edge of 4 adjacent chains 	Na, K Ca, Mn, Fe, Mg
Y	M_1, M_2, M_3	6 FCN	5	++ to +++	front of 2 facing chains 	Fe, Mg, Ti Fe, Al[c]
Z	Si_I, Si_{II}	4 FCN	4	+++ to ++++	forming single chain unit 	Al[d] Si

[a] Ordering of size of sites: $M_4 > M_3 > M_2 > M_1$

[b] A-sites frequently vacant; if $M_4 > 2$, A-site is filled (Whittaker, 1960)

[c] Y-sites can also be filled by Mn, Cr, Li, Zn

[d] Al substitutes for Si at up to 1 in 4

Table 7

Chemical range of the asbestos types[a]

	Amosite	Anthophyllite	Crocidolite	Actinolite	Tremolite
SiO_2	49-53	56-58	49-53	51-56	55-60
Al_2O_3	-	0.5-1.5	0-0.2	1.5-3	0-2.5
Fe_2O_3	-	-	17-20	0-3	0-0.5
FeO	34-44	3-12	13-20	5-15	0-4
MgO	1-7	28-34	0-3	15-20	21-26
CaO	-	-	0.3-2.7	10-12	11-13
Na_2O	trace	-	4-8.5	0.5-1.5	0-1.5
K_2O	0-0.4	-	0-0.4	0-0.5	0-0.6
H_2O	2.5-4.5	1-6	2.5-4.5	1.5-2.5	0.5-2.5
Common trace elements Ag, Ba, Ce, Co, Cr, Cu, Li, Mn, Mo, Nb, Ni, Sc, Sr, Th, V, Zr					

[a] Based on superior analyses of Museum quality representative fibres

(iii) Minerals similar to the amphibole asbestos types: Because of the complexity of the structure of the amphiboles and the wide range of possible cation substitutions in terms of size and valence, it is important to note that a number of minerals should be regarded as akin to asbestos types. Table 4 includes a partial list of rock-forming minerals which may form fibres that possess properties similar to those of amphibole asbestos types occurring in exploited areas.

(iv) Physical properties: The biological activity of the amphibole asbestos types is possibly related to physical properties as well as to chemical properties. The wide variation in chemical structure of the amphibole varieties suggests that biological activity is not restricted to any one chemical variety (Langer *et al.*, 1974; Pooley *et al.*, 1970; Timbrell *et al.*, 1970). For example, crocidolite tends to form thinner

fibres than amosite; in general, amosite tends to form thinner fibres than anthophyllite. Diameter is the determining factor in the ability of a fibre to penetrate the lung airways.

The surface charges of all of the amphibole asbestos fibres are negative in aqueous media (Prasad & Pooley, 1973). The magnitude of the surface charge is different for each of the different fibre types. Stability in alkaline and acid environments also varies considerably and has been studied in detail (Speil & Leineweber, 1969).

The earth's crust, a complex of multiple rock types, is composed primarily of silicate minerals (Wahlstrom, 1956). Although the physical and chemical natures of these rocks vary greatly (Poldervaart, 1955), perhaps only six mineral groups constitute the 'rock-forming assemblage' (Wahlstrom, 1956), classified on the basis of their atomic structures and chemistry. It is of great importance to note that chrysotile, the asbestos fibre used most widely throughout North America, is not considered to be an 'abundant' mineral phase. Rather, almost 8% of the earth's crust is composed of amphiboles (Wahlstrom, 1956). Since most of the asbestos fibre types are members of that mineral class, this fact is of particular importance. Asbestos terminology is not commonly used to describe the rock-forming counterpart; therefore, one might suspect that many mining areas of the world represent sources of potential asbestos exposure and disease because of their content of these fibrous gangue minerals (see section 3.4c).

2. Production, Use, Occurrence and Detection

2.1 Production and use

Asbestos has been used intermittently in small amounts for thousands of years. Modern industrial use dates from about 1880, when the Quebec chrysotile fields began to be exploited (Hendry, 1965; Hueper, 1965). During the next 50 years there were gradual increases in production and use: a cumulative total of somewhat less than 5000 million kg had been mined by 1930.

World production has accelerated over the past four decades (Table 8); for example, world mine production increased by 50% between 1964 and 1973. In the latter year, the two major producing countries were Canada (sales were 1790 million kg) and the USSR (estimated production, 1280 million kg); other countries with significant mine production were the Republic of South Africa, Rhodesia, the People's Republic of China, Italy and the USA (US Bureau of Mines, 1975).

Table 8

World production of asbestos

Year	World production (million kg)	% Canada	% USSR
1960[1]	2 210	45	29
1970[2,3]	3 490	44	30
1973[2]	4 093	41	31
1974[2]	4 115	40	33
1975[4]	4 560	23	48
1976[4]	5 178	29	44

[1] From May, 1965
[2] From Clifton, 1974
[3] From Clifton, 1972
[4] From Fagan, 1976

Most asbestos is used in the construction industry, in general, accounting for two thirds of the usage. Over 3000 uses of asbestos have been identified (Rosato, 1959); important uses include asbestos cement

sheets and pipes, insulation materials, taping compounds and floor and ceiling tiles (Hueper, 1965) (see also Table 9). The asbestos content of a product is not necessarily an indication of its relative health risk, for in many products the fibres are tightly bound to the matrix or are encapsulated. A potential health risk arises when asbestos fibres are set free, e.g., during the drilling or sawing of asbestos cement sheets.

Friction materials constitute an important class of asbestos materials. These include not only clutch facings and brakes for cars, lorries, railway carriages and aeroplanes but also braking materials widely used in industry for machinery. Asbestos-containing gaskets are also often used.

Insulation materials often contain asbestos. Asbestos materials have been applied in blocks, or pipe-sections, or as asbestos cement, or sprayed on in compounds which often contain rock wool, binders and other agents. Sprayed asbestos materials are used for decorative and acoustic purposes, as well as for the fireproofing of structural elements in buildings.

An extraordinary variety of other uses of asbestos are known, ranging from papier maché materials used by school children and fireproof clothing and gloves to fillers for plastics. Such uses may be found to have considerable impact in terms of public health terms, since large numbers of people may be exposed. The same perspective may be valid in considering end-product use of asbestos materials, especially in the construction industry or in ship-building and ship repair. A single insulation worker, cutting asbestos block or mixing asbestos cement, may cause the exposure of many other workers roundabout, e.g., electricians, plumbers, masons, bricklayers, sweepers and others. The importance of such 'bystander' exposure has been emphasized by the observations of Harries (1976) and Skidmore & Jones (1975).

Tremolite is not at present exploited as an asbestos mineral in its own right. Materials that include tremolite as a major component are, however, produced in many parts of the world. These include many

Table 9[a]

Asbestos distribution by end use, grade and type in the US, 1974

(million kg)

	Chrysotile	Crocidolite	Amosite	Anthophyllite	Total
Asbestos cement pipe	168	33	0.9	0.18	202
Asbestos cement sheet	82		3.9		86
Flooring products	139				139
Roofing products	66		1.5		67
Packing & gaskets	26	0.09			26
Insulation, thermal	6.6		1.6		8
Insulation, electrical	4.2				4
Friction products	72			0.18	72
Coatings and compounds	34				34
Plastics	15	0.18		0.63	16
Textiles	18				18
Paper	57	0.18			57
Other	33	0.36	0.45		34
Total					763

[a] From Clifton, 1974

industrial powders referred to as talcs or tremolitic talcs (Pooley & Rowlands, 1977; Rohl *et al.*, 1975).

Anthophyllite is a talc-like form of asbestos; it is used as an industrial talc and in paper-processing, plastic products, asbestos cement pipes and friction materials (Clifton, 1974). Other uses are described by Rosato (1959).

Known commercially exploited deposits

Chrysotile: The largest commercial deposits of this mineral are in the USSR and Canada. It is also mined in the People's Republic of China, Cyprus, Italy, southern Africa and the USA. Recently, an open-pit mine has begun production in Australia. In the past, small amounts were mined in Corsica (Boutin *et al.*, 1976).

Crocidolite: Most of this fibre comes from the north-western Cape and Transvaal areas of South Africa. In the past, small amounts were mined in Western Australia (Wittenoom Gorge) and Bolivia (Chichabamba).

Amosite: Transvaal, South Africa, is the main source of this type of fibre. An identical fibre has been found in India and will be produced under the name of mysorite.

Anthophyllite: This form of asbestos was exploited in Finland until 1974; smaller quantities are found in a number of other countries. It is a common contaminant of talc deposits in the US (Kleinfeld *et al.*, 1974; Pooley & Rowlands, 1977; Rohl *et al.*, 1975).

Tremolite: Some limited mining of tremolite fibres was carried out in the US and in the Far East. The fibre now exists primarily as a natural contaminant in other exploited materials, e.g., talc (Kleinfeld *et al.*, 1974; Pooley & Rowlands, 1977; Rohl *et al.*, 1975).

2.2 Occurrence

The occurrence of asbestos in the general or occupational environment has been reported in various units of measurement; in workplaces, air units include million particles per cubic foot (mppcf) or, more recently, number of fibres > 5 µm per ml and million fibres per m^3;

in ambient air samples, values are generally recorded on a gravimetric basis, e.g., ng/m^3.

It would be desirable to have a conversion factor in order to relate ambient asbestos levels to occupational levels; however, attempts to formulate such a conversion factor have generally been unsuccessful because of large variability (NIOSH, 1977). This is to be expected, as ambient levels are generally determined by transmission electron microscopy, whereas phase contrast optical microscopy is used to measure occupational exposures. In addition, techniques used to prepare samples for electron microscopic observation may cause alterations in fibre size (diameter and length) distributions. However, the direct transfer technique may overcome these difficulties (Sebastien *et al.*, 1976a).

Measurements of asbestos in fluids, including water, beverages, etc., have been expressed as fibres per ml, fibres per l or ng per g of sample. For more details concerning the problems in detecting asbestos, see section 2.3.

(a) Asbestos in the general environment

Air: Concentrations not exceeding 100 ng/m^3, and usually less than 10 ng/m^3, asbestos fibres are present in the general urban atmosphere (Holt & Young, 1973; Nicholson & Pundsack, 1973; Sebastien & Bignon, 1974; Sebastien *et al.*, 1976a; Selikoff *et al.*, 1972a). However, concentrations of 10-5000 ng/m^3 asbestos fibres have been reported near some factories using asbestos (Nicholson *et al.*, 1975; Rickards, 1973).

Contamination of the air inside buildings can occur from damage or erosion of asbestos-sprayed materials or from working with asbestos-containing materials. Nicholson *et al.* (1975) found, in 19 buildings investigated, values ranging from 2-200 ng/m^3. Sebastien *et al.* (1976a) found levels as high as 800 ng/m^3.

In an elementary school in the US with a spray-formed, domed asbestos roof, asbestos fell intermittently to leave dust on the surface of the furniture. The intake filters of the ventilation system which recirculated the school-room air were clogged with asbestos fibres, and personal samplers

on school children showed that up to 3.8 asbestos fibres greater than 5 μm in length per ml of air occurred within the school (US Department of Health, Education and Welfare, 1972a; Young, 1972).

Levels of asbestos fibre contamination in buildings appear to be related to the application process used on interior surfaces (Nicholson *et al.*, 1976). 'Dry' processes, in which no liquid is added to matrix binders, tend to deposit the insulation material as a loose 'fluff'. This material disintegrates on touch and cannot withstand the abrasion of air movement.

The lengths and diameters of asbestos fibres found inside such buildings are similar to those described by Gibbs & Hwang (1975) for fibres sampled in various work environments (Sebastien *et al.*, 1976a). In both situations, the percentage of fibres with diameters less than 0.5 μm and with lengths greater than 5 μm was about 20% for amphibole and 1% for chrysotile.

Table 10 indicates various exposure levels in the air to which the general population may be exposed.

Table 10

Examples of exposure levels in air[a]

Exposure	Asbestos concentration (ng/m^3)	
	USA	Paris
Ambient air (urban)	0.1-100	0.1-10
Buildings sprayed with asbestos	0.1-800	0.1-800
Near asbestos spraying	10-1000	-
Near asbestos factory	10-5000	10-3000

[a] From Nicholson *et al.* (1975) and Sebastian *et al.* (1976a)

The presence of asbestiform minerals in non-commercial deposits is widespread in many geological formations; the fact that fibres can be

released when the rocks are crushed provides a further source of contamination (for discussion of other fibrous minerals, see section 3.3 d). In this regard, the use of asbestos mine tailings on roads may prove to be an important hazard to the general public, and the use of asbestos-containing, quarried, crushed rock may also be a potential risk. This question was raised in a recent community survey of lung cancer (Newman *et al.*, 1976). Similarly, the use of asbestos stucco, employed as cladding for buildings, may result in environmental exposure. The incipient danger from discarded asbestos is indicated by the finding of 60-100 million asbestos fibres/m^3 in the ambient air in the vicinity of waste dumps (Harwood & Blaszak, 1974).

Water: Average concentrations of asbestos in drinking-water ranged from 0.3-1.5 µg/l as measured in eastern US river water (Nicholson & Pundsack, 1973). Levels of 2-173 million fibres/l were found in Canadian tap-water, the highest levels being found in unfiltered tap-water near a mining area (Cunningham & Pontefract, 1971).

Levels of up to 12.46 µg/l chrysotile asbestos, as determined by electron microscopy, were found in the Jumata and Connecticut rivers (American Water Works Association, 1974). A study of the Great Lakes and St Lawrence River bywaters showed average concentrations of about 1.7 million asbestos fibres/l. Locations with higher counts were found along the north shore of Lake Superior between Silver Bay and Duluth, along the St Clair River, downstream from Montreal, and in the asbestos mining district in the province of Quebec (Cook *et al.*, 1974; Zielhuis, 1977).

Food: The asbestos contents of food have not been well investigated; asbestos filters and talc, which may contain asbestos as an impurity, may be used in the manufacture of processed foods, e.g., sugar, vegetable oil, lard and coated rice (Merliss, 1971; Wolff & Oehme, 1974).

Beverages: Asbestos fibrils, considered to be chrysotile, at levels of 13-24 million fibres/l have been found in samples of one type of spirit probably filtered with asbestos filters (Wehman & Plantholt, 1974).

Biles & Emerson (1968) and Cunningham & Pontefract (1971) also reported the occurrence of asbestos fibres in British, Canadian and American beer (1-6.6 million fibres/l). Asbestos fibres were found in various sherries, ports, vermouths and soft drinks (1.7-12.2 million fibres/l) (Cunningham & Pontefract, 1971).

Pharmaceuticals: Chrysotile asbestos has been found in some samples of parenteral drugs (range, 1-1000 ng/g) (Nicholson *et al.*, 1972). In the US, no asbestos-containing or other fibre-releasing filter may be used in the manufacture, processing or packaging of such products, unless it is not possible to manufacture that drug product or component without the use of such a filter (US Food and Drug Administration, 1976).

Dental practice and dental school laboratories: Asbestos-containing periodontal packs are sometimes used after gingival surgery (Infante & Lemen, 1976). In dental schools, asbestos tape is used to hold gold that is heated and then cast into moulds during dental laboratory procedures. This may be a potential problem and has not been evaluated by adequate industrial hygiene monitoring.

(b) Asbestos in the work environment

Asbestos contamination of the air can be caused by spraying of asbestos material either for fire protection or for decorative or acoustical purposes; contamination was found to be high during the application of sprayed mineral fibre (Nicholson & Pundsack, 1973). A comparison of asbestos concentrations in air under different circumstances as measured by electron microscopy is as follows: near asbestos spraying, 10-1000 ng/m^3; during a milling operation, 10-5000 ng/m^3; in other occupational exposures, 1000-> 100,000 ng/m^3 (Nicholson *et al.*, 1975).

Fibre concentrations in various asbestos-using industries in the US prior to 1971, as determined by optical and electron microscopy, are given in Table 11.

Table 11

Concentrations of fibres in various asbestos-using industries in US before 1971[a]

Industry	Range of means (fibres > 5 μm/ml)	Range of individual samples (fibres > 5 μm/ml)
Textile	0.1-29.9	0.0-143.9
Insulation	0.1-74.4	0.0-208.4
Paper packing and asphalt production	0.2-13.6	0.0-18.9
Cement shingles, mill-board and gasket	0.1-4.4	0.0-16.6
Friction	0.1-14.4	0.1-32.4
Cement pipe	0.2-6.3	0.0-13.4

[a] From US Department of Health, Education & Welfare (1972b)

Airborne asbestos sampling programmes do not at present, however, attempt to discriminate between the various fibrous minerals present in dust samples. Table 12 gives a comparison of the length distributions of airborne asbestos fibres, as determined by electron miscroscopy, in various industries in the US.

Table 13 gives the contents of asbestos fibres, by products and fibre type, in asbestos products produced in various EEC countries.

Occupational exposure in situations other than the traditional asbestos processes (mining, milling, factory production and handling of asbestos products) has been shown to be of increasing importance. Such exposures occur during end-product use, as among asbestos insulation workers (Selikoff *et al.*, 1964), among brake repair and brake maintenance workers (Lorimer *et al.*, 1976; Rohl *et al.*, 1976, 1977), and as the result of indirect occupational exposures, particularly in ship building and ship repair (Harries, 1968, 1976), and in the construction industry. Other exposures occur in relation to inspection, repair and maintenance work on asbestos-containing structures and

Table 12

Lengths of asbestos fibres in air near various US industries [a]

Operation	Fibre type	Median length (μm)	% > 5 μm
Textile	chrysotile		
Fibre preparation & carding		1.4	4
Spinning, twisting, weaving		1.0	2
Friction	chrysotile		
Mixing		0.9	2
Finishing		0.8	2
Asbestos-cement pipe	chrysotile		
Mixing		0.9	2
Finishing		0.7	1
Pipe insulation	amosite		
Pipe forming		4.9	51

[a] From Dement *et al.* (1976)

equipment, in refineries and chemical plants, buildings, railway locomotives and wagons, shipyards and power plants. Increasingly important exposures can be expected to result from building demolition and waste disposal (US Environmental Protection Agency, 1975). These could pose a considerable problem, in view of the very large amount of asbestos now in place as the result of the cumulative use of the material during the past century. Exposures may also occur during the wearing of asbestos safety garments (Gibbs, 1975), during cleaning operations on buildings formerly sprayed with asbestos (Skidmore & Jones, 1975) and during the handling of bags formerly used in the transport and storage of raw or milled asbestos (US Department of Labor, 1975).

(c) Domestic exposure

Domestic exposure of household contacts to asbestos may occur from dusts brought home on workers' clothes, shoes, hair, equipment, etc. (Anderson *et al.*, 1976; Newhouse & Thompson, 1965; Wagner *et al.*, 1960). Nicholson *et al.* (1975) found asbestos levels ranging from 100-500 ng/m^3 in the houses of workmen.

Table 13

Asbestos products and their asbestos contents in EEC countries [a]

Product	Approx. asbestos content (% wt.)	Asbestos fibre type [b]
Asbestos-cement building products	10-15	C,A,Cr
Asbestos-cement pressure, sewage and drainage pipes	12-15	C,Cr,A
Fire-resistant insulation boards	25-40	A,C
Insulation products, including sprays	12-100	A,C,Cr
Jointings and packings	25-85	C,Cr
Friction materials	30-70	C
Textile products not included above	65-100	C,Cr
Floor tiles and sheets	5-7.5	C
Moulded plastics and battery boxes	55-70	C,Cr
Fillers and reinforcements and products made thereof (felts, millboard, paper, filter pads for wines and beers, underseals, mastics, adhesives, coatings, etc.)	25-98	C,Cr

[a] From Zielhuis (1977)

[b] A = amosite; C = chrysotile; Cr = crocidolite (not used in all EEC countries)

Other domestic exposures, also widespread, are para-occupational exposures from household repairs and do-it-yourself construction using asbestos-containing materials, such as asbestos cement sheets, plaster fillers and wall-joining compounds (Rohl *et al.*, 1975), furnace and heating equipment cements and other repair materials. Such exposures may increase as more and more householders undertake their own maintainance repairs.

2.3 Detection of asbestos

Procedures for the sampling and measurement of airborne asbestos dust by the membrane filter method have been described (Asbestosis Research Council, 1971a,b). These procedures have been evaluated in detail by the National Institute for Occupational Safety and Health (NIOSH, 1977). A report on inter-laboratory comparison of the counting of samples obtained by this method is given by Beckett & Attfield (1974).

Phase contrast-optical microscopy is used in the routine examination of dust samples because of its low cost and speed of performance. However, it can provide only an index of fibre presence and of the size and optical properties of particles that may be used to identify individual fibres. The technique is limited, since only the largest fibres in a sample can be seen, and, when employed for identification purposes, it is cumbersome and requires an expert microscopist to interpret the results.

X-ray diffraction techniques have been used to establish the presence of asbestos, but they cannot differentiate between the fibrous and non-fibrous forms of these minerals. Quantitative asbestos determination, using X-ray techniques, is complicated by the methods used for sample preparation and by the presence of minerals which may display X-ray reflections in similar positions to those of the asbestos minerals (Keenan & Lynch, 1970; Rohl & Langer, 1974; Rohl *et al.*, 1976). It also requires the preparation of standards for calibration purposes. Minimum detection levels of 2.0 % weight for anthophyllite, 0.25 % for chrysotile and 0.1 % for tremolite have been reported in talc (Rohl & Langer, 1974). The techniques require bulk samples which are not available in most environmental situations.

Differential thermal analysis has been used to determine chrysotile asbestos fibres in bulk talc samples but has not been used for environmental samples. Differential thermal analysis, like X-ray diffraction, is not capable of differentiating between asbestos fibres and their non-fibrous mineralogical polymorphs. A minimum detection

level of 1% chrysotile by weight has been reported in talc (Schelz, 1974). This level of contamination has, however, rarely been observed in natural talcs.

Both transmission and scanning electron microscopy have been used to identify and quantify asbestos fibres. The scanning electron microscope can give only morphological information, unless it is fitted with energy or wave-length dispersive X-ray spectrometers with which microchemical analysis of single particles can be performed; this technique was used by Beckett (1973). Transmission electron microscopy is a much more versatile technique, since with this method particle morphology can be accurately observed and electron diffraction patterns are displayed (NIOSH, 1977). Microchemical analysis of particles (electron microprobe analysis) can be obtained when the technique is used in conjunction with X-ray analytical equipment (Jaurand *et al.*, 1975· Langer & Pooley, 1973; Langer *et al.*, 1972a,b; Pooley, 1975). The latter technique allows the collection of morphological, structural and chemical data that allow unique identification of all single sub-microscopic fibres that occur in the environment.

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Man

3.1 Carcinogenicity and related studies in animals

(a) Oral administration

Rat: Groups of 32 Wistar SPF rats were fed 100 mg/day Italian talc or UICC Canadian chrysotile in malted milk powder on 5 days/week for 100 days over a 6-month period; 16 controls were fed only malted milk. The mean lengths of survival from the start of feeding were 614 days for those given talc, 619 days for those given chrysotile and 641 days in controls. Two gastric leiomyosarcomas were observed, 1 in an animal fed talc and the other in 1 fed chrysotile. None of these tumours occurred in the controls (Wagner *et al.*, 1977a).

Three groups of 25 male and 25 female 10-week old Wistar rats were either untreated, given 50 mg/kg bw/day asbestos filter material containing 52.6% chrysotile asbestos which was powdered and added as a water suspension to the diet, or given 50 mg/kg bw/day talc in the diet for life. In the group given asbestos filter material, the average survival time was 441 days. Among 42 animals available for study, 12 malignant tumours with metastases were found (4 kidney carcinomas, 1 lung carcinoma, 3 reticulum-cell sarcomas and 4 liver-cell carcinomas). One lung adenoma, 2 cholangiomas, 2 papillomas of the forestomach and 2 mammary fibroadenomas were also observed. In the group receiving talc in the diet, the average survival time was 649 days; among 45 rats examined, 3 liver-cell carcinomas and 4 mammary fibroadenomas were seen. In untreated controls average survival time was 702 days; 2 liver-cell carcinomas and 5 mammary fibroadenomas occurred among 49 animals. The increased incidence of malignant tumours in rats given asbestos filter material in the diet was significant compared with that in controls ($P < 0.01$) (Gibel *et al.*, 1976) [The Working Group noted that the exact composition of the asbestos filter material was not given].

(b) Inhalation

Mouse: Nordman & Sorge (1941) exposed 100 white mice to a high concentration of chrysotile dust for 72 hours. After 6 weeks, asbestos bodies and fibrosis were observed in the lungs of all mice, and after 13 weeks about 50% had hyperplasia of the epithelial cells of the lungs. Two carcinomas were seen in 10 mice surviving 240 days.

Lynch *et al.* (1957) exposed 8-week old AC/F_1 hybrid mice by inhalation to a commercial preparation of chrysotile asbestos for 8-12 hours/day on 5 days/week for 17 months. In animals killed at the end of exposure, a higher incidence of multiple pulmonary adenomas was observed in the exposed group (46%, 58/127), than in the controls (36%, 80/222) [This result is not statistically significant ($P > 0.05$)].

Rat: Gross *et al.* (1967) observed tumours of the lung in rats exposed repeatedly to a mean concentration of 86 mg/m^3 chrysotile dust for 30 hours/week. Twenty-five of 72 rats surviving for 16 months (time of appearance of first tumour) or longer developed 28 lung tumours (17 adenocarcinomas, 4 squamous-cell carcinomas and 7 fibrosarcomas), whereas no such tumours occurred in 39 controls. The authors suggested that the presence of trace metals from the hammers of the mill used to prepare the fibre was a factor in the induction of these tumours. However, this suggestion was not confirmed by subsequent experiments (Wagner *et al.*, 1974).

Reeves *et al.* (1971) found squamous-cell carcinomas of the lungs in 2 of 31 rats which survived exposure to crocidolite for 2 years at a concentration of 49 mg/m^3 for 16 hours/week. Five rats in a group of 40 exposed to chrysotile developed pulmonary adenomatosis, but no malignant tumours were observed among rats exposed to either chrysotile or amosite.

In a subsequent experiment, Reeves *et al.* (1974) exposed groups of 69 Charles River CD rats to ball-milled crocidolite, amosite and chrysotile for 4 hours/day on 4 days/week for 2 years, at mean concentrations of about 50 mg/m^3. The results are given in Table 14.

Table 14

Inhalation carcinogenesis from various forms of asbestos in rats[a]

Form of asbestos	Number of tumours
None	None
Amosite	2 pleural mesotheliomas
Crocidolite	3 squamous-cell carcinomas, 1 papillary carcinoma and 1 adenocarcinoma, all of lungs
Chrysotile	1 papillary carcinoma and 1 squamous-cell carcinoma of lungs and 1 pleural mesothelioma

[a] From Reeves *et al.* (1974)

[It is important to note that these materials were comminuted by vigorous mechanical milling (ball-milling for up to 240 hours), which undoubtedly altered the fibre properties (Langer *et al.*, 1977; Occella & Maddalon, 1963)].

Reeves (1976) produced pulmonary tumours in rats with all three major types of asbestos following exposures of 4 hours/day on 4 days/week for 6-24 months to dust prepared by hammer-milling, at mean concentrations of approximately 50 mg/m^3. Exposure to chrysotile yielded 2 lung carcinomas and a mediastinal fibrosarcoma (a 5% incidence of malignancy among surviving animals); exposure to amosite produced the same 5% incidence of malignancy (1 lung carcinoma, 1 fibrosarcoma and 1 mesothelioma); and exposure to crocidolite yielded lung carcinomas in 14%. It is interesting to note that optically visible fibre counts were 54 million/m^3, 864 million/m^3 and 1105 million/m^3 for the 3 different types of asbestos, respectively, indicating that while the atmospheric concentrations were the same in terms of weight/volume, the optical fibre counts were dissimilar.

Wagner *et al.* (1974) exposed groups of CD Wistar rats to the five UICC asbestos samples (amosite, anthophyllite, crocidolite and Rhodesian and Canadian chrysotiles) at concentrations of about 12 mg/m^3 respirable dust for 7 hours/day on 5 days/week, for several lengths of exposure:

one day (7 hours), 3 months, 6 months, 12 months or 24 months. At the end of the exposures, the amount of dust in the lungs of animals exposed to the two chrysotile samples was much less than that in animals exposed to the three amphibole samples. However, all types of fibre produced asbestosis, which was progressive after removal from the dust. Furthermore, whereas no carcinomas of the lung were found in the control group, carcinomas of the lung and mesotheliomas were demonstrated in the groups exposed to Canadian chrysotile and to the amphiboles. Only carcinomas of the lung were seen with Rhodesian chrysotile (see Table 15). An increasing incidence of neoplasms was observed with increasing exposures to each form of asbestos. Even as little as one day of exposure - providing the animals were allowed to survive and were observed - produced neoplasia (see Table 16).

Wagner *et al.* (1977a) compared rats exposed for 2 years to a pure, non-fibrous cosmetic talc with another group of rats exposed to superfine chrysotile. Similar degrees of fibrosis were found in each group, while one adenocarcinoma was found in an animal exposed to the chrysotile.

Other species: Groups of 20 rabbits, 32 guinea-pigs and 68 gerbils were exposed to about 48 mg/m^3 balled-milled crocidolite, amosite and chrysotile for 4 hours/day on 4 days/week for 18 months. No tumours were seen; however, survival times after 18 months were not reported (Reeves *et al.*, 1974).

(c) Intrapleural administration

Rat: All commercial types of asbestos have produced mesotheliomas in CD Wistar rats (Wagner *et al.*, 1973). A dose of 20 mg of the 5 UICC standard reference samples - crocidolite, amosite, anthophyllite, Canadian and Rhodesian chrysotiles - produced various numbers of mesotheliomas (Table 17) (Wagner *et al.*, 1977b).

Stanton & Wrench (1972), using a dose of 40 mg asbestos dust on gelatin-coated fibre-glass pledgets, found that 3 of the UICC samples, crocidolite, amosite and Rhodesian chrysotile, all produced mesotheliomas in about 60% of Osborne-Mendel rats. Pylev & Shabad (1973) induced 37.5% mesotheliomas with 3 doses of 20 mg of a Russian chrysotile.

Table 15

Numbers of rats with lung tumours or mesotheliomas after exposure to various forms of asbestos through inhalation[a]

Form of asbestos	No. of animals	Adenocarcinomas	Squamous-cell carcinomas	Mesotheliomas
Amosite	146	5	6	1
Anthophyllite	145	8	8	2
Crocidolite	141	7	9	4
Chrysotile (Canadian)	137	11	6	4
Chrysotile (Rhodesian)	144	19	11	0
None	126	0	0	0

[a] From Wagner *et al.* (1974)

Table 16

Numbers of rats with lung tumours or mesotheliomas after various lengths of exposure to various forms of asbestos through inhalation[a]

Length of exposure	No. of animals	No. with lung carcinomas	No. with pleural mesotheliomas	% of animals with tumours
None	126	0	0	0.0
1 day	219	3[b]	2[c]	2.3
3 months	180	8	1	5.0
6 months	90	7	0	7.8
12 months	129	35	6	31.8
24 months	95	37	2	41.0

[a] From Wagner *et al.* (1974)

[b] 2 exposed to chrysotile and 1 to crocidolite

[c] 1 exposed to amosite and one to crocidolite

Table 17

Percentage of rats developing mesotheliomas after intrapleural administration of various materials[a]

Material	% of rats with mesotheliomas
SFA chrysotile (superfine Canadian sample)	66
UICC crocidolite	61
UICC amosite	36
UICC anthophyllite	34
UICC chrysotile (Canadian)	30
UICC chrysotile (Rhodesian)	19
Fine glass fibre (code 100), median diameter, 0.12 μm	12
Ceramic fibre, diameter, 0.5-1 μm[b]	10
Glass powder	3
Coarse glass fibre (code 110), median diameter, 1.8 μm	0

[a] From Wagner *et al.* (1977b)

[b] Wagner *et al.* (1973)

Donna (1970) also observed mesotheliomas in Sprague-Dawley rats treated with a single dose of 67 mg of chrysotile, amosite or crocidolite. Similar results were obtained by Reeves *et al.* (1971) with chrysotile and crocidolite. Evidence that the response to chrysotile and crocidolite was dose-related was provided by Stanton & Wrench (1972) and Wagner *et al.* (1973) (see Table 18).

The suggestion has been made that natural oils and waxes (Harington, 1962; Harington & Roe, 1965) and contaminant oils from milling of the fibre (Roe *et al.*, 1966) or from jute or plastic storage bags (Commins & Gibbs, 1969; Harington, 1965) contributed to the incidence of pleural tumours. However, samples from which the oils had been removed gave very

Table 18

Dose-response data following intrapleural administration of asbestos to rats

Material	Dose (mg)	No. of rats with mesotheliomas	Total no. of rats	% of rats with tumours	Reference
SFA chrysotile	0.5	1	12	8	Wagner *et al.* (1973)
	1	3	11	27	
	2	5	12	42	
	4	4	12	33	
	8	8	12	62	
Crocidolite	0.5	1	11	9	
	1	0	12	0	
	2	3	12	25	
	4	2	13	15	
	8	5	11	45	
UICC-SRAS crocidolite	1	2	25	8	Stanton & Wrench (1972)
	2	5	23	22	
	10	11	27	41	
	20	12	25	48	
	40	14	23	61	
Hand-cobbed virgin crocidolite	1	4	30	13	
	20	10	24	42	
	40	18	27	67	

similar results to those obtained with untreated fibre (Wagner & Berry, 1969; Wagner *et al.*, 1973).

The fibre diameter, length and shape may be important. All of the 8 separate sub-samples which were pooled in the UICC Canadian chrysotile reference sample (Timbrell & Rendall, 1971/72), when ground separately to a finer powder, produced a higher incidence of mesotheliomas than did the pooled sample. The highest incidence (69%) was produced by 20 mg of a separate, superfine chrysotile sample fractionated from commercial grade 7 asbestos by water sedimentation (Wagner *et al.*, 1973). Using UICC crocidolite, Stanton & Wrench (1972) found that partially pulverized material induced fewer mesotheliomas than did the standard, unpulverized fibre. Prolonged grinding to fine sizes is known to destroy crystalline structure (Langer *et al.*, 1977; Occella & Maddalon, 1963). Stanton (1973) showed that fibres of other materials, including glass, could induce mesotheliomas, but only when the diameter was of the same order as that of asbestos, when measured by light microscopy.

Other fibres, in addition to the UICC standard reference samples, were inoculated intrapleurally into rats by Wagner *et al.* (1973). Mesotheliomas occurred in 18/32 animals injected with a sample of brucite (nemalite, which may be contaminated with chrysotile), in 3/31 injected with a ceramic fibre, in 1/30 injected with barium sulfate, in 1/35 injected with glass powder and in 1/35 injected with aluminium oxide. No mesotheliomas occurred in animals injected with a coarse glass fibre.

Wagner *et al.* (1977a), in a series of experiments to compare the biological effects of a pure, asbestos-free cosmetic talc with those of the superfine chrysotile asbestos used in previous experiments, inoculated 48 Wistar rats intrapleurally with each of the two dusts. Eighteen of those receiving chrysotile developed mesotheliomas, but no mesotheliomas were seen in those given talc.

Further evidence of the importance of fibre diameter was provided by Wagner *et al.* (1977b) who reported on rats injected intrapleurally with glass fibre (Table 17). Two samples of glass fibre were used, one with a median fibre diameter of 0.12 μm and the other with a median

diameter of 1.8 μm. Four mesotheliomas were observed in 32 rats injected with the finer fibre and none in those given the coarser fibre. Also, the degree of mesothelial cell hyperplasia was more pronounced in the rats injected with the finer fibre. These results were comparable with those of the previous experiment.

Shabad *et al.* (1974) reported that when 20 mg Russian chrysotile were injected intrapleurally 3 times into 67 rats, 31 developed mesotheliomas within 2 years.

Hamster: In groups of 50 hamsters given a single intrapleural injection of 1, 10 or 25 mg chrysotile, 0, 4 and 9 mesotheliomas occurred, respectively; with 1 or 10 mg amosite, 4/50 hamsters developed mesotheliomas at the highest dose only. UICC crocidolite, given at a dose of 10 mg induced mesotheliomas in 10/50 hamsters; a dose of 1 mg induced mesotheliomas in 2/50 hamsters; UICC anthophyllite (10 mg) produced mesotheliomas in 3/50 hamsters (Smith & Hübert, 1974).

Rabbit: Intrapleural injection of 16 mg crocidolite into 13 rabbits induced mesotheliomas in 2 surviving 22-24 months (Reeves *et al.*, 1971).

(d) Intratracheal injection

This technique has been used to study co-carcinogenesis of chrysotile asbestos with benzo[a]pyrene (BaP) in rats (IARC, 1972; Pylev, 1972; Pylev & Shabad, 1973; Salk & Vosamäe, 1975; Shabad *et al.*, 1974) and in hamsters (Miller *et al.*, 1965; Smith *et al.*, 1970).

Rat: Shabad *et al.* (1974) showed that intratracheal injection of 2 mg Russian chrysotile on which 0.144 mg BaP was adsorbed (3 times at monthly intervals) or of 2 mg Russian chrysotile together with 5 mg BaP (single injection) produced lung papillomas, epidermoid carcinomas, reticulosarcomas or pleural mesotheliomas in 6/21 and 6/11 rats, respectively, within 9-28 months. No lung tumours or mesotheliomas occurred in 49 rats given 3 doses of 2 mg chrysotile alone or in 19 rats given a single dose of 5 mg BaP alone, during, or up to, 28 months of observation.

Hamster: Smith *et al.* (1970) showed that among 31 hamsters receiving a total dose of 4.5 mg BaP plus 12 mg chrysotile over a period of 12 weeks, 7 developed pulmonary adenomas, 7, pulmonary carcinomas, 9, tracheal papillomas and 1, a laryngeal papilloma. No lung tumours were observed in 17 hamsters receiving chrysotile alone, and only 1 pulmonary carcinoma but 9 tracheobronchial papillomas were found among 38 hamsters receiving BaP alone.

(e) Intraperitoneal administration

Mouse: Pott *et al.* (1976) injected 540 NMRI mice intraperitoneally with 2 or 6 mg chrysotile, crocidolite or glass fibre and observed mesotheliomas. No mesotheliomas occurred in controls or in mice given haematite.

Rat: Reeves *et al.* (1971) gave i.p. injections of 20 mg amosite, crocidolite or chrysotile into groups of 11, 13 and 13 Charles River CD rats, respectively. Three peritoneal mesotheliomas were observed with chrysotile, 3 with crocidolite and none with amosite, after 7-17 months.

Maltoni & Annoscia (1974) injected 25 mg crocidolite intraperitoneally into 50 male and 50 female 17-week old Sprague-Dawley rats and observed 65 peritoneal mesotheliomas, 31 in males and 34 in females.

Pott & Friedrichs (1972) induced peritoneal tumours in Wistar rats by i.p. injections of chrysotile and fibrous glass. Tumours were also observed with crocidolite (Pott *et al.*, 1976). The dosage and results after i.p. administrations of several fibrous and granular dusts are shown in Tables 19 and 20.

After i.p. injection of powdered chrysotile (fibre lengths, 99% < 3μm, 93% < 1 μm and 60% < 0.3 μm), ball-milled for 4 hours, the latent period for the induction of tumours was found to be longer than after i.p. injection of standard chrysotile (95% < 5 μm). The rate of tumour occurrence after injection of chrysotile was not distinctly influenced by the addition of benzo[*a*]pyrene. In another group, benzo[*a*]pyrene without asbestos induced tumours in 10% of the animals. Histologically, the types of tumours observed were connected with structures of the

Table 19

Tumours in abdomen and/or thorax after intraperitoneal injection of different fibrous or granular dusts in rats[a]

Dust	Form[b]	I.p. dose (mg)	Effective number of dissected rats	No. of days before first tumour	Average survival time of rats with tumours (days after injection)	Rats with tumours (%)	Tumour type					
							Mesothelioma	Spindle-cell sarcoma	Polym-cell sarcoma	Carcinoma	Reticulum-cell sarcoma[c]	Benign[c]
UICC Rhodesian chrysotile	f	2	37	431	651	16.2	4	2	-	-	1	-
"	f	6.25	35	343	501	77.1	24	3	-	-	-	-
"	f	25	31	276	419	80.6	21	2	1	1	-	-
"	f	4 x 25	33	323	361	54.5	16	2	-	-	-	-
"	f	3 x 25 s.c.	33	449	449	3.0	-	-	1 s.c.	-	-	-
" milled	f	4 x 25	37	400	509	32.4	9	3	-	-	-	-
Palygorscite	f	3 x 25	34	257	348	76.5	24	2	-	-	-	-
Glass fibres S + S 106	f	2	34	692	692	2.9	1	-	-	-	-	-
"	f	10	36	350	530	11.1	2	2	-	-	1	-
"	f	4 x 25	32	197	325	71.9	20	3	-	-	-	-
Gypsum	f	4 x 25	35	579	583	5.7	-	-	1	1	1	-
Hemalite	f	4 x 25	34	249	315	73.5	17	8	-	-	-	-
Actinolite	g	4 x 25	39	-	-	-	-	-	-	-	-	-
Biotite	g	4 x 25	37	-	-	-	-	-	-	-	-	-
Haematite (precipit.)	g	4 x 25	34	-	-	-	-	-	-	-	-	-
Haematite (mineral	g	4 x 25	38	-	-	-	-	-	-	-	-	-
Pectolite	g	4 x 25	40	569	569	2.5	-	-	-	1	1	1
Sanidine	g	4 x 25	39	579	579	2.6	-	1	-	-	-	-
Talc	g	4 x 25	36	587	587	2.8	1	-	-	-	-	-
NaCl (control)	-	4 x 2ml	72	-	-	-	-	-	-	-	-	-

[a] From Pott et al. (1976) ; [b] f, fibrous; g, granular; [c] Not evaluated in tumour rates

Table 20

Tumours in abdomen and/or thorax after intraperitoneal injection of glass fibres, crocidolite or corundum in rats[a]

Dust	Form[b]	I.p. dose (mg)	Effective number of dissected rats	No. of days before first tumour	Average survival time of rats with tumours (days after injection)	Rats with tumours (%)	Tumour type					
							Mesothelioma	Spindle-cell sarcoma	Polym.-cell sarcoma	Carcinoma	Reticulum-cell sarcoma[c]	Benign[c]
Glass fibres MN 104	f	2	73	421	703	27.4	17	3	-	-	1	1
"	f	10	77	210	632	53.2	36	4	-	1	3	-
"	f	2 x 25	77	194	367	71.4	47	6	2	-	-	-
Glass fibres MN 112	f	20	37	390	615	37.8	12	1	-	1	-	1
Crocidolite	f	2	39	452	761	38.5	12	3	-	-	2	1
Corundum	g	2 x 25	37	545	799	8.1	1	-	-	2	2	2

[a] From Pott *et al.* (1976); [b] f, fibrous; g, granular; [c] Not evaluated in tumour rates

Table 21

Summary of most relevant animal experiments

Reference	Findings	Animal species	Dosage	Type of fibre
A. ORAL				
Gibel *et al.*, 1976	With asbestos filter material, 12/42 animals with malignant tumours (4 kidney carcinomas, 1 lung carcinoma, 3 reticulum-cell sarcomas, 4 liver-cell carcinomas) With talc, 3/45 rats with liver-cell carcinomas 2 liver-cell carcinomas in 49 controls	Groups of 50 Wistar rats	50 mg/kg bw/day administered in the diet for life	Asbestos filter material containing 52.6% chrysotile, talc
Wagner *et al.*, 1977a	2 gastric leiomyosarcomas, 1 in a rat fed chrysotile and 1 in a rat fed talc None in controls	Groups of 32 Wistar rats	100 mg/day on 5 days/week for 100 days over a 6-month period	Chrysotile, talc
B. INHALATION				
Lynch *et al.*, 1957	Pulmonary adenomas in 46% (58/127) of chrysotile-exposed group and in 36% (80/222) of controls	AC/F_1 hybrid mice	150-300 million particles/ml 8-12 hr/day on 5 days/week for 17 months	Chrysotile

Reference	Findings	Animal species	Dosage	Type of fibre
Gross *et al.*, 1967	25/72 rats surviving 16 months or longer developed lung tumours (17 adenocarcinomas, 4 squamous-cell carcinomas, 7 fibrosarcomas) No such tumours in 39 controls	Rats	80 mg/m^3, 30 hrs/week	Chrysotile
Reeves *et al.*, 1971	2/31 rats developed carcinomas of the lung after crocidolite exposure 5/40 rats developed adenomatosis after chrysotile exposure	Rats	49 mg/m^3, 16 hrs/week for 2 years	Crocidolite, chrysotile, amosite
Reeves *et al.*, 1974	5 lung carcinomas with crocidolite, 2 lung carcinomas and 1 pleural mesothelioma with chrysotile and 2 pleural mesotheliomas with amosite	Groups of 69 Charles River CD rats	5 mg/m^3, 4 hrs/day on 4 days/week for 2 years	Crocidolite, chrysotile, amosite
Wagner *et al.*, 1974	Asbestosis produced with all types of fibres lung cancer / mesothelioma / fibre 11/146 — 1/146 — amosite 16/145 — 2/145 — anthophyllite 16/141 — 4/141 — crocidolite 17/137 — 4/137 — chrysotile (Canadian) 30/144 — 0/144 — chrysotile (Rhodesian)	CD Wistar rats	12 mg/m^3, 7 hrs/day on 5 days/week for 1 day, 3, 6, 12 or 24 months	5 UICC asbestos samples
Reeves, 1976	With crocidolite, 14% incidence of malignant tumours of the lung With chrysotile, 5% incidence of malignant tumours of the lung and mediastinum With amosite, 5% incidence of malignant tumours of the lung and pleura	Rats	50 mg/m^3, 4 hrs/day on 4 days/week for 2 years	Crocidolite, chrysotile, amosite
Wagner *et al.*, 1977a	1 adenocarcinoma of the lung with superfine chrysotile in 24 rats exposed for 12 months	CD Wistar rats	10.8 mg/m^3, 7.5 hrs/day on 5 days/week for 3, 6 or 12 months	Chrysotile

Reference	Findings	Animal species	Dosage	Type of fibre
C. INTRAPLEURAL				
Donna, 1970	Mesotheliomas	Sprague-Dawley rats	67 mg	Chrysotile, amosite, crocidolite
Reeves *et al.*, 1971	1/3 mesothelioma with crocidolite, 2/12 mesotheliomas with chrysotile	Rats	10 mg	Crocidolite, chrysotile
Reeves *et al.*, 1971	2/130 mesotheliomas	Rabbit	16 mg	Crocidolite
Stanton & Wrench, 1972	Mesotheliomas in 60% of rats	Osborne-Mendel rats	40 mg	Crocidolite, amosite, Rhodesian chrysotile
Pylev & Shabad, 1973	Mesotheliomas in 37.5% of rats	Rats	3 x 20 mg	Russian chrysotile
Shabad *et al.*, 1974	31/67 mesotheliomas within 2 years	Rats	3 x 20 mg	Russian chrysotile
Smith & Hubert, 1974	Chrysotile, 1 mg, 0/50 mesotheliomas 10 mg, 4/50 mesotheliomas 25 mg, 9/50 mesotheliomas Amosite, 1 mg, 0/50 mesotheliomas 10 mg, 4/50 mesotheliomas Crocidolite, 1 mg, 2/50 mesotheliomas 10 mg, 10/50 mesotheliomas Anthophyllite, 10 mg, 3/50 mesotheliomas	Groups of 50 hamsters	Single dose of 1, 10 or 25 mg chrysotile, 1 or 10 mg amosite, 1 or 10 mg crocidolite, or 10 mg anthophyllite	Chrysotile, amosite, crocidolite, anthophyllite
Wagner *et al.*, 1977a	18/48 mesotheliomas with chrysotile, 0/48 mesotheliomas with talc	Group of 48 Wistar rats	20 mg	Chrysotile, talc
Wagner *et al.*, 1977b	61% mesotheliomas with crocidolite, 36% mesotheliomas with amosite, 34% mesotheliomas with anthophyllite, 30% mesotheliomas with Canadian chrysotile, 19% mesotheliomas with Rhodesian chrysotile	CD Wistar rats	20 mg	5 UICC asbestos samples

Reference	Findings	Animal species	Dosage	Type of fibre
D. INTRATRACHEAL				
Smith *et al.*, 1970	7 pulmonary adenomas, 7 pulmonary carcinomas, 10 tracheobronchial papillomas among 31 hamsters	Hamsters	12 mg chrysotile + 4.5 mg benzo[*a*]pyrene	Chrysotile
Shabad *et al.*, 1974	Lung papillomas, epidermoid carcinomas reticulosarcomas, pleural mesotheliomas in 6/21 and	Rats	2 mg Russian chrysotile with 0.144 mg benzo[*a*]pyrene 3 times at monthly intervals	Russian chrysotile
	6/11 rats within 9-28 months		2 mg Russian chrysotile + 5 mg benzo-[*a*]pyrene (single dose)	
E. INTRAPERITONEAL				
Reeves *et al.*, 1971	After 7-17 months, 3/11 peritoneal mesotheliomas with chrysotile, 3/13 peritoneal mesotheliomas with crocidolite, 0/13 peritoneal mesotheliomas with amosite	Charles River CD rats	20 mg	Amosite, crocidolite, chrysotile
Pott *et al.*, 1972	40% tumours	Wistar rats	100 mg	Chrysotile, milled to 99% < 3 µm
Maltoni & Annoscia, 1974	31/50 mesotheliomas in males, 34/50 mesotheliomas in females	Groups of 50 Sprague-Dawley rats	25 mg	Crocidolite
Pott *et al.*, 1976	16% tumours 77% tumours 81% tumours 55% tumours 39% tumours	Wistar rats	2 mg 6.25 mg 25 mg 100 mg 2 mg	UICC Rhodesian chrysotile UICC crocidolite
F. SUBCUTANEOUS				
Pott *et al.*, 1976	1/33 local tumours	Wistar rats	75 mg	UICC Rhodesian chrysotile

abdominal wall, including the serosa, and, in isolated cases, with those of the intestinal wall (Pott *et al.*, 1972).

(f) Subcutaneous administration

Rat: Pott *et al.* (1976) observed a single local tumour after s.c. administration of 75 mg Rhodesian chrysotile to 33 Wistar rats.

3.2 Other relevant biological data in animals

(a) Retention

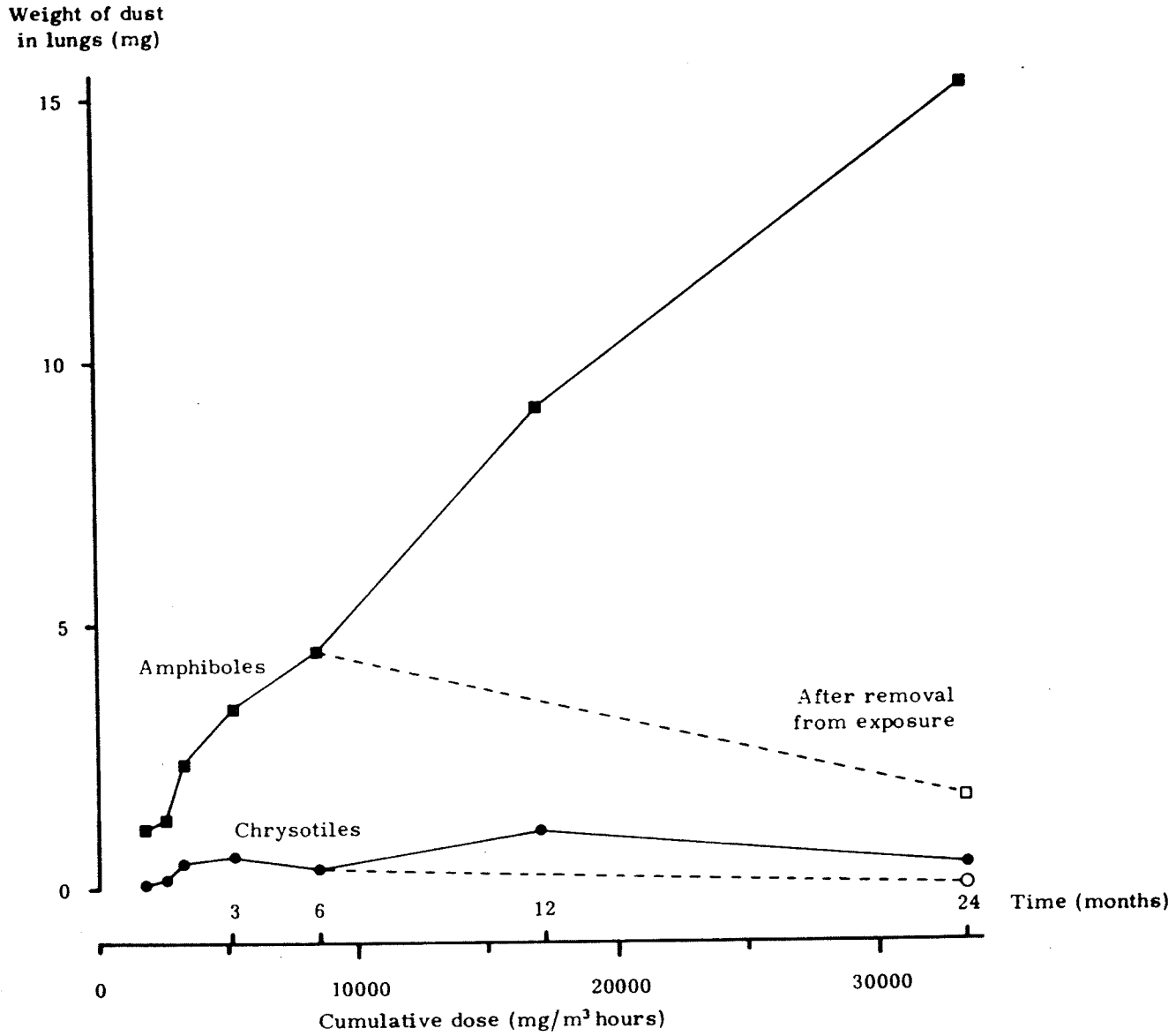
The penetration and clearance of radioactive UICC crocidolite has been studied in rats. Of 35% of inhaled crocidolite deposited onto respiratory tissues, approximately half lodged in the upper airways and was cleared to the gastrointestinal tract within an hour. The remainder in lungs and trachea was reduced after 30 days to 73% of the initial value (Evans *et al.*, 1973).

The retention of different types of asbestos in rats following exposure to the same concentrations of respirable dust was described by Wagner *et al.* (1974). For the amphiboles, there was a similar pattern with an almost proportional increase of lung dust with dose. Much less dust was found for the chrysotiles, and no increase of dust content was shown in the lungs. Dust in the lungs of animals with 6 months' exposure had been partially cleared 18 months after the inhalation period. About 74% of the amosite and crocidolite and 41% of the anthophyllite were eliminated. The elimination rate of chrysotiles could not be determined exactly, because of their low occurrence in the lung (Fig. 1).

(b) Migration of fibres from sites of entry

The question of whether asbestos fibres can move from their site of primary deposition in the body and induce cancer at other sites is still a vexing one. Volkheimer (1973, 1974) and Schreiber (1974) have reported that particles and plant fibres ingested by experimental animals and man can penetrate the wall of the gastrointestinal tract and be transported throughout the body, possibly appearing in the urine. Westlake *et al.* (1965) fed a diet containing 6% chrysotile to rats and reported that the

Figure 1. Effects of inhalation of asbestos in rats[a]



[a] From Wagner *et al.* (1974)

animals had fibres in the wall of the colon. Cunningham & Pontefract (1973) performed a similar experiment and reported that asbestos fibres appeared in the blood and various tissues. The more recent report by Gross *et al.* (1974) concluded, however, that there was no satisfactory evidence from their study of transmigration of fibres outside the gastro-intestinal tract.

In studies in which chrysotile, labelled intrinsically with radio-active trace metals by neutron irradiation, was injected intrapleurally into rats, Holmes & Morgan (1967) found evidence for passage of a small amount of the fibre from the pleural cavity and lungs into such other organs as the liver: after intrapleural inoculation of chrysotile into rats, as much as 22% of the administered dose was found later in the liver (Morgan *et al.*, 1971). In a similar experiment, Morgan *et al.* (1971) reported that a population of radionuclides, consistent with that expected on the basis of the labelled chrysotile, was found in the heart, lungs, diaphragm and chest muscles.

Karacharova *et al.* (1969) and Friedrichs *et al.* (1971) found some evidence for movement of asbestos fibres from an intraperitoneal site of injection into various tissues of the rats used. The latter group of investigators reported that movement was inversely related to the length of the fibre, becoming essentially zero for fibres 20 μm or more in length.

Intravenously-injected asbestos is found mostly in the liver and lungs in rats (Cunningham & Pontefract, 1973); chrysotile injected intravenously into pregnant rats crossed the placenta and appeared in the livers and lungs of the foetuses (Cunningham & Pontefract, 1974).

(c) Association of scarring with tumour development

In early experiments, it was demonstrated that guinea-pigs and monkeys exposed to the four commercial types of asbestos developed fibrotic lesions of the lung and pleura similar to those seen in human cases of asbestosis (Holt *et al.*, 1965; Vorwald *et al.*, 1951; Wagner, 1963). In more recent experiments, this finding has been confirmed in rats and hamsters (Smith *et al.*, 1970; Wagner *et al.*, 1974).

(d) Other experimental systems

Several authors have demonstrated the cytotoxicity of asbestos fibres in *in vitro* systems. This toxicity is thought to be due to the interaction of fibres with plasma membranes. Beck & Bruch (1974) and Beck *et al.* (1971, 1972) investigated the effects of chrysotile and glass fibres on L-cells and peritoneal and alveolar macrophages *in vitro*. They demonstrated, by electron microscopy, incomplete phagocytosis, disturbed permeability of cell membranes and loss of enzyme activity. Powdered chrysotile or glass fibres had more effect on the cells than did unpowdered fibres.

Allison (1973) detected two types of cytotoxic effect: an early effect due to interaction with the plasma membrane and a late one due to an interaction of ingested asbestos particles with the membranes around secondary lysosomes. Interactions of asbestos particles with macrophages and mesothelial cells are similar, but there is less effect with fibroblasts. Asbestos was found to be cytotoxic for malignant P388D1 cells, which have macrophage-like characteristics (Wade *et al.*, 1976).

The induction of interferon by influenza virus was depressed in asbestos-treated monkey kidney-cell monolayers. This also suggests that asbestos fibres act on cell membranes (Hahon & Eckert, 1976).

Sincock & Seabright (1975) reported that chrysotile and crocidolite asbestos dusts in concentrations of 0.01 mg/ml induced chromosomal aberrations in cultured Chinese hamster cells; these changes were not observed with glass powder or glass fibre of 2 μm diameter. Chromosomal aberrations were found in 30% of cells exposed to glass fibres of less than 2 μm diameter (Sincock, 1977).

3.3 Case reports and epidemiological studies

(a) Occupational exposure to commercially exploited sources

Historical background

In 1935, over one-half a century since asbestos began to be used in industry, suspicion of an association between asbestosis and lung cancer was reported by Lynch & Smith (1935) in the USA and by Gloyne (1935) in the UK. About 10-15 years later, case reports of neoplasms involving pleural tumours associated with asbestos exposure appeared (Wedler, 1943a,b; Weiss, 1953; Wyers, 1946), and a peritoneal tumour was reported in an asbestos worker by Leicher (1954). Epidemiological evidence from Doll (1955) showed a ten-fold excess risk of lung cancer in those UK asbestos textile workers who had been employed before 1930 and for 10 or more years. Mesotheliomas were reported to occur in miners of crocidolite and in non-mining populations in the region of the mines (Wagner *et al.*, 1960). Similar findings were reported in the USA, where lung tumours and mesotheliomas were reported in asbestos workers (Mancuso & Coulter, 1963; Selikoff *et al.*, 1964). Possible variations in risk with different types of fibre were rarely considered in the early reports; however, Selikoff *et al.* (1965) did so in one paper. In 1964, the UICC Working Group on Asbestos and Cancer (UICC, 1965) made a number of recommendations, and in the last decade there has been an expansion in the number of epidemiological studies in many parts of the world.

Epidemiological studies

(i) Lung cancer, pleural and peritoneal mesotheliomas

Mixed types of fibre: In most industrial enterprises different types of fibre are used, so exposures to a single asbestos type are unusual. Mortality studies of asbestos manufacturing, insulating and shipyard workers have provided the most concrete evidence concerning an association between lung cancer, pleural and peritoneal mesotheliomas and exposure to asbestos. Reports have come from several countries: the Federal Republic of Germany (Bohlig *et al.*, 1970); Italy (Rubino *et al.*, 1972); The Netherlands (Stumphius, 1971); the UK (Elmes & Simpson, 1971; Newhouse, 1969); and the USA (Selikoff, 1976a; Selikoff *et al.*, 1964, 1970).

The study of Doll (1955), continued by Knox *et al.* (1968) and then by Peto *et al.* (1977), has demonstrated that there is a 2-3-fold excess of lung cancer in those workers first employed between 1933 and 1950 and in those first exposed in 1951 or later. A seven-fold excess of lung cancer was found in a group of insulation workers exposed to chrysotile and amosite but not to crocidolite (Selikoff *et al.*, 1973). Enterline *et al.* (1972) reported a 4.3-times increased risk of respiratory cancer mortality among maintenance service workers and a 1.7-times increased risk among production workers who had reached retirement age and had been exposed to mixed asbestos fibres. Among men in the asbestos cement industry with mixed exposures to crocidolite and chrysotile, the rate was 6.1 times that expected (Enterline & Henderson, 1973).

Enterline *et al.* (1973) suggested that there is no direct dose response for respiratory cancer below 125 mppcf-years, but this suggestion was challenged by Schneiderman (1974).

Harries (1976), De Lajartre *et al.* (1976) and Biava *et al.* (1976) have shown that there has been a steep rise in the incidence of mesotheliomas since 1962. Edge (1976) reported that shipyard workers with pleural plaques who had mixed exposure to asbestos (without evidence of pulmonary fibrosis) have a 2.5-times increased risk of developing carcinoma of the bronchus, when compared with the general population; furthermore, 17 of 70 deaths among the 235 men under observation between 1970-74 were due to mesothelioma. In a second group of 156 men the same author showed a 2.6-fold increased risk of carcinomas of the bronchus in former shipyard workers who had pleural plaques as compared with controls without pleural plaques.

In a study of 2 cohorts of sheet-metal workers who had worked for 5 or more years between 1950 and 1970 in the construction industry and who had measurable and mixed asbestos exposure, Cooper *et al.* (1975) observed an excess of deaths due to malignant neoplasms (24.8 and 26.5% of total deaths in the 2 cohorts, respectively, compared to 19.1% of deaths in a group with death claims; 14.6% and 16.2 would have been expected in US males in 1959 and 1967, respectively). This increase was attributed largely to an excess of malignant tumours

of the respiratory tract. Of the 307 deaths in the first cohort, the 32 lung cancer deaths were significantly in excess (1.7 times) of the number expected. One pleural mesothelioma was observed.

In a study of 689 asbestos workers exposed to mixed fibres for 20 years and observed during 1959-75, 35 lung cancer and 26 pleural or peritoneal mesotheliomas were observed among 274 deaths (Nicholson *et al.*, 1977).

Newhouse (1969, 1973a) and Newhouse *et al.* (1972) showed that the cancer risk following mixed exposure of factory workers to chrysotile, amosite and crocidolite is dose related. Those workers reported to have had heavier exposures (as judged by their occupations) showed an excess of lung cancer (6-fold for men, 12-fold for women) after 15 years, whereas those with moderate or low exposures required 25 years to demonstrate an excess. The rate of mesothelioma increased with both the severity and the length of exposure; 22 mesotheliomas were observed in those exposed for less than 2 years (Newhouse & Berry, 1976).

Additional confirmatory evidence of the association between mesotheliomas and past exposure to asbestos comes from many institutes, departments of pathology and cancer registries in, e.g., Australia (Milne, 1976); the Federal Republic of Germany (Hain *et al.*, 1974); Finland (Nurminen, 1975); France (De Lajartre *et al.*, 1973); the German Democratic Republic (Sturm & Bittersohl, 1975); Italy (Gobbato & Ferri, 1973; Puntoni *et al.*, 1976); The Netherlands (Zielhuis *et al.*, 1975); South Africa (Webster, 1973); and the UK (Greenberg & Lloyd Davies, 1974). These studies have shown an association between asbestos and mesothelioma, some with exposures as brief as one day; however, in approximately 15% of mesothelioma cases no evidence of exposure to asbestos could be ascertained. Three studies (Greenberg & Lloyd Davies, 1974; McDonald *et al.*, 1973; Newhouse *et al.*, 1972) showed a poor correlation between certified cause of death and histological diagnosis of mesothelioma.

The reported ratio of pleural to peritoneal tumours varies widely in different studies; peritoneal tumours appear to be associated with heavier exposure (Newhouse *et al.*, 1972; Selikoff *et al.*, 1970).

Among a number of occupationally exposed groups studied, approximately 5-10% of deaths have been due to mesothelioma (Gilson, 1973; Hammond & Selikoff, 1973; Selikoff, 1976a). More recently, however, an estimate has projected that the deaths of between 8-11% of former asbestos workers from a particular factory in the UK will be due to mesothelioma (Newhouse & Berry, 1976).

Martischnig *et al.* (1977) found that 58 out of 201 men with lung cancer admitted to a thoracic surgical centre gave, after careful questioning, a history of exposure to asbestos, compared with only 29 of the matched controls, although none were ostensibly 'asbestos workers' and none had evidence of asbestosis.

Analyses of lung parenchymal tissues obtained from men employed in the Canadian chrysotile mining industry who had been clinically diagnosed as asbestotic have shown the presence of tremolite and other amphibole fibres, often in excess of chrysotile (Pooley, 1976). The analyses illustrated that the presence of amphibole fibres in commercial chrysotile material may be involved in the etiology of subsequent disease from exposure to dust arising from chrysotile materials.

Individual types of fibre

Crocidolite: In 1956, Wagner started investigating the occurrence of pleural mesotheliomas in the crocidolite mining areas of the North-west Cape Province in South Africa. It was shown that these tumours occurred in the non-mining population living in the vicinity as well as among men working in the mines, mills and in the transportation and handling of the fibre. Asbestosis was present in 8/33 cases. The latent period between first exposure and clinical recognition of the tumour was long - a mean of 40 years (Wagner *et al.*, 1960). Subsequent surveillance of the mining population in all the asbestos-producing areas of South Africa has demonstrated that mesotheliomas occur chiefly in the crocidolite mining areas of that country (Harington *et al.*, 1971; Webster, 1973). The mining of crocidolite in north-west Australia has been associated with mesotheliomas (McNulty, 1962). Jones *et al.* (1976) have reported a high incidence of mesotheliomas among women who worked with crocidolite in a factory producing gas-mask canisters during World War II.

Chrysotile: McDonald *et al.* (1973, 1974) reported that the overall death rate among 11,572 workers born between 1891 and 1920 and observed from 1945 onwards and employed in the chrysotile mines and mills of Quebec province was lower than that for the province as a whole. However, an increased risk of lung cancer was found. The authors considered that those men who had been most heavily exposed to the asbestos dust showed about a 5-fold risk compared with that of those least exposed. Of 3270 deaths that had occurred in this group up to the end of 1969, 134 were due to respiratory cancer, 129 of which were lung cancer and 5, pleural mesothelioma. More recently, the authors (McDonald & McDonald, 1976) have observed 3938 total deaths among males up to 1973, of which 224 were due to lung cancer and 7 to mesothelioma. The authors suggest that the mesothelioma mortality in the Quebec chrysotile industry as a whole was greater than that expected on the basis of regional mortality data. The ratio of lung cancer deaths to all deaths occurring in the four years 1970-1973 is 14%.

Kogan *et al.* (1972) investigated the cancer mortality among workers in asbestos mining and milling industries between 1948 and 1967. The total cancer mortality rate among workers was 1.6 times higher than in the general male population; for female workers the rates were 0.8 for those in mines and 1.3 for those in mills. The lung cancer risk for male miners and millers was two times that of the general male population. For females in mines and mills the risks were 2.1 and 1.4 times that of the general female population, respectively. For those workers over 50 years of age, the lung cancer risk was greater: for men in mining, 4.9; those in milling, 5.9; for women in mining, 9.5; and for women in milling, 39.8 times that in the general population. No mesotheliomas were reported. The numbers of people in the study populations were not reported.

Wagoner *et al.* (1973) reported on the cancer risk among a cohort of workers in a major manufacturing complex utilizing predominantly chrysotile asbestos in textile, friction and packaging products. An excess of respiratory cancer occurred among asbestos workers in each duration-of-employment category down to and including 1-9 years. They observed

a statistically significant standard mortality ratio of 122 for all malignant neoplasms and 244 for malignant neoplasms of the respiratory system. The asbestos workers in this study were located in an area of predominantly Dutch Amish population with known low frequencies of smoking.

Enterline & Henderson (1973) found that for retired men who had worked as production or maintenance employees in the asbestos industry and who had reached 65 years of age, those who had been exposed only to chrysotile had a respiratory cancer risk 2.4 times that expected. Among men within the asbestos cement industry exposed only to chrysotile a 1.4-fold excess of respiratory cancer was found. Of 822 deaths, for which 802 death certificates were found (including those for workers exposed to amosite or mixed fibres), only one mesothelioma had been recorded (Enterline *et al.*, 1972). In contrast, a subsequent investigation by Borow *et al.* (1973) found 72 cases of mesothelioma in one plant, where chrysotile was the main fibre used. The discrepancy may have been due to methodological variations; for instance, Enterline *et al.* (1972) had limited their investigation to men of age 65 or over, while many of the mesothelioma cases reported by Borow *et al.* (1973) had died before that age.

Amosite: Exposures to amosite in a factory making insulation materials were reported by Selikoff (1976a). Ten mesotheliomas were found, and there was an increased risk of lung cancer in workers followed up for 20 years or longer. The excess lung cancer risk in the amosite workers was shown to increase with duration of employment. There was a 3.87-fold increase in lung cancer among those with less than three months' employment.

In a retrospective study of 914 men who had worked for various periods of time during World War II in a plant manufacturing insulating materials from amosite for the US Navy, Seidman *et al.* (1977) reported that the group of 65 men who had worked for less than 1 month had an excess mortality from lung cancer (but not from all cancers or all causes) which became discernible only 30 years after the exposure.

Excess mortality from lung cancer and all cancers that showed up after progressively shorter intervals after the exposure was reported in men who had worked for periods ranging from 1 month to more than 2 years.

Anthophyllite: In Finland, anthophyllite mining has been associated with an excess lung cancer risk of 1.4; the risk is 2.7 after allowing for smoking habits in workers with more than 10 years' exposure. There was also a higher prevalence of dyspnoea and cough in the miners. No mesotheliomas were found (Meurman *et al.*, 1974). The occurrence in Finland of an unusually high incidence of pleural thickening and calcification, as detected by radiographical and pathological surveys, has, however, been reported (Kiviluoto, 1960; Meurman, 1966).

(ii) Other cancers : Epidemiological studies have consistently shown an excess risk of other cancers, especially of the gastrointestinal tract, following exposure to mixed fibres (Elmes & Simpson, 1971; Enterline, 1965; Hammond *et al.*, 1965; Kogan *et al.*, 1972; Mancuso & El-Attar, 1967; Newhouse, 1973b; Nicholson *et al.*, 1977; Selikoff, 1974; Selikoff *et al.*, 1964), to amosite (Selikoff, 1976b; Selikoff *et al.*, 1972b) or to chrysotile (Wagoner *et al.*, 1973). However, such risks have been less than that for lung cancers. Schneiderman (1974), analysing data from the literature, came to the conclusion that 'increased exposure to inhaled asbestos particles leads to increased digestive system cancer'.

Stell & McGill (1973) found that of 100 men with squamous-cell carcinomas of the larynx, 31 had known exposure to asbestos, compared with only three in matched controls. Similar associations have been reported by Morgan & Shettigara (1976) and Shettigara & Morgan (1975). Newhouse & Berry (1973) found two cases of cancer of the larynx (ICD 161) in their cohort of over 4000 workers, compared with an expected incidence of 0.4.

The incidence of oropharyngeal cancer also appears to be increased among asbestos workers (Selikoff *et al.*, 1970); however, these cancers occur relatively rarely in relation to other asbestos cancers.

(iii) Multiple primary cancers : Multiple primary tumours have been reported in 5 shipyard workers exposed to asbestos; 2 had both a lung

carcinoma and a colon carcinoma and 3 had 2 distinct pulmonary carcinomas each (Dohner *et al.*, 1975).

(b) Smoking and occupational exposure to asbestos

In most studies of asbestos workers, smoking habits have not been known. Selikoff *et al.* (1968) first took account of smoking and calculated that asbestos workers who smoke had 8 times the lung cancer risk of all other smokers and 92 times the risk of non-smokers who did not work with asbestos. This study has been continued and the data interpreted as being consistent with a multiplicative (synergistic) effect of the carcinogens, smoking and asbestos (Doll, 1971; Hammond & Selikoff, 1973), a view supported by another study (Berry *et al.*, 1972).

Some of the above studies and recent studies from NIOSH (1977) and of Martischnig *et al.* (1977) are consistent with the occurrence of an increased risk among non-smokers, which is, however, of a lower order of magnitude. Smoking has not been found to be associated with an increased risk of mesotheliomas or cancers of the stomach, colon and rectum, which occur with equal frequency among smoking and non-smoking asbestos workers.

(c) Non-occupational exposure to commercially exploited sources

Household contact with asbestos is associated with an increased risk for mesothelioma. Mesotheliomas have occurred in household contacts and in non-occupationally exposed individuals living in the neighbourhood of industrial sources of asbestos (Bohlig & Hain, 1973; Newhouse & Thompson, 1965; Wagner *et al.*, 1960). Anderson *et al.* (1976) have recently reviewed 37 such cases of mesothelioma from nine countries and reported 4 new cases among family contacts of asbestos workers. Studies of the geographical distribution of cases of non-occupational mesotheliomas in the UK over a 2-year period indicate that the new cases are nearly all from areas in which there has been a recognized industrial source of asbestos (Greenberg & Lloyd Davies, 1974).

Results have been reported among non-occupationally exposed persons in Finland living where anthophyllite asbestos is mined. In this study, 118 of the total of 126 cases of roentgenologically diagnosed pleural

calcification, excluding those individuals with haemothorax, empyema and tuberculosis, lived or had lived in areas immediately adjacent to asbestos mines (Kiviluoto, 1960). The results of this study suggest a health hazard due to ambient community exposure to asbestos.

(d) Exposure to asbestiform minerals other than mined asbestos

A number of fibrous minerals other than the asbestos varieties exist in nature. Some of these occur as natural contaminants of rocks and ores which are released during mining, milling or processing (See also sections 1.2(a) and (b) and Tables 3 and 4). For example, talc may be contaminated with asbestiform (fibrous) tremolite, anthophyllite and chrysotile, in total concentrations greater than that of the talc mineral itself (Kleinfeld *et al.*, 1973, 1974; Rohl & Langer, 1974). Excess deaths due to malignancies have occurred in workmen exposed to aerosols during the mining and milling of these materials, in addition to pneumoconiosis. Nineteen of 91 deaths recorded were due to lung carcinoma (9), pleural fibrosarcoma (1), peritoneal mesothelioma (1), gastrointestinal tract cancer (6) and other cancers (Kleinfeld *et al.*, 1967). Asbestos disease stigmata have been reported in association with fibrous talc exposure (Rohl & Langer, 1974).

These observations serve to highlight the important question of a relationship between exposure to asbestiform minerals (not asbestos *per se*) and the occurrence of excess malignant disease. This problem is global in scope and potentially important. For example, iron-ore deposits may present such a problem. Wagner (1928) demonstrated that the extensive iron deposits of the southern hemisphere, produced as a result of bacterial action, are similar in nature to those iron deposits making up the Mesabi Range in the US and to those found in ranges the world over (French, 1968). Wagner emphasized that these iron formations would contain fibrous iron silicates; and fibrous silicates are indeed scattered throughout these deposits and occasionally occur in large foci. In the southern hemisphere, these deposits have or are being mined for amphibole asbestos, including the crocidolite deposits of the Cape Province, the amosite and crocidolite areas in the Transvaal in South Africa, the

mysorite deposits in Mysore in southern India and the crocidolite in Western Australia and in Bolivia.

The Transvaal iron formation is also exploited for iron ore itself and was the main source of iron ore in South Africa. In recent years, the increased demand for iron ore has led to the opening up of large-scale surface mining of the banded ironstone in Sishen in South Africa (Webster, 1973) and the Hamersley deposit, Western Australia; both these deposits are in the vicinity of known occurrences of crocidolite fibre. In northern US, asbestos fibre has not been exploited from the Mesabi Range. Although iron ore is mined along this range, fibres similar to and in some instances identical with the amphibole asbestos variety exploited in the southern hemisphere are found. These are inevitably mined with the iron ore. Similar problems exist with other ores. Recent concern about the potential carcinogenicity of non-commercially exploited materials of an asbestos nature has been raised with regard to these ores and associated amphibole fibres.

Mean air concentrations of amphibole fibres in communities surrounding milling operations have been reported to range from 2.6-8.9 $\times 10^3$ fibres/m^3. Chrysotile concentrations in individual samples ranged from none detected to 10.4 $\times 10^4$ fibres/m^3. Concentrations of as high as 11 $\times 10^6$ amphibole fibres/m^3 of air were reported near specific point emission sources (NIOSH, 1977).

Studies of communities in geographical areas near these mining operations, who are exposed to amphibole fibres in drinking-water (Levy *et al.*, 1976; Masson *et al.*, 1974), demonstrate no increased risk of cancer as of 1971. However, since these mining operations began in approximately 1955, the period of observation is insufficient to evaluate the presence or absence of an associated carcinogenic risk.

Studies using X-ray diffraction, optical microscopy and electron-beam instrumentation have demonstrated the presence of cummingtonite and grunerite (amosite) fibres in a hard rock gold mine (Dement *et al.*, 1976). A study of underground miners in this mine has demonstrated a 3-fold excess risk of mortality from respiratory cancer (Gillam *et al.*, 1976).

Yazicioglu (1976) has conducted a radiographic survey of 15,239 people living around the city of Diyarbakir in south-east Turkey and found 389 (2.6%) with evidence of pleural calcification. It has long been customary to paint the walls and floors of houses in this area with a material easily dug from local rocks. Samples of this material have been identified by the State Mining Investigation Institute in Ankara as containing chrysotile fibre as one of the constituents.

Pleural plaques have been observed in agricultural workers engaged in growing tobacco on stony mountainous soil in Bulgaria; anthophyllite, tremolite and sepiolite have been found in regions where endemic pleural calcification occurs (Burilkov & Babadjov, 1970; Burilkov & Michailova, 1970, 1972).

3.4 Analyses of fibres in tissues

The physical characteristics of asbestos fibres that penetrate to the lung parenchyma have been studied by Timbrell (1965, 1972), who demonstrated that fibre respirability was largely a function of fibre diameter (Timbrell *et al.*, 1970).

Two kinds of data are relevant; Timbrell (1972) has shown that the crocidolite mined in Northern Cape Province and in Western Australia is associated with a frequent occurrence of pleural mesothelioma. This crocidolite had thinner and shorter fibres than the crocidolite or amosite mined in the Transvaal Province, where fewer cases of pleural mesothelioma have been reported. It has been proposed that the reported risk difference may be attributable to the differing physical characteristics of the fibres (Langer *et al.*, 1974).

A study (Sebastien *et al.*, 1977) concerning diameter and length of 5000 asbestos fibres from the lungs of 10 deceased persons who had been occupationally exposed to asbestos showed that these were all less than 0.5 μm in diameter. The proportion of fibres shorter than 5 μm ranged from 70% to 90%.

Numerous asbestos fibres, either of chrysotile or amphibole or both types, have been found by electron microscopy in the lungs of industrially

exposed men (Pooley, 1972, 1973; Fondimare & Desborde, 1974). A quantitative topographic study of asbestos fibres in the lung that has been carried out in 12 industrially exposed men showed that heavily exposed cases with lung fibrosis and carcinomas have fewer fibres in the fibrotic lower lobes than in the less fibrotic upper lobes. The fibres were mostly of the amphibole type. In cases of lung cancer without lung fibrosis, a higher concentration of asbestos fibres, mostly of the chrysotile type, was clearly demonstrated in peripheral areas of the lung (Sebastien *et al.*, 1977).

Optical and transmission electron microscopic study of lung and pleura revealed a preferential accumulation of chrysotile *versus* amphibole fibres in the pleura; the mean length of the fibres was greater in the lung and visceral pleura than in the parietal pleura, this being particularly the case for the amphiboles (Le Bouffant *et al.*, 1977). There was no relationship between the numerical concentration of fibres in lung parenchyma and that in parietal pleura. Generally, the concentration was always less in pleura than in parenchyma; however, the distribution of chrysotile microfibrils in the pleura was not homogeneous, and in some areas high concentrations identical to those in the parenchyma could be observed (Sebastien *et al.*, 1976b).

In a series of studies in London (Pooley *et al.*, 1970), New York (Langer *et al.*, 1971) and Le Havre (Sebastien *et al.*, 1977), chrysotile fibres or fibrils were demonstrated by transmission electron microscopy in the lungs of most consecutive autopsy cases.

Pooley (1973) found that the lungs of 93% of 120 mesothelioma cases studied had asbestos fibres visible by electron microscopy, as compared to less than 50% of 135 cases obtained at random autopsies. Higher concentrations of fibres were observed in mesothelioma than in non-mesothelioma cases. In mesothelioma cases the fibre types were either amphibole or chrysotile, or both, but amphibole was predominant; in non-mesothelioma cases, chrysotile fibres were predominant. In the three cases of mesothelioma included in the study of Sebastien *et al.* (1977), the percentage of chrysotile fibres was from 44-97% in the peripheral

areas of the lung. The ratio of amphibole to chrysotile has been found to decrease from the central toward the peripheral areas of the lung (Fondimare *et al.*, 1977; Le Bouffant *et al.*, 1977).

Asbestos bodies have been found, by light microscopy, in large numbers in occupationally exposed individuals (Ashcroft & Heppleston, 1973) and by optical and electron microscopy in the lungs of most adults who have lived in urban areas (Bignon *et al.*, 1970; Davis & Gross, 1973; Oldham, 1973; Selikoff *et al.*, 1972a; Thomson & Graves, 1966). The number of coated fibres in lungs has been compared in persons with and without lung carcinoma. Meurman *et al.* (1970), who took into account cigarette consumption, could find no significant difference.

Doniach *et al.* (1975) found an increased incidence of asbestos bodies in men with stomach cancer and in women with breast cancer, but not in lung cancer cases. Contrasting observations with regard to lung were made by Warnock & Churg (1975), who found that lung cancer cases had more asbestos bodies in their lungs than those without lung cancer, even though only one case had had known occupational exposure to asbestos. It has long been known that inhalation of other fibres may result in the formation of bodies resembling asbestos bodies (Williams, 1934).

Simultaneous studies by optical and electron microscopy in 18 lungs from subjects with various degrees of asbestos exposure showed that light microscopy could identify 41-100% of fibres as coated, whereas with electron microscopy only 10% of all fibres were coated in subjects heavily exposed and only 0.21% in subjects with moderate exposure (Sebastien *et al.*, 1977).

In persons occupationally exposed to asbestos, smaller numbers of asbestos bodies or fibres than are seen in lung tissue have been found in extra-pulmonary tissues, including tonsils, thoracic and abdominal lymph nodes, pleura, peritoneum, liver, spleen, kidney and small intestine (Godwin & Jagatic, 1970; Zielhuis, 1977).

3.5 Asbestosis

Asbestosis is a progressive, irreversible lung disease caused by the inhalation of asbestos dust and is characterized by diffuse intestinal fibrosis. The pathological features have been described by Wagner (1965), and radiological features defined by Gilson (1971). A combined pathological-radiological correlation has been undertaken (Caplan *et al.*, 1965).

Early reports of an association between asbestos dust exposure and pulmonary disease were given by Murray (1907) in the UK, Hoffman (1918) in Canada and Pancoast *et al.* (1917) in the US. However, the first complete descriptions of asbestosis were not made until 1927, by Cooke (1927) and McDonald (1927) in the UK, and 1930, by Mills (1930) in the US. Early studies led many investigators to conclude that people exposed to asbestos dust developed the disease, 'asbestosis', if the dust concentration were high or if their exposure were long (Beintker, 1931; Dreessen *et al.*, 1938; Fulton *et al.*, 1935; Merewether, 1947; Merewether & Price, 1930).

As to a relationship between asbestosis and bronchial carcinoma, there is at present no scientific documentation indicating that these entities are interrelated in any way other than that they constitute disease outcomes that may be associated causally with exposure to asbestos as a common environmental factor.

Recent reports (Edge, 1976; Martischnig *et al.*, 1977) support the hypothesis that an excess of bronchial carcinomas exists in groups of persons exposed to asbestos without concomitant radiological signs of lung asbestosis.

Table 22

Summary of studies of carcinogenicity in human populations

Reference	Finding	Group and exposure
A. OCCUPATIONAL EXPOSURE		
Historical studies		
Lynch & Smith, 1935 Gloyne, 1935	Suspicion of association between asbestos and lung cancer	Asbestos workers
Wedler, 1943a,b Wyers, 1946 Weiss, 1953	Case reports of pleural and peritoneal tumours associated with asbestos	
Leicher, 1954	A peritoneal tumour	
Doll, 1955	Lung cancer	Asbestos textile workers employed before 1930
Wagner *et al.*, 1960	Mesotheliomas	Miners and non-mining population
Mancusco & Coulter, 1963	Lung cancer and mesothelioma	Asbestos workers
Selikoff *et al.*, 1964	Lung cancer and mesothelioma	Asbestos workers
Epidemiological studies		
Lung, pleura and peritoneum Mixed types of fibres		
Knox *et al.*, 1968		Asbestos textile workers employed after 1933
Newhouse, 1969 (UK) Bohlig *et al.*, 1970 (FRG) Selikoff *et al.*, 1970 (USA) Elmes & Simpson, 1971 (UK) Stumphius, 1971 (The Netherlands) Rubino *et al.*, 1972 (Italy)	Lung cancer, pleural and peritoneal mesotheliomas	Asbestos manufacturing, insulation and shipyard workers
Selikoff *et al.*, 1973	Lung cancer	Insulation workers; chrysotile and amosite asbestos exposure

Reference	Finding	Group and exposure
Enterline *et al.*, 1972 Enterline & Henderson, 1973	Respiratory cancer	Retired production and maintenance workers in asbestos industry
Cooper *et al.*, 1975	Lung cancer	Sheet-metal workers
De Lajartre *et al.*, 1976	Mesothelioma	Shipyard workers
Biava *et al.*, 1976		Shipyard workers
Harries, 1976		Naval dockyard workers
Edge, 1976	Carcinoma of bronchus	Shipyard workers
Newhouse, 1973a Newhouse & Berry, 1976	Lung cancer	Asbestos workers
De Lajartre *et al.*, 1973 (France) Gobbato & Ferri, 1973 (Italy) Puntoni *et al.*, 1976 (Italy) Webster, 1973 (South Africa) Greenberg & Lloyd Davies, 1974 (UK) Hain *et al.*, 1974 (FRG) Nurminen, 1975 (Finland) Sturm & Bittersohl, 1975 (GDR) Zielhuis *et al.*, 1975 (The Netherlands) Milne, 1976 (Australia)	Evidence of association between mesothelioma and past exposure to asbestos	Occupational exposures, in some cases as brief as one day
Newhouse *et al.*, 1972 Selikoff *et al.*, 1970	Peritoneal tumours associated with heavy exposures	
Gilson, 1973 Hammond & Selikoff, 1973 Selikoff, 1976a	5% to 10% asbestos workers' deaths due to mesothelioma	
Newhouse & Berry, 1976	8-11% asbestos workers' deaths due to mesothelioma	
Martischnig *et al.*, 1977	Lung cancer	Asbestos workers
Peto *et al.*, 1977		Asbestos textile workers
Nicholson *et al.*, 1977	Lung cancer, mesothelioma	Asbestos workers
Single types of fibres		
Crocidolite		
Wagner *et al.*, 1960	Pleural cancer	Workers in mines, mills and transportation and handling of crocidolite and population in vicinity of mines

Reference	Finding	Group and exposure
Harington *et al.*, 1971 Webster, 1973	Mesothelioma	Mining population of crocidolite mines
McNulty, 1962	Mesothelioma	Miners of crocidolite
Jones *et al.*, 1976	Mesothelioma	Women working with crocidolite in WWII gas-mask canister factories
Chrysotile		
McDonald *et al.*, 1973, 1974 McDonald & McDonald, 1976	Lung cancer, mesothelioma	Chrysotile mine and mill workers
Kogan *et al.*, 1972	Total cancer, lung cancer	Workers in asbestos mining and milling, men and women
Wagoner *et al.*, 1973	Respiratory cancer	Workers in manufacturing of textile, friction and packaging products, using chrysotile
Enterline & Henderson, 1973 Enterline *et al.*, 1972	Respiratory cancer	Men 65 years and older, retired production or maintenance employees in asbestos industry exposed only to chrysotile
Borow *et al.*, 1973	Mesothelioma	Workers at plant using chrysotile, all ages
Amosite		
Selikoff, 1976a Seidman *et al.*, 1977	Mesothelioma, lung cancer Lung cancer	Insulation workers in factory using amosite
Anthophyllite		
Meurman *et al.*, 1974	Bronchial cancer, dyspnoea and cough	Anthophyllite mining employees

Reference	Finding	Group and exposure
Other cancers		
Enterline, 1965 Hammond *et al.*, 1965 Mancuso & El-Attar, 1967 Elmes & Simpson, 1971 Kogan *et al.*, 1972 Newhouse, 1973b Wagoner *et al.*, 1973 Selikoff, 1974, 1976b Selikoff *et al.*, 1964, 1972b Nicholson *et al.*, 1977	Cancer of gastrointestinal tract	Asbestos workers
Stell & McGill, 1973 Morgan & Shettigara, 1976		Workers with exposure to asbestos
Newhouse & Berry, 1973	Laryngeal cancer	Asbestos workers
Shettigara & Morgan, 1975		
Selikoff *et al.*, 1970	Oropharyngeal cancer	
Dohner *et al.*, 1975	Multiple primary cancers	Shipyard workers
B. SMOKING AND ASBESTOS		
Selikoff *et al.*, 1968 Doll, 1971 Berry *et al.*, 1972 Hammond & Selikoff, 1973	Lung cancer	Asbestos workers
C. NON-OCCUPATIONAL EXPOSURES		
Anderson *et al.*, 1976	Mesothelioma	Family members of asbestos workers
Wagner *et al.*, 1960 Newhouse & Thompson, 1965 Bohlig & Hain, 1973		Individuals in neighbourhood of industrial sources of asbestos
Greenberg & Lloyd Davies, 1974		New cases from areas with recognized industrial source of asbestos
D. ASBESTIFORM MINERALS		
Kleinfeld *et al.*, 1967	Lung, pleural, peritoneal, gastro-intestinal tract cancers	Talc miners and millers
Gillam *et al.*, 1976	Respiratory cancer	Underground gold mines

4. Comments on Data Reported and Evaluation

All commercial forms of asbestos tested are carcinogenic in mice, rats, hamsters and rabbits. In mice, mesotheliomas were induced following intraperitoneal injection of asbestos fibres. In rats, various types of asbestos produced lung carcinomas and mesotheliomas following their inhalation and mesotheliomas and sarcomas following their intrapleural or intraperitoneal injection. The oral administration of asbestos filter material to rats also resulted in an increased incidence of tumours. Mesotheliomas were produced in hamsters and rabbits after intrapleural injection of a number of types of asbestos fibre.

The size and shape of the fibres influence the incidence of tumours; fibres less than 0.5 μm in diameter are more active in producing tumours. Glass fibres and nemalite of a similar size can also produce mesotheliomas following their intrapleural or intraperitoneal injection in rats.

In humans, occupational exposure to chrysotile, amosite, anthophyllite and mixed fibres containing crocidolite has resulted in a high incidence of lung cancer; a predominantly tremolitic material mixed with anthophyllite and small amounts of chrysotile has also caused an increased incidence of lung cancer. Many pleural and peritoneal mesotheliomas have been observed after occupational exposure to crocidolite, amosite and chrysotile. An excess risk of gastrointestinal tract cancers has been demonstrated in groups exposed occupationally to amosite, chrysotile or mixed fibres containing crocidolite. An excess of cancers of the larynx was also observed in exposed workers. Mesotheliomas also occur in individuals living in the neighbourhood of asbestos factories and crocidolite mines and in household contacts of asbestos workers.

Occupational exposure to asbestos may occur during the mining of fibrous minerals, as well as of minerals embodied in rocks, which may contain asbestiform fibres as a contaminant.

Both cigarette smoking and occupational exposure to asbestos fibres independently increase lung cancer incidence, but when they are present together they act in a multiplicative fashion.

The general population may also be exposed to asbestos fibres in air, beverages, drinking-water, food and pharmaceutical and dental preparations and by consumer use of asbestos-containing products. The presence of asbestos and asbestiform minerals from natural sources in the environment, other than mines or quarries, has only recently shown itself to be a further potential problem.

At present, it is not possible to assess whether there is a level of exposure in humans below which an increased risk of cancer would not occur.

APPENDIX A

The criteria for the evaluation of the carcinogenic risk of chemicals to man were established at a number of meetings held prior to the publication of Volume 1 of the IARC Monograph series. All volumes published since that time have followed essentially the same format and are based on the same criteria. Working Groups have been limited to the assessment of published data, on which the final evaluation in terms of carcinogenic potential is based. In order to ensure, however, that the monographs will continue to provide accurate and extensive evaluations in changing circumstances, it has been decided to convene a Working Group to review the criteria used up until now.

The present Working Group, convened to evaluate asbestos, felt, however, that in view of the importance of this substance, this monograph should also present a quantitative evaluation of the future scope of the problem in terms of society as a whole. Such forecasts are dependent on several variables which cannot be predicted with certainty.

Without implying disagreement with the views of the Working Group, the Director of IARC has requested that this section appear as an Appendix to the main text of the monograph.

SCOPE OF THE PROBLEM RELATED TO ASBESTOS EXPOSURE

In the first half century of modern commercial use of asbestos (1878-1927), there were only sporadic reports of associated health risks, and these were concerned with pneumoconiosis, in particular asbestosis (Cooke, 1927). During those years the use of this versatile material expanded greatly; with few precautions against exposure. In spite of the fact that the hazards from exposure to asbestos dust had been clearly defined by Merewether & Price (1930) in the UK, by Dreessen *et al.* (1938) in the US and by Nordmann (1938) in Germany, insufficient action was subsequently taken. By the time the cancer potential had been recognized and defined (1935-1960), asbestos had permeated much of modern industry,

and, indeed, modern society, with thousands of products being manufactured and utilized throughout the world, in circumstances that we now understand were inadequate for the control of occupational disease, including cancer. As a result, we are now faced with a double dilemma, of how to deal with the consequences of previous inattention and error, in terms of human disease, and of how to avoid further exposure which could produce disease in the future.

The results of failures in the past spur efforts for control [See, e.g., Senior Medical Inspector's Advisory Panel (1968)]. In many studies of groups of asbestos workers, for example, approximately 20% of all deaths are the result of lung cancer, three-quarters of which are attributable to their work with asbestos (Selikoff, 1976b). Among such groups, pleural and peritoneal mesotheliomas have become common; estimates for certain groups suggest that as many as 7-11% may die of these diseases (Newhouse & Berry, 1976), which otherwise occur only rarely. Excess incidences of gastrointestinal, laryngeal and oropharyngeal cancer will claim further lives. There are few accurate estimates of the numbers of persons at risk from exposure to asbestos in the various countries of the world. Attempts to do so have been made in the US (Wagoner, 1976), and it is sobering to realize that there are now in the US approximately one million men and women who work regularly in manufacturing asbestos products or who were so employed in the past. Should the foregoing estimates hold for them as well, some 200 thousand deaths from lung cancer and 50 or more thousand deaths from mesotheliomas will occur (See also Newhouse & Berry, 1976). However, to the extent that we fail to control further exposures, these will be underestimates of the occupational cancer incidence.

Another factor that could lead to their being underestimates is that such figures may not include cancers that result from the mining and milling of asbestos or from indirect occupational exposures (as in the shipyard and construction industries), from a number of specific uses of asbestos materials (as in brake repair and brake maintainance work), or from para-occupational exposure or uncontrollable consumer use of asbestos materials; nor do they include cancers that will result from household

contact or neighbourhood exposures. Indeed, no population exposed to the industrial use of asbestos has escaped this hazard; it is also likely that every country in the world has experienced this public health problem.

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