Importance of Mineral Type, Form and Dimensions in Carcinogenic Responses

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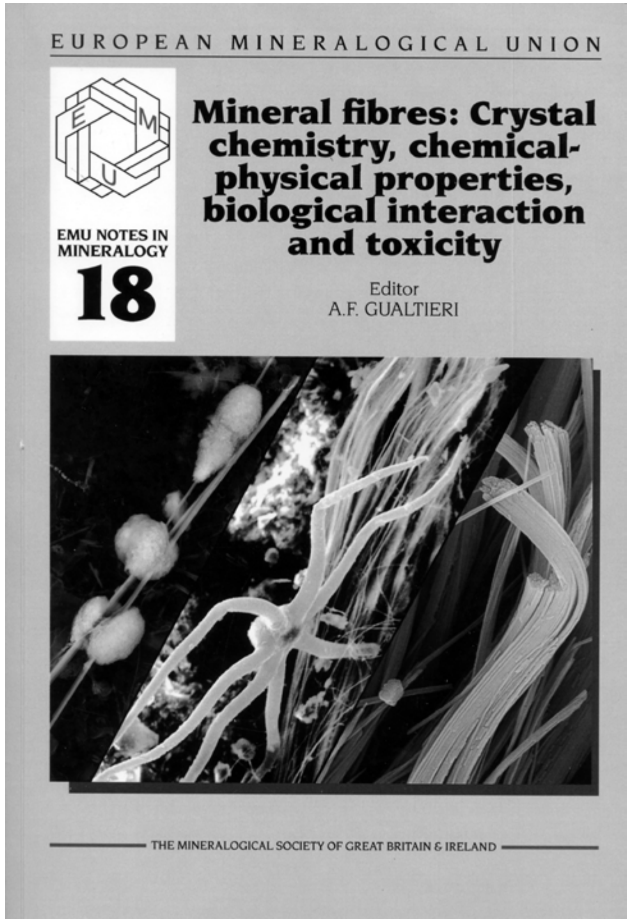
Many properties of minerals OTHER than dimensions are important in carcinogenesis

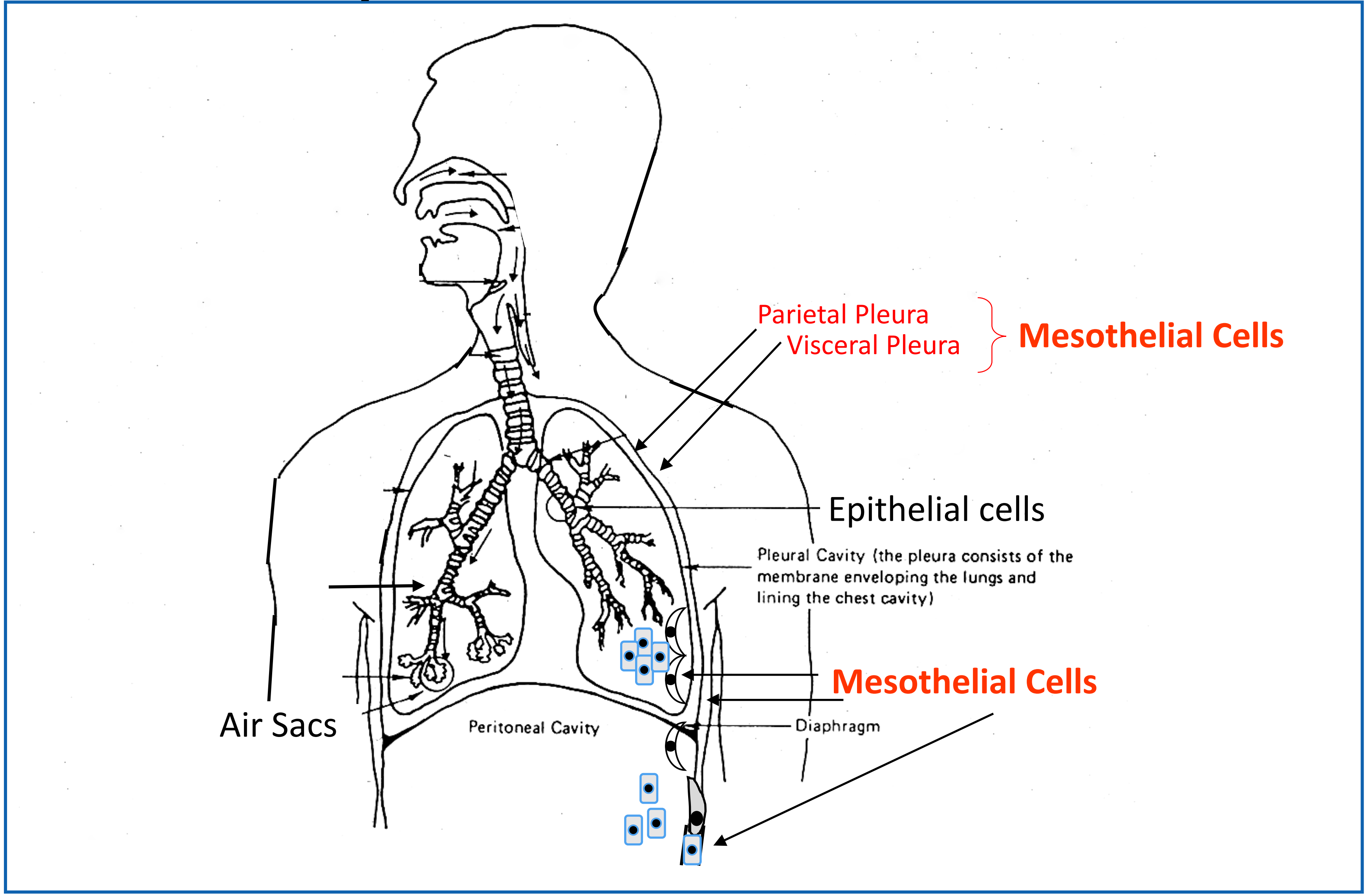


Gualtieri, Mossman and Roggli, Towards a general model for predicting the toxicity and pathogenicity of mineral fibers, 2017

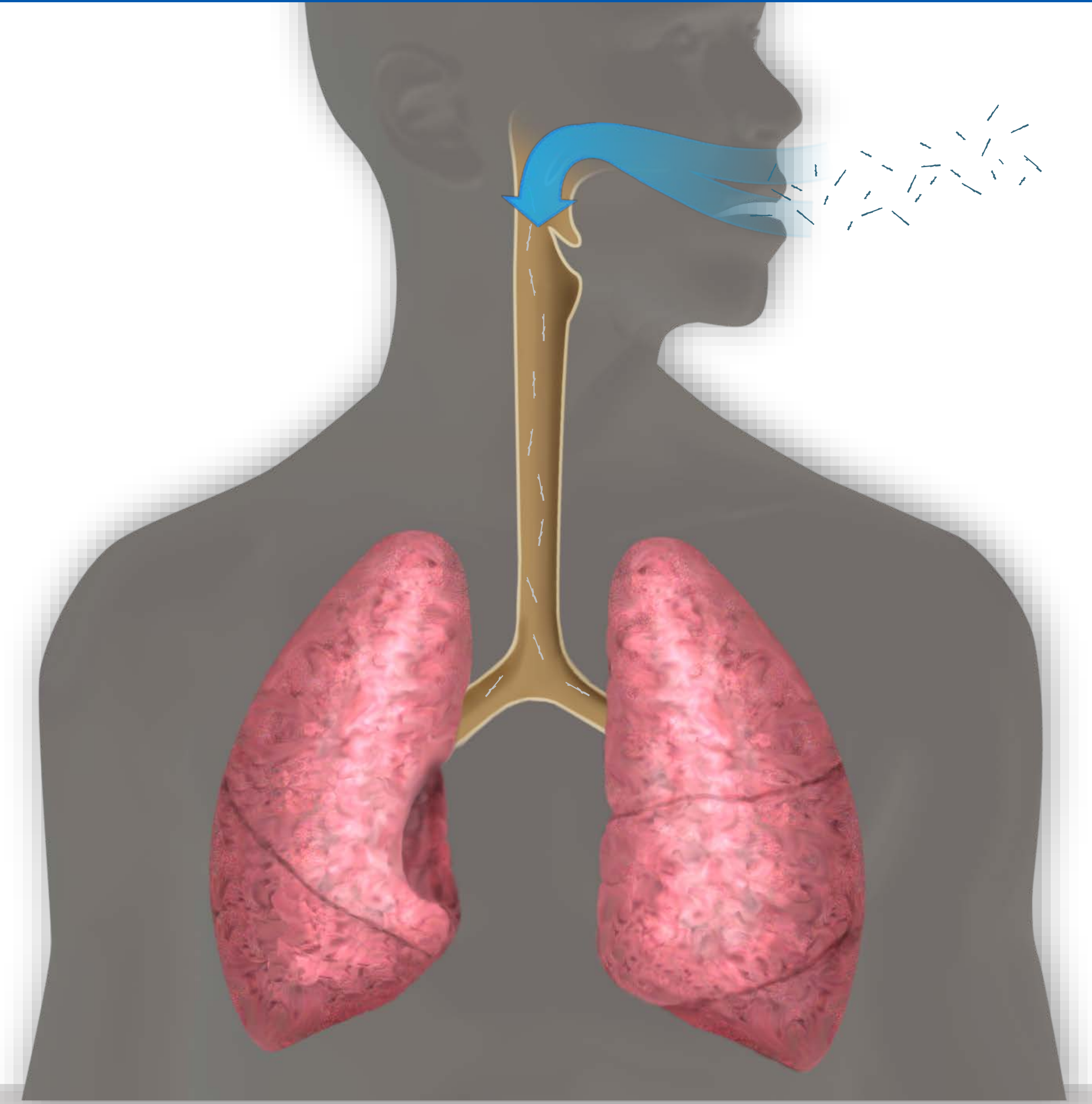
Table 2. A sample correlation matrix of all the parameters that play a role in the toxicity of mineral fibres (the explanation of each code is in the text).

	1a	1b	1c	1d	1e	1f	2a	2b	2c	2d	3a	3b	3c	3d	4a	4b
1a		X				X		X			X	X		X	X	X
1b				X							X	X		X	X	X
1c					X											X
1d																
1e											X	X		X	X	X
1f								X			X	X	X	X		
2a								X	X							
2b									X		X	X				
2c											X	X				
2d																
3a												X	X	X		
3b																
3c																
3d																
4a																X
4b																

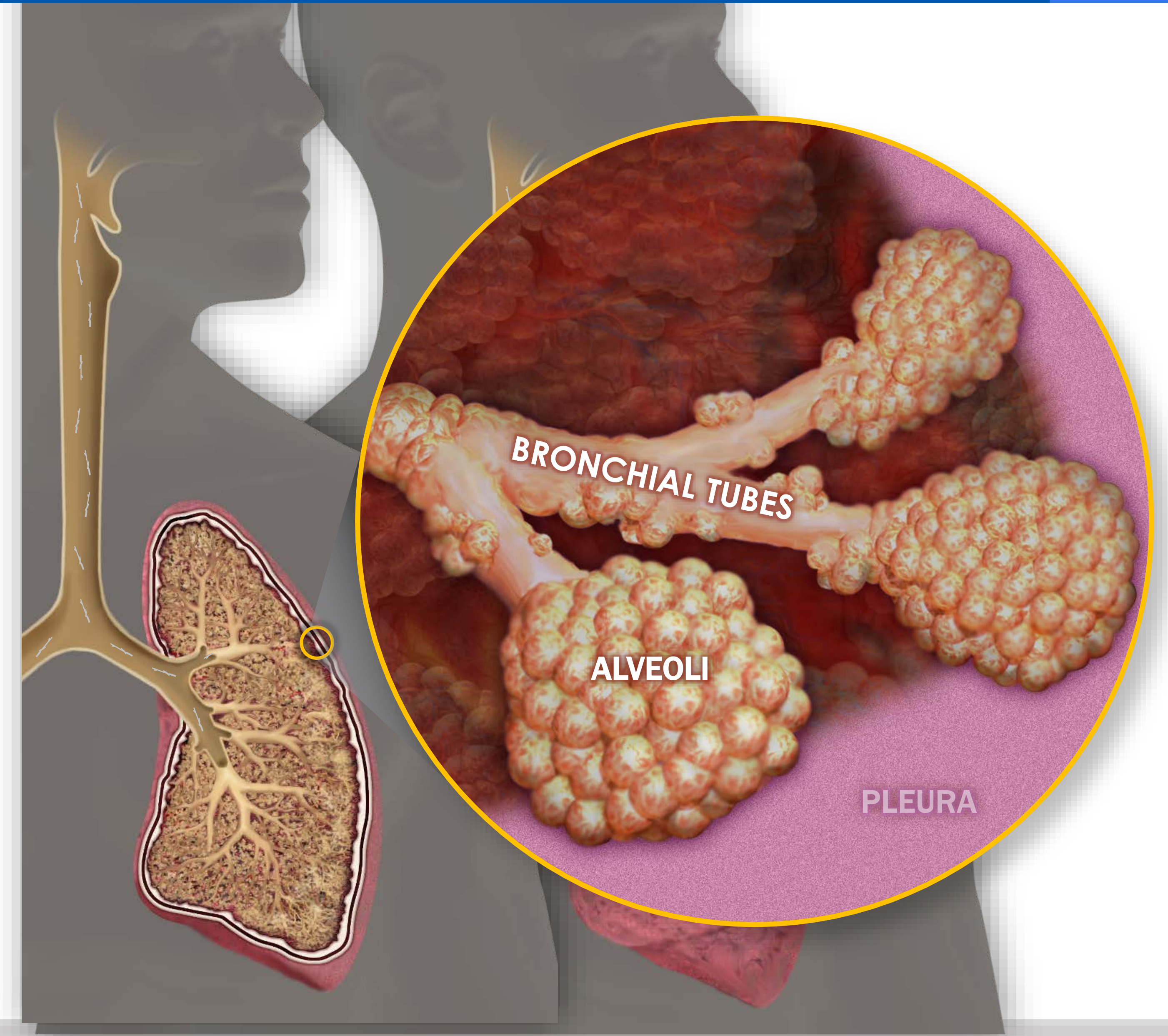
What features of amphibole asbestos are important in mesothelioma development ?



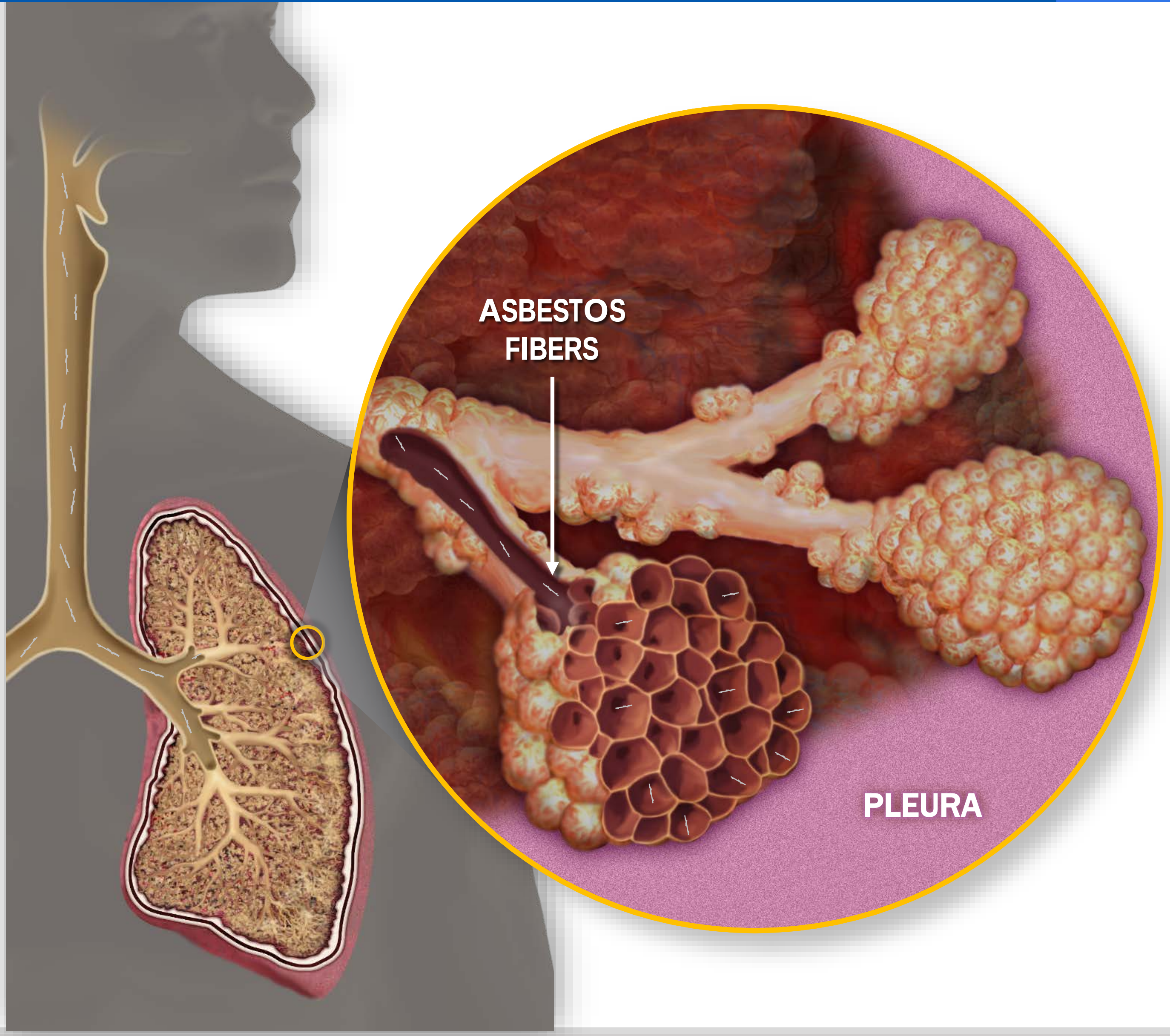
Dimensions are Important in Aerodynamics of Fibers vs Fragments:



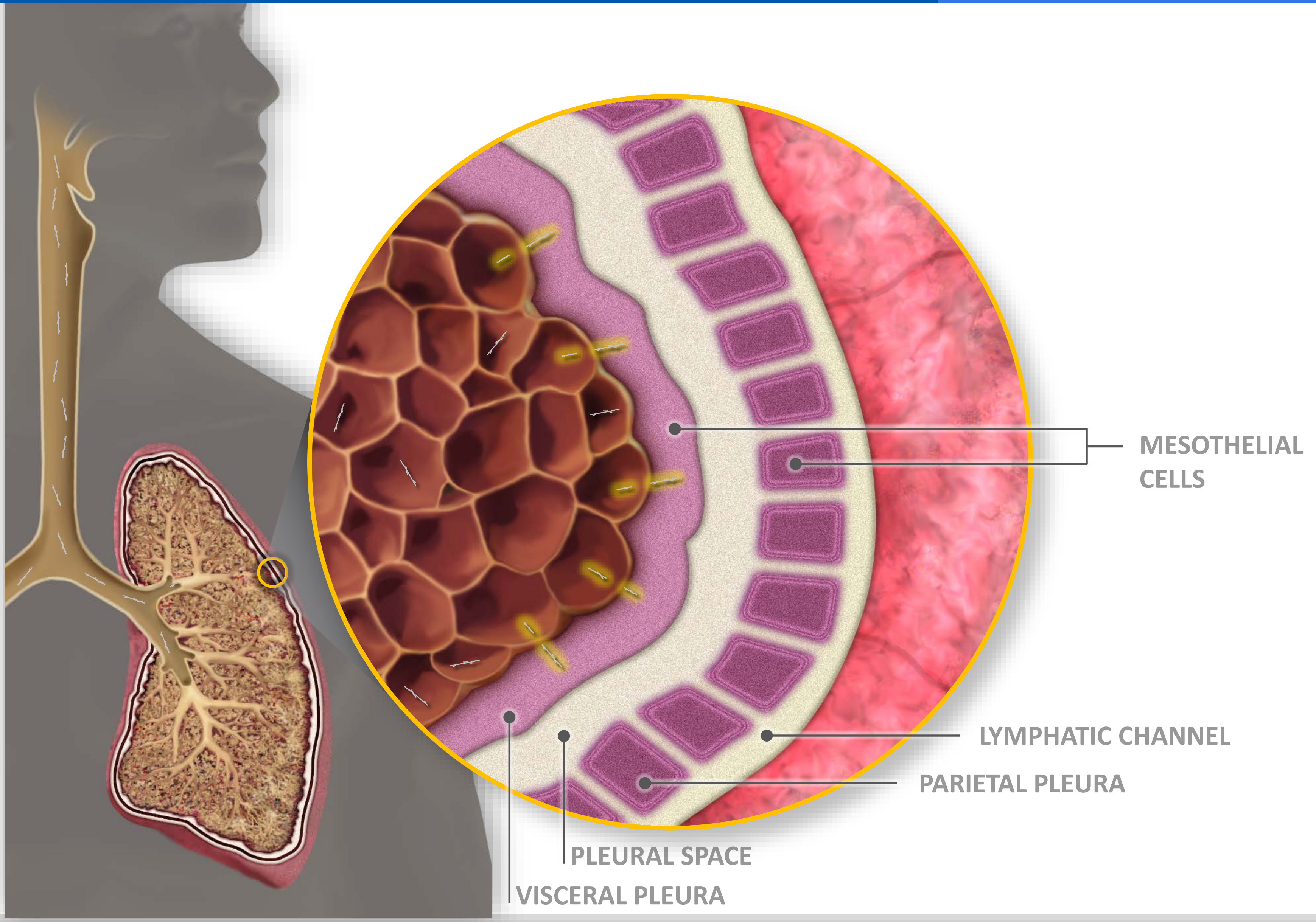
Long, thin amphibole asbestos fibers align themselves with narrow bronchioles to enter the deep lung



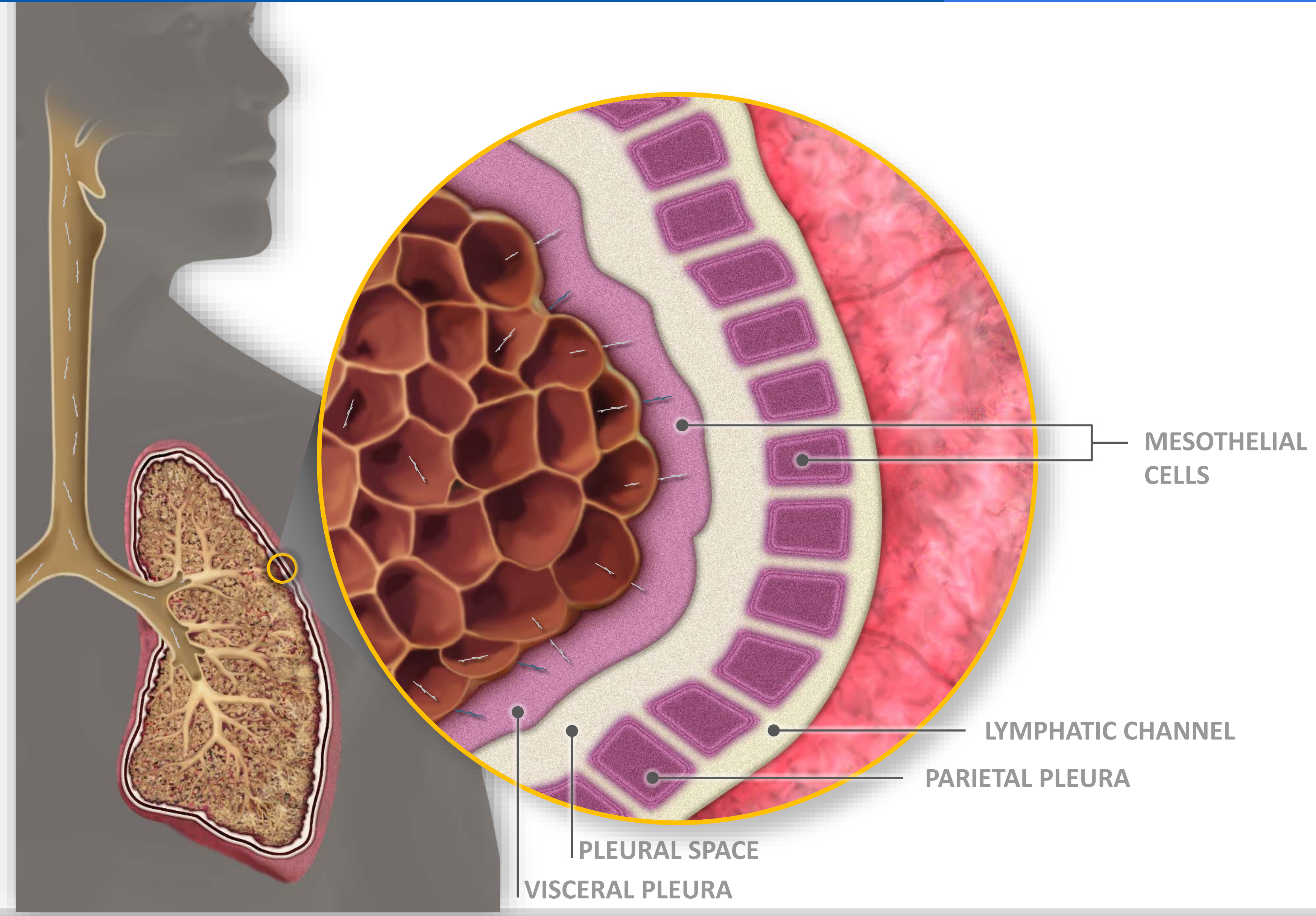
Bronchiolar ducts carry respirable fibers and particles to the air sacs of the lungs



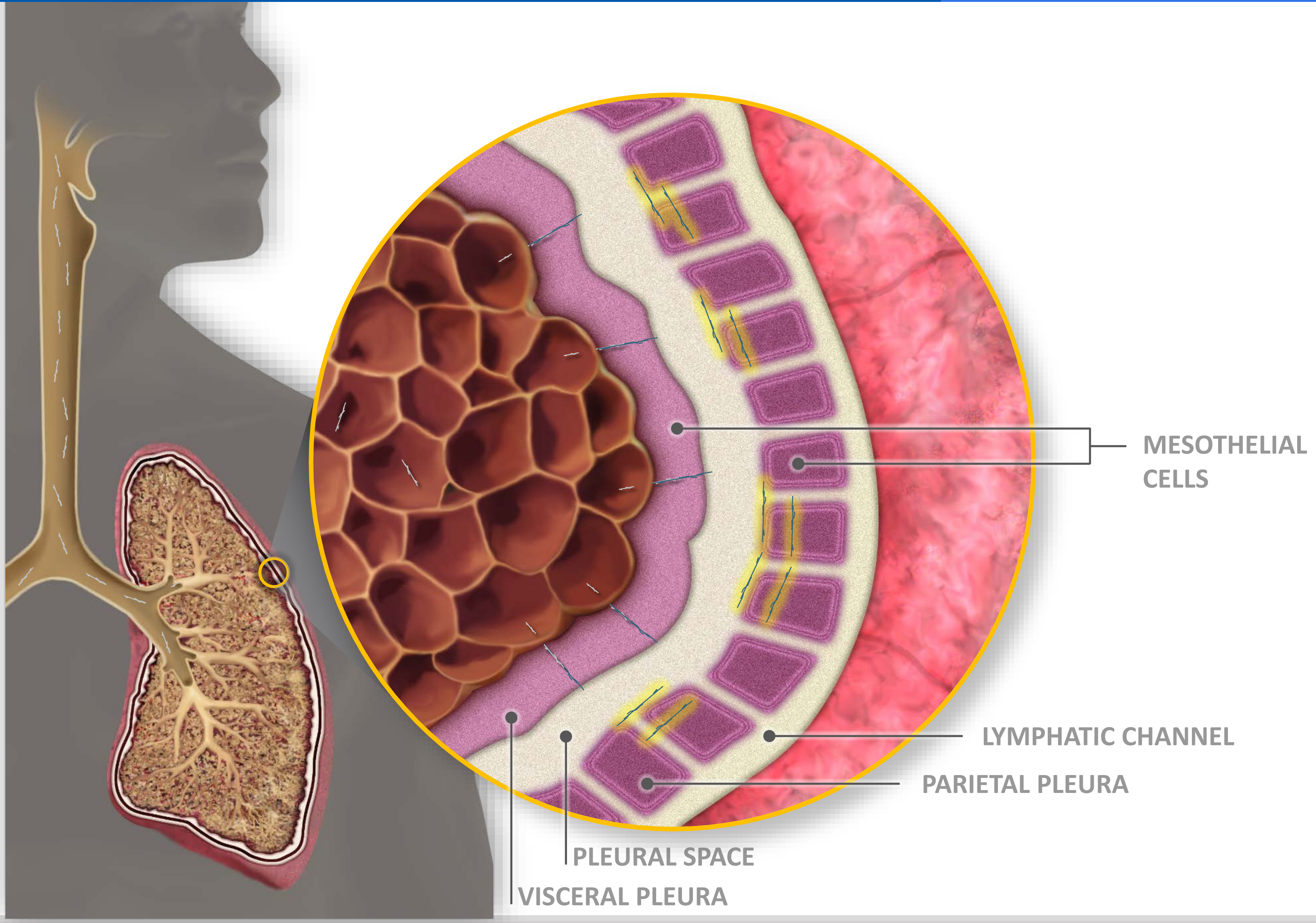
Long, Thin Asbestos Fibers Can Penetrate Air Sacs to Reach Parietal Mesothelial Cells (Rigidity and Flexibility)



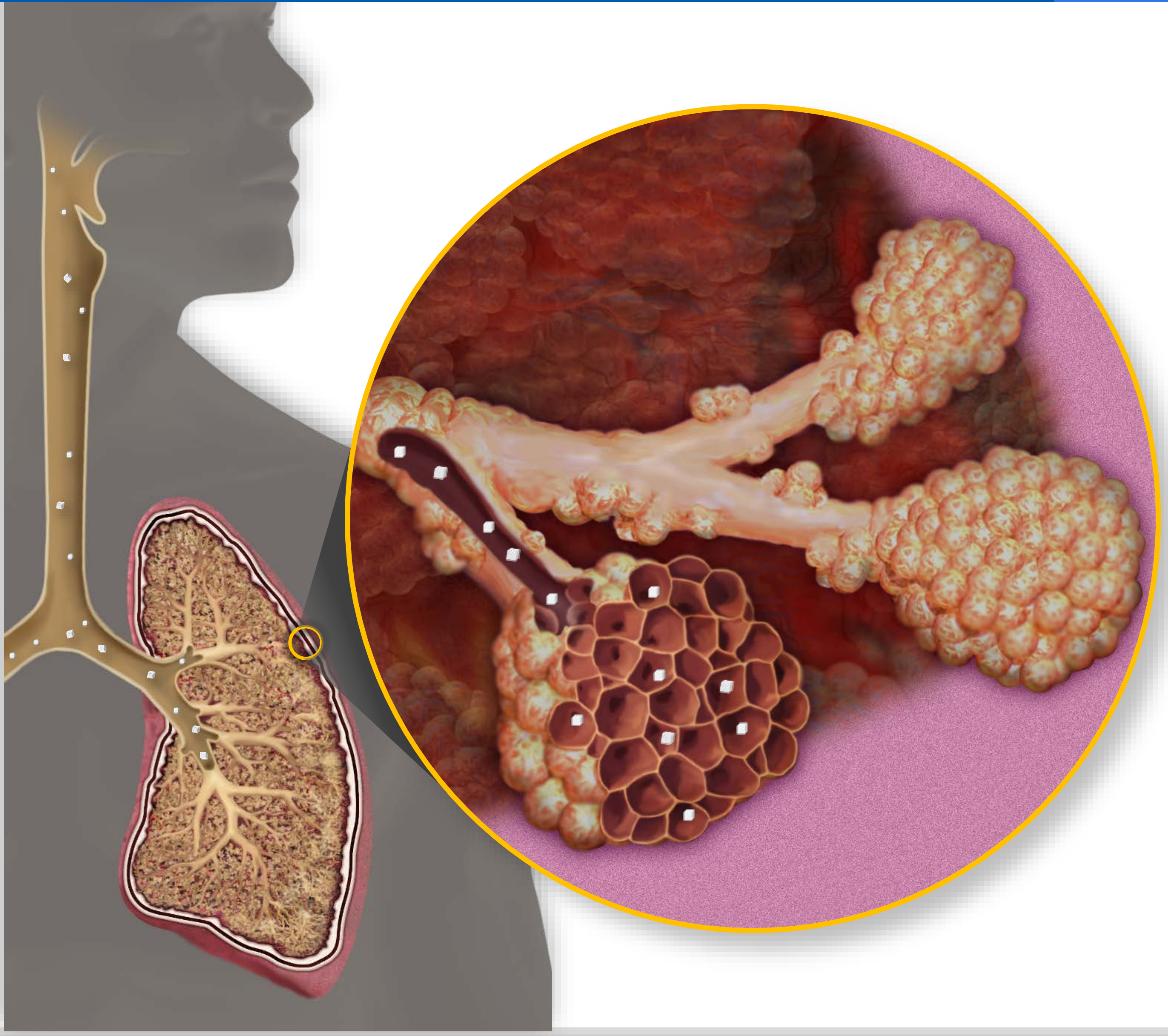
Short Asbestos Fibers and Non-Asbestos Fragments Drain out Through Stomata to Lymphatic System



Dose, Dimension and Durability: Asbestos Fibers Become Lodged at Mesothelial Cells in the Pleura and Persist

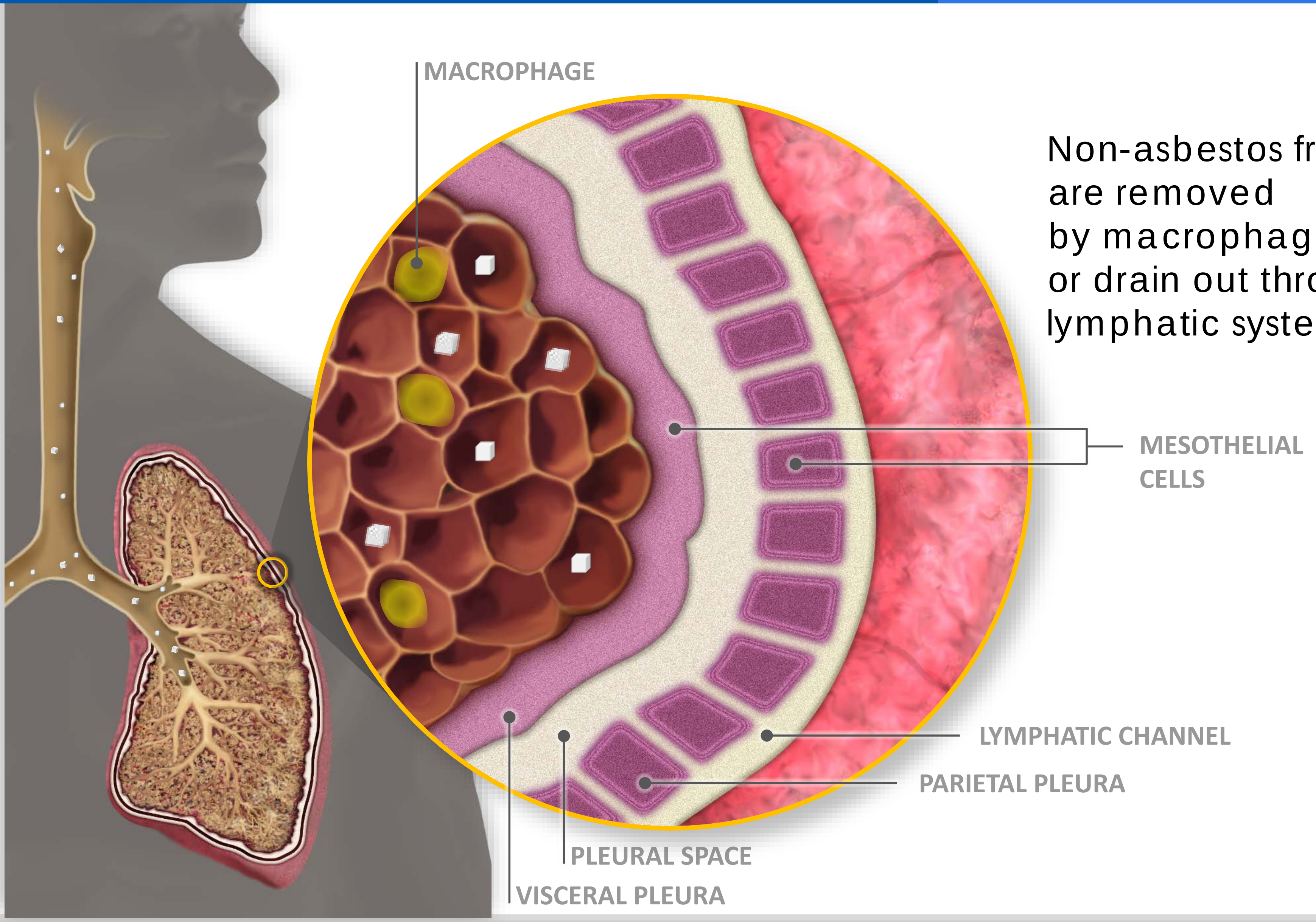


Short Fragments Do Not Become Lodged at Mesothelial Cells (Schinwald et al., 2012; Murphy et al., 2011)



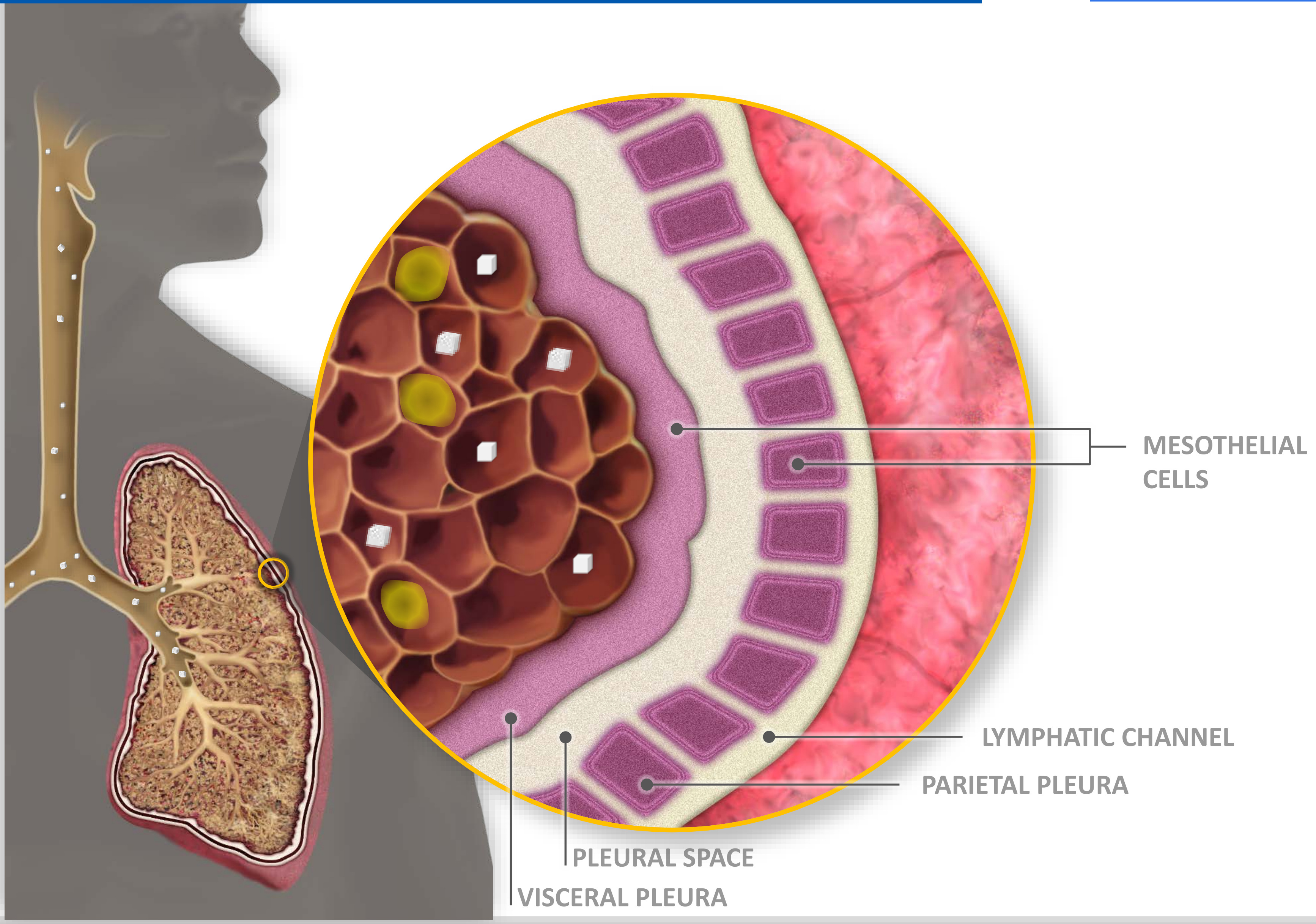
Particles and short fibers will reach the air sacs of the lungs but are effectively removed by macrophages

Chemistry, surface charge, and dimensions affect clearance mechanisms

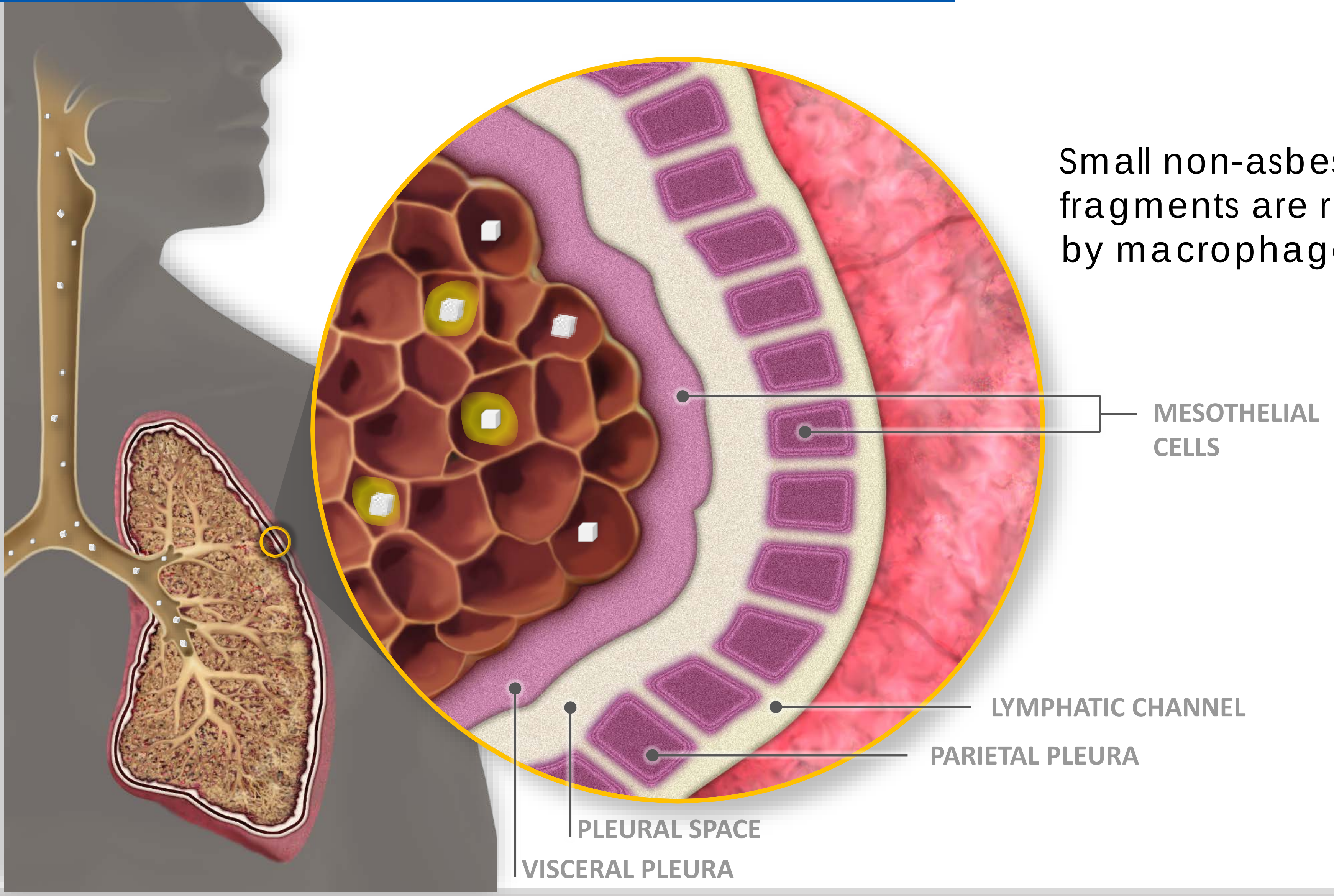


Non-asbestos fragments are removed by macrophages or drain out through lymphatic system

Dissolution Kinetics of Asbestos Fibers and Fragments Differ (Guthrie, 1997)

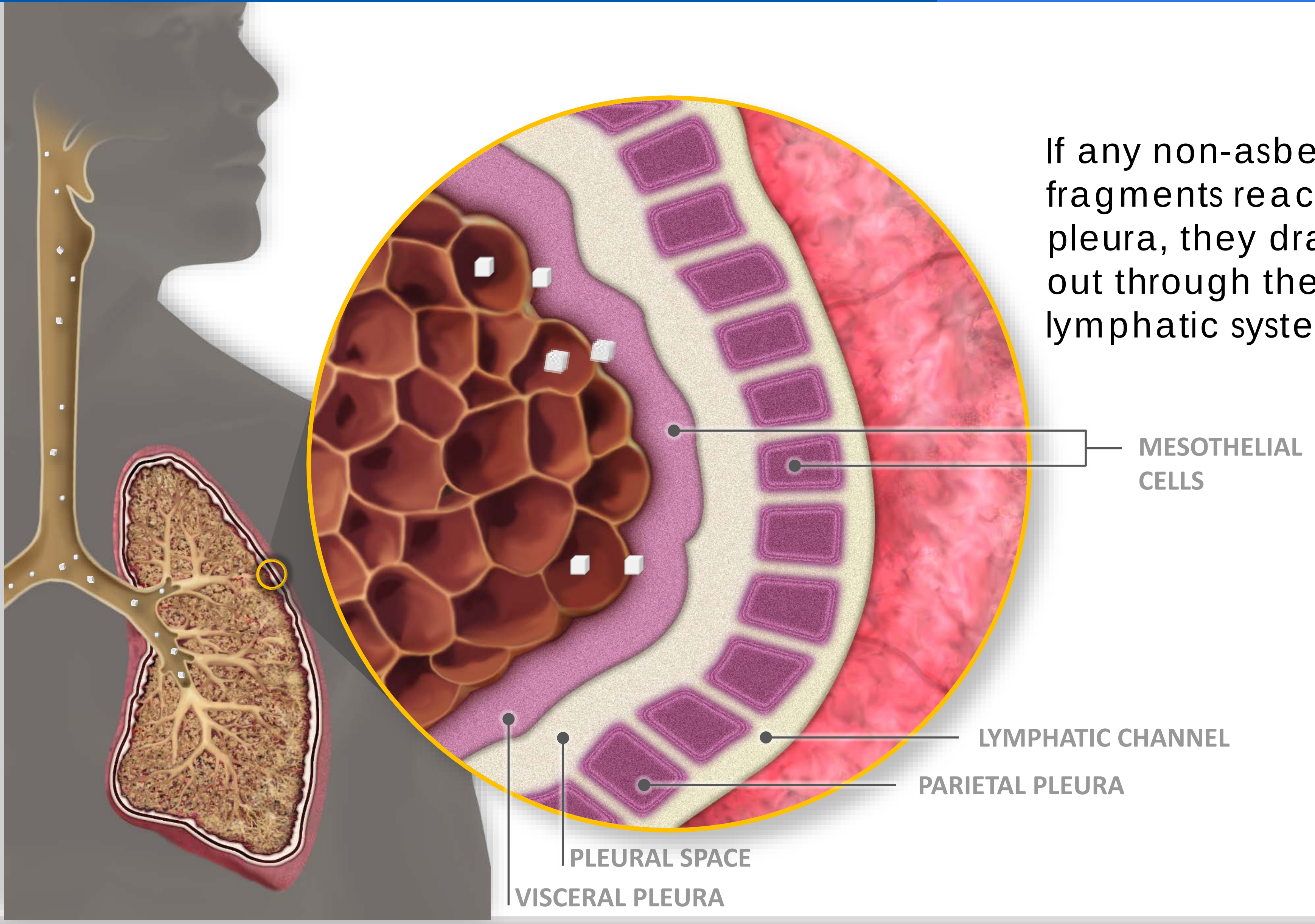


Non-toxic fragments are taken up by macrophages effectively



Small non-asbestos fragments are removed by macrophages

Non-Asbestos Fragments Are Removed Through Lymphatic Channels



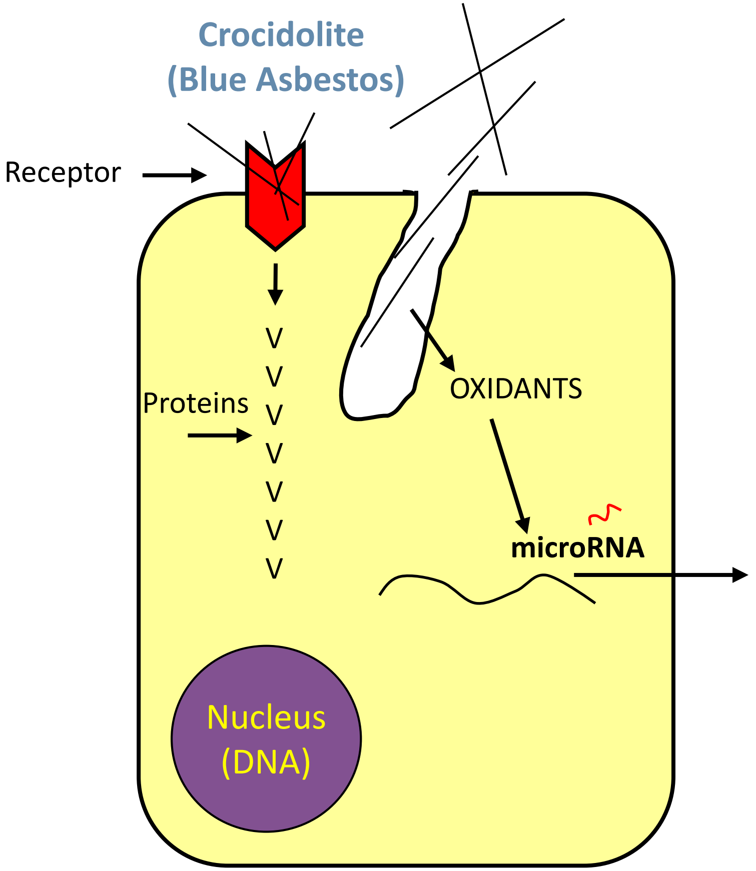
If any non-asbestos fragments reach the pleura, they drain out through the lymphatic system

Emphasis: What are the properties of minerals associated with cancer development?

- Focus on early hallmarks of cancer/mesothelioma development.
  - ↑ Cell Proliferation
  - ↑ Cell Survival
  - Gene/Proteins regulating mesothelial cell proliferation and survival.
  - Properties of minerals (emphasis on talcs) causing these changes.
- Correlations with animal models and humans.

High Iron-containing Amphibole Asbestos Fibers Cause Hallmarks of Cancer Development

- Crocidolite Asbestos Causes Signals From Outer Membranes Of Mesothelial Cells To Activate Proteins Causing Cell Division And Other Steps In Cancer Development.



Proteins → Cell Division/Survival → **CANCER**

V = Cell signaling chain of proteins

What We Learned About Asbestos: Chemistry Matters

ASBESTOS

- **SERPENTINE**
  - White - Chrysotile
    - $Mg_6Si_4O_{10}(OH)_8$
- **AMPHIBOLE**
  - Blue - Crocidolite
    - $Na_2(Fe^{3+})_2(Fe^{2+})_3Si_{18}O_{22}(OH)_2$
  - Brown - Amosite
    - $(Fe^{2+},Mg)_7Si_8O_{22}(OH)_2$
  - (Crocidolite and Amosite: **High Iron Containing**)

Anthophyllite

$(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2$

Tremolite

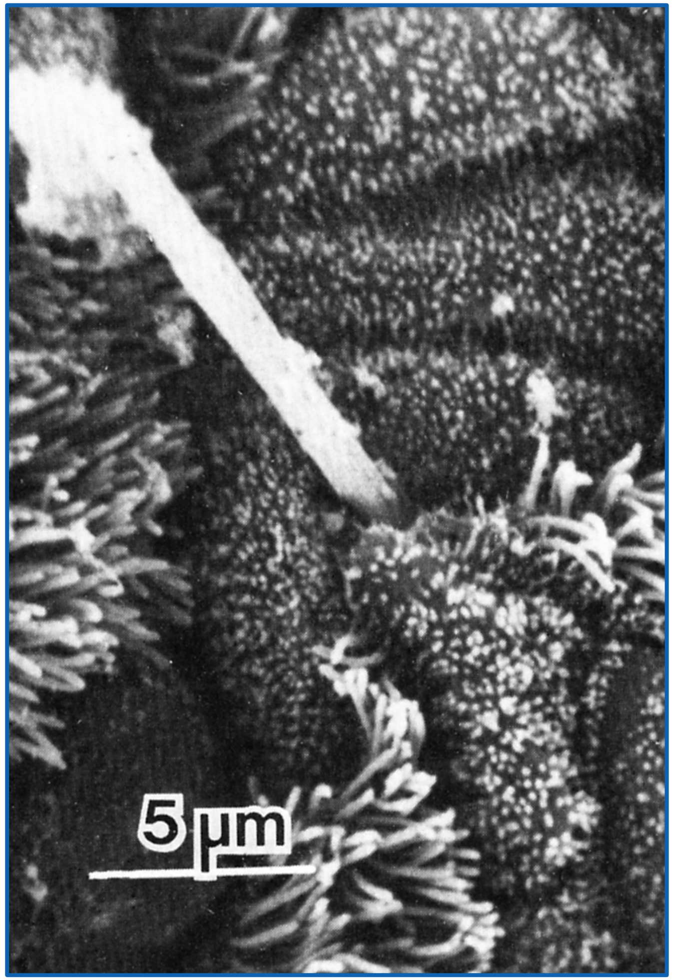
$Ca_2(Mg_{5)},Si_8O_{22}(OH)_2$

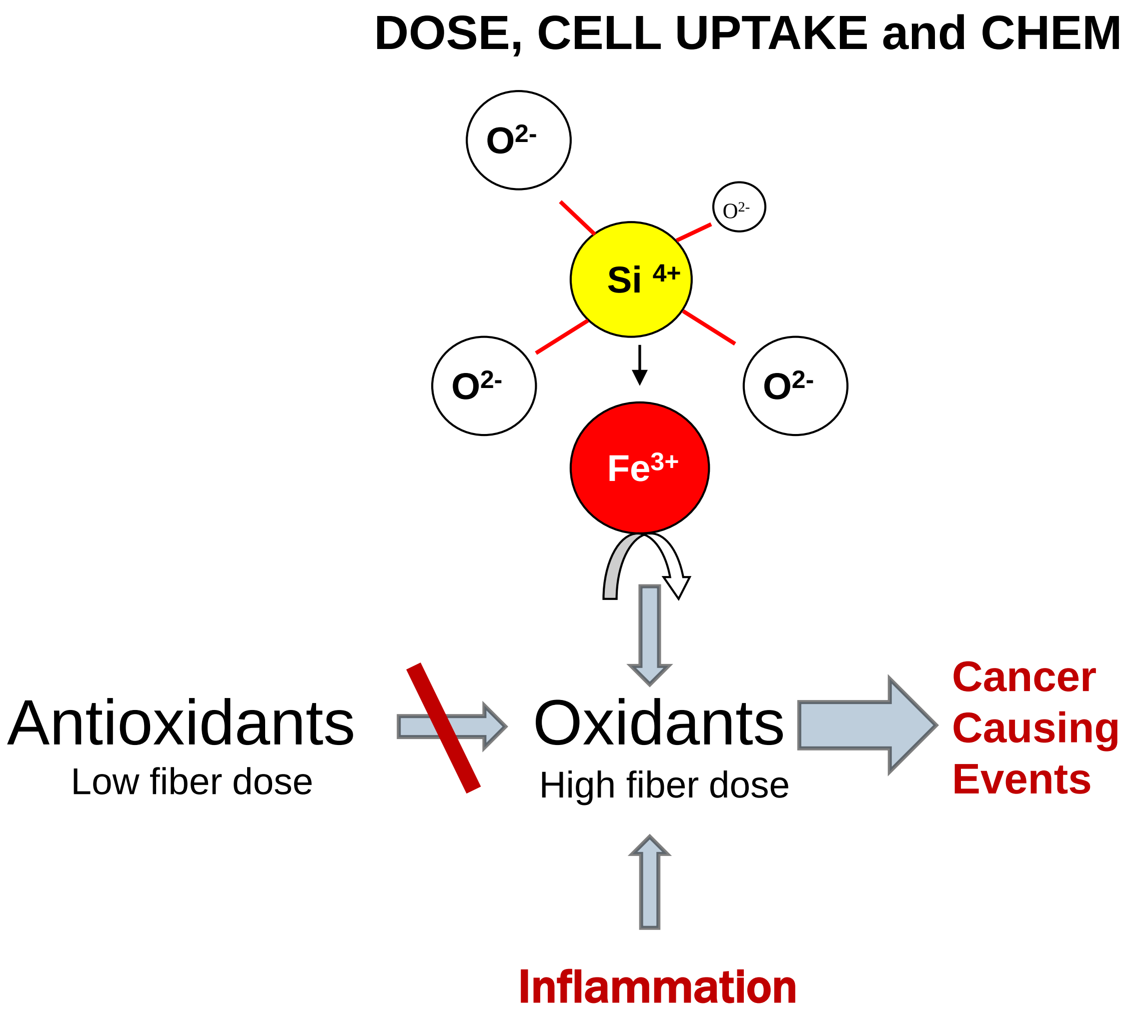
Actinolite

$Ca_2(Mg,Fe^{2+})_5Si_8O_{22}(OH)_2$

Fe=Iron

How Crocidolite and Amosite Asbestos Cause Persistent Release of Oxidants: Multiple Mechanisms

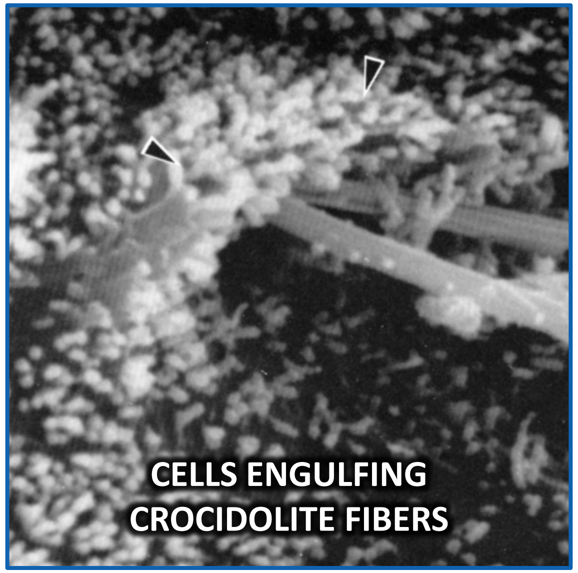


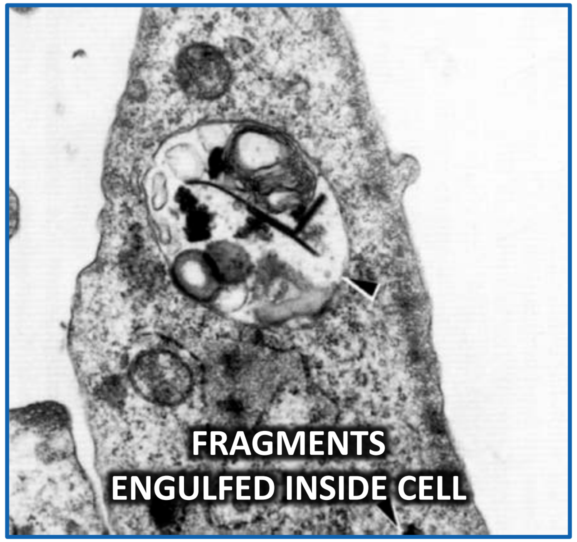


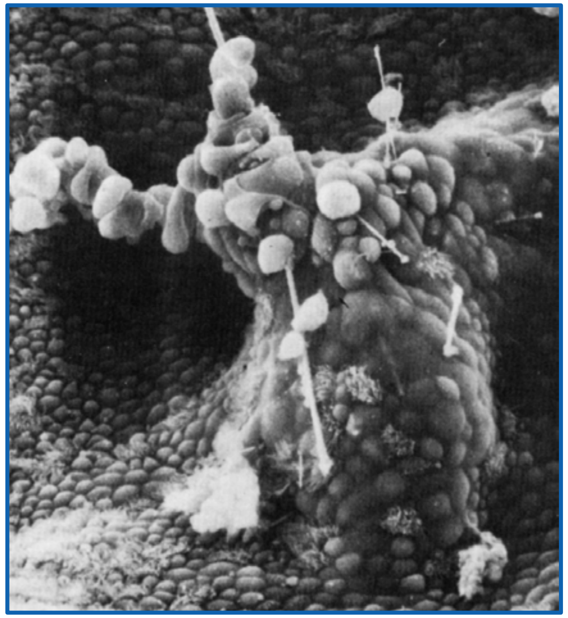
Multiple Properties of Crocidolite Asbestos Cause Oxidant Release

Abnormal Cell / Tissue Response

NORMAL CELL







CROCIDOLITE ASBESTOS FIBERS AND PRE-CANCEROUS CELLS

↑ Cell Division
↑ Cell Survival
↑ Inflammation

Do Non-Asbestiform Minerals Elicit Hallmarks of Cancer Development ?

MINERAL FAMILY	ASBESTIFORM	NON-ASBESTIFORM (including cleavage fragments)
Serpentine	Chrysotile	Antigorite/Lizardite
Amphibole	Crocidolite	Riebeckite
	Amosite	Cummingtonite-Grunerite
	Tremolite Asbestos	Tremolite
	Anthophyllite Asbestos	Anthophyllite
	Actinolite Asbestos	Actinolite

Asbestos vs. Non-Asbestos Fragments (Mossman Studies)

Study	Asbestos Fibers	Non-Asbestos Fragments
Cancer Res., 1983, Cell Division, Metaplasia	Crocidolite +	Riebeckite -
Cancer Res., 1987, Oxidant release	Crocidolite +	Riebeckite -
Cancer Res., 1988, Tumor promoting protein	Crocidolite +	Riebeckite -
PNAS USA, 1993, Antioxidant enzymes	Crocidolite +	Riebeckite -
Am. J. Resp. Crit. Care Med., 1994, c-fos, c-jun, AP-1	Crocidolite +	Riebeckite -
Am. J. Resp. Cell Mol. Biol., 1994, Early response genes	Crocidolite +	Riebeckite -
Cancer Res., 1996, ERK1/2 proteins	Crocidolite +	Riebeckite -
Carcinogenesis, 1996, Oxidative DNA damage	Crocidolite +	Riebeckite -

Asbestos vs. Non-Asbestos Fragments (Mossman Studies)

Study	Asbestos Fibers	Non-Asbestos Fragments
Am. J. Path., 1997, Cell survival protein	Crocidolite +	Riebeckite -
Am. J. Resp. Cell Mol. Biol., 1997, Programmed cell death	Crocidolite +	Riebeckite -
Toxic. Appl. Pharm., 1997, Cell survival	Crocidolite +	NYS* Talc (11%, 37%, 59% fibers)
Am. J. Physiol., 1997, Cell receptor interference	Crocidolite +	Riebeckite -
Am. J. Resp. Cell Molec. Biol., 2009, Increased gene expression	Crocidolite +	Talc -
J. Toxic. Environ. Health, 2010, Differential gene expression	Crocidolite +	Talc -
Langmuir, 2013 Receptor stimulation	Crocidolite +	Riebeckite -

*NYS = 3 New York State Gouvenor Mine samples containing nonasbestiform tremolite and anthophyllite.

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Mineralogical Features Associated with Cytotoxic and Proliferative Effects of Fibrous Talc and Asbestos on Rodent Tracheal Epithelial and Pleural Mesothelial Cells

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- Crocidolite and chrysotile asbestos or 3 New York fibrous talcs (11, 37, 59%) added for 7 days. Multiple doses and parameters considered.
- ‘Fiber’ defined as particles with aspect ratio of at least 5.
- Cells examined for increases and decreases in colonies (toxicity).
- Only asbestos caused significant increases in cell survival.

TABLE 1

Characterization of Talc and Asbestos Samples

Sample	Mineralogy
	Mineral composition (% of sample)
FD14	Talc (37), tremolite (35), serpentine (15), other (<2), unknown (12)[a]
S157	Talc (60), tremolite (12), unknown (21), other (4), anthophyllite (3), quartz (1)
CPS183	Talc (50), quartz (12), unknown (28), tremolite (4), other (4), anthophyllite (3)
NIEHS crocidolite	Riebeckite (100)
NIEHS chrysotile	Chrysotile (100)
	Mineralogy of fibers >5 μm (% of fibers)
FD14	Talc (62), amphibole (24),[b] talc/amphibole (14)
S157	Talc (84), amphibole (11), talc/amphibole (5)
CPS183	Talc (99), amphibole (1), talc/amphibole (<1)
NIEHS crocidolite	Crocidolite (100)
NIEHS chrysotile	Chrysotile (100)

Wylie et. al. Toxicol Appl Pharmacol. 1997 Nov;147(1):143-50

Life-time Rodent Studies Show That Non-Asbestos Fragments and Talcs Do Not Cause Mesotheliomas

Study	Asbestos	Non-Asbestos Fragment*
Stanton and Wrench 1972,1981	All amphiboles **+**	Fibrous and platy talcs **-**
Wehner et al. 1972		Cosmetic talc **-**
Stenback + Rowland, 1978		Fibrous talc **-**
Wagner et al., 1982	Tremolite **+**	Tremolite **-**

* Numerous additional negative studies summarized in IARC, 2010

Life-time Rodent Studies Show That Non-Asbestos Fragments and Talcs Do Not Cause Mesotheliomas

Study	Asbestos	Non-Asbestos Fragment*
Smith et. al., 1979		Fibrous talcs **-**
McConnell et al., 1983 (feeding studies)	Tremolite **-**	Tremolite **-**
Coffin et al., 1992	Amosite **+**	Grunerite **-**
Cyphert et al., 2016	Libby amphibole **+**	Ontario ferroactinolite **-**

* Numerous additional negative studies in animal models and cells (Endo-Capron et al., 1993) summarized in IARC, 2010

Conclusions: Many Properties of Minerals are Important in the Development of Mesothelioma

- Dimensions (Long, Thin)
- Crystal Structure and Growth
- Flexibility/Tensile Strength
- Chemical Composition
- Surface Area Chemistry/Charge
- Durability*

* All these properties are interlinked to durability of fibers at sites of cancer development.

What We Have Learned About Mesothelioma in Humans:

- Dimensions alone do not explain the ability of a fiber to cause mesothelioma.
- **Many long thin fibers do not cause mesothelioma in man.**
  - Glass and synthetic vitreous fibers
  - Rutile
  - Sepiolite
  - Wollastonite
  - Palygorskite
  - Micas
  - Mordenite
  - Potassium titanate
  - Cotton and cellulose

Suggestions:

- Focus on characterizing mineral properties that might explain the lack of carcinogenicity of non-asbestiform fragments such as tremolite.
- Use methods that distinguish between asbestiform and non-asbestiform amphiboles.
- Dose response is important in assessing numbers/concentrations of fibers with carcinogenic potential.