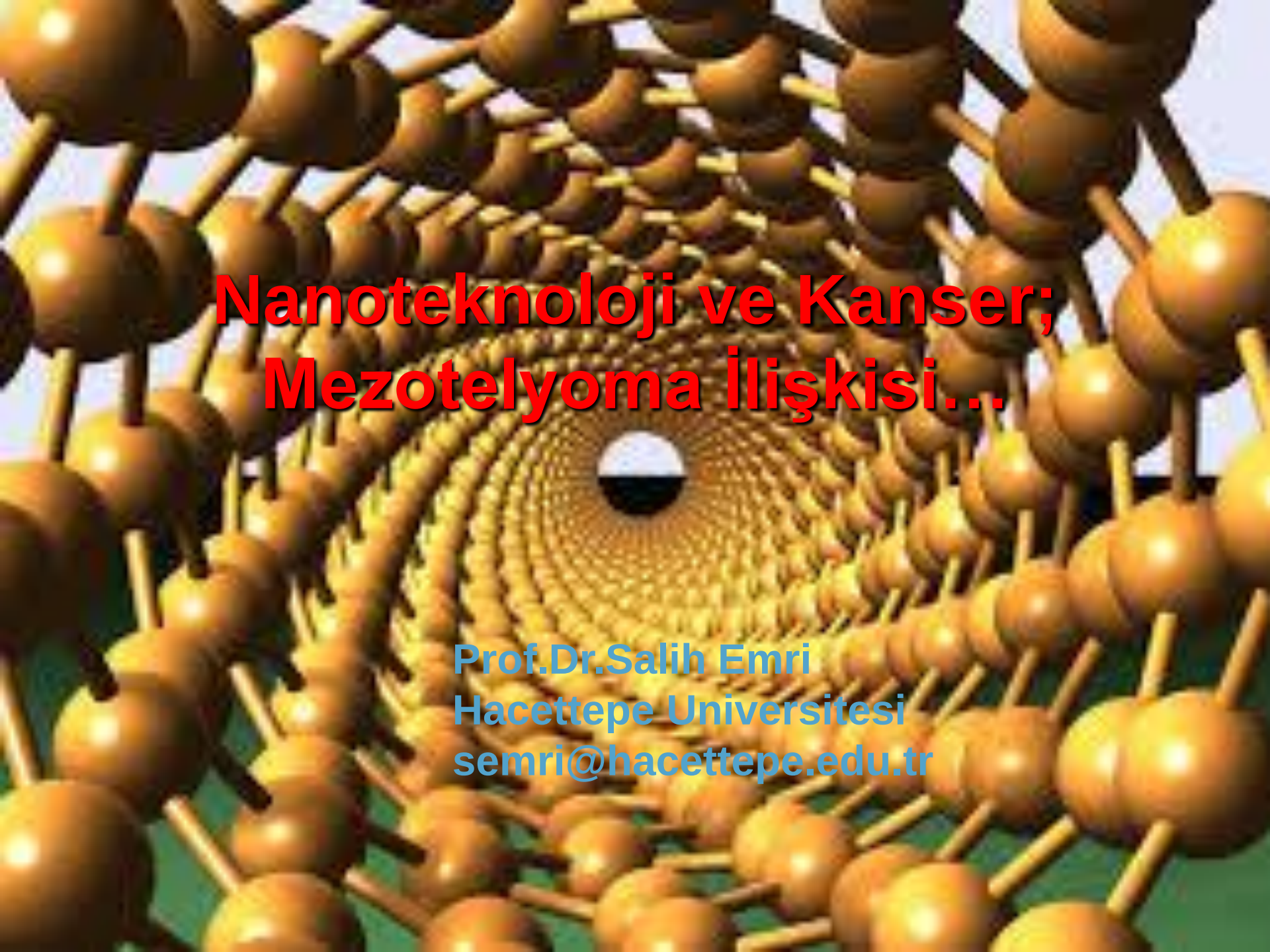


Nanoteknoloji ve Kanser; Mezotelyoma İlişkisi…

Prof.Dr.Salih Emri
Hacettepe Universitesi
semri@hacettepe.edu.tr

Nanopartikül Nedir?

Basic definition: based on the size (between 1-100 nm)

1 nanometric dimension: nanosheet

2 nanometric dimensions: nanotube

3 nanometric dimensions: nanoparticle

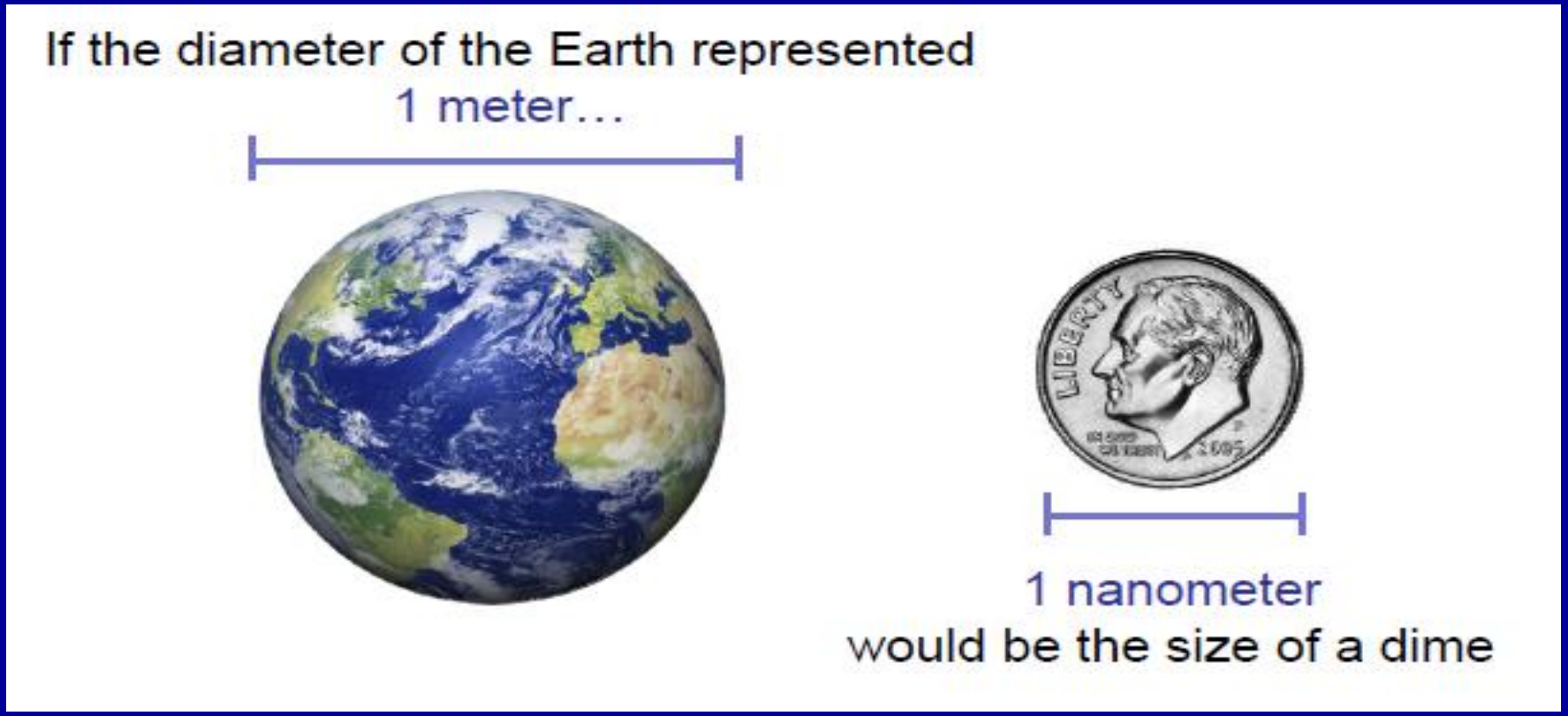
Nanomaterial: a material composed by nanoparticles

ISO (International Organization for Standardization) ISO/TS 27687:2008 Nanotechnologies - Terminology and definitions for nano objects - nanoparticle, nanofibre and nanoplate (http://www.iso.org/iso/iso_catalogue.htm)

ASTM (formerly American Society for Testing and Materials) 2456-06 Standard Terminology Relating to Nanotechnology (http://www.astm.org/Standard/index.shtml)

SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risk) Scientific Basis for the Definition of the Term "nanomaterial", ISSN 1831-4783 ISBN 978-92-79-12757-1, doi:10.2772/39703 ND-AS-09-004-EN-N.

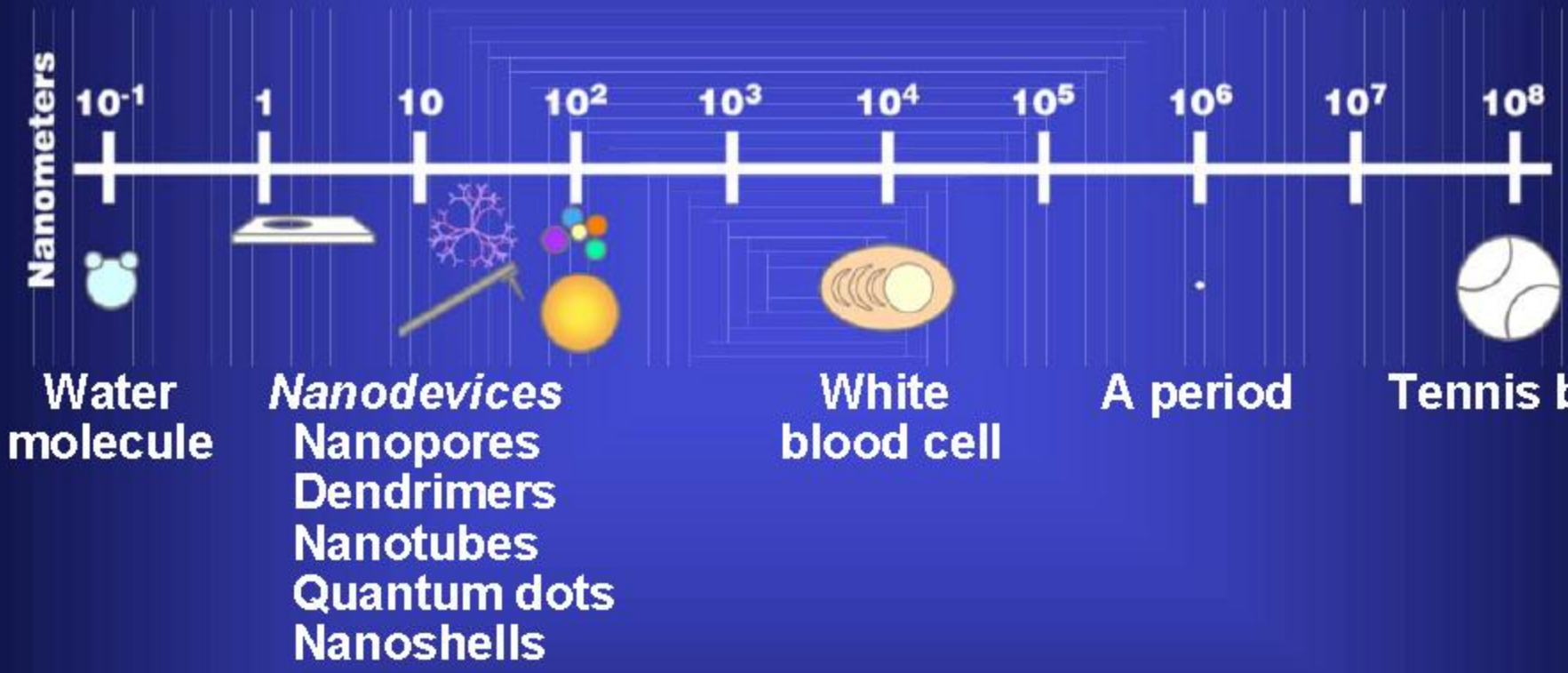
Nanoteknoloji, Nanopartikül,



Tanım:

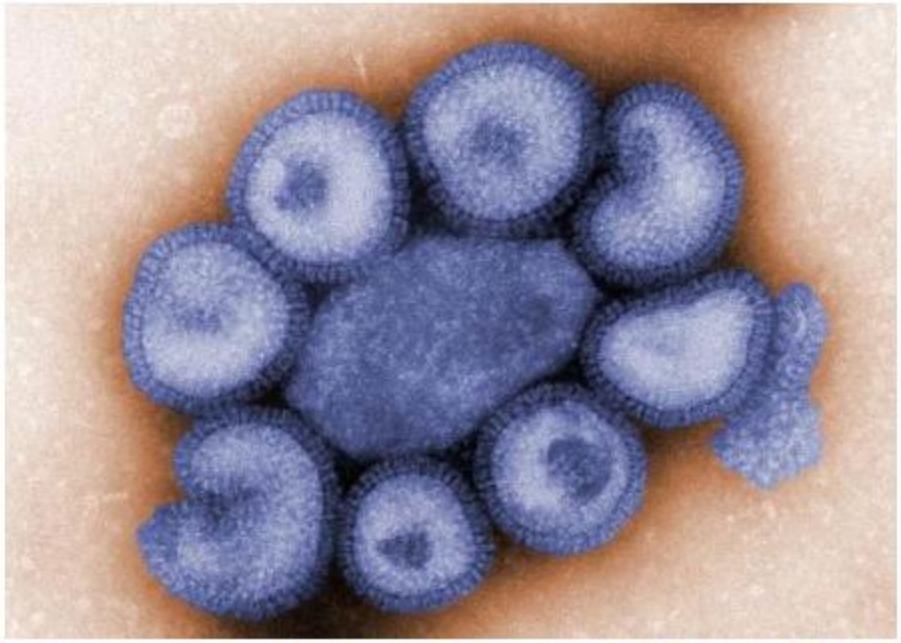
Nanometre büyüklüğündeki partiküller optik, manyetik, kimyasal ve yapısal özellikleri ile kendilerine ait geniş büyüklükteki,eşdeğerlerinden ayrılırlar.

Nanoteknoloji Nedir?
3. Endüstri Devrimi!..



Bir nanometre,bir metrenin milyarda biridir. İnsan saçının 1/80.000 kalınlığını düşünün. 10 H^+ atomu yan yana geldiğinde 1 nanometredir.

Nanopartiküllerin büyüklüklerinin karşıl
Mikroorganizma ve hücreler



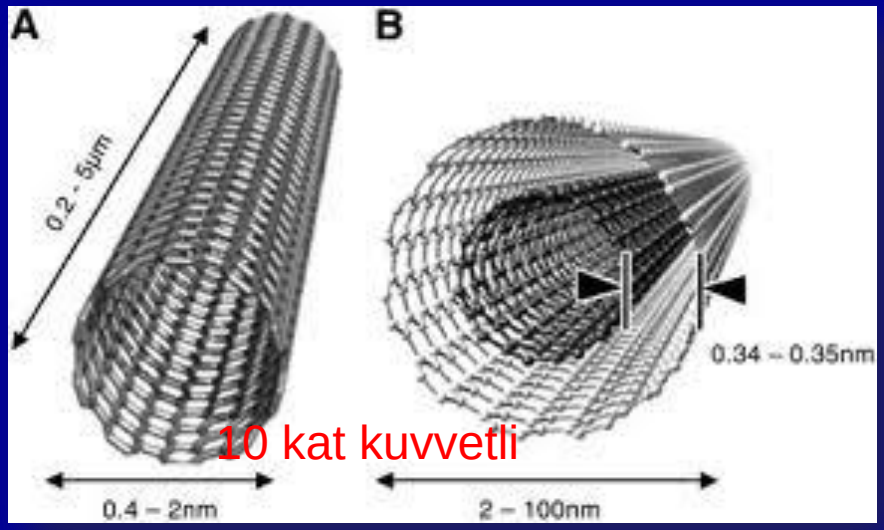
Influenza virus
75-100 nM

Nanoteknolojiye niçin bu kadar önem atfediliyor?

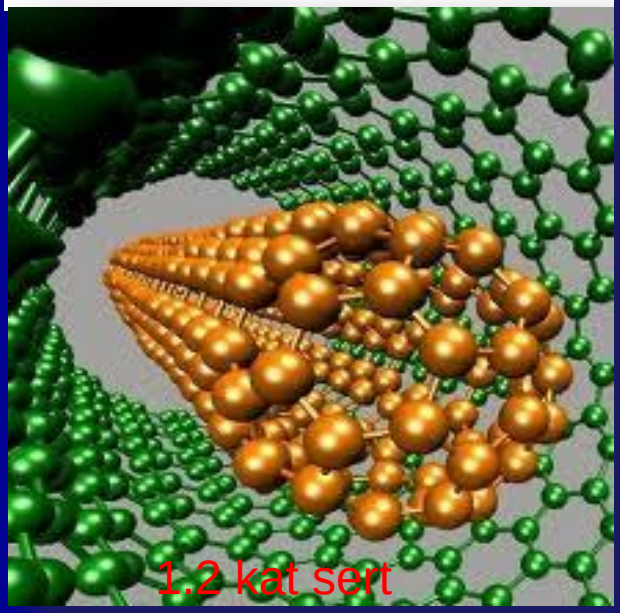
Hangisi Daha Kuvvetli?

Hangisi Daha Sert?

Çok hafif ve alışılmışın dışında elektrik ve ısı iletimi sağlıyorlar

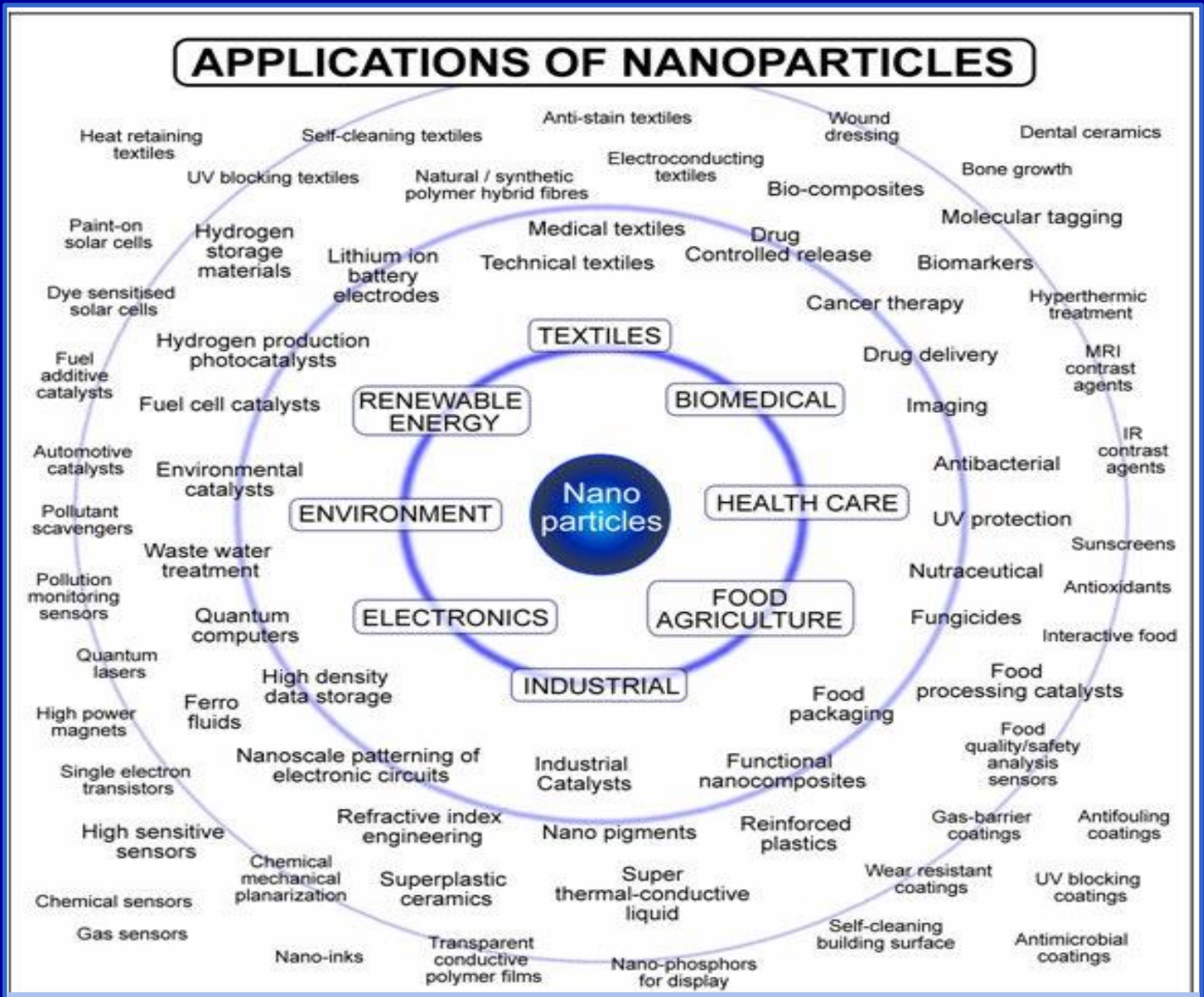


10 kat kuvvetli



1.2 kat sert

Nanoteknoloji kullanılan ve pazarda olan ürünler:

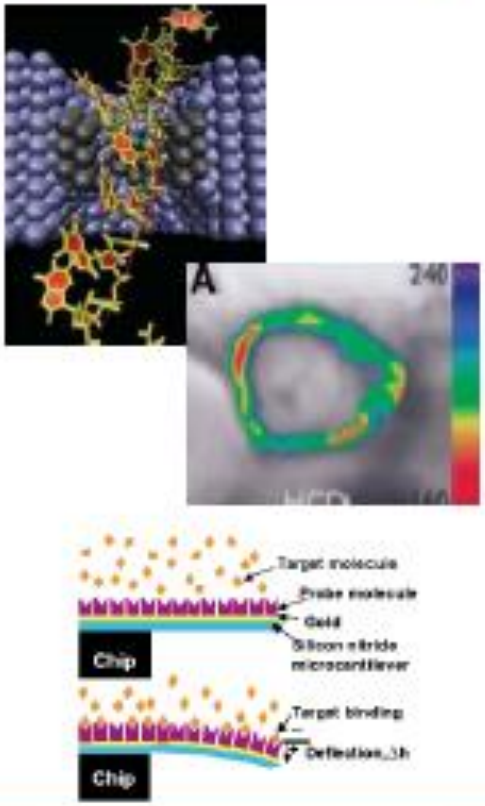


Multimilyar dolarlık bir endüstri ve 2015 yılı için trilyon dolara ulaşacağı tahmin ediliyor !..

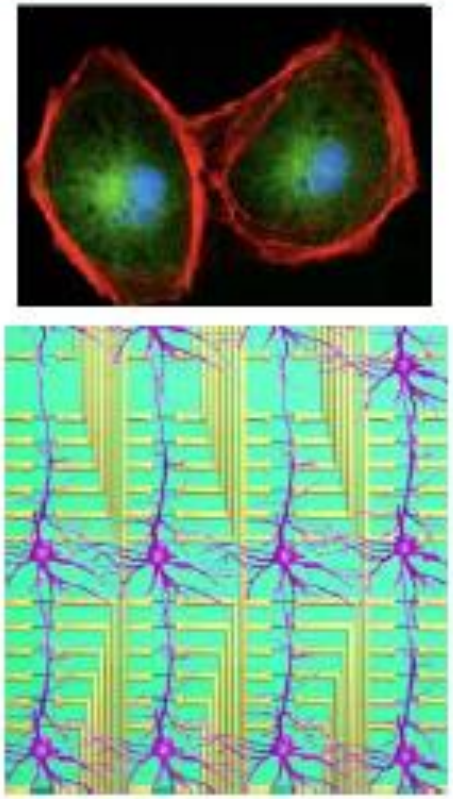
Elektronik sigaralar yüksek düzeylerde toksik metal nanopartikülleri içermektedir!..

Nanoteknoloji Biyomedikal Çözümler Üretmekte de Yoğun Olarak Kullanılmaya Başlamıştır!..

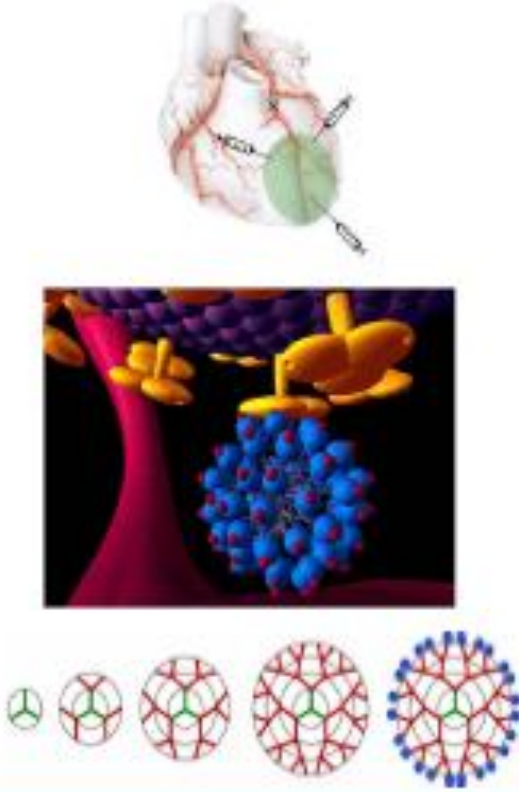
Diagnosis Early Detection



Cellular and Organ System Function



Therapeutics Intervention



Ne biliyoruz?

- Nanopartiküllerin özellikleri nanotıpta kullanımını özendirmektedir.
- Antikorlar ile fonksiyonilize edilerek spesifik hücrelere bağlanabilirler.
- Nanopartiküller biomarkır yolu ile tanıda kullanılabilir.

Ne biliyoruz?

- Nanopartiküller eksternal radyasyona cevap vererek ısı üretip, çevresindeki hücreleri öldürebilirler.
- Lipit ve polimer yapısındaki nanopartiküller hedefe vardıklarında dekompose olarak ilacı hücreye verebilirler.
- Quantum dots'ları çaplarına göre değişik renkte ışık saçarlar ve komplex tanılarda kullanılabilirler.

Ne biliyoruz?

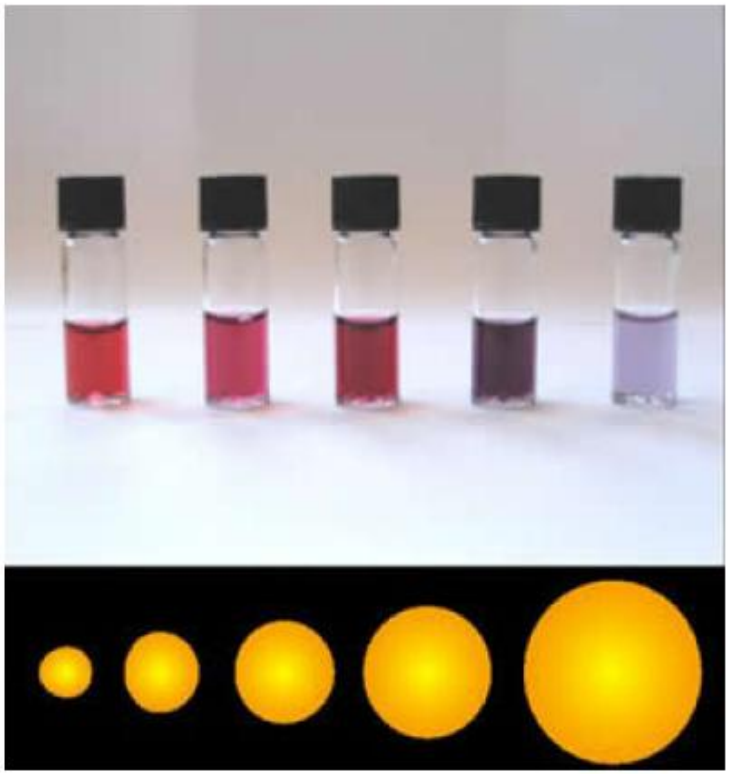
PEG, nanopartikülleri örtmede en sık kullanılan polimer olup, biyo-uygunluk ve biyo-mobiliteyi sağlar.

Hedefe yönelik olarak tasarlanan nanopartiküllerin kanser tedavisinde kullanılması yakındır.

En ideal nanopartikülün 3 fonksiyonu da içermesi beklenir; saptar, tanır ve tümör hücrelerini attake eder.

Niçin Dikkatli Olmalıyız?

- Çünkü şeyler(partiküller) bu ölçekte farklı davranırlar!..
- Burada kuantum mekanikleri önemli bir rol oynuyor.



Nanopartiküllerin boyutu büyüdükçe çözeltideki altın partiküllerin rengi berraktan pembe mor renk almaktadır.

http://www.webexhibits.org/causesofcolor/9.html

Niçin Dikkatli Olmalıyız?

Çünkü biyolojik işlemlerin ölçeği ile ilgili bir durum bu.

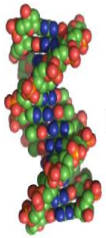
Why else do we care?

This is the scale of biological processes

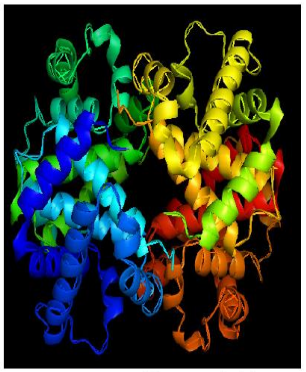
- Human cells and bacteria have diameters around 1-10 *micro*meters

BUT

- Cellular machinery is on the *nano*scale
  - Diameter of DNA is ~2 nanometers
  - Hemoglobin, the protein that carries oxygen through the body, is 5.5 nanometers in diameter



Structure of DNA
PDB ID: 1 BNA



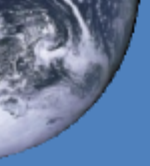
Structure of hemoglobin
PDB ID: 1 BUW

Nanopartiküllerin Sağlık Üzerine Yan Etkileri Va mıdır?

- **Findings from air pollution epidemiology**
  - Particles < 2.5 µm associated with respiratory and cardiovascular effects
- **Studies of industrial fumes (e.g., welding fumes) and combustion (e.g., diesel) products**
  - Wide range of effects: pulmonary and eye irritation, fever, lung canc
- **Initial animal inhalation studies of engineered nanomaterials**
  - Pulmonary fibrosis, granulomas, and inflammation
  - Lung cancer, mesothelioma-like effects
  - Cardiovascular effects: oxidative stress, plaque

15,000 excess deaths over a 2-week period

65,000 vehicles / day
4-5% heavy duty vehicles
17% of 78% cars – diesel
Diesel – very low sulphur
6°C, wind speed: 5m/s, RH: 87%



affect occupational health?

m NIOSH:

ed on results from human and animal studies, airborne nanoparticles can be
leposit in the respiratory tract; and based on animal studies, nanoparticles c
lood stream, and translocate to other organs." [1]

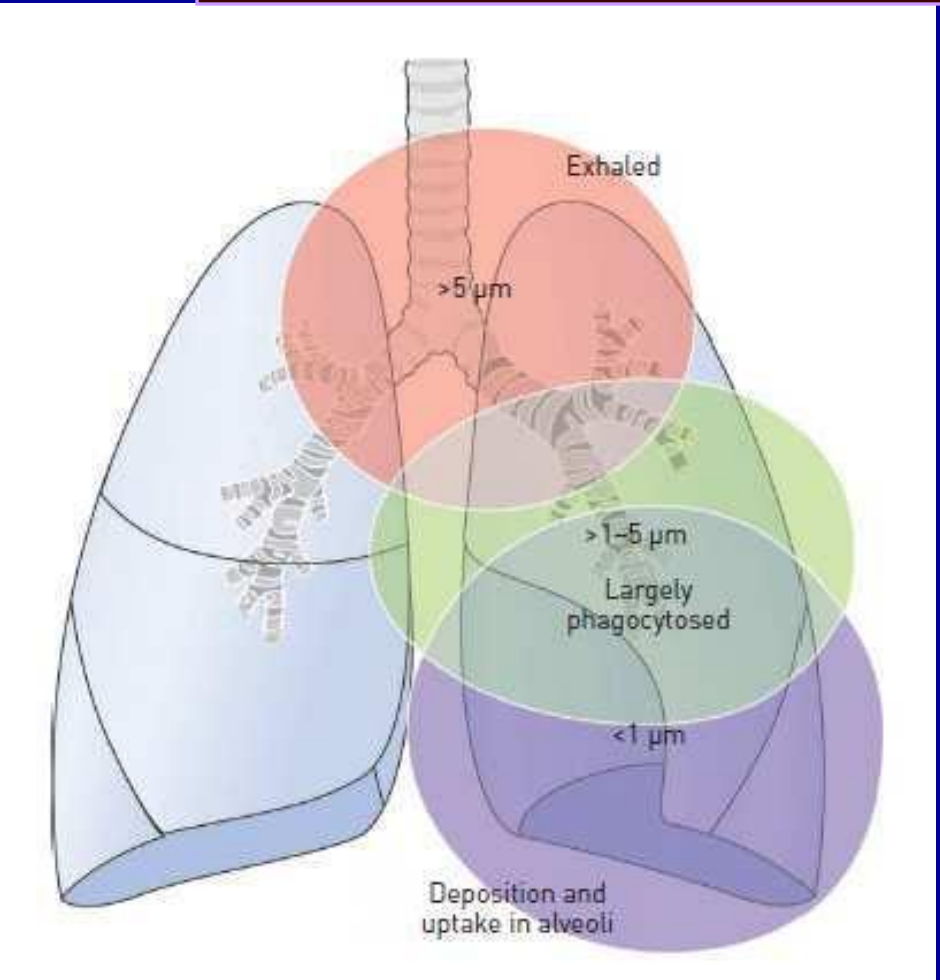
n other words, human and animal studies have shown that inhaled nanopar
nd up in the lungs, and nanoparticles in the blood can find their way to oth
possibly unintended) organs.

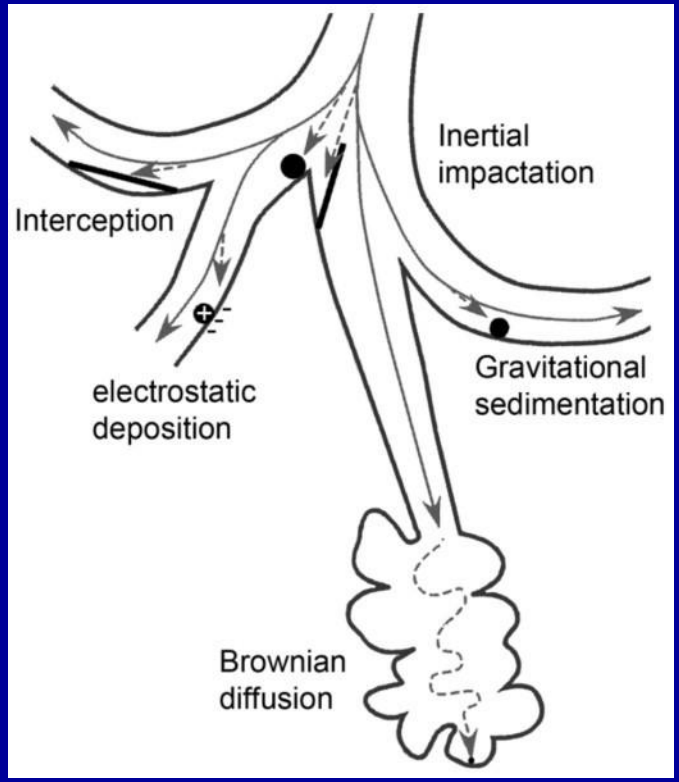
ies in workers exposed to aerosols of some manufactured or incidental micr
and nanoscale (ultrafine) particles have reported adverse lung effects inclu
ion decrements and obstructive and fibrotic lung diseases. The implications
es to engineered nanoparticles, which may have different particle properties
tain." [1]

asically, studies have shown that workers that inhaled incidentally created
anoparticles have reported health problems, but this may not be the case f
ype of nanoparticle.

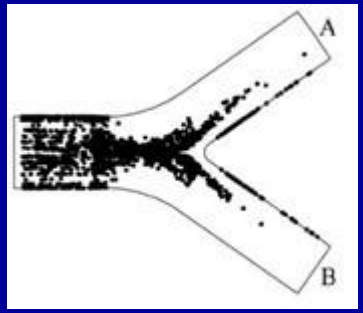
earch is needed to determine the key physical and chemical characteristics

Partikül Büyüklğü ve Akciğer Birikimi

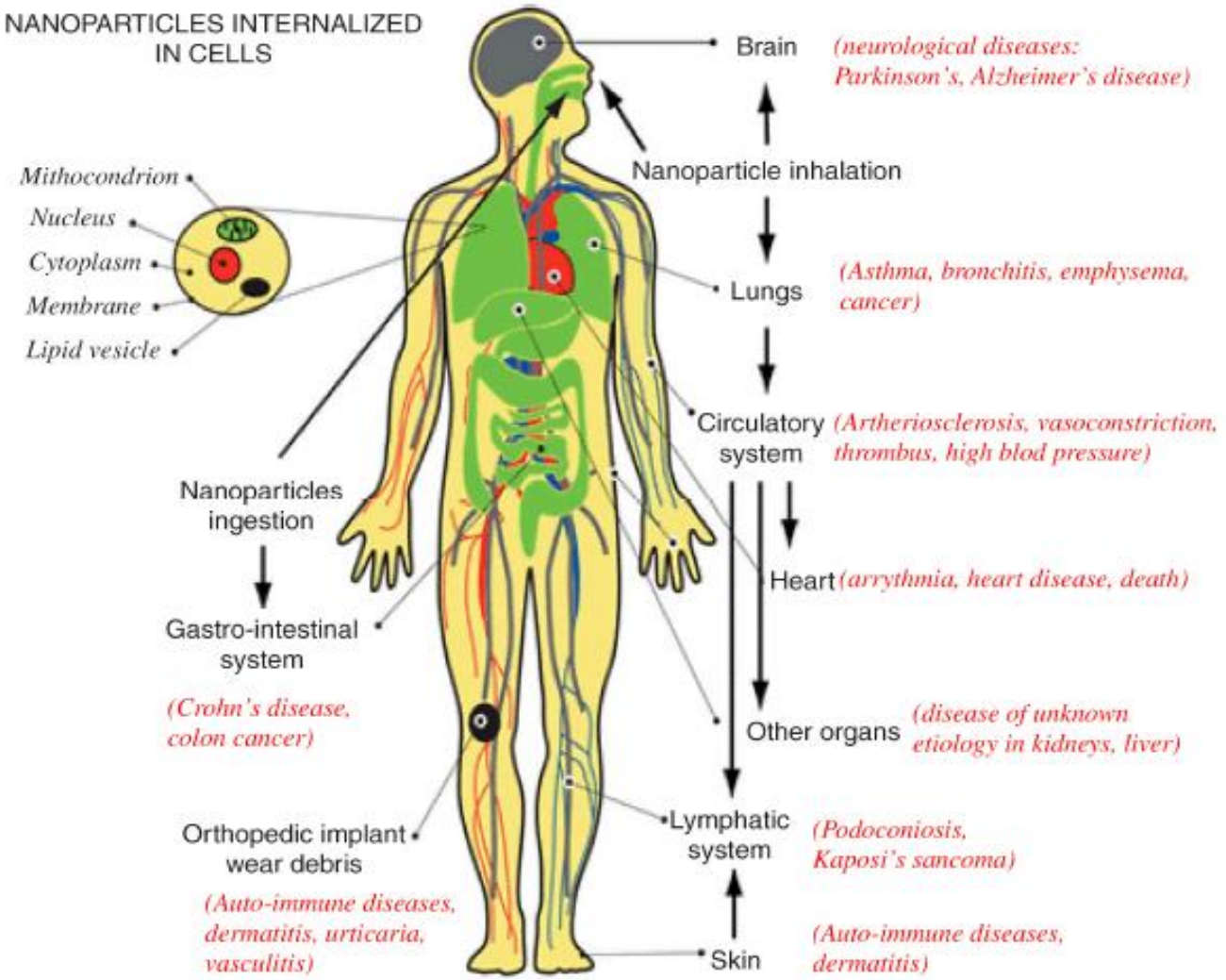




(van Rijt SH et al, ERJ 2014; 44(3): 765-774)

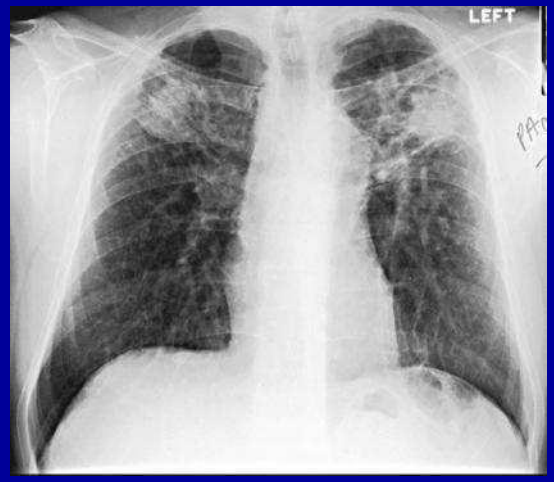


Nanopartiküller burundan beyine, akciğerlerden diğer organlara ve deri yolu ile penentre olabilirler



Nanopartiküllerin Yol Açtığı Pulmoner Fibrozis

Silicosis

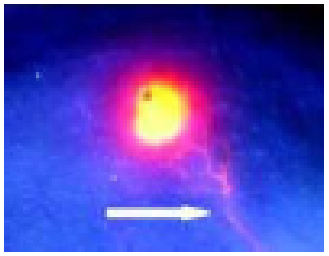


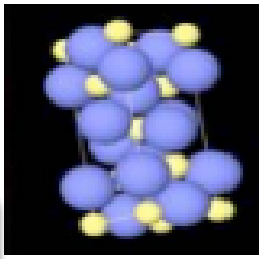
Asbestosis

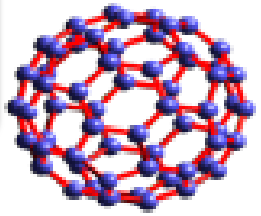
Aluminum welding pneumoconiosis

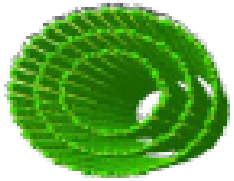
National Toxicology Program

- **Cadmium based "quantum dots"**
  - Role of skin integrity on pharmacokinetic studies after dermal exposure
- **Titanium dioxides**: Dermal pharmacokinetics
  - Impact of coatings and crystal state
- **Carbon based fullerenes**: Pulmonary and oral toxicity
  - Impact of size of C60 aggregates
- **Multiwalled carbon nanotubes**
  - Influence of length and diameter on pulmonary toxicity
- **Ceric oxide**
  - Role of particle size on pulmonary toxicity
- **Nanosilver**
  - Role of particle size and shape on PK and toxicity









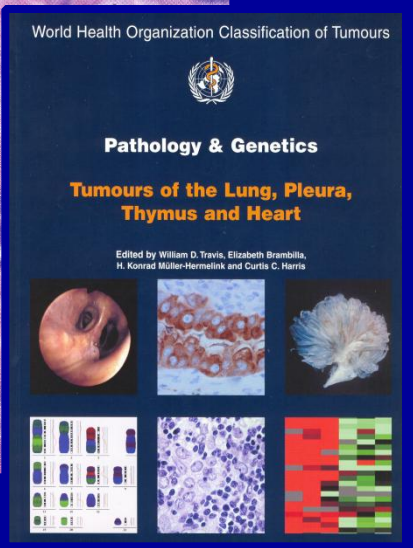
CHAPTER 2

Tumours of the Pleura

Mesothelioma is the most frequent neoplasm affecting the pleura and remains a major health threat for many years to come. Although the causation by asbestos is firmly established since more than 50 years, in many world regions, the use of this dangerous carcinogen peaked [illegible] and also the incidence and mortality rates are still climbing. In Western countries, the USA and most European countries, incidence and mortality rates are still climbing. In Western countries, approximately 300 000 mesothelioma deaths have been predicted to occur during the next 25 years. Despite this grim outlook, the worldwide production of asbestos has not declined significantly.

Less is known about the cellular and molecular mechanisms operative in the evolution of asbestos-induced mesothelioma. Clastogenic effects are well documented, but the sequential acquisition of genetic alterations which typically form the basis of tumour development, are still poorly understood. During the past decade, several studies have identified sequences of the oncogenic SV40 virus in human mesotheliomas, but it remains to be shown whether or not SV40 is causally involved in their etiology.

Mezotelyoma; pleural, perikardial ve peritoneal yüzeyleri döşeyen mezotel hücrelerinden köken alan bir kanserdir.



MPM-Epidemiyoloji

- Nadir, ama agresif bir kanser
- Son 20 yılda artış;WHO Mortalite İstatistikleri 2000-2004:
  - USA: 2433/yıl
  - Batı Avrupa: 2966/yıl
  - Doğu Avrupa: 340/yıl
  - UK; 1820 /yıl
  - Japonya: 825/yıl
- 2000-44 yılları arasında tüm Avrupa'da 168.000 ölüm olacağı tahmin ediliyor.Batı Ülkelerinde erkeklerde daha sıktır (5:1). Risk yaşla artıyor. Median yaş US için 72 yaş.

1.Julian Peto,IMIG 2008, Amsterdam

MPM;Nedenleri

- **Asbest teması**
  - % 70-80 (% 50-60 mesleksel, % 20 meslek dışı ve çevresel)
    - Kohort çalışmalarında asbest işçilerinin % 10 ‘u MPM’den ölmektedir.
- **Asbest dışı diğer doğal lifsel yapılı mineraller**
  - Erionite; İç Anadolu(Nevşehir)
  - Fluoro-edenite; Biancovilla,Sicily,IT
  - Winchite;Zonolite miners&millers, in Libby,MT,US
- **SV40 DNA virus (simian virus 40)**
- **Genetic yatkınlık;**
  - **BAP1 Somatik Mutasyon**
- **Radyasyon (Hodgkin Lenfomalı hastalarda 30 kat risk artımı)**
- **Carbon Nanotubes**

1. Emri S,et al. Anticancer Research. 2000; 20: 891-894.
2. Yang H et al. Oncology. 2008;9:147-157.
3. Bruin De MU, et al. Blood. 2009;16:3679-3681.
4. Public health assessment: Libby asbestos site, Libby, Lincoln County, Montana 2002. Agency for Toxic Substances and Disease Registry. Available from: http://www.atsdr.cdc.gov/ HAC/pha/libby3/lby_p1.html
5. Paoletti L, et al. Arch Env Health. 2000; 55:392-398.
6. Jasani B, et al. Arch pathol Lab Med.2012;136:262-267.
7. Testa JR. IMIG 2012.

Non-Asbestos Malignant Mesothelioma;Kapadokya Bölgesinde MPM.

Thorax, 1978, **33**, 181–192

An outbreak of pleural mesothelioma and chronic fibrosing pleurisy in the village of Karain/Ürgüp in Anatolia

Y. I. BARIS, A. A. SAHIN, M. OZESMI, I. KERSE, E. OZEN, B. KOLACAN, M. ALTINÖRS, AND A. GÖKTEPELI

From the Departments of Chest Diseases, Histology, and Pathology, Hacettepe University School of Medicine, and the Institute of Mineral Research and Exploration, Ankara, Turkey

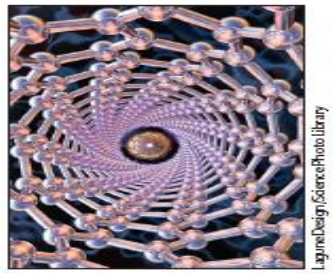
- Following initial observations of cases of malignant pleural mesothelioma in Karain village of Central Anatolia (1,2).

1. Baris Yi, et al. Kanser 1975; 5: 1-4
2. Baris Yi, et al. Thorax 1978; 33: 181-192.

Non-asbestos Mezotelyomalar

- MMMF ile ilişkili MPM rapor edilmemiştir!..
- Son zamanlarda carbon nanotube(CNT's) ve diğer high-aspect ratio olan ve silica, silver ve nickel den yapılan nanopartüküllerin MPM patogenezinde potansiyel riskleri olduğuna dair yayınlar mevcuttur.

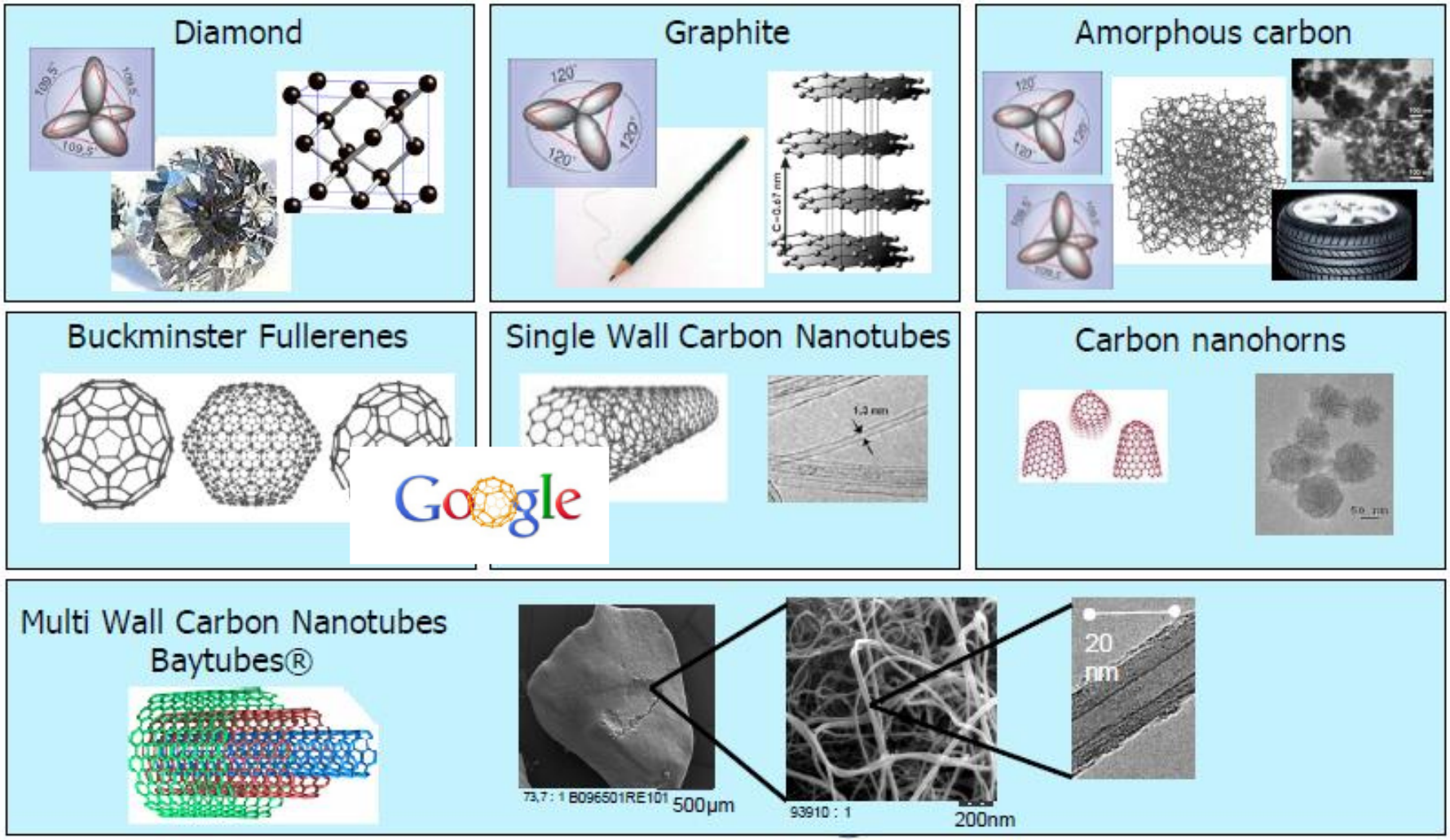
Space elevators, tennis racquets, and mesothelioma



Laguna Design/Science Photo Library

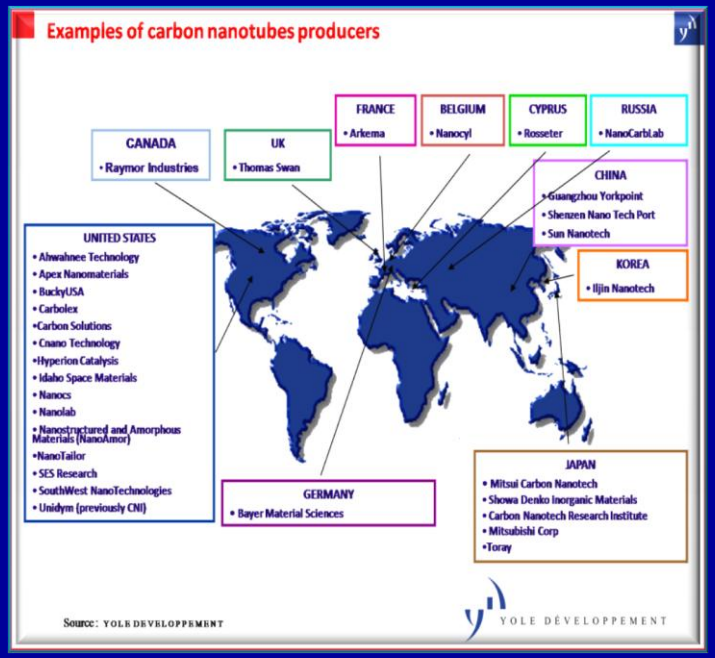
For more on the biological effects of carbon nanotubes see *Nature Nanotechnol* published online May 20, 2008; DOI:10.1038/nnano.2008.111; *J Toxicol Sci* 2008; 33: 105–16; and *J Mater Sci: Mater Med* 2008; 19: 1523–27

Karbon birçok kimyasal form ve şekilde karşımıza çıkmaktadır!..



Carbon Nanotubes(CNT)

- Nanoteknoloji ürünü olup, elektronik, uzay teknolojisi,GDO,optik ve tıpta çok geniş kullanım alanı bulmuştur.
- Silindirik moleküller olup nm. çap ve microm. veya mm. uzunlukta olabilirler
- 2006 yılında 270 milyon $US, 2014'de 2 milyar $US



Donaldson *et al. Particle and Fibre Toxicology* 2010, **7**:5
http://www.particleandfibretoxicology.com/content/7/1/5

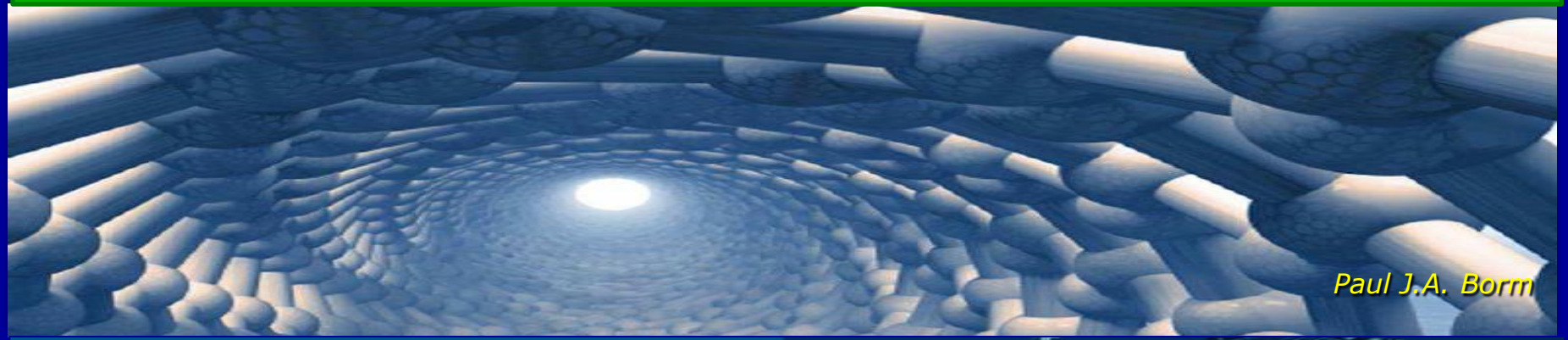
pft PARTICLE AND FIBRE TOXICOLOGY

REVIEW Open Access

Asbestos, carbon nanotubes and the pleural mesothelium: a review of the hypothesis regarding the role of long fibre retention in the parietal pleura, inflammation and mesothelioma

Ken Donaldson*, Fiona A Murphy, Rodger Duffin, Craig A Poland

The structure of carbon nanotubes (CNT) and why they might cause mesothelioma



ERS | EUROPEAN RESPIRATORY SOCIETY BARCELONA 2010

NANO REVIEWS COACTION

REVIEW ARTICLE

A concise review of carbon nanotube's toxicology

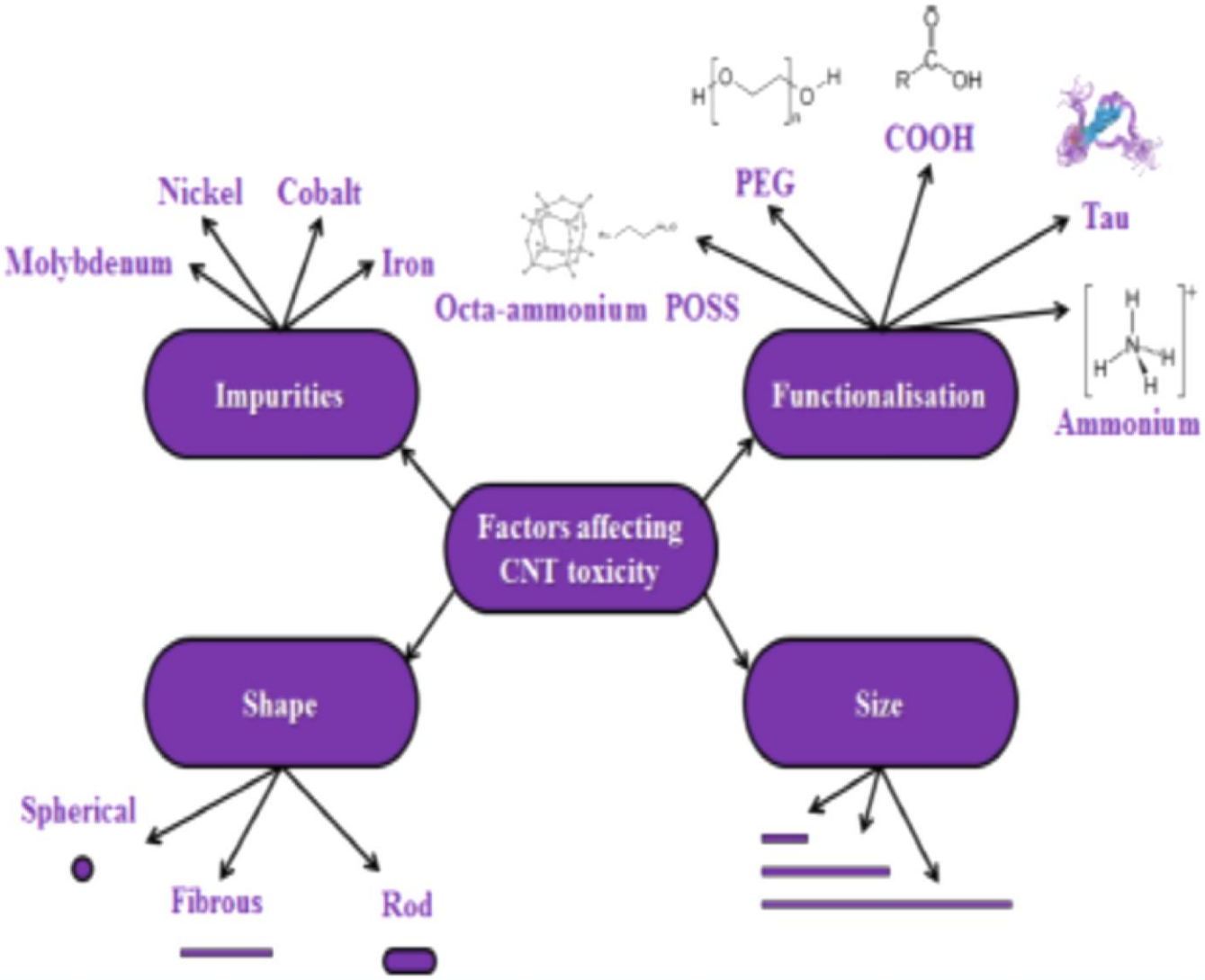
Seyed Yazdan Madani[1†], Abraham Mandel[1†] and Alexander M. Seifalian[1,2*]

[1]UCL Centre for Nanotechnology & Regenerative Medicine, UCL Division of Surgery & Interventional Science, University College London, London, UK; [2]Royal Free London NHS Foundation Trust Hospital, London, UK

Received: 23 May 2013; Revised: 3 October 2013; Accepted: 3 October 2013; Published: 3 December 2013

Niçin MPM Yapabilir?

- Nanopartiküller büyük partikülleren daha toksik
- Lifsel yapılı maddeler
  - Demetler halinde bulunuyorlar böylece daha kalın ve uzun hale geliyorlar
- Grafitik oldukları için biyolojik olarak biyopersistan yani durabl
- CNT's boyutlarına bağlı olarak çok geniş yüzeye sahipler ;SWCNT ~300m^2/g
- Fonksiyonlaştırme ve kimyasal modifikasyonlar toksisiteyi arttırıyor


Factors affecting CNT toxicity
Impurities
Nickel
Cobalt
Molybdenum
Iron
Functionalisation
PEG
COOH
Tau
Octa-ammonium POSS
Ammonium
Shape
Spherical
Fibrous
Rod
Size

Erionit

- Erionite fiberleri, her biri yaklaşık 0.5 µm çapında olan fibrillerden meydana gelmiş , 5-6µm çapında ve 30-40µm uzunluğunda bir mineraldir (1).

- Üç çeşit erionite tanımlanmıştır: erionite-Na, erionite-K, ve erionite-Ca, hepsi karsinojendir. (2-4).

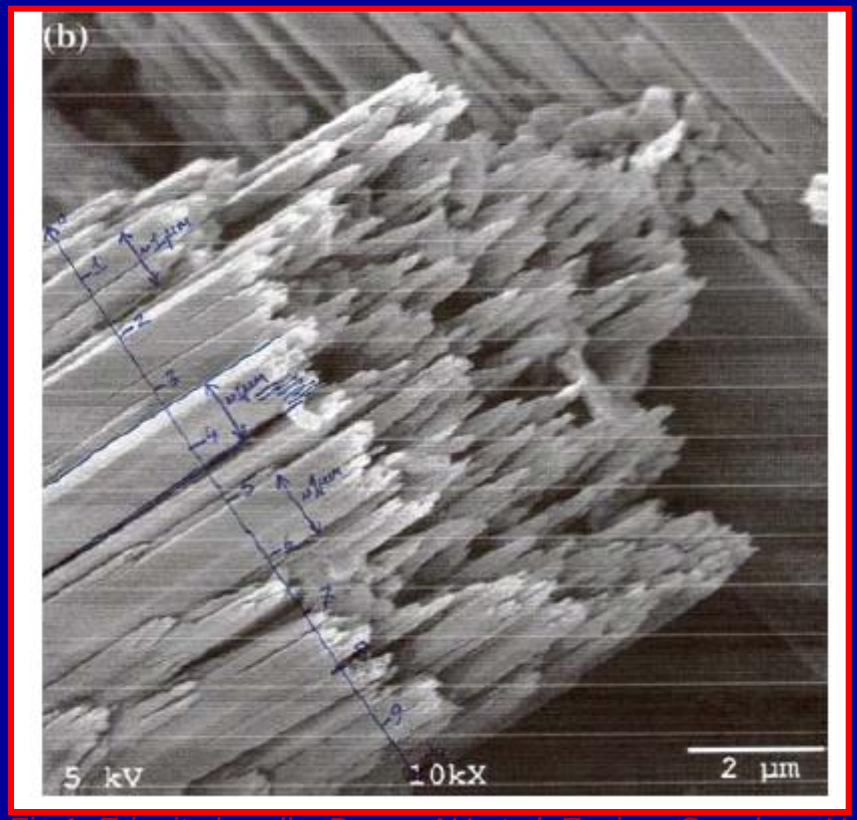
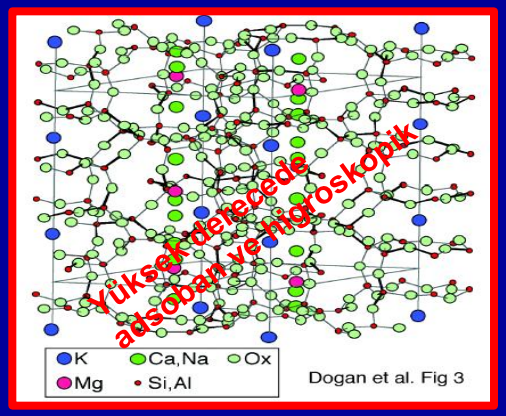


Fig 1: Erionite bundle. Dogan AU et al, Environ Geochem Health 2008, 30:367-381..

1. Coombs DS and et al. The Canadian Minerologist 1997; 33: 1571-1606,
2. Maltoni C, et al. Environ Res 1982; 29: 238-244.
3. Wagner JC, et al. Br J Cancer 1985; 51: 727-730.
4. IARC 1987;42:287.
5. Dogan AU. Cappadocian mesothelioma villages.The symposium on nutrition,environment, and cancer. March 31-April 3, 2002, Ankara, Turkey.

Çok Güçlü Bir Karsinojen;Erionite

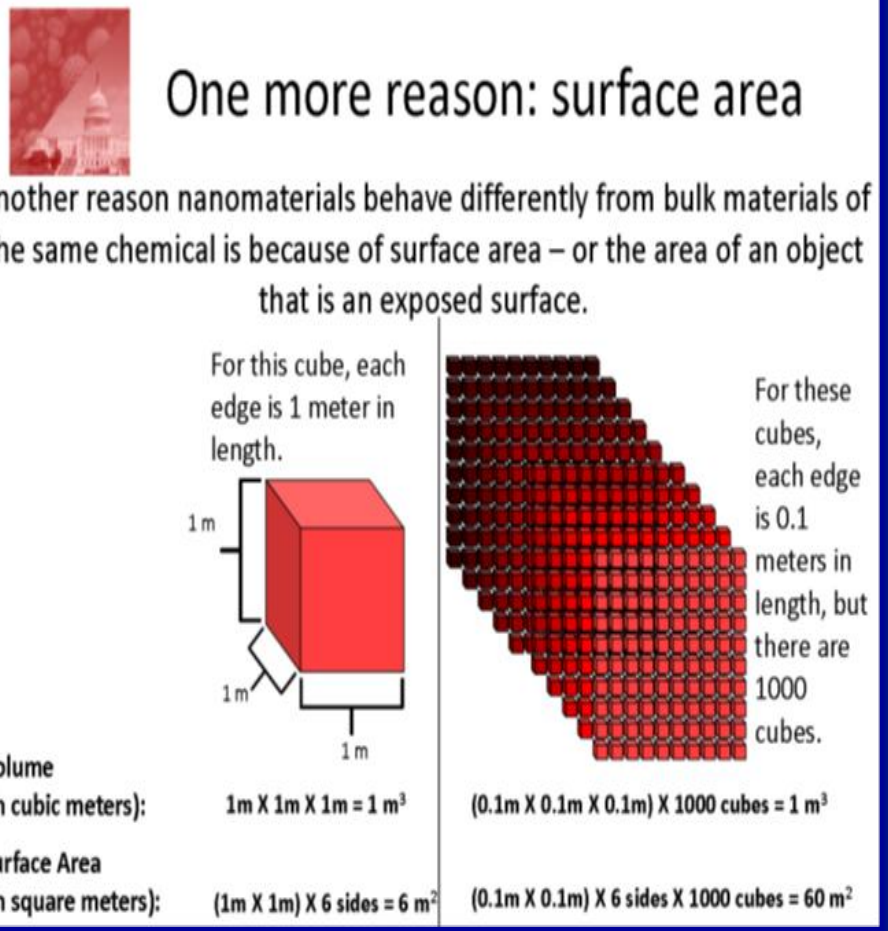
- Erionite, fibröz ve, hexagonal yapıdadır.
- İç yüzeyi 200 m^2/g olup, crocidolite asbestten 20 kat büyüktür.
- Küçük molekülleri adsorbe ederek yüksek katalitik aktivite göstermektedir.



Resim 1. Erionite'in molekül yapısı
$K2Ca1.5NaMg(Al8Si28)O72.28H2O$

1. Coffin DL, et al. IARC Sci Publ 1989; 90:167-172.
2. Dogan UA.Cancer Research 2006.

Nano farklı kimyasal yığın malzemelerden yüzey alanı nedeniyle farklı davranır!.



Zeolit Köylerinde Lif Analizi Çalışmaları

- Erionite retention is in the same range as tremolite in the BALF of tremolite exposed subjects analysed by TEM.
- The geometric mean of lung tissue fibre content was higher in patients from zeolite villages($130x10^6$ fibres.g^{-1} dry lung) than in the pts from asbestos villages ($11x10^6$ fibre.g^{-1} dry lung).
- The environment in tremolite villages was 8-1020 times more dustier

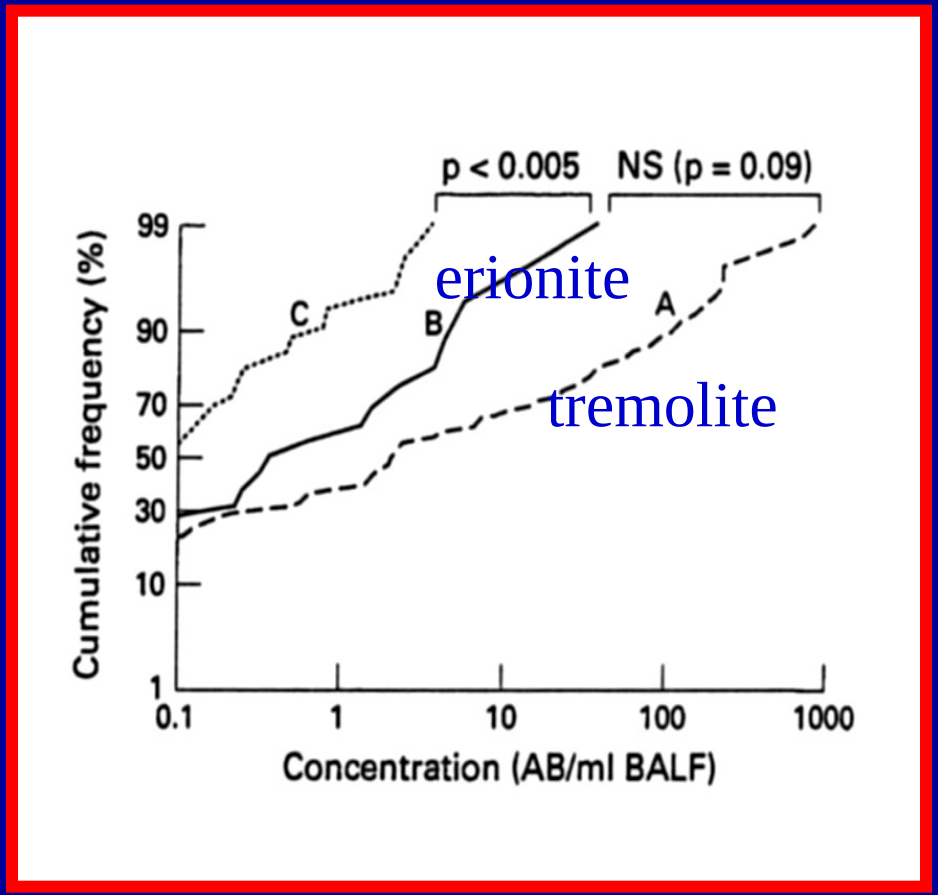


Fig. 1: The cumulative curve for concentration of FBs in the erionite group is compared with the curves recorded for concentration of ABs in control and tremolite group.

1. Dumortier P, et al. Occup Environ Med 2001;58:261-266.
2. Karakoca Y,et al. Indoor Built Environ 1997; 6: 100-105
3. Simonato L, et al. iARC Scientific Publication No.90, 1989.
4. Pooley FD. Dust and Disease. 1979.
5. Sebastien P, et al. Lab invest 1981; 44: 420-425.

Animal studies with CNT- initial focus on inflammation.

Exposure + model	material	outcome	reference
Intracheal instillation, guinea pigs (12.5 mg)	NanoLab CNT	Granuloma, Fibrosis (lung)	Huzcko 2005
Intracheal instillation, (0.25 and 1.25 mg/rat)	SWCNT	Inflammation Mutiple granuloma	Warheitet al 2004
Intracheal instillation, mice (0.1, 0.5 mg/mouse)	SWCNT	Granuloma Inflammation> CB	Lam et al, 2004
Intracheal instillation, rats (0.5- 5 mg/rat)	MWCNT	Inflammation Fibrosis	Muller et al, 2005
Pharyngeal aspiration (10- 40 ug/mouse)	SWCNT	Progressive fibrosis Granulomas	Shevdova et al, 2005
Inhalation, mice (0.3- 5 mg/m^3, 12 wks)	MWCNT	Systemic immune effects	Mitchell et al, 2007
Intraperitoneal injection P53 +/- mice	MWCNT C60	Granuloma formation	Takagi et al, 2008
Intraperitoneal injection Mice (C57BI/6)	SWCNT, MWCNT (specially fabricated)	Granuloma formation with MWCNT	Poland et al, 2008

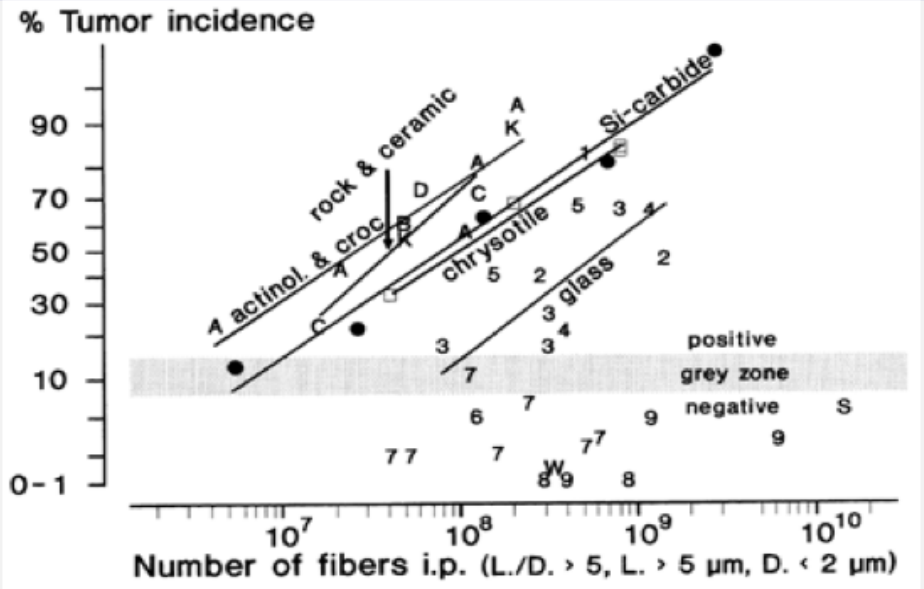
Animal studies with CNT- continued

Exposure + model	material	outcome	reference
Inhalation, mice (30 mg/m^3 for 6 hours)	MWCNT (Helix Materials)	Reach subpleural tissue, causing fibrosis	Ryman-Rasmussen 2009
Inhalation, Wistar rats (11 and 241 mg/m^3 for 6 hours), 3 months follow-up	MWCNT BayTubes, Micronized Quartz as reference	Dose-response inflammation. Septic fibrosis. Role of Co	Ellinger-Ziegelbauer & Pauluhn (2009)
Inhalation, Wistar rats (13 weeks, 0.1-6 mg/m^3)	MWCNT BayTubes, micronized	Granuloma and hyperplasia at overload conditions (> 0.4 mg/m^3)	Pauluhn, 2010

Based on the sub-chronic study, Bayer has suggested a OEL of 0.05 mg BayTubes/m^3 (Pauluhn et al, Reg Toxicol Pharmacol).

Animal studies with CNT- Focus on MPM.

Exposure + model	material	outcome	reference
Single intrascrotal injection,Fisher 344 rats	MWCNT 1mg/kg, 7 animals, Crocidolite and vehicle as reference	6/7; 85.7% i.p. disseminated meso. With bloody ascites	Sakamoto Y, et al, 2009
Single i.p. injection,19 p53 heterozygous mice	MWCNT $1X10^9$ (3mg/head)in1 ml suspension, crocidolite and fullerene as reference	14/16; 87.5% i.p. mesothelioma	Tagagi A, et al.2008



Sargent et al. Particle and Fibre Toxicology 2014, 11:3
http://www.particleandfibretoxicology.com/content/11/1/3

pft PARTICLE AND FIBRE TOXICOLOGY

RESEARCH Open Access

Promotion of lung adenocarcinoma following inhalation exposure to multi-walled carbon nanotubes

Linda M Sargent[1*], Dale W Porter[1], Lauren M Staska[2], Ann F Hubbs[1], David T Lowry[1], Lori Battelli[1],

- Bu çalışmada ilk kez inhale edilen MWCNT'lerin farelerde adeno ca ve adenom açısından kuvvetli promoter olduğunu gösteriyor.
- Yine bu çalışmada inhale edilen MWCNT'lerin sarkomatöz mezotelyoma gelişimini promot etiğini gösteriyor.
- Bundan dolayı MWCNT'lerin sigara veya diğer inisiyatörlere temas edenlerdende promoter olarak etki edebileceğini göstermektedir.
- Rijit MWCNT çap 40-50 nm ve 4 micm uzunluk en fazla inflamatuvar özelliğe sahip.

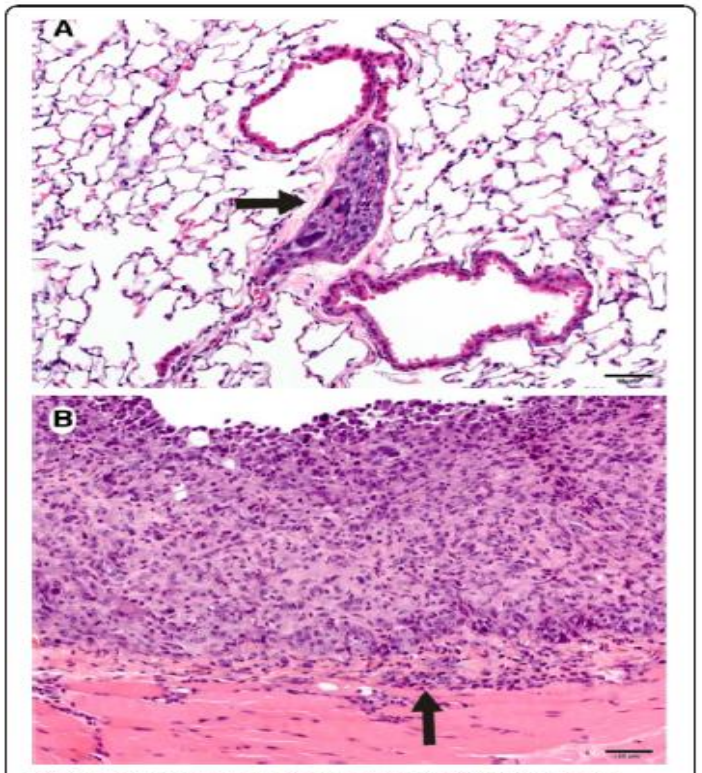
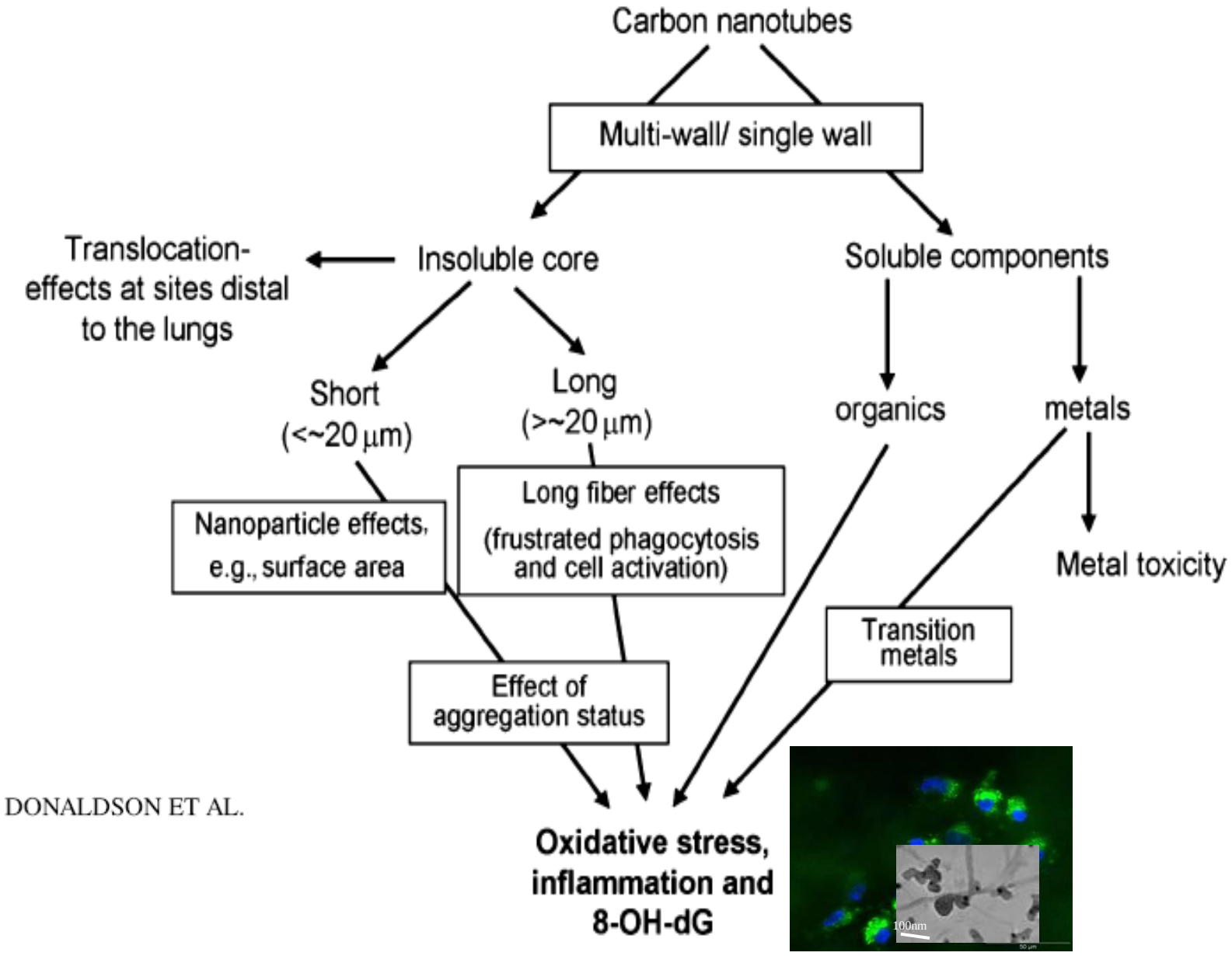


Figure 8 Malignant serosal tumors in the lung (A) and the diaphragm (B) in mice exposed to MC followed by MWCNT. A. The photomicrograph shows a pulmonary vein in the right cardiac lung lobe that contained variably-sized polygonal to spindloid cells similar to those on the diaphragm (Figure 8B). The arrow indicates a metastasis of the malignant serosal tumor (20×). The magnification bar is 50 microns. B. The skeletal muscle of the diaphragm in the photomicrograph is infiltrated by a nodular mass composed of variably-sized polygonal to spindloid cells (malignant serosal tumors). (20×). The magnification bar is 50 microns.

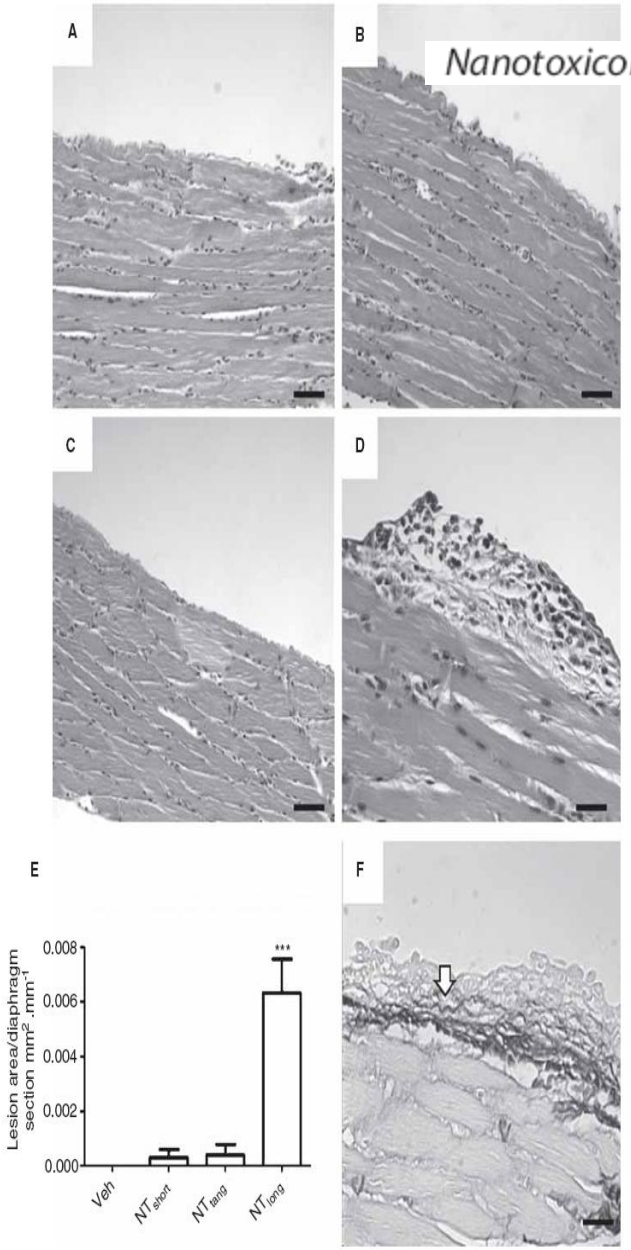
Sadece İnhale Edilebilen Lifler Sağlığa Zararlıdır!

Çap ≤1μ [Lif Boyutu] Uzunluk ≥10μ

Biyodurability


Carbon nanotubes
Multi-wall/ single wall
Translocation-
effects at sites distal
to the lungs
Insoluble core
Soluble components
Short
(<~20 μm)
Long
(>~20 μm)
organics
metals
Nanoparticle effects,
e.g., surface area
Long fiber effects
(frustrated phagocytosis
and cell activation)
Metal toxicity
Transition
metals
Effect of
aggregation status
DONALDSON ET AL.
Oxidative stress,
inflammation and
8-OH-dG
100nm

Nanotoxicology, 2012; Early Online, 1–11



5. Lesion formation along the diaphragm after pulmonary exposure to CNT. Histological sections through the diaphragm showing normal l pleura in the case of the vehical control (A) and the short CNT (B) and tangled CNT (C). Only the mice treated with the long CNT showed onal aggregations of inflammatory cells along the mesothelium (D). The extent of these lesions was quantified and is shown in (E). On g with picrosirius red, reticular collagen fibres could be seen stained red (F, arrow). Scale bar = 50 µm. Significance indicated compares ent groups with vehicle control *** indicates $p < 0.0001$.

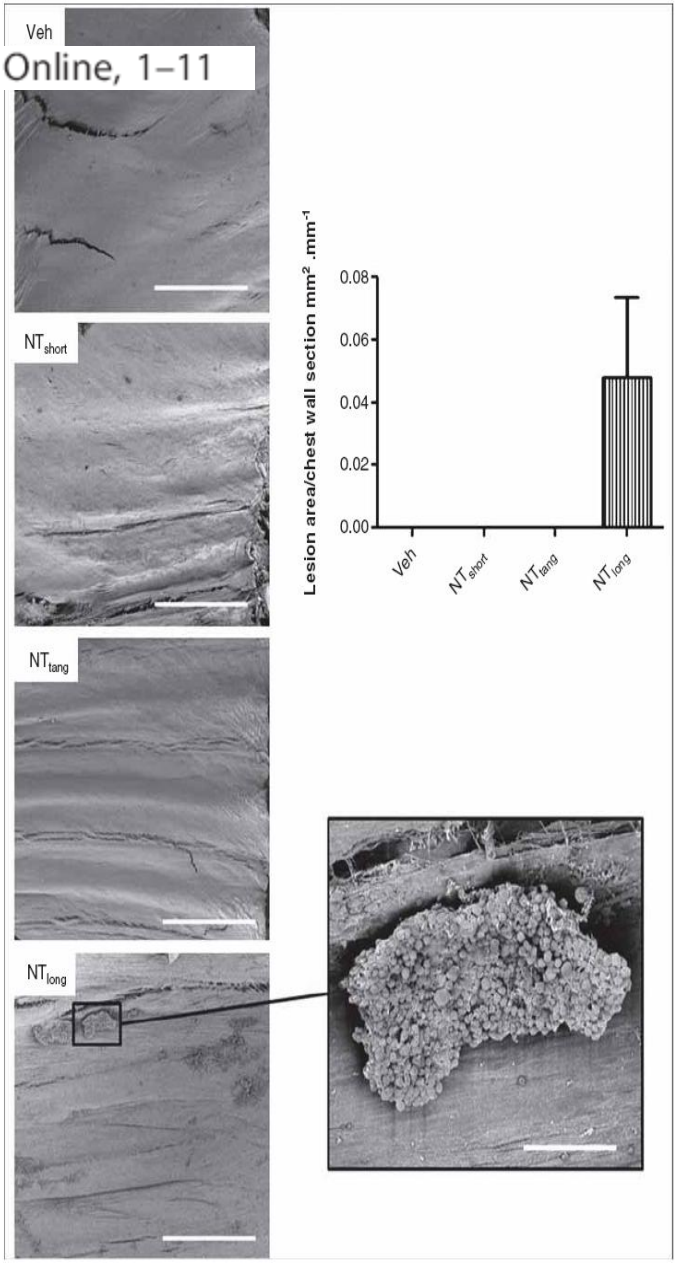
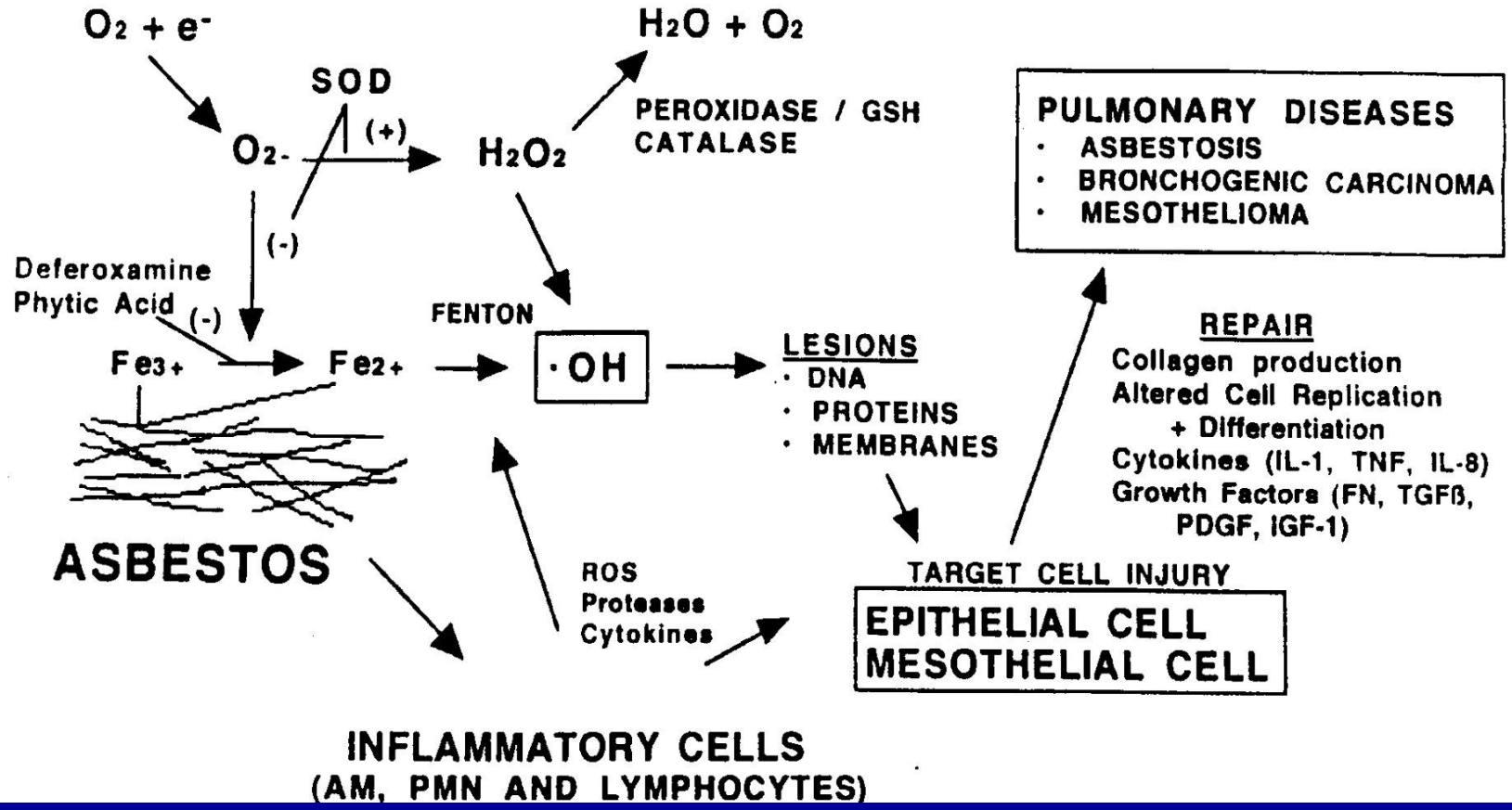
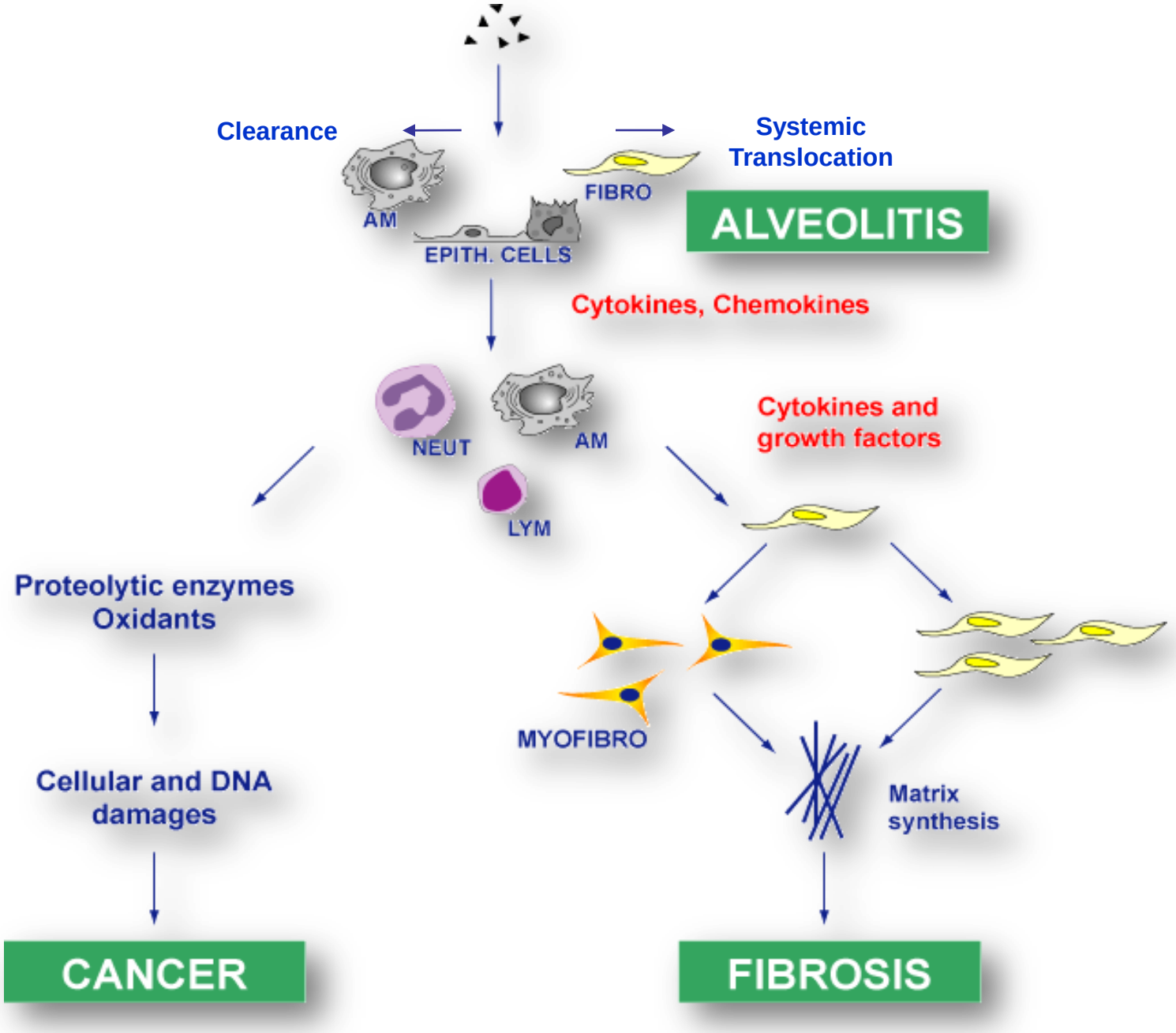


Figure 4. Lesion formation along the chest wall after pulmonary exposure to CNT. The chest wall was examined by scanning electron microscopy 6 weeks after the mice were exposed to the CNT panel by aspiration. Vehicle control, NT_{short}- and NT_{tang}-treated mice (see labels on images) had normal mesothelium. Aggregates of cells were identified overlying the mesothelium in the mice treated with the NT_{long} sample (see image labelled NT_{long} and callout showing a higher magnification). Scale bar = 1 µm.

Hücre Hasarının Mekanizması



KAMP AND WEITSMAN



dominique.lison@uclouvain.be

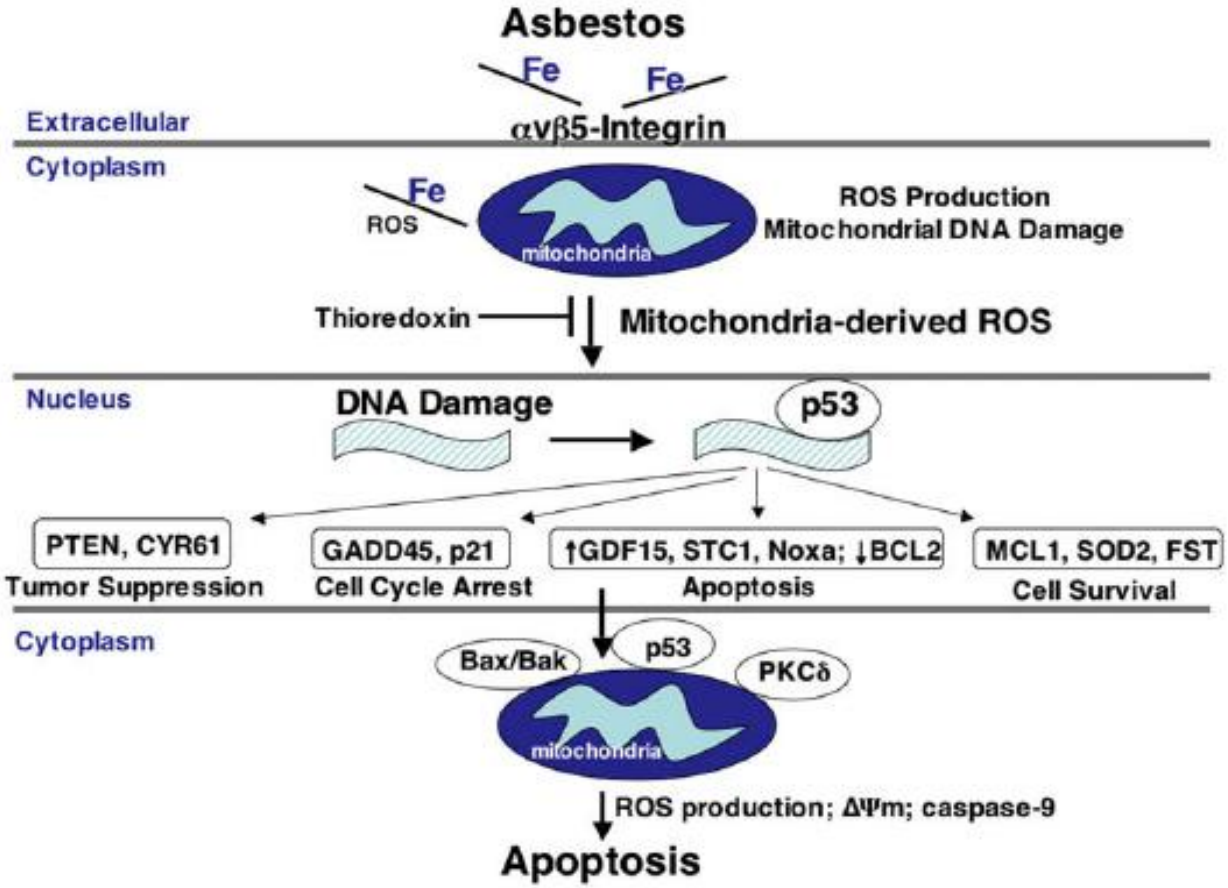


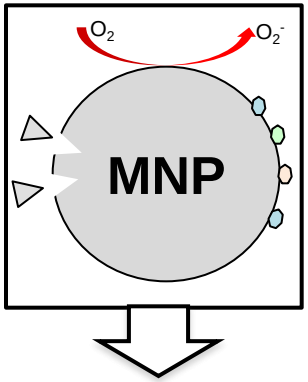
Fig 1. Hypothetical model depicting some of the crucial events that lead to asbestos-induced alveolar epithelial cell mitochondria-regulated apoptosis. Asbestos, which is an iron containing fiber, is rapidly internalized via the $\alpha v\beta 5$ integrin receptor and induces mitochondria-derived ROS production. By mechanisms that are still uncertain, mitochondrial ROS signaling that results from asbestos exposure stabilizes p53 and promotes p53-dependent transcription of a variety of important proteins involved with tumor suppression, cell cycle arrest, apoptosis, and cell survival. Asbestos-induced AEC intrinsic apoptosis is augmented by mitochondrial translocation of proapoptotic Bcl-2 family members (eg, Bax and Bak) p53 and PKCδ. The model is a modified version of one initially developed by Hevel et al[81] that incorporates their findings as well as the work of others.[52,59-62,64,81,82] (Color version of figure is available online.)

Determinants of the potential toxicological effects of MNP: *a proposed pathway*

Physico-chemical characteristics

⇩

Mechanisms of interaction of MNP with cells and tissues leading to toxicity



Alterations of cell viability	Inflammation, oxidative stress	Alterations of endogenous molecules

⇩

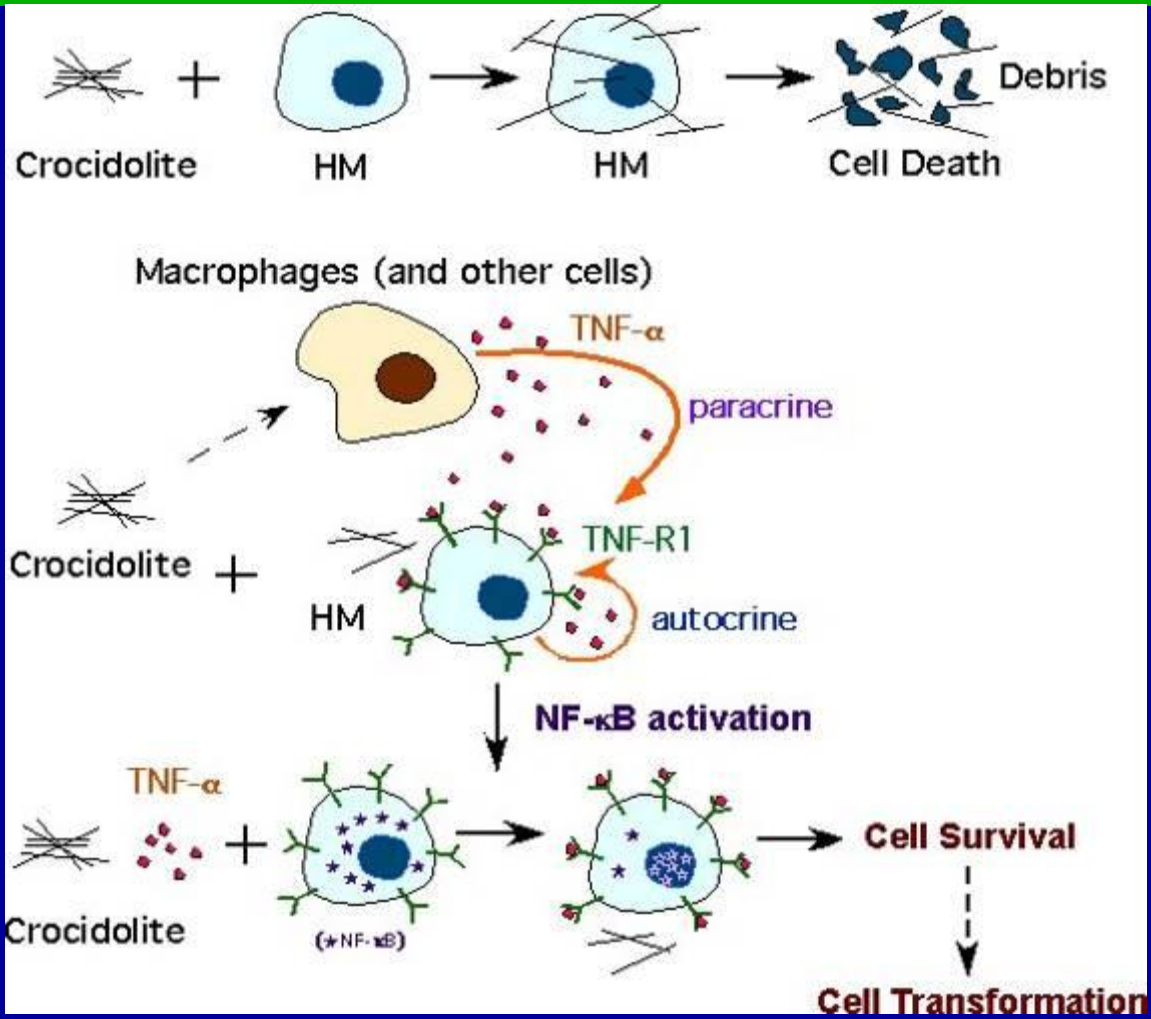
Tissue remodelling	Cancerogenesis	Other effects?

Fibre Analysis Studies in Zeolite Villages

Fibre Content$X10^6$ per gram dry tissue

Name	Sex	Information	CRY	CROC	FIBZ	Others
AA	M	Pleural plaque no tumor cells, S	(+)			
FA (BALF)	F	Lung tissue,Tube A no tumor cells,	3,42	N.D	17,08	N.D
GB	F,44	Normal lung	1,33	N.D	1,67	N.D
KS	F, 45	Interstitial fibrosis	1,55	N.D	4,51	1
SG	F, 65	MM patient + fresh frozen tumor tissue and normal tissue #B5, B6, B7, B8, Family (18) + #44 DNA from whole blood. Very conjested lung + areas of desquamatous pneumonia and atelectasis	1,37	N.D	1,37	0
AI		Lung and tumor but 80% lung tissue.	1,75	N.D	13,75	2
AI	F,46	(S)Pleural plaque with foci of inflammation and epitheliod epith 90% is PP	3,63	N.D	N.D	1

TNF-a inhibits asbestos induced cytotoxicity via a NF-kB dependent pathway: a possible mechanism for asbestos induced oncogenesis.



Yang H, Bocchetta M, Kroczynska B, Elmishad AG, Chen Y, Liu Z, Bubici C, Mossman BT, Pass HI, Testa JR, Franzoso G and Carbone M, Proceedings of the National Academy of Sciences USA, 2006.

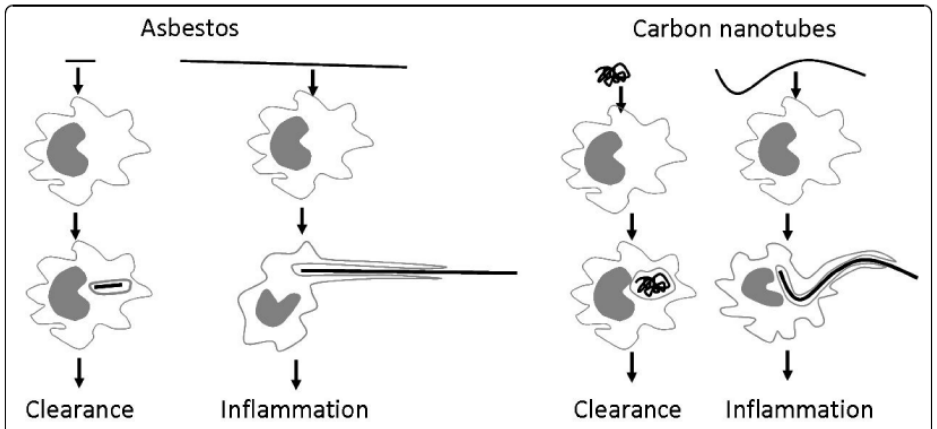


Figure 2 The frustrated phagocytosis paradigm as it relates to long and short fibres of asbestos (left) and various forms of carbon nanotubes (right). When confronted by short asbestos fibres or tangled, compact carbon nanotube 'particles' the macrophage can enclose them and clear them. However the macrophage cannot extend itself sufficiently to enclose long asbestos or long nanotubes, resulting in incomplete or frustrated phagocytosis, which leads to inflammation.

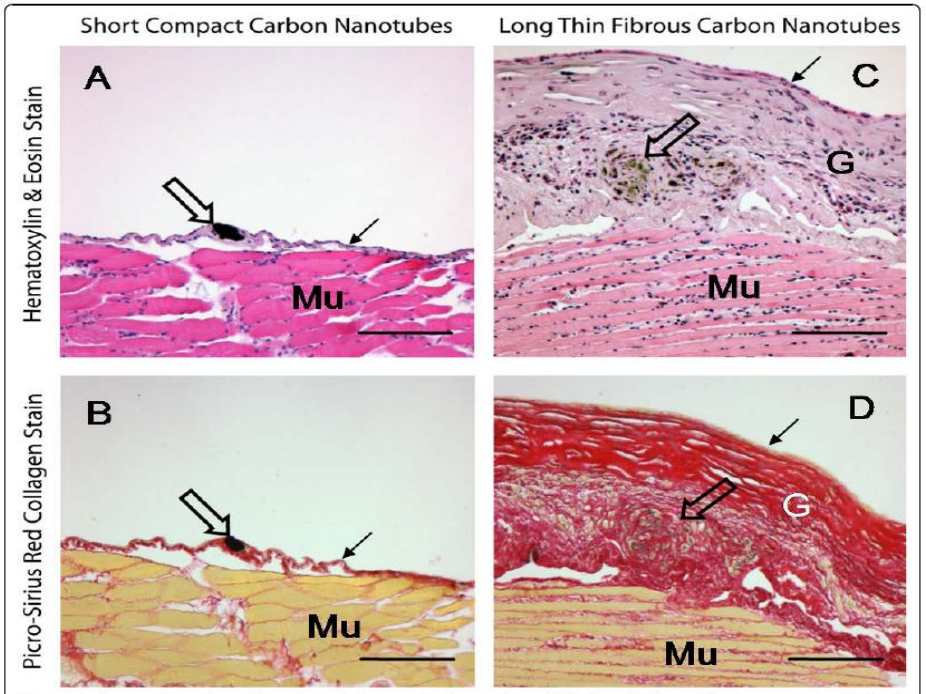


Figure 6 Lesions on the peritoneal face of the diaphragm after intra-peritoneal injection of 2 forms of carbon nanotube differing in aspect ratio. The figure shows sections through the peritoneal aspect of the diaphragm of C57BL/6 mice 6 months after intra-peritoneal injection of 10 μg of two separate forms of multi-walled carbon nanotube (CNT). Sections are stained with Haematoxylin & Eosin (panels A and C) or Picro-sirius red stain which stains collagen bright red (panels B and D). Mu = Muscle of diaphragm; G = granuloma; small arrows = mesothelium; large arrows = carbon nanotubes. C and D show a large granuloma sitting atop the muscle layer, caused by the presence of CNT in the form of long fibres (open arrows). A and B show the contrasting response to CNT in the form of tightly bound dense spherical aggregates (open arrows) which produces minimal tissue reaction. All images are taken at ×100 magnification bar = 100 μm.

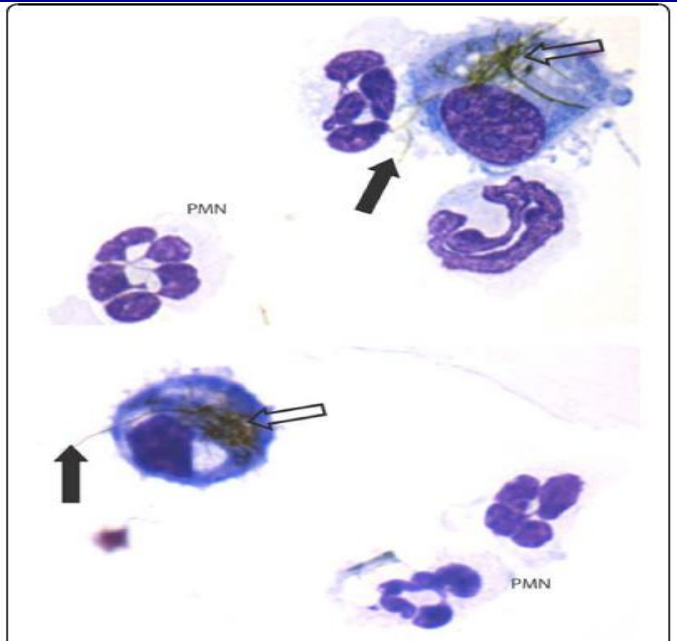


Figure 3 Frustrated phagocytosis (arrows) and the associated acute inflammatory reaction in the bronchoalveolar lavage of mice whose lungs have been instilled with long nanotubes. Aspiration of 50 μg of long fibrous multi-walled carbon nanotubes (CNT) into the lungs of C57BL/6 mice caused an acute inflammatory reaction at 24 hrs typified by a large influx of inflammatory neutrophils (PMN) into the bronchoalveolar lavage. CNT bundles and singlet fibres were seen both within macrophages (hollow arrow) and extending outside the macrophage in the process of incomplete or frustrated phagocytosis (black arrows). All images at taken at ×1000 magnification.

Donaldson et al (2010).
Particle & Fibre Toxicology

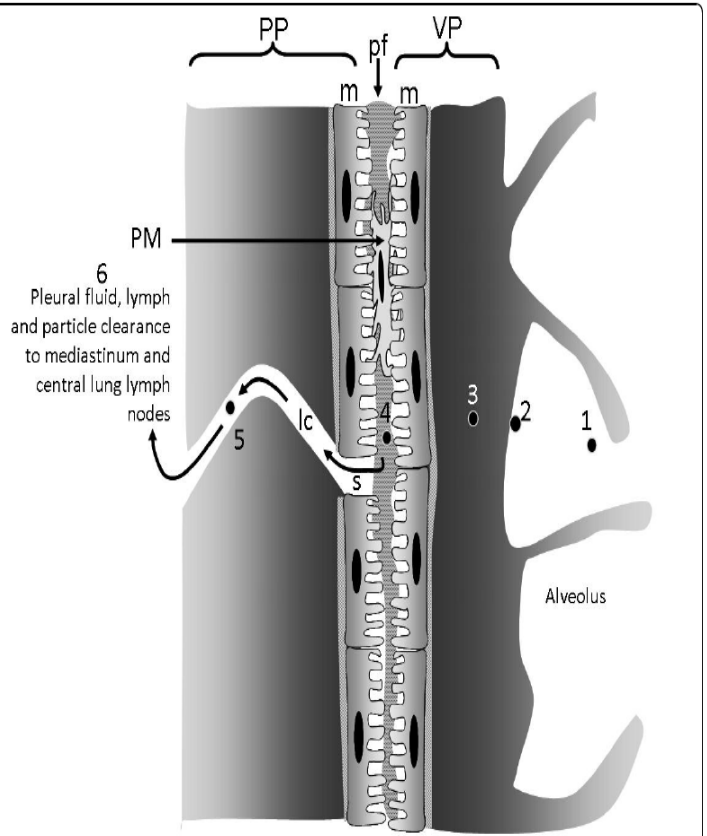


Figure 7 Diagrammatic representation of the relationship between the visceral and parietal pleurae. The visceral pleura (VP) and the parietal pleura (PP) are seen in close apposition separated by a pleural space that contains a small volume of pleural fluid (pf). Contact between the 2 pleurae is made via the mesothelial cell layers (m) on the surface of the parietal and visceral pleurae. Pleural macrophages (PM) are present in the pleural space. The rigid chest wall is tightly locked to the lungs by the adherence of the visceral pleura to the parietal pleura allowing movements of the chest wall caused by the action of the diaphragmatic muscle and intercostal muscle (IM) to expand and relax the lungs, allowing pulmonary inspiration and expiration. The pathway for particles to reach the pleural space is unknown but the path for an airborne particle (1) that deposits in the distal alveoli (2) is shown as it passes into the interstitium (3) enters the pleural space (4) and exits through a stoma in the parietal pleura (s) into a lymphatic capillary (lc, 5) to enter the lymph flow to the lymph nodes in the mediastinum and central lung.

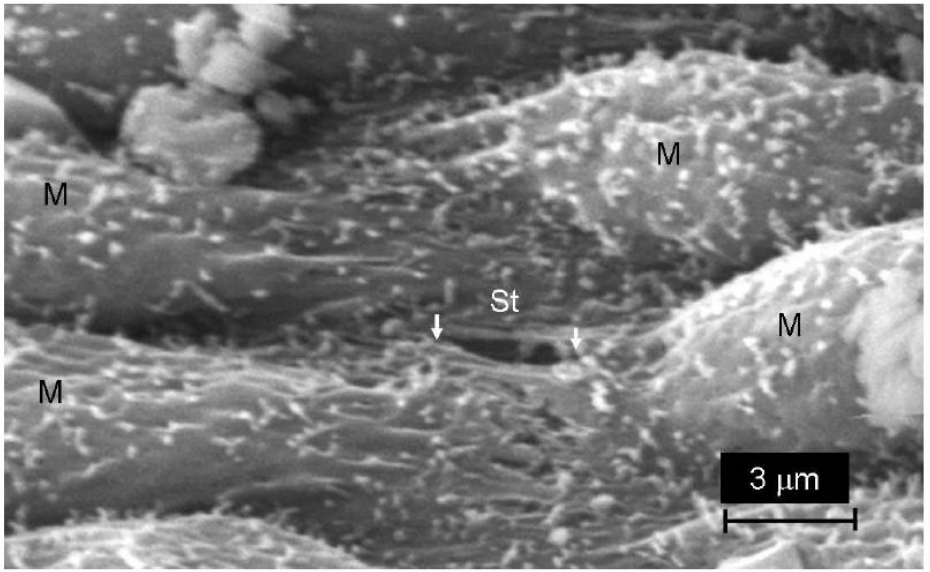


Figure 8 Scanning electron micrograph image of chest wall from a normal rat showing the parietal pleural surface with mesothelial cells (M) and a stoma (white arrows, St) that is approximately 3 µm in diameter.

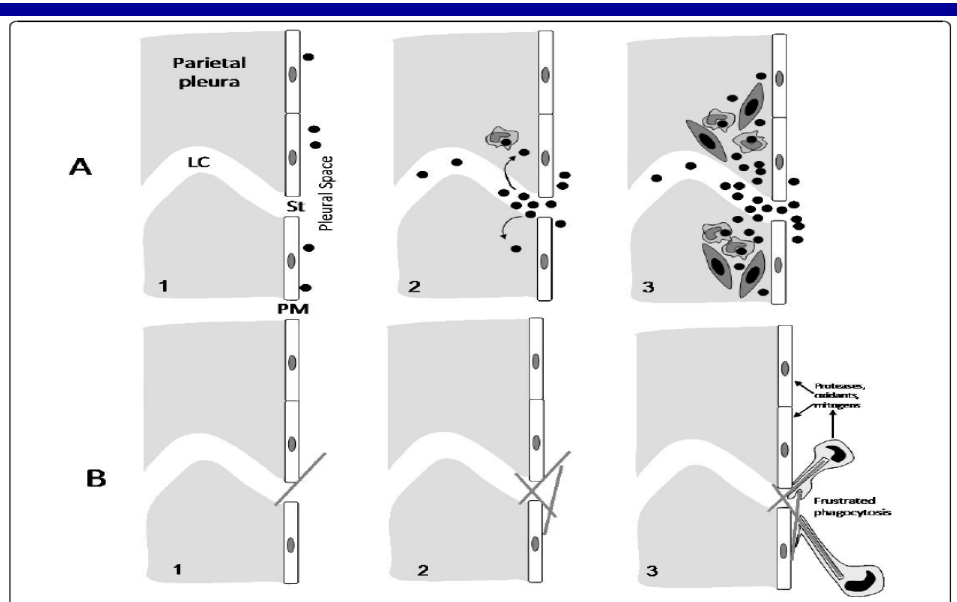
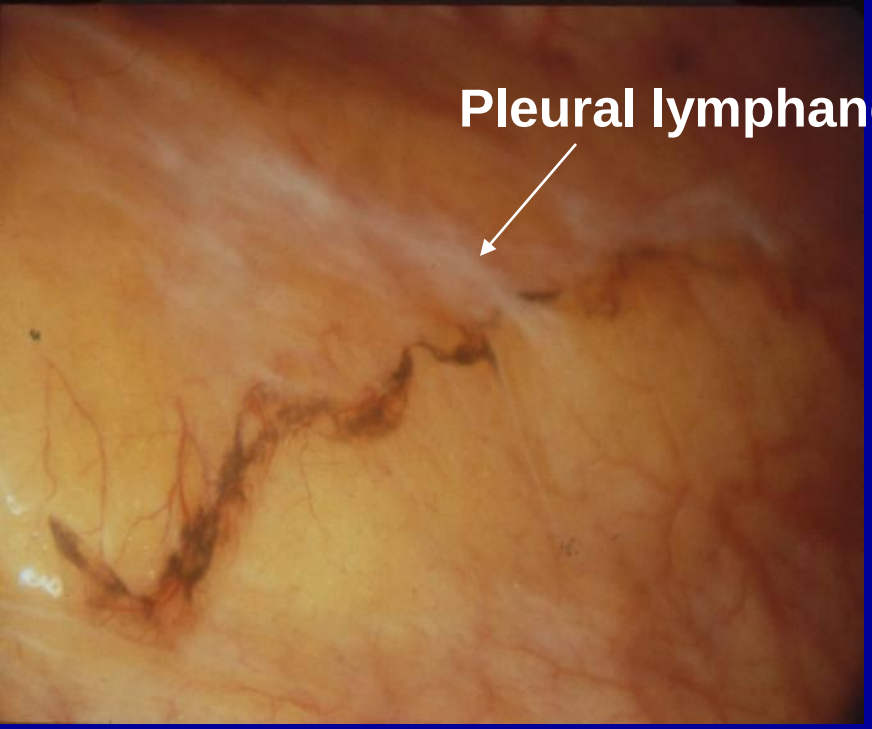
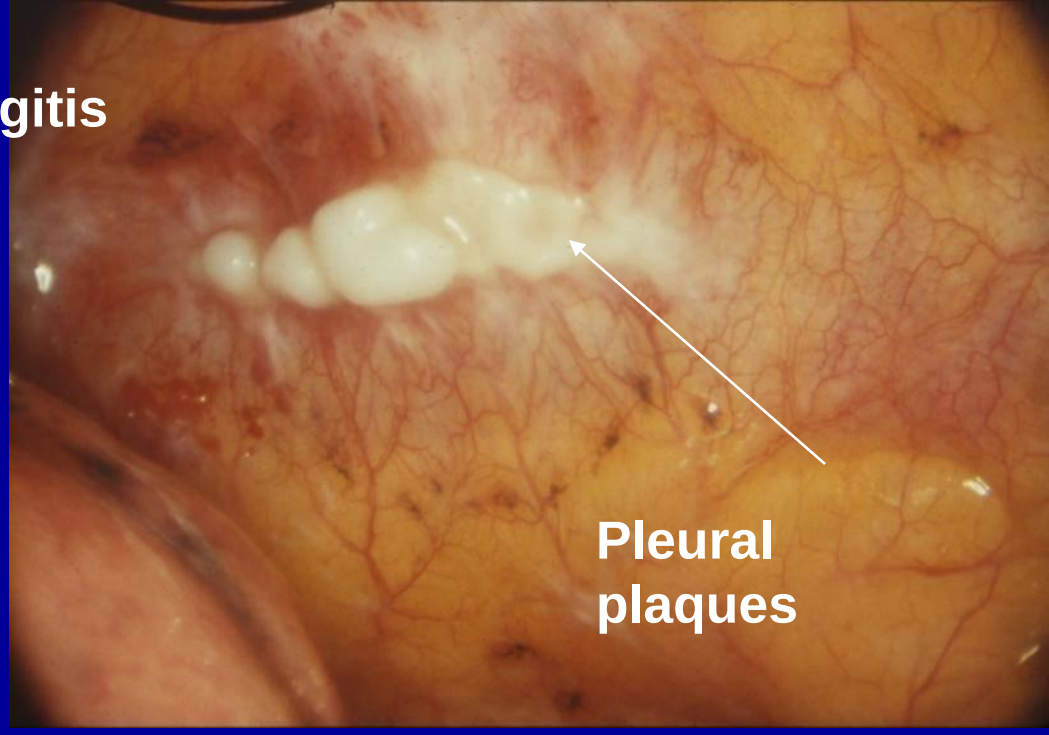


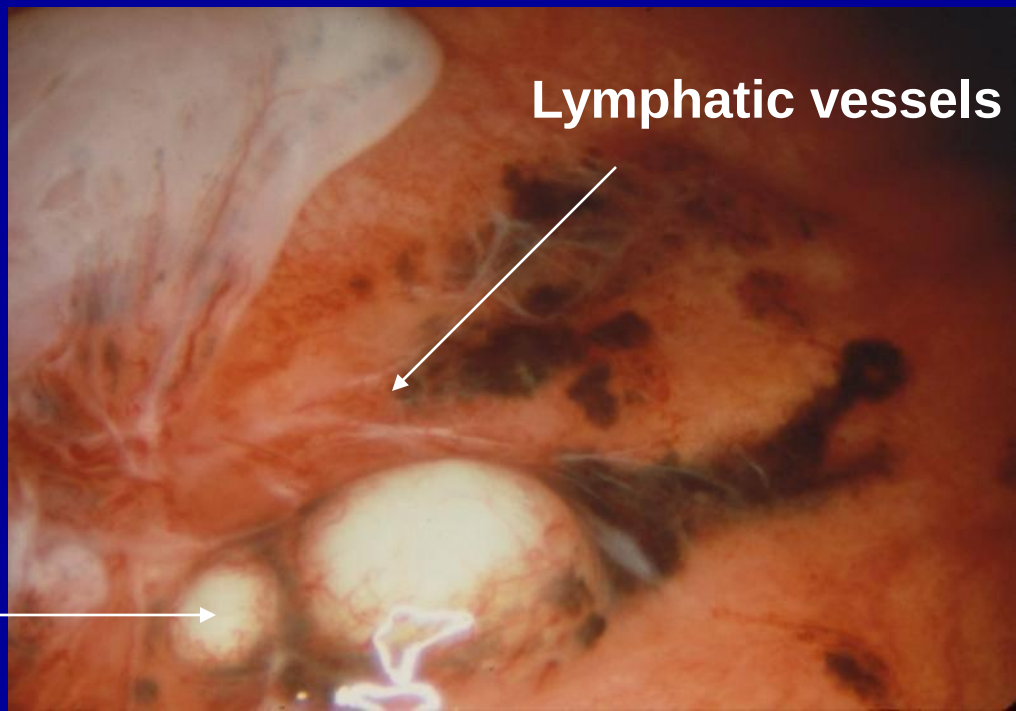
Figure 9 A) diagram showing the events leading up to formation of black spots. A1) particles enter the pleural space; A2) in focusing to exit via the stoma (St) some particles interstitialise through the loose lymphatic capillary endothelium and macrophages begin to accumulate in response; A3) macrophages and particles form a mature 'black spot' with mesenchymal cell activation and proliferation depending on the toxicity and dose of the particle. B) In B1 a single long fibre is intercepted as it attempts to negotiate the stomatal opening and is retained; 2) other fibres are caught up and there is an accumulation of retained long fibres; 3) macrophages attempt to phagocytose the fibres and undergo frustrated phagocytosis releasing a range of pro-inflammatory, genotoxic and mitogenic mediators close to the pleural mesothelial cells. PM = pleural mesothelium; St = stoma; LC = lymph capillary.



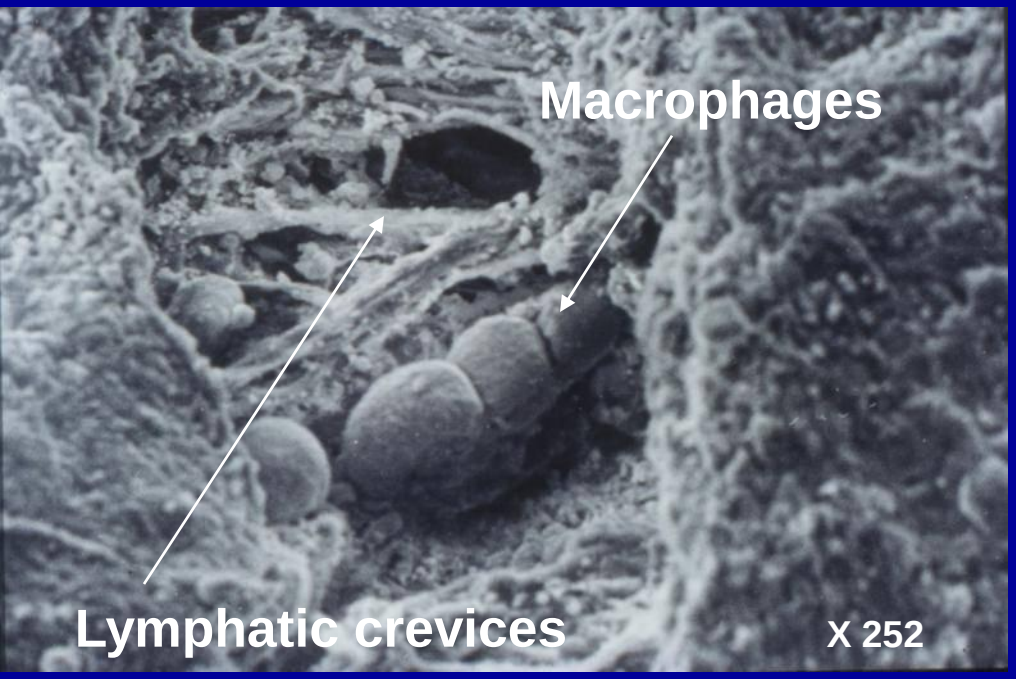


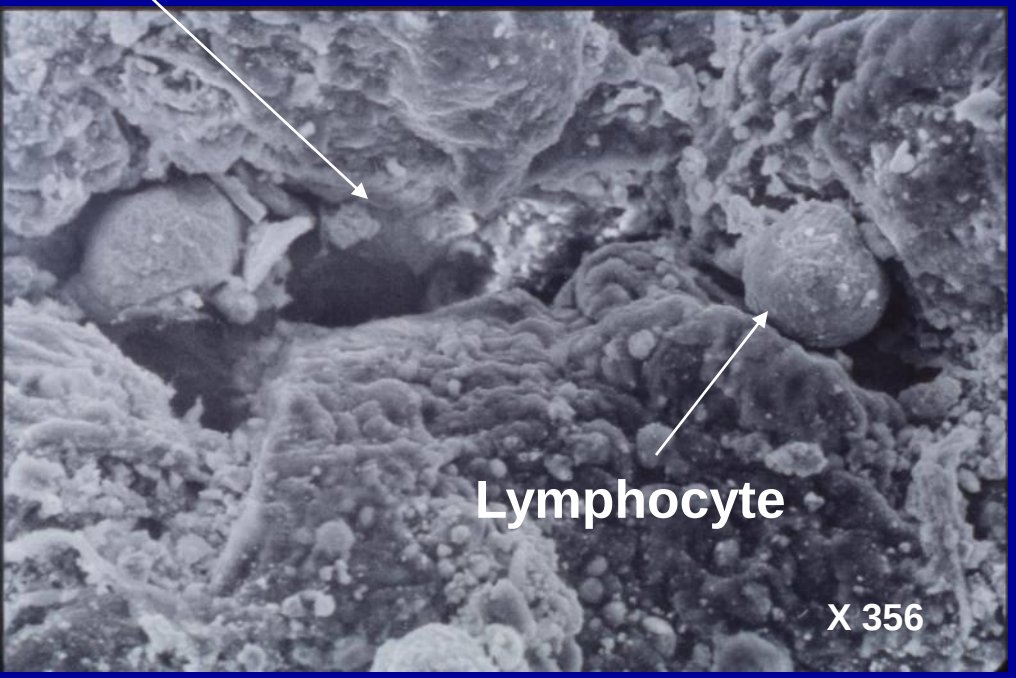
PARIETAL PLEURA

Anthracotic deposits



Malignant nodules

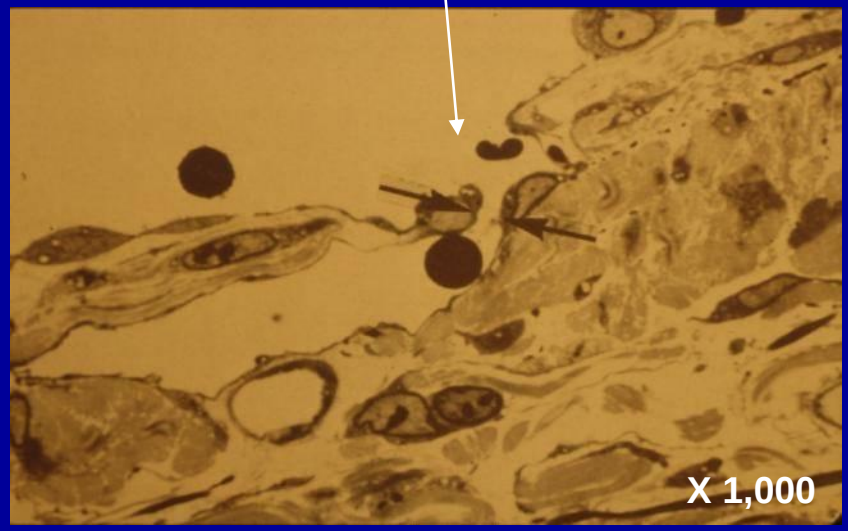




Boutin C, et al.
Am J Respir Crit Care Med 1996; 153: 444-9

PARIETAL PLEURA

‘ Wang ’ stoma



Wang NS. Diseases of the pleura. Masson.. Nex York, 1983

Table 4: Comparison between physical and chemical parameters of asbestos and CNTs

Parameter	*Comparison*
Shape	Both are elongated particles; fibre shaped.
Dimensions	Asbestos fibre diameter: range of 100 nm. Chrysotile fibrils: ≅ 50 nm of diameter. Same order as MWCNTs.
Structure	Chrysotile: multi-layered rolled sheets of brucite ($MgOH_2$) and silicon oxide (SiO_2). Important aggregation with CNTs, which may form more entangled bundles, ropes, than asbestos.
Chemistry	Different chemistry. Possibility of metal impurities in both asbestos and CNTs.
Surface reactivity	Both show sorptive properties to biological molecules. ROS production: no definitive answer for CNTs.

Table 5: Comparison between biological effects of asbestos and CNTs

Cell/tissue response	*Comparison*
Particle uptake	Demonstrated with both types. Conflicting results with CNTs. Exocytosis found with CNTs, so far not investigated with asbestos.
Cytotoxicity	Both cytotoxic.
DNA damage, mutation, gene interaction	Found with both asbestos and CNTs.
Transfection	Gene transfer is with asbestos. CNT gene knockdown.
Biodistribution	Both types are cleared *via* the lymphatic system and found in different organs
Inflammation, granulomas, fibrosis	Found with both asbestos and CNTs. Both types show dependence of biological effects with fibre dimensions: bioactivity of long fibres.
Cancer	MM found with both asbestos and CNTs by peritoneal exposure.

Sonuç

- CNT; uzunluk:çap >3 high aspect ratio, sert ve fleksibl,
- Teknolojik olarak kullanılma potansiyelleri hayellerin ötesinde,
- Lif paradigmasını sağlıyorlar,
- İnhalasyonla plevral boşluk ve plevraya ulaşıyorlar
- Dissolusyon ve eksresyonları hakkında tam bilgi mevcut değil,
- Regülasyonu nasıl olacak, toz ölçümü ve lif sayımı ve çalışanların periyodik takipleri çok belli değil,

(OSHA müsaade edilebilir(PNOR) limit 5 mg/mm3, NIOSH tavsiye edilen temas limiti 1 micg/mm3)

- Lancet oncology dergisinin aralık 2014 sayısında IARC adına rapor hazırlamakla yükümlü bir grup araştırıcı ***çok tabakalı 7 nolu karbon tüpün (MWCNT-7)*** elde mevcut hayvan deneylerine dayanarak(rodentler üzerinde yapılan invitro çalışmalar) ***insanlar için muhtemel kanser yapıcı (karsinojenik) bir madde olarak yani Grup 2b altında sınıflandırıldığını belirtmektedirler.*** IARC'ın sayfasında ise bu madde hakkında 20 yıl önce muhtemel karsinojenik etkisi hakkında uyarı yapıldığını ve bunun sonunda kanıtlandığını otoritelerin bu nedenle diğer toksik ve zehirli yeni maddelerin markete girmesi konusunda uyanık olunması gerektiği ve karbon nanotüp üretimi ve yaygınlaştırılması konusunda büyük dikkat gerektiğini vurgulamaktadırlar.

1. http://www.psr.org/environment-and-health/environmental-health-policy-institute/responses/iarcs-review-carbon-nanotubes.html
2. www.thelancet.com/oncology Vol 15 December 2014


Protecting the Nanotechnology Workforce
NIOSH Nanotechnology Research and Guidance Strategic Plan, 2013–2016
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health
NIOSH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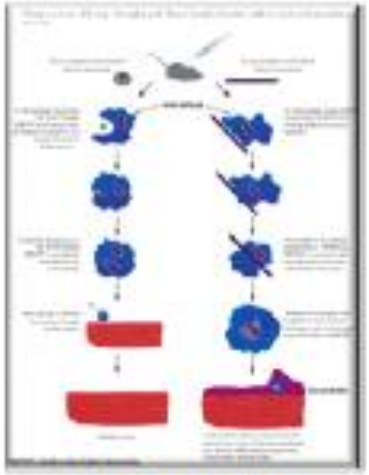
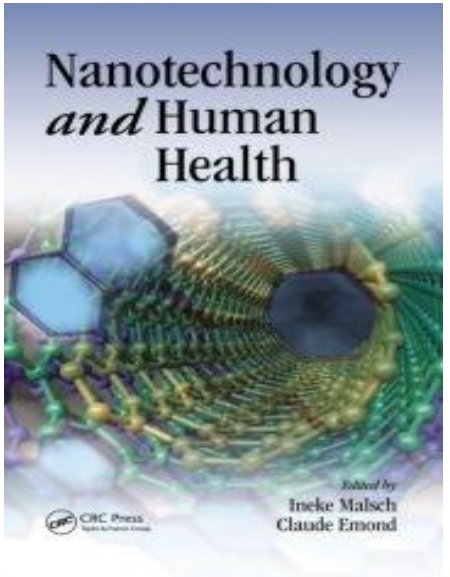


Backgrounders

nanoEHS VIRTUAL JOURNAL

Knowledge Base



http://icon.rice.edu

CDC

Rereferanslar:

1. **Deposition of ultrafine particles in the human lung and the mechanisms behind their health effects**

Dr Sundeep Salvi MD, PhD(UK), FCCP(USA)

Director, Chest Research Foundation, Pune, INDIA,ERS 2014

2. **Nanoparticle toxicology: a scientific state-of-the-art**

Jorge Boczkowski, MD PhD
UMR 955 (Inserm-Université Paris Est)
Créteil, France,ERS 2014

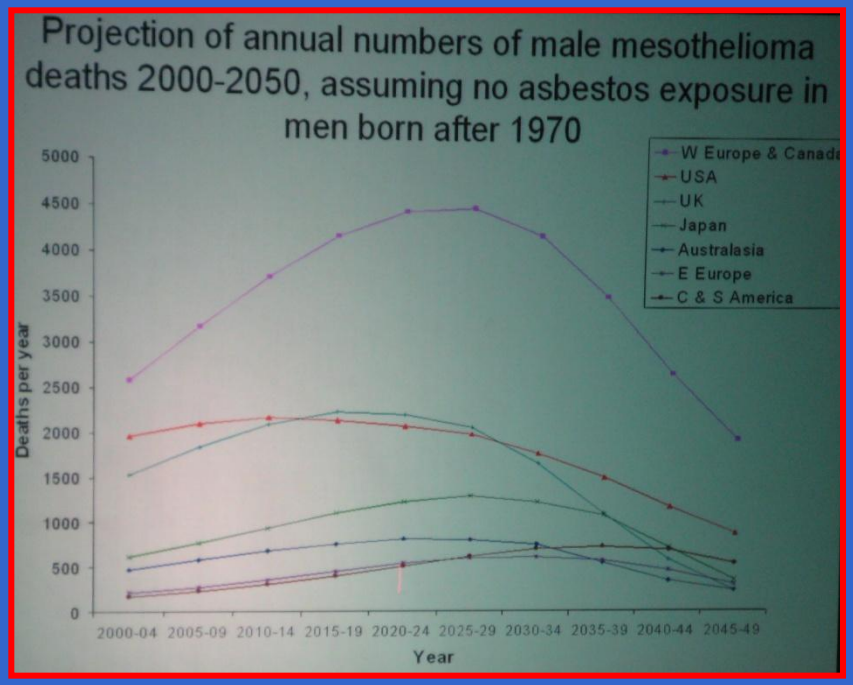
3. Nanoparticles and Respiratory Health *In vitro* and *in vivo* studies of nanoparticles and the
Prof. Dr. Peter S. Thorne
Dept. of Occupational and Environmental Health
University of Iowa,ERS 2014


Dikkatiniz İçin Teşekkürler

Malignant Pleural Mesothelioma(MPM):Epidemiology

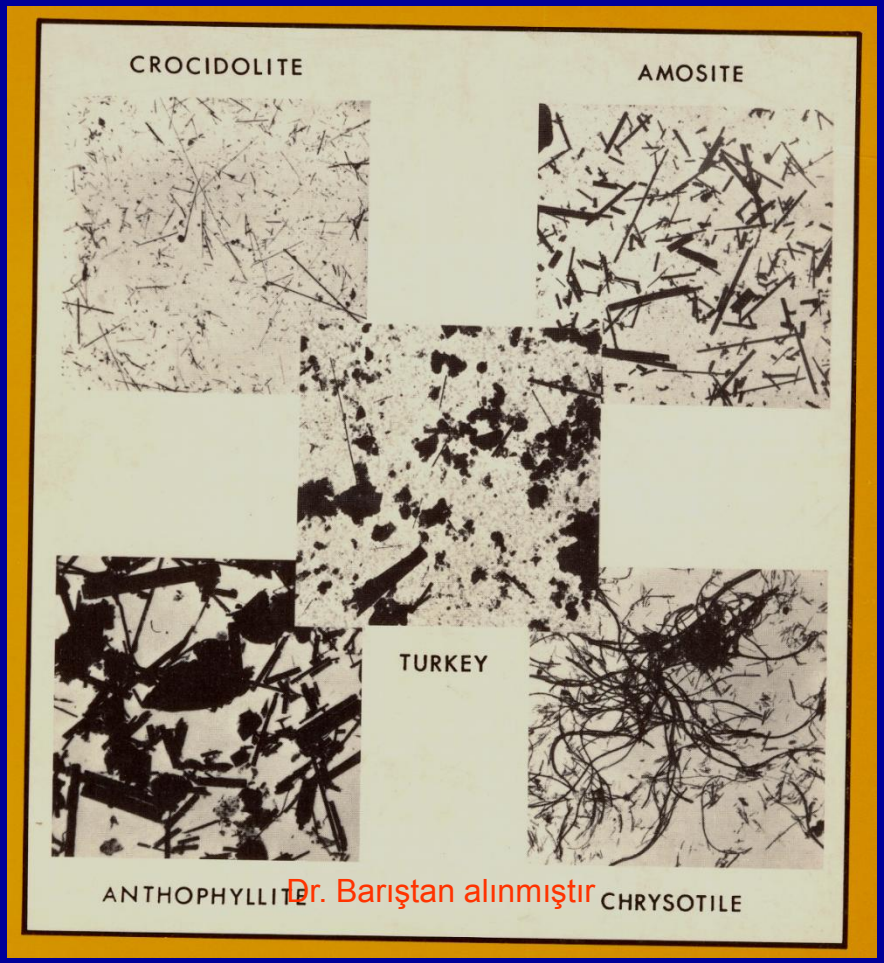
Tahmini MPM İnsidansı

Ülke	Tahmini yıllık kaba insidans/milyon kişi	Kaynak
Avustralya	30	Mezotelyoma kayıt
UK	30	Mezotelyoma martalite kayıt
Belçika	29	Araştırıcı tahminleri
Hollanda	23	Mortalite isrtatistikleri
Türkiye	7.8	Araştırıcı tahminleri



Julian Peto, IMIG 2008, Amsterdam

Bianchi C and Bianchi T. Industrial Health. 2007;45:379-387



Dr. Barıştan alınmıştır

Mean dimensions (⌠m) and proportions of fibers in lung samples and pleural black spots

	Lung	Black spots	p Value
Mean length*	4.45 +/- 0.45 (2.9)	3.82 +/- 0.22 (3.03)	NS
Mean diameter*	0.13 +/- 0.01 (0.10)	0.19 +/- 0.01 (0.13)	p<0.001
Maximum length	90	26	
Length > 5 ⌠m	21.7%	22.5%	
Length > 8 ⌠m	11.4%	10%	
Length > 15 ⌠m	3.9%	2.1%	

Mean +/- SEM

Boutin C, et al. Am J Respir Crit Care Med 1996; 153: 444-9

Potential Zeolite Mexican Mesothelioma Epidemic

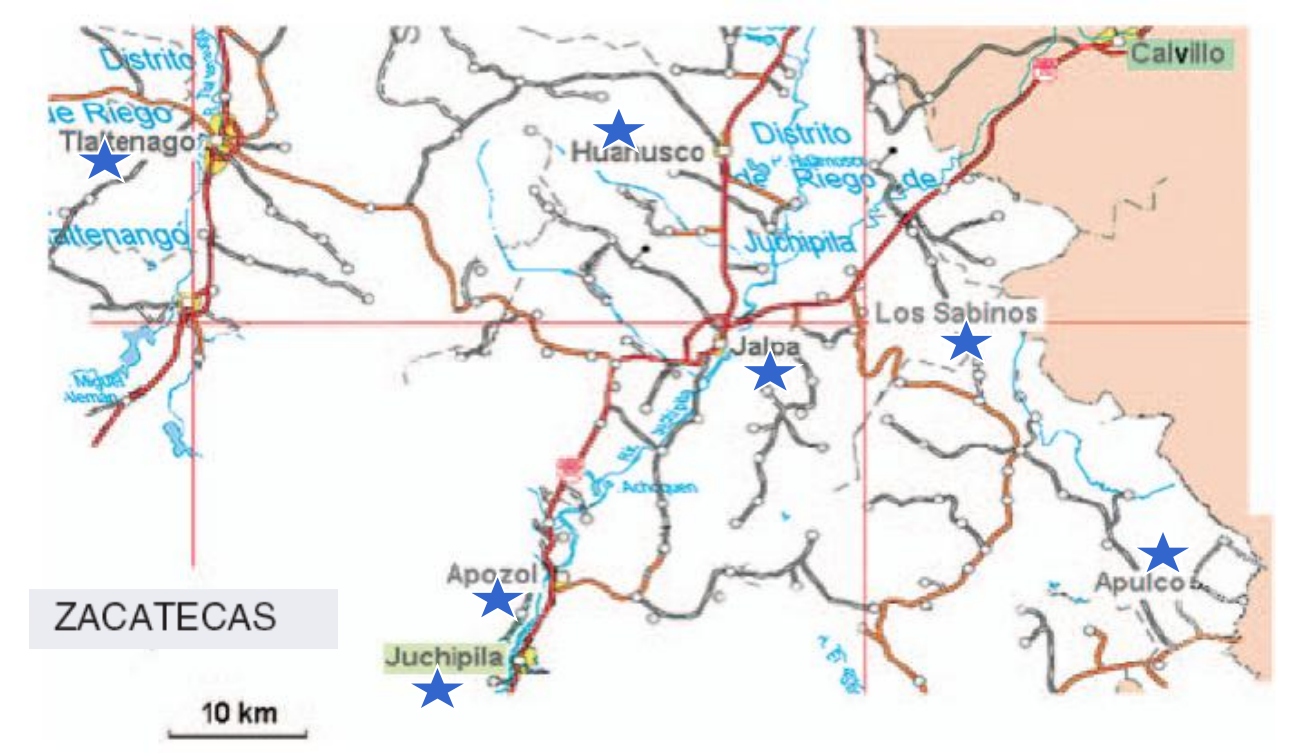


Fig. 5. Map of the Valley of Jalpa (SGM) showing the sites of the villages from whence nine cases came: 1. Los Sabinos; 2. Jalpa; 3. Apulco; 4. Apozol; 5. Tlaltenang; 6. Huanesco; 7. Guadalupe. The valley runs from Juchipila in the south to Calvillo in the north.

Indoor Built Environ 2008;17:496–515

İlgren EB and et al, recently reported a mesothelioma cluster in the Southern part of the State of Zacatecas.This is the first study that came from outside of Turkey…

#FS Sunday

BanasbestosNOW

"Asbestos, a known carcinogen, claims more than 107,000 lives every year."

#BANASBESTOSNOW

AsbestosDiseaseAwareness.org

NIOSH Hazard Assessment Research Priorities

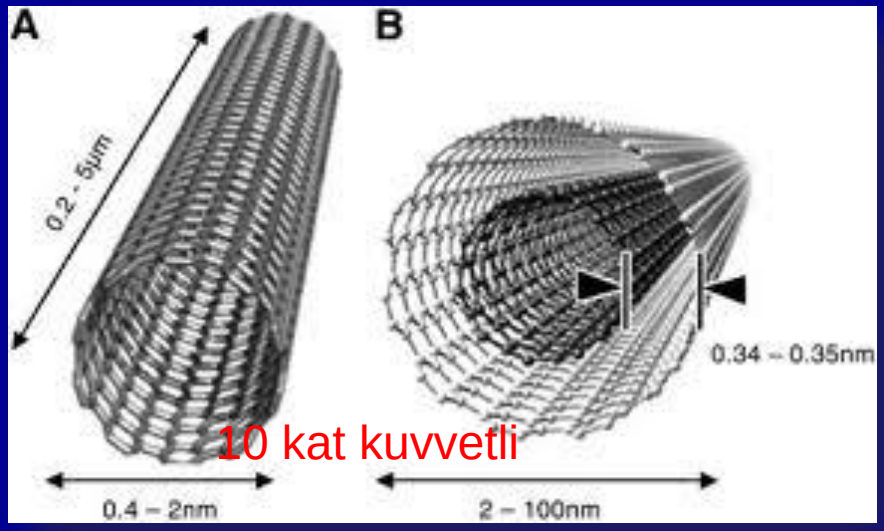
- **Studying carbon black, single-walled carbon nanotubes (SWCNT), multi-walled carbon nanotubes (MWCNT), TiO_2spheres and wires, silicon nanowires, silver, nickel, quantum dots, ZnO, WC-Co, etc**
- **Evaluating**
  - Exposure routes: pulmonary and dermal
  - Biological endpoints: pulmonary, cardiovascular, CNS, and dermal
- **Determining the relationship between given physicochemical properties of a nanoparticle and its bioactivity**
- **Developing *in vitro* screening tests for rapid prediction of the bioactivity of a given nanoparticle**

TIO2, titanium dioxide
ZnO, zinc oxide
WC-Co, tungsten carbide/cobalt

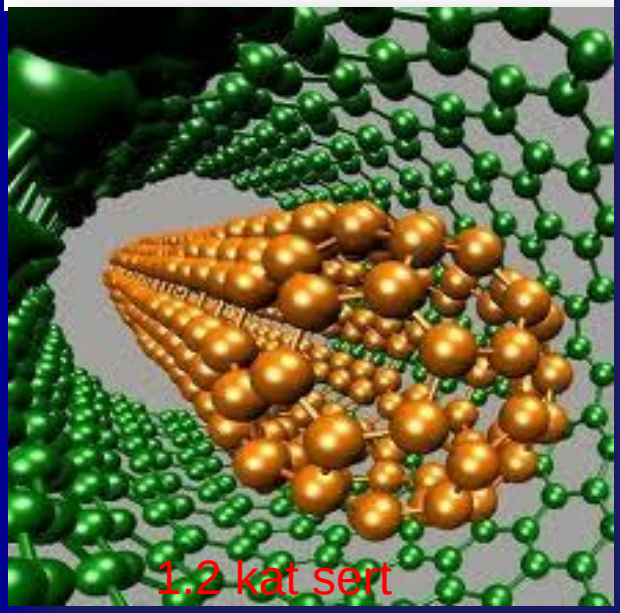
Hangisi Daha Kuvvetli?

Hangisi Daha Sert?

Çok hafif ve alışılmışın dışında elektrik ve ısı iletimi sağlıyorlar



10 kat kuvvetli

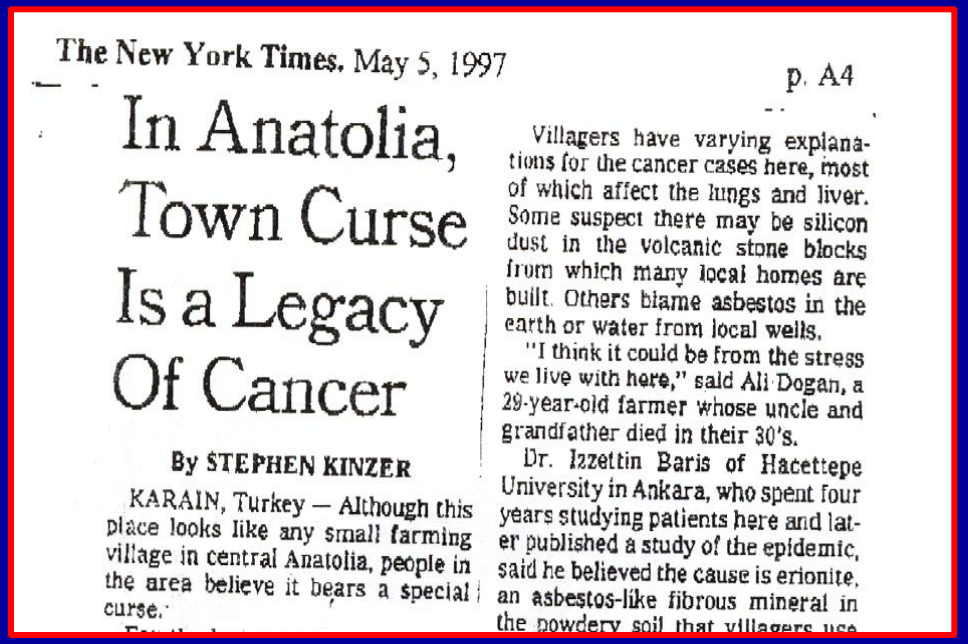


1.2 kat sert

Kapadokya Bölgesinde MPM: Insidans

- Erionite köylerinde, erionite olan **1f.ml^{-1}-yıl kümülatif temas sonucu mezotelyoma insidansı 996/100.000 kişi-yıl olarak tahmin edilmektedir** (1).

- Bu risk amphibole teması olan asbest işçilerinden çok daha fazladır! (2).



The New York Times, May 5, 1997 p. A4

In Anatolia, Town Curse Is a Legacy Of Cancer

By STEPHEN KINZER

KARAIN, Turkey — Although this place looks like any small farming village in central Anatolia, people in the area believe it bears a special curse.

Villagers have varying explanations for the cancer cases here, most of which affect the lungs and liver. Some suspect there may be silicon dust in the volcanic stone blocks from which many local homes are built. Others blame asbestos in the earth or water from local wells.

"I think it could be from the stress we live with here," said Ali Dogan, a 29-year-old farmer whose uncle and grandfather died in their 30's.

Dr. Izzettin Baris of Hacettepe University in Ankara, who spent four years studying patients here and later published a study of the epidemic, said he believed the cause is erionite, an asbestos-like fibrous mineral in the powdery soil that villagers use

1. Baris YI, et al. Int J Cancer 1987; 39: 10-17.
2. Simonato L, et al. IARC Scientific Publication No.90, 1989.