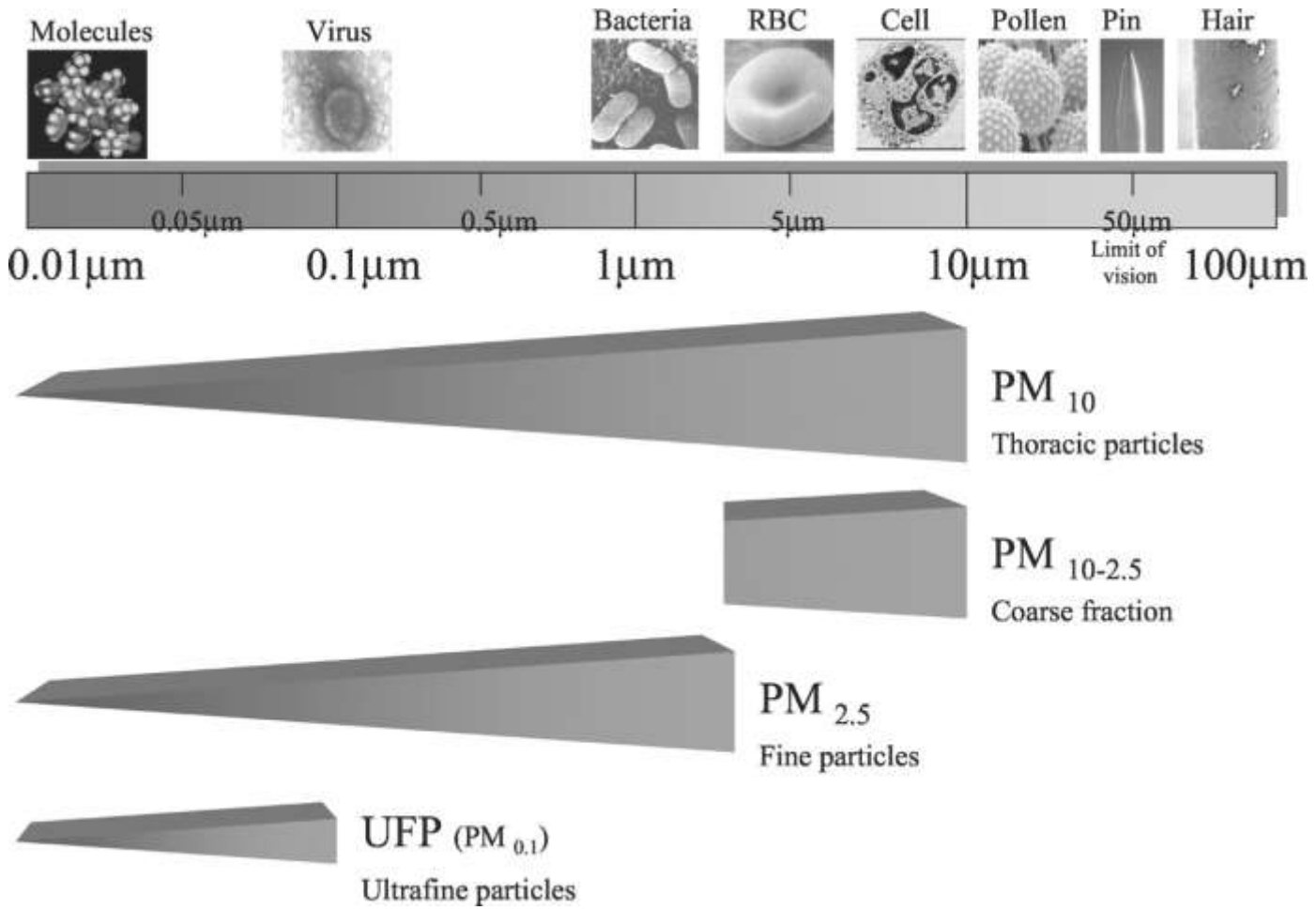
奈米科技與健康

國家衛生研究院環醫所

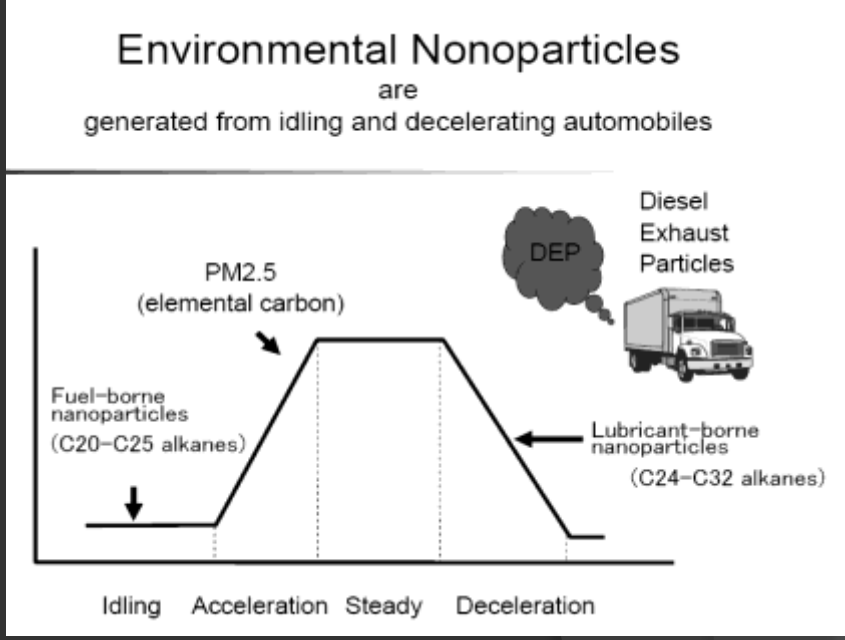
劉紹興研究員

內容

- 奈米之特性
- 疑似奈米微粒造成之健康影響的病例報告
- 奈米作業人員之流行病學研究
- 結論


Molecules
Virus
Bacteria
RBC
Cell
Pollen
Pin
Hair
0.05µm
0.5µm
5µm
50µm
0.01µm
0.1µm
1µm
10µm
Limit of vision
100µm
PM 10
Thoracic particles
PM 10-2.5
Coarse fraction
PM 2.5
Fine particles
UFP (PM 0.1)
Ultrafine particles

奈米微粒之分類



→非蓄意製造奈米

◉ 從空氣污染流行病學研究結果

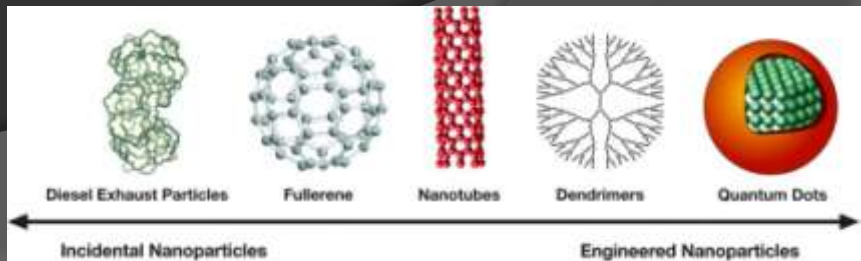
◉ 從燃燒（如柴油廢氣和焊接燻煙）研究結果

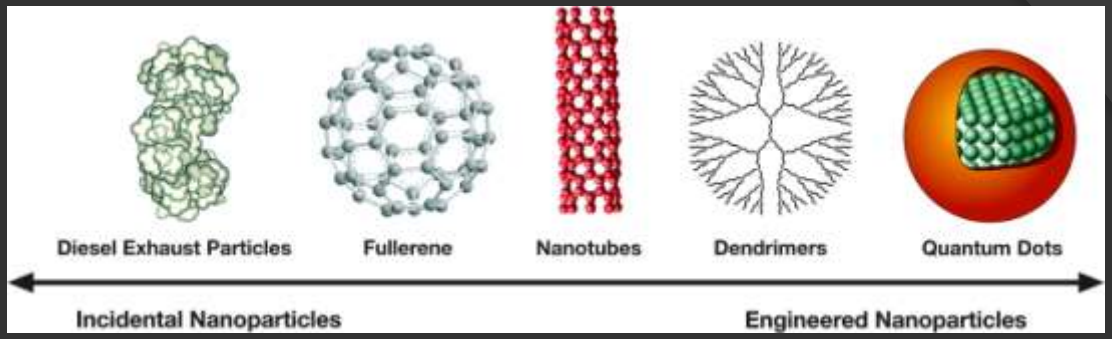
☆肺部發炎，心臟疾病，動脈硬化，哮喘和肺癌。

→蓄意製造(工程)奈米

◉ 製造已經上市的奈米粒子（碳米碳管，二氧化鈦，二氧化矽，氧化鋁）

☆健康風險(??)





蓄意製造(工程)奈米
-市場已使用(TiO2, AgN)
-新興製造(工程)奈米

非蓄意製造奈米
-燃燒Combustion
-核化Nucleation

新產品, 新使用
高附加價值

無附加價值, 無額外支出
健康風險大

暴露低 (mg/m^3 → < ug or ng/m^3)
健康風險低

Stern, S. T. et al. Toxicol. Sci. 2008
101:4-21; doi:10.1093/toxsci/kfm169

Critical Reviews in Toxicology, 2009; 39(3): 195–227

informa
healthcare

REVIEW ARTICLE

Non-cancer health effects of diesel exhaust: A critical assessment of recent human and animal toxicological literature

Thomas W. Hesterberg[1], Christopher M. Long[2], William B. Bunn[1], Sonja N. Sax[2], Charles A. Lapin[3], and Peter A. Valberg[2]

Inhalation Toxicology, 2010; 22(8): 679–694

informa
healthcare

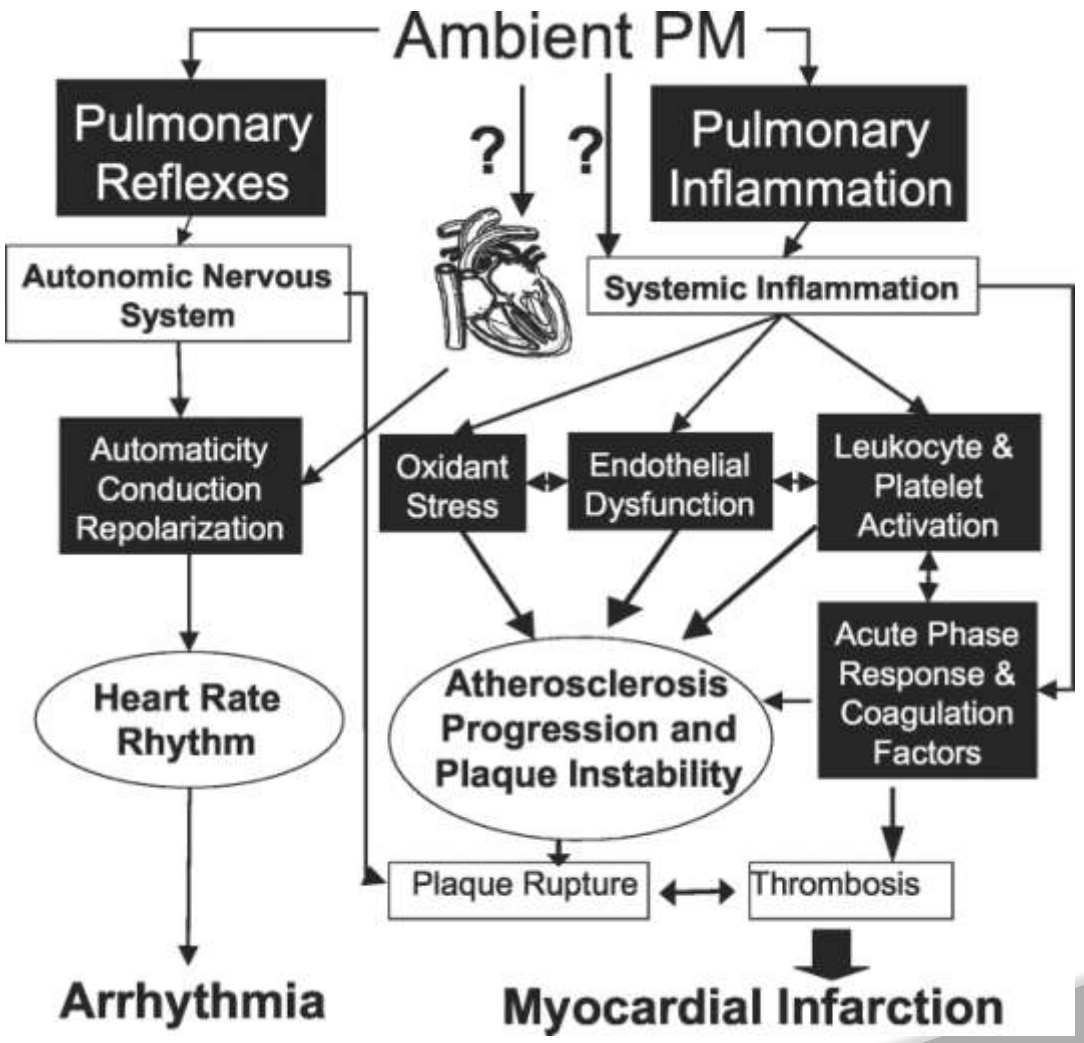
RESEARCH ARTICLE

Diesel exhaust particulate (DEP) and nanoparticle exposures: What do DEP human clinical studies tell us about potential human health hazards of nanoparticles?

Thomas W. Hesterberg[1], Christopher M. Long[2], Charles A. Lapin[3], Ali K. Hamade[2], and Peter A. Valberg[2]

[1]Navistar, Inc., Chicago, Illinois, USA, [2]Gradient, Cambridge, Massachusetts, USA, and [3]Lapin & Associates, Glendale, California, USA

Possible biological mechanisms linking PM with cardiovascular disease



Circulation

奈米之使用

Early Nano-enabled Consumer Products Are on the Market Now

Mercedes
CLS-class

Mercedes-Benz

Eddie Bauer
Ruston Fit Nano-Care khakis

Eddie Bauer

3M Adper Single Bond Plus dental adhesive

3M

Samsung Nano SilverSeal Refrigerator

SAMSUNG

Wyeth Rapamune immuno-suppressant

Wyeth

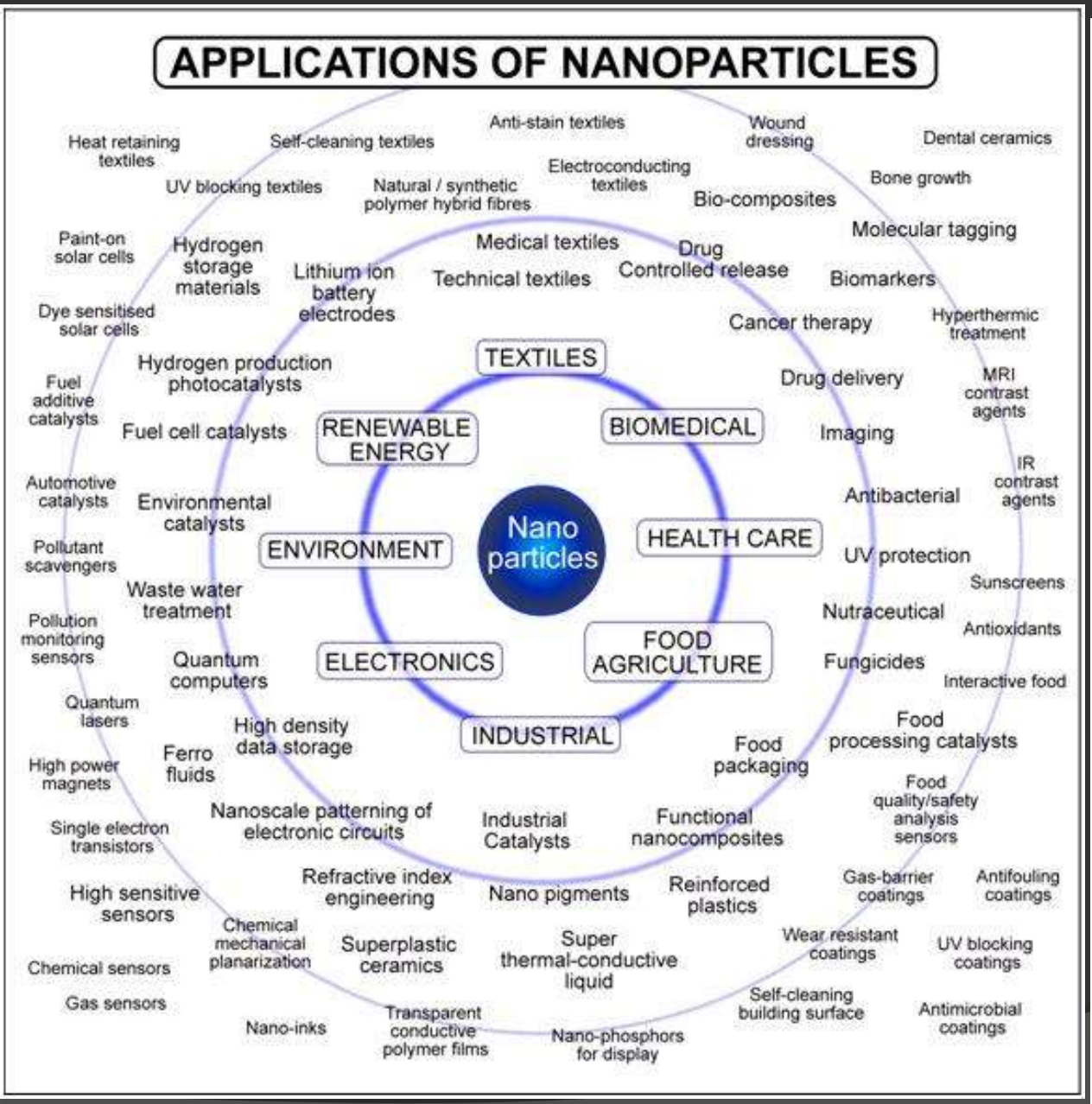
Wilson Double Core tennis balls

Consumer products with nanoclaim

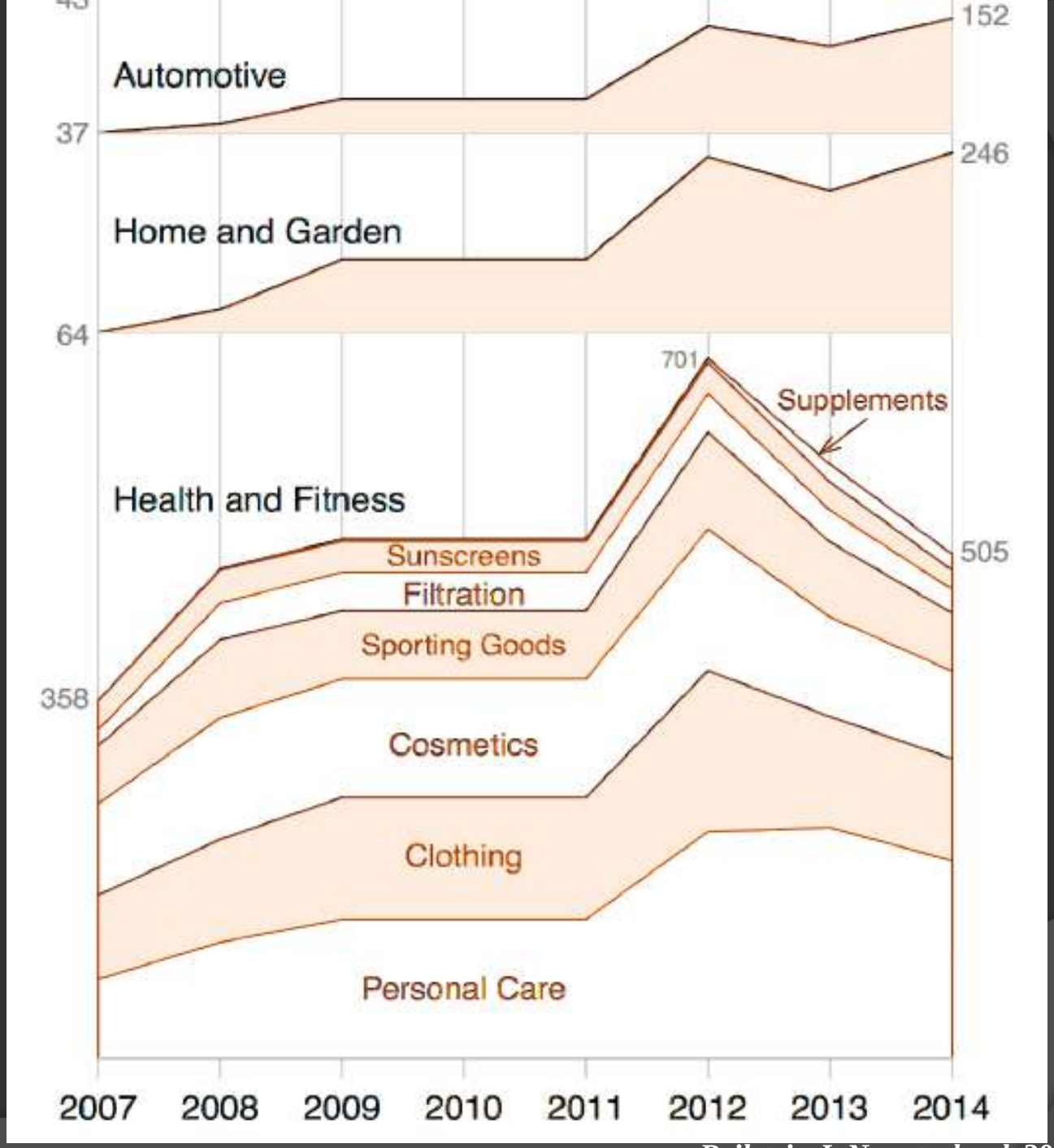
rivm

Scientific Committees

Global Market for Nanotechnology to Reach $3.3 Trillion by 2018



https://www.linkedin.com/pulse/global-nanotechnology-market-reach-us-758-billion-2020-jon-klein?trk=pulse-det-nav_art



Beilstein J. Nanotechnol. 2015, *6*, 1769–1780

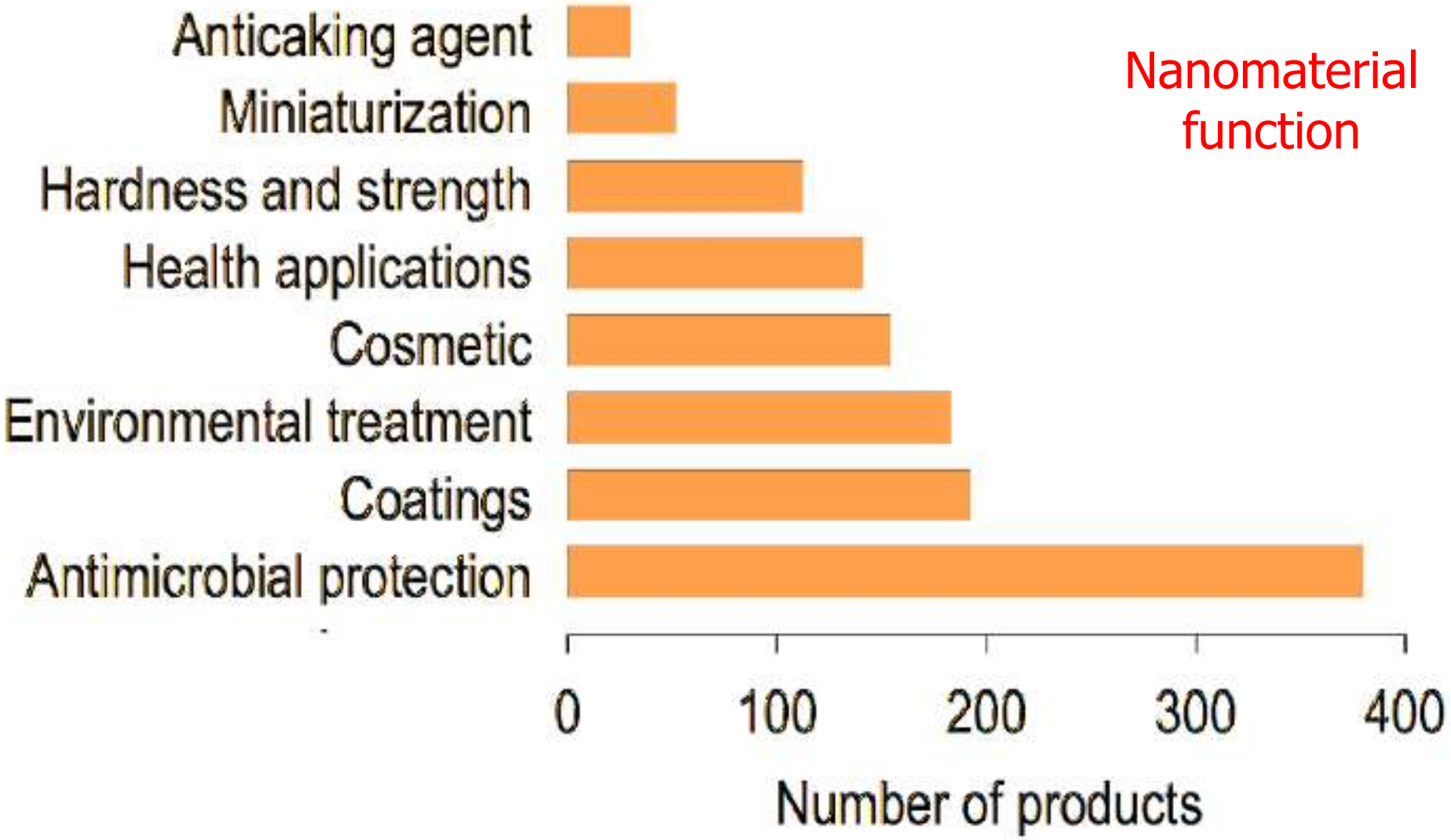
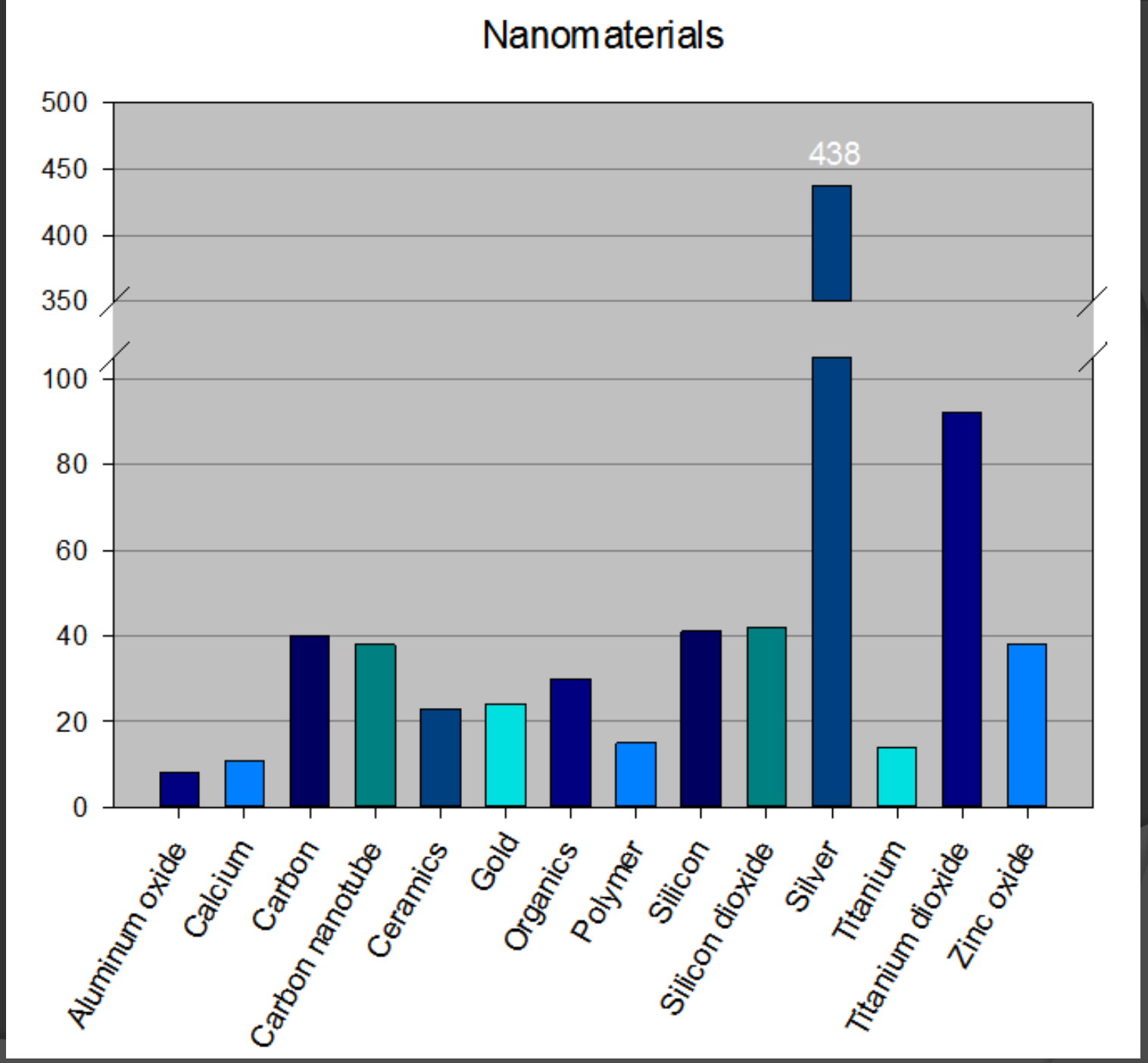


Figure 6: Expected benefits of incorporating nanomaterial additives into consumer products.



http://www.nanotechproject.org/inventories/consumer/browse/products/

Behavior of Inhaled Nanoparticles

- 1.<100nm nanoparticles deposit mainly in the alveolar regions.
- 2. Clearance of nanoparticles from the lung is more slowly than fine particles.
- 3. More nanoparticles translocate to interstitial sites and to blood circulation compared to the larger particles.
- 4. Inhaled nanoparticles may migrate from the lungs to other organs.

Oberdörster G, et al. **2005**

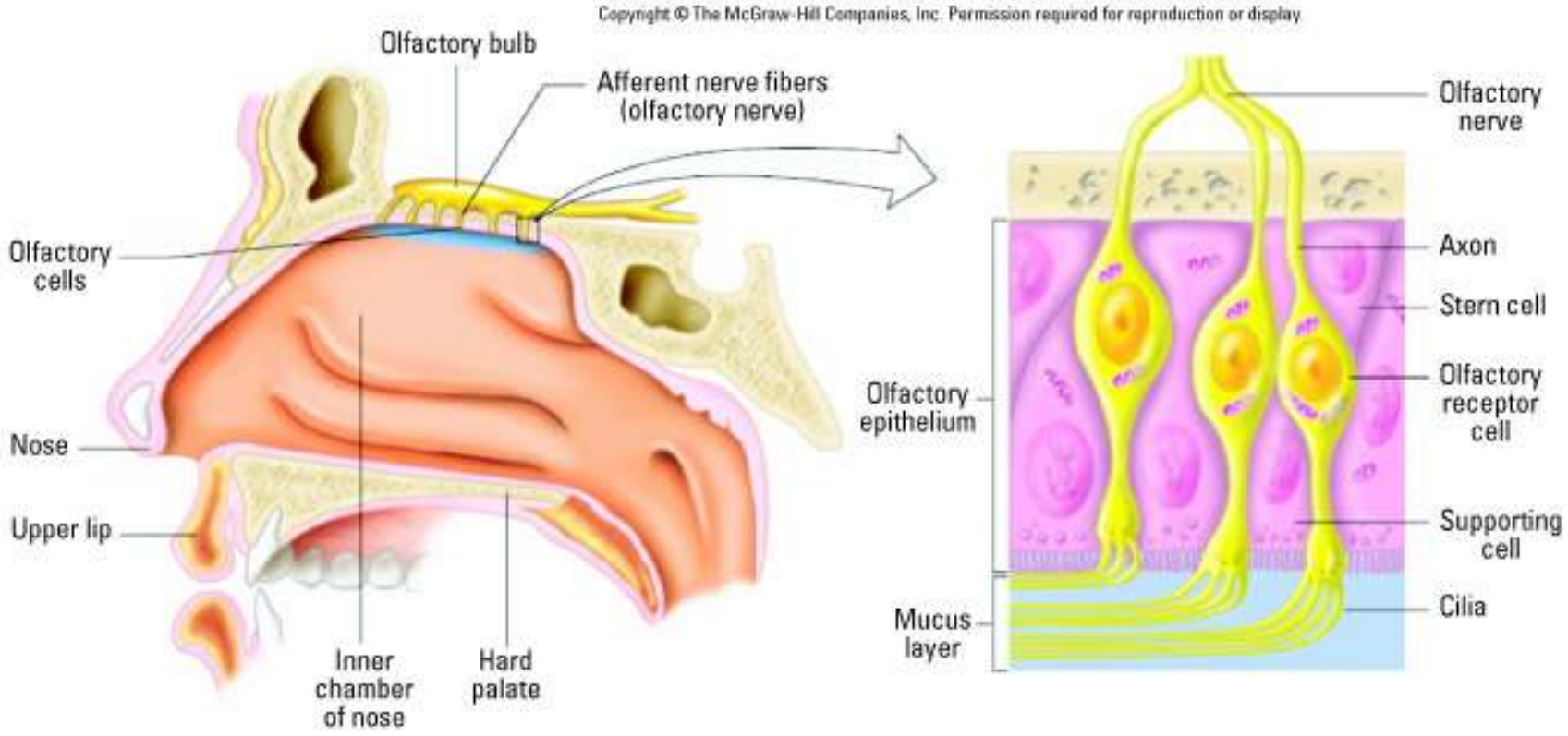


Figure 12. Close proximity of olfactory mucosa to olfactory bulb of the CNS. Inhaled NSP[s], especially below 10 nm, deposit efficiently on the olfactory mucosa by diffusion, similar to airborne "smell" molecules which deposit in this area of olfactory dendritic cilia. Subsequent uptake and translocation of solid NSP[s] along axons of the olfactory nerve has been demonstrated in non-human primates and rodents. Surface chemistry of the particles may influence their neuronal translocation. Copyright © the McGraw-Hill Companies, Inc. Reproduced from Widmaier et al. (2004) with permission from McGraw-Hill.

4. Inhaled nanoparticles may migrate from the lungs to Brain.

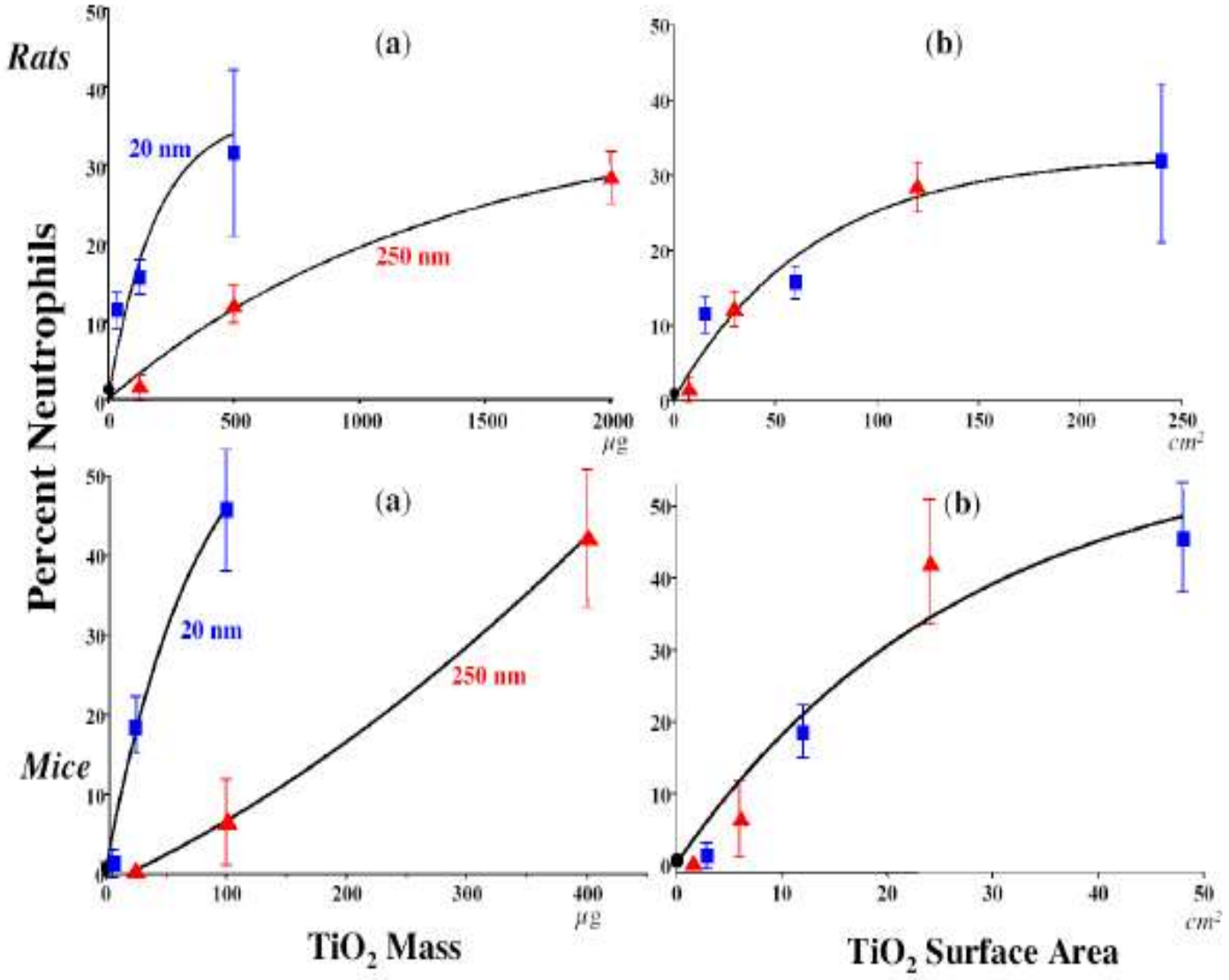
Oberdörster G, et al. *Environ Health Perspect* 113:823-839 (2005)

Toxicities of Inhaled Nanoparticles

- Have an active and large surface that can interact with many targets in the body
- Can cause acute inflammation with secondary effects such as cancer.
- Nanoparticles cause worsening of heart disease, atherosclerosis and asthma.
- Are in the size of proteins and can interfere with normal cellular signaling pathways.
- Poor recognition by our immune system and even enhance response to antigens

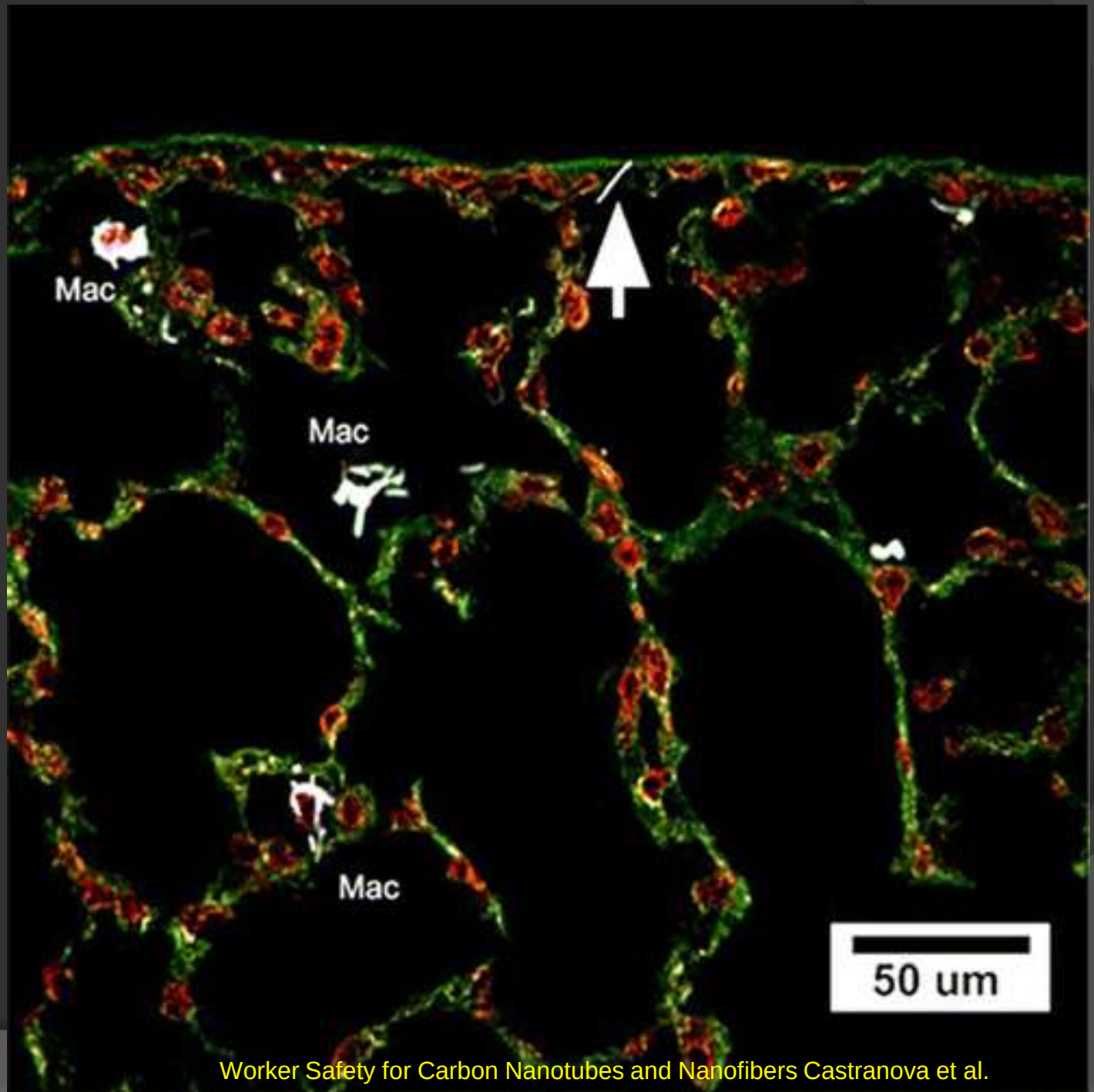
Oberdörster G, et al. **2005**

Inflammatory response in animals



Surface shows good correlation to effect

Environ Health Perspect. 2005 Jul;113(7):823-39.



Worker Safety for Carbon Nanotubes and Nanofibers Castranova et al.


S4800 5.0kV
x15.0k SE(M)

Suspected cases caused by nanoparticles
疑似奈米微粒造成之職業病病例報告

- **Occup exposure to "spray paint" in China in 2009**
  Polyacrylate , Silica nanoparticles (Song et al. 2009)
- **Acute respiratory distress syndrome (ARDS) and kidney tubular necrosis : case report (South Africa, 2010)**
  nickel nanoparticle (Phillips et al, 2010)
- **Submesothelial deposition of carbon nanoparticles after toner exposition: case report (Germany, 2011).**
  carbon black (Theegarten et al, 2011)
- **Allergic dermatitis, asthma, rhinitis: case report (Canada, 2014)**
  nickel nanoparticle (Journeay et al, 2014)

這些女工在一個70平方米、沒有窗戶的房間工作，而且通風設備損壞。她們工作的主要內容，是將聚丙烯酸酯(Polyacrylate)混合物塗到一台機器的底盤上，這台機器再將這種黏合劑噴塗在有機玻璃板之上。 噴塗過程中，經常會有原料噴濺到工人們的身上。

這些女工幾乎沒有職業安全衛生防護。 她們只有棉紗口罩，而且很少佩戴。

2007年至2008年，朝陽醫院職業病科收治了7名18歲至47歲的女性，她們在同一個印刷廠車間工作了5至13個月後，相繼發病。

女工們表現出同樣的症狀：呼吸困難，胸腔積液和心包積液。 一名19歲的病人接受手術後不久即去世，另一名29歲的病人後來也死於呼吸衰竭。其他人也患上了永久性肺損傷。

Song Y, et al. Eur Respir J 2009 34(3): 559-567

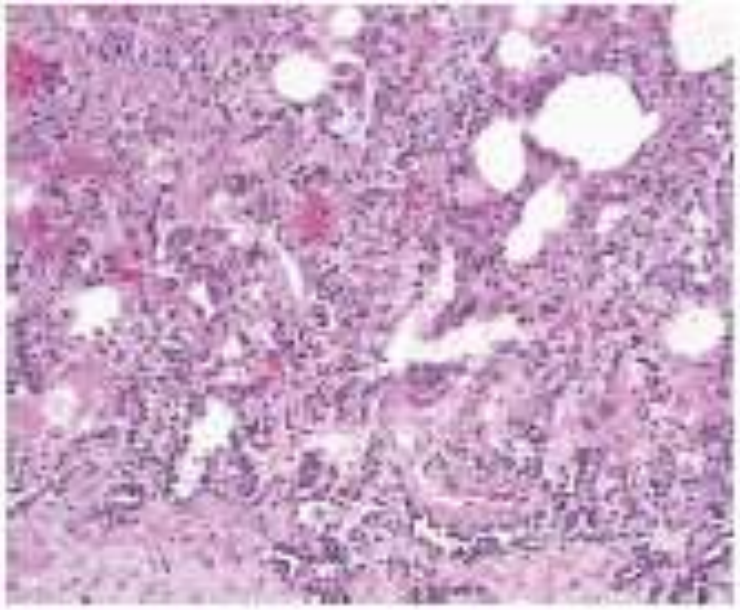


图1 经支气管肺活检结果

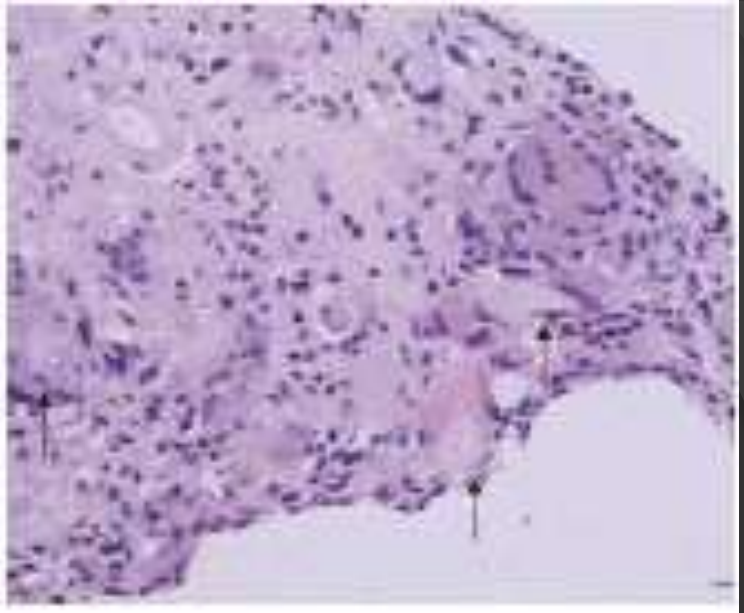
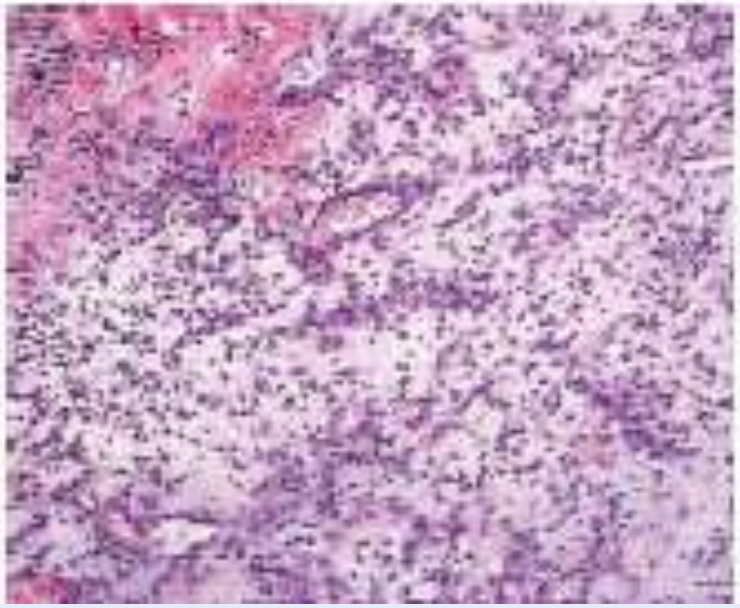
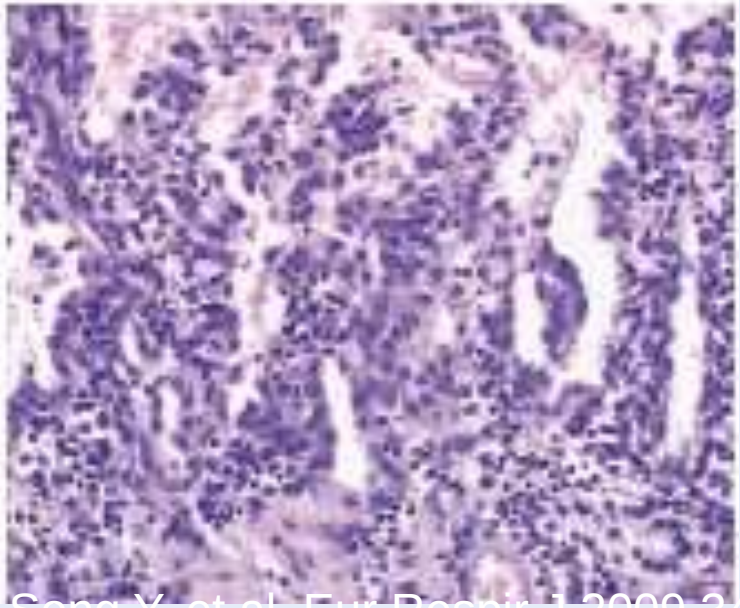


图2 胸腔镜检查结果

nonspecific pulmonary inflammation, pulmonary fibrosis and foreign-body granulomas of pleura

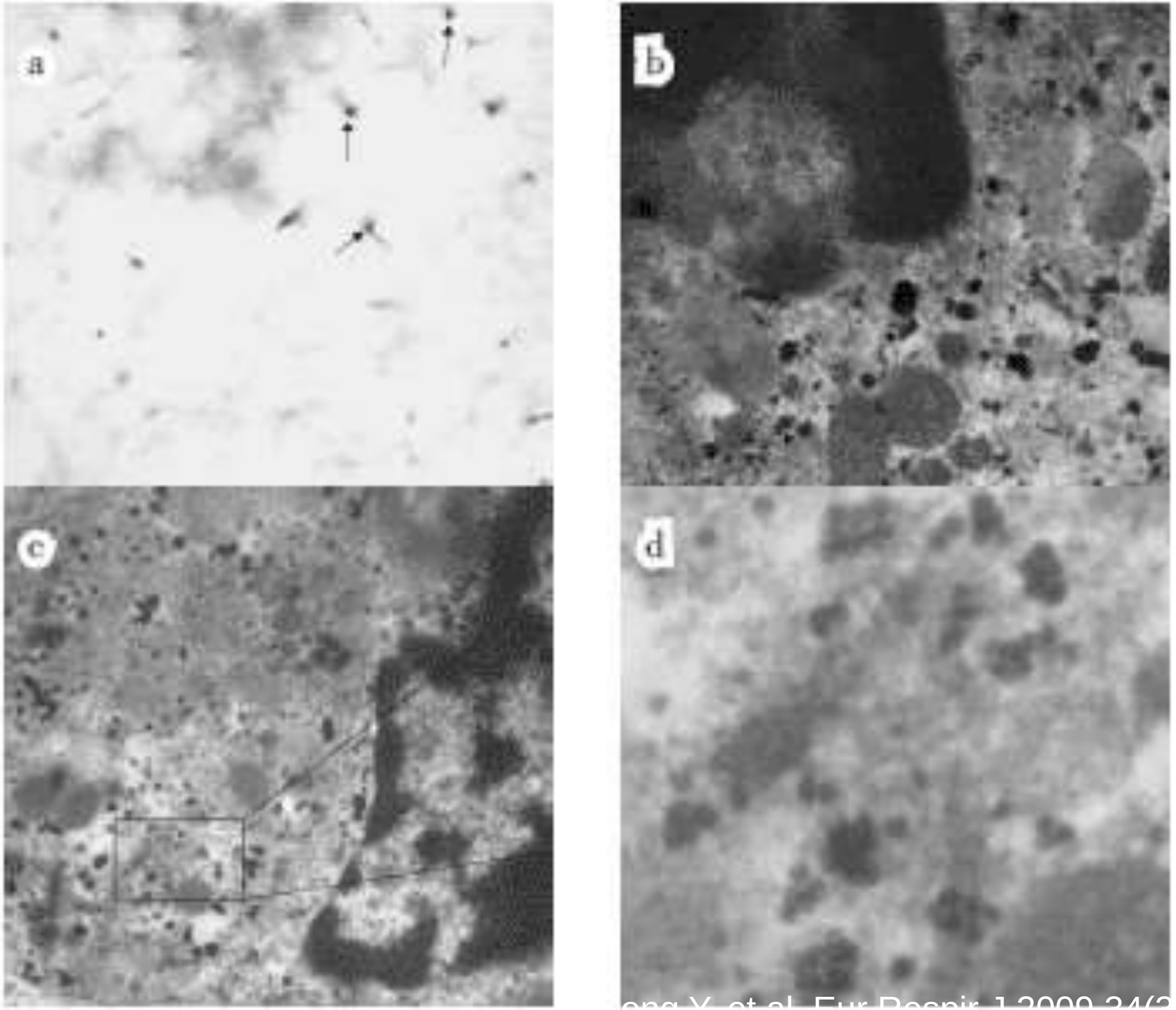
Case 1





Song Y, et al. Eur Respir J 2009; 34(3): 559-567

圖3 18個月後胸腔膜病理檢查結果圖4 18個月後肺部病理檢查結果



nanoparticles were observed in pulmonary epithelial and mesothelial cells, and chest fluid

Case 1

Cong X, et al. Eur Respir J 2009 34(3): 559-567

圖5電鏡下觀察胸腔積液結果

長期暴露在沒有保護措施的奈米粒子下可能嚴重損害人體肺部

long-term exposure to some nanoparticles without protective measures may be related to serious damage to human lungs

Song Y, et al. Eur Respir J 2009 34(3): 559-567

Theegarten *et al. Diagnostic Pathology* 2010, **5**:77
http://www.diagnosticpathology.org/content/5/1/77

Case 3

DIAGNOSTIC PATHOLOGY

影印碳粉沉積於腹膜中皮層

CASE REPORT Open Access

Submesothelial deposition of carbon nanoparticles after toner exposition: Case report

Dirk Theegarten[1*], Smail Boukercha[2], Stathis Philippou[3], Olaf Anhenn[1,4]

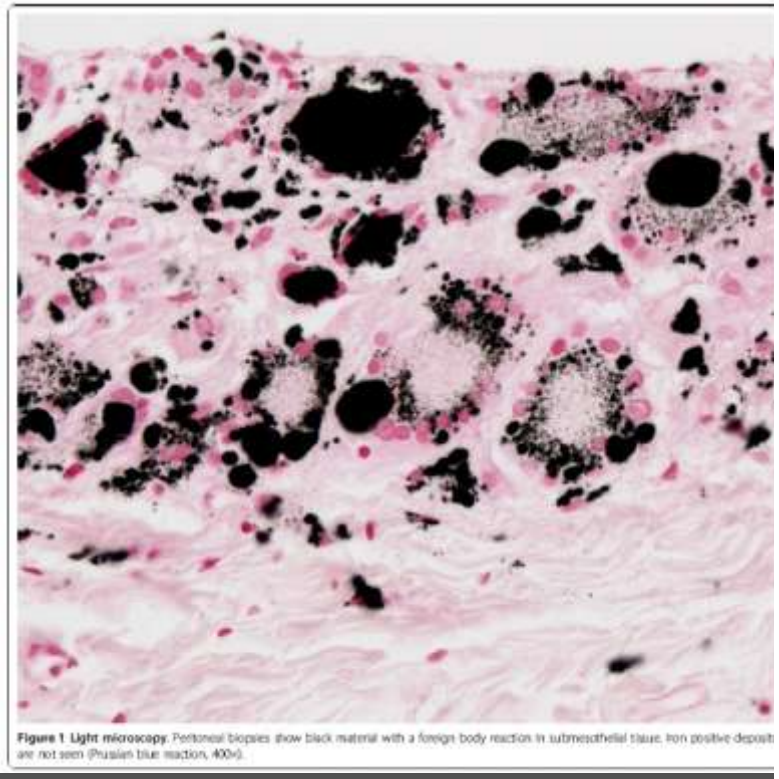


Figure 1 Light microscopy. Peritoneal biopsies show black material with a foreign body reaction in submesothelial tissue. Iron positive deposits are not seen (Prussian blue reaction, 400×).

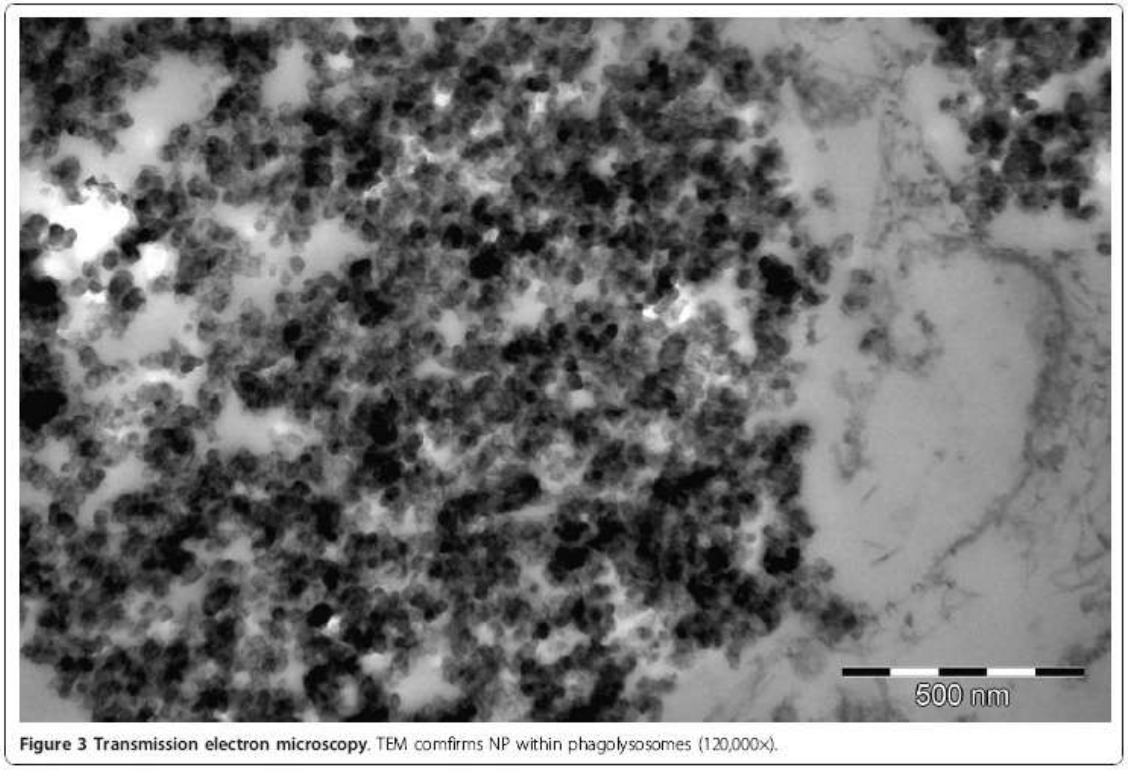


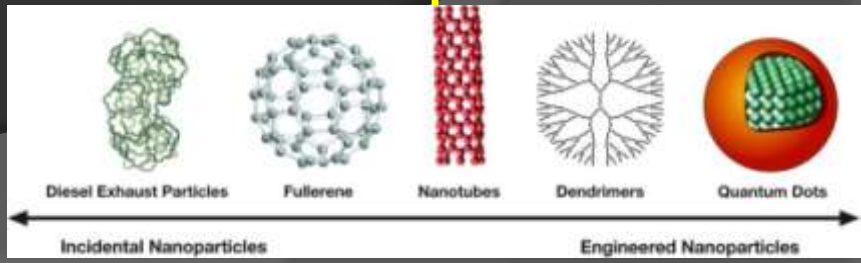
Figure 3 Transmission electron microscopy. TEM comfirms NP within phagolysosomes (120,000×).

Toxicity of Engineered Nanoparticles

- Animal inhalation studies of engineered nanoparticles based on the unrealistic large-dose hazards
  - Inflammation, Granuloma, Pulmonary fibrosis
  - Cardiovascular effects
  - Oxidative stress
  - Plaque, Mesothelioma-like effects
  - Lung cancer

Oberdörster et al. 2005; Hesterberg et al. 2006; Borm et al. 2006; Stern et al. 2008; Hesterberg et al. 2009; Hesterberg et al. 2010; Hubbs et al. 2011

- Occup. Disease Report: Four cases;
- Epidemiological Study on low dose exposure: Some;



Biomonitoring of Exposure and Health Effects in Nanomaterials Workers:

Updated Status of Nanoepidemiology

Epidemiological Studies of Nanomaterial Workers

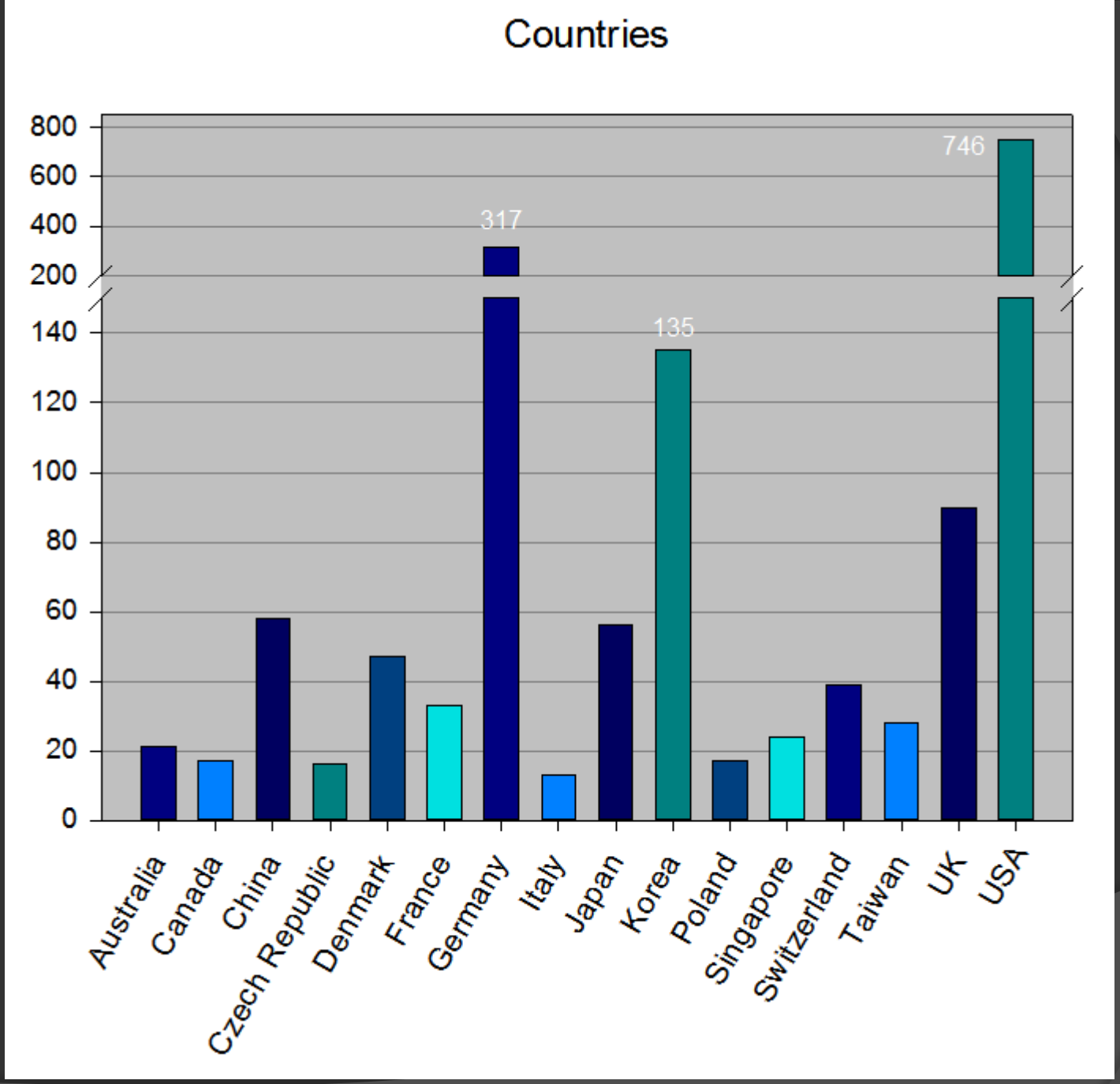
- 17 nanoepidemiologic studies, including
- 13 published peer-reviewed articles;
- 4 unpublished articles;
  - -- 1 doctoral dissertation;
  - -- 1 conference paper; and
  - -- 2 conferences abstracts.

- Exclude natural (legacy) nanomaterial (carbon black)
- 3 additional ongoing studies in the USA, France, and Australia

Liou et al. [2015]

13 published epidemiological studies on nanomaterials handling workers

Author(Year) (Journal)	Country	Nanomaterials	Sample size (exposed/ control)
DESCRIPTIVE STUDY			
Lee et al, 2012 (Nanotoxicology 2012;6:667-9)	Korea	nanosilver	2
Pelclova et al, 2015 (J. Breath Res. 9 (2015) 036008)	Czech Republic	TiO_2 (70-90% TiO_2 <100 nm.)	20/20
CROSS-SECTIONAL STUDY			
Liou et al, 2012 (J Nano Res 2012;14:878-892)	Taiwan	Various (carbon nanotubes, silica dioxide, titanium dioxide, nanosilver, nanoresin)	227/137
Liao et al, 2014 (Ind Health 2014;52:199-215)	Taiwan	Various (ditto)	258/200
Wu et al, 2014 (Int. J. Mol. Sci. 2014, 15, 878-894)	Taiwan	Various (ditto)	241/196
Lee et al, 2015 (Nanotoxicology, 2015;9(6):802-11)	Korea	MWCNT	9/4
Ichihara et al, 2016 (J Nanopart Res 2016;18:52)	China	TiO_2 The particle diameter ranged from 46 to 560 nm.	16(4)/?
Fatkhutdinova et al. 2016 (Toxicology and Applied Pharmacology 2016;299:125–131)	Russia	multiwalled carbon nanotubes	11/14
Pelclova et al, 2016 (Occup Environ Med 2016;73:110–118.	Czech Republic	TiO_2 (70-90% TiO_2 <100 nm.)	36/45
Pelclova et al, 2016 (J. Breath Res. 10 (2016) 016004)	Czech Republic	Fe oxides (81-98% <100 nm)	14/14
Liou et al, 2016 (Biomarkers, 2016;24:1-7)	Taiwan	TiO_2, SiO_2, Indium Tin Oxide (ITO)	127 (32, 39, 56)/100
Pelclova et al, 2016 (J. Breath Res. 10 (2016) 036004)	**Czech Republic**	**TiO_2 (80%** TiO_2 <100 nm.)	52(30 exposed/22 office workers)/45
LONGITUDINAL STUDY			
Liao et al, 2014 (Nanotoxicology 2014;8(S1):100-110)	Taiwan	Various (ditto)	124/77



http://www.nanotechproject.org/inventories/consumer/browse/products/

4 unpublished epidemiological studies on nanomaterials handling workers

Study type, authors, year (presentation)	Country	Nanomaterials	Sample size (no. exposed/no. controls)
CROSS-SECTIONAL			
Cui, 2013 (PhD thesis, UW)	China	Calcium carbonate	66-102/?
Vermeulen et al., 2014 (2014 EPICOH)	Netherlands	CNTs	8 operators + 16 R&D workers/43
LONGITUDINAL			
Liou et al., 2013 (2013 EPICOH)	Taiwan	Various	206/140 followed up no less than 2 times
Cui, 2013 (PhD thesis)	China	Calcium carbonate	66-102/?
Pelclova et al., 2014b (EUROTOX)	Czech Republic	TiO_2 (70–90% of particles <100 nm)	14/25

Study design

- 12 cross-sectional studies;
- 4 longitudinal studies with repeated measurements (panel study);
- 2 descriptive epidemiological study;

- Total=17
- 1 study had both cross-sectional and longitudinal study design.

Liou et al. [2015, in process]

Nanomaterial studied

- MWCNT: 3 (+ USA)
- TiO2: 3

- Fe_2O_3: 1
- Ca carbonate: 1;
- Mixed: 1 (Taiwan)

Major findings of 12 cross-sectional epidemiological studies

Author(Year) (Journal)	**Country**	Nanomaterials	Major findings
CROSS-SECTIONAL			
Liou et al, 2012	Taiwan +	Various (carbon nanotubes, silica dioxide, titanium dioxide, nanosilver, nanoresin)	Decreased antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPX) and increased cardiovascular markers, fibrinogen, intercellular adhesion molecule (ICAM), and interleukin 6 in exposed workers
Liao et al, 2014	Taiwan +	Various (ditto)	The only symptom identified as significantly work-related was sneezing. The only disease significantly worsened by work was allergic dermatitis.
Wu et al, 2014	Taiwan +	Various (ditto)	A significant association between risk level 2 of NP exposure and FENO. nano-TiO2 in all of the NM exposed categories had a significantly increased risk in FENO > 35 ppb.
Lee et al, 2015	Korea +	MWCNT	The malondialdehyde (MDA), 4-hydroxy-2-hexenal (4-HHE), and n-hexanal levels in the EBC of MWCNT manufacturing workers were significantly higher than those in the office workers. .
Ichihara et al, 2016	China +	TiO_2 (46 to 560 nm)	The study showed that exposure to particles with a diameter <300 nm might affect HRV in workers handling TiO2 particles.
Fatkhutdinova et al.	Russia +	multiwalled carbon nanotubes	Exposure to MWCNTs caused significant increase in IL-1β, IL6, TNF-α, inflammatory cytokines and KL-6, a serological biomarker for interstitial lung disease in collected sputum samples.
Pelclova et al, 2016	Czech Republic +	TiO_2 (70-90% TiO_2 <100 nm.)	Accordingly, most EBC oxidative stress markers, including in the preshift samples, were higher in production workers than in the two other groups. Multiple regression analysis confirmed an association between the production of TiO2 and the levels of studied biomarkers.
Pelclova et al,	Czech Republic +	Fe oxides (81-98% <100 nm)	Almost all markers of lipid, nucleic acid and protein oxidation were elevated in the EBC of workers comparing with control subjects. Markers in urine were not elevated.
Liou et al, 2016	Taiwan +	TiO_2, SiO_2, Indium Tin Oxide (ITO)	Exposure to TiO2, SiO2, and ITO resulted in significant lower antioxidant enzymes (glutathione peroxidase and superoxide dismutase) and higher oxidative biomarkers 8-hydroxydeoxyguanosine (8-oxodG) than comparison workers.
Pelclova et al, 2016	Czech Republic +	**TiO_2 (8**0% TiO_2 <100 nm.)	All LT levels in workers' EBC were elevated relative to the controls ($p < 0.01$). LTs in the EBC sample were correlated with titanium levels.
Cui, 2013 (PhD thesis, UW)	China +	Calcium carbonate	IL1β and IL8 in sputum ↑
Vermeulen et al., 2014 (2014 EPICOH)	Netherlands +	CNTs	Immuno-cytokines ↑

Analysis of 12 cross-sectional studies

- All 12 cross-sectional studies showed biological changes that might be indicative of early adverse health effects with exposure to engineered nanomaterials.
- In addition, Taiwan's study found excessive sneezing and allergic dermatitis in nanomaterial workers.

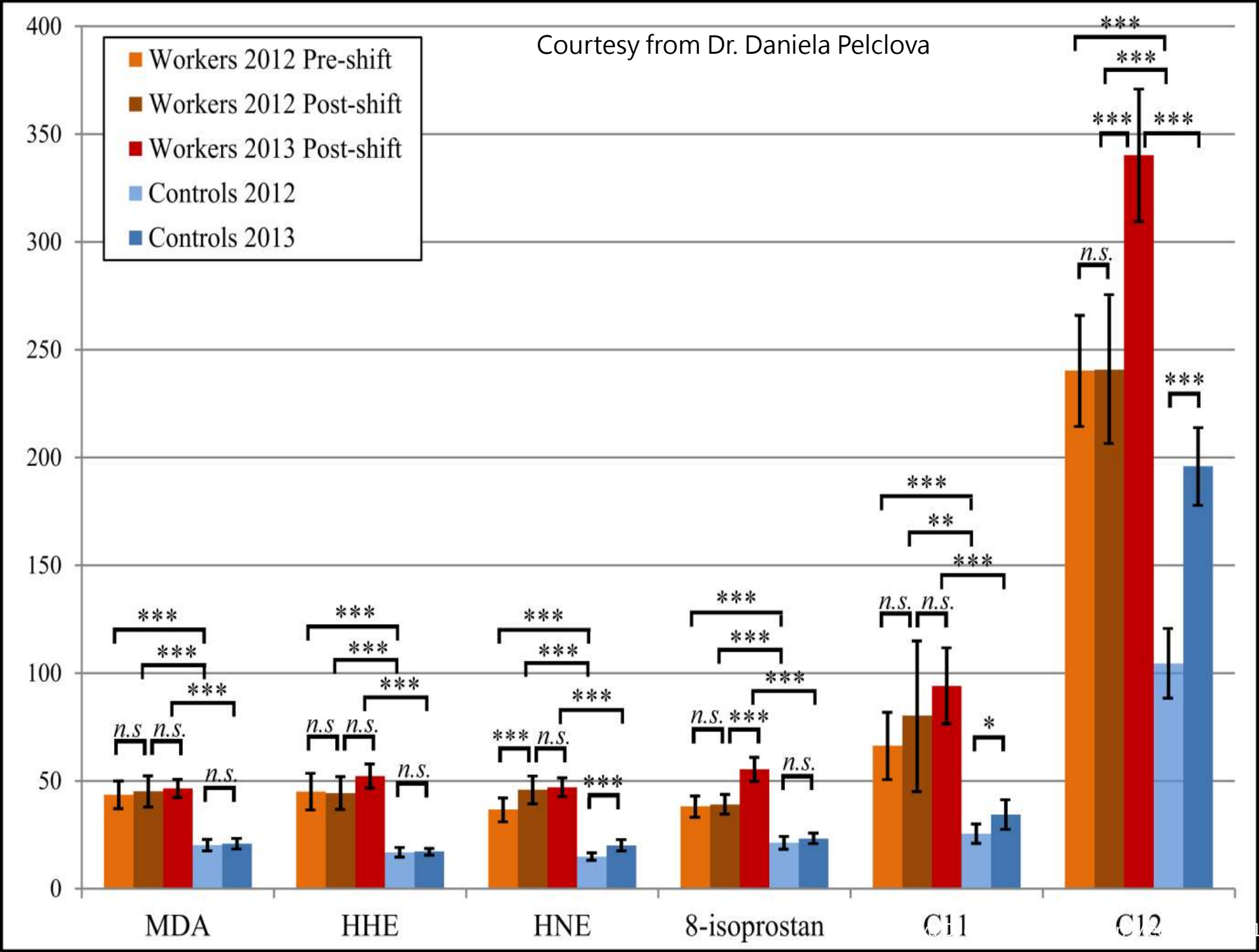
(weakness of cross-sectional study: lack of temporality and causal)

Biological markers were categorized into four organs/systems

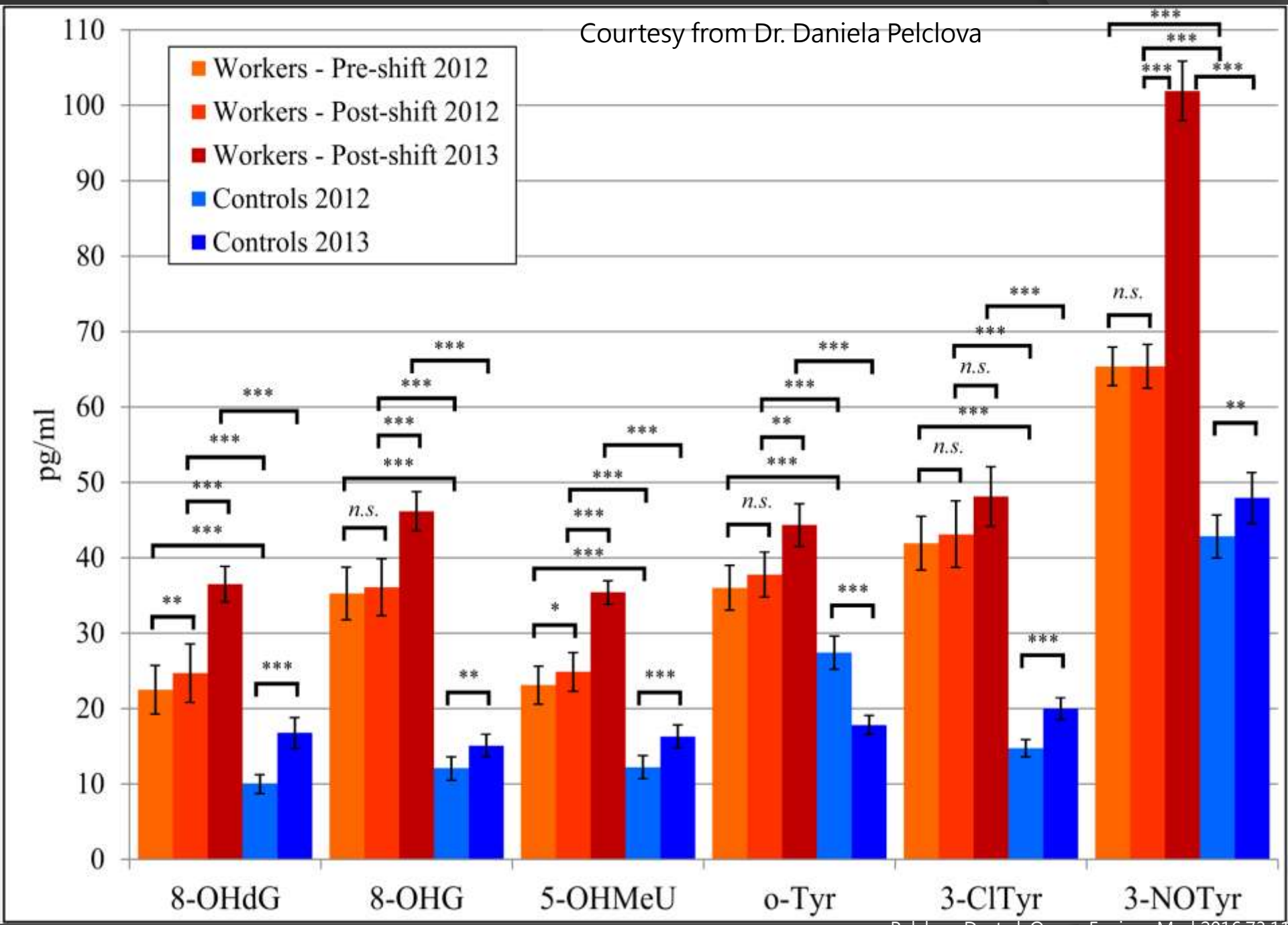
- 1. Oxidative damage: increased EBC markers of lipid oxidation, including MDA, HNE, HHE, and 8-isoprostane, n-hexanal, C_6-C_{12}; markers of oxidation of nucleic acids and proteins, including 8-OHdG, 8-OHG, 5-OHMeU, 3-ClTyr, 3-NOTyr, o-Tyr; and urine C_6, C_7, C_{10}, C_{12}, HHE, 8-OHG and 3-ClTyr., decreased anti-oxidant enzymes (superoxide dismutase (SOD) and glutathione peroxidase (GPX)).
- (5 positive in EBC or sputum; 1 positive in plasma or urine);

- 2. Lung: increased lung fibrosis markers (serum TGF-β1 and sputum KL-6), increased lung inflammation markers (sputum IL-1β and IL-8, FeNO), increased EBC LT B_4, C_4, and E_4, reduction of lung function (FEV1%, FEV1/FVC, MMF, PEFR, and FEF25%), and increased pro-inflammatory cytokines (IL-1β, IL-6, IL-8, MIP-1β, and TNFα);

- 3. Cardiovascular: increased cardiovascular effect markers (fibrinogen, intercellular adhesion molecule (ICAM), and interleukin 6), total number or percentage of RR 50+/- in HRV;


Courtesy from Dr. Daniela Pelclova
Workers 2012 Pre-shift
Workers 2012 Post-shift
Workers 2013 Post-shift
Controls 2012
Controls 2013
400
350
300
250
200
150
100
50
0
MDA
HHE
HNE
8-isoprostan
C11
C12
n.s.
***
**
*

Courtesy from Dr. Daniela Pelclova



Pelclova D, et al. Occup Environ Med 2016;73:11

Courtesy from Dr. Daniela Pelclova

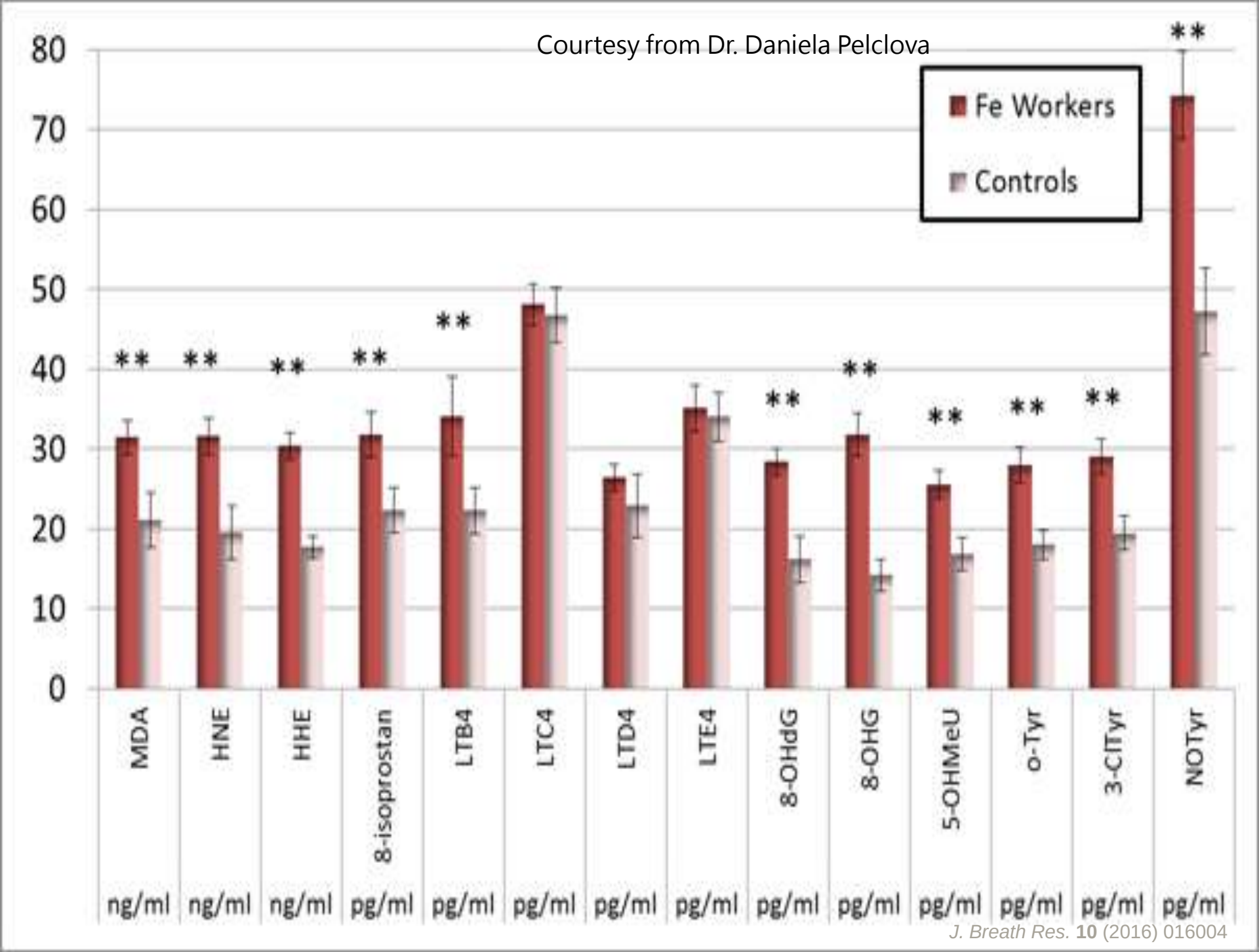


Table 6. A. Levels of biomarkers related to MWCNT exposure. B. Median levels of biomarkers related to MWCNT exposure and diurnal variation (work-shift).

A. Levels of biomarkers related to MWCNT exposure.

		Manufacturing		*p* values	
	Office (4)	Total ($N=9$)	Day shift ($N=5$)	$p1$[a]	$p2$[b]
Blood Mo (μg/L)	0.60 ± 0.11 (0.61)	0.86 ± 0.42 (0.72)	0.55 ± 0.19 (0.63)	0.199	0.905
Blood Co (μg/L)	0.14 ± 0.03 (0.15)	0.16 ± 0.05 (0.14)	0.16 ± 0.06 (0.14)	0.710	0.905
EBC H_2O_2 (μM)	0.41 ± 0.19 (0.39)	0.44 ± 0.39 (0.30)	0.58 ± 0.46 (0.30)	0.710	0.905
EBC MDA (nM)	2.29 ± 0.64 (2.25)	4.11 ± 1.29 (4.15)	3.28 ± 0.74 (3.18)	0.011	0.063
EBC 4-HHE (nM)	1.34 ± 1.36 (1.16)	6.32 ± 4.12 (4.53)	7.84 ± 4.85 (7.69)	0.020	0.032
EBC n-Hexanal (nM)	13.0 ± 9.2 (13.6)	34.5 ± 11.8 (35.0)	28.2 ± 9.8 (26.5)	0.020	0.111

Calculated by the Mann-Whitney U-test, arithmetic mean±standard deviation (median).
aOffice versus total manufacturing workers.
bOffice versus day shift manufacturing workers.

MDA: malondialdehyde
4-HHE:4-hydroxy-2-hexenal

Lee et al. [2015, in press]

Table 2
The content of the cytokines/proteins in serum and sputum samples in exposure and control groups.

Cytokines/proteins, pg/ml	Sputum		Serum	
	Control	Exposed group	Control	Exposed group
IL-1β	646.90 ± 188.18	1988.70 ± 205.71*	36.61 ± 3.86	90.08 ± 23.29*
IL-4	299.33 ± 108.77	818.86 ± 57.34*	19.46 ± 8.30	47.38 ± 6.30*
Il-5	436.43 ± 173.40	1764.37 ± 424.12*	15.24 ± 2.83	22.02 ± 3.77
Il-6	47.98 ± 40.79	262.75 ± 22.34*		
IL-8	863.84 ± 222.37	1753.51 ± 201.91*	769.87 ± 214.95	1217.98 ± 237.00
TNF-α	321.41 ± 156.34	1512.67 ± 271.88*	20.98 ± 3.66	52.47 ± 9.19*
IL-10			8.40 ± 3.24	18.05 ± 0.41*
Il-2	374.16 ± 128.07	887.59 ± 354.36	80.62 ± 12.73	88.70 ± 3.92
IFN-γ	992.15 ± 510.59	2635.29 ± 958.51	19.47 ± 5.12	29.15 ± 1.47
IL-12			11.14 ± 2.26	17.37 ± 0.72
KL-6	12.20 ± 8.69	220.50 ± 95.06*	248.35 ± 37.81	313.52 ± 29.46
TGF-β1	4.90 ± 0.34	5.0 ± 0.95	20.06 ± 0.31	21.82 ± 1.23
Osteopontin			59.19 ± 5.37	68.98 ± 7.20

* $p < 0.05$, *t*-test.

Table 2. Comparison of 8-oxodG in various biospecimens between exposed and non-exposed groups and stratified by exposed materials.

Characteristic/biomarker	Urinary 8-oxodG (ng/mL)	Plasma 8-oxodG (ppt, pg/mL)	WBC 8-oxodG ($1/10^6$dG)	Plasma SOD (U/mL)	Plasma GPx (nmol/min/mL)
Median (IQR)					
Non-exposed ($n = 100$)	2.61 (2.58)[a]	12.63 (8.51)	2.26 (1.59)	14.68 (9.88)	143.89 (44.14)
Exposed ($n = 127$)	4.77 (4.38)	16.34 (8.30)	3.50 (2.26)	10.09 (4.78)	120.00 (28.93)
p Value[b]	<0.001	<0.001	<0.001	<0.001	<0.001
TiO_2 exposure ($n = 32$)	4.59 (3.16)	16.53 (8.46)	2.57 (2.57)	12.88 (5.93)	123.82 (56.92)
p Value[b]	0.003	0.012	0.033	0.042	0.033
SiO_2 exposure ($n = 39$)	3.93 (3.21)	14.74 (7.47)	2.47 (1.23)	12.16 (6.76)	122.93 (51.83)
p Value[b]	0.003	0.034	0.039	0.047	0.02
ITO exposure ($n = 56$)	5.38 (4.37)	16.35 (8.72)	4.11 (1.23)	8.81 (2.62)	118.52 (18.44)
p Value[b]	<0.001	<0.001	<0.001	<0.001	<0.001

[a]Median (IQR); IQR: interquartile range.
[b]Mann–Whitney U tests.

Major findings of 4 longitudinal (panel) epidemiological studies

Study type, authors, year (presentation)	Country	Nanomaterials	Major findings	Sample size (no. exposed/no. controls)
LONGITUDINAL				
Liao et al, 2014	Taiwan +	Various (ditto)	Changes of the antioxidant enzymes (decreased SOD and GPX), cardiovascular markers (increased VCAM, decrease of paraoxonase), the small airway damage marker (decreased Clara cell protein 16), and lung function parameters (decreased MMF, PEFR and FEF25%) were significantly associated with nanomaterial-handling	122/77
Liou et al., 2013 (2013 EPICOH)	Taiwan -	Various	No significant difference in 4-year follow-up study	206/140 followed up no less than 2 times
Cui, 2013 (PhD thesis)	China -	Calcium carbonate	No significant cross-shift effect for FEV1, BP, and FENO.	66-102/?
Pelclova et al., 2014b (EUROTOX)	Czech Republic -	TiO_2 (70–90% of particles <100 nm)	Ihe post-shift markers in 2013 were elevated versus post-shift markers in 2012 for all markers of oxidation of lipids, nucleic acids, and proteins .	14/25

Summary of Health Hazards of Nanomaterials Handling

	Anti-oxidant Enzymes (Oxidative stress markers)	Lung / systemic Inflam. markers	Cardio-vascular markers (HRV)	Genotoxic markers	Brain function
Cross-Sectional	SOD ↓ (X)	X	Fibrinogen, ICAM ↑ (X)	X	Memory ↓
6 months FU	SOD ↓ (X)	V (CC16 and lung function)	VCAM ↑ (X)	X	X
30-month FU	SOD ↑ (X)	X	X (X)	X	X
42-month FU	SOD ↑ (X)	X	X (X)	X	X

follow-up >= 2 times, X: negative

Liou et al, 2014

Emission of nanomaterials in different operations or industries in Taiwan

Operation	Emission of Nanomaterials
Coating of nanomaterials (Enclosed)	Very low
Mixing/grinding of nanopigments (Enclosed)	Very low
Synthesis of nanomaterials (Wet process)	Very low
Centrifuge of nanomaterials (wet process)	Very low
Spray drying of nanomaterials	Yes
Welding	Yes
Polishing	Yes
Milling	Yes
Grinding	Yes
Foundry Industry	Yes

Tsai et al, 2012

Analysis of 4 longitudinal studies

- Only 1 (Taiwan study) of the 4 longitudinal panel studies indicated increased markers of biological changes in the exposed group during a 6-month follow-up study.
- However, extended four-year follow-up study has shown to be negative in Taiwan.

- → None of longitudinal study is positive
- (GEE analysis for repeated measurements)
- GEE: Generalized Estimating Equation

結　　論

- 目前流行病學研究發現橫斷面結果皆顯示奈米顆粒可能對人體有氧化性傷害、肺部傷害、及心血管系統傷害等毒性。**但縱斷面之追蹤研究尚未發現奈米顆粒可能對人體有傷害。**
- 尚需要更多的縱斷面追蹤研究來回答奈米顆粒長期慢性、低濃度暴露對人體的影響。**尤其來自奈米大國如美國、德國、英國和韓國。**
- 流行病學研究及劑量效應關係有賴於暴露評估，但職場之奈米暴露評估有其技術上的限制，**生物偵測方法如測量呼氣濃縮物(EBC)中的奈米顆粒數 或許可反映奈米之暴露。**並可配合呼氣濃縮物中的效應指標來探討劑量效應關係。
- 由於缺乏縱斷面追蹤研究的數據無法執行量化風險評估，為謹慎起見，還是**需要防止風險的預防措施/法規**。

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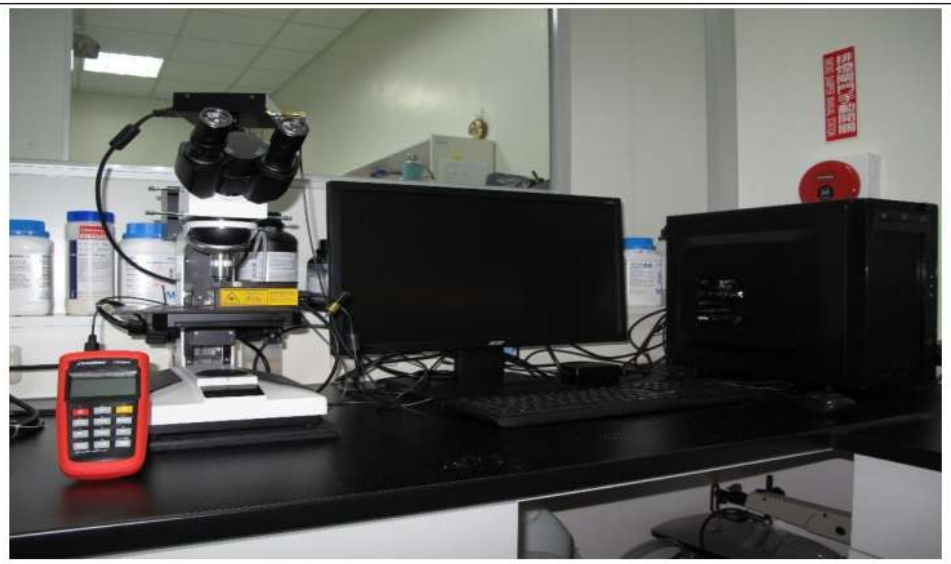
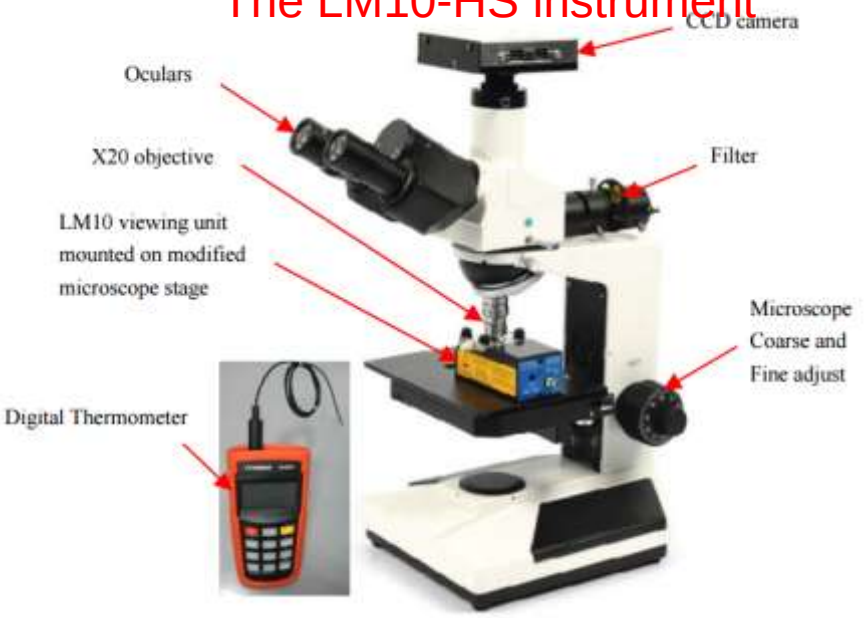
Center for Micro/Nano Science and Technology, National Cheng Kung University



NanoSight

Nanoparticles tracking Analysis (NTA)

The LM10-HS instrument



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- University of Massachusetts Lowell
  Drs. Ellenbecker M. and Tsai SJ

Thanks For Your Attention