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Professor
Nanosafe 2018

Cardiovascular disease as a (nano)particle-induced occupational disease

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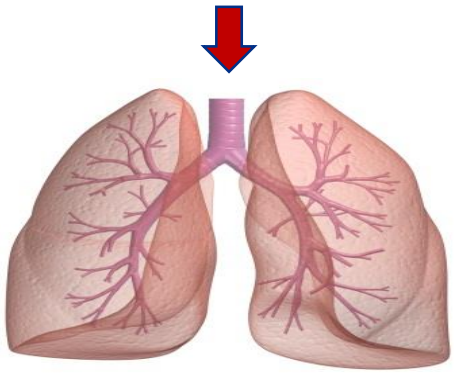
DTU Nanotech
Department of Micro- and Nanotechnology

Proposed mechanism of action for particle-mediated cardiovascular disease

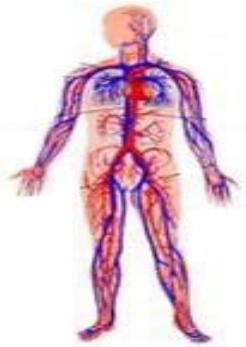
Inhaled particles promote atherosclerosis via acute phase response

Inhalation of (nano)particles

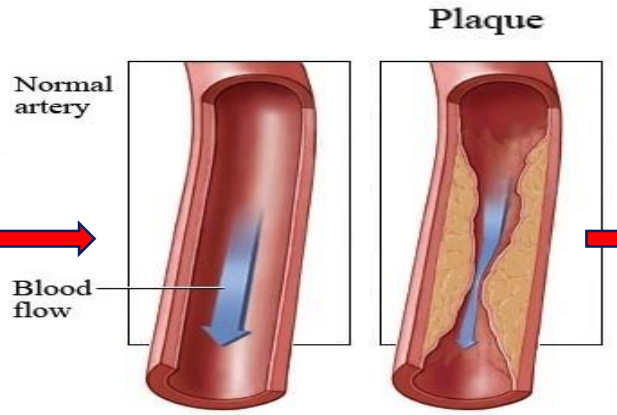


Inflammatory & acute phase response

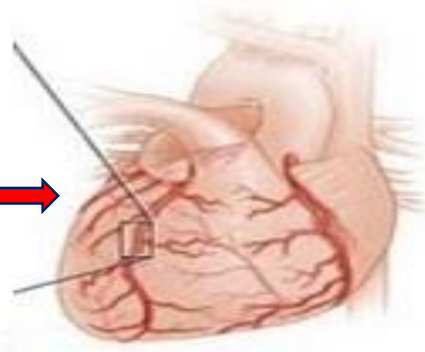
Systemic circulation of acute phase proteins



Atherosclerosis



Cardiovascular disease



New knowledge

Established fact

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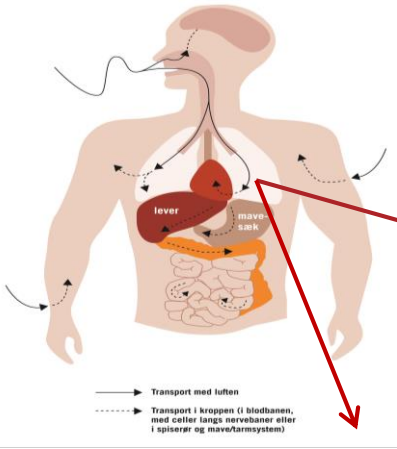
Inhalation of nanoparticles: particle accumulation and inflammation



Nanoparticles

Ultrafine particles

Fine particles

Airways

Particle deposition and removal by mucociliar clearance

Particle phagocytosis by macrophage

INFLAMMATION

release of mediators

ROS

Chemo/cytokines

TNF, MIP, ILs etc.:

ROS/RNS

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Time- and dose-dependent pulmonary acute phase response in mice following exposure to nanomaterials

TABLE 1 | Differential Expression of Murine Acute Phase Genes and *Saa3* Expression Levels after Exposure to Different Nanomaterials and at Different Time Points

Post Exposure Day	1			3			28			
Dose/Animal	18 μg	54 μg	162 μg	18 μg	54 μg	162 μg	18 μg	54 μg	162 μg	Ref
TiO_2 nanoparticles										
N acute phase genes[1]	0	5	10	3	1	3	1	2	3	28
Fold increase of *Saa3* mRNA[2]	1.8	87	368	1.1	2.6	19	1	1.8	5.5	11
Carbon Black nanoparticles										
N acute phase genes[1]	0	7	10	0	0	4	0	0	2	42
Fold increase of *Saa3* mRNA[2]	63	237	294	8.3	24	51	1.1	5	22	11
Multiwalled Carbon nanotubes										
N acute phase genes[1]	5	5	10	ND	ND	ND	ND	1	ND	35
Fold increase of *Saa3* mRNA[2]	52	151	95	39	152	612	7.9	29	88	11

Saber *et al.* 2014

WIREs Nanomed nanobiotech

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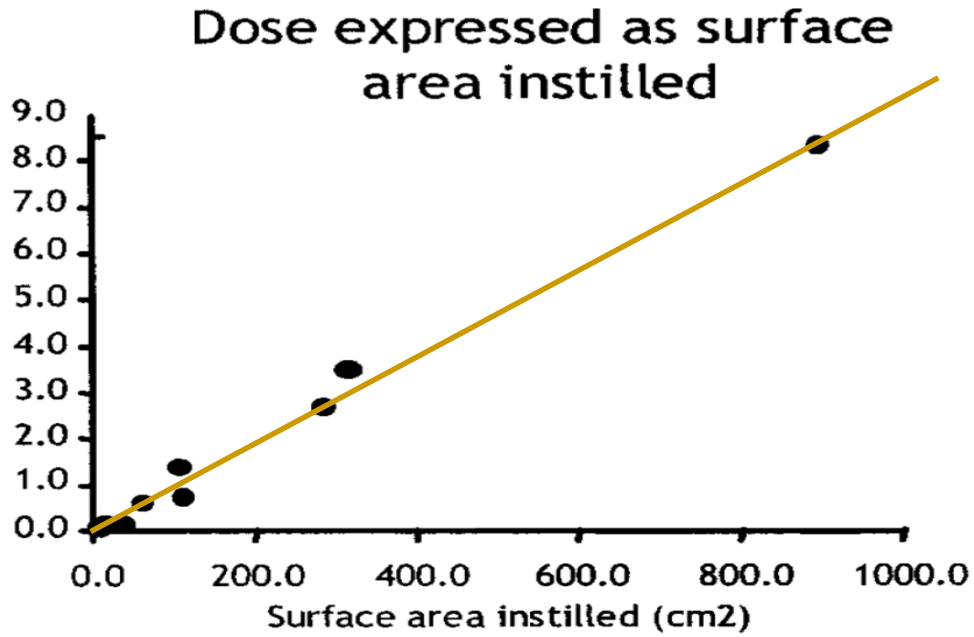
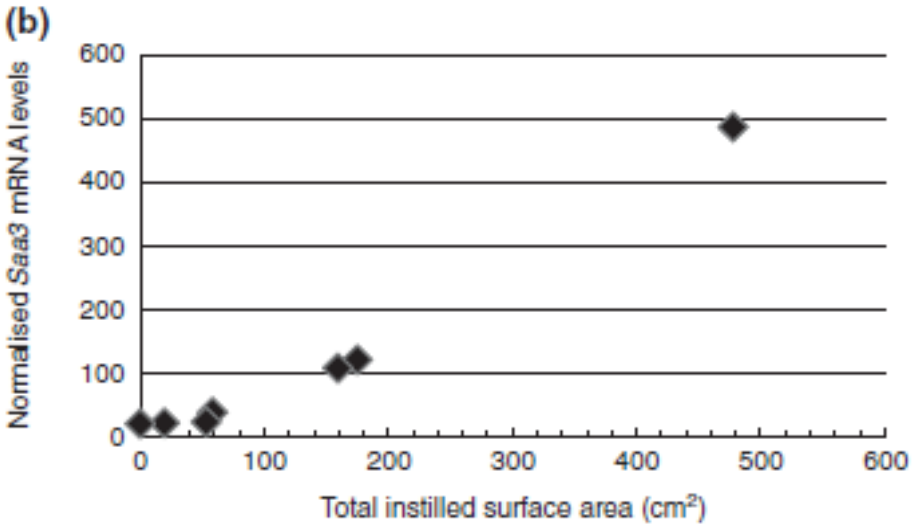
Deposited surface area of insoluble particles is a predictor of pulmonary inflammation and pulmonary acute phase response



Donaldson et al., 2002



Saber AT et al, 2014

Cardiovascular disease is a major cause of (occupational) morbidity

- Prospective cohort of 5866 Danish welders (1986-2006)
- Expected cardiovascular morbidity based on the general population : 1587 affected (27%)
- Observed cardiovascular morbidity: 1760 (30%)
- Excess cases: 173/5866= 2.9% of the cohort

EVEN VERY SMALL EFFECTS ON CARDIOVASCULAR RISK HAS LARGE IMPACT

Table 2 Standardised incidence ratios (SIRs) and 95% CIs for selected cardiovascular diseases among 5866 male Danish welders followed up from 1986 to 2006 and compared with the general male population

Cardiovascular disease	Cumulative particulate exposure ($mg/m^3 \times years$)	Observed	Expected	SIR	95% CI
Acute myocardial infarct	All	377	337.4	1.12	1.01 to 1.24
	0–10	11	8.7	1.26	0.63 to 2.26
	10–50	40	42.7	0.94	0.94 to 1.28
	50–100	80	63.3	1.26	1.00 to 1.57
	>100	76	77.3	0.98	0.77 to 1.23
	Missing data*	170	145.4	1.17	1.00 to 1.36
Angina pectoris	All	437	394.5	1.11	1.01 to 1.22
	0–10	9	11.3	0.80	0.36 to 1.52
	10–50	65	57.6	1.13	0.87 to 1.44
	50–100	87	82.1	1.06	0.85 to 1.31
	>100	101	90.4	1.12	0.91 to 1.36
	Missing data*	175	153.1	1.14	0.98 to 1.33
Chronic ischaemic heart disease	All	326	277.6	1.17	1.05 to 1.31
	0–10	5	7.3	0.68	0.22 to 1.59
	10–50	42	36.7	1.14	0.82 to 1.55
	50–100	68	55.3	1.23	0.95 to 1.56
	>100	65	65.3	1.00	0.77 to 1.27
	Missing data*	146	15.2	1.29	1.09 to 1.52
Cerebral infarct	All	169	136.5	1.24	1.06 to 1.44
	0–10	2	3.4	0.58	0.07 to 2.10
	10–50	21	16.7	1.26	0.78 to 1.92
	50–100	30	25.6	1.17	0.79 to 1.67
	>100	46	32.1	1.43	1.05 to 1.91
	Missing data*	70	58.7	1.19	0.93 to 1.51
Other acute ischaemic heart disease	All	14	13.02	1.08	0.59 to 1.80
Cardiac arrythmias	All	237	233.5	1.01	0.89 to 1.15
Cardiac arrest	All	32	33.7	0.95	0.65 to 1.34
Heart failure	All	157	148.8	1.05	0.90 to 1.23
Arterial embolism and thrombosis	All	11	15.3	0.72	0.36 to 1.29

*Welders for whom we had either incomplete information on duration of welding or no information on welding in the period 1980–86 for calculation of cumulative particulate exposure after baseline (from 1 January 1987).

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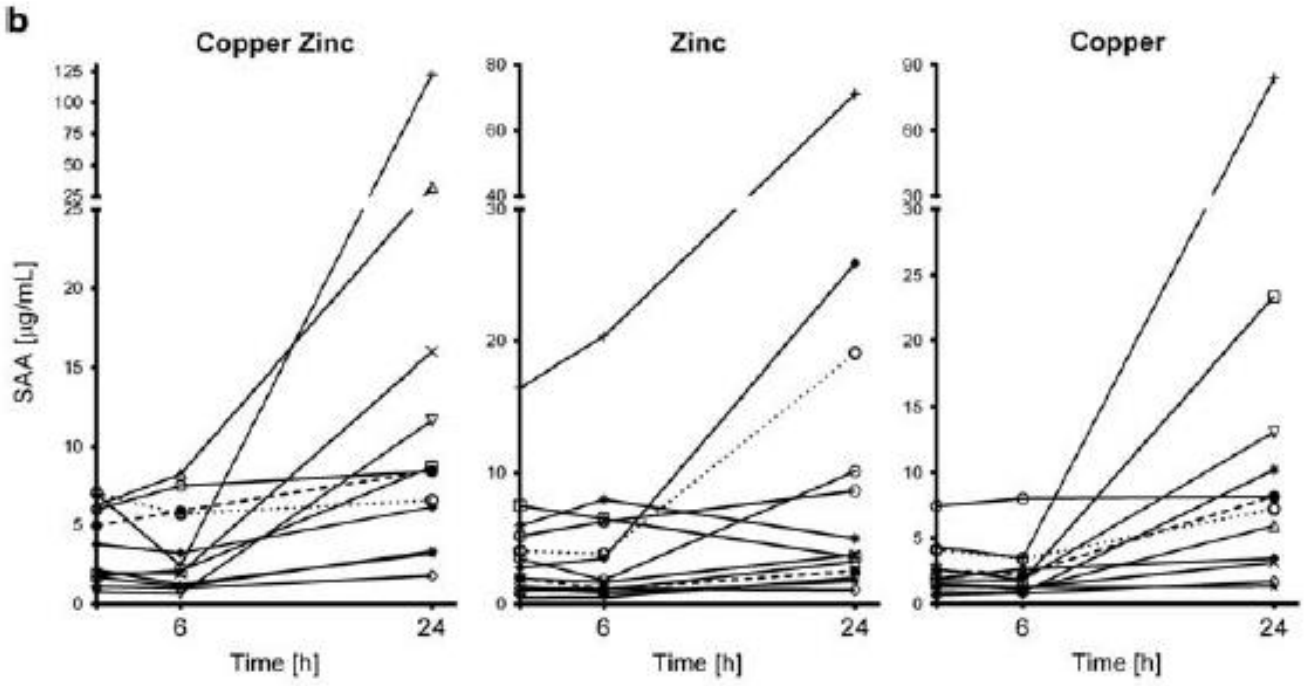
Ibfelt et al, OEM 2010)

Acute phase response induced by welding fumes containing Cu and

- 15 healthy male volunteers
- 6 h exposure to welding fumes:
- 1.5 mg/m^3 Zn
- 0.4 mg/m^3 Cu
- Acute phase protein SAA measured in blood



Baumann et al JESEE 2018

Acute phase proteins CRP & SAA levels are associated with risk of CVD in prospective epidemiological studies

Nurses' Health Study : 120.000 participants

TABLE 3. RELATIVE RISK OF CARDIOVASCULAR EVENTS ACCORDING TO BASE-LINE PLASMA LEVELS OF MARKERS OF INFLAMMATION AND LIPIDS.*

VARIABLE	QUARTILE OF PLASMA LEVEL				P VALUE FOR TREND
	1	2	3	4	
High-sensitivity C-reactive protein					
Median — mg/dl	0.06	0.19	0.38	0.85	
Relative risk (95% CI)	1.0	2.1 (1.0–4.5)	2.1 (1.0–4.4)	4.4 (2.2–8.9)	<0.001
Serum amyloid A					
Median — mg/dl	0.25	0.43	0.62	1.17	
Relative risk (95% CI)	1.0	1.8 (0.9–3.6)	1.9 (0.9–3.8)	3.0 (1.5–6.0)	0.002

Ridker *et al.* 2000, NEJM

Inhalation of ZnO NPs induces acute phase response in human volunteers below current occulational exposure limits

Vogel and Cassee *Particle and Fibre Toxicology* (2018) 15:7
DOI 10.1186/s12989-018-0247-3

Particle and Fibre Toxicology

EDITORIAL Open Access

Editorial: dose-dependent ZnO particle-induced acute phase response in humans warrants re-evaluation of occupational exposure limits for metal oxides

Ulla Vogel[1,2*] and Flemming R. Cassee[3,4]

RP

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well below incurrent OEL

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Adapted from Monsé et al Part Fibre Toxicol. 2018 15(1):8

Example of insoluble particles: Association between air pollution levels and CRP

Association between PM2.5 and CRP levels in 30 000 Taiwanese:
0.014 mg/L CRP pr 5 ug/m^3 increment in PM 2.5

Table 2. Associations of CRP with long-term exposure to $PM_{2.5}$ in baseline analysis among Taiwanese adults

	Crude model			Model 1[a]			Model 2[a]		
	Mean (SE)[b]	% difference (95% CI)	*P*	Mean (SE)[b]	% difference (95% CI)	*P*	Mean (SE)[b]	% difference (95% CI)	*P*
Men ($N = 17761$)									
1st quartile	0.96 (1.01)	Ref	Ref	0.92 (1.03)	Ref	Ref	0.98 (1.05)	Ref	Ref
2nd quartile	0.96 (1.01)	0.34 (−1.36, 2.05)	0.69	0.95 (1.03)	1.18 (−0.01, 2.89)	0.18	1.01 (1.05)	1.49 (−0.01, 3.05)	0.06
3rd quartile	0.98 (1.01)	0.93 (−0.77, 2.62)	0.28	0.97 (1.03)	1.94 (0.23, 3.65)	0.03	1.03 (1.05)	2.19 (0.63, 3.76)	0.006
4th quartile	1.07 (1.01)	4.78 (3.09, 6.48)	< 0.001	1.03 (1.03)	4.71 (3.01, 6.41)	< 0.001	1.08 (1.05)	4.27 (2.72, 5.82)	< 0.001
trend test[c]	-	-	< 0.001	-	-	< 0.001	-	-	< 0.001
every 5 $\mu g/m^3$ increment[d]	-	1.42 (0.96, 1.87)	< 0.001	-	1.35 (0.89, 1.81)	< 0.001	-	1.21 (0.79, 1.63)	< 0.001
Women ($N = 12273$)									
1st quartile	0.76 (1.02)	Ref	Ref	0.70 (1.06)	Ref	Ref	0.85 (1.07)	Ref	Ref
2nd quartile	0.68 (1.02)	−4.79 (−0.01, -2.42)	< 0.001	0.67 (1.06)	−1.52 (−0.01, 0.78)	0.19	0.84 (1.07)	−0.82 (−0.01, 1.23)	0.43
3rd quartile	0.70 (1.02)	−3.54 (−5.91, -1.16)	0.004	0.70 (1.06)	0.37 (−1.95, 2.70)	0.75	0.88 (1.07)	1.44 (−0.63, 3.51)	0.17
4th quartile	0.82 (1.02)	3.30 (0.92, 5.68)	0.006	0.79 (1.06)	5.19 (2.88, 7.5)	< 0.001	0.95 (1.07)	4.89 (2.84, 6.95)	< 0.001
trend test[c]	-	-	< 0.001	-	-	< 0.001	-	-	< 0.001
Every 5 $\mu g/m^3$ increment[d]	-	1.27 (0.66, 1.89)	< 0.001	-	1.64 (1.04, 2.24)	< 0.001	-	1.62 (1.09, 2.15)	< 0.001

Zhang et al, Int J Epidemiol. 2017

Acute phase response 24 h after firing of mililary arms

1 h shooting sessions in semi-enclosed tents

Exposure: 15 mg/m^3 PM, 5.3 mg/m^3 Cu, 1.1 mg/m^3 Zn

Table 2. Levels and delta values of the different inflammation markers in lung and blood for the different ammunition types

		All		Leaded ammunition		Unleaded ammunition		
		Levels	delta	Levels	delta	Levels	delta	P-value†
Blood		n=54		n=17		n=37		
Leukocyte markers								
sCD14 (µg/mL)	BL	1.26 (1.03, 1.41)	0.28 (0.03, 0.54)	1.18 (1.07, 1.51)	0.23 (-0.02, 0.46)	1.28 (1.03, 1.39)	0.37 (0.08, 0.55)	0.376
	d1	1.47 (1.33, 1.75)*		1.42 (1.30, 1.66)*		1.49 (1.35, 1.75)*		
MPO (ng/mL)	BL	327 (192, 429)	340 (121 ,474)	267 (192, 397)	317 (121, 478)	360 (201, 461)	342 (154, 469)	0.918
	d1	705 (407, 903)*		660 (366, 874)*		712 (408, 903)*		
sCD25 (ng/mL)	BL	326 (231, 424)	85 (23, 149)	332 (264, 424)	90 (33, 127)	324 (222,424)	82 (23, 149)	0.985
	d1	392 (339, 476)*		397 (354, 490)*		388 (333,435)		
Acute phase proteins								
CRP (mg/L)	Baseline	0.9 (0.5,1.8)	14.8 (9.0, 21.4)	0.8 (0.5, 1.1)	11 (7.3, 12.5)	1.1 (0.5, 2.2)	17.9 (12.4, 24.8)	0.014
	Day 1	15.8 (10.4,23.2)*		12.1 (7.8, 14.1)*		20.3 (14.2,25.3)*		
PTX3 (ng/mL)	BL	0.8 (0.6, 1.1)	0.5 (0.3, 0.7)	0.8 (0.6, 1.0)	0.4 (0.2, 0.6)	0.8 (0.6, 1.2)	0.5 (0.3, 0.8)	0.099
	d1	1.4 (1.1, 1.7)*		1.3 (1.1, 1.5)*		1.4 (1.1, 1.8)*		

Borander et al, OEM, 2017, Sikkeland, AJRCCM 2017

MWCNT physico-chemical predictors of inflammation (neutrophil influx)

- 10 different MWCNT
- All relatively short
- Varying diameter, surface modification (OH, COOH), level and type of metal contaminations
- 3 dose levels, 1, 28 and 90 days post-exposure
- Regression analysis of physico-chemical properties that predict neutrophil influx

MWCNT Physico-chemical predictors of Neutrophil influx

In bronchoalveolar lavage

Day	Exposure Variable	Multiplicative Effect	LowerCL	UpperCL	Probt
1	**Per doubling in Dose**	**2.763**	**2.286**	**3.199**	**<.0001**
	Per doubling in Fe_2O_3	0.927	0.858	1.002	0.0562
	Per doubling in OH	0.869	0.718	1.053	0.151
	Per doubling in Length	1.164	0.776	1.746	0.462
	Per 25% difference in BET	**1.212**	**1.070**	**1.373**	**0.003**
28	**Per doubling in Dose**	**4.342**	**3.360**	**5.611**	**<.0001**
	Per doubling in Fe_2O_3	0.951	0.832	1.086	0.457
	Per doubling in OH	**0.394**	**0.278**	**0.558**	**<.0001**
	Per doubling in Length	**3.537**	**1.782**	**7.020**	**0.0003**
	Per 25% difference in BET	**1.908**	**1.528**	**2.383**	**<.0001**
92	**Per doubling in Fe_2O_3**	**0.657**	**0.503**	**0.858**	**0.003**
	Per doubling in OH	1.214	0.650	2.266	0.538
	Per doubling in Length	2.176	0.603	7.850	0.230
	Per 25% difference in BET	**3.053**	**1.942**	**4.800**	**<.0001**

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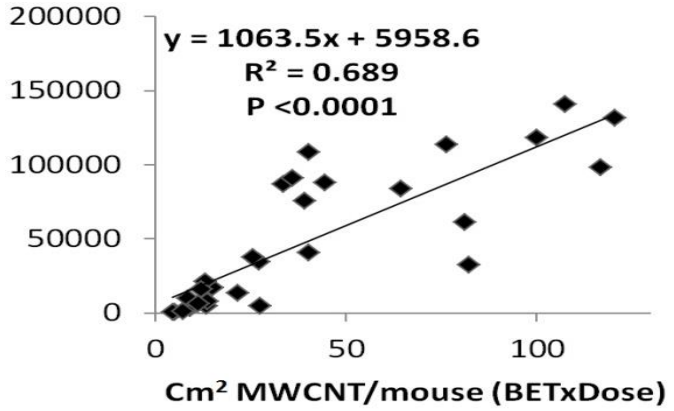
Poulsen SS et al, Nanotoxicology 2016

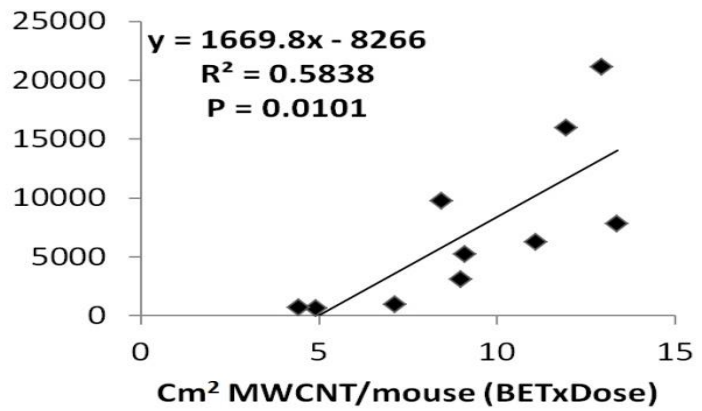
Surface area/diameter correlates with inflammatory response for CNTs

Correlation between neutrophil influx and total deposited surface area of the CNTs

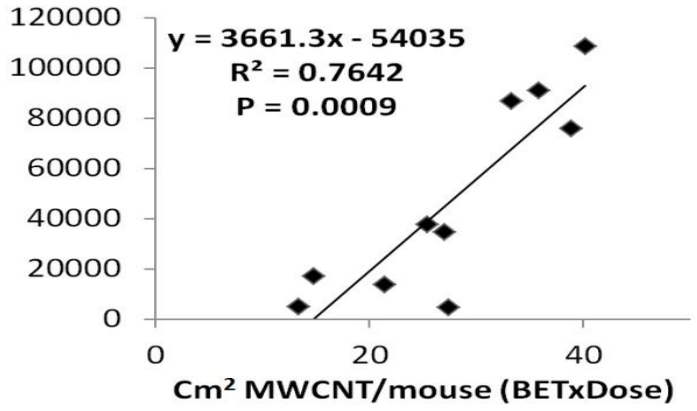
All doses



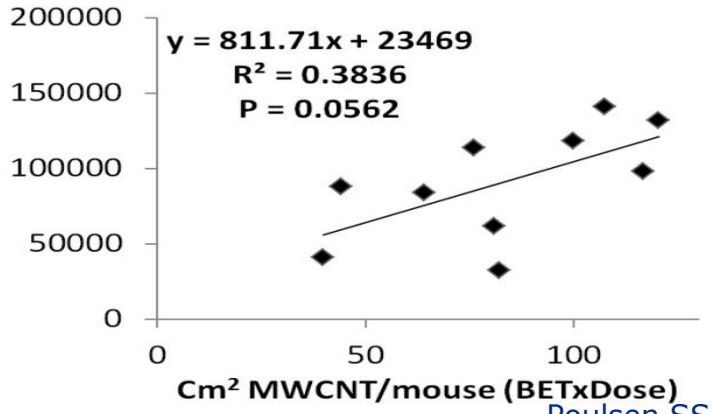
6 µg



18 µg



54 µg



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Poulsen SS et al, Nanotoxicology 2016

Acute phase proteins as biomarkers of risk of cardiovascular disease?

YES:

- Acute phase protein SAA is causally related to atherosclerosis
- Large dynamic range
- Rutinely measured as diagnotic marker (crp)
- Human and mice express acute phase protein SAA
- In mice, SAA is closely associated with neutrophil influx and with total surface area of deposited particles
- Acute phase proteins can be used in controlled studies of volunteers with low basal levels (young, fit, non-smokers)
- Acute phase proteins can be used as biomarker in studies with many participants

NO:

- Large inter-individual variation in baseline levels
- Baseline levels depends on lifestyle factors such as BMI, fitness state, smoking, cholestrol levels,
- Acute phase response is induced by bacteria, virus, infarction
- Particle-mediated effects may be (too) small compared to baseline levels for detection

Summary

- Acute phase response may be a mechanism of action of particle-induced cardiovascular disease
- Exposure to particles induces time- and dose-dependent acute phase response
- For insoluble particles, acute phase response is predicted by deposited surface area and by pulmonary inflammation
- The findings underscore cardiovascular disease as particle-related occupational disease

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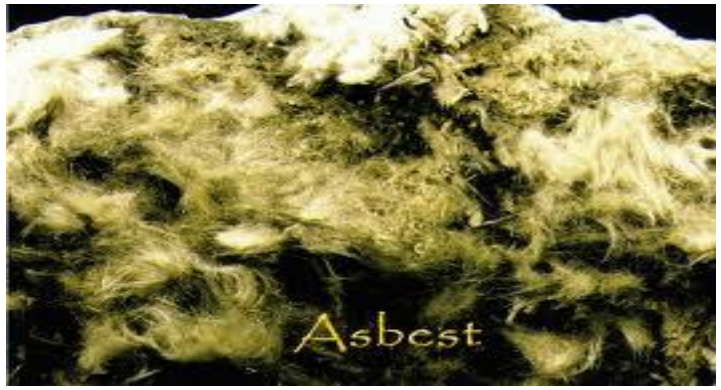
- European Union's Horizon 2020 research and innovation programme under grant agreement No 686239 (caLIBRAte)
- European Union's Horizon 2020 research and innovation programme under grant agreement No 760813 (PATROLS)

SmartNanoTox
Smart Tools for Gauging Nano Hazards

caLIBRAte
nano risk governance

PATROLS
Advanced Tools for NanoSafety Testing

Safe-by-design:



Lung cancer
Fibre-paradigm

Mineralwool

Painters syndrome
Organic solvents

Water-based paint
MAL kodes

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Cardiovascular disease constitutes a major fraction of preventable air pollution-induced morbidity

EXAMPLE:

- Heating with coal in private households was banned in Dublin, Ireland in 1991:
- Black smoke levels in ambient air were reduced by 0.036 mg/m^3

- Mortality rates were reduced by 75 per 100 000 person-years
- 77% cardiovascular (!)

- Effects were adjusted for death rates in the rest of Ireland

- Morbidity was not assessed

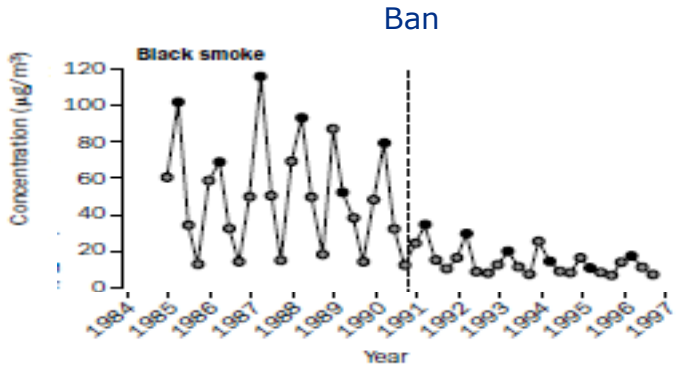
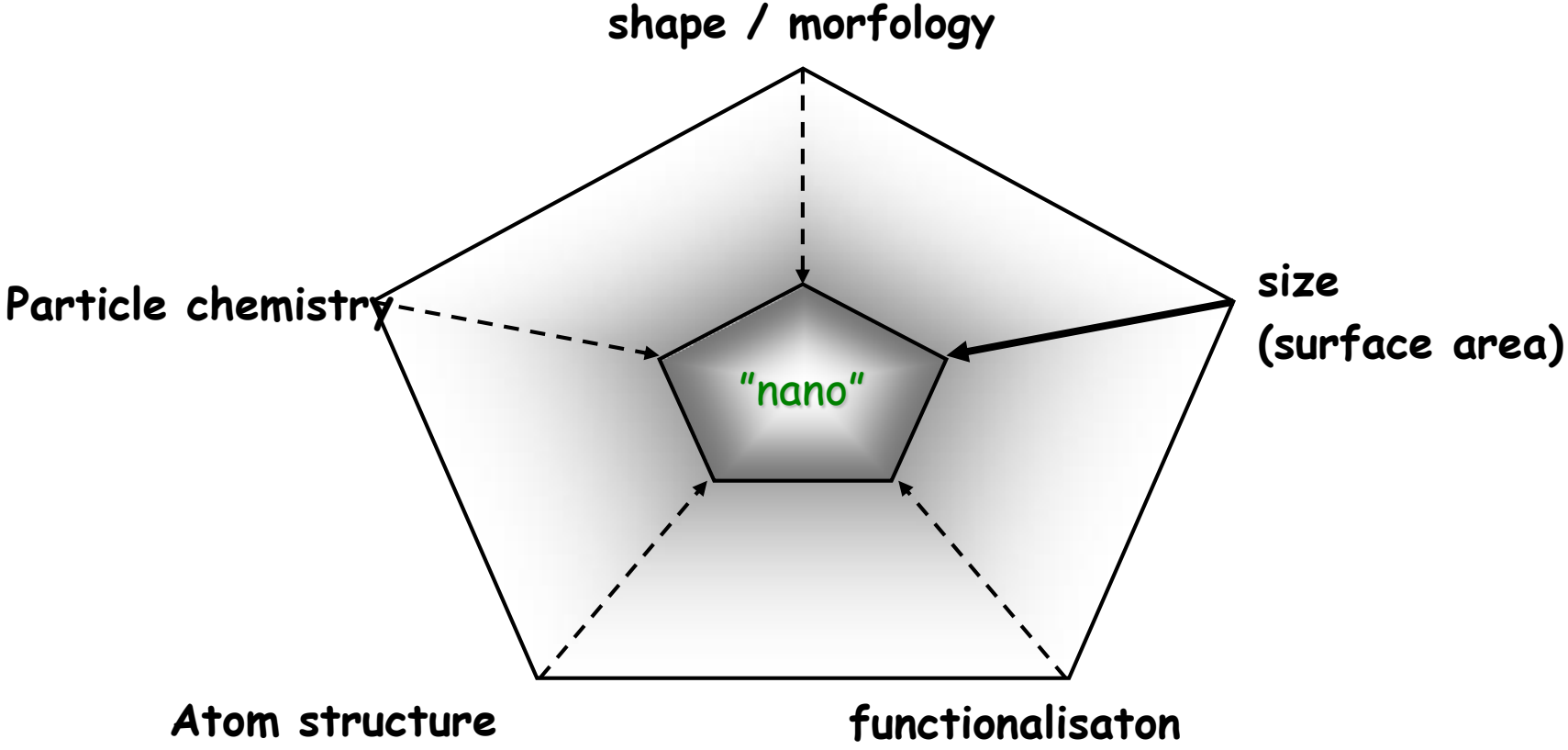


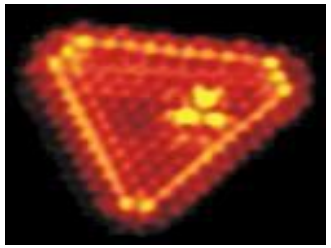
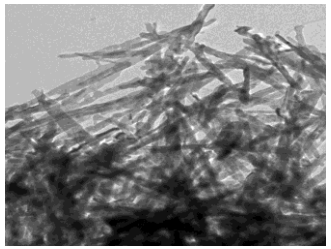
Table 2: **Age-standardised mortality rates for Dublin County Borough before (1984–90) and after (1990–96) ban of sale of coal, by season**

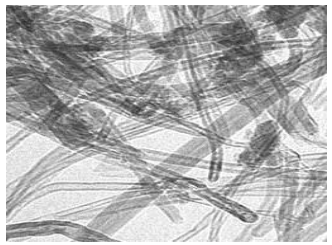
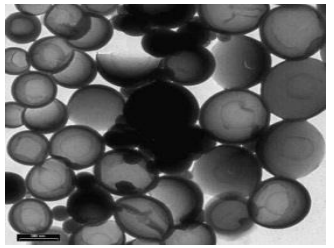
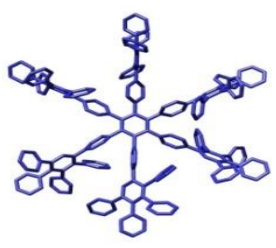
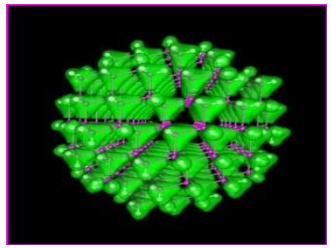
	1984–90	1990–96	Change	p
Deaths per 1000 person-years				
Non-trauma				
Autumn	8·73	8·54	–0·19	<0·0001
Winter	11·03	9·88	–1·15	<0·0001
Spring	9·49	8·66	–0·83	<0·0001
Summer	8·40	7·56	–0·85	<0·0001
Total	9·41	8·65	–0·75	<0·0001
Cardiovascular				
Autumn	4·01	3·67	–0·34	<0·0001
Winter	5·18	4·47	–0·71	<0·0001
Spring	4·41	3·71	–0·69	<0·0001
Summer	3·89	3·29	–0·59	<0·0001
Total	4·37	3·78	–0·58	<0·0001

(Adapted from Clancy et al, Lancet, 2002)

Many different nanomaterials



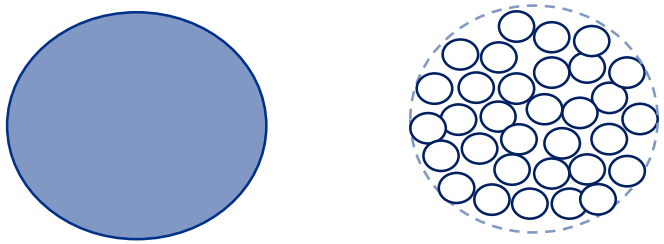
Inhalation of particles and risk of cardiovascular disease

- Epidemiological studies show associations between air pollution and risk of cardiovascular disease
- Several different mechanisms have been proposed related to
  - Inflammation
  - Inflammation-induced hepatic acute phase response
  - Direct effect of translocated particles
  - Vascular function

The Known: Nanomaterial-induced pulmonary inflammation

- Inhalation of inert and insoluble nanoparticles induces pulmonary inflammation in terms of neutrophil influx and increased pulmonary transcription and expression of cytokines
- Inflammation (neutrophil influx) correlates with the total surface area of deposited particles

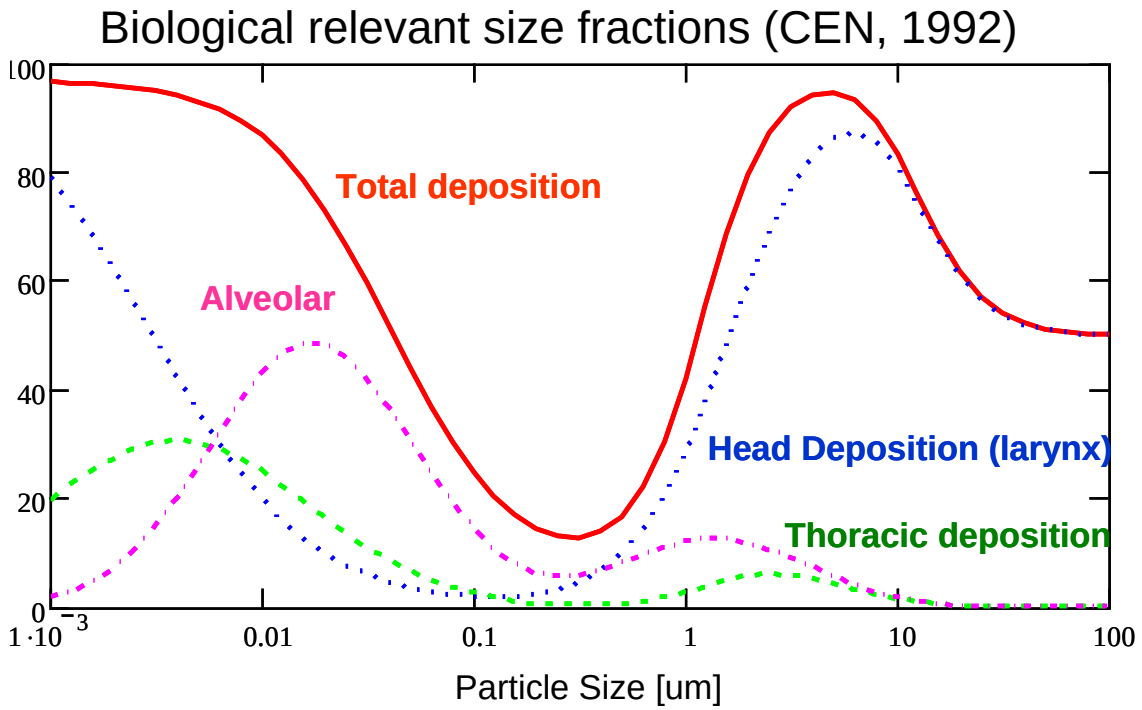
The Nano Issue: More particles & larger total surface area per mass unit, and more alveolar deposition after inhalation



Smaller particles:

More particles pr mass unit

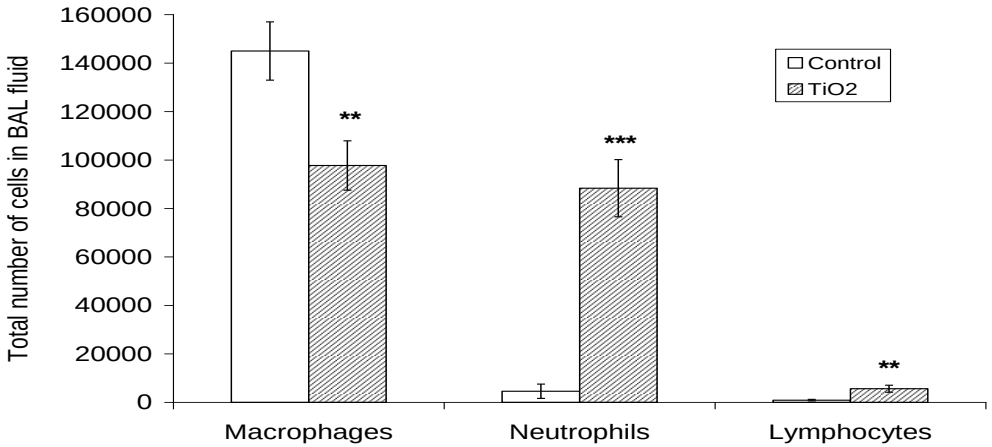
Larger surface area pr mass unit



Inhalation of nano-TiO_2 induces pulmonary inflammation in mice

Mice inhaled 40 mg/m^3 nanosized TiO_2 1 hour daily for 11 days.
Types and numbers of cells in lung fluid:

Cell composition in bronchoalveolar lavage fluid 5 days post-exposure



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Hougaard et al, PT&T 2010

The acute phase response: A risk factor for cardiovascular disease

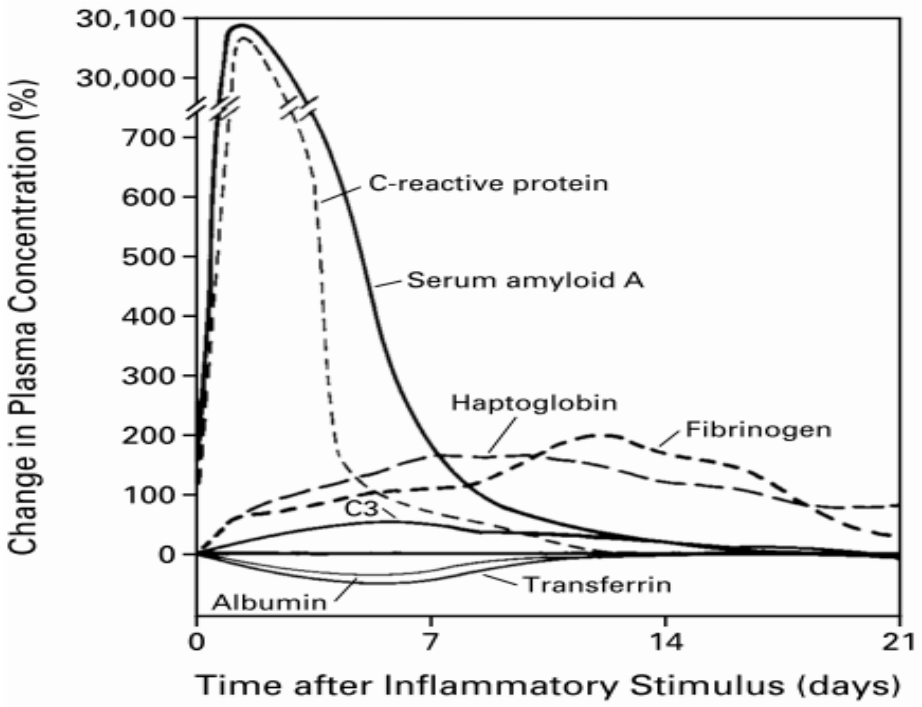


Figure 1. Characteristic Patterns of Change in Plasma Concentrations of Some Acute-Phase Proteins after a Moderate Inflammatory Stimulus.
Modified from Gitlin and Colten[5] with the permission of the publisher.

- The acute phase response is the systemic response to acute and chronic inflammatory states caused by fx bacterial infection, trauma and infarction.

- Conditions that induce acute phase response are associated with risk of cardiovascular disease, including asthma and air pollution exposure.

Gabay and Kushner 1999, NEJM

Acute phase proteins CRP & SAA are associated with risk of CVD in prospective epidemiological studies

Nurses' Health Study : 120.000 participants

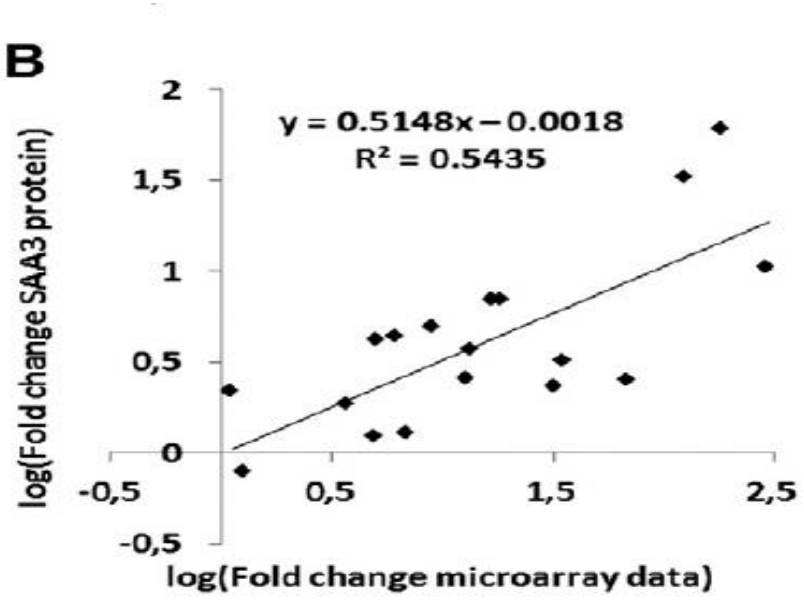
TABLE 3. RELATIVE RISK OF CARDIOVASCULAR EVENTS ACCORDING TO BASE-LINE PLASMA LEVELS OF MARKERS OF INFLAMMATION AND LIPIDS.*

VARIABLE	QUARTILE OF PLASMA LEVEL				P VALUE FOR TREND
	1	2	3	4	
High-sensitivity C-reactive protein					
Median — mg/dl	0.06	0.19	0.38	0.85	
Relative risk (95% CI)	1.0	2.1 (1.0–4.5)	2.1 (1.0–4.4)	4.4 (2.2–8.9)	<0.001
Serum amyloid A					
Median — mg/dl	0.25	0.43	0.62	1.17	
Relative risk (95% CI)	1.0	1.8 (0.9–3.6)	1.9 (0.9–3.8)	3.0 (1.5–6.0)	0.002

Ridker *et al.* 2000, NEJM

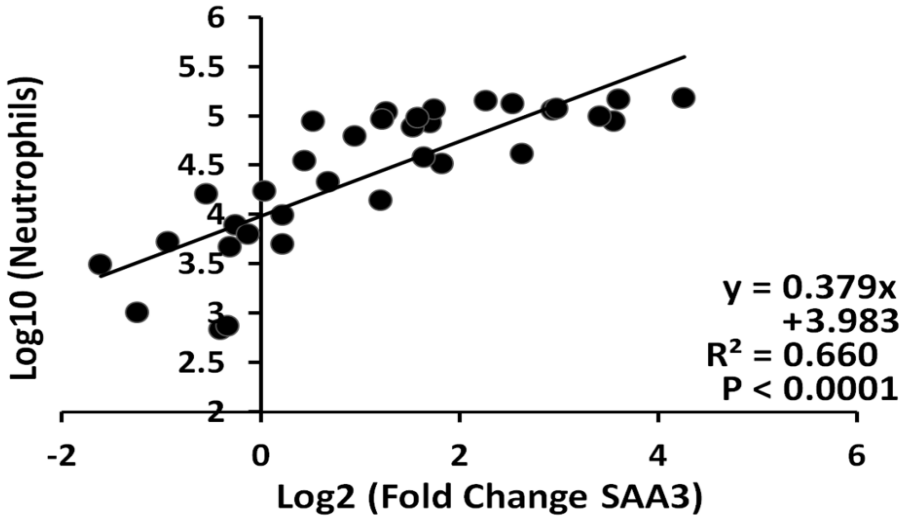
Plasma levels of acute phase protein SAA3 correlates with lung responses

Saa3 mRNA in lung correlates with plasma SAA3



Poulsen *et al* 2015, TAAP

Plasma SAA3 levels and neutrophil influx



Poulsen *et al.* 2017, Plos One

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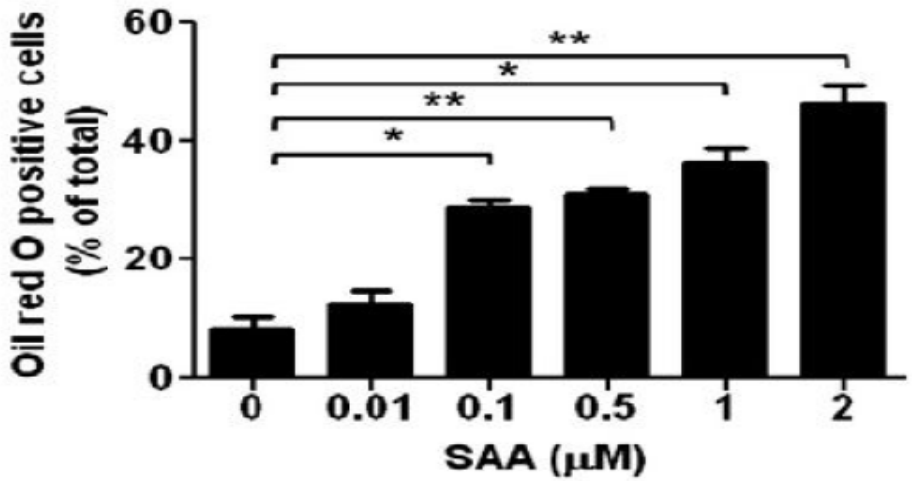
SAA: an acute phase protein that directly promotes formation of foam cells

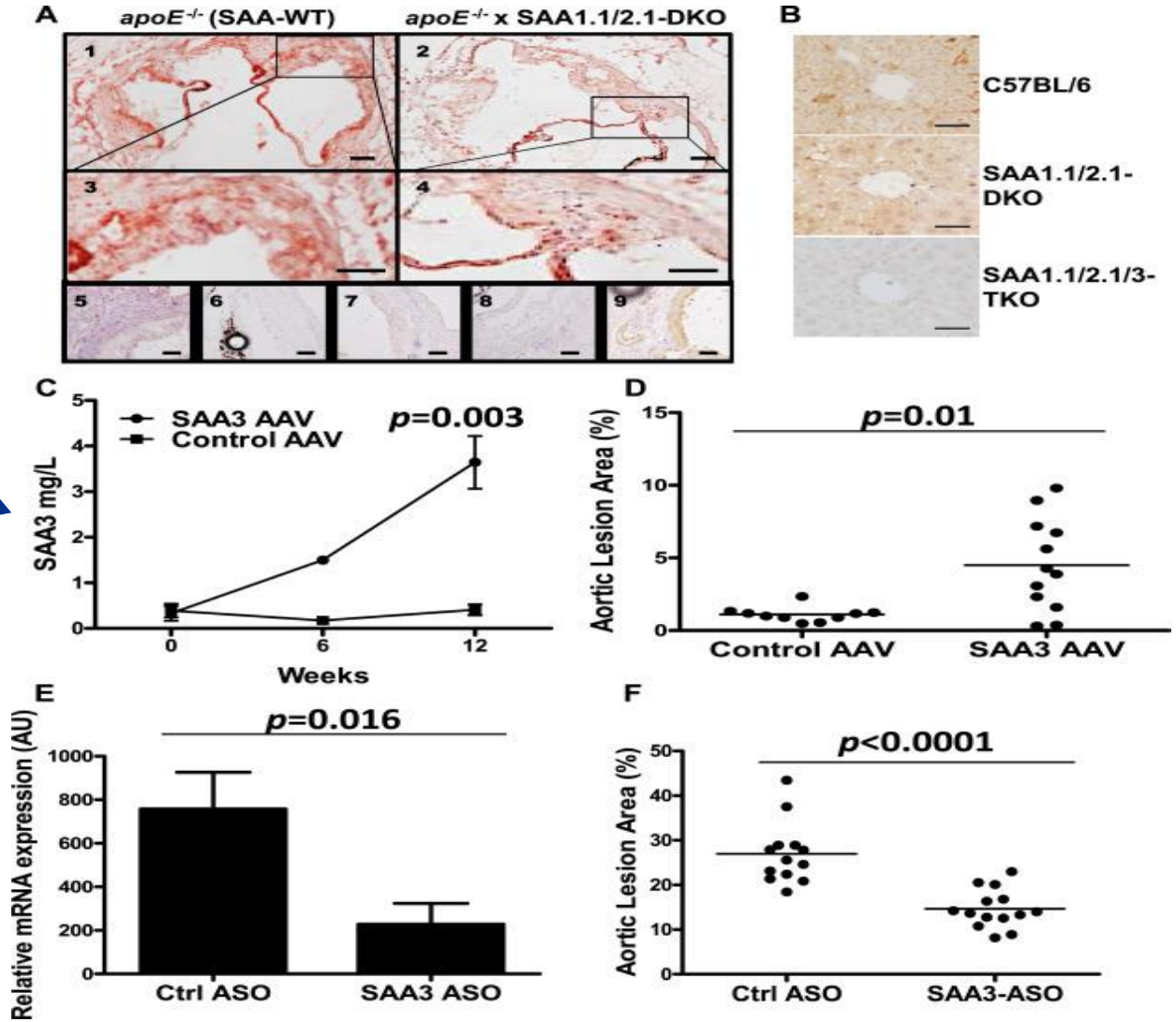
- SAA can replace ApoA-1 as the major HDL protein.
- This inhibits HDLs role in reverse cholesterol transport.
- SAA induces foam cell formation in macrophages [1].



[1] Lee et al, 2013, BBRC

Acute phase protein SAA is causally implicated in plaque progression

- Mice have 3 inducible SAA isogenes (*Saa1, Saa2, Saa3*)
- Over-expression of SAA3 increases plaque progression (Thompson 2018)
- Inactivation (KO) of all SAA isogenes results in reduced plaque progression (Thompson 2018)



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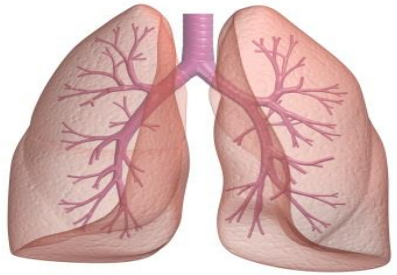
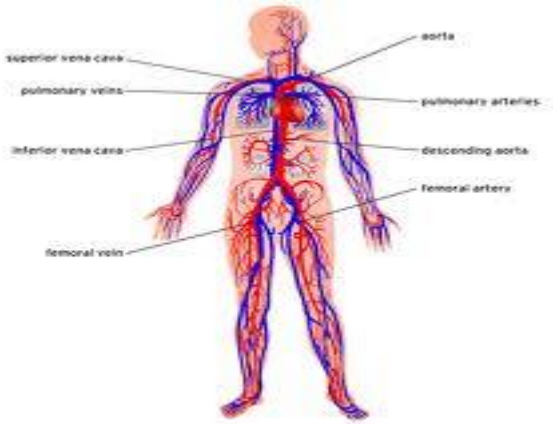
Particle-induce atherosclerosis

Particles

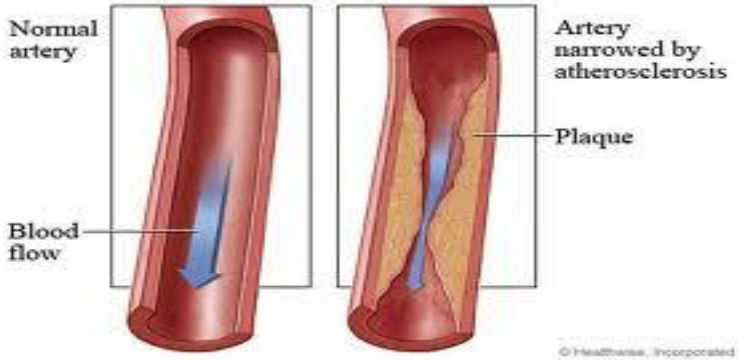


Inflammatory & acute phase response

Systemic circulation of acute phase proteins



Atherosclerosis



Coronary heart disease

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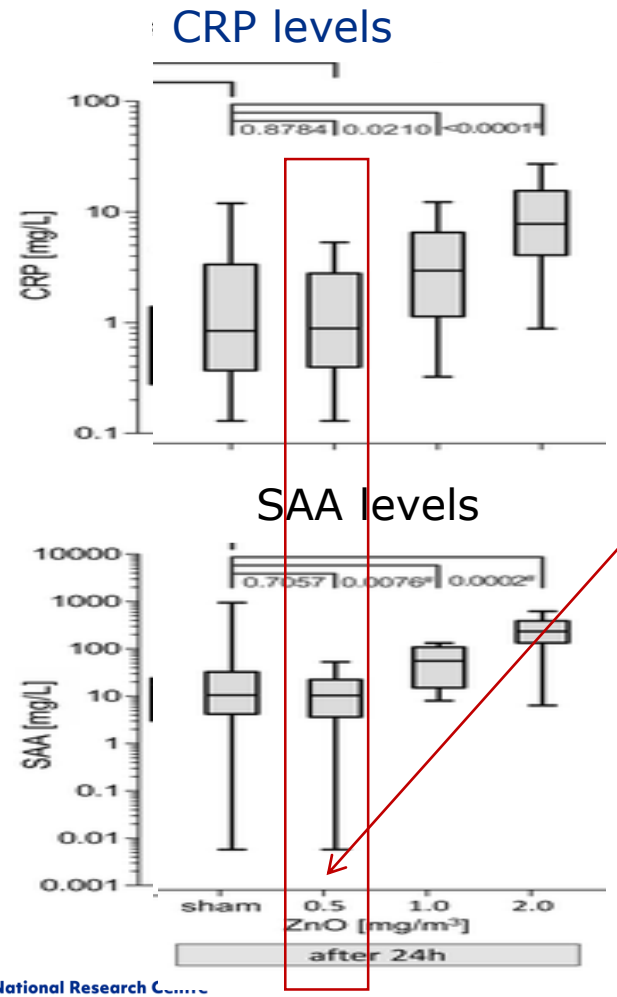
Any Human relevance ?: Yes; inhalation of ZnO induces acute phase response in human volunteers



- No effect level:
- 0.5 mg/m^3

Study set up:

- 16 volunteers
- Exposed to 0, 0.5, 1 or 2 mg/m^3 ZnO particles for 4 h
- OEL: 5 mg/m^3 for 8 h
- Acute phase response proteins CRP and SAA

Acute phase response was induced after ZnO inhalation at concentrations well below incurrent OEL

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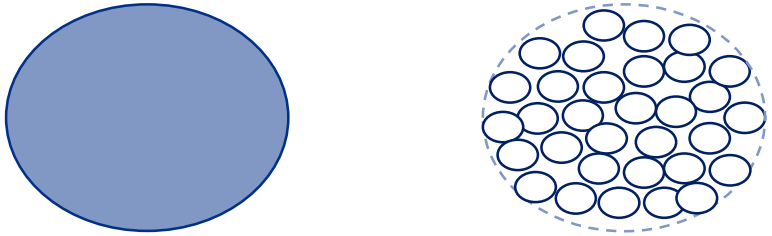
Adapted from Monsé et al Part Fibre Toxicol. 2018 15(1):8

And more..

- Correlation between exposure to organic dust and serum levels of acute phase proteins SAA and CRP among 33 greenhouse workers (Madsen et al, 2016, Environmental Health)
- Correlation between exposure to respirable dust and serum levels of SAA among 101 welders (Li et al, 2015, Plos One)
- Correlation between occupational exposure to paper mill dust and SAA and CRP levels (Westberg, Int Arch Occup Environ Health. 2016)
- Exposure to welding fumes with ZnO and/or CuO increase CRP and SAA levels in human volunteers (Baumann R et al, J Expo Sci Environ Epidemiol, 2018)
- Exposure to fumes from military small arms increased CRP levels in human volunteers (Sikkeland et al, Am J Respir Crit Care Med. 2017)

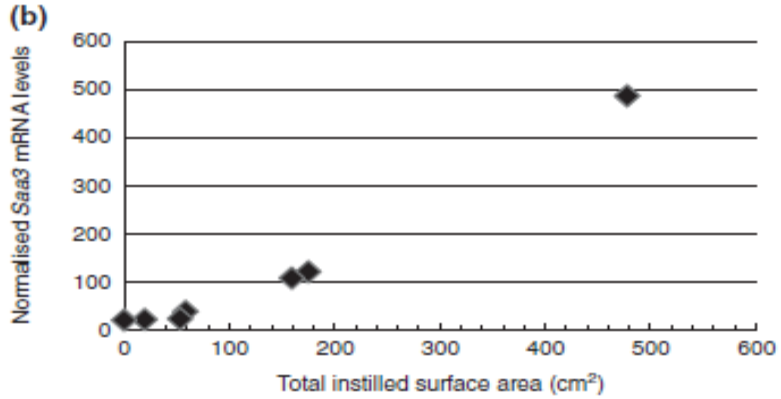
Risk assessment of nanoparticles



10 times smaller particles:

1.000 more particles pr mass unit

10 times larger surface area pr mass unit



Correlation between deposited surface area and pulmonary acute phase response

Summary

- Acute phase response is causally related to atherosclerosis and cardiovascular disease
- Airway exposure to nanoparticles and nanomaterials induces a time- and dose dependent acute phase response in mice
- The acute phase response correlates with markers of lung inflammation and deposited surface area
- Cardiovascular disease is an important particle-related occupational disease

Thank you for your attention!

Danish Centre for Nanosafety 2012-2016

National Research Centre for the Working Environment

Thank you for your attention

Danish Centre for Nanosafety

Colaborators:

- Health Canada
  - Sabina Halappanavar
  - Carole Yauk
  - Andrew Williams

Funding:

- Danish Centre for Nanosafety
- NanoReg
- SmartNanotox

SmartNanoTox
Smart Tools for Gauging Nano Hazards

NANOREG

Acute phase response levels in blood as biomarker ?

Many factors influence blood levels of acute phase proteins

- Acute phase response is induced by pro-inflammatory cytokines IL6, TNF, IL1b and by low inflammatory states
- Acute phase response levels are also predicted by a number of lifestyle factors including BMI, waist circumference, leptin levels
- Particle-dependent changes in acute phase response can probably only be detected in persons with low basal levels (ie fit, healthy non-smokers) and in well-powered studies

Table 2 Correlates of clinical and biochemical parameters with (log)SAA in women and men

	Women (n = 618)		Adjusted for BMI		Men (n = 891)		Adjusted for BMI	
Variable	r^a	P	r^a	P	r^a	P	r^a	P
Body mass index (BMI)	0.328	<0.001			0.281	<0.001		
Waist circumference	0.334	<0.001	0.093	0.021	0.312	<0.001	0.138	<0.001
Waist-hip ratio	0.214	<0.001	0.034	0.405	0.250	<0.001	0.092	0.006
Age	0.025	0.732			0.074	0.028	0.026	0.434
Total cholesterol	0.189	<0.001	0.147	<0.001	0.099	0.003	0.032	0.348
HDL cholesterol	0.056	0.163			−0.066	0.049	0.010	0.776
LDL cholesterol	0.144	<0.001	0.094	0.021	0.071	0.035	0.010	0.766
(log)Triglycerides	0.170	<0.001	0.059	0.144	0.180	<0.001	0.077	0.022
ApoA1	0.121	<0.001	0.205	<0.001	0.010	0.766		
ApoB	0.219	<0.001	0.066	0.152	0.165	<0.001	0.060	0.073
Systolic blood pressure	0.163	<0.001	0.048	0.235	0.080	0.017	−0.006	0.869
Diastolic blood pressure	0.157	<0.001	0.052	0.202	0.104	0.002	0.028	0.438
(log)Insulin	0.183	<0.001	0.014	0.765	0.206	<0.001	0.077	0.032
Glucose	0.022	0.593			0.068	0.042	0.024	0.512
(log)Leptin	0.390	<0.001	0.236	<0.001	0.342	<0.001	0.217	<0.001
HOMA-IR	0.191	<0.001	0.002	0.968	0.200	0.001	0.075	0.025
(log)Adiponectin	0.100	0.016	−0.021	0.611	−0.051	0.131		
Homocysteine	−0.009	0.830			0.023	0.492		
Physical activity index	−0.036	0.438			−0.072	0.043	−0.068	0.058
Alcohol	−0.015	0.707			−0.001	0.978		
(log)CRP	0.650	<0.001	0.585	<0.001	0.703	<0.001	0.672	<0.001

The significant correlations were adjusted for BMI.

[a]Pearson's correlation.

ApoA1, apolipoproteinA1; ApoB, apolipoproteinB; BMI, body mass index; CRP, C-reactive protein; HOMA-IR, homeostasis assessment of insulin resistance; SAA, serum amyloid A.