Oxidative stress: the missing link between PM toxicology and epidemiology?

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Can toxicology resolve the following question arising from epi-studies?

- Though consistent across studies, the strength of the association between ambient particle mass and the observed health effects varies markedly between different locations

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This suggest that particle mass alone is not driving the effect

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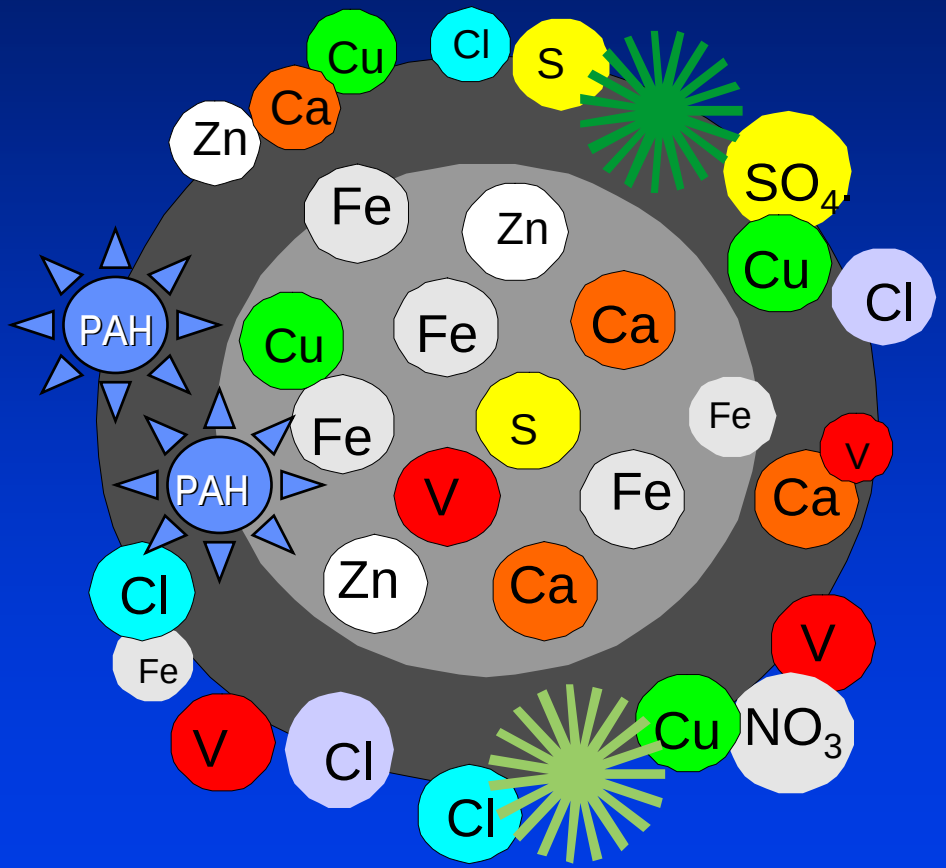
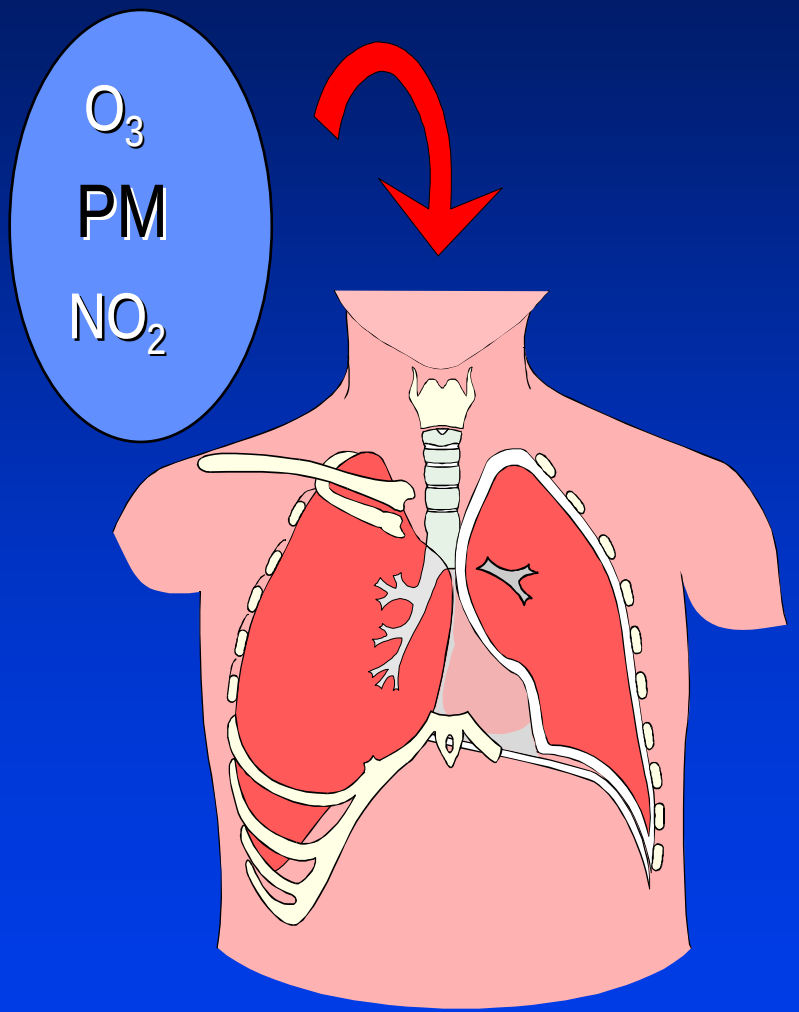
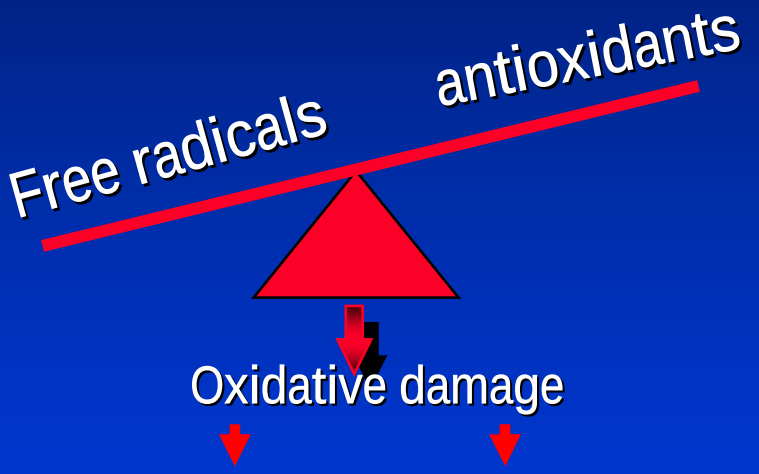
Particle toxicity

Particle toxicity via oxidative stress



‘Oxidant’ or free radical theory of PM toxicity





lung injury & inflammation

Cardiopulmonary effects

Occupational Environmental Health 60: 612-616; 2003

Oxidative theory of PM toxicity

Does it stand close examination within an epidemiological setting ?

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HEPMEAP

Health Effects of Particles from Motor Exhausts & Ambient Pollution

Dutch ISAAC II study:

Sites:

24 Schools close to highways with varying traffic densities throughout the Netherlands

Health assessment of school children:

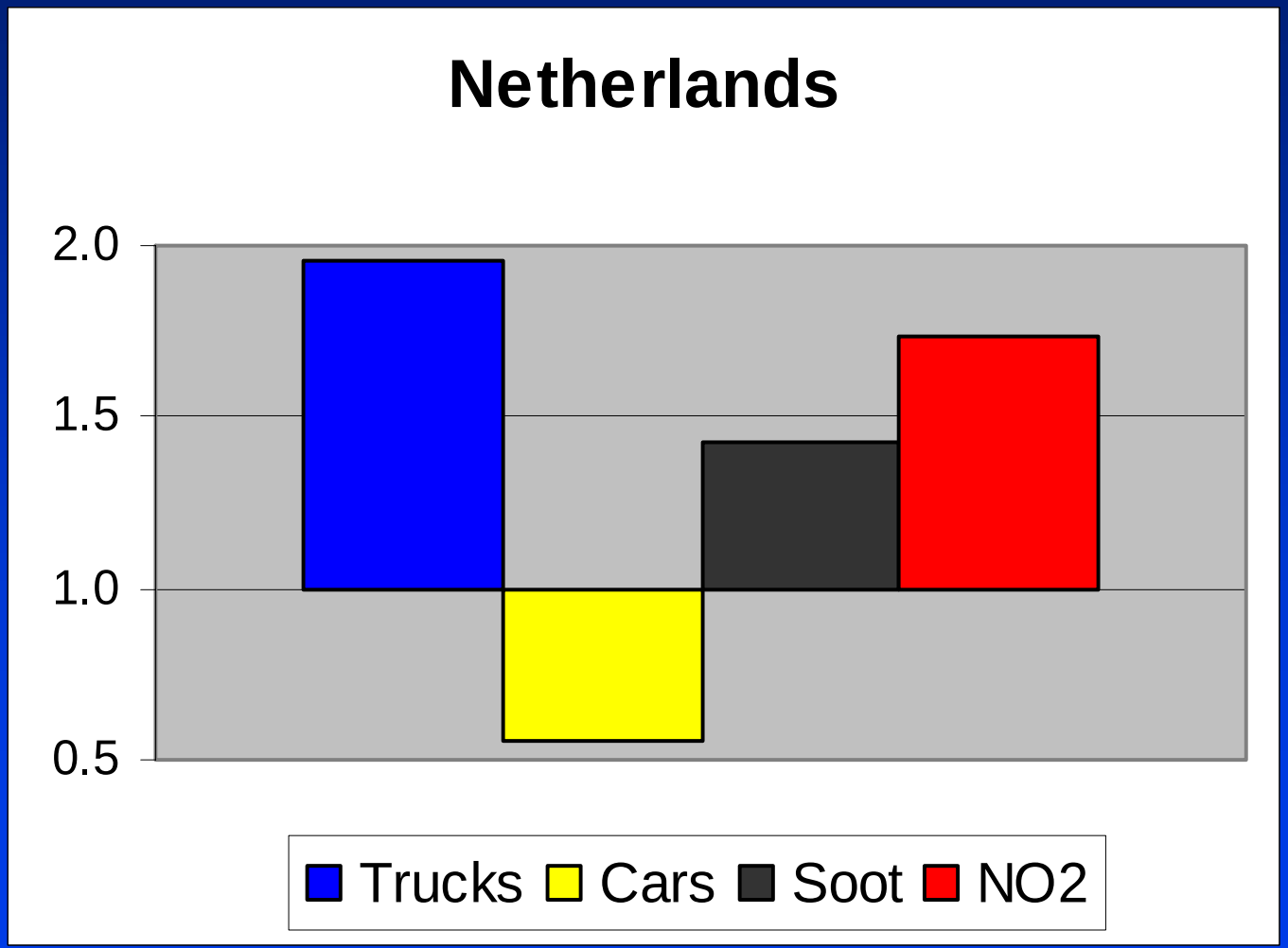
ISAAC II protocol (questionnaire, IgE, BHR)

Exposure assessment:

- Traffic characteristics: traffic counts for cars and trucks separately, distance of the school and home to the highway
- Annual average concentrations of PM2.5, Soot, NO_2 at the school

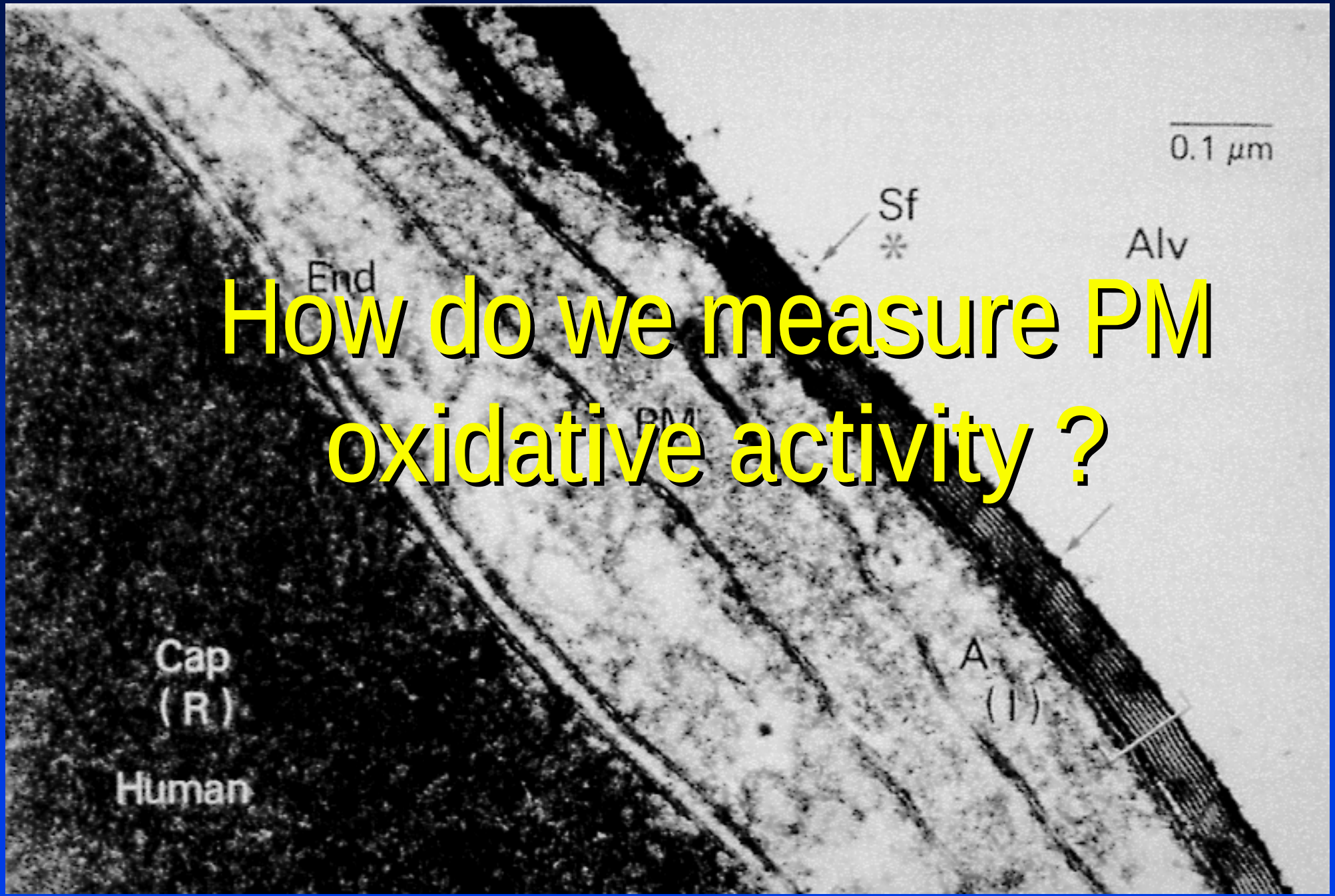
(Janssen et al. 2001; 2003)

Odds ratio for current wheeze in the Dutch ISAAC II study

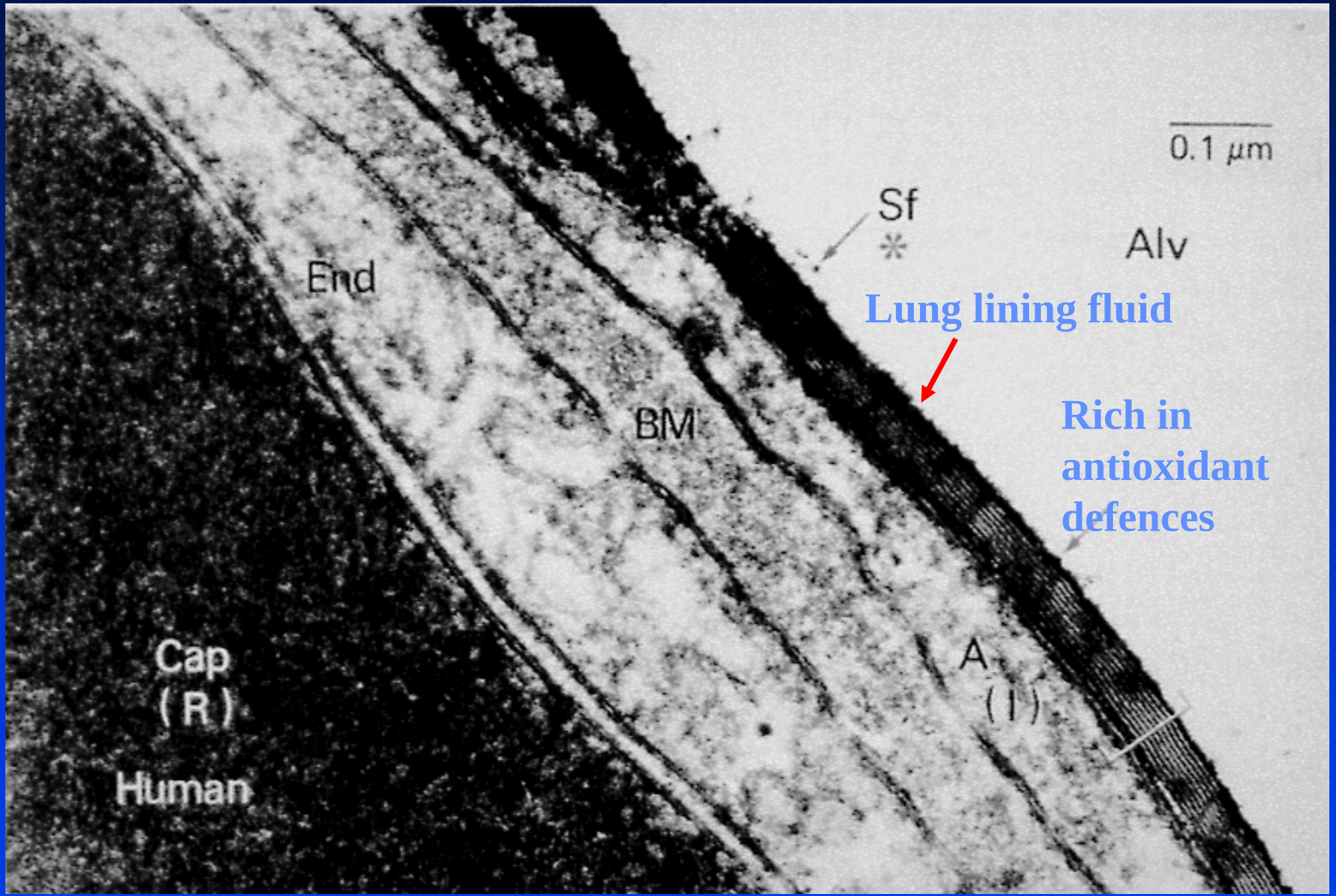


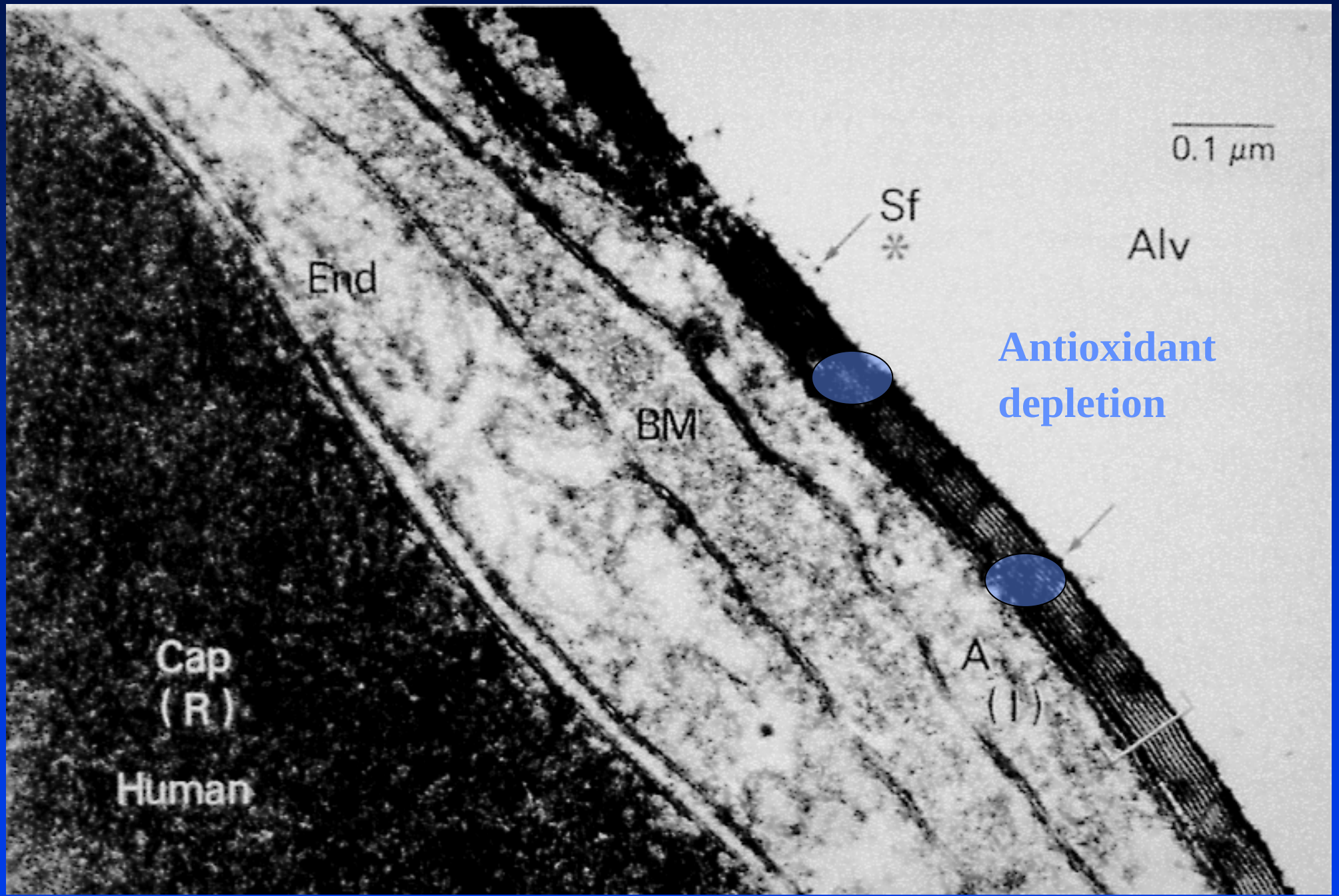
HEPMEAP study:

- 4 school sites selected based on annual average “soot” concentration
- Traffic counts etc also made for back comparison to ISAAC II study
- 6 two-week measurements per site, spaced over a one-year period (each site measured once every 8-weeks)
- both high volume (UF, $PM_{0.1\text{-}2.5}$, $PM_{2.5\text{-}10}$) and low volume sampling ($PM_{2.5}$ and PM_{10})



How do we measure PM oxidative activity ?


0.1 μm
Sf
*
Alv
End
Lung lining fluid
BM
Rich in
antioxidant
defences
A
(I)
Cap
(R)
Human


0.1 μm
Sf
*
Alv
End
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depletion
A
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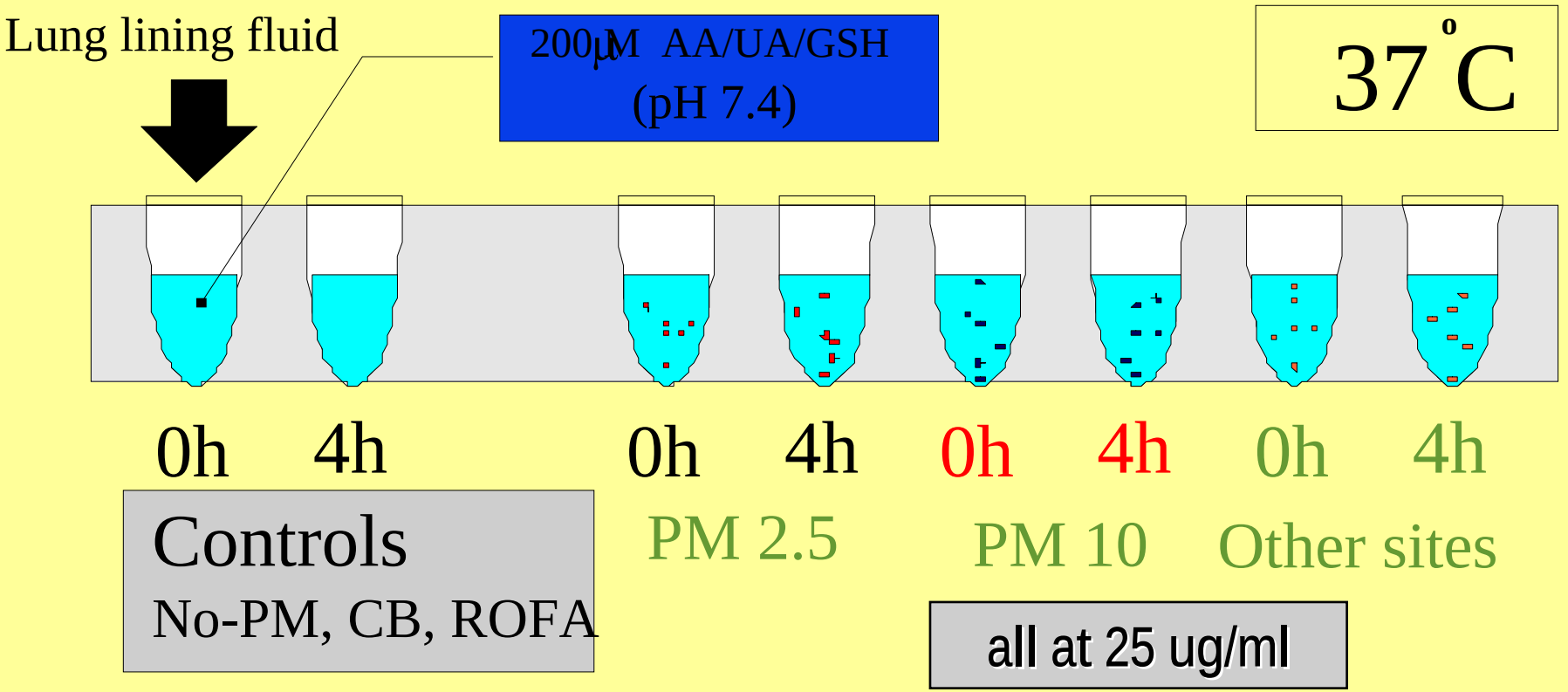
Particle Exposure Model

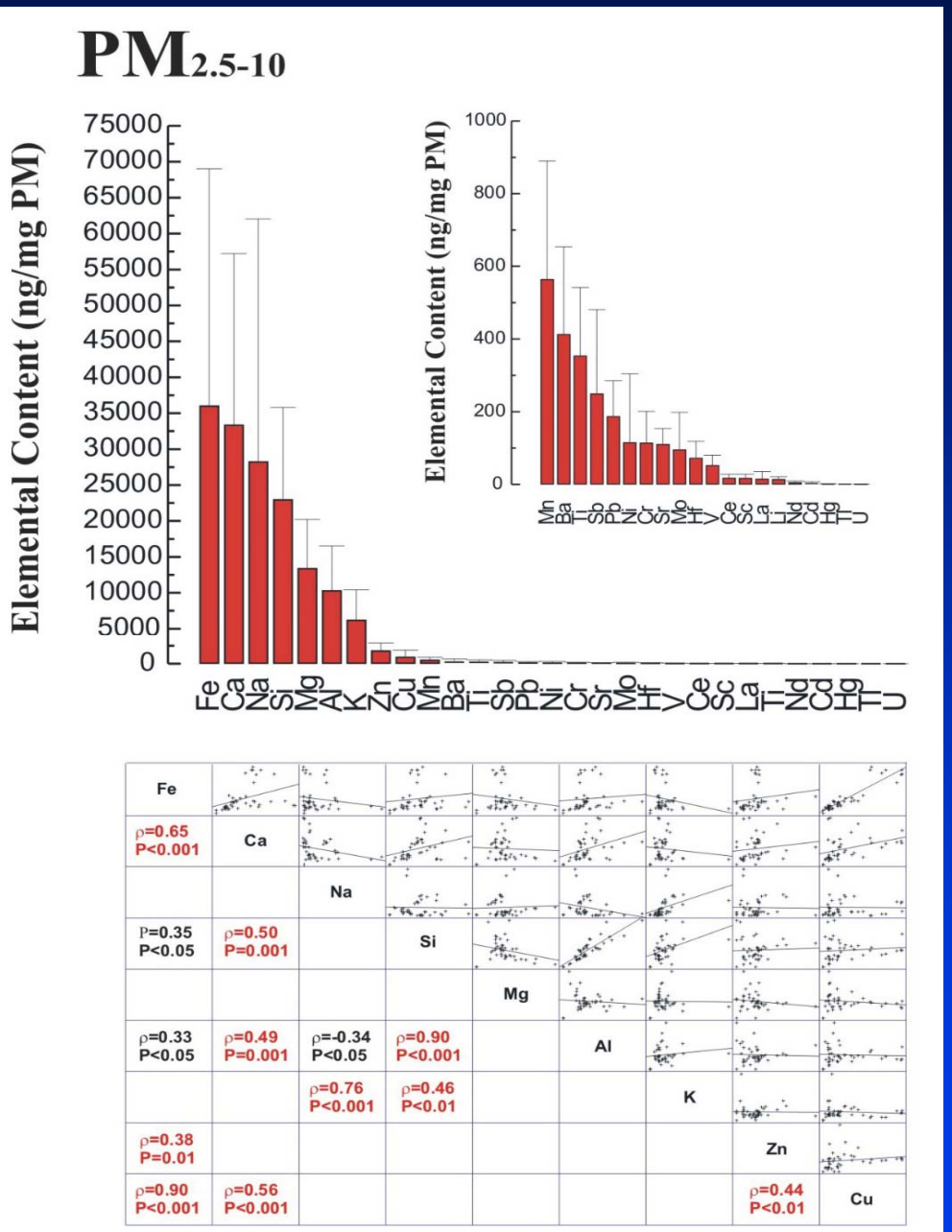


PM compared on a equal mass basis

Ascorbate Depletion (%)
100
80
60
40
20
0
PM0.1-2.5
PM2.5-10
Amsterdam
Sassenheim
Badhoevedorp
Dordrecht
Amsterdam
Sassenheim
Badhoevedorp
Dordrecht

Which PM components drive the oxidative activity?

Elements (total)			Light PAHs	Heavy PAHs	Traffic tracers
Li	Al	NH4	Naftalene	Anthracene	
Be	Si	Cl	1-Methyl-naftalene	1-Methyl-fenantrene	
Sr	Ca	NO3	Bifenyl	Fluorantene	**Hopanes**
Mo	Sc	SO4	2,6-Dimethyl-naftalene	Pyrene	17a(H)-22,29,30-Trisnorhopane
Cd	Ti	Br	Acenaftylene	Benz[a]antracene	17a(H)-21b(H)-Hopane
Sb	V		Acenaftene	Chrysene	
Ba	Cr		2,3,5-Trimethyl-naftalene	Benzo[b]fluorantene	
La	Mn		Fluorene	Benzo[k]fluorantene	
Ce	Fe		Fenantrene	Benzo(e)pyrene	**Steranes**
Nd	Co			Benzo[a]pyrene	
Sm	Ni			Perylene	abb-20R-Cholestane
Hf	Cu			Indeno[1,2,3-cd]-pyrene	5a-Cholestane
Hg	Zn			Dibenzo[a,h]antracene	abb-20R-24S-Methylcholestane
Tl	Na			Benzo[g,h,i]perylene	abb-20R-24R-Ethylcholestane
Pb	K		**Bio organics**		
U	As				
Mg	Se		Lipopolysaccharide (LPS)		



Transition metals vs. AA

Fe: r=0.67, P<0.001

Cu: r=0.63, P<0.001

Ni: r=0.50, P=0.001

Cr: r=0.65, P<0.001

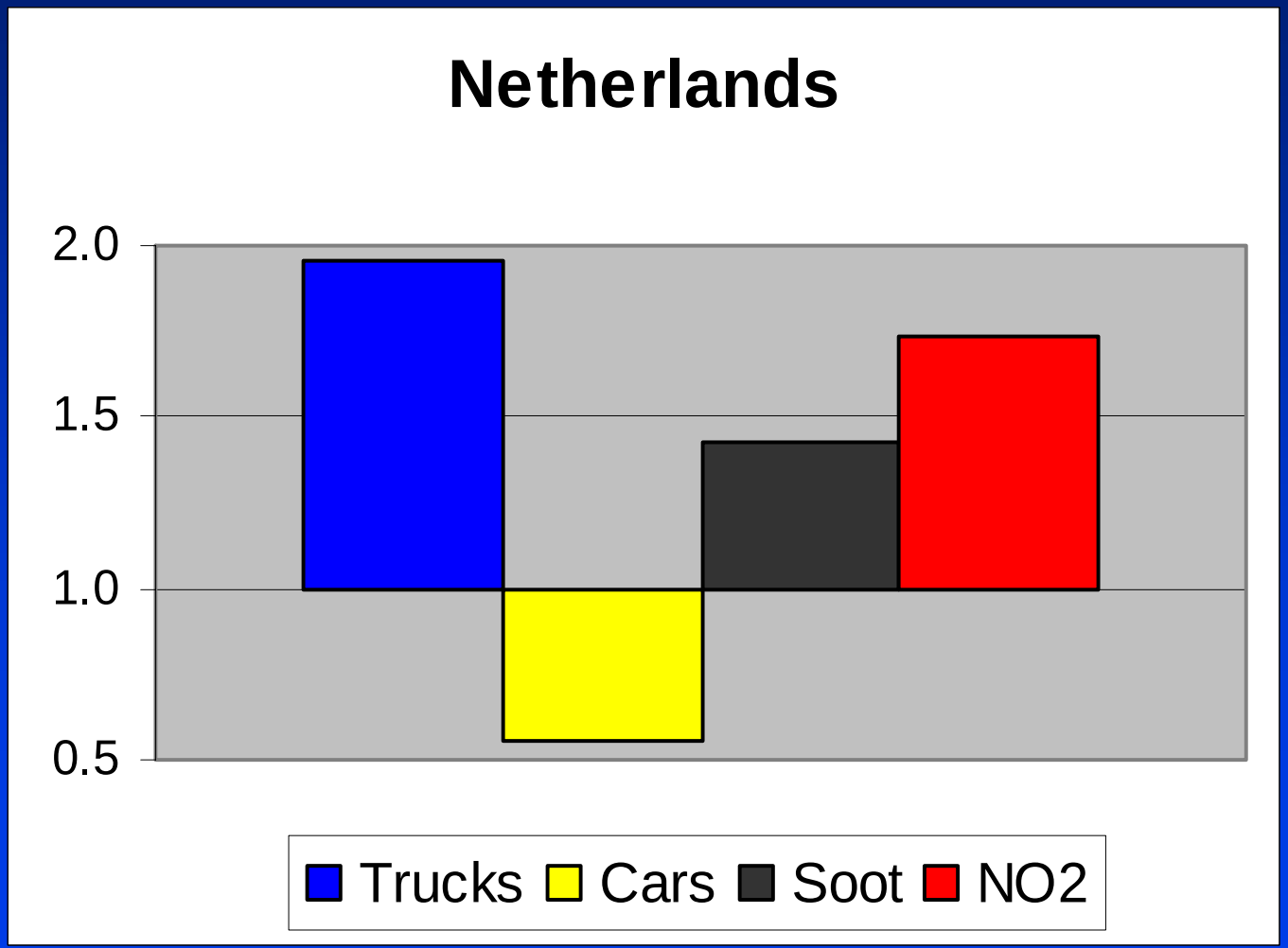
Al: NS

Zn: NS

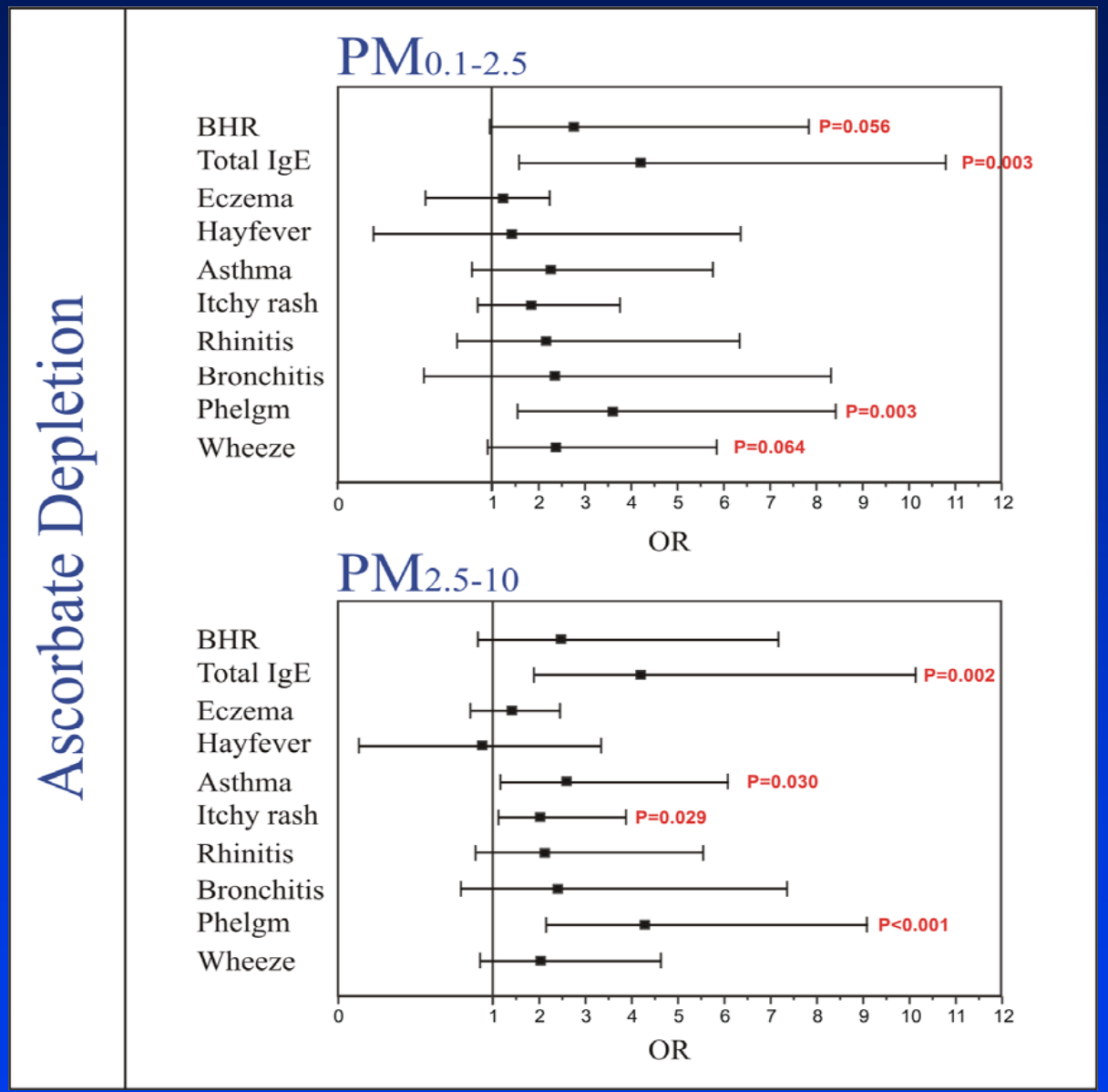
Summary of HEPMEAP findings

- **PM display a range of oxidative activities**
- **Clear location dependent contrasts exist despite within site variations across time**
- **Much of the oxidative activity appear attributable to redox active metals (Fe and Cu)**

Odds ratio for current wheeze in the Dutch ISAAC II study



PM oxidative capacity & symptoms in ISAAC II



Conclusions

- HEPMEAP has succeeded in building a bridge between PM toxicology and epidemiology
- Crude, site-specific averages of PM oxidative activity were associated with respiratory symptoms, total IgE and BHR
- For some health endpoints, these associations are stronger than the associations with the exposure variables used in the original ISAAC II study (Soot, NO_2)
- Both fine and coarse fractions were found to have oxidative activity and often the activity of the coarse fraction was greater than that of the fine fraction

Acknowledgements

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HEPMEAP partners

Henk Bloemen, Flemming Cassee (PM collection and characterisation)

Thomas Sandstrom (Project coordinator)

Nicole Janssen, Bert Brunekreef (Epidemiology)

PM- what do we know: 1993-2004

1. The epidemiologically observed association between premature death and long term residence in areas with high PM concentrations is robust.
2. The deaths appear due to cardiopulmonary causes
3. Similar associations have been observed with asthma exacerbations, aggravation of other respiratory disease, incidence of respiratory symptoms and the prevalence of asthma and allergy.
4. Proximity to busy roads, with a high density of diesel vehicles increases the risk of negative health effects

PM – some of the unresolved problems

1. How does inhaling relatively low concentrations of ambient particles result in the wide range of effects reported?
2. What are the mechanisms of this effect?
3. Are all particles equally active and where does the toxicity reside?
4. To what extent are vehicle-derived particles responsible for the observed health effects?