Local and systemic effects of inhaled particles and the role of size and composition

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View of Mexico City in the late 1990's

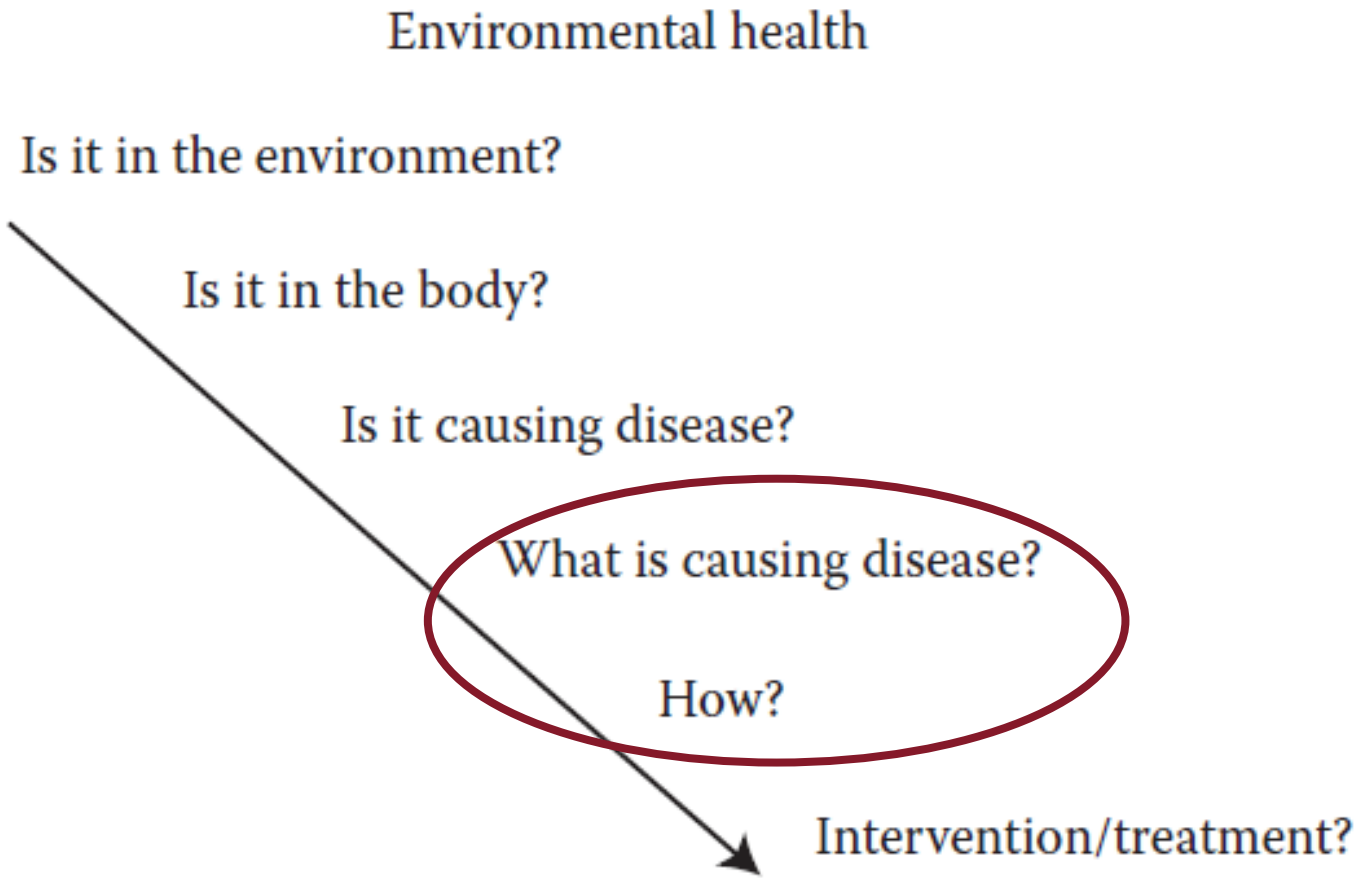
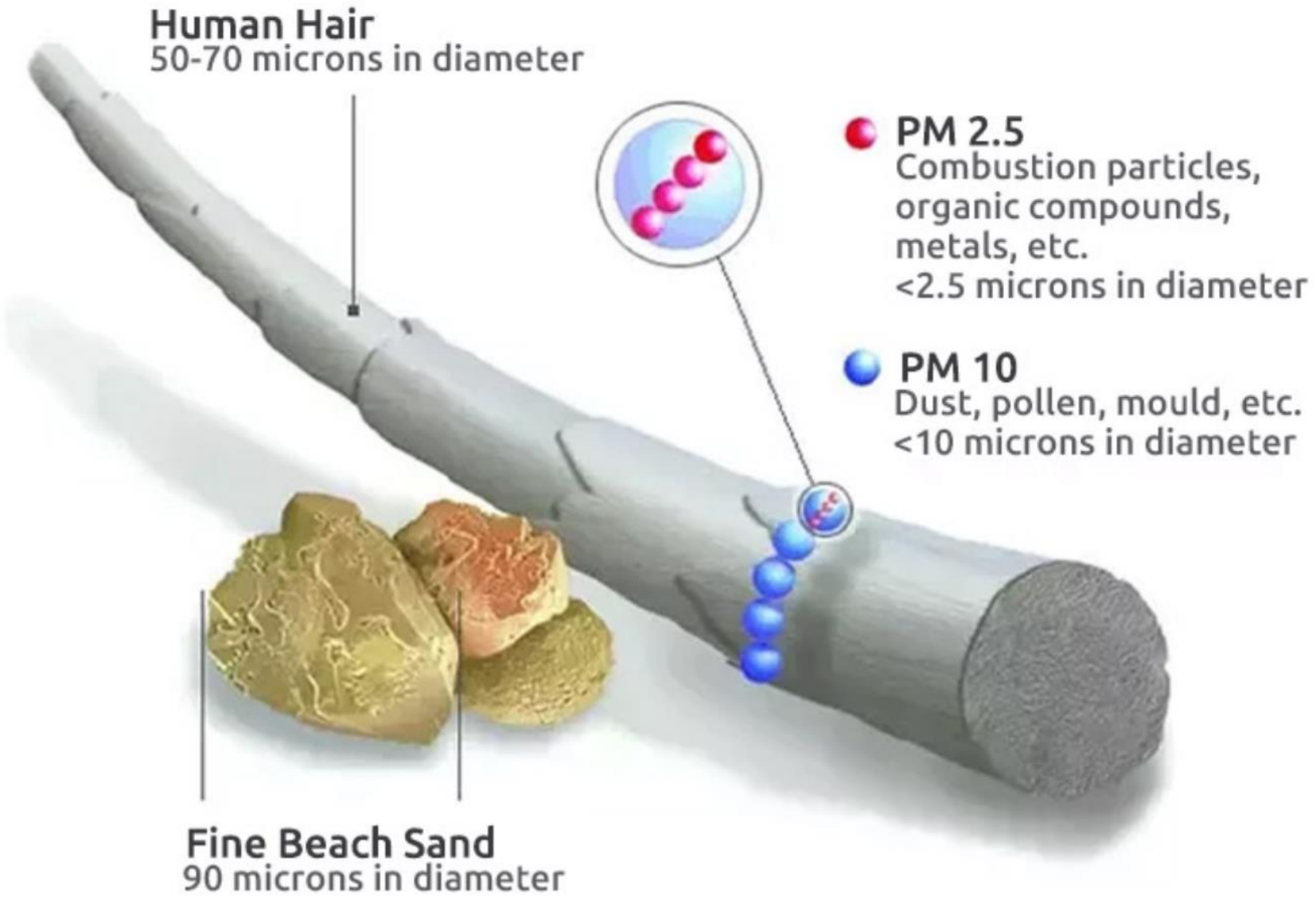


FIGURE 9.1 Schematic representation of the major steps of a theoretical pathway useful in the study of environmentally related health effects; these steps can be applied to air pollution.

Alfaro-Moreno et al. "Air Pollution: Health & Environmental Impacts" Taylor & Francis, 2010

PM 2.5 & PM 10



Source : US EPA

SWETOX

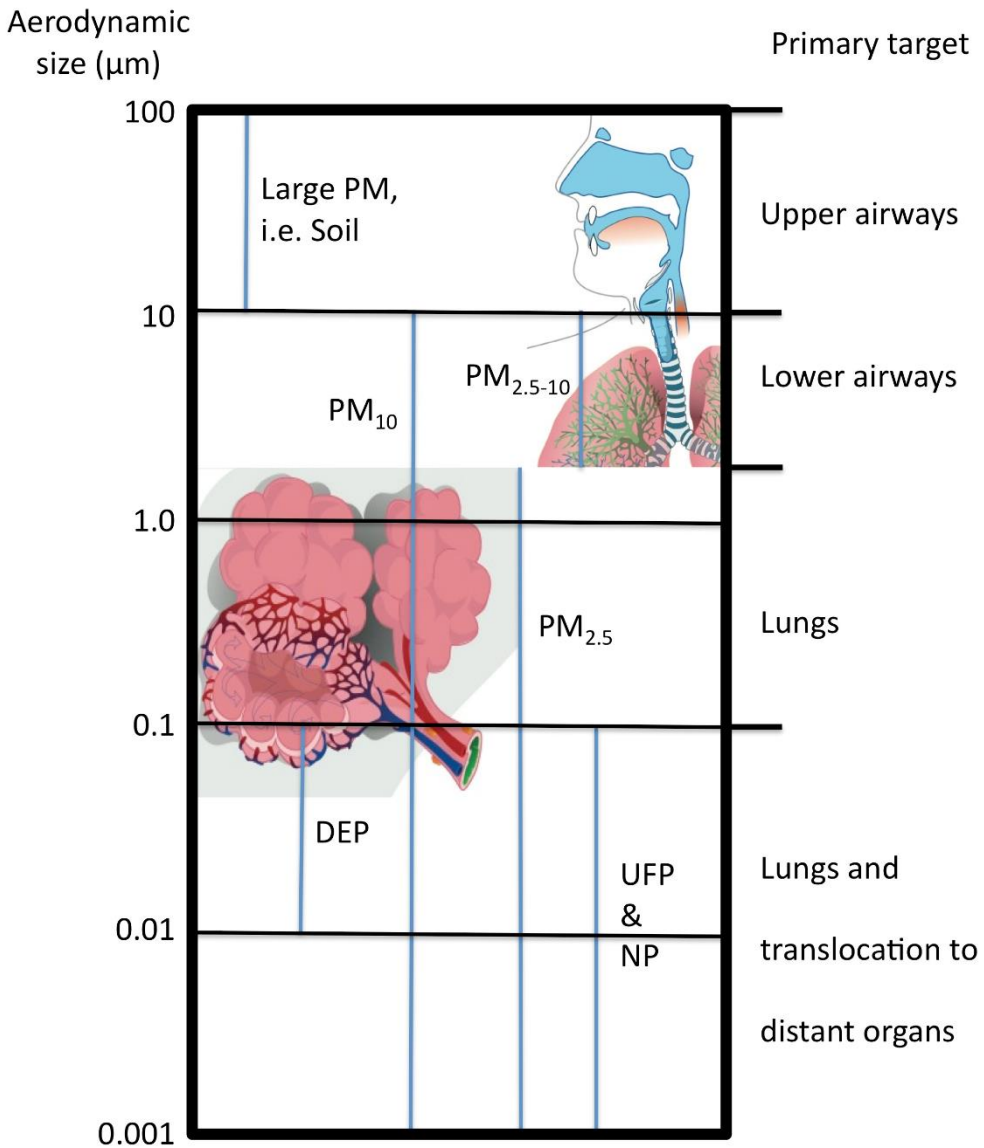
Definition of PM_{10} and $PM_{2.5}$

- *PM_{10} – particles which pass through a size-selective inlet with a 50 % efficiency cut-off at 10 µm **aerodynamic diameter**. PM_{10} corresponds to the "thoracic convention" as defined in ISO 7708:1995, Clause 6.*

- *$PM_{2.5}$ – particles which pass through a size-selective inlet with a 50 % efficiency cut-off at 2.5 µm **aerodynamic diameter**. $PM_{2.5}$ corresponds to the "high-risk respirable convention" as defined in ISO 7708:1995, 7.1.*

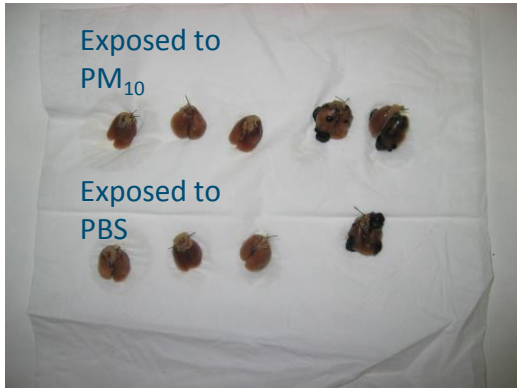
SWETOX

Inhaled particles, sizes and targets

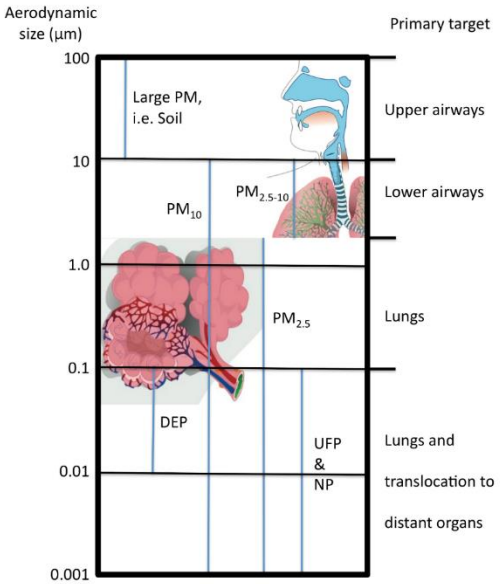


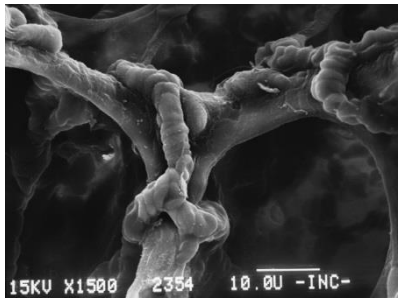
Inhalation toxicology

In vivo

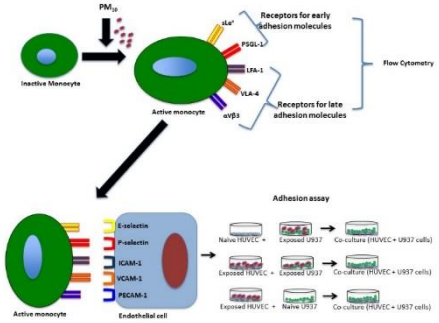


Inhaled particles, sizes and targets

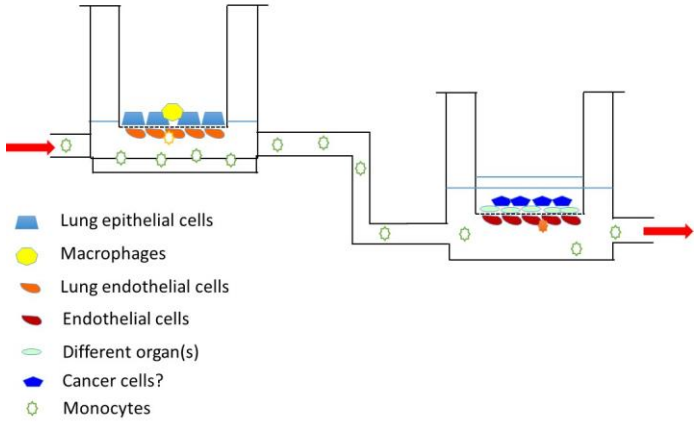




In vitro



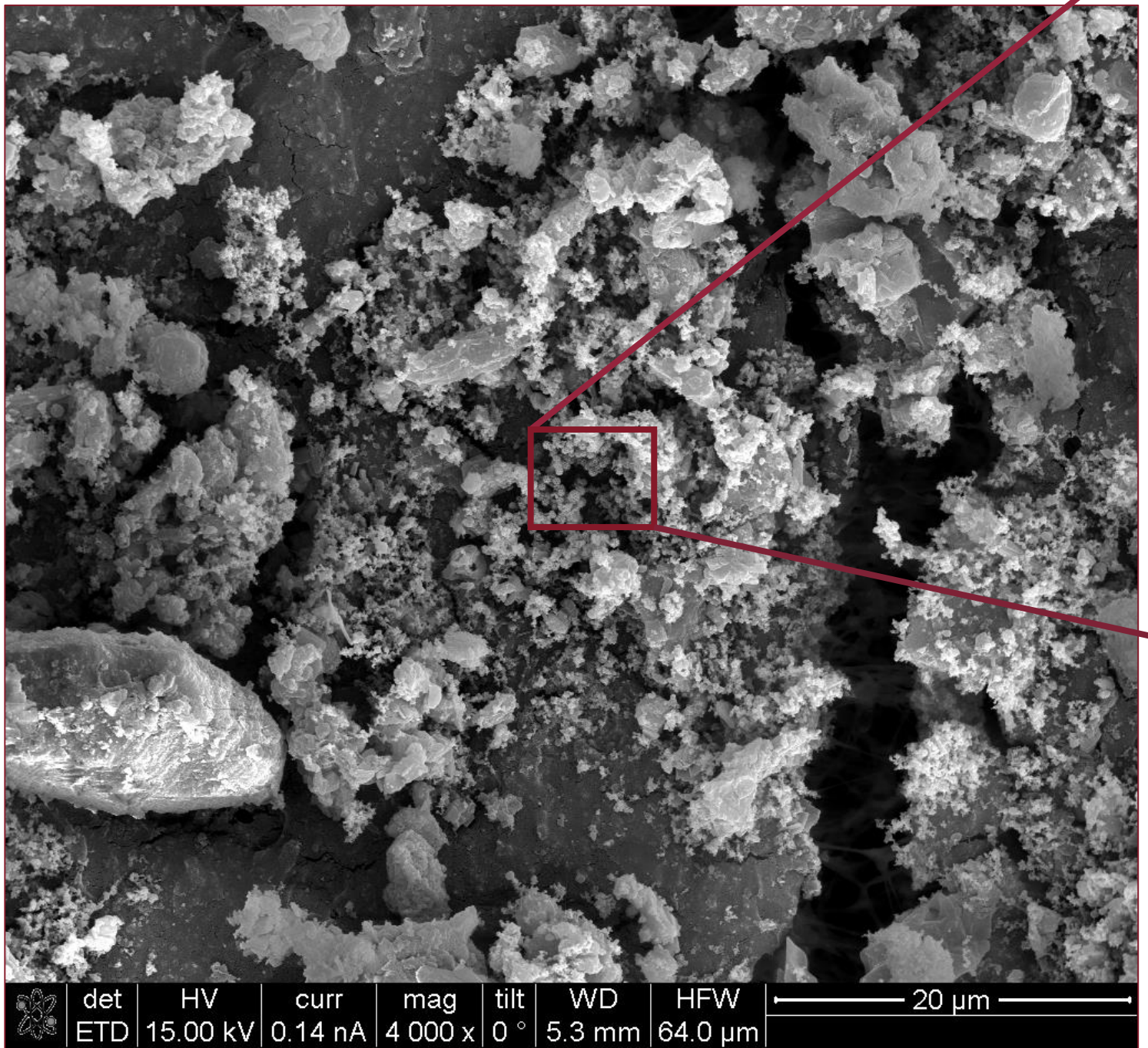
Developing new models

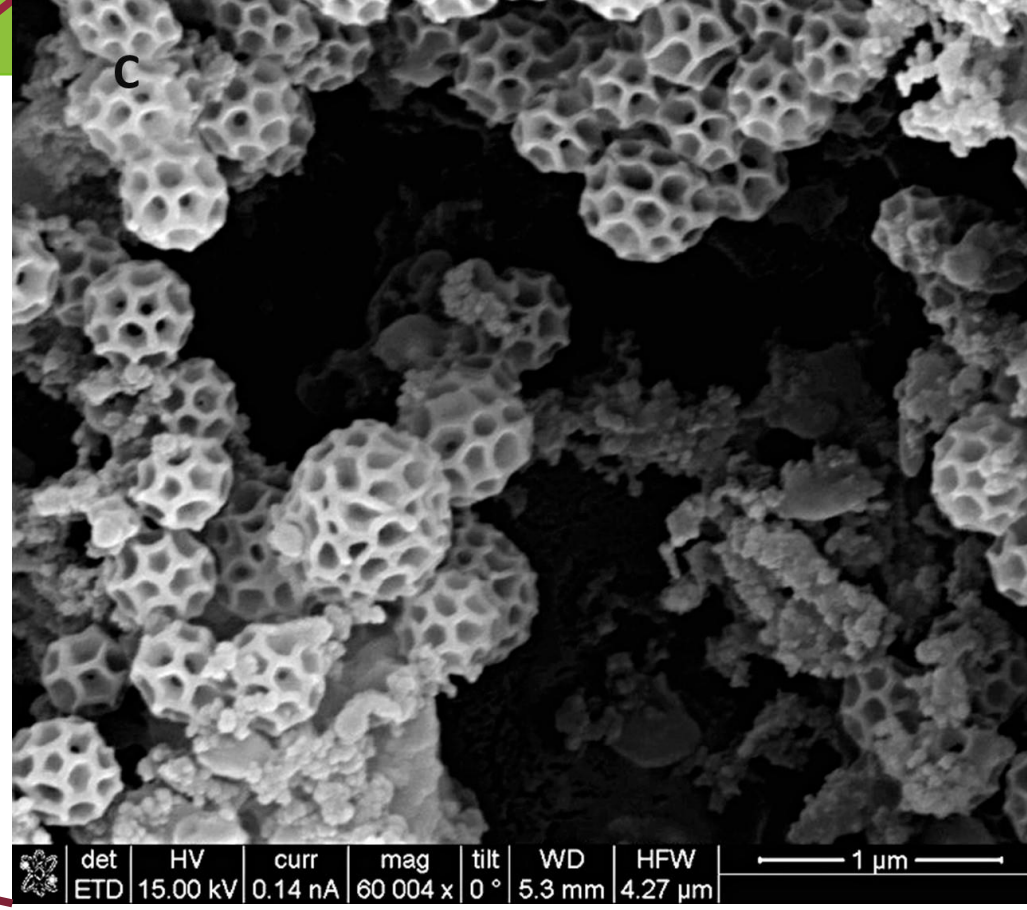


SWETOX

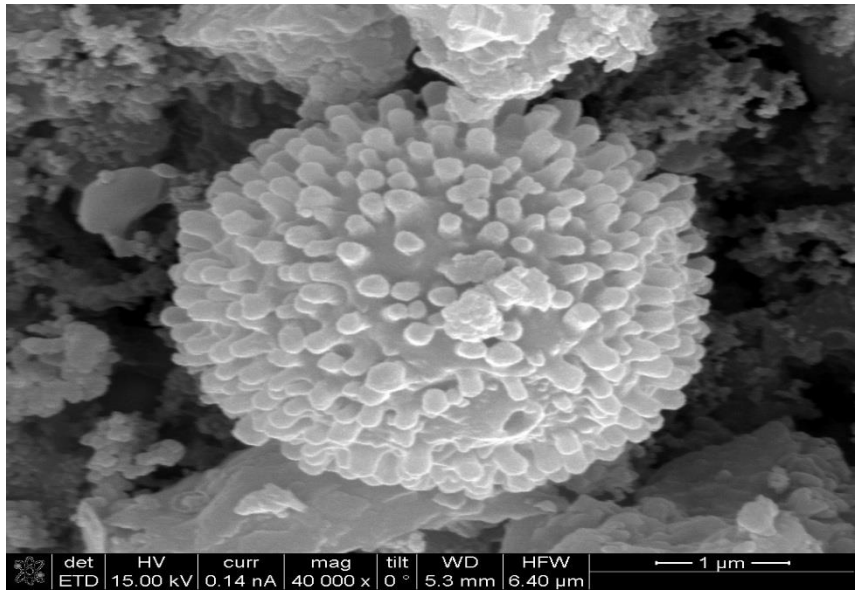
Characterization of Particulate Matter

- Physical
- Chemical
  - Raúl Omar Quintana-Belmares
  - Annette Krais


det
ETD
HV
15.00 kV
curr
0.14 nA
mag
4 000 x
tilt
0 °
WD
5.3 mm
HFW
64.0 µm
20 µm


C
det
ETD
HV
15.00 kV
curr
0.14 nA
mag
60 004 x
tilt
0 °
WD
5.3 mm
HFW
4.27 µm
1 µm

SWETOX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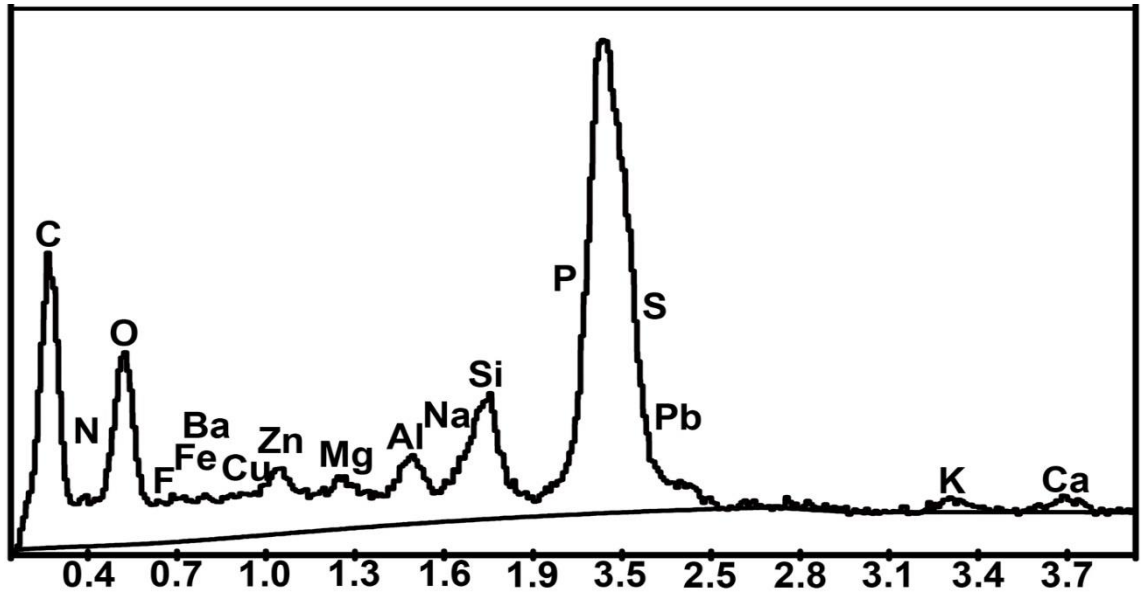
ETD 15.00 kV 0.14 nA 40 000 x 0 ° 5.3 mm 6.40 µm
1 µm


C
O
N
F
Ba
Fe
Cu
Zn
Mg
Al
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Si
P
S
Pb
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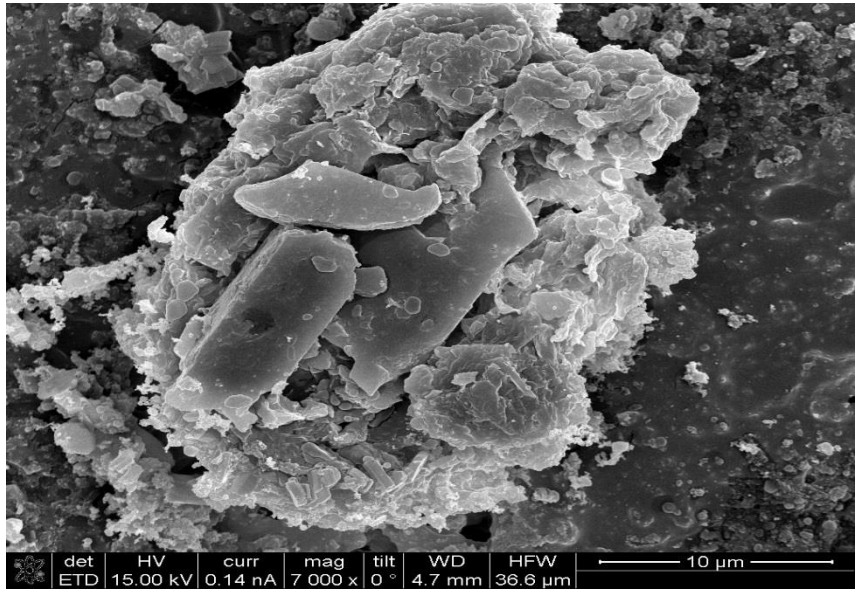
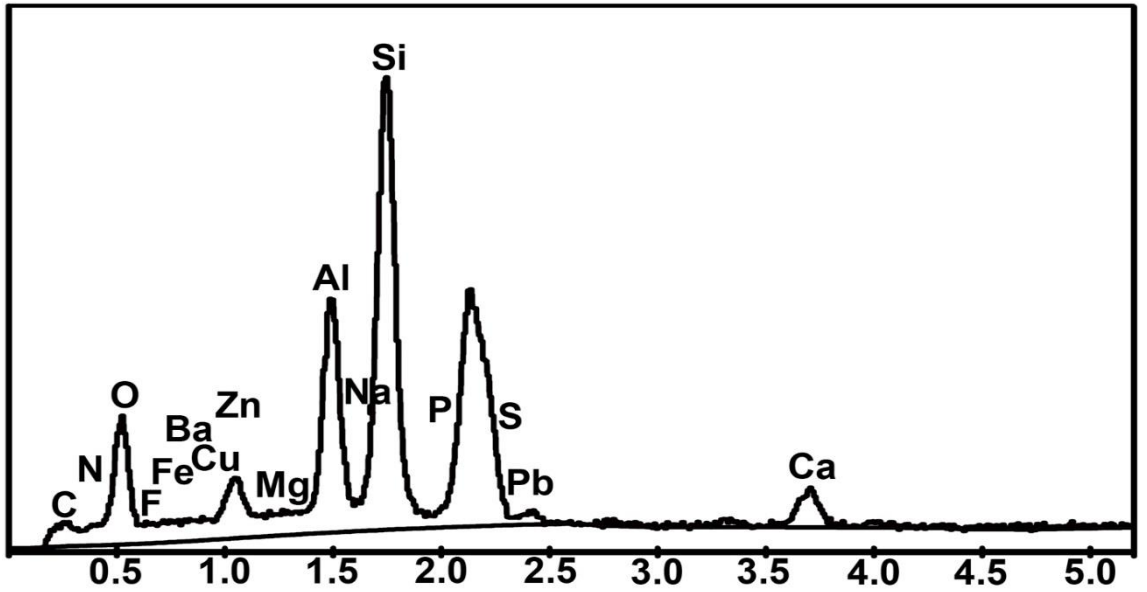
Ca
0.4 0.7 1.0 1.3 1.6 1.9 3.5 2.5 2.8 3.1 3.4 3.7


det HV curr mag tilt WD HFW
ETD 15.00 kV 0.14 nA 7 000 x 0 ° 4.7 mm 36.6 µm
10 µm


Si
Al
O
Zn
Na
Ba
Cu
P
S
N
Fe
Mg
C
F
Pb
Ca
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0

PM_{10} (µg/mg of PM)

Month	Al	Si	P	S	Cl	K	Ca	Ti	V	Cr	Mn	Fe	Ni	Cu	Zn	Se	Br	Sr	Pb
November 2012	37.60	55.97	2.23	21.78	2.66	18.15	82.39	5.52	1.68	0.44	1.81	69.99	0.01	2.96	10.10	0.17	0.34	0.75	1.05
December 2012	24.07	35.08	1.37	11.09	2.27	14.73	47.19	3.39	0.81	0.20	0.98	40.36	0.00	1.48	2.81	0.10	0.17	0.41	0.74
January 2013	28.46	39.70	1.85	15.29	2.36	16.89	59.59	4.04	1.73	0.29	1.25	51.33	0.12	1.94	4.82	0.07	0.20	0.53	0.73
February 2013	35.13	50.53	2.00	13.71	3.06	18.58	75.75	5.85	1.87	0.36	1.90	75.40	0.00	3.23	5.78	0.05	0.30	0.73	0.89
March 2013	36.80	50.76	2.13	16.87	3.01	20.28	71.76	5.78	1.94	0.41	1.79	67.55	0.08	2.31	4.73	0.06	0.22	0.75	0.74
April 2013	20.36	27.92	1.17	7.97	2.03	8.93	31.75	2.64	0.60	0.20	0.86	29.15	0.00	2.24	1.51	0.03	0.11	0.35	0.23
May 2013	22.67	27.91	1.42	12.49	2.02	11.00	38.87	3.17	0.74	0.25	0.95	39.35	0.00	4.56	2.67	0.03	0.13	0.44	0.43

PM_{10} (ng/mg of PM)

Month	Naftalene	Acenaftilene	Acenaftene	Fluorene	Fenantrene	Antracene	1-Metilantracene	3,6-Dimetilfenantrene	Fluorantene	Pirene	Tripticene	Benzo[a]fluorene	Benzo[a]antracene	Trifenilen+Crisene	Benzo[b]fluorantene	Benzo[k]fluorantene	Benzo[e]pirene	Benzo[a]pirene	Perilene	Indeno[1,2,3-cd]pirene	Dibenzo[ac]antracene+Dibenzo[ah]antraceno	Benzo[ghi]perilene
November 2012	1.30	0.25	0.30	0.30	1.59	0.20	0.42	0.03	1.65	2.58	0.00	0.31	1.79	2.49	4.38	5.56	3.48	2.31	0.59	3.84	1.54	14.38
December 2012	1.37	0.29	0.00	0.40	1.63	0.20	0.00	0.16	1.86	2.75	0.00	0.30	1.91	2.56	5.03	6.62	3.82	2.71	0.67	4.80	0.53	36.94
January 2013	1.60	0.39	0.00	0.38	2.00	0.24	0.00	0.11	2.24	3.63	0.00	0.53	2.60	2.68	4.55	7.94	5.04	3.24	0.84	5.34	1.71	50.09
February 2013	1.61	0.39	0.00	0.32	1.82	0.16	0.00	0.29	1.95	3.35	0.00	0.45	2.07	2.12	4.03	6.61	4.56	2.65	0.81	4.13	1.43	21.31
March 2013	1.29	0.28	0.00	0.26	1.55	0.21	0.00	0.16	2.03	3.42	0.00	0.41	1.84	2.00	3.18	5.44	3.71	2.30	0.59	4.00	1.34	45.37
April 2013	1.57	0.25	0.00	0.31	1.50	0.20	0.00	0.41	1.38	2.60	0.00	0.38	1.28	1.50	2.39	4.09	2.83	1.65	0.47	3.01	0.21	81.58
May 2013	1.67	0.21	0.00	0.30	1.49	0.00	0.14	0.32	1.04	2.02	0.00	0.27	0.86	1.12	1.69	2.75	2.00	1.02	0.27	1.98	1.69	10.96

Table 2. Semiquantitative comparative appreciation of cellular effects induced by PM_{10} from Mexico City.

	Cytotoxic effects			Proinflammatory effects			
Zone	Toxicity	Apoptosis	DNA damage	TNFα	IL-6	PGE_2	E-selectin
Northern	+++	+++	+++	++	++	+	++
Central	++	++	+++	+++	+++	+++	++
Southern	++	+	++	+	+	++	++

The number of + symbols indicates the magnitude of the observed effects.

TABLE 4
Multiple linear regression analysis and stepwise analysis

	Viability		TNFα		IL-6		E-Selectin		DNA damage	
Component	β	p	β	p	β	p	β	p	β	p
Ni	−51.7	0.000	18.6	0.113	−.76	0.39	Exc.	Exc.	−20.2	0.000
Zn	−45.6	0.000	−9.98	0.36	−2.8	0.001	−17.7	0.14	−17.9	0.000
Pb	43.5	0.008	31.4	0.11	10.6	0.000	22.3	0.35	75.6	0.000
N	45		36		54		9		895	
R^2	0.86		0.44		0.81		0.18		0.222	
p	<.0001		.0001		<.0001		0.231		.0001	
SW	Ni, Zn, Pb		Ni, Pb		Pb, Zn		None		Ni, Zn, Pb	

p: probability of the whole model. SW: stepwise procedure results. Exc: excluded from the analysis.

Table 3
Factor loadings for three extracted principal components found in th
analysis of PM_{10} composition measurements

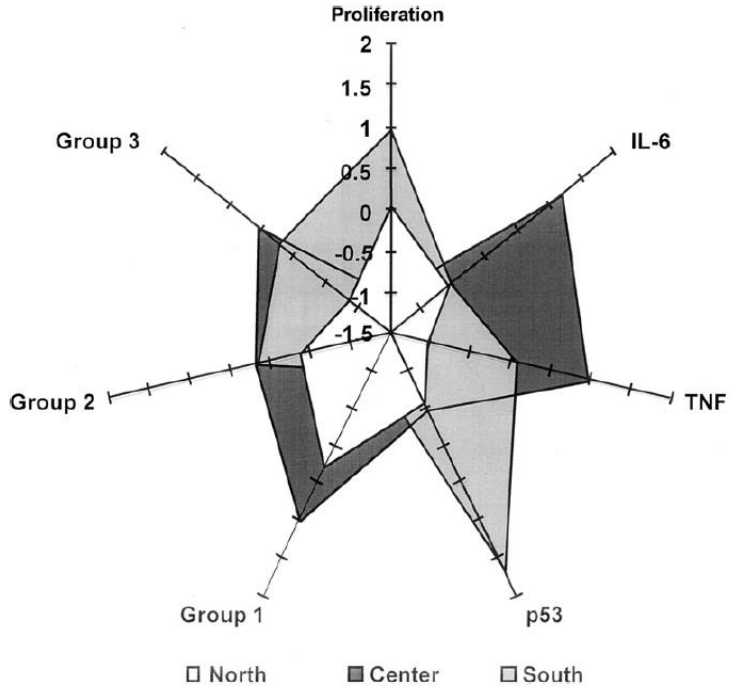
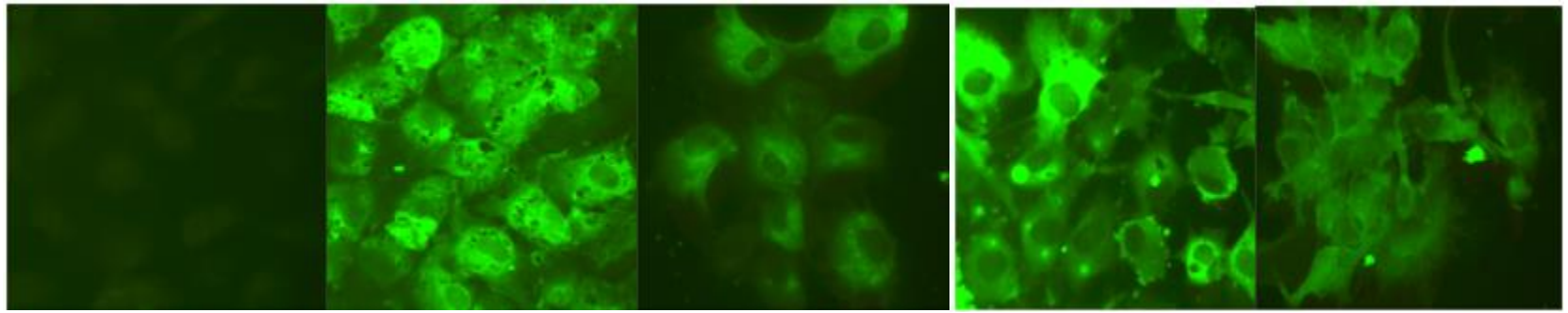


Fig. 5. This radial plot shows the relationship between PM_{10}-component groups and biological effects, stratified by sampling site.

-Ctr. PM10 PM10+PolymixinB Insoluble fraction Soluble fraction



n.d. - not detactable.

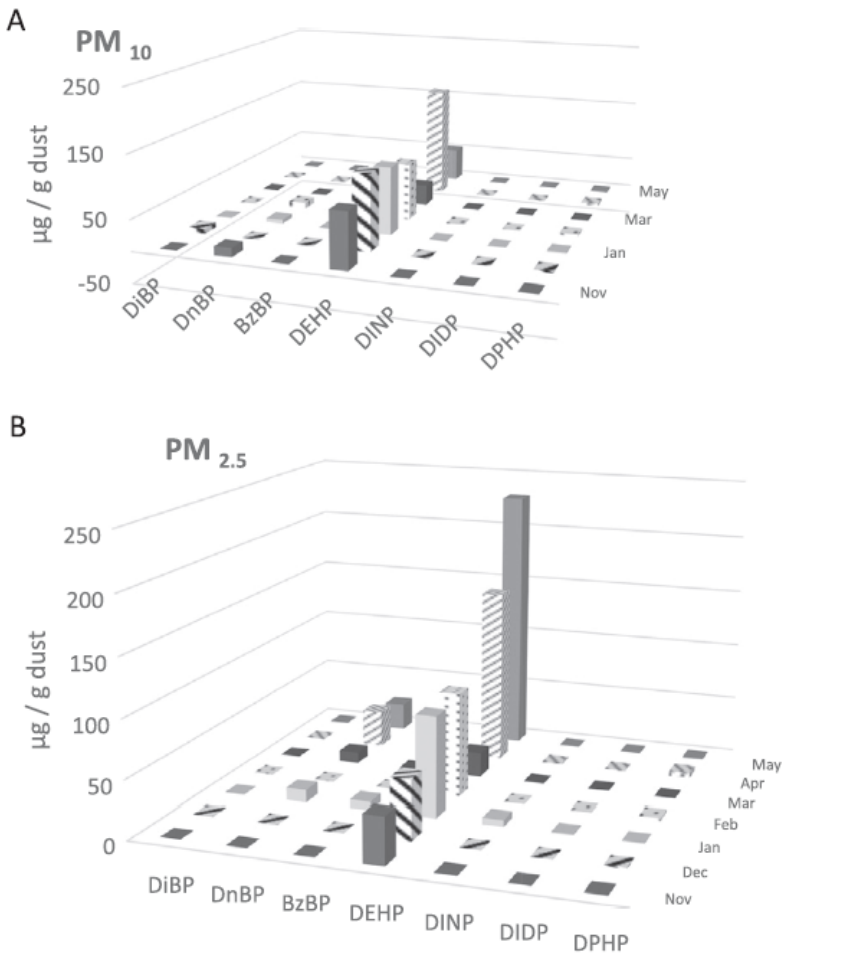


Fig. 3. Levels of phthalate esters (µg/g particles) on airborne pollution particles PM_{10} (A) and $PM_{2.5}$ (B) as analyzed by GC-MS/MS.

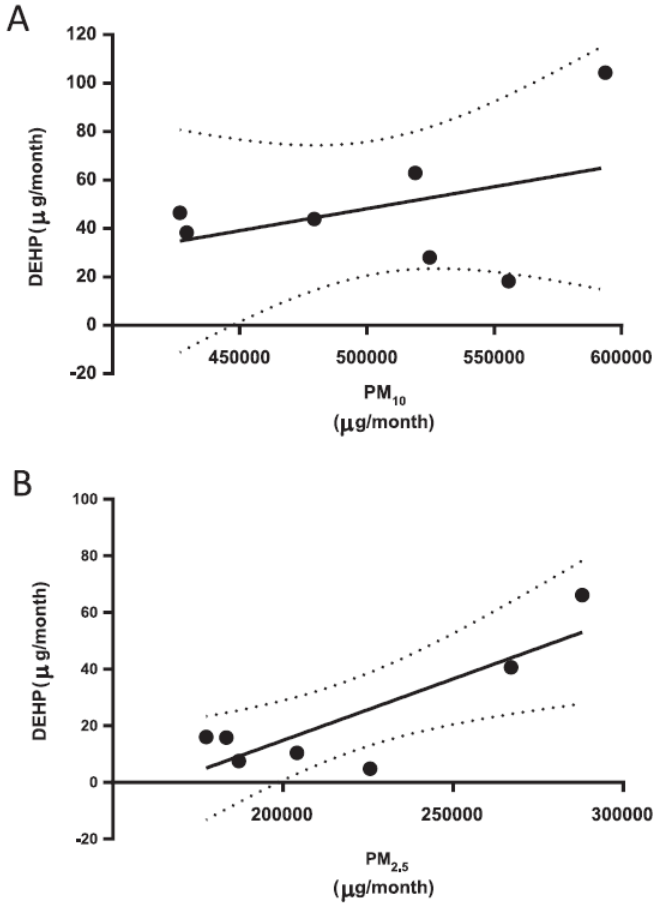


Fig. 4. Correlation of estimated concentrations of DEHP and monthly concentrations of PM_{10} (A) and $PM_{2.5}$ (B). (A) Pearson's r = 0.402, r^2 = 0.1619, p > 0.05; (B) Pearson's r = 0.8449, r^2 = 0.7138, p = 0.0167. The regressions are shown with the 95% confidence bands.

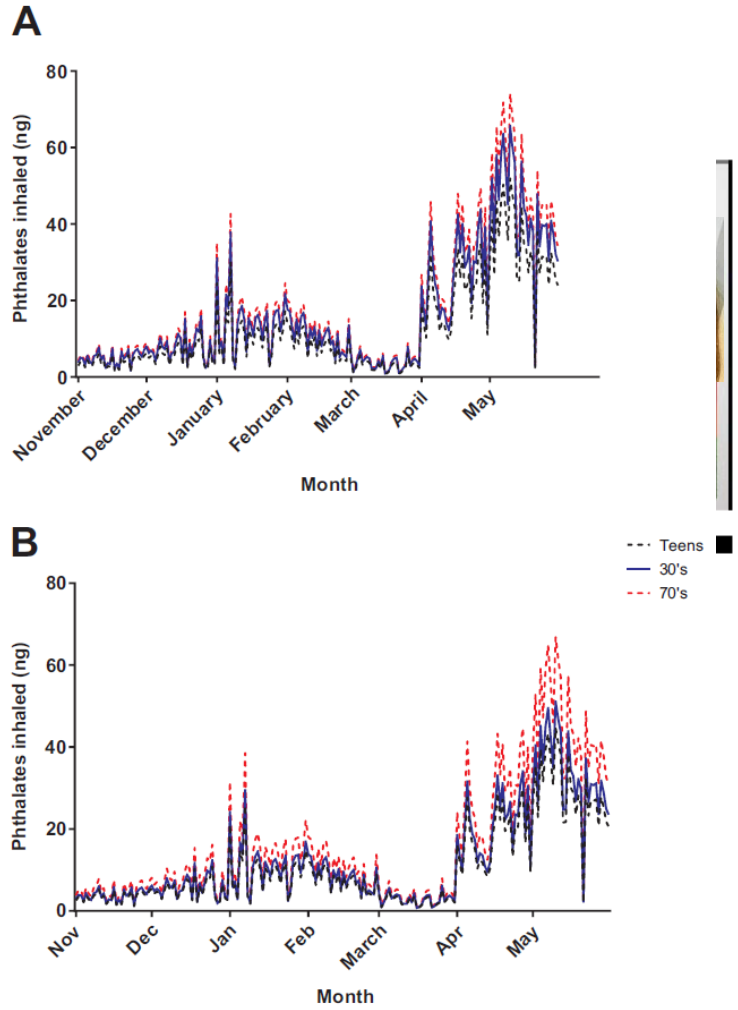
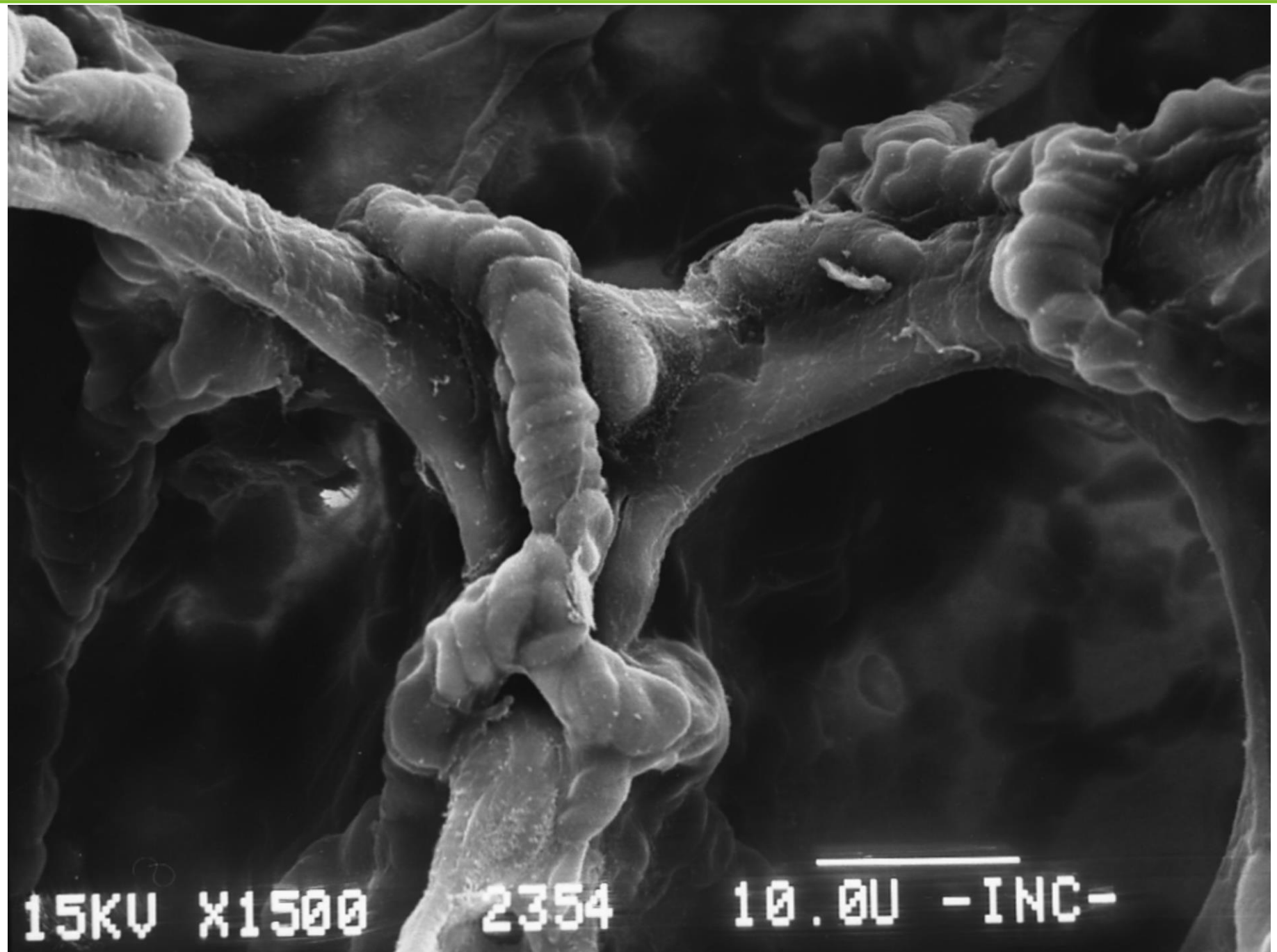


Fig. 6. Sum of exposure to phthalates in $PM_{2.5}$ for males at different ages, from 7 a.m. to 3 p.m. every day over 7 months. A) Males; B) Females.


15KV X1500 2354 10.0U -INC-

Coat membranes with gelatin for 2h

Add Hulec-5[a] (endothelial cells)

Let the cells to attach for 3 h at RT

Flip membranes back into the well

Add A549 cell (pneumocytes)

24 h later, add differentiated THP-1 (macrophages)

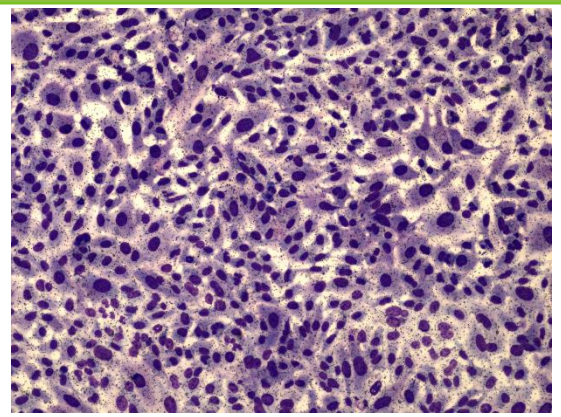
Next morning, remove the medium

Leave under ail-liquid conditions for 48h

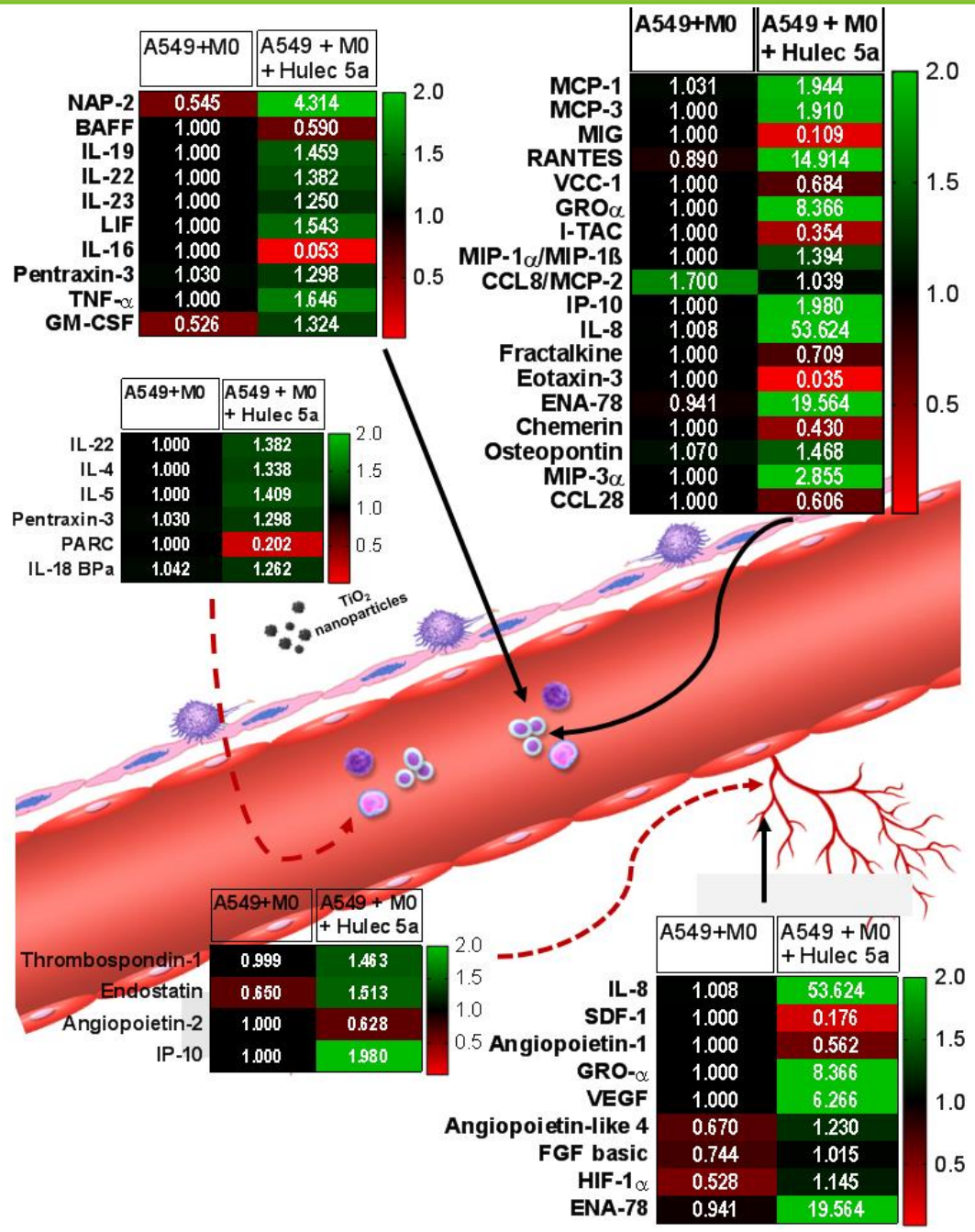
Expose to particles (TiO_2)

Recover supernatants for evaluation

SWETOX

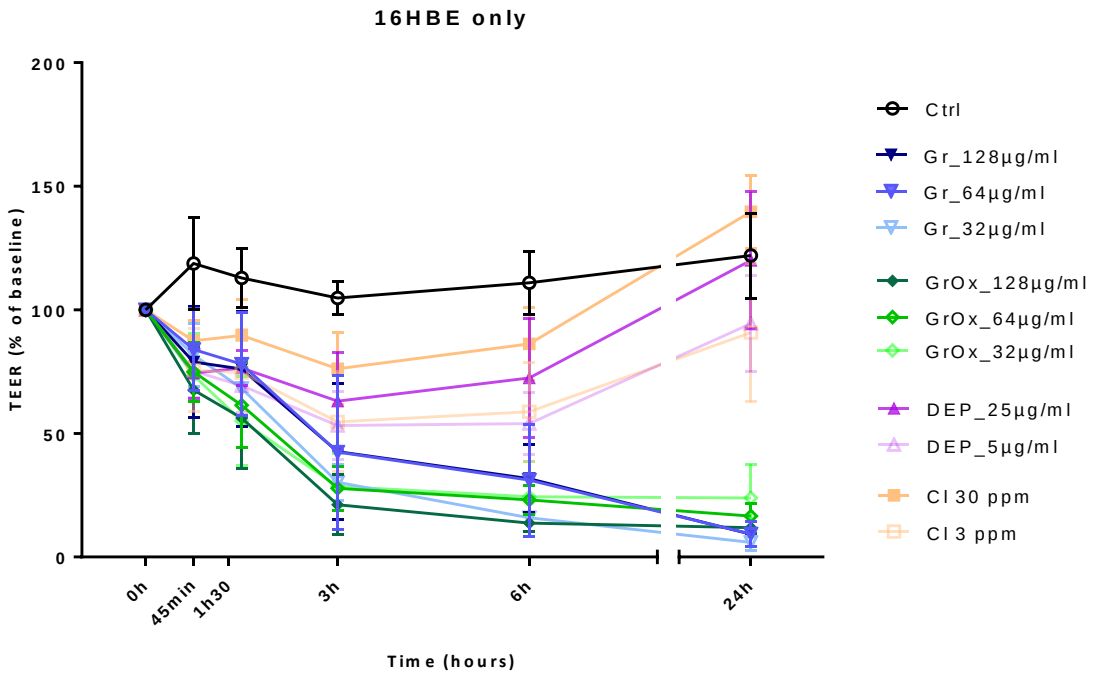


A549 type II pneumocytes + THP-1 macrophages co-cultered at air-liquid interface for 48 hours.

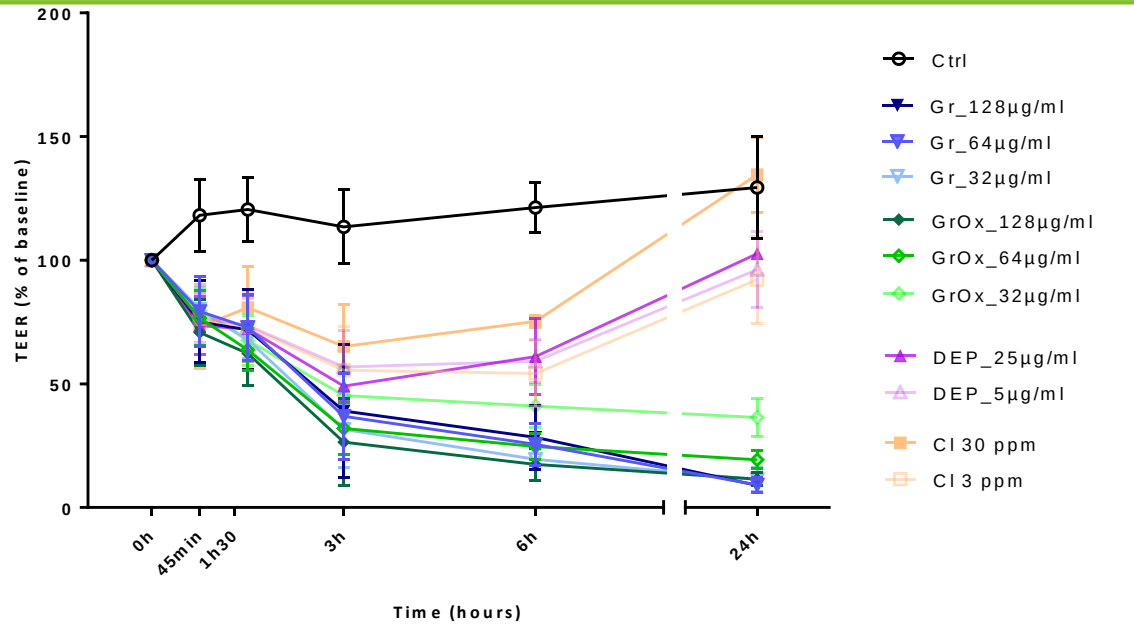


Cytokines, chemokines and growth factors secretion on cultures exposed or unexposed to TiO_2. The co-culture of epithelial cells and macrophages did not show a large shift in the expression of these molecules. When endothelial cells were included in the model, a large amount of molecules show variations from 30% up to several fold increases.

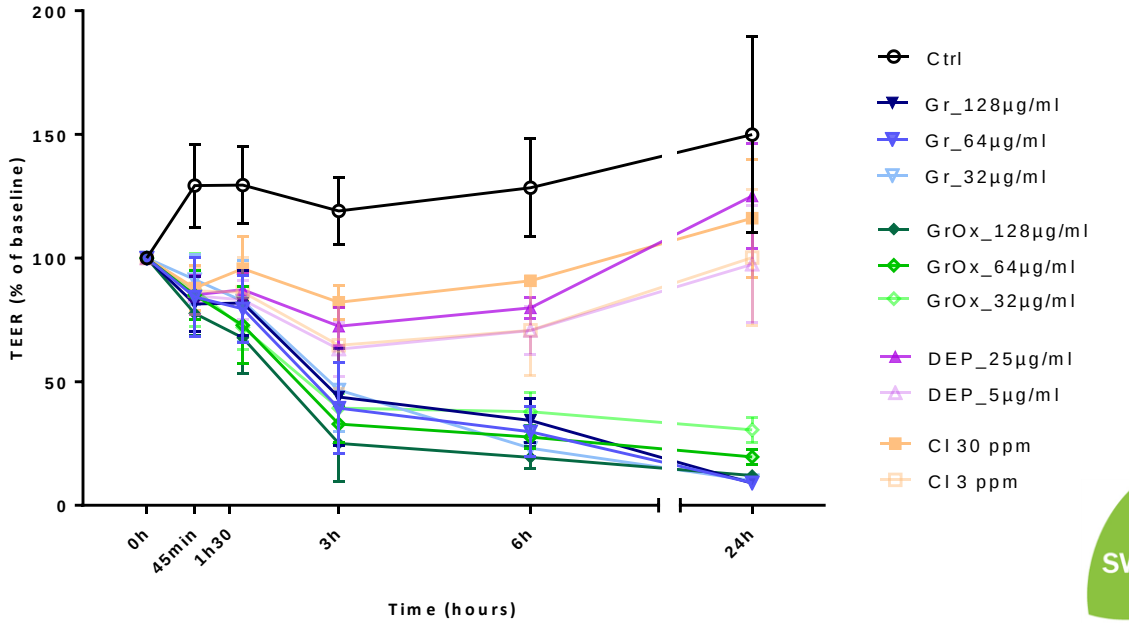
% of baseline TEER at diffrent timepoints



1/10 HMC1/16HBE Apical



1/10 HMC1/16HBE Basolateral



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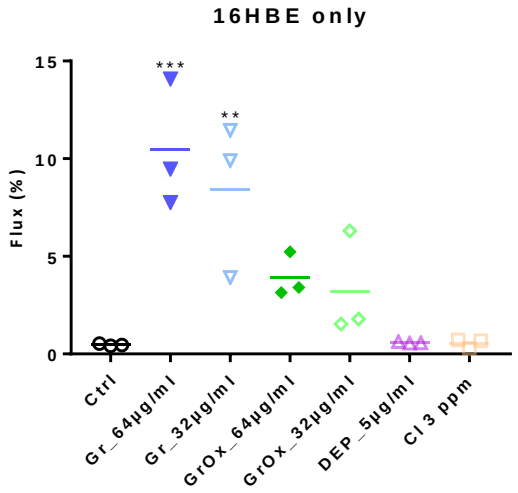
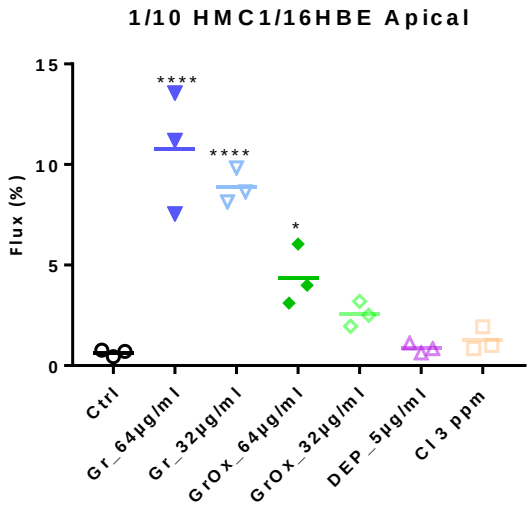
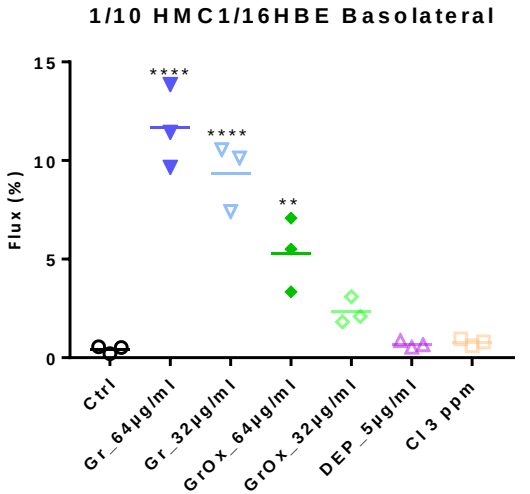
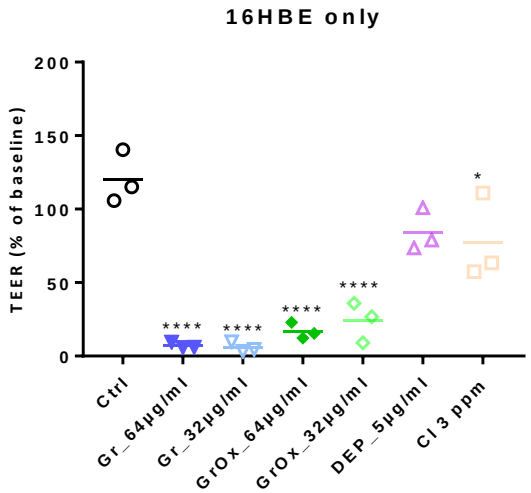
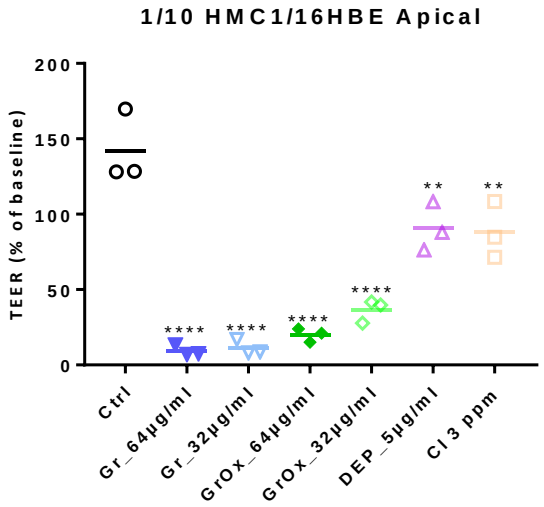
Flux FITC-dextran

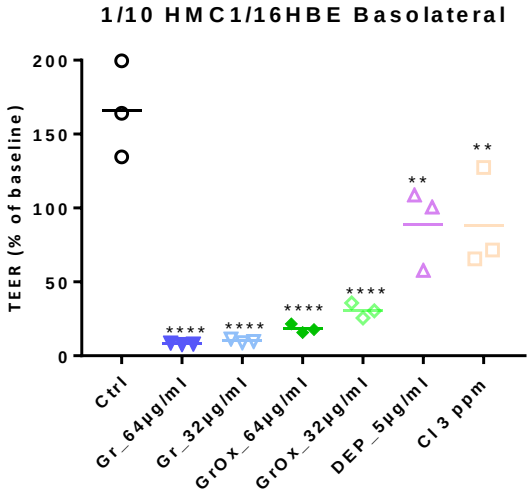




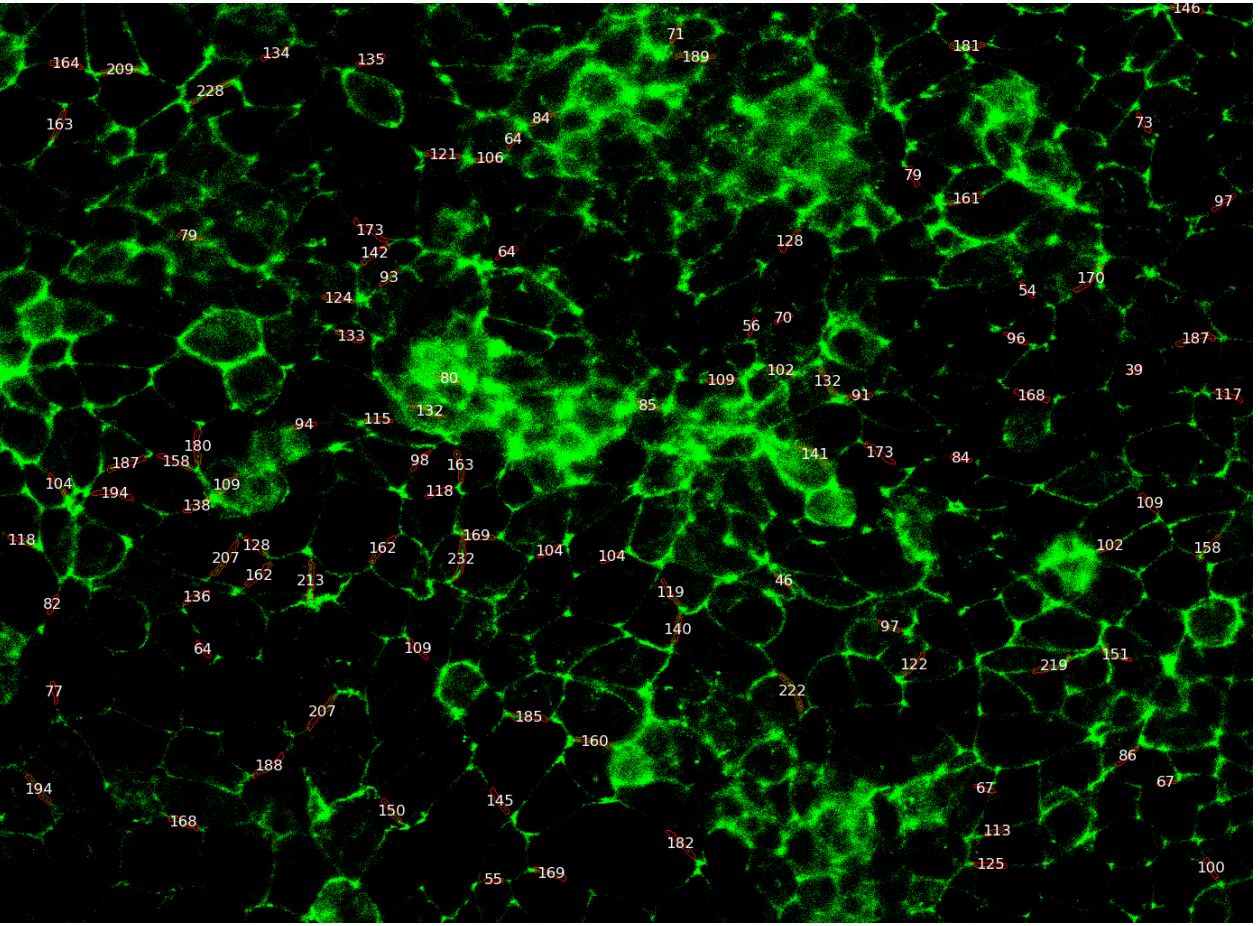


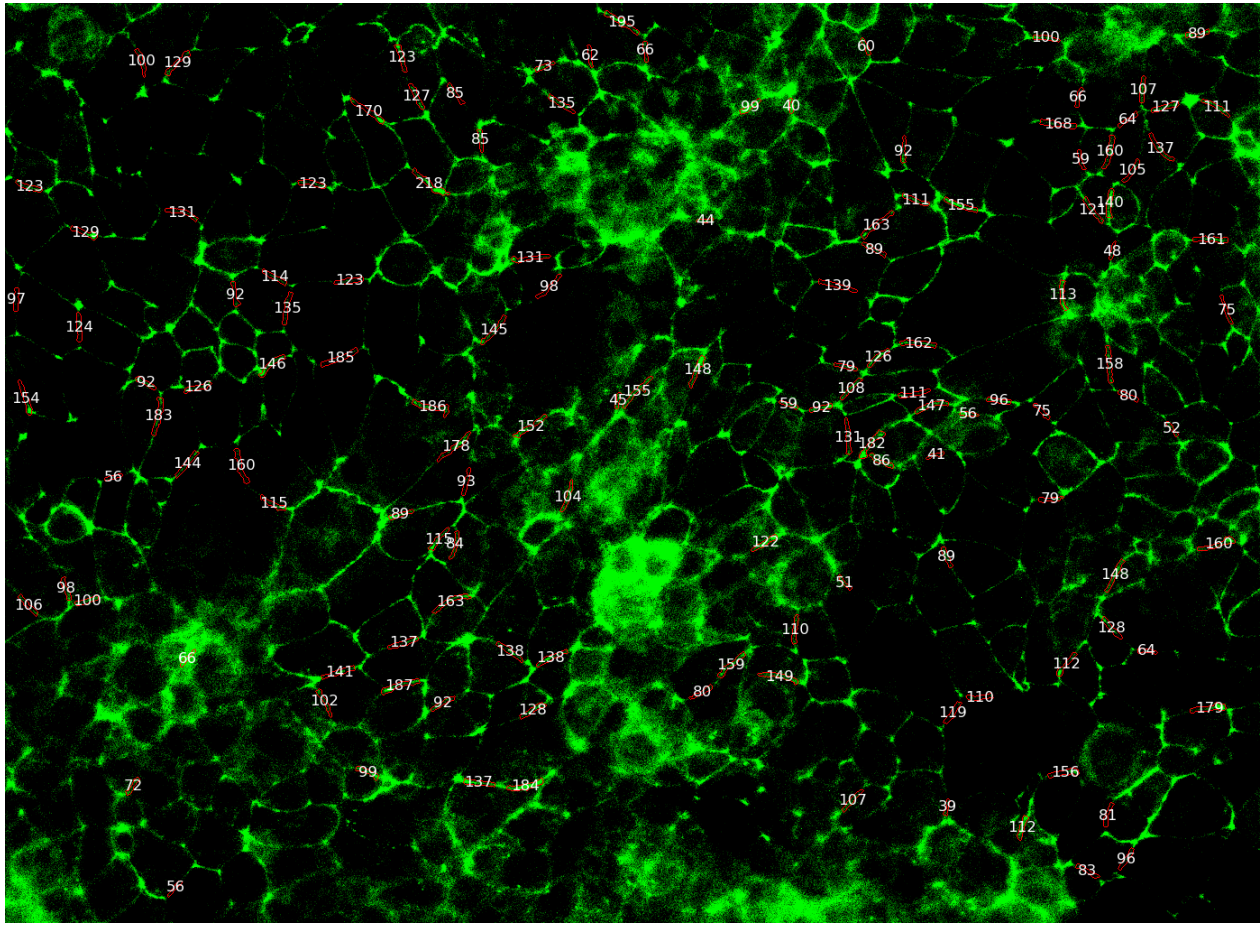




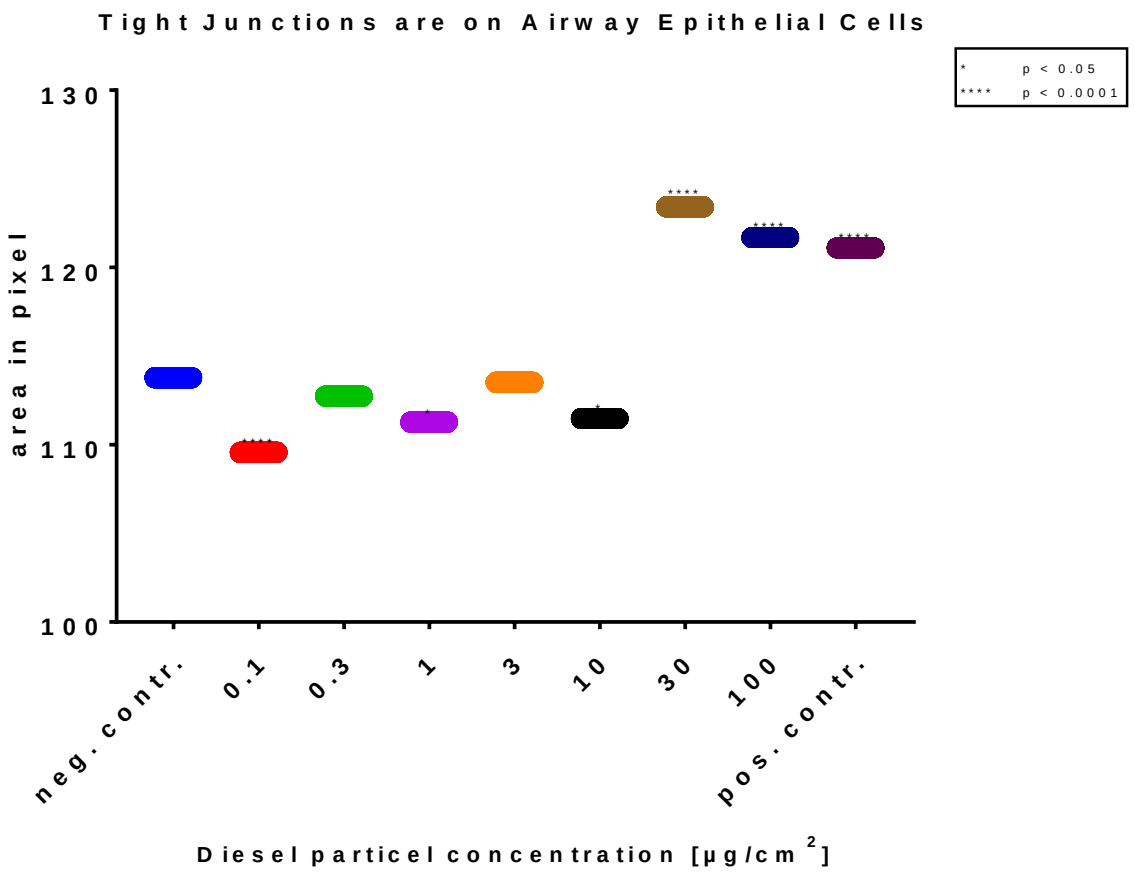


Diesel - Ctrl.

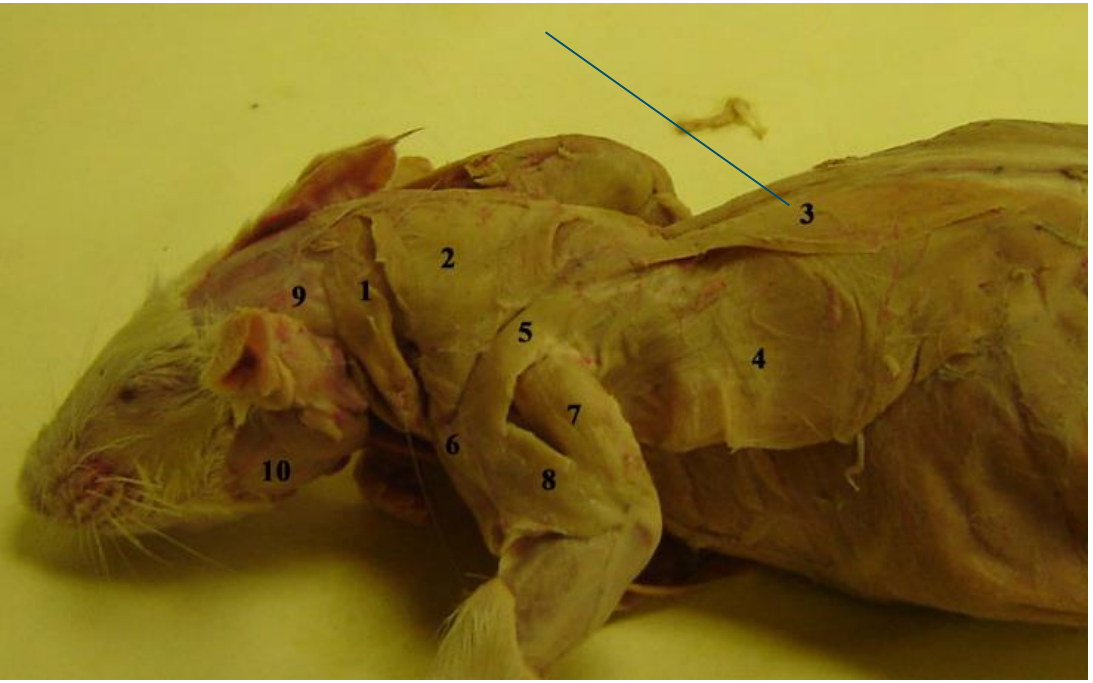




Diesel


Tight Junctions are on Airway Epithelial Cells
* p < 0.05
**** p < 0.0001
area in pixel
130
120
110
100
neg. contr.
0.1
0.3
1
3
10
30
100
pos. contr.
Diesel particel concentration [µg/cm²]

Spinotrapezius



Adhesion of PMN cells to blood vesels in the spinotrapezius muscle, after intratacheal instilation of ROFA.

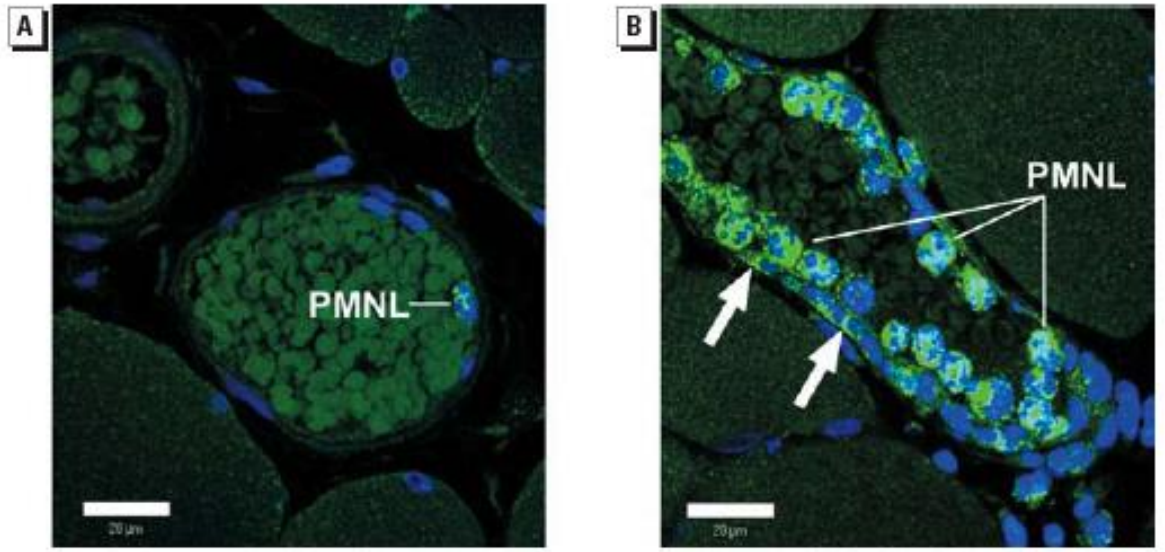
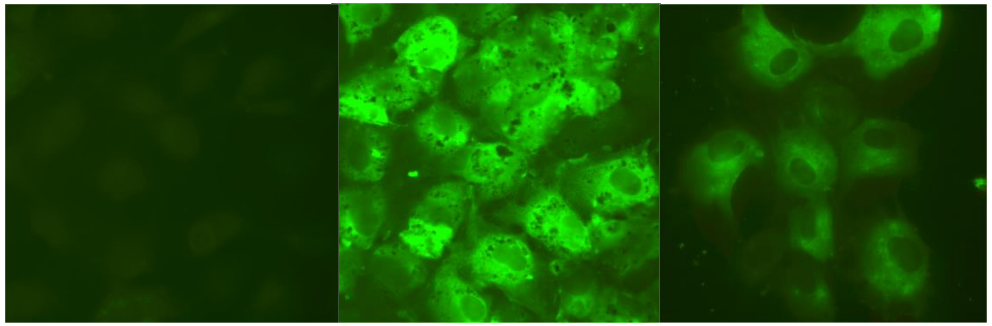


Figure 7. Localization of MPO in the spinotrapezius muscle microcirculation 24 hr after ROFA exposure. Fluorescent antibodies targeted a polyclonal antibody against MPO; nuclei are counterstained blue with DAPI. (*A*) Representative confocal fluorescent image of a venule from a saline-treated rat. (*B*) Representative confocal image of a venule from a rat exposed to 0.25 mg ROFA. Note the fluorescence in the microvascular wall indicating the presence of MPO (arrows). Bars = 20 µm; similar results were obtained with TiO_2.

Nurkiewicz et al., Environ Healt Perspect 114:412-419 (2006)

SWETOX



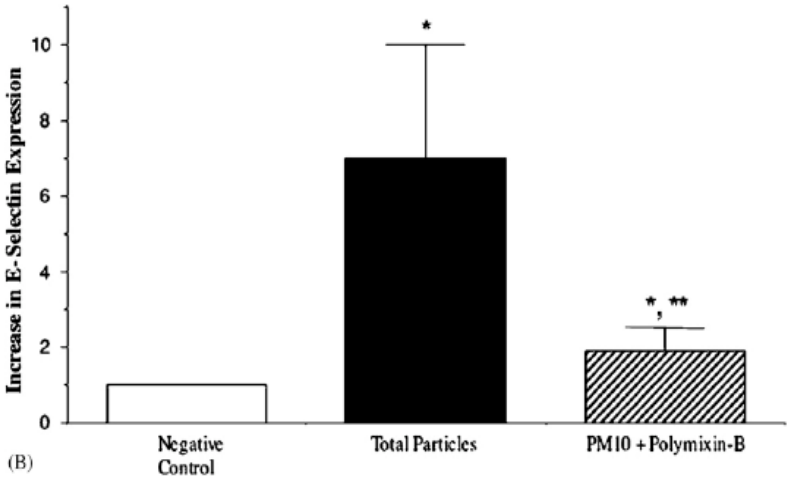
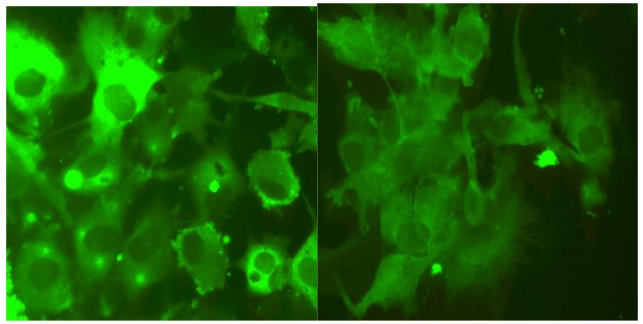


Fig. 2. Effect of particles from Mexico City on E-Selectin expression. HUVEC were exposed to 40 μg/cm^2 of total PM_{10} or preincubated with polymixin-B. The fluorescence increase was detected by fluorescence microscopy (A) or by flow cytometry (B). In B, the fold-increase in mean fluoresecence intensity is shown. Mean ± SD, $n = 3$. * Significantly different from control (unexposed) cells ($P < 0.05$). ** Significant difference between polymixin-B-treated cultures and cells exposed to particles ($P < 0.05$).



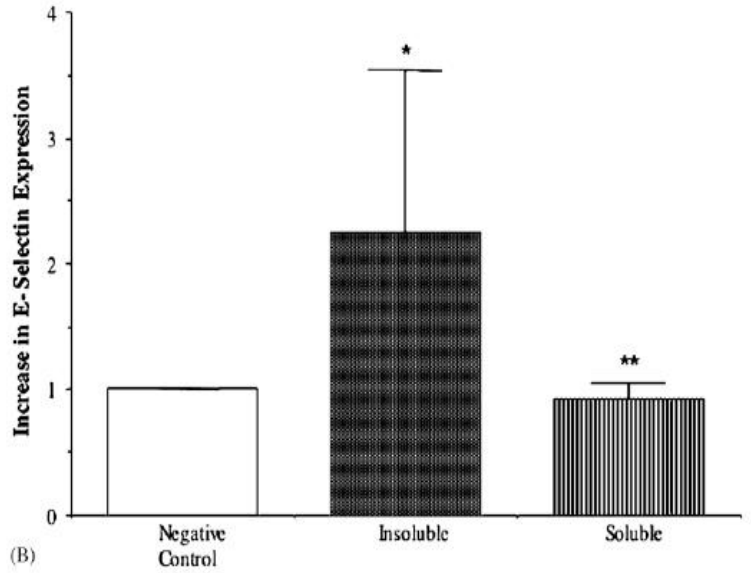
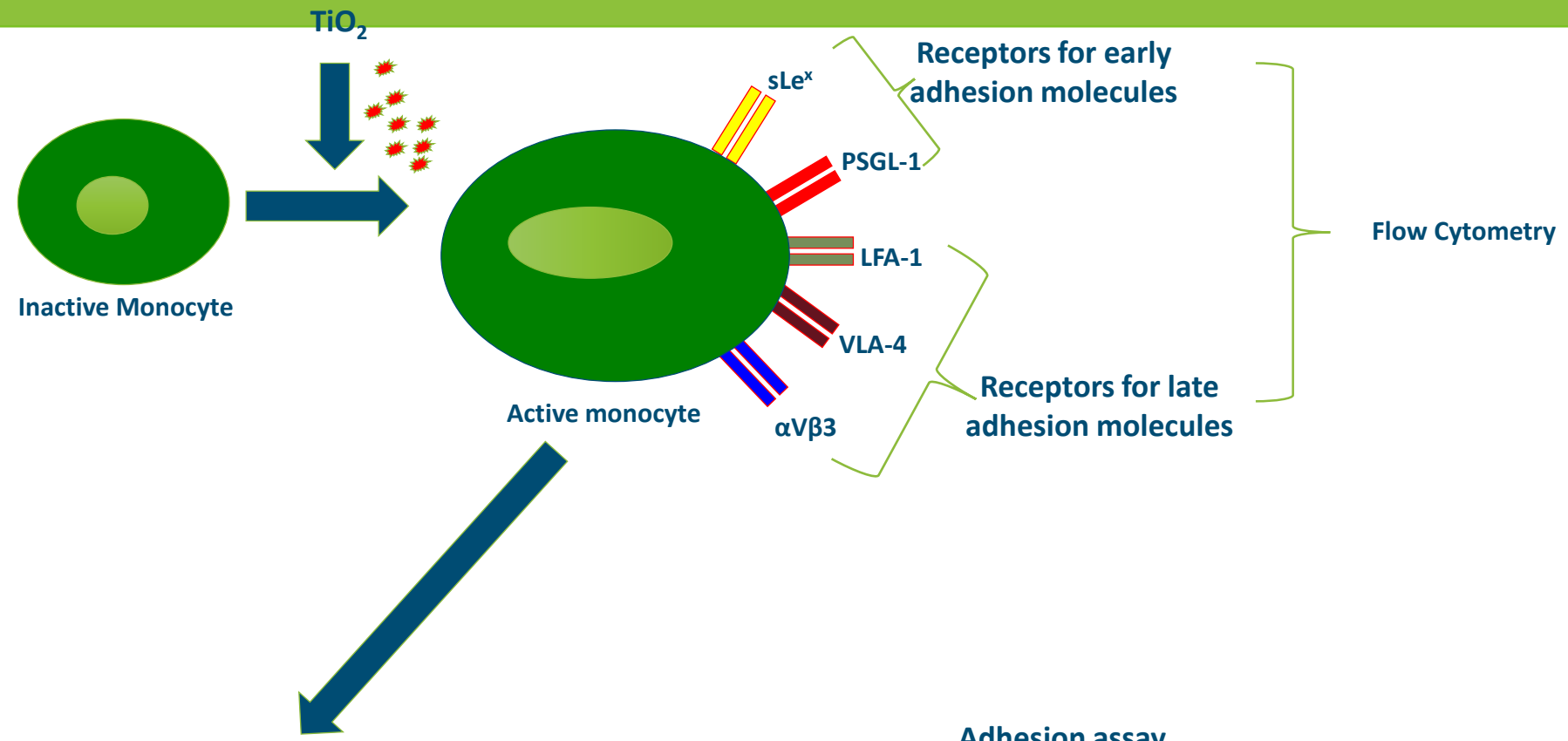


Fig. 3. Effect of different particle fractions on E-Selectin expression in HUVEC. HUVEC were exposed to the equivalent of 40 μg/cm^2 of soluble and insoluble fractions of PM_{10} from Mexico City. The fluorescence increase was detected by fluorescence microscopy (A) or flow cytometry (B). In B, the fold-increase in expression is shown. Mean ± SD, $n = 3$. * Significant difference between particle-exposed cells and control cells ($P < 0.05$). ** Significant difference between cells exposed to soluble fraction and cells exposed to insoluble fraction ($P < 0.05$).

Alfaro-Moreno E, et al. Environ Res 2007; 103 (2): 221-228


TiO_2
Inactive Monocyte
sLe^x
PSGL-1
LFA-1
VLA-4
αVβ3
Active monocyte
Receptors for early adhesion molecules
Receptors for late adhesion molecules
Flow Cytometry

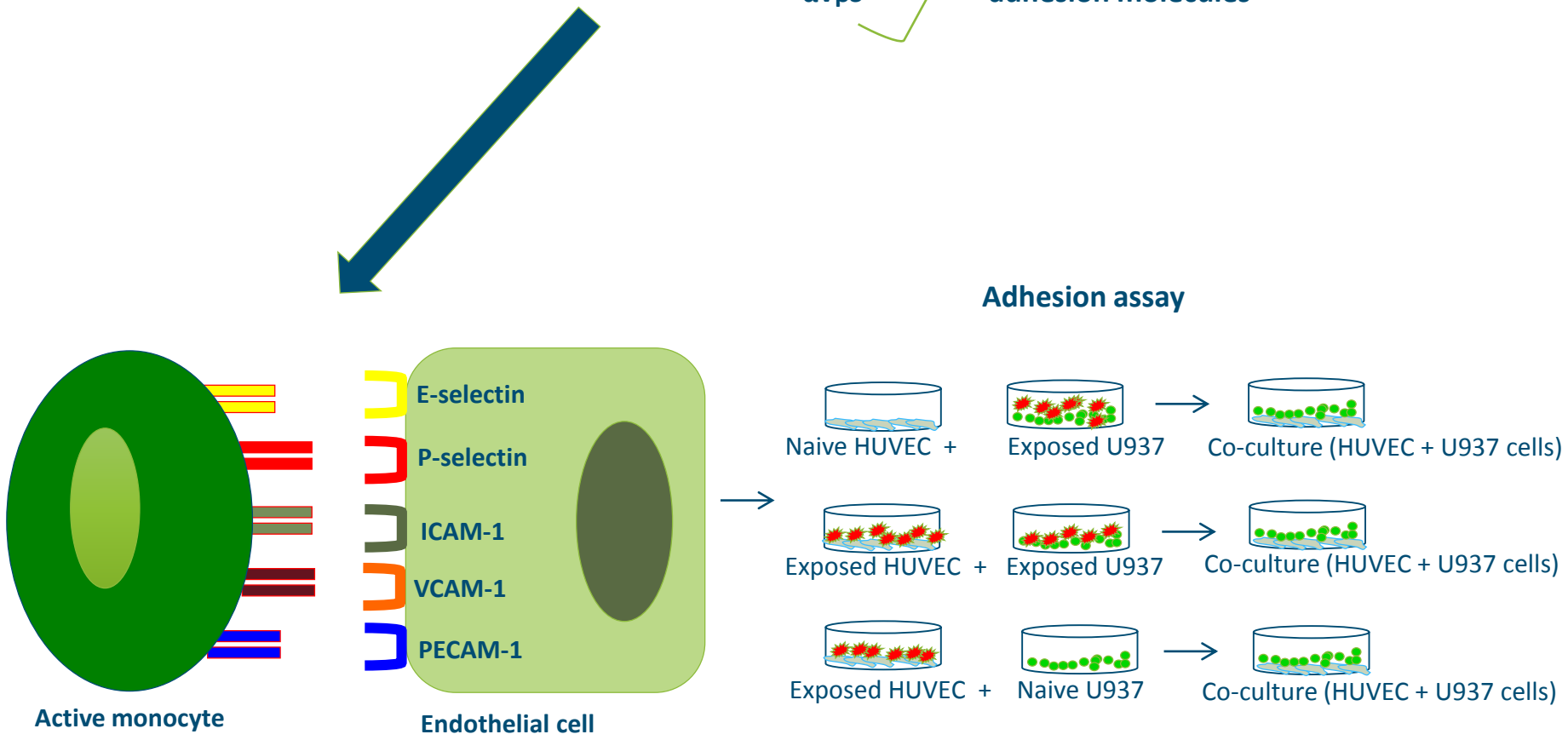

Adhesion assay
E-selectin
P-selectin
ICAM-1
VCAM-1
PECAM-1
Active monocyte
Endothelial cell
Naive HUVEC +
Exposed U937
Co-culture (HUVEC + U937 cells)
Exposed HUVEC +
Exposed U937
Co-culture (HUVEC + U937 cells)
Exposed HUVEC +
Naive U937
Co-culture (HUVEC + U937 cells)

Figure 2: Receptors for late adhesion molecules (LFA-1, VLA-4 and αVβ3)

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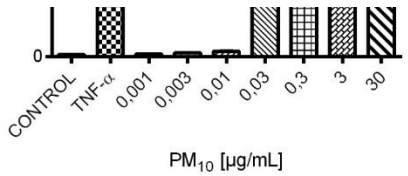
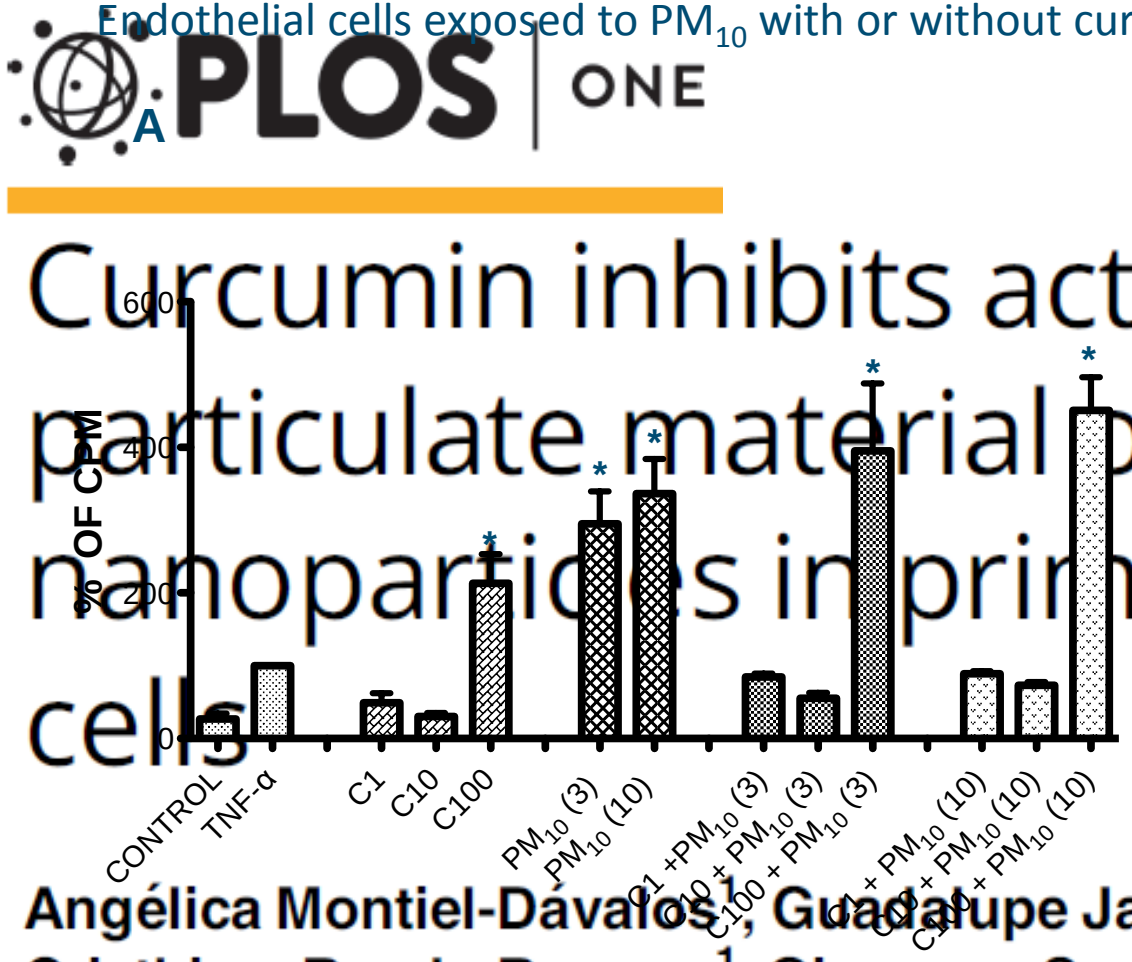
Urban particulate matter induces the expression of receptors for early and late adhesion molecules on human monocytes

Raúl Quintana-Belmares[a,1], Guillermina Hernández-Pérez[a,1], Angélica Montiel-Dávalos[a], Åsa Gustafsson[b], Javier Miranda[c], Irma Rosas-Pérez[d], Rebeca López-Marure[e], Ernesto Alfaro-Moreno[b,*]

Figure 1: Receptors for early adhesion molecules (sLex and PSGL-1) were induced in cells exposed to PM_{10} for 3 h, from 0.03 μg/mL.
* $p < 0.05$ vs. Negative control.

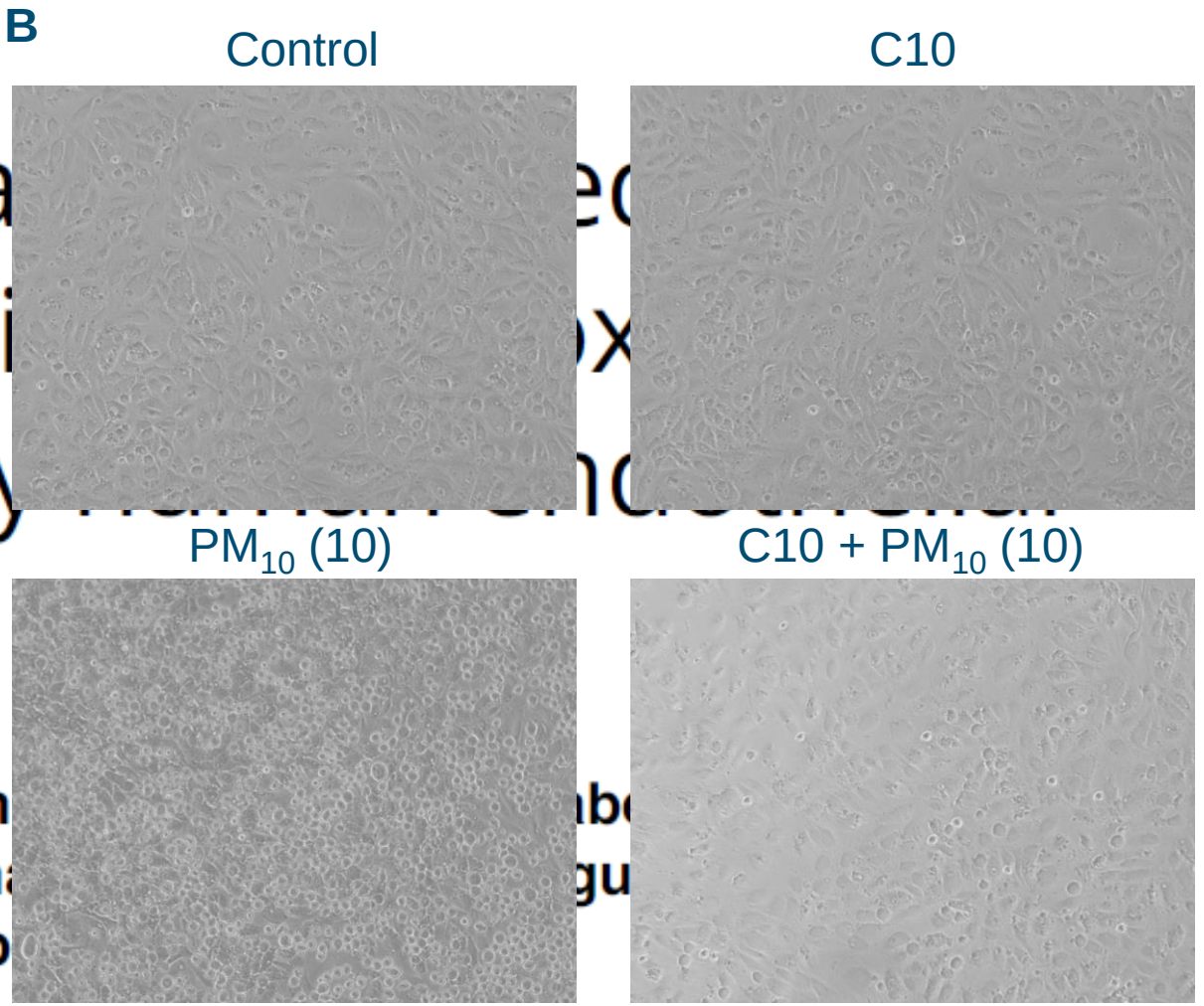


Endothelial cells exposed to PM_{10} with or without curcumin



Curcumin inhibits activa… particulate material or ti… nanoparticles in primary … cells

Angélica Montiel-Dávalos[1], Guadalupe Jazmin…
Cristhiam Rueda-Romero[1], Giovanny Soca Cha…
Moreno[4], José Pedraza-Chaverri[5], Rebeca Lóp…



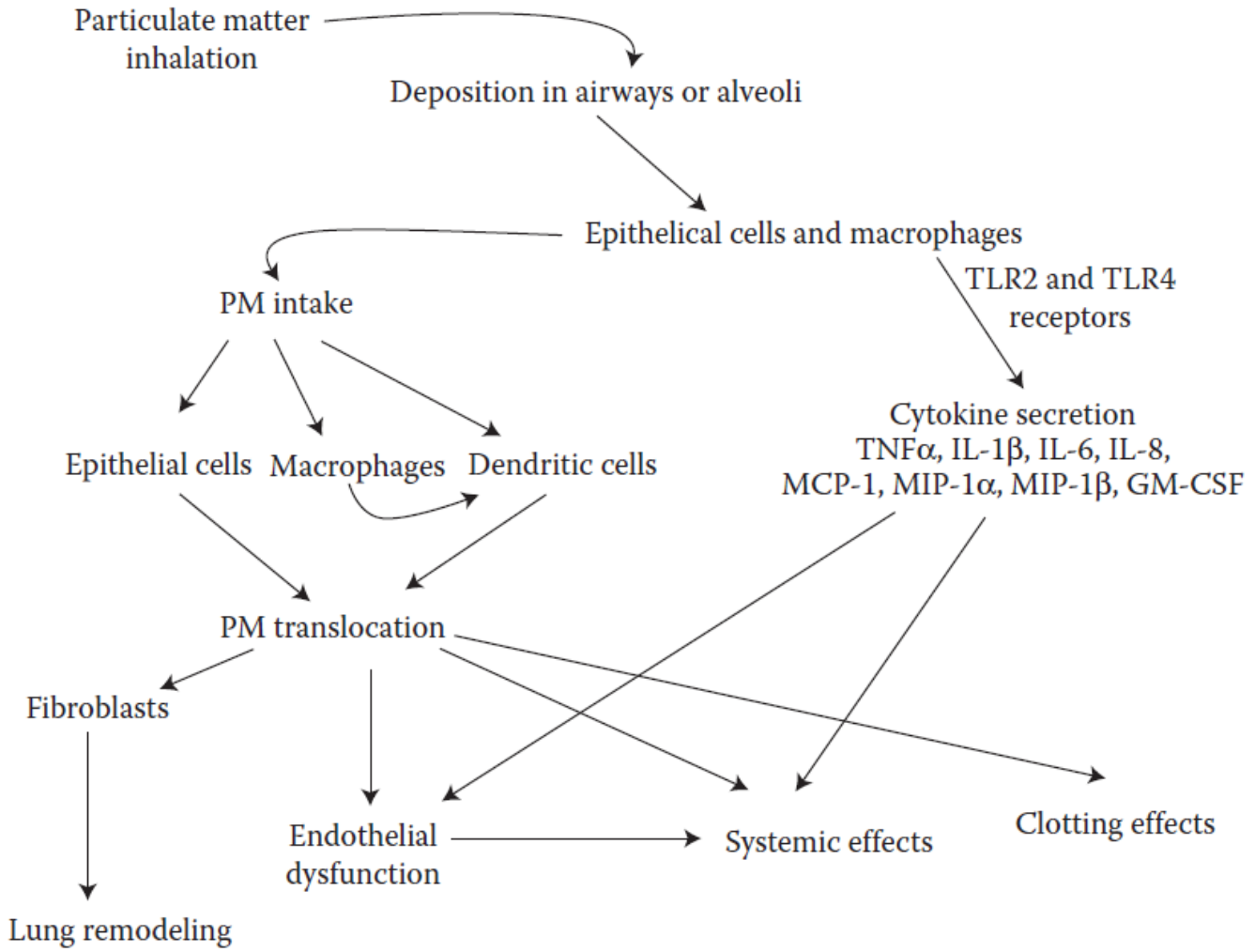
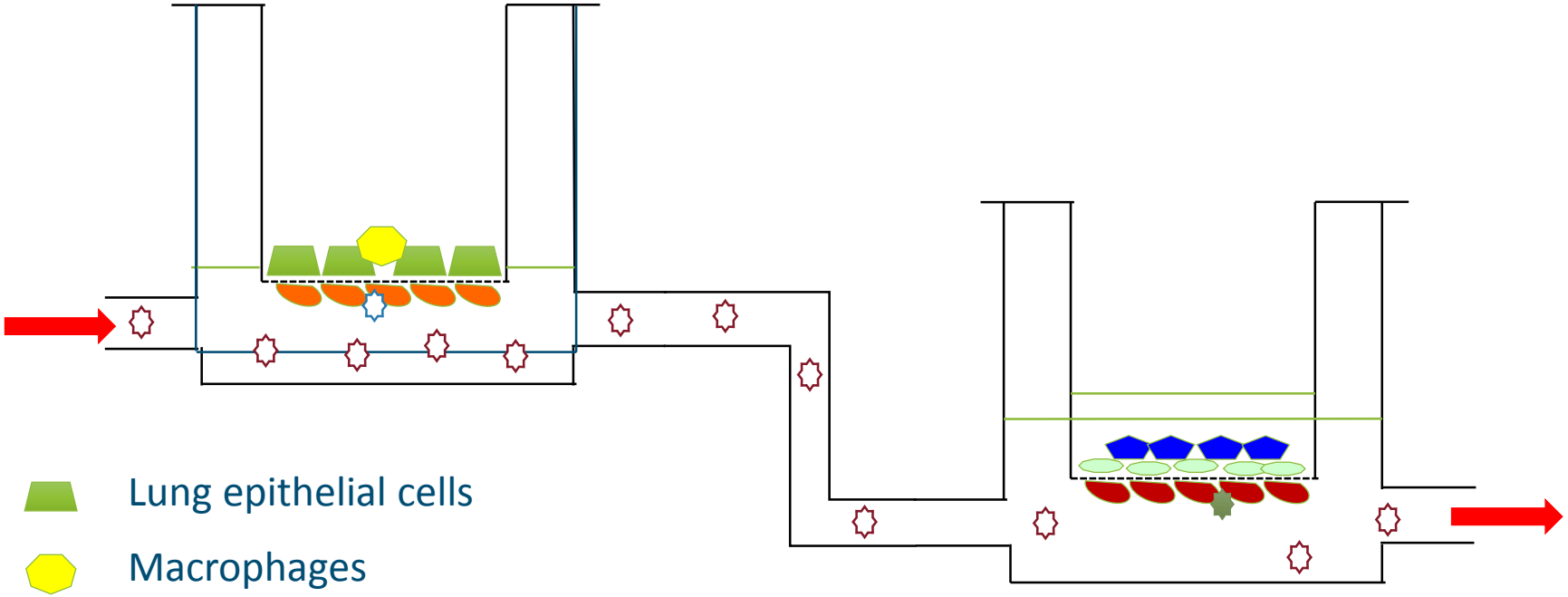


FIGURE 9.3 Possible chain of events related to PM exposure. Deposited PM in the airways or the alveoli can induce the production of cytokines that will activate other cells creating local or even a systemic effect. The translocation of the PM may explain effects induced by PM at distant sites.

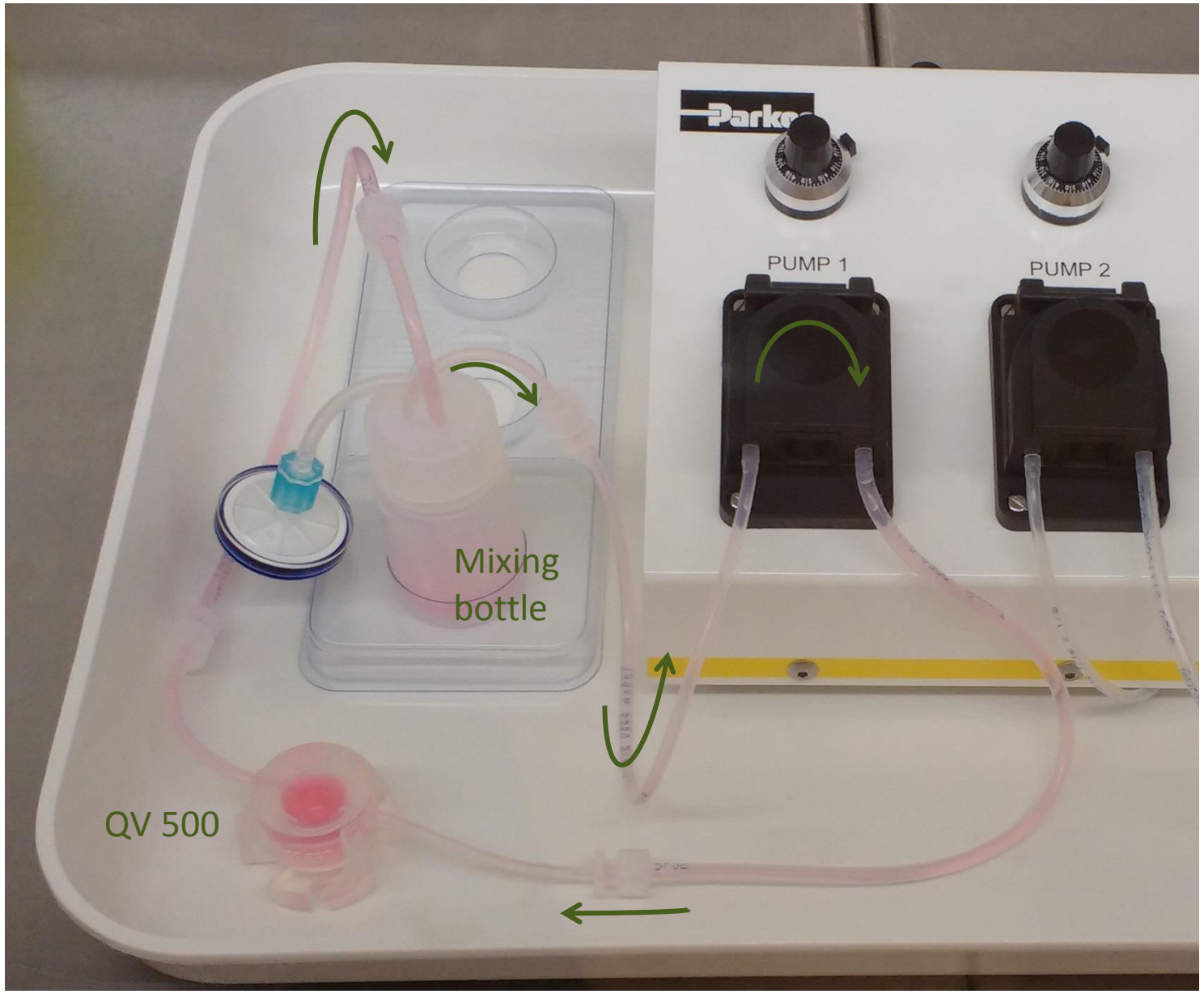
Alfaro-Moreno et al. "Air Pollution: Health & Environmental Impacts" Taylor & Francis, 2010

Developing new models



- Lung epithelial cells
- Macrophages
- Lung endothelial cells
- Endothelial cells
- Different organ(s)
- Cancer cells?
- Monocytes

Set up:
Single QV500 chamber



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