Border Air Quality Strategy

Toxicology of Urban Particulate Matter: In Vitro and In Vivo Bioassays

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Healthy Environments and Consumer Safety Branch

Second BAQS Investigator Workshop
Detroit, 21 October 2005

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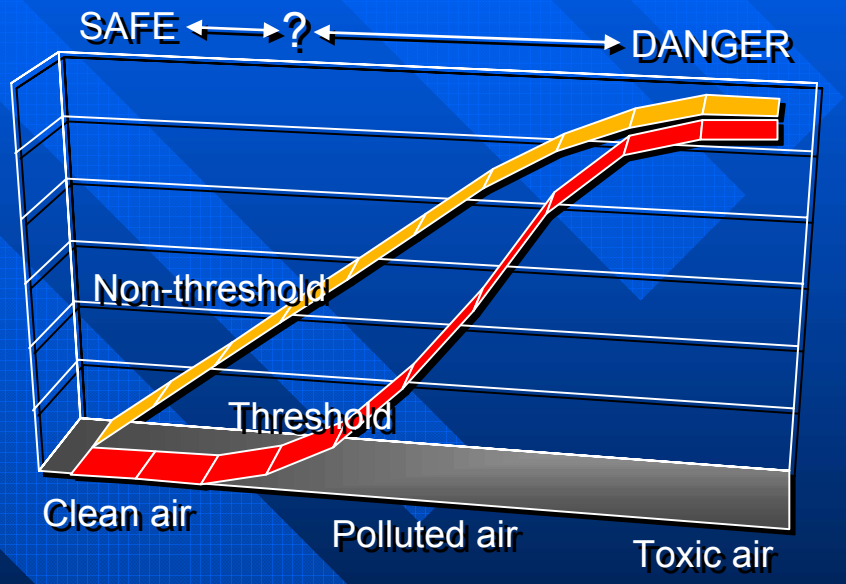
Low Levels of Air Pollution Cause Health Effects

Increase of +30 µg/m^3 $PM_{2.5}$ in southern Ontario associated the next day with +4% cardiac and +3% respiratory hospital admissions (Burnett et al, Am J Epidemiol 142:15-22, 1995)



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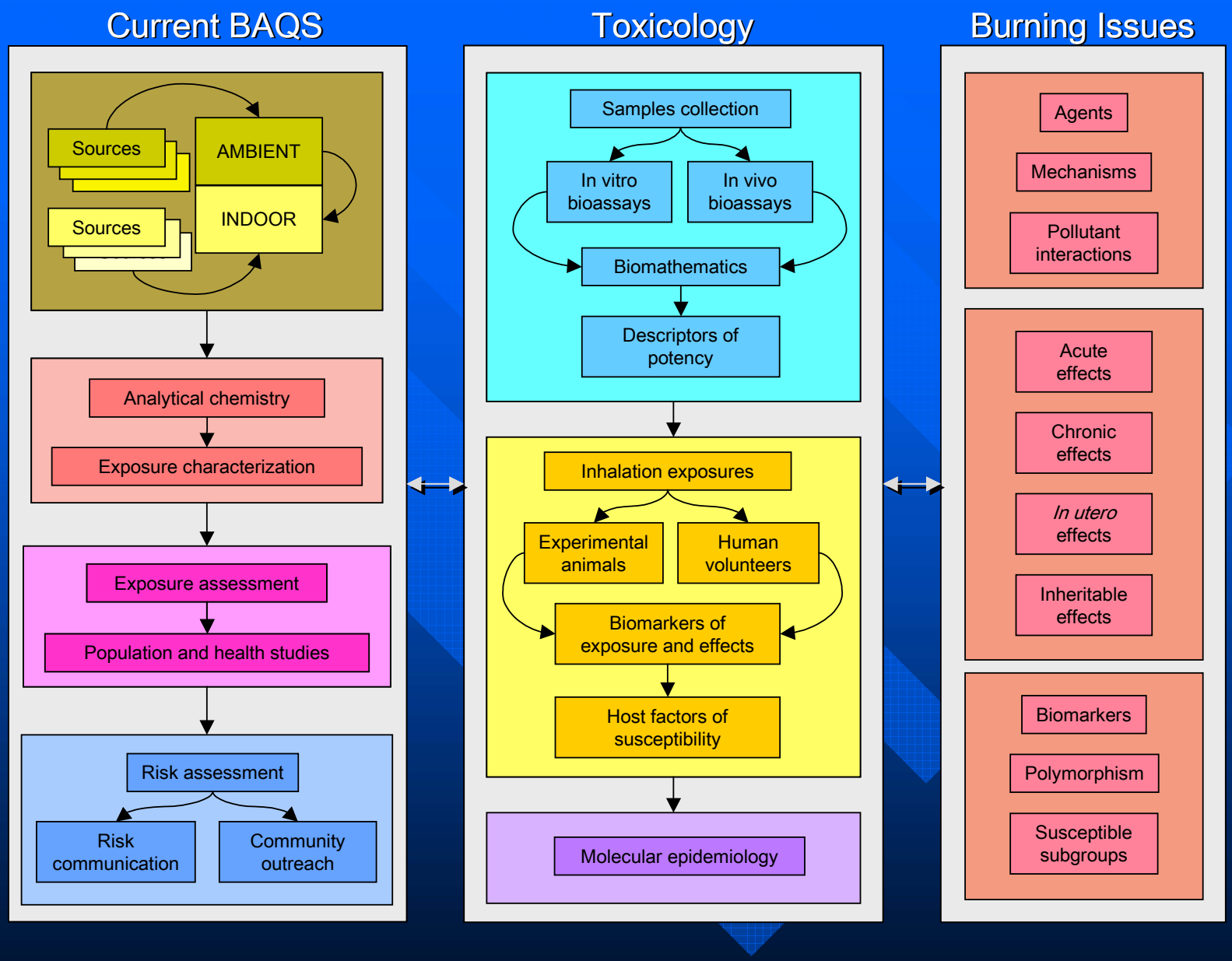

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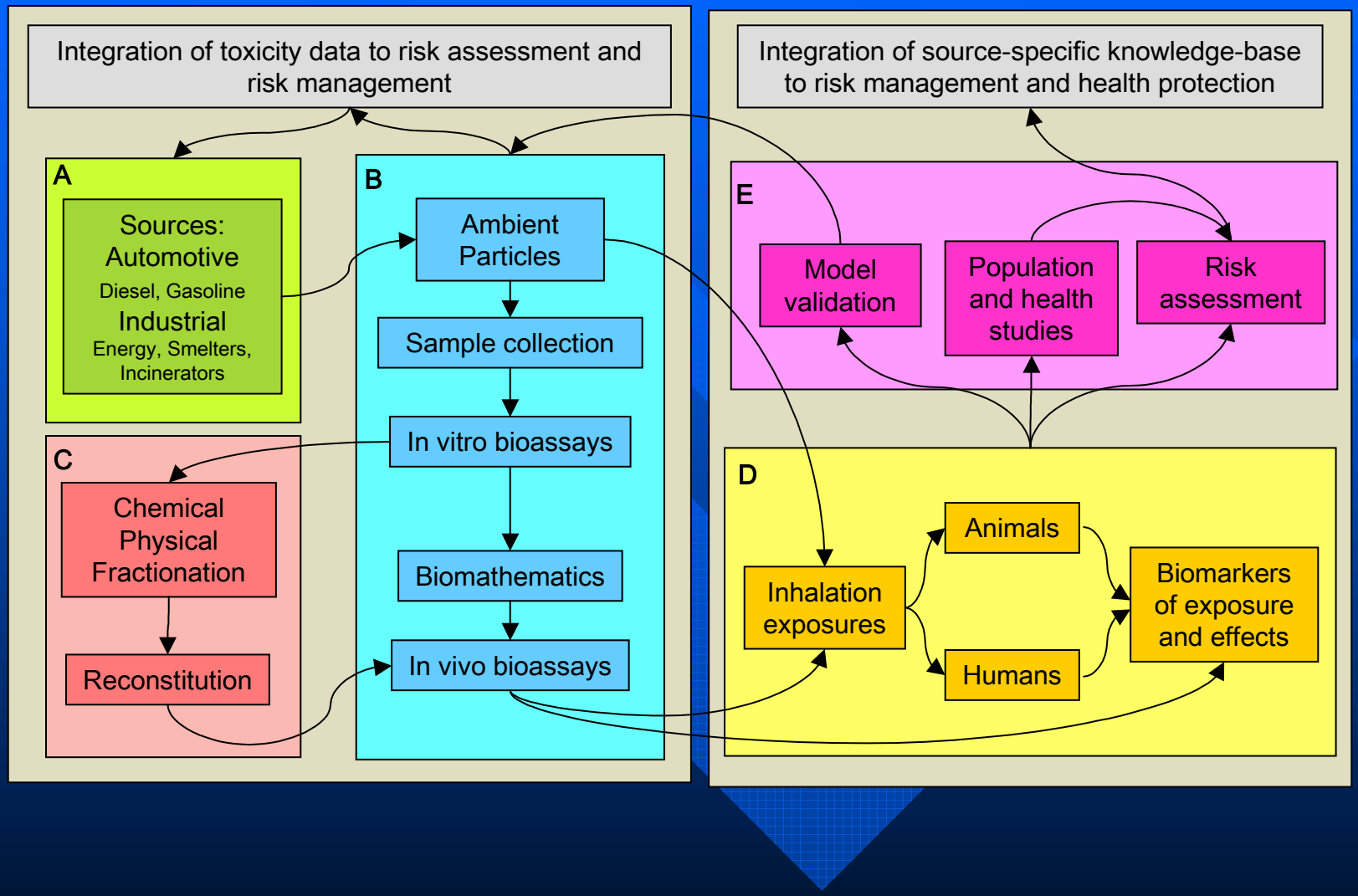
BAQS Project Strategy



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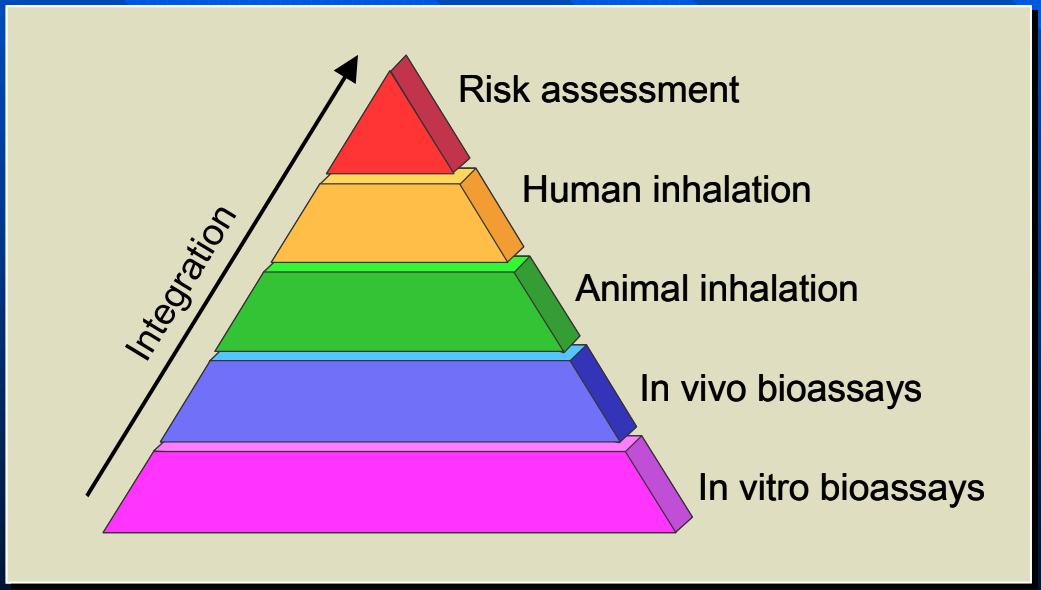
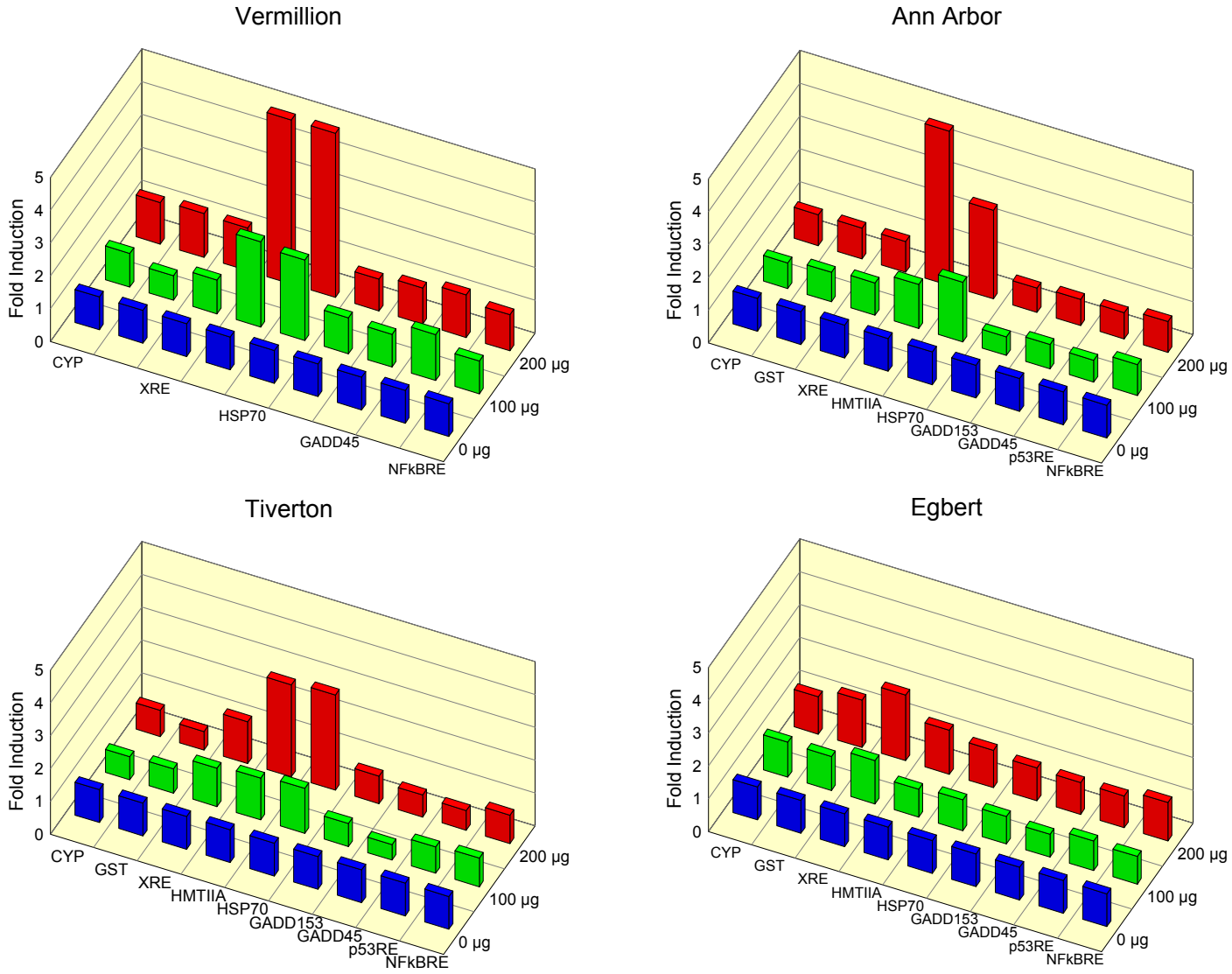
Strengths and Limitations of Assessment Approaches

	Throughput	Technical challenge	Health relevance
In vitro bioassays	*Very high*	*Very low*	*Low*
In vivo bioassays	*Medium*	*Low*	*Medium*
Animal Inhalation	*Low*	*Medium*	*High*
Human Inhalation	*None*	*High*	*Direct*





Vincent et al, Fund Appl Toxicol **39**, 18-32, 1997

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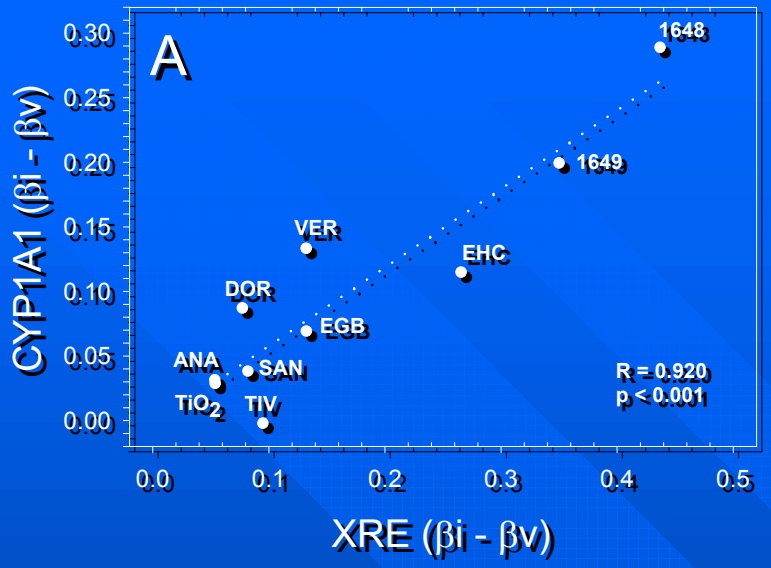

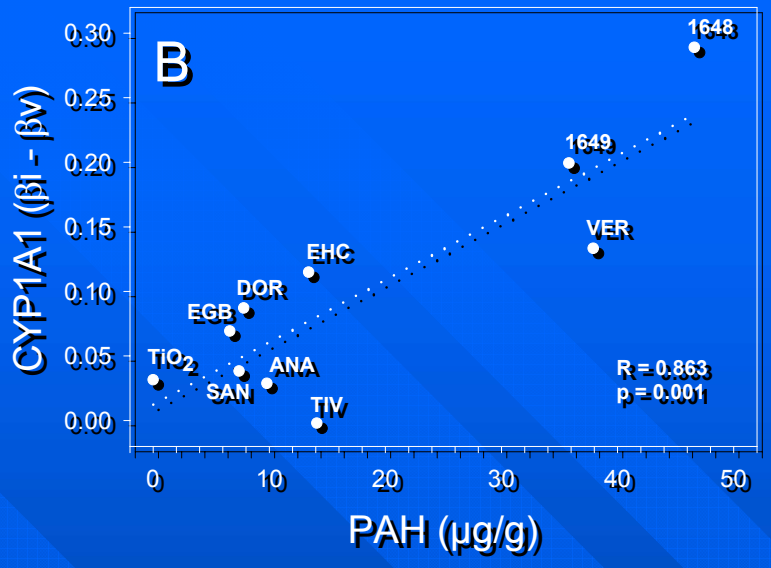

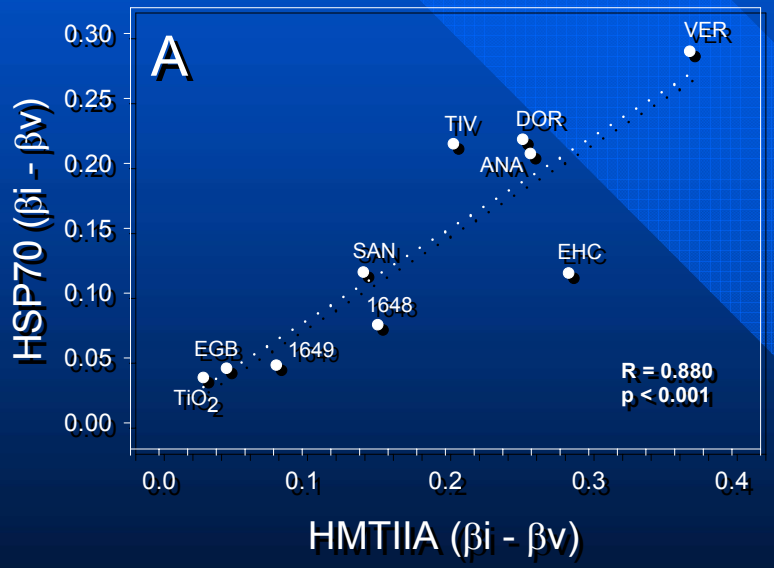

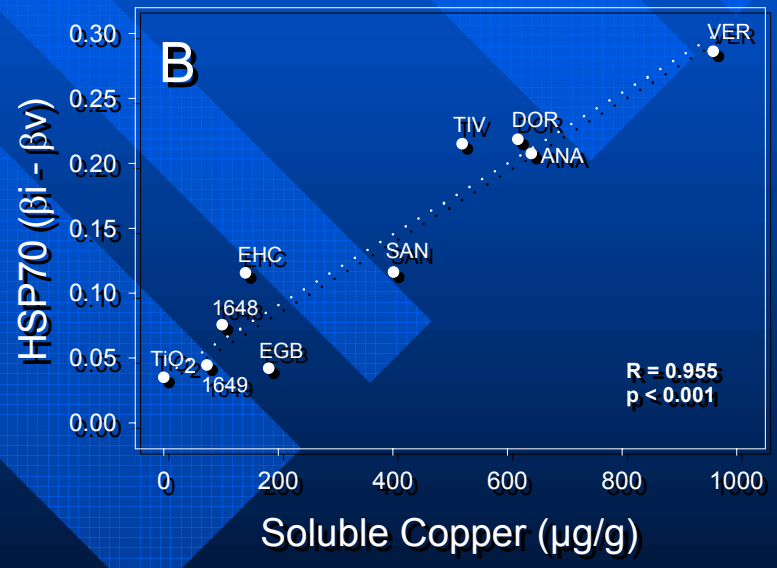

Vincent et al, Fund Appl Toxicol **39**, 18-32, 1997

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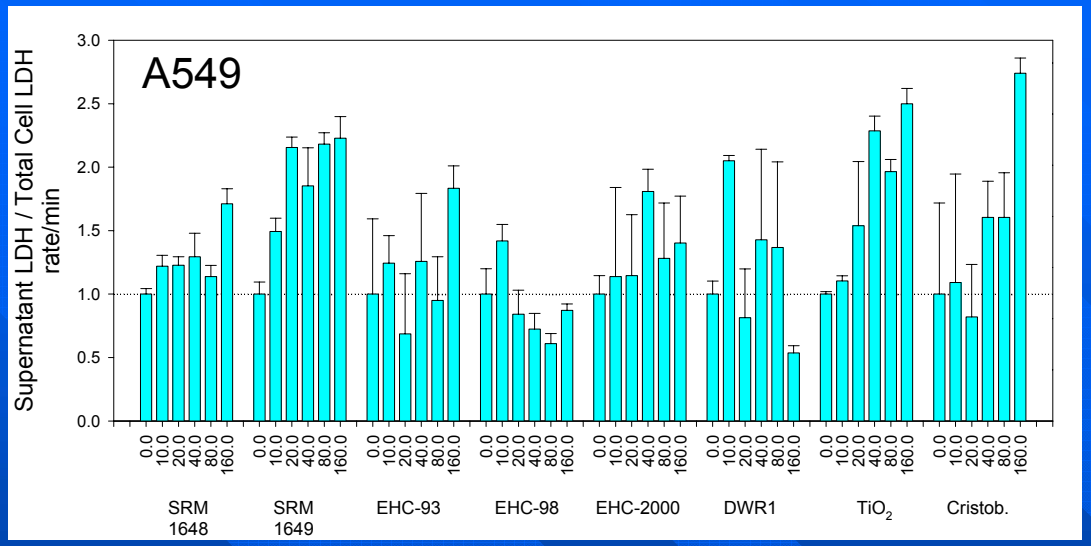
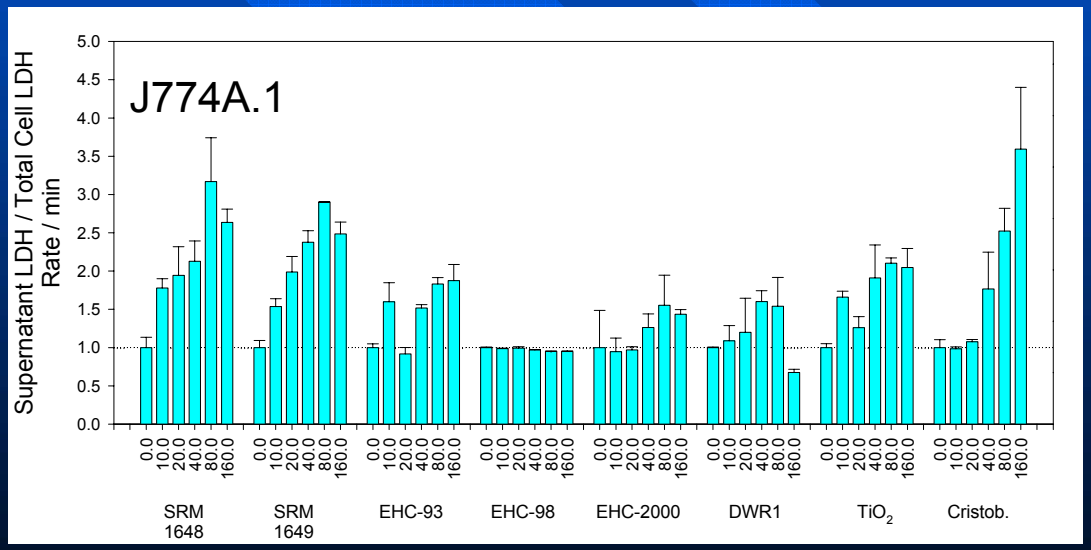
LDH permeability assay
(PM 24 h, n=3)





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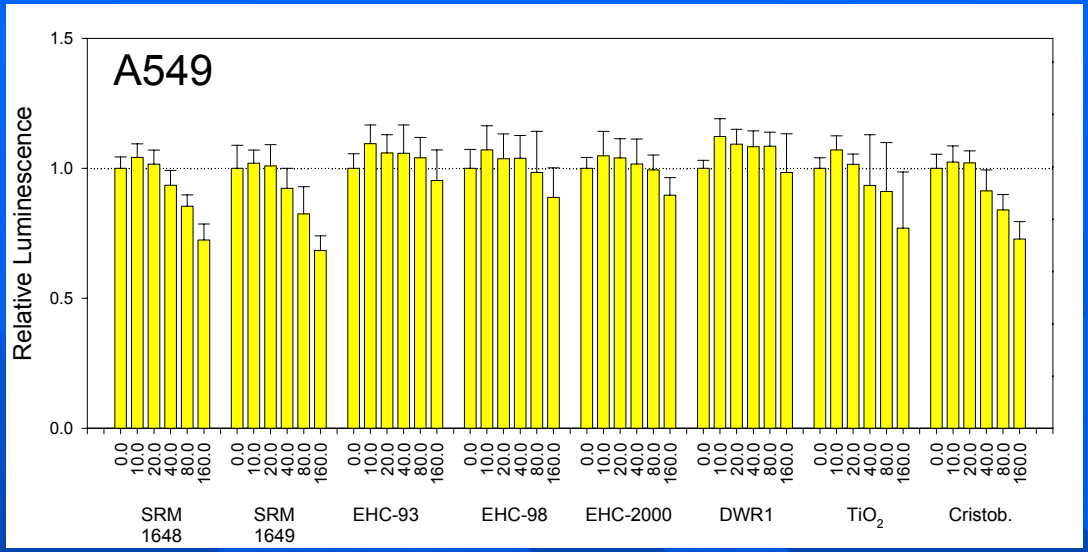
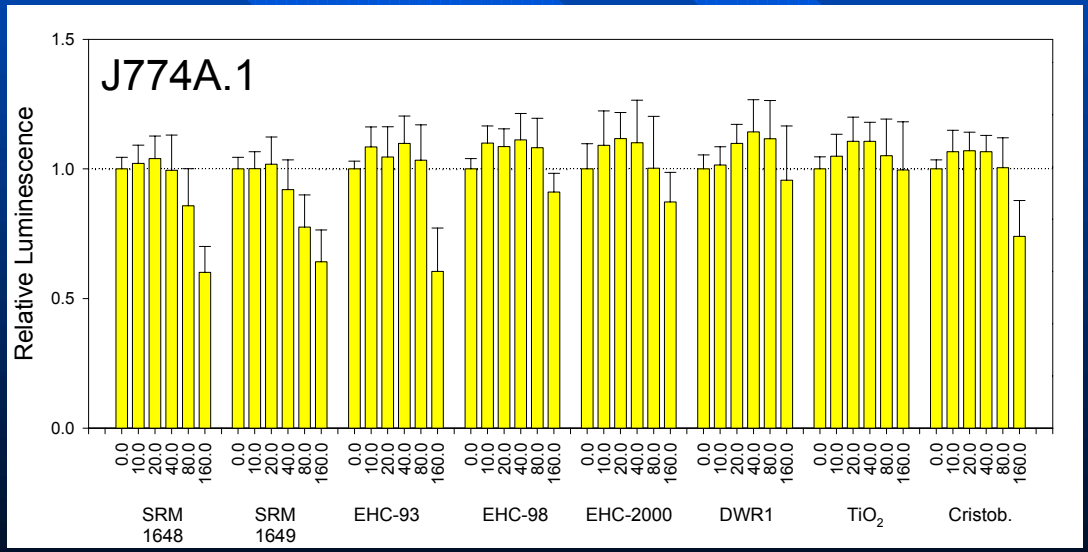
ATP metabolic assay
(PM 24 h, n=3)





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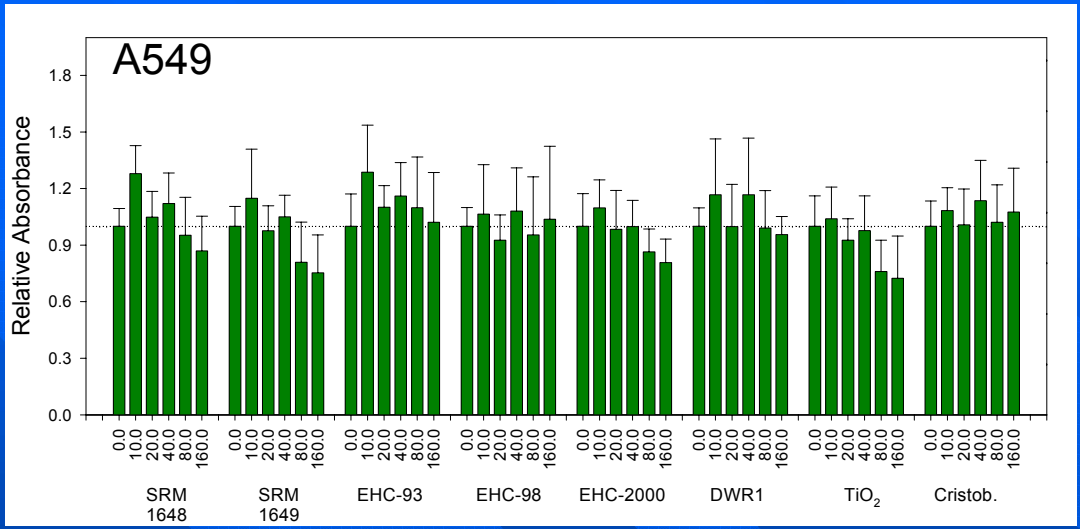
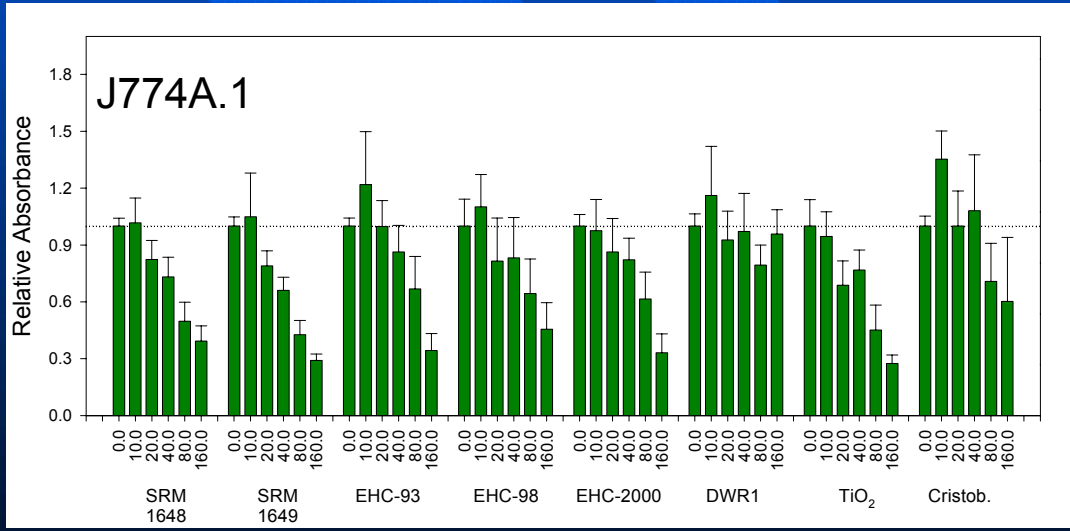
BrdU proliferation assay
(PM 24 h, n=3)





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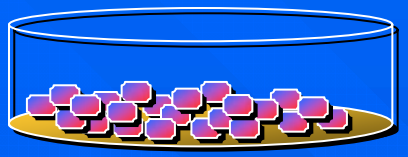
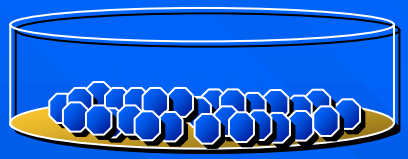
particulate matter



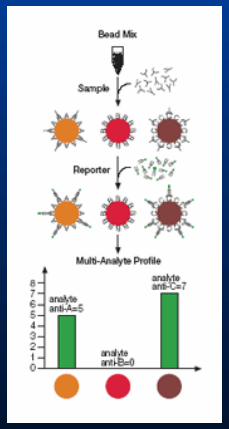
J774A.1 mouse macrophages



A549 human lung epithelial cells

cell culture supernatants

Bioplex cytokine / chemokine analysis



	IL-1β	IL-2	IL-4	IL-5	IL-6	IL-7	IL-8	IL-10	IL-12 (p70)	IL-13	IL-17	G-CSF	GM-CSF	IFN-γ	MCP-1 (MCAF)	MIP-1β	TNF-α
Human cytokine	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

	IL-1α	IL-1β	IL-2	IL-3	IL-4	IL-5	IL-6	IL-10	IL-12 (p40)	IL-12 (p70)	IL-17	G-CSF	GM-CSF	IFN-γ	KC	MIP-1α	RANTES	TNF-α
Mouse cytokine	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

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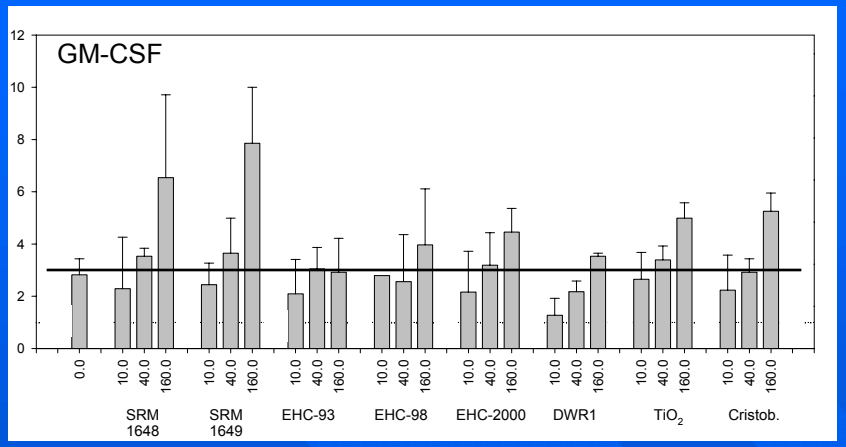
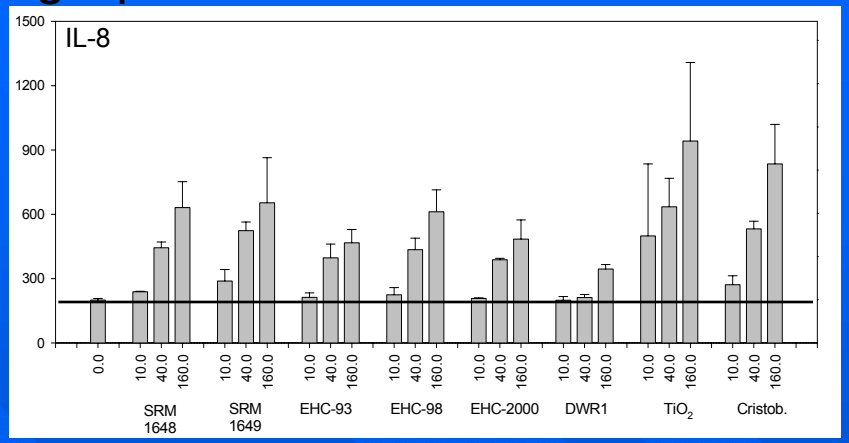
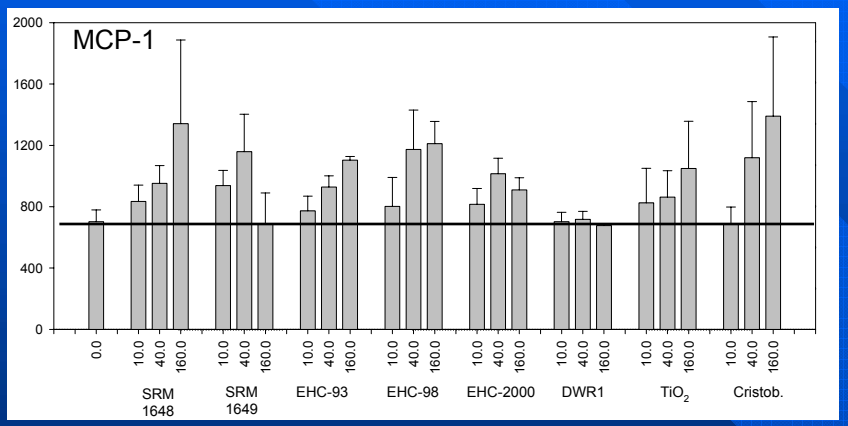
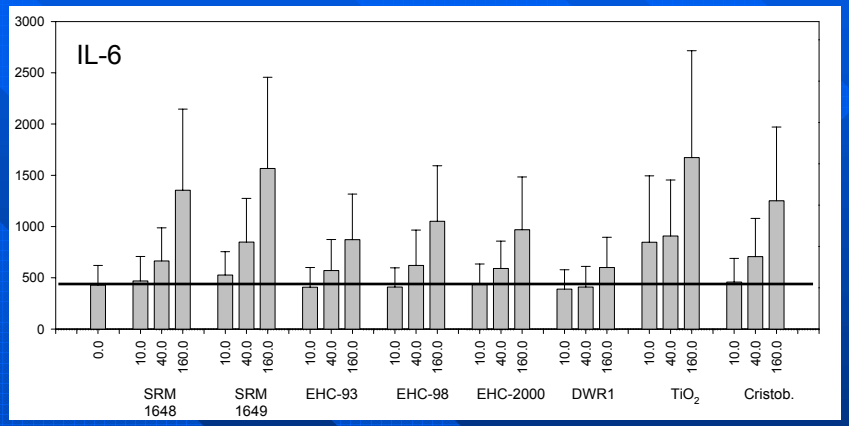
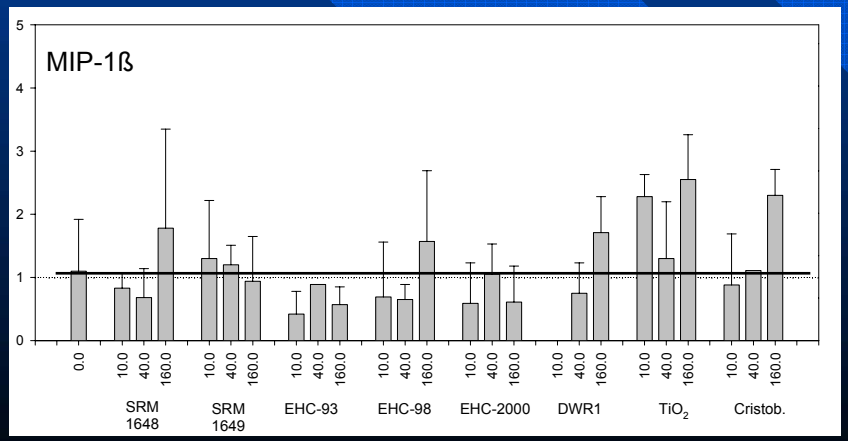
A549 Human Lung Epithelial Cells











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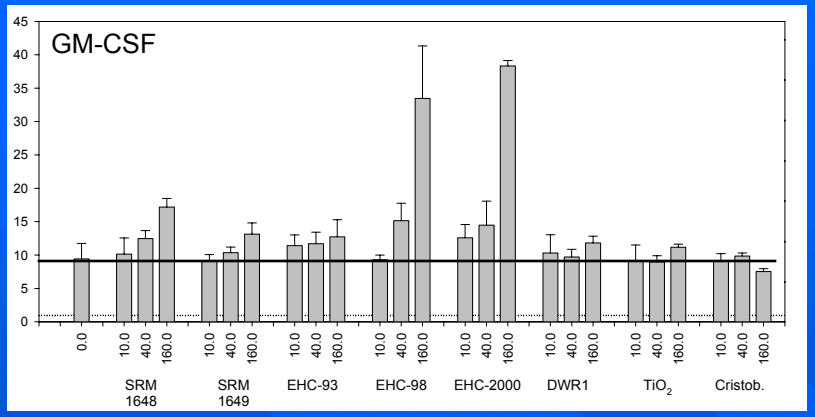
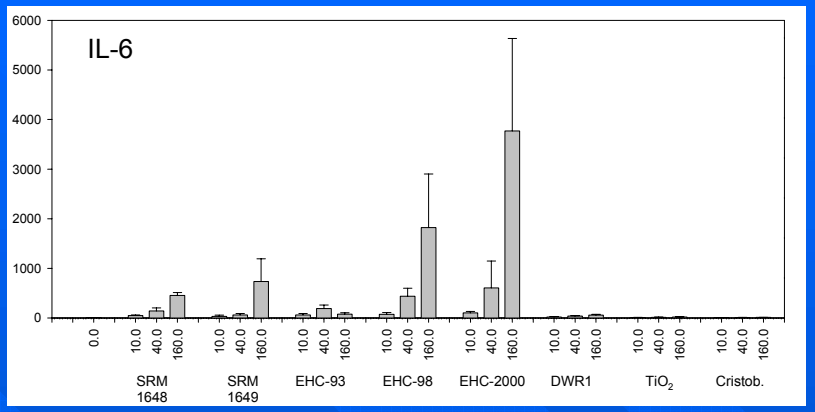
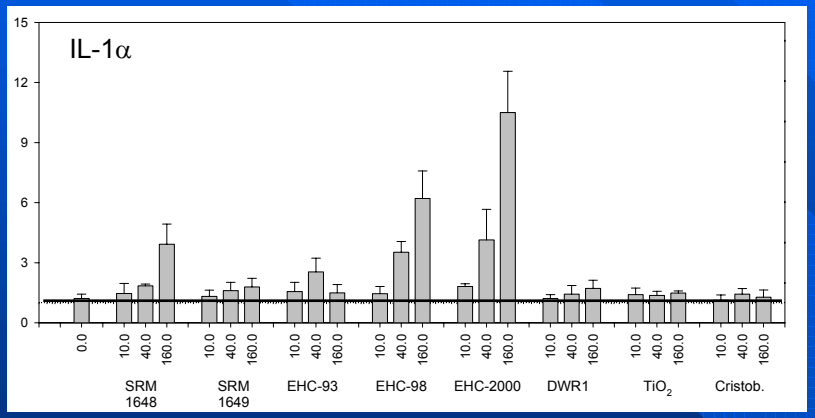
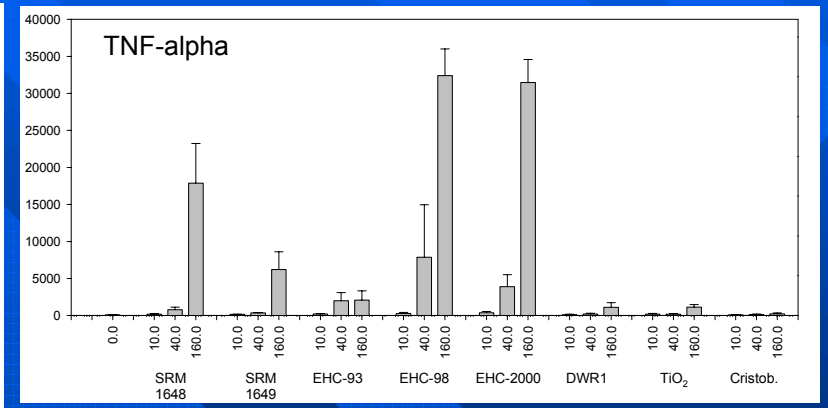
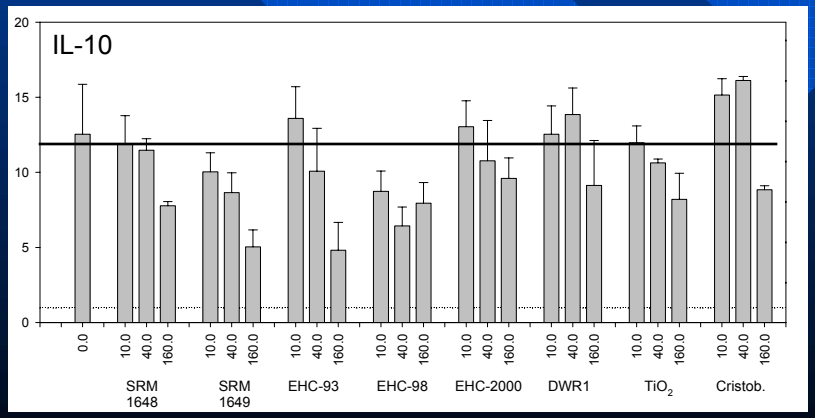
J774A.1 Mouse Monocyte Cell Line











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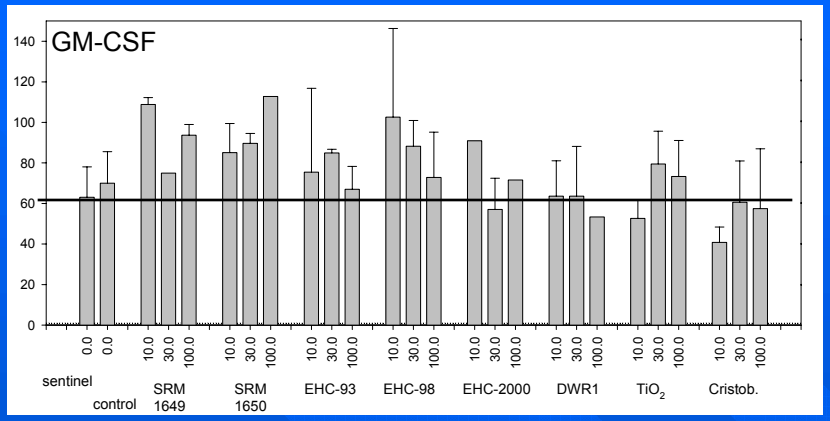
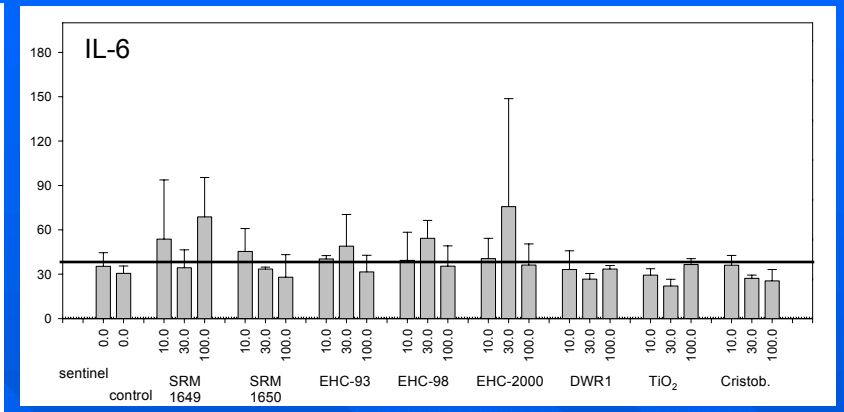
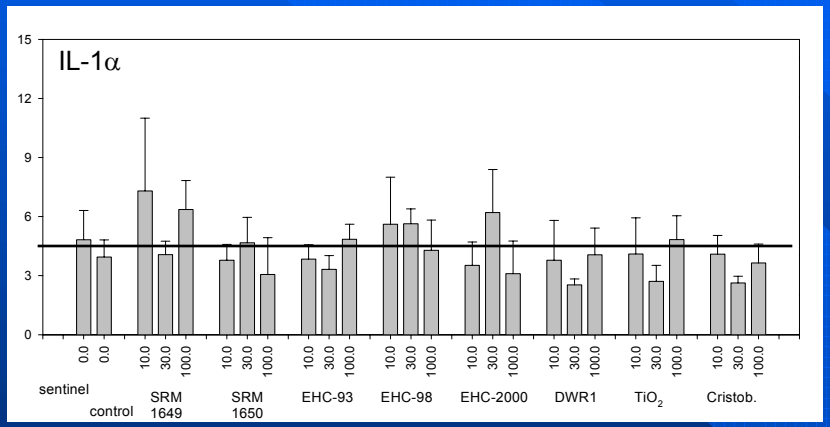
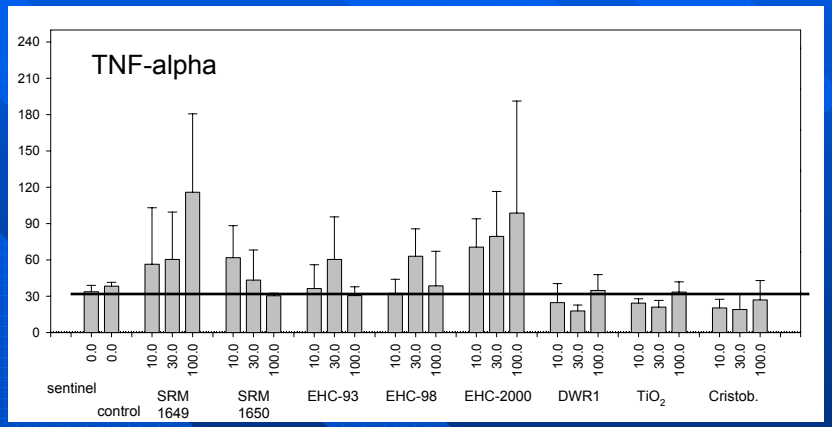
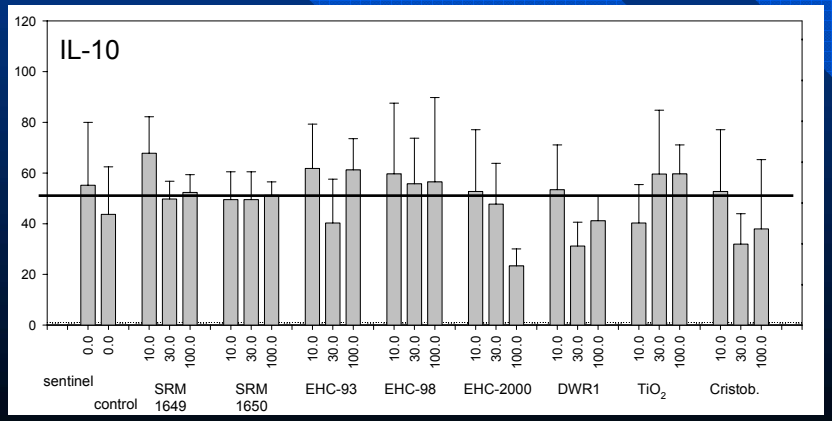
Mouse In Vivo Bioassay (BALF)











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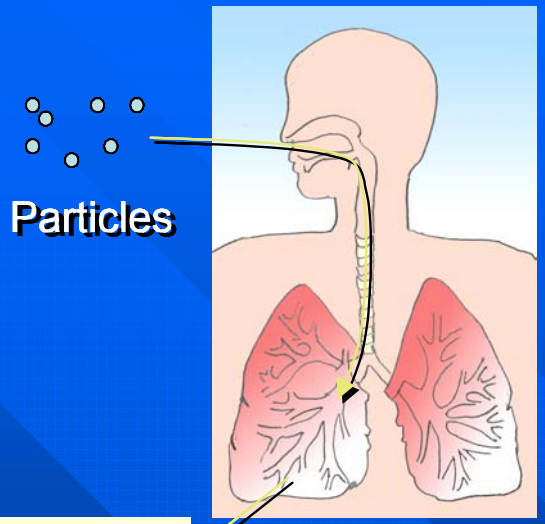
Biological Plausibility

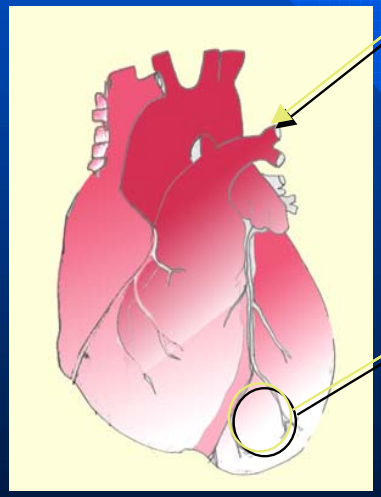
Urban particles cause elevation of circulating ET-1

Changes are sufficient to induce systemic vasoconstiction

May be compensated in healthy individuals

May not be compensated in individuals with heart diseases





Endothelin-1
Sustained higher plasma ET-1

Vasoconstriction
Hemodynamic changes

Electrophysiology
ST-segment area depression

Evidence in Rats
Correlate in time
Maximal effects 36h post

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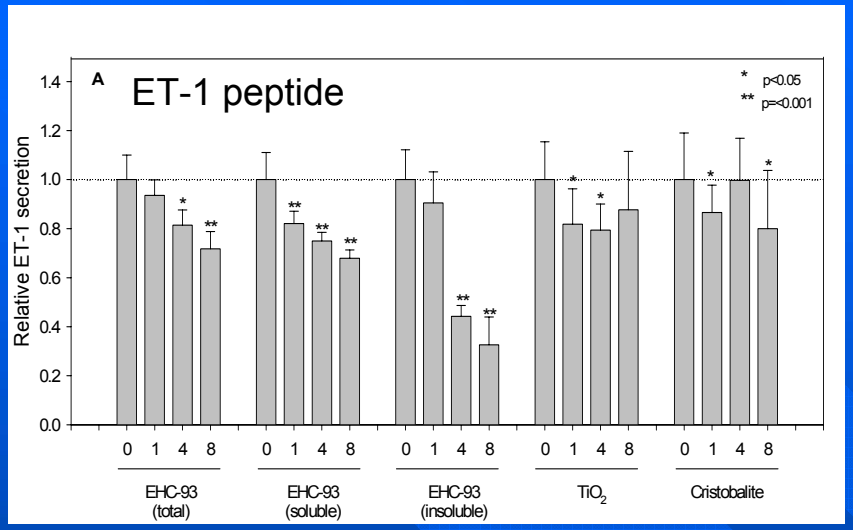
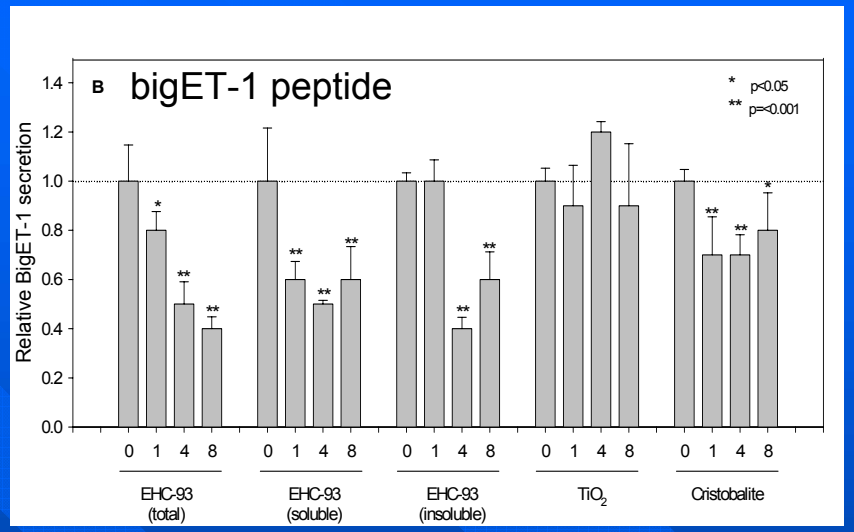
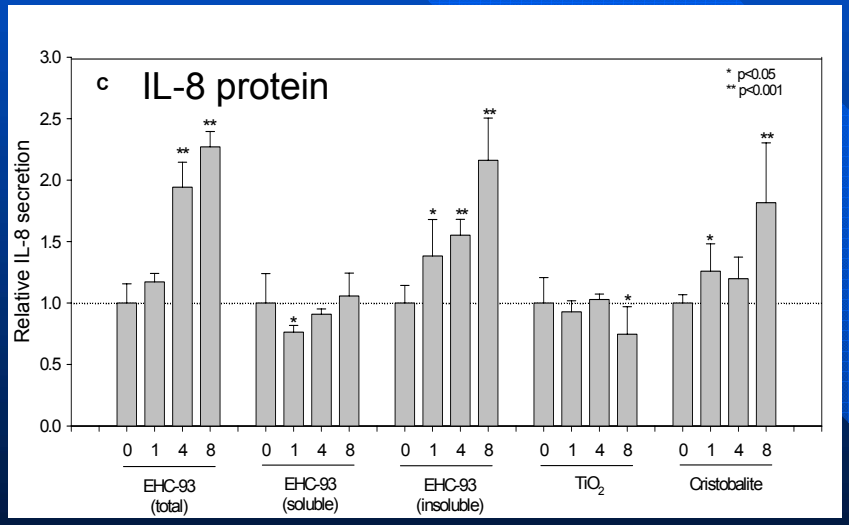
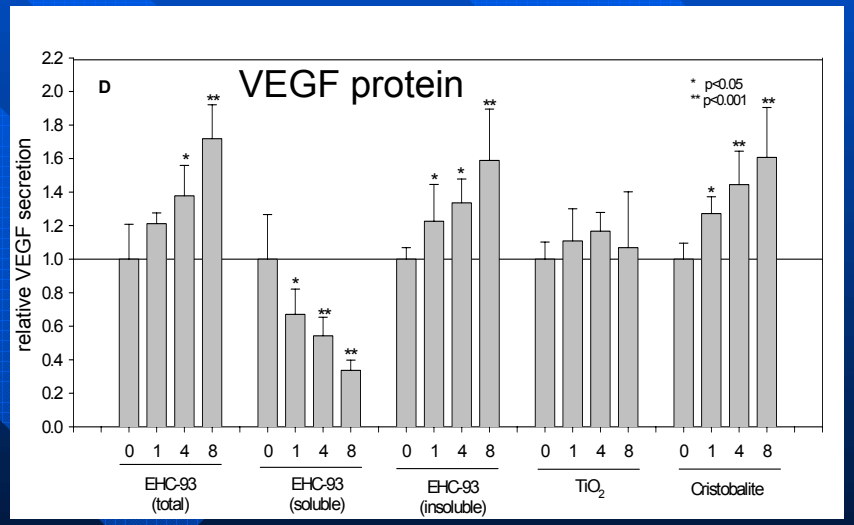
A549 Human Lung Epithelial Cells









Chauhan et al, Cell Biol Toxicol 2005 (in press)

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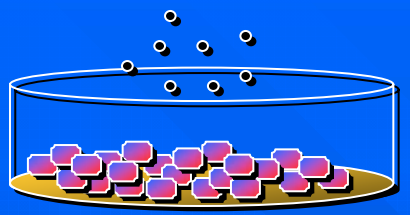
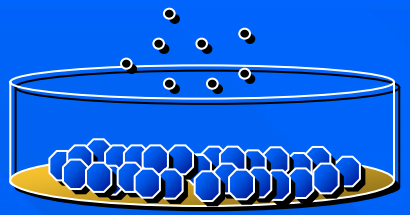
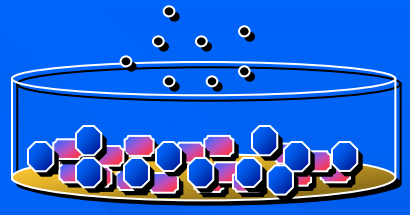
In Vitro Cardiovascular Model



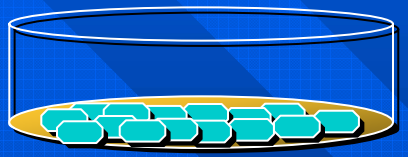
Human macrophages
THP-1



Human lung epithelial
cells A549

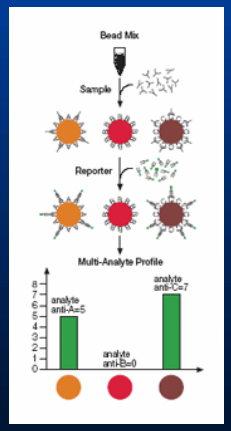


A549 + THP-1
Co-culture

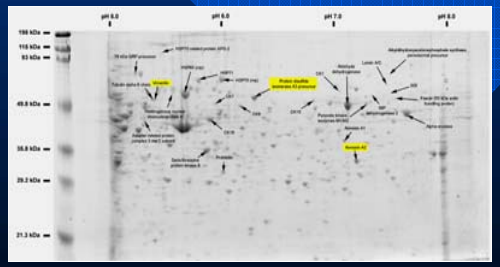


Human pulmonary artery
endothelial cells
HPAE

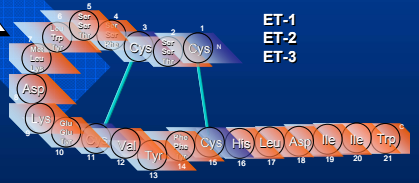
Bioplex protein
liquid arrays



Proteomics



Endothelin
isoforms



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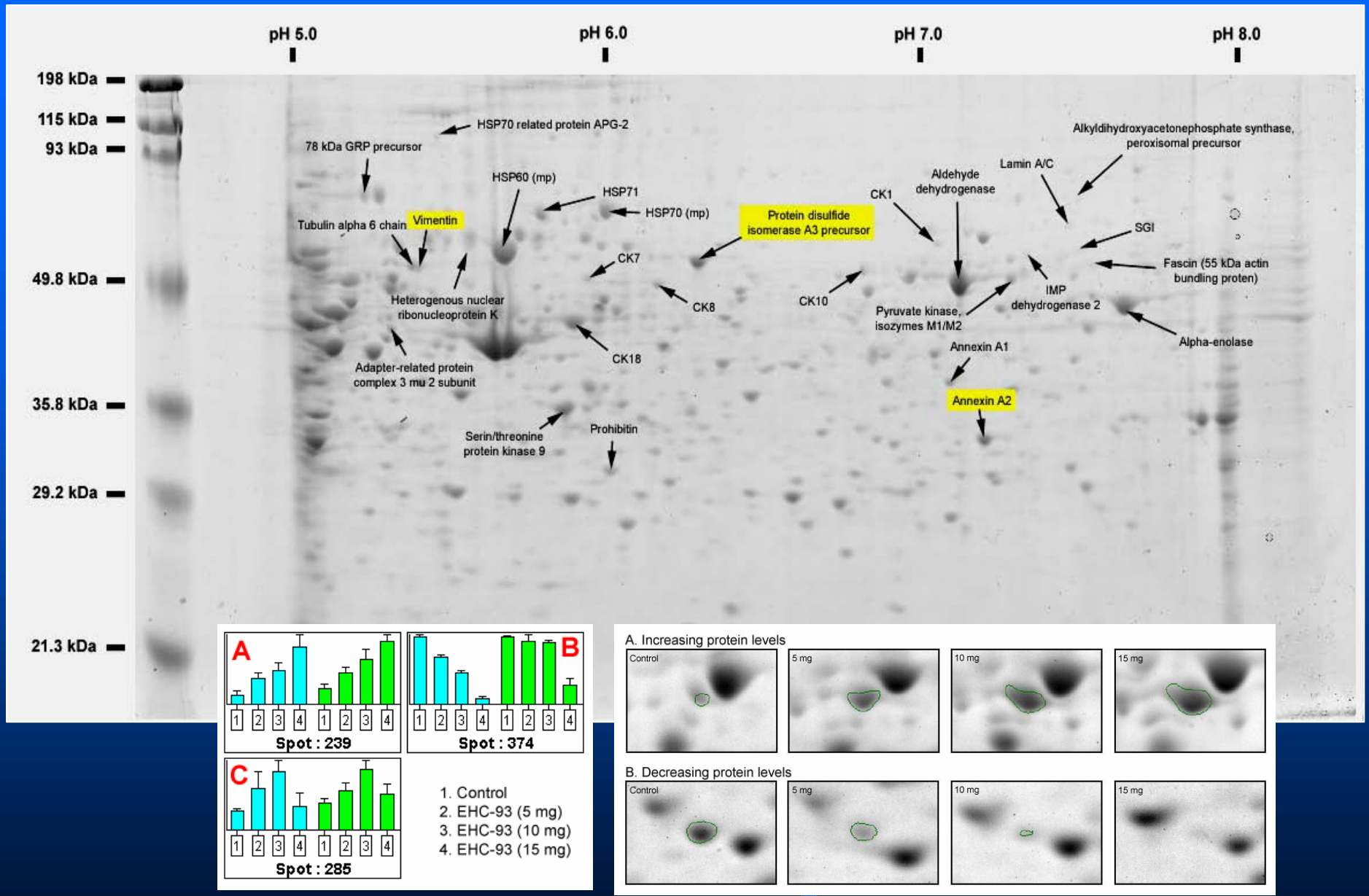

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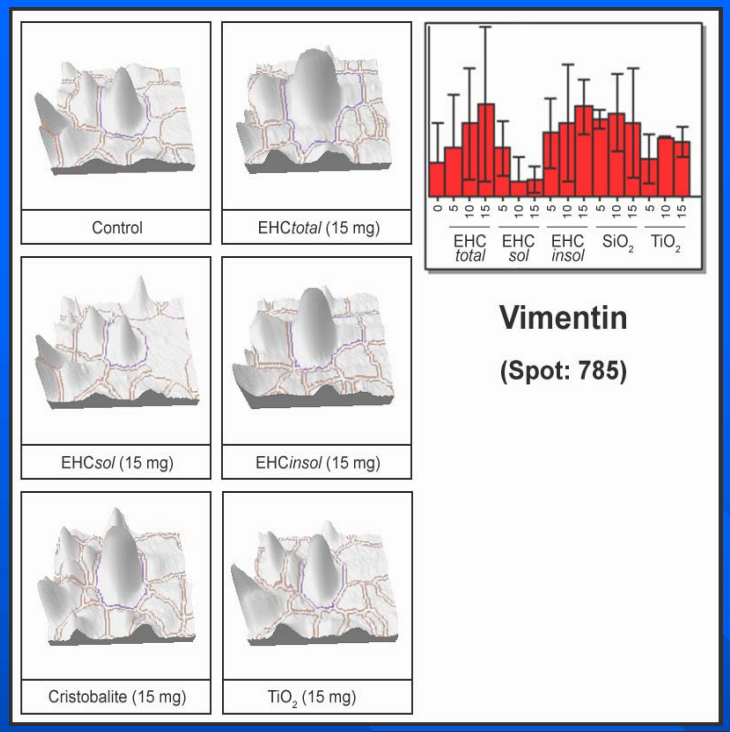
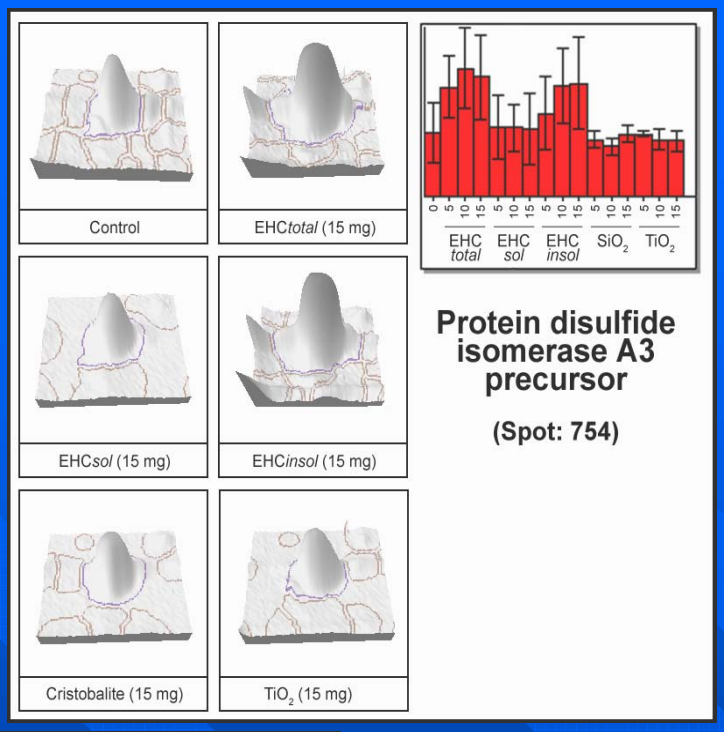


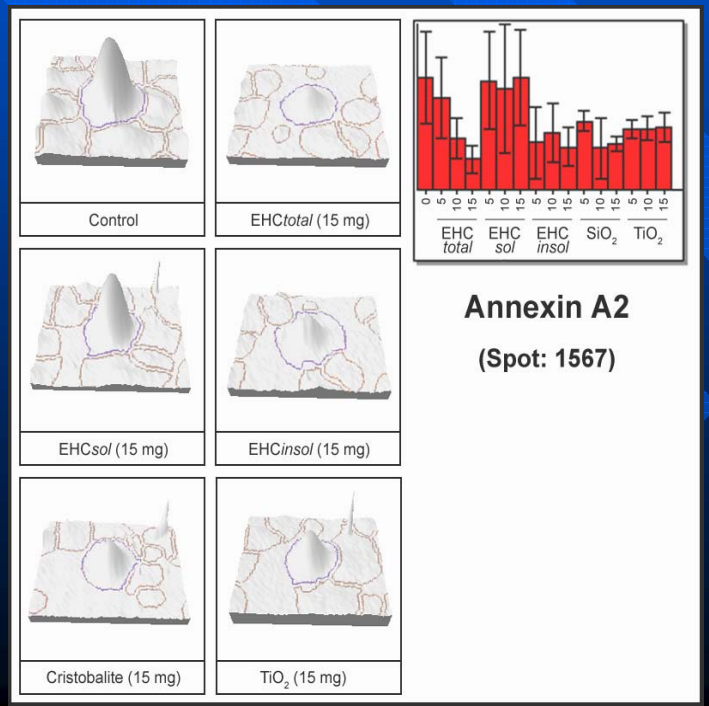
Vimentin

(Spot: 785)



Protein disulfide isomerase A3 precursor

(Spot: 754)



Annexin A2

(Spot: 1567)

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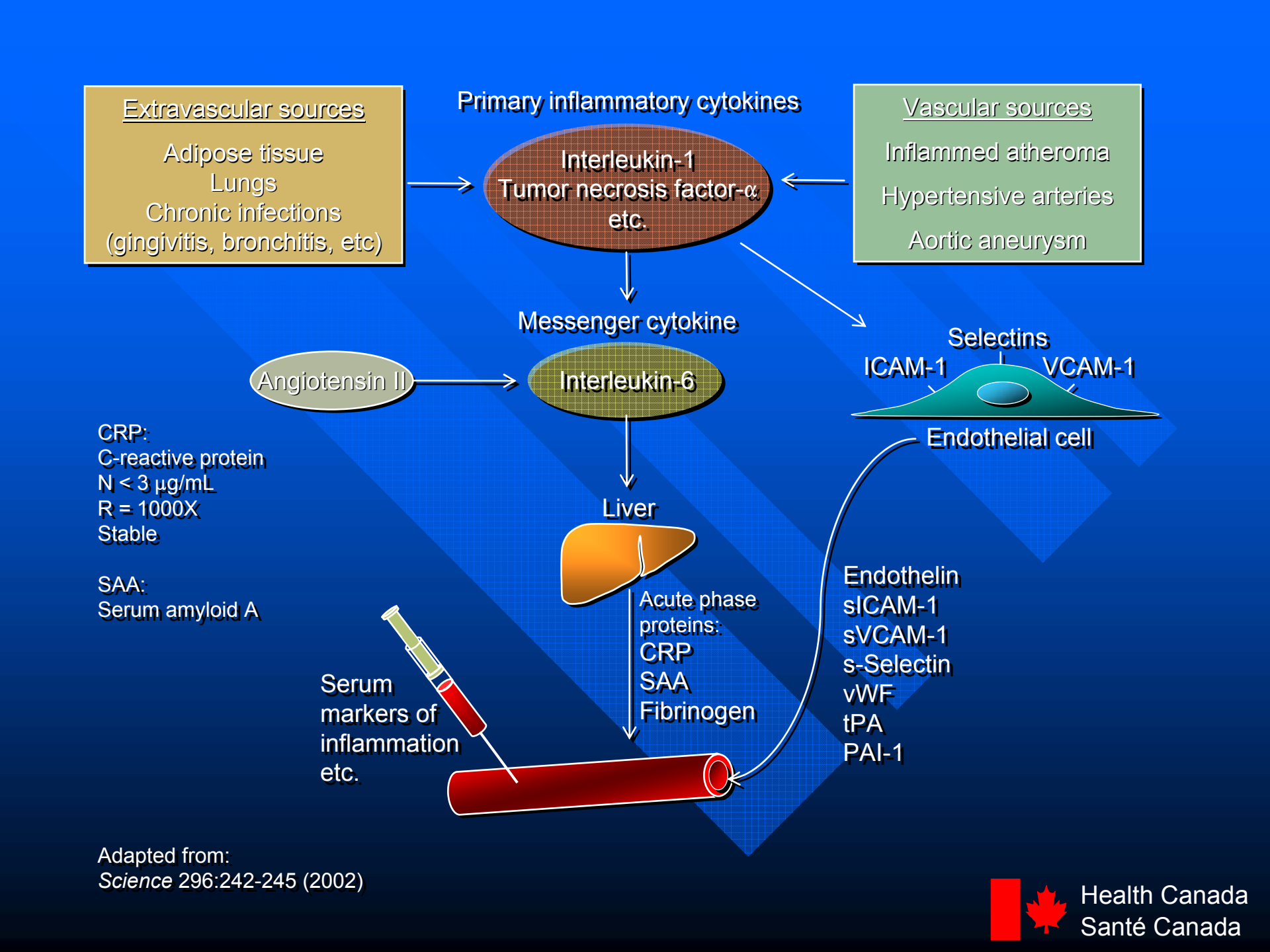
Extravascular sources
Adipose tissue
Lungs
Chronic infections
(gingivitis, bronchitis, etc)
Primary inflammatory cytokines
Interleukin-1
Tumor necrosis factor-α
etc.
Vascular sources
Inflammed atheroma
Hypertensive arteries
Aortic aneurysm
Messenger cytokine
Angiotensin II
Interleukin-6
Selectins
ICAM-1
VCAM-1
Endothelial cell
CRP:
C-reactive protein
N < 3 µg/mL
R = 1000X
Stable
SAA:
Serum amyloid A
Liver
Acute phase proteins:
CRP
SAA
Fibrinogen
Endothelin
sICAM-1
sVCAM-1
s-Selectin
vWF
tPA
PAI-1
Serum markers of inflammation etc.
Adapted from:
Science 296:242-245 (2002)
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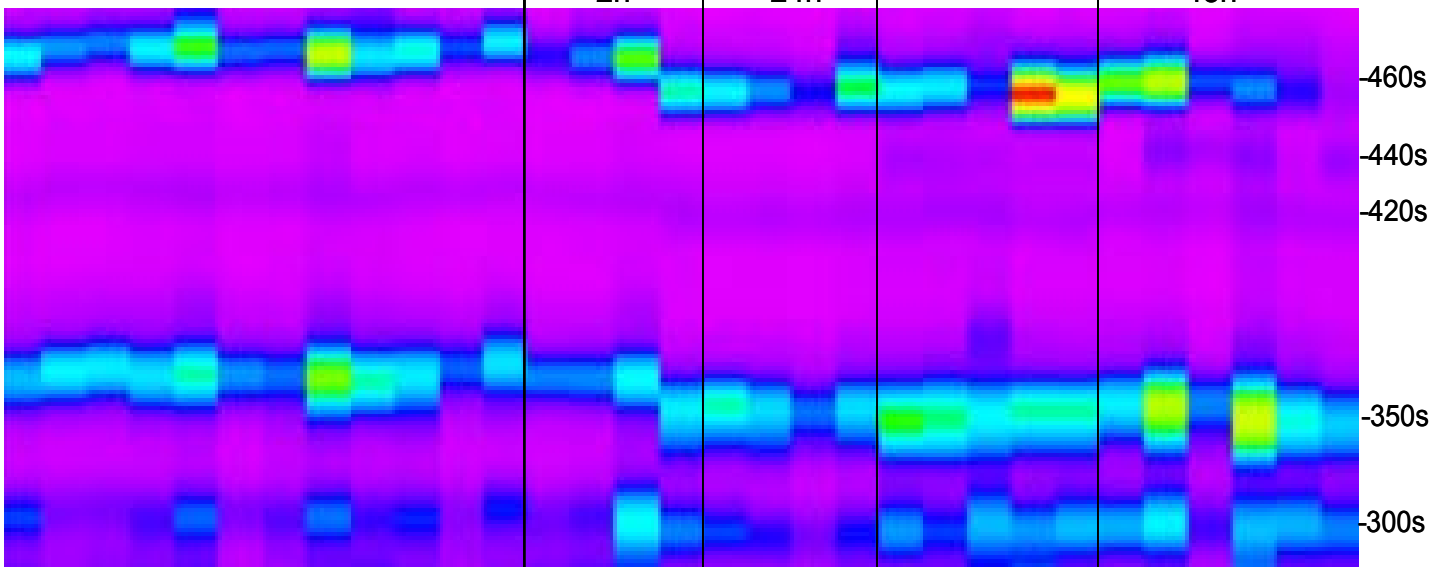

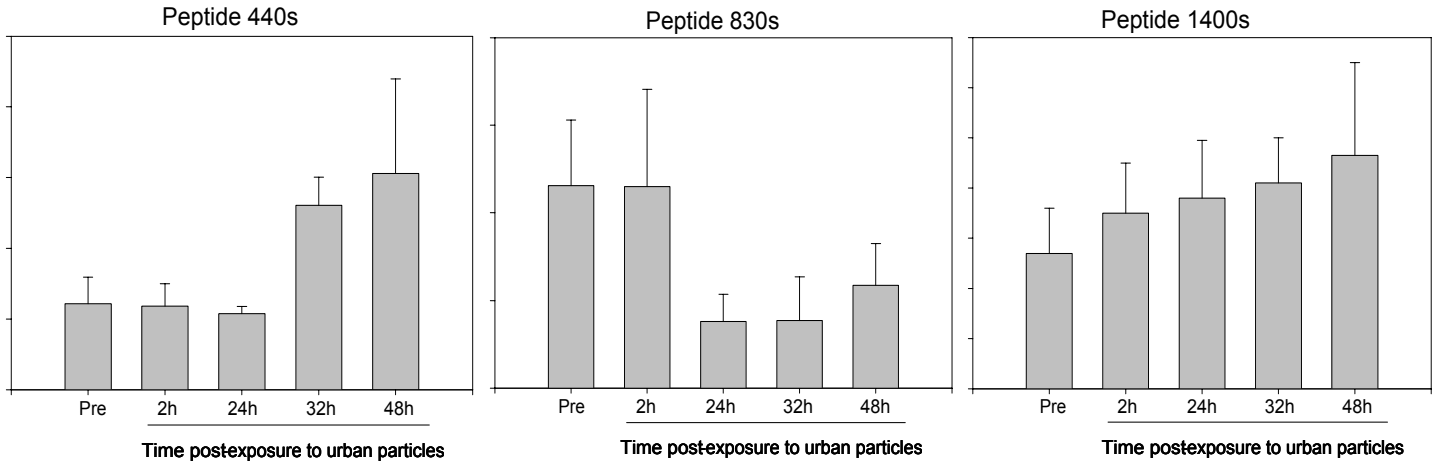

Health Canada
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Support

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Border Air Quality Strategy

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