Health Effects from Exposure to Ultrafine Particles

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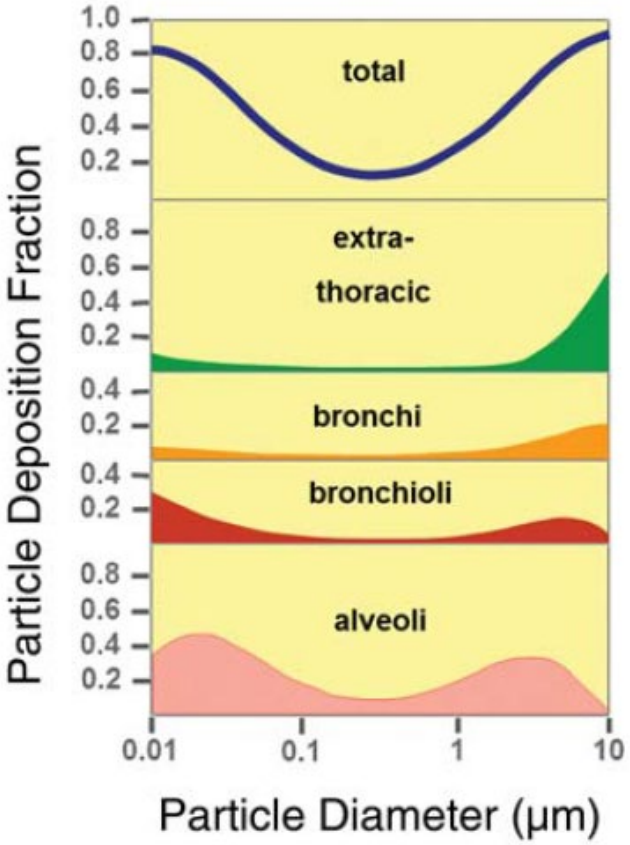
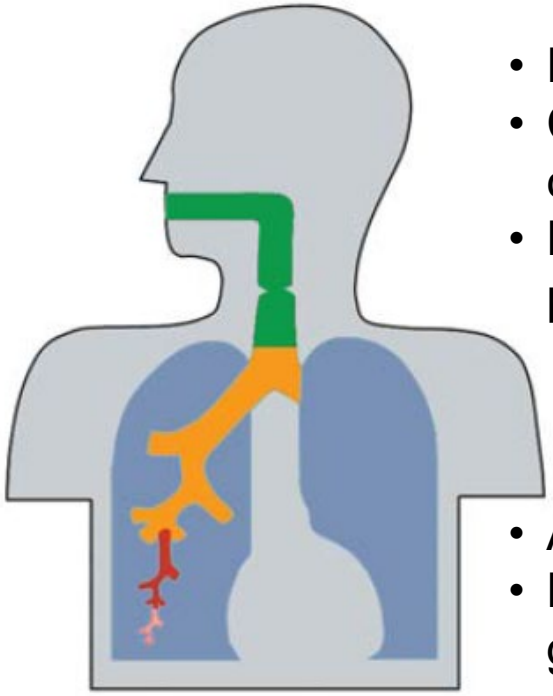
Physical characteristics lead to alveoli deposition





Particle density: 1 g cm^{-3}
Respiratory flow rate: 300 cm^3 s^{-1}
Mouth breathing at rest, cycle period: 5 s

Small size

- High alveolar deposition
- Can escape alveolar clearing mechanisms
- Diffusion through physiologic membranes

High surface area

- Adsorption of toxins
- Place for oxygen radical generation

Kreyling et al. 2006

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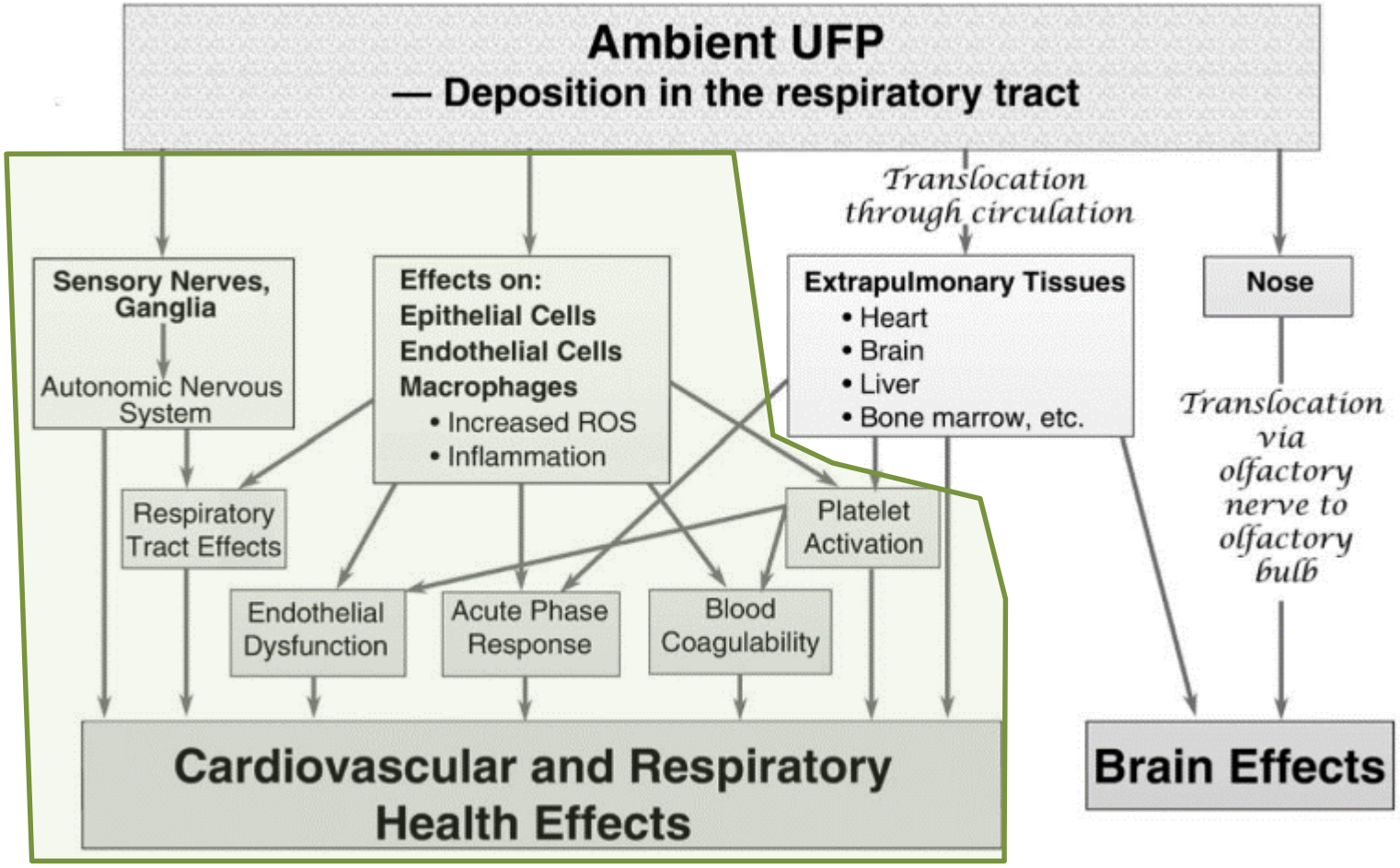
Biological mechanisms



HEI Perspectives 3, 2013

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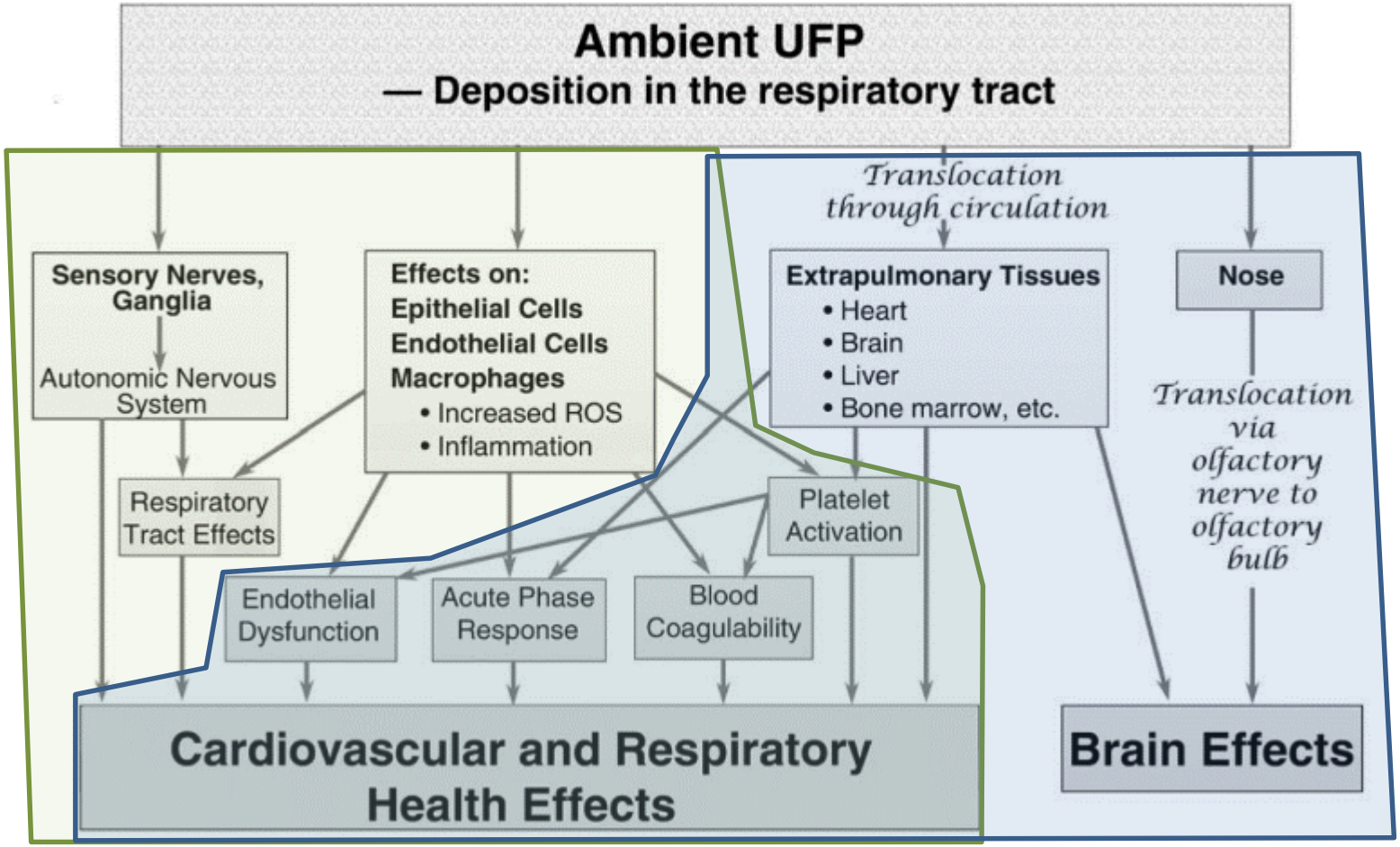
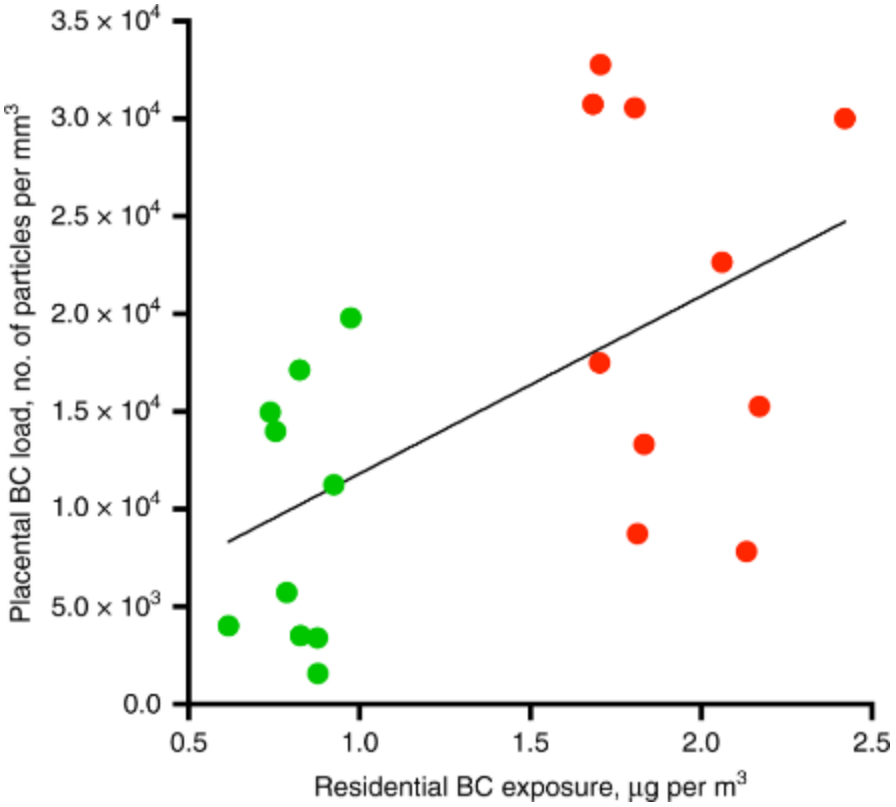
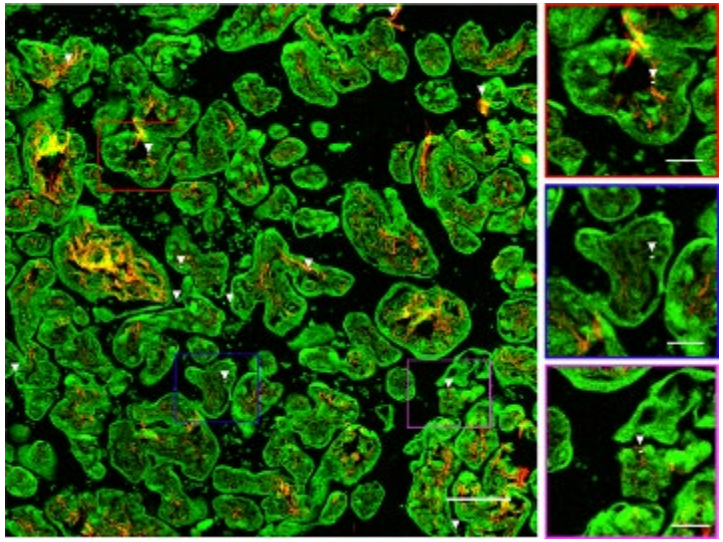
Biological mechanisms



HEI Perspectives 3, 2013

UFP-related black carbon found in human placenta





Bové et al. *Nature Communications* **10**, 3866, 2019

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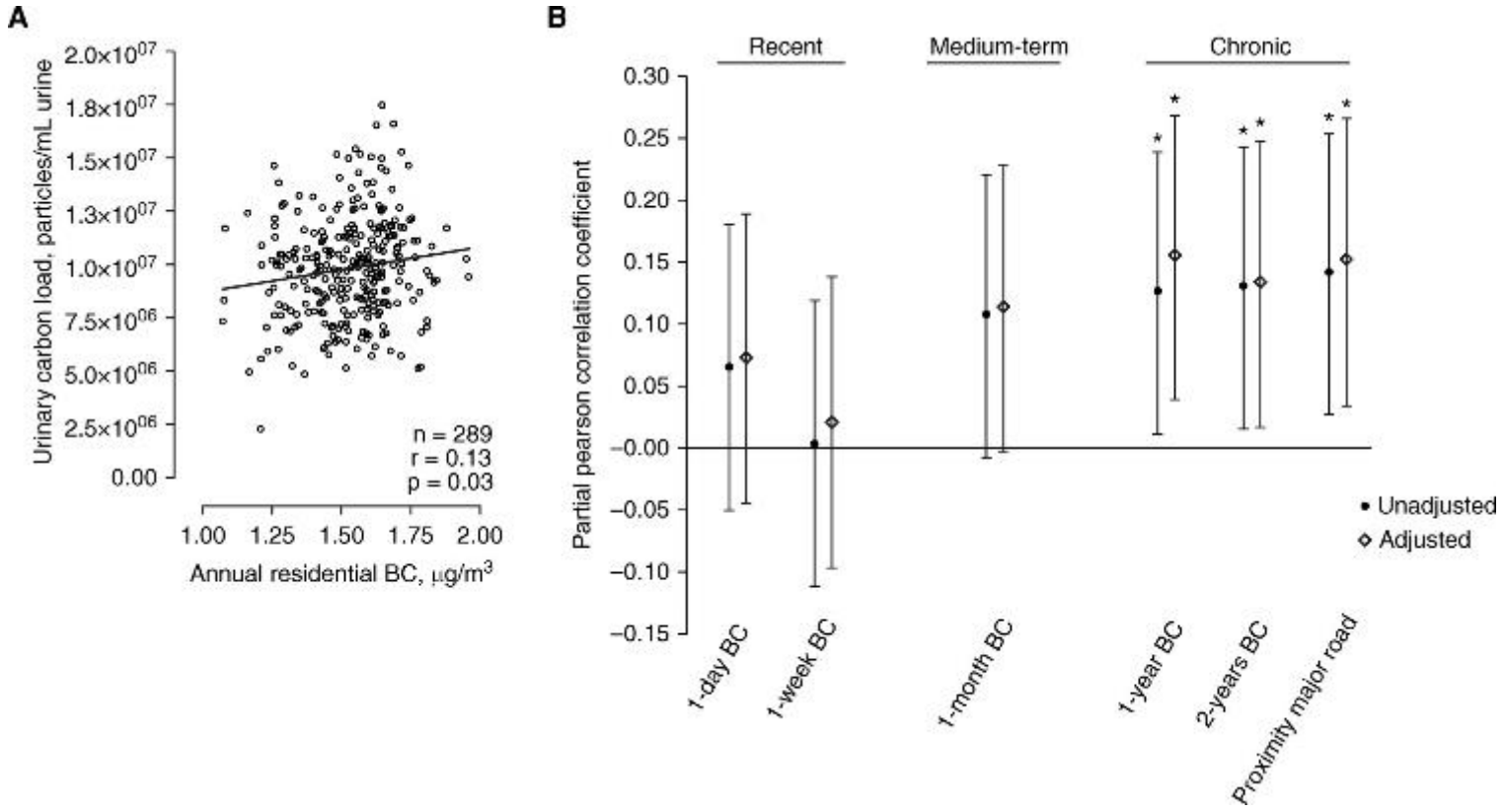
UFP-related black carbon in child urine



Saenen et al. AJRCCM 196, 7, 2017

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Health Effects Institute Special Report 2013

- Some studies show evidence for UFP effects
  - lung function changes, airway inflammation, enhanced allergic responses, vascular thrombogenic effects, altered endothelial function, altered heart rate and heart rate variability, accelerated atherosclerosis, and increased markers of brain inflammation
- Relatively few studies have directly compared UFPs with other particle size fractions.
- Evidence not sufficiently strong to conclude that short-term exposures to UFPs have effects that are dramatically different from those of larger particles
- Limitations and inconsistencies in the findings from short-term studies on UFP health effects, and there are no long-term animal exposure studies of UFP health effects.
- These factors constrain our ability to draw definitive conclusions about the specific consequences of exposure to UFPs

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Health Effects Institute Special Report 2013

- The available observational study designs have not been able to clearly determine whether UFPs have effects independent of those for related pollutants.
- Where studies have measured UFPs, few have assessed whether the effects associated with UFPs are independent of other pollutants.
  - When they have, the effects of UFPs have not been consistently discernible from those of other pollutants with which they often occur or share similar sources (e.g., traffic).
- Of 42 articles published since 1997 that cited any significant health associations with UFPs measured as number concentration, 37 articles also noted significant effects for other particle size fractions or traffic-related pollutants, and 10 articles did not consider any traffic-related gases in the analysis.

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Health Effects Institute Special Report 2013

- Several factors — the unique physical properties of UFPs, their interactions with tissues and cells, their potential for translocation beyond the lung — have led scientists to expect that UFPs may have specific or enhanced toxicity relative to other particle size fractions and may contribute to effects beyond the respiratory system.
- However, the considerable body of research that has been conducted has not provided a definitive answer to this question.
- Toxicologic studies in animals, controlled human exposure studies, and epidemiologic studies to date have not provided consistent findings on the effects of exposures to ambient levels of UFPs, particularly in human populations.
- The current evidence does not support a conclusion that exposures to UFPs alone can account in substantial ways for the adverse effects that have been associated with other ambient pollutants such as $PM_{2.5}$.

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Health effects of ultrafine particles: a systematic literature review update of epidemiological evidence

- Ohlwein S, Kappeler R, Kutlar Joss M, Künzli N, Hoffmann B

- Int J Public Health. 2019 May;64(4):547-559.

RESULTS:
We identified 85 original studies, conducting short-term (n = 75) and long-term (n = 10) investigations. Panel (n = 32), scripted exposure with predefined settings (n = 16) or time series studies (n = 11) were most frequent. Thirty-four studies adjusted for at least one other pollutant. Most consistent associations were identified for short-term effects on pulmonary/systemic inflammation, heart rate variability and blood pressure.
CONCLUSIONS:
The evidence suggests adverse short-term associations with inflammatory and cardiovascular changes, which may be at least partly independent of other pollutants. For the other studied health outcomes, the evidence on independent health effects of UFP remains inconclusive or insufficient.

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Subclinical Effects of UFPs

Outcome	Number of studies		
Respiratory indices	11		
Blood pressure	13		
HRV	16		
Arrhythmia	1		
Vascular function	7		
Pulmonary inflammation	12		
Systemic inflammation	18		
Neurocognitive outcomes	2	1	-

Ohlwein et al. 2019

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Subclinical Effects of UFPs

Outcome	Number of studies	Number of studies with associations in expected direction without co-pollutant adjustment
Respiratory indices	11	4/11
Blood pressure	13	9/13
HRV	16	12/16
Arrhythmia	1	1/1
Vascular function	7	4/7
Pulmonary inflammation	12	12/12
Systemic inflammation	18	7/18
Neurocognitive outcomes	2	1

Ohlwein et al. 2019

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Subclinical Effects of UFPs

Outcome	Number of studies	Number of studies with associations in expected direction without co-pollutant adjustment	Number of studies with associations in expected direction with co-pollutant adjustment
Respiratory indices	11	4/11	3/3
Blood pressure	13	9/13	2/4
HRV	16	12/16	3/5
Arrhythmia	1	1/1	-
Vascular function	7	4/7	1/2
Pulmonary inflammation	12	12/12	2/2
Systemic inflammation	18	7/18	2/5
Neurocognitive outcomes	2	1	-

Ohlwein et al. 2019

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Few Long -Term Studies

Outcome type/ study	Outcome
Mortality Ostro et al. 2015	All-cause and cause-spec.
Morbidity Li et al. 2017	Cardiometabolic
	Low birth weight
Laurent et al. 2014/2016b	Preterm birth
Laurent 2016a	
Subclinical	
Aguilera et al. 2016	Atherosclerosis
Viehmann et al. 2015	Inflammation
Lane et al. 2015	Inflammation
Lane et al. 2016	Inflammation
Sunyer et al. 2016	Cognitive function

Ohlwein et al. 2019

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Few Long -Term Studies

Outcome type/ study	Outcome	Associations w/o co-pollutant adjustment	Associations with co-pollutant adjustment
Mortality Ostro et al. 2015	All-cause and cause-spec.	0	Not conducted
Morbidity Li et al. 2017	Cardiometabolic	(+)	Not conducted
	Low birth weight	(+)	Not conducted
Laurent et al. 2014/2016b Laurent 2016a	Preterm birth	-/+	Not conducted
Subclinical			
Aguilera et al. 2016	Atherosclerosis	+	(+)
Viehmann et al. 2015	Inflammation	(+)	Not conducted
Lane et al. 2015	Inflammation	(+)	Not conducted
Lane et al. 2016	Inflammation	(+)	Not conducted
Sunyer et al. 2016	Cognitive function	+	Not conducted

Ohlwein et al. 2019

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Summary

Outcome	Single pollutant effect
Short-term	**49/79**
Mortality	5/7
Morbidity	3/7
Hospital admission	4/10
Subclinical	37/55
Long-term	**8/10**
Mortality	1/1
Morbidity	3/4
Hospital admission	-
Subclinical	4/5

Ohlwein et al. 2019

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Summary

Outcome	Single pollutant effect	Multi-pollutant effect	Consistency of general pattern in multipollutant models
Short-term	**49/79**	**18/32**	**7/18**
Mortality	5/7	4/6	1/4
Morbidity	3/7	-	-
Hospital admission	4/10	0/5	-
Subclinical	37/55	14/21	6/14
Long-term	**8/10**	**0/1**	**-**
Mortality	1/1	-	-
Morbidity	3/4	-	-
Hospital admission	-	-	-
Subclinical	4/5	0/1	-

Ohlwein et al. 2019

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Challenges

- Lack of exposure data – measurements
- Correlations among air pollutants in time and space
- Difficulty in laboratory generation or collection and re-use of real world UFPs for toxicology or clinical studies

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UFPs part of a complex mixture

- These correlations must be taken into account when evaluating exposure to sources such as traffic, or when designing epidemiologic studies and interpreting their results.
- Temporal variability in UFP number concentration can be similar to that of other PM size fractions and gaseous pollutants, making it difficult to differentiate the effects of UFP number concentration in such study designs.
- Reliance on measurements at central-site monitors to represent broad population exposure — a central feature in epidemiologic studies of long-term exposures to $PM_{2.5}$ and other pollutants — is likely to lead to errors in estimates of exposure to UFPs.

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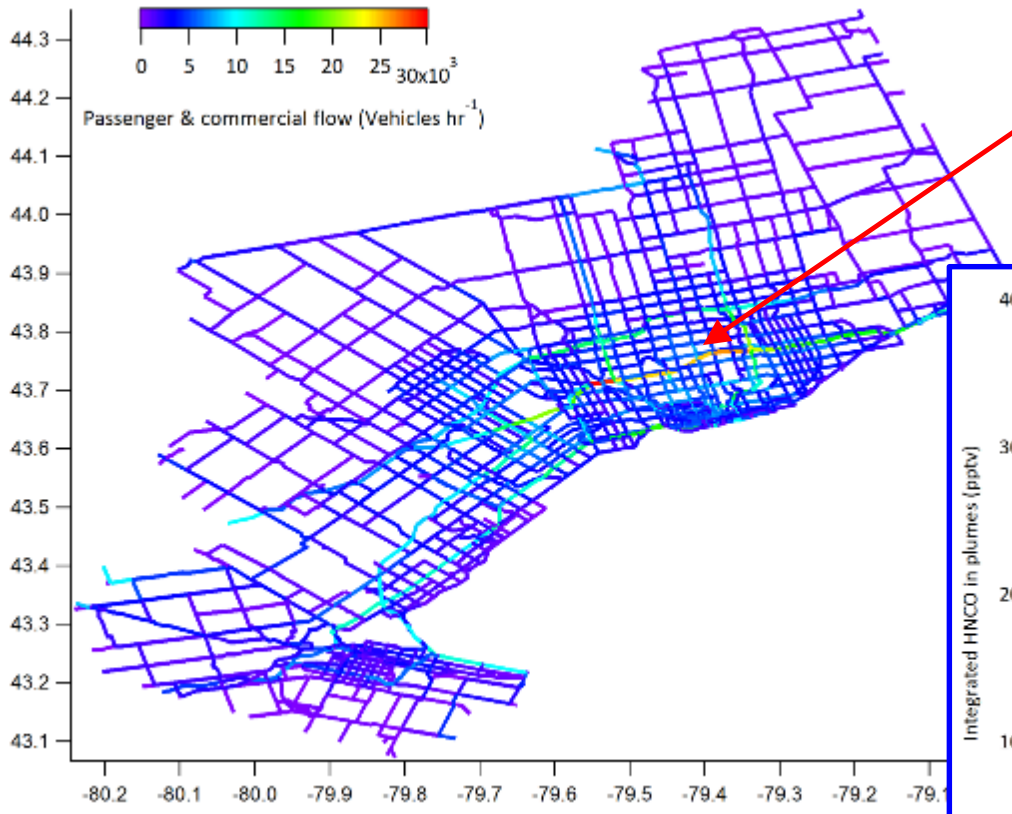
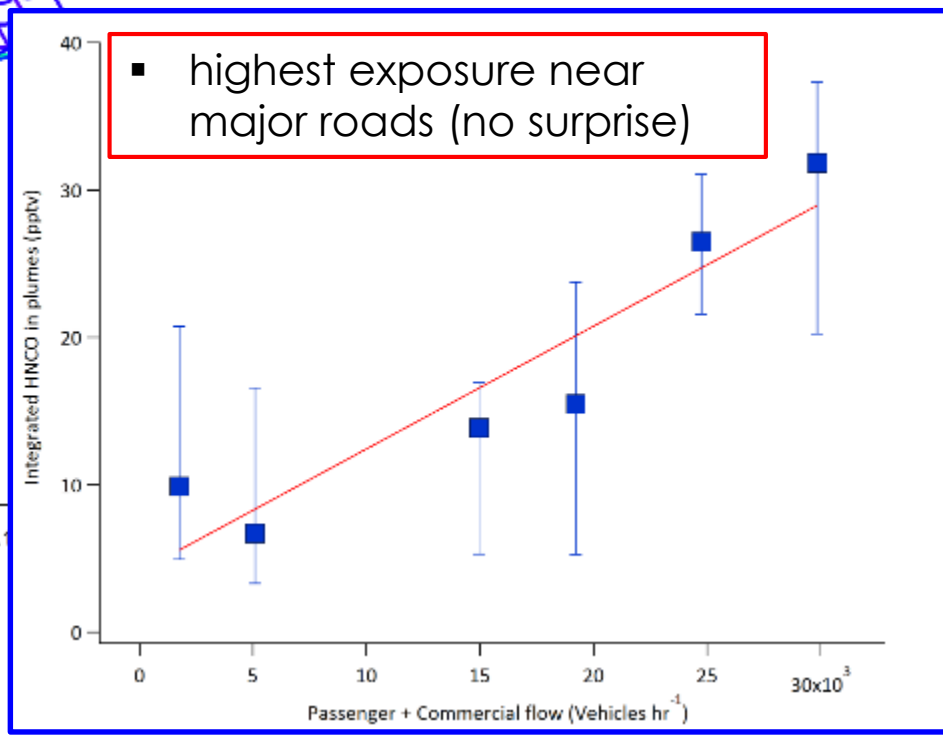
Unmeasured compounds in TRAP

- HNCO and HCN shown to be in primary vehicle emissions in the lab and field
- modelled passenger and commercial vehicle flow for GTA road segments



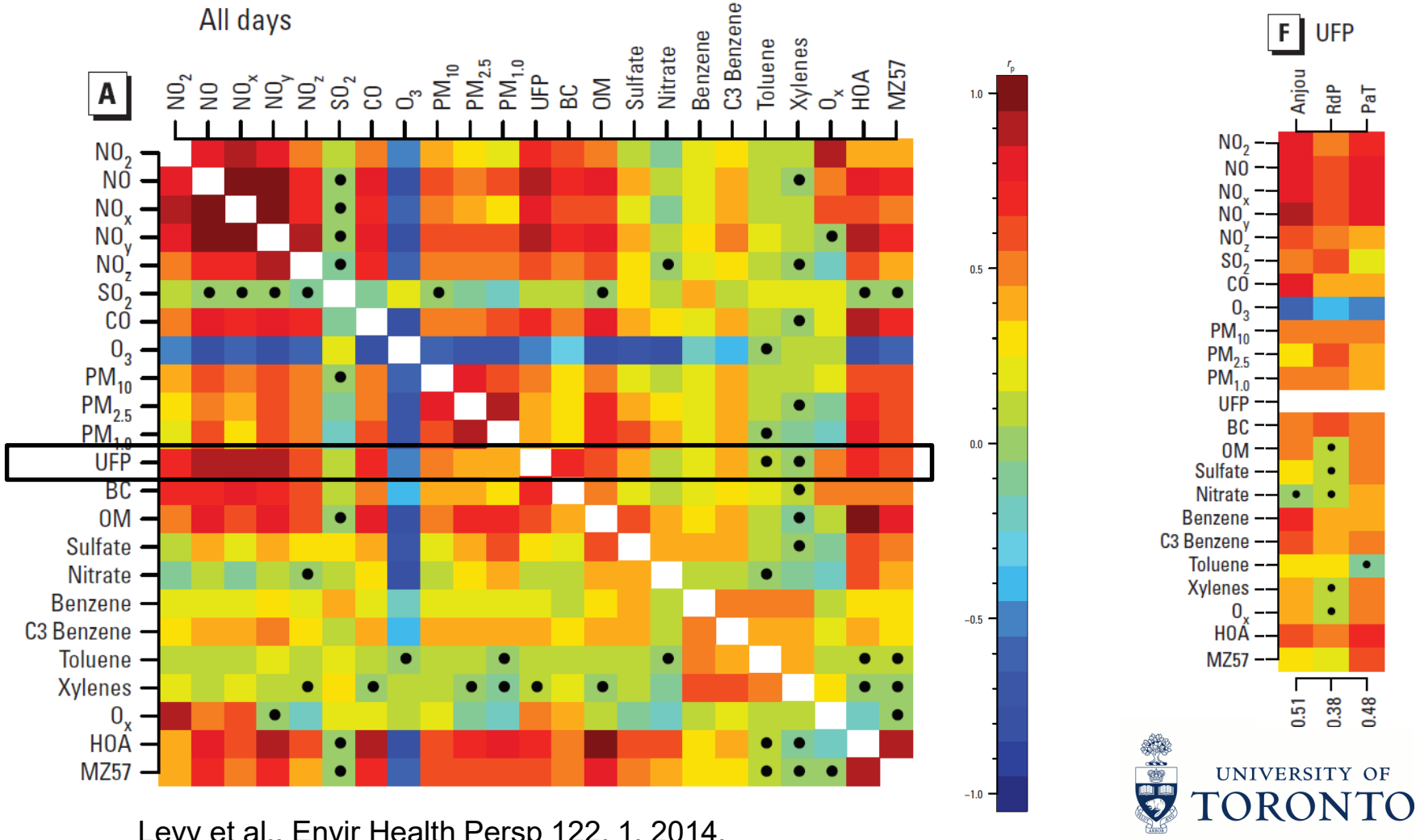
- Highest flow for major roads
- Highest HNCO seen on these roads too



- highest exposure near major roads (no surprise)

Wren et al., Atmos Chem Phys, 2018.

Correlation in high resolution spatial patterns – Montréal mobile measurements



Levy et al., Envir Health Persp 122, 1, 2014.

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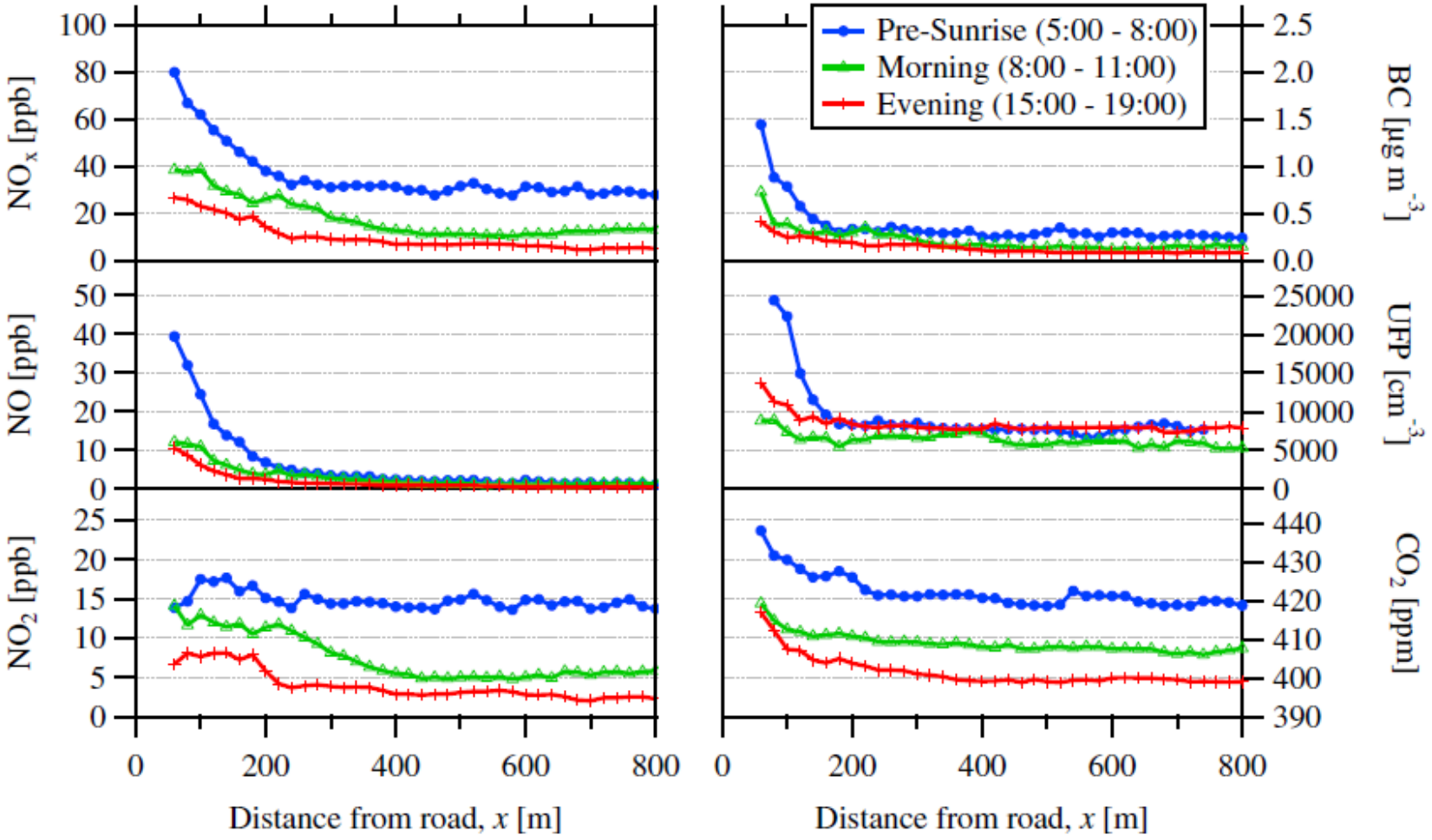
Near-highway (400) gradients by time of day



Gordon et al., 2012, Atmos. Env.

CDN Within -City Epidemiological Studies

- In **Toronto,** we did not observe clear evidence of positive associations between long-term exposure to ambient UFPs and respiratory disease incidence independent of other air pollutants. *Weichenthal et al. J Environ Epi, 2017*
  - In single pollutant models, each interquartile increase in ambient UFPs was associated with incident COPD (HR = 1.06, 95% CI: 1.05, 1.09) but not asthma (HR = 1.00, 95% CI: 1.00, 1.01) or lung cancer (HR = 1.00, 95% CI: 0.97, 1.03).
  - Additional adjustment for NO_2 attenuated the association between UFPs and COPD and the HR was no longer elevated (HR = 1.01, 95% CI: 0.98, 1.03).
  - $PM_{2.5}$ and NO_2 were each associated with increased incidence of all three outcomes but risk estimates for lung cancer were sensitive to indirect adjustment for smoking and body mass index.

- In **Montreal,** ambient UFP concentrations were associated with an increased risk of prostate cancer (OR=1.10, 95% CI: 1.01, 1.19) in fully adjusted models when exposures were assigned to residences 10-years prior to diagnosis.
  - No adjustments for other pollutants

Weichenthal et al. Environmental Research 156:374-380, 2017

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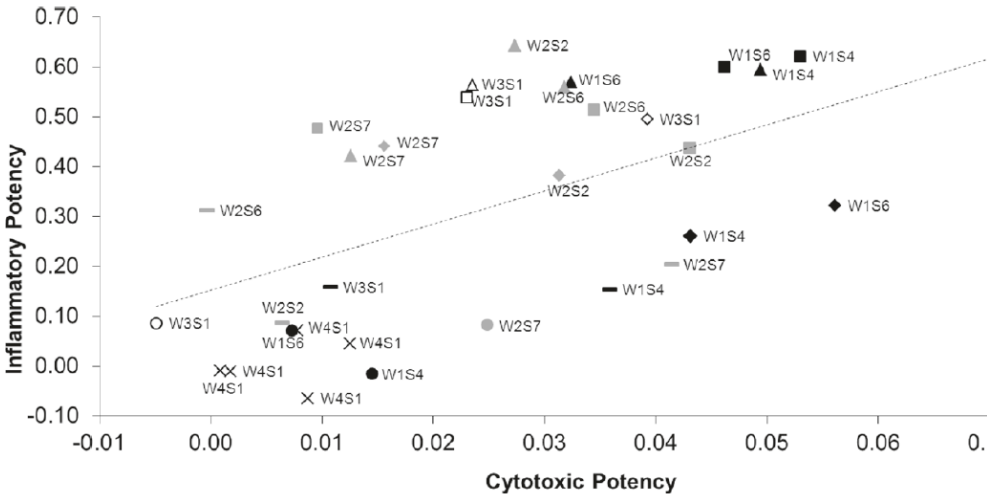
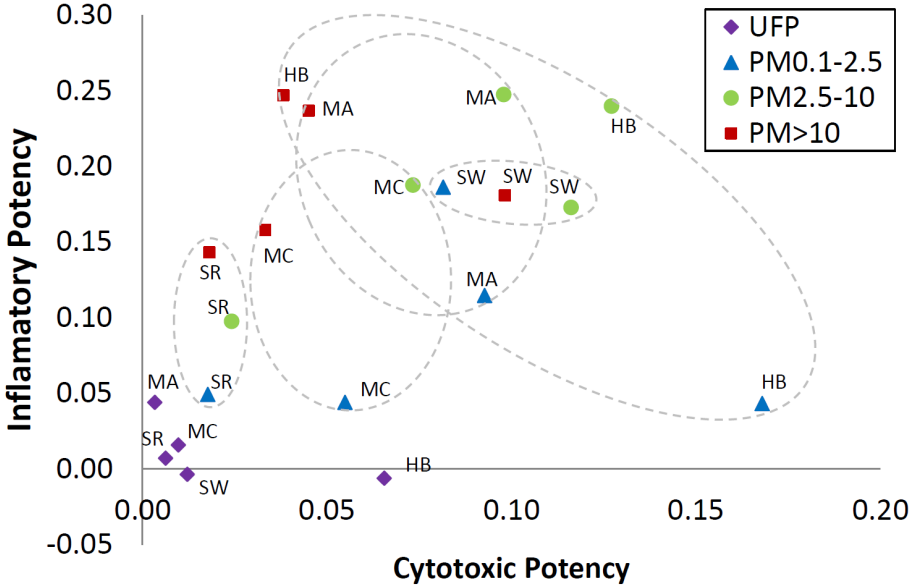
In vitro testing of different PM sizes

Three sites in Windsor, ON



Thomson et al., Particle and Fibre Toxicology **12**, 24, 2015

Five Industrial Locations



Thomson et al., Particle and Fibre Toxicology **13**, 65, 2016

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Controlled Human Exposures

	Number of Missing Observations	Mean ± Standard Deviation	Median	25th percentile	75th percentile	Minimum/ Maximum	
PM Mass							
Coarse	0	214 ± 52.7	207	193	225	66.4/ 514	
Fine	0	243 ± 52.1	234	209	260	158/ 405	
Ultrafine	0	122 ± 69.6	112	64.9	183	21.9/ 283	
PM Number							
Ultrafine	7	215,000 ± 58,800	221,000	185,000	256,000	116,000/ 332,000	
BC Mass							
Coarse	4	1.36 ± 0.85	1.22	0.61	1.95	0.18/ 3.54	
Fine	3	5.10 ± 3.74	3.71	2.31	8.07	0.78/ 13.7	
Ultrafine	6	10.3 ± 8.55	6.77	3.57	16.6	0.08/ 31.1	

Godri et al. in preparation

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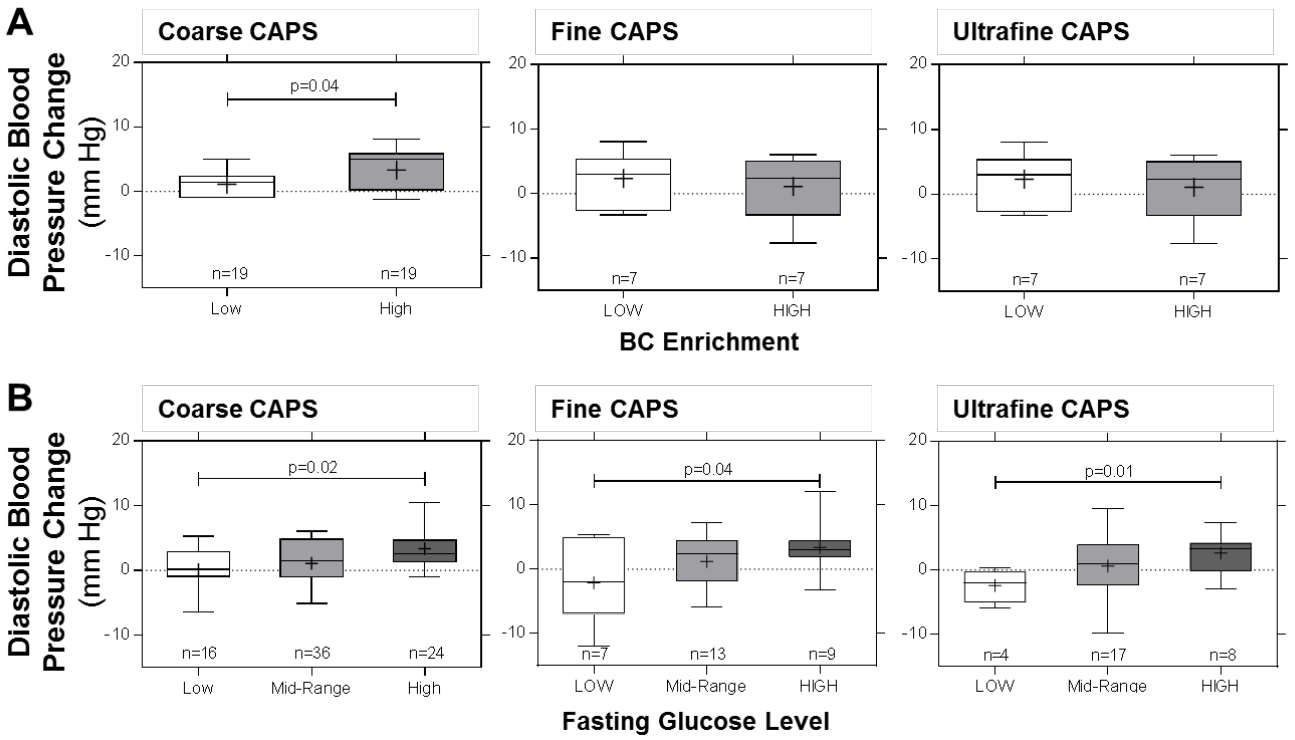
Controlled Human Exposures



Godri et al. in preparation

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Conclusions

- Identifying and isolating the specific health effects of UFPs and comparing to other air pollutant risks is a considerable challenge
- Overall, the evidence remains inconsistent
- UFP's ability to migrate to organs beyond the lungs is a significant concern and represents an additional biological mechanism for effects
- Considerable research required to determine what might be a harmful dose and to assess what UFP characteristics are most harmful

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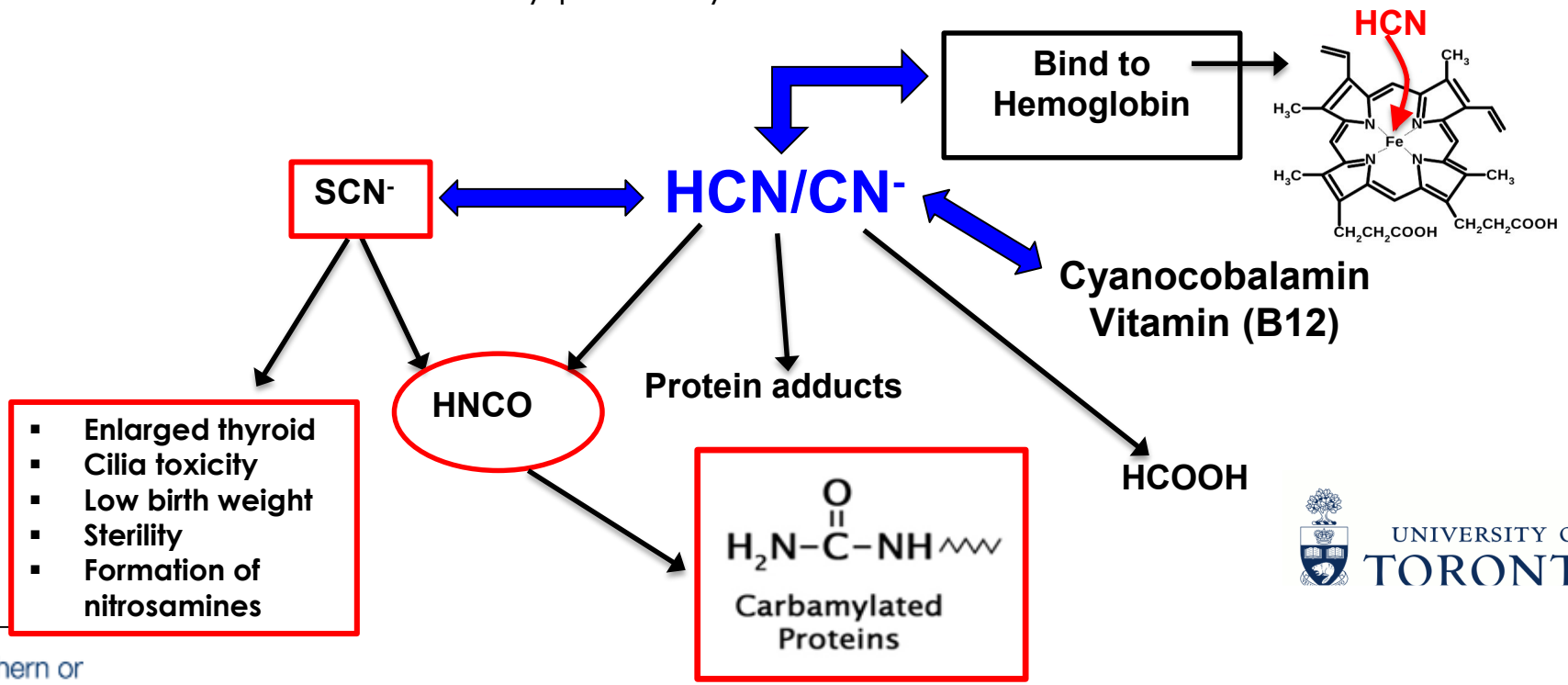
Unmeasured compounds in TRAP

- HCN is a highly toxic and leads to death: inhaled concentration of 270 ppm can lead to immediate death (obviously not relevant).
- HCN is on the EPA list of toxic compounds. The reference concentration (RfC) for hydrogen cyanide is 0.003 mg/m3 (~3 ppb).
- The Ontario Ambient Air Quality Criteria (AAQC): 7.2 ppb (24 –hour basis).
- Part of the HCN toxicity pathway can be similar to HNCO:



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