Biological Monitoring of Human Exposure to Diesel Exhaust

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Diesel exhaust (DE)

- DE is a major component of ambient PM
- DE is a complex mixture of gases and particles, including many known toxic substances:
- Acute exposure to high concentrations of DE can lead to:
  - Irritation, headache, weakness, chest tightness
- Long term exposure has caused lung cancer and skin cancer in laboratory animals.
- Recently classified as carcinogenic to humans by IARC
  - Also evidence of reduced immunity

Challenges in exposure assessment for DE

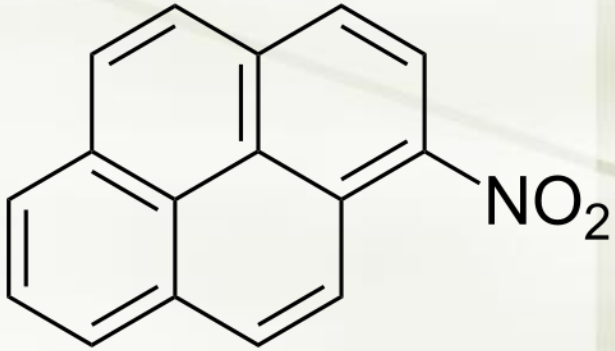
- Lack of a specific marker for DE
  - Elemental carbon commonly used
- Spatial and temporal variability in DE emissions
- Environmental measurements don’t account for modifying effect of behavior on exposure
  - Ventilation rate, protective equipment

Biological monitoring of DE exposure?

- Potential Advantages:
  - Measure of absorbed (bioavailable) dose
  - Integrates multiple routes of exposure (inhalation and dermal)
  - Accounts for differences in exposure due to breathing rate
  - Easier to implement on a large scale than personal environmental monitoring

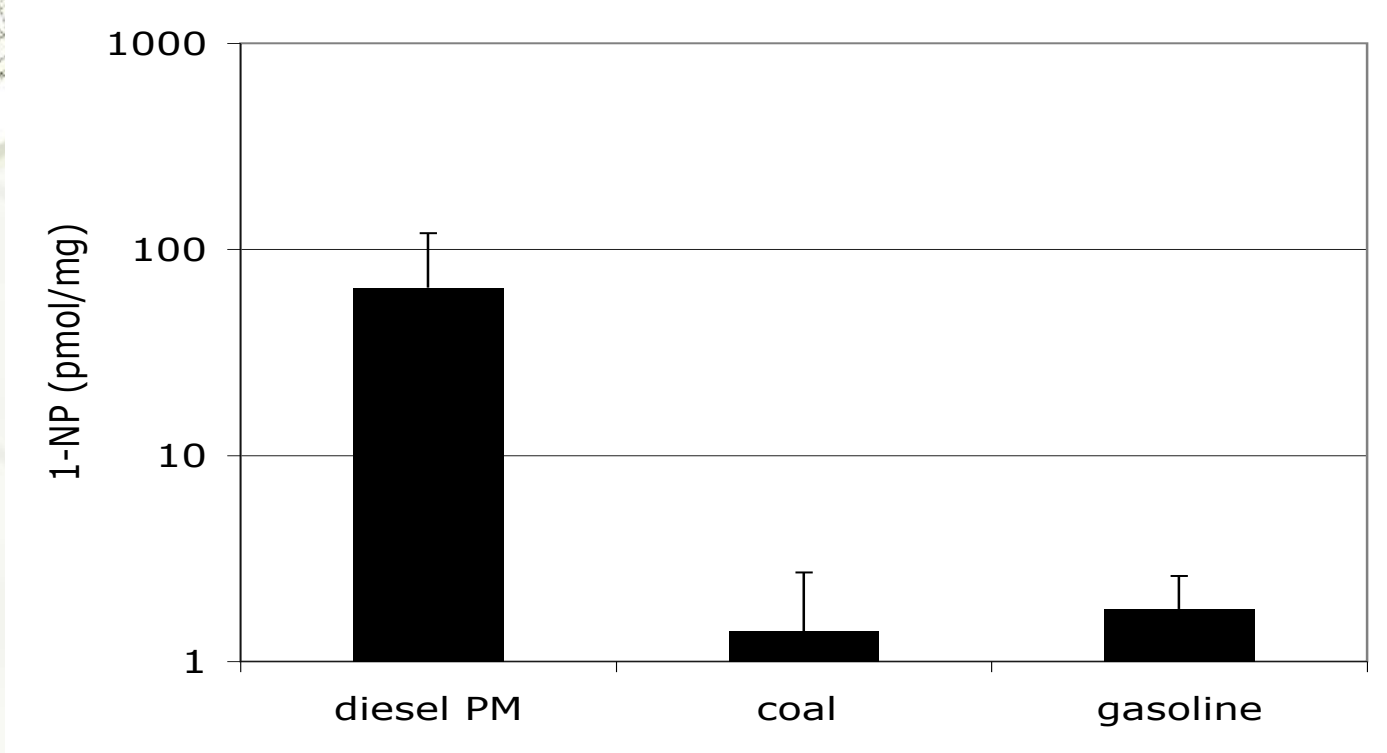
1-Nitropyrene (1-NP)

- 1-NP is formed by nitration of poly aromatic hydrocarbons (PAHs) within diesel engines
  - 1-NP is the most abundant particle-associated nitro-PAH in DE.
- It is a much more specific measure of DE
- Metabolites of 1-NP can be measured in urine as an exposure biomarker



Scheepers et al. 1995; Toriba et al. 2007; http://en.wikipedia.org/wiki/1-Nitropyrene

1-NP emission factors for different combustion sources



Tang et al, Atmos. Environ. ***39,*** *pp5817-5826,* ***2005***
Murahashi et al., Jap, J. Toxicol. Environ. Health 41(5):pp328-333 ***1995***

Contribution of DE to ambient 1-NP concentrations

City	Diesel vehicles (% of fleet)	Contribution of DE to 1-NP
Kanazawa	27	99.9
Sapporo	41	100
Tokyo	20	99.4

Kakimoto et al., J. Health Sci. 46(1): 5-15. ***2000***

Source apportionment of PM In Seattle's Duwamish Valley

- 1-NP was measured on teflon filters using standard FRM sampling protocols in 2008-2009
- Daily 1-NP was significantly associated with heavy truck counts on the highway adjacent to the monitoring site.
- The weekday-weekend ratio of 1-NP paralleled the equivalent ratio for heavy truck counts.
- A PMF analysis identified seven source contributions to $PM_{2.5}$. 1-NP was only associated with the diesel source (rho = 0.86)

Evaluation of new methods for source apportionment using real time continuous monitoring methods. Report to Puget Sound Clean Air Agency, October 2010.

FRM: Federal Reference Method
PMF: positive matrix factorization

Spatial modeling of 1-NP

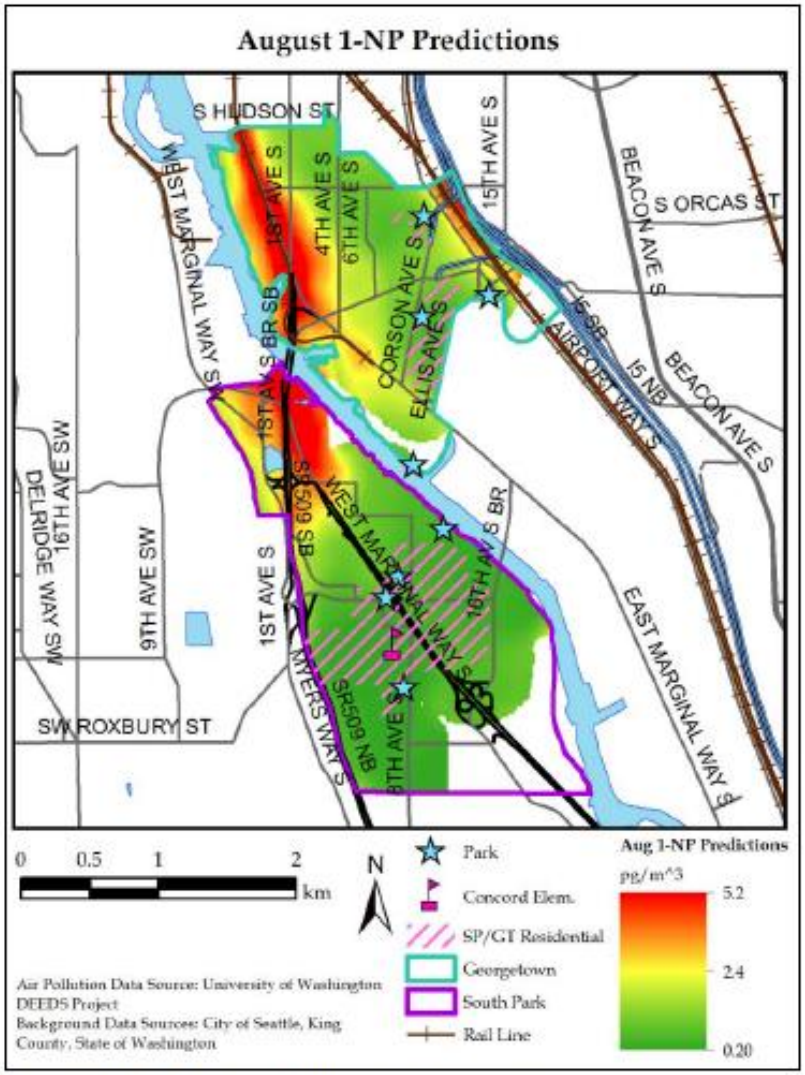
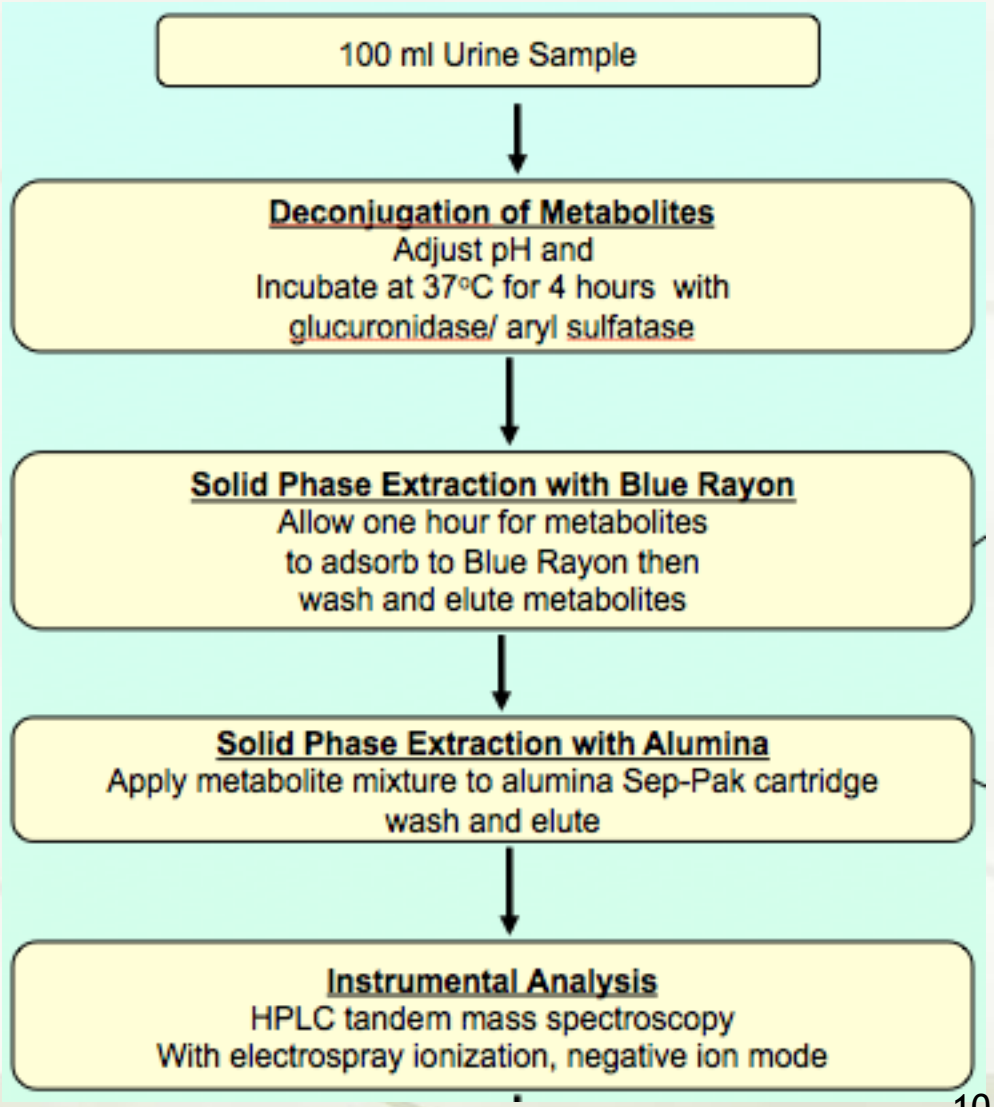


Figure 1. Map of August 1-NP prediction gradient

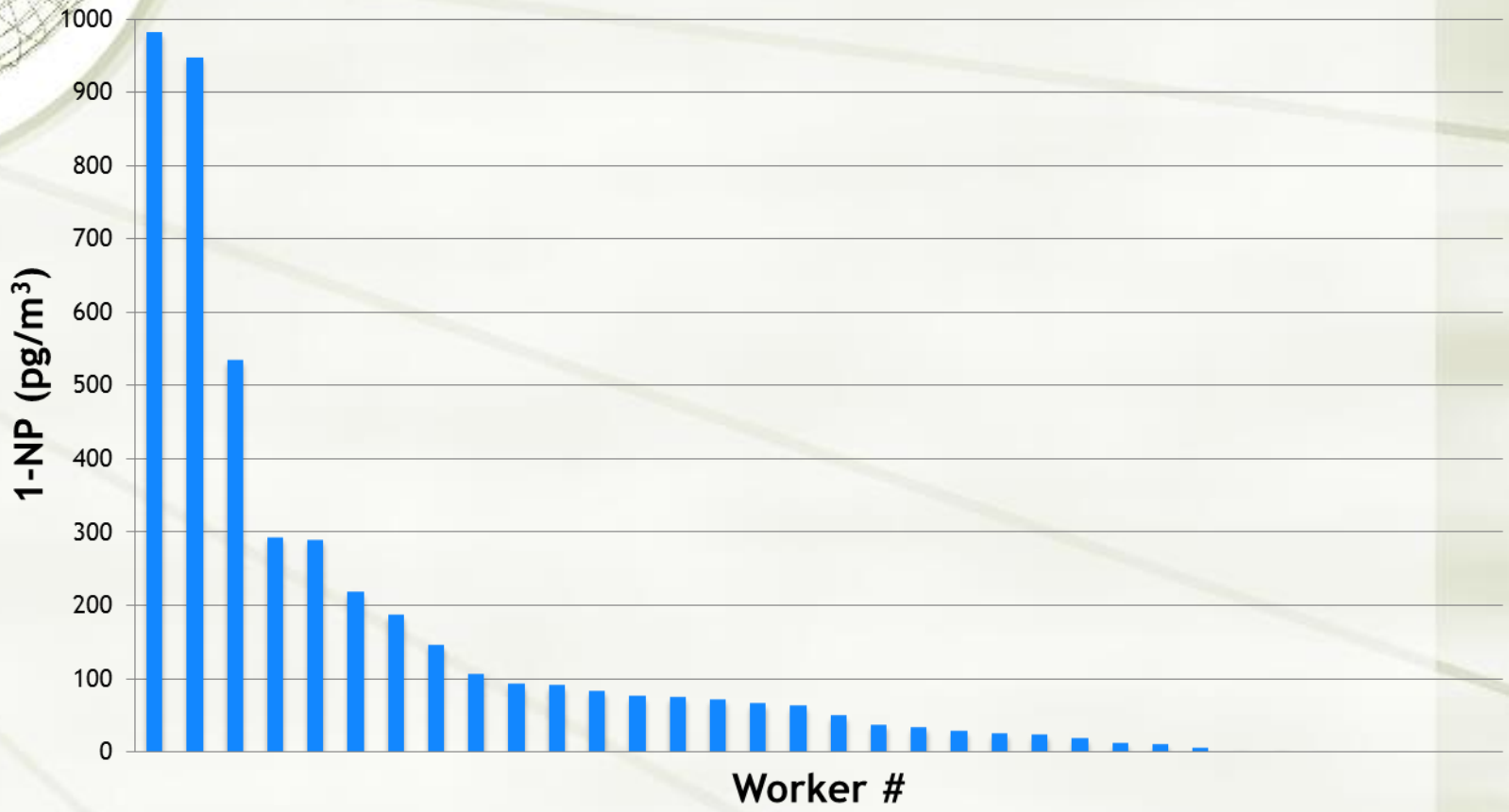
Variable	Coefficient	Std. Error	t-value	p-value[1]	95% CI
Log_{10} meters to railroad	-0.18	0.081	-2.2	0.04	(-0.36, -0.0061)
High-intensity development[2] in 150m	0.0025	0.0010	2.4	0.03	(0.00030, 0.0047)
Log_{10} CAL3QHCR truck emission predictions in 4500m	0.29	0.20	1.5	0.16	(-0.13, 0.71)
Mean log_{10} mobile black carbon in 300m	1.3	0.41	3.2	0.01	(0.43, 2.2)
Model $R^2 = 0.87$ Cross-validated $R^2 = 0.73$ Cross-validated RMSE = 0.12 log_{10} pg/m^3					

Schulte, J.K., Magzamen, S., Oron, A.P., Beaudet, N., Kaufman, J.D., Larson, T.V., & Fox, J.R. (2013). Diesel Exhaust Exposure in the Duwamish Study: Technical Report. Seattle, WA: University of Washington School of Public Health, Department of Environmental Health Sciences.

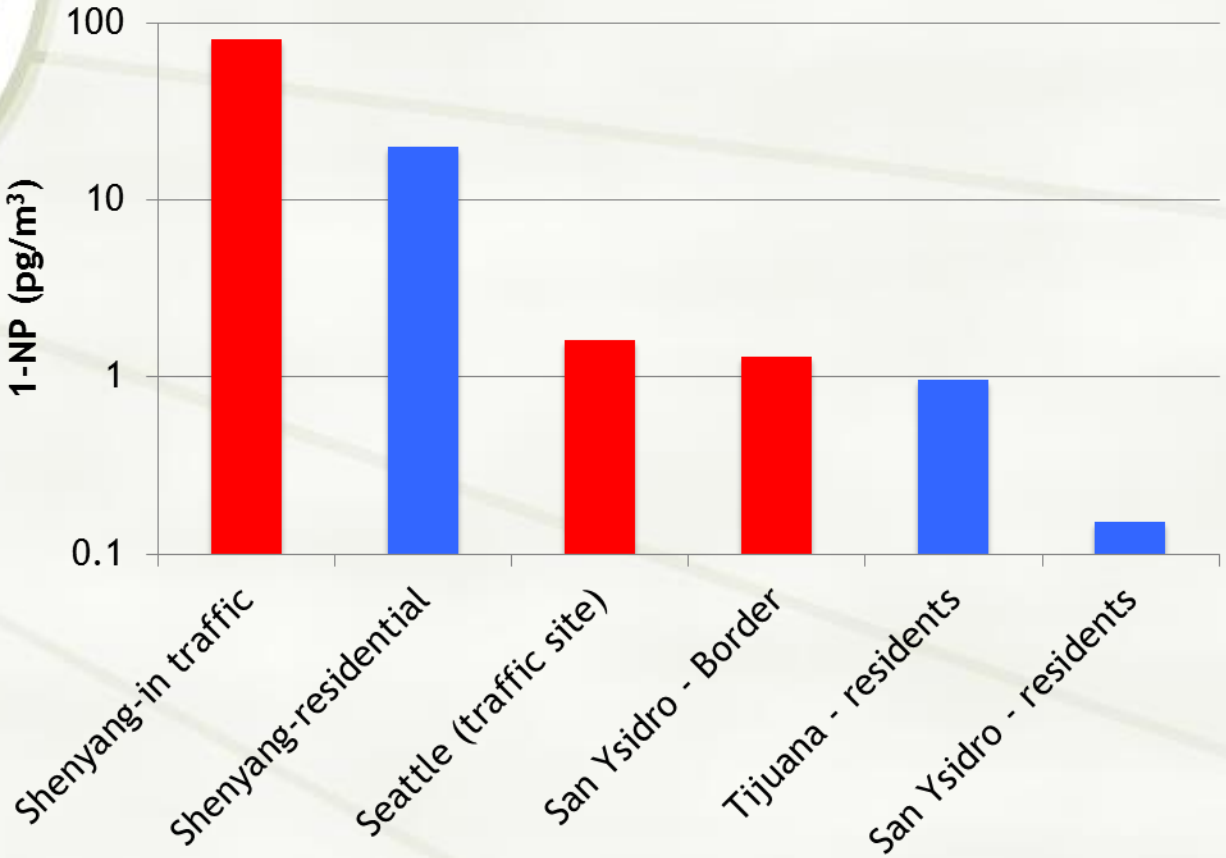
Sample preparation and analysis for 1-NP metabolites



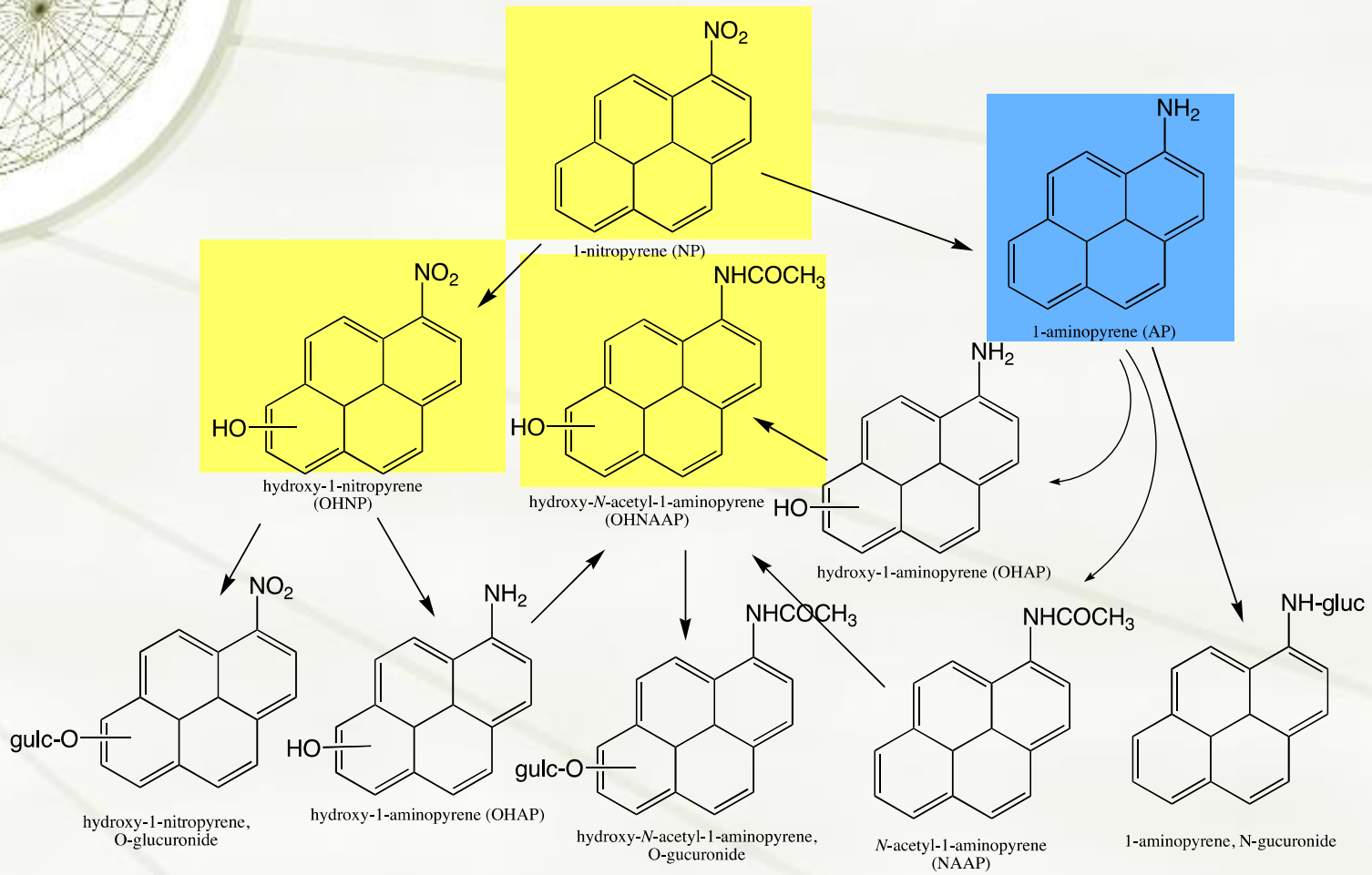
1-NP exposures in underground miners



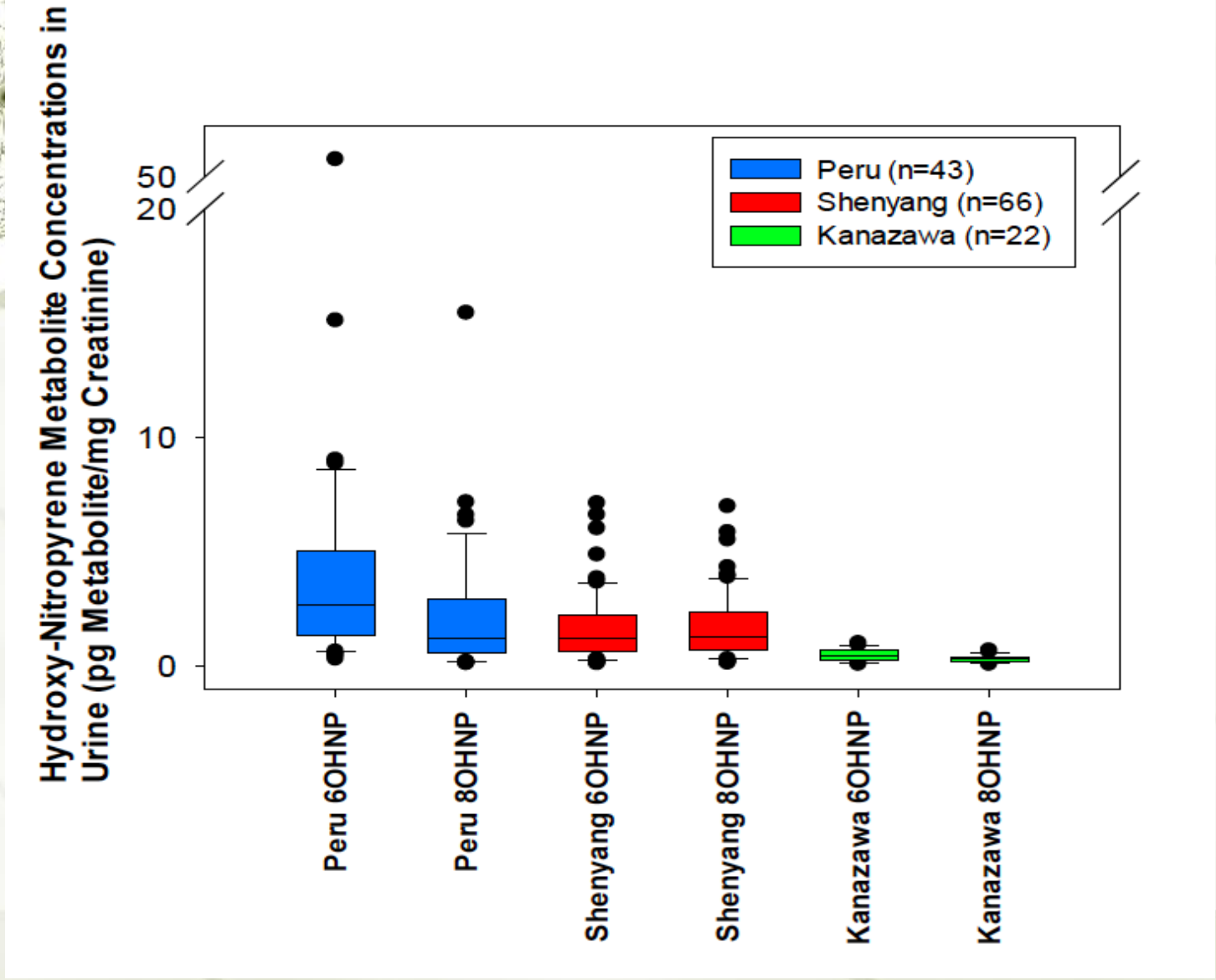
Air measurements



Biological monitoring of exposure to 1-NP

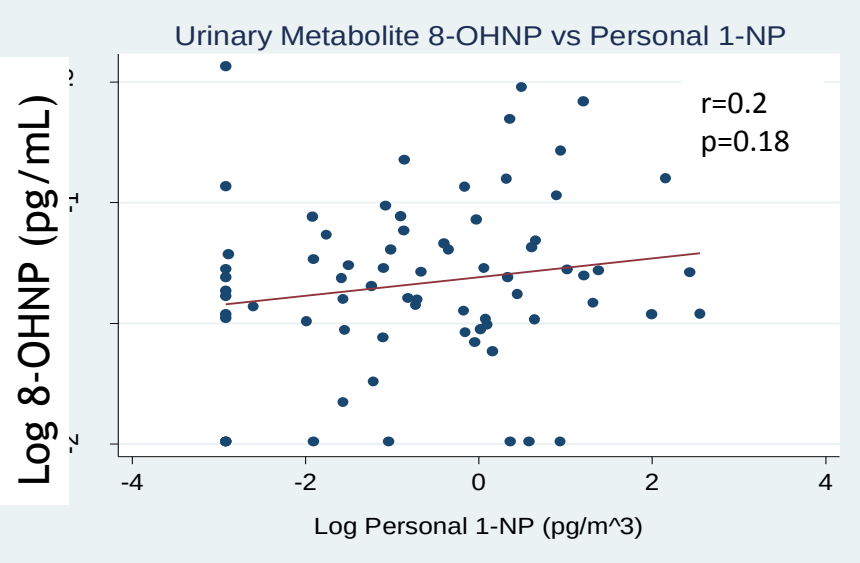


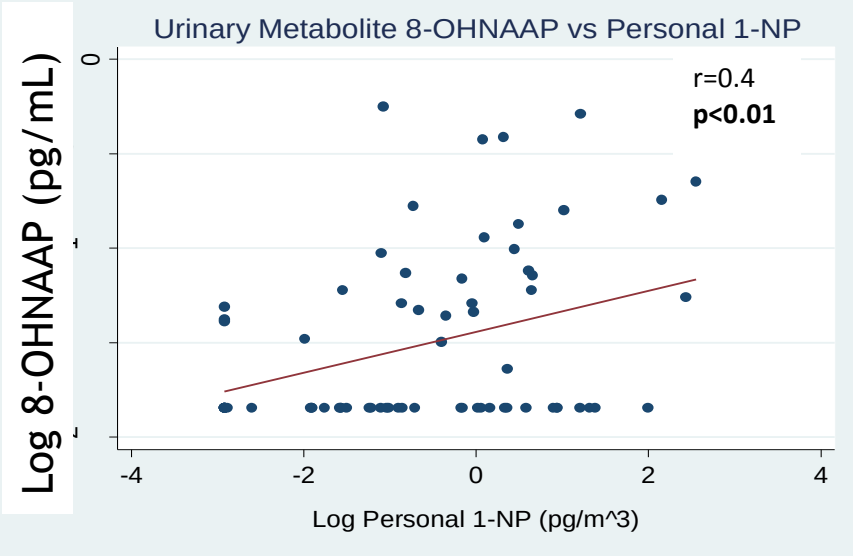
1-NP metabolite levels



1-NP exposures & metabolite levels : pedestrian commuters, Tijuana

- Biomarker levels in first morning void compared to personal 1-NP exposure over preceding 24 hours
  - Weak to moderate associations observed with 1-NP





1-AP as a biomarker for DE exposure

- Seidel at al measured 2-200 ng of 1-AP in 24 hr urine specimens from underground miners. Corresponding 1-NP exposures ~0.5-3 ng/m^3
- Laumbach observed ~10x increase in urinary 1-AP in human volunteers exposed to DE containing 2.7 ng/m^3 1-NP.
  - 50th percentile urinary 1-AP post exposure ~1-3 ng/L
  - Mass balance on Laumbach study indicates mass 1-NP inhaled 2.7 ng; mass excreted/24hrs ~1-3ng

Seidel A, Dahmann D, Krekeler H, Jacob J (2002). Int J Hyg Environ Health, 204: 333–338.
Laumbach et al, (2009) J. Environ. Monit., 11: 153–159

Unanswered Questions

- 1-NP exposure is associated with urinary 1-NP metabolites at the group and individual level. However:
  - What period of exposure is represented by a spot urine sample?
  - Is there a strong enough relationship between inhaled 1-NP and urinary metabolite levels, such that urinary biomarker levels can usefully predict inhalation exposure?
  - Are other routes of exposure to 1-NP important?
    - Diet, dermal
  - Are inter-individual differences in uptake and metabolism important confounders?
    - e.g. P450 or NAT polymorphisms

Temporal changes in biomarker levels in blood and urine

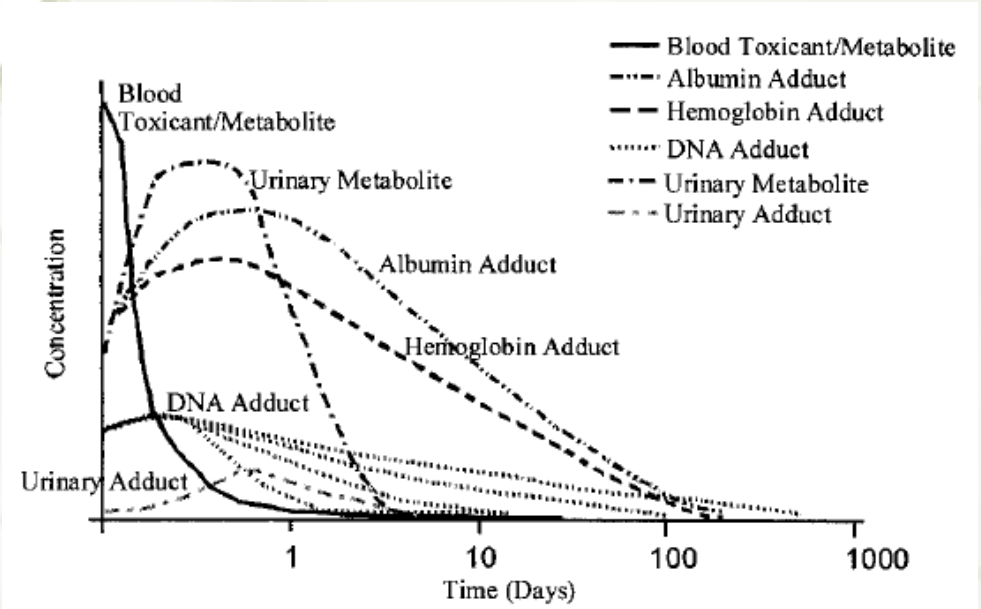


Figure 4. Post-exposure fate of a nonpersistent toxicant in blood and urine.

Needham, L.L. and sexton, K. J. Exposure Anal. Environ Epi. 2000 10 611-629

Conclusions

- 1-NP metabolites can be reliably detected in human urine samples, including from individuals exposed to ambient concentrations of DE
  - Levels of metabolites are in the low pg/mL range; the analytical method – at least for the hydroxylated metabolites - is sophisticated and requires expensive instrumentation
- The existing data strongly suggest that urinary 1-NP metabolites increase as exposure to DE increases
- We don't yet know the extent to which exposures other than DE contribute to urinary 1-NP metabolite levels
- We don't yet know how strong the relationship is between inhaled 1-NP and urinary metabolite levels, nor how reliably urinary biomarker levels might predict inhalation exposure.