

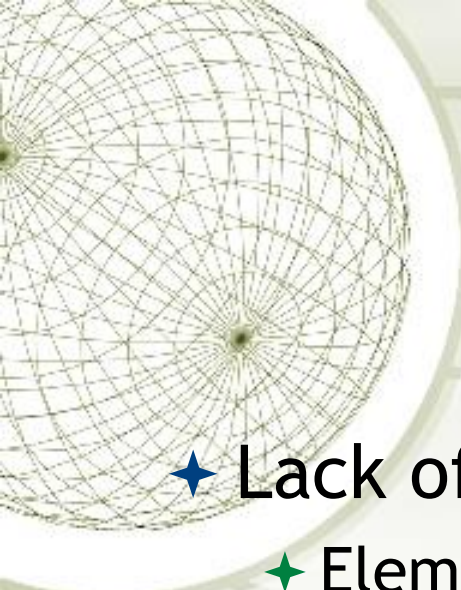
Biological Monitoring of Human Exposure to Diesel Exhaust

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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



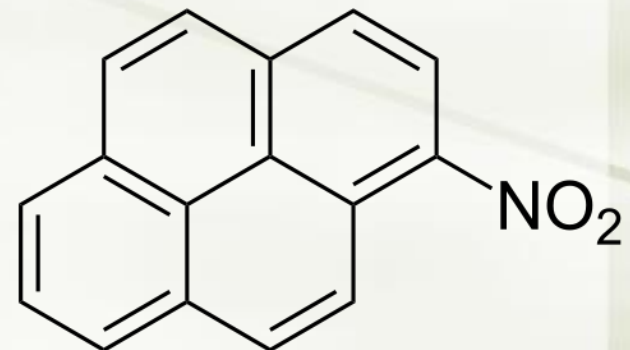
Biological monitoring of DE exposure?

★ Potential Advantages:

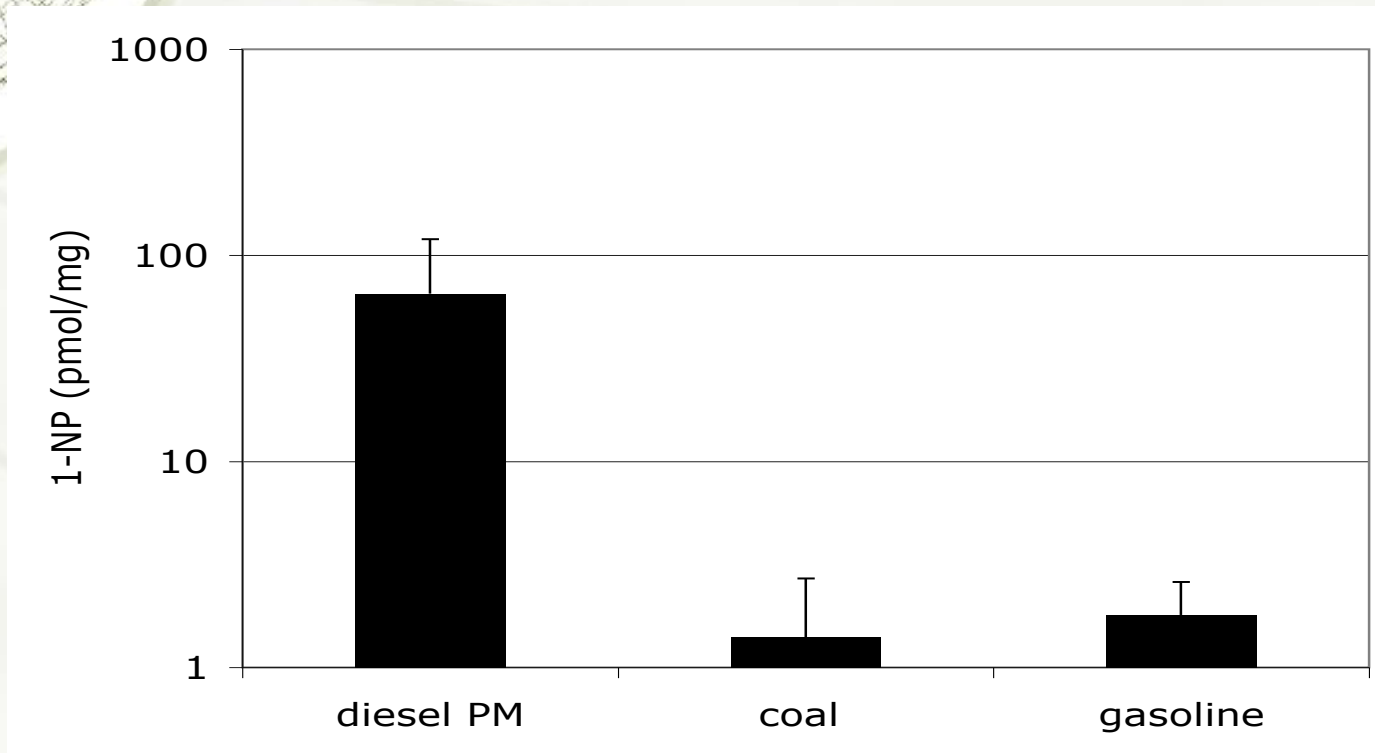
- ★ Measure of absorbed (bioavailable) dose
- ★ Integrates multiple routes of exposure (inhalation and dermal)
- ★ Accounts for differences in exposure due to breathing rate
- ★ Easier to implement on a large scale than personal environmental monitoring

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



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



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

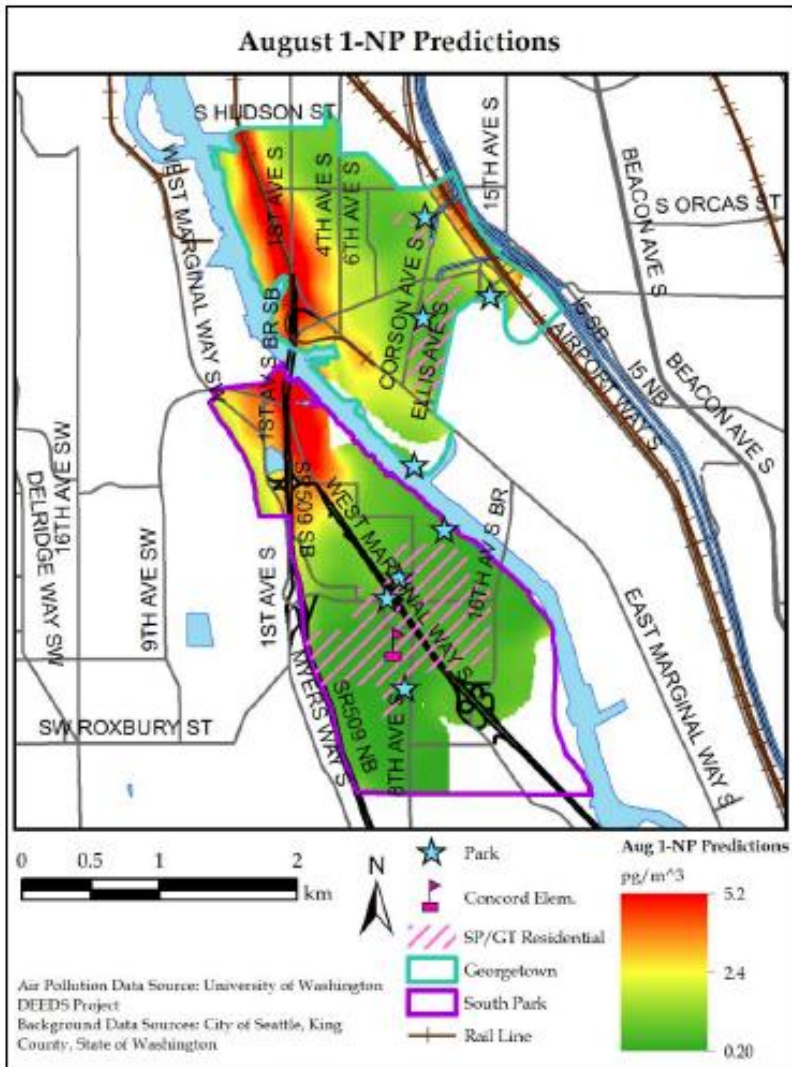
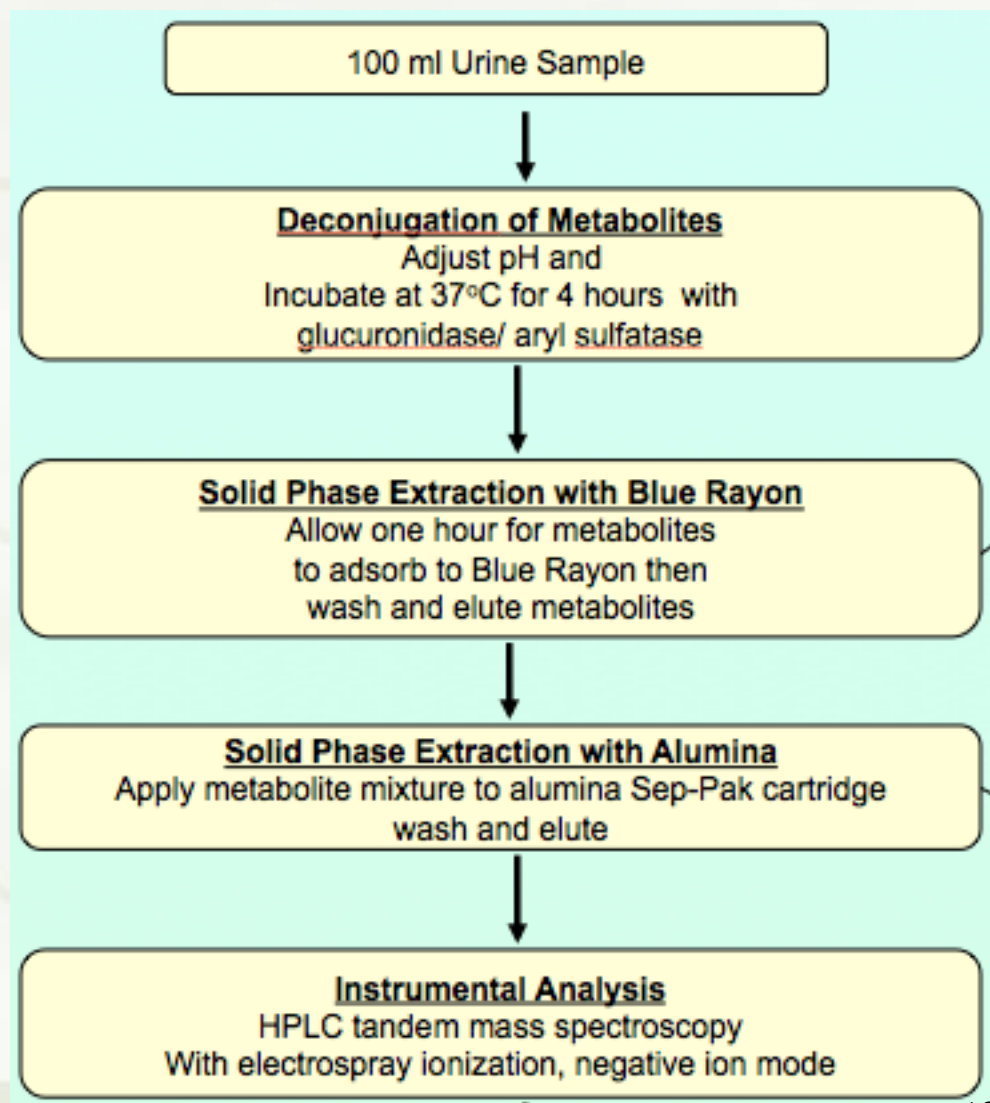


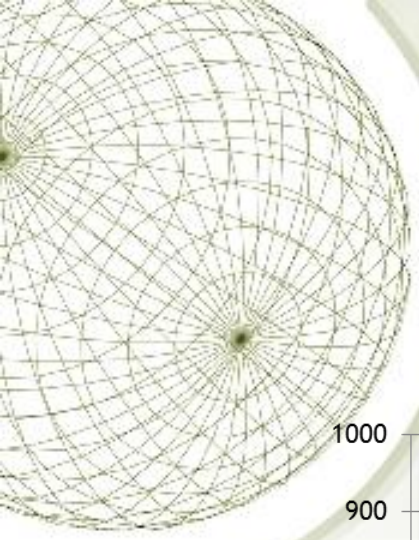
Figure 1. Map of August 1-NP prediction gradient

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					

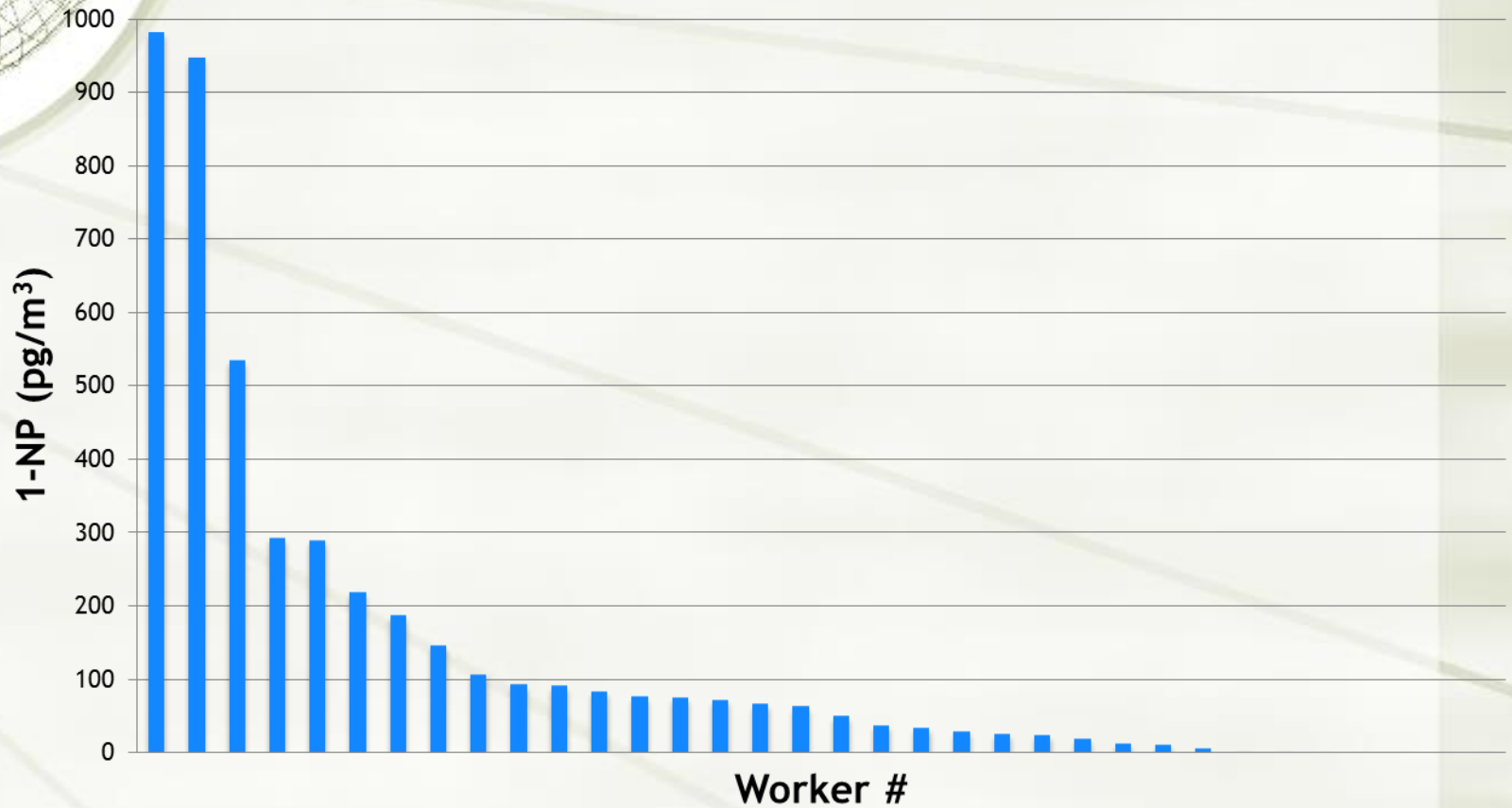


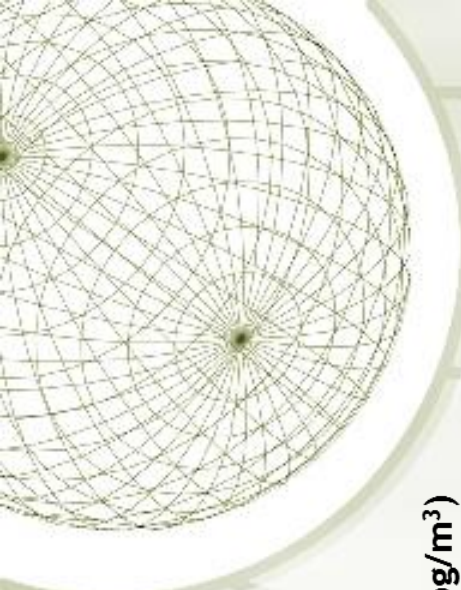
Sample preparation and analysis for 1-NP metabolites



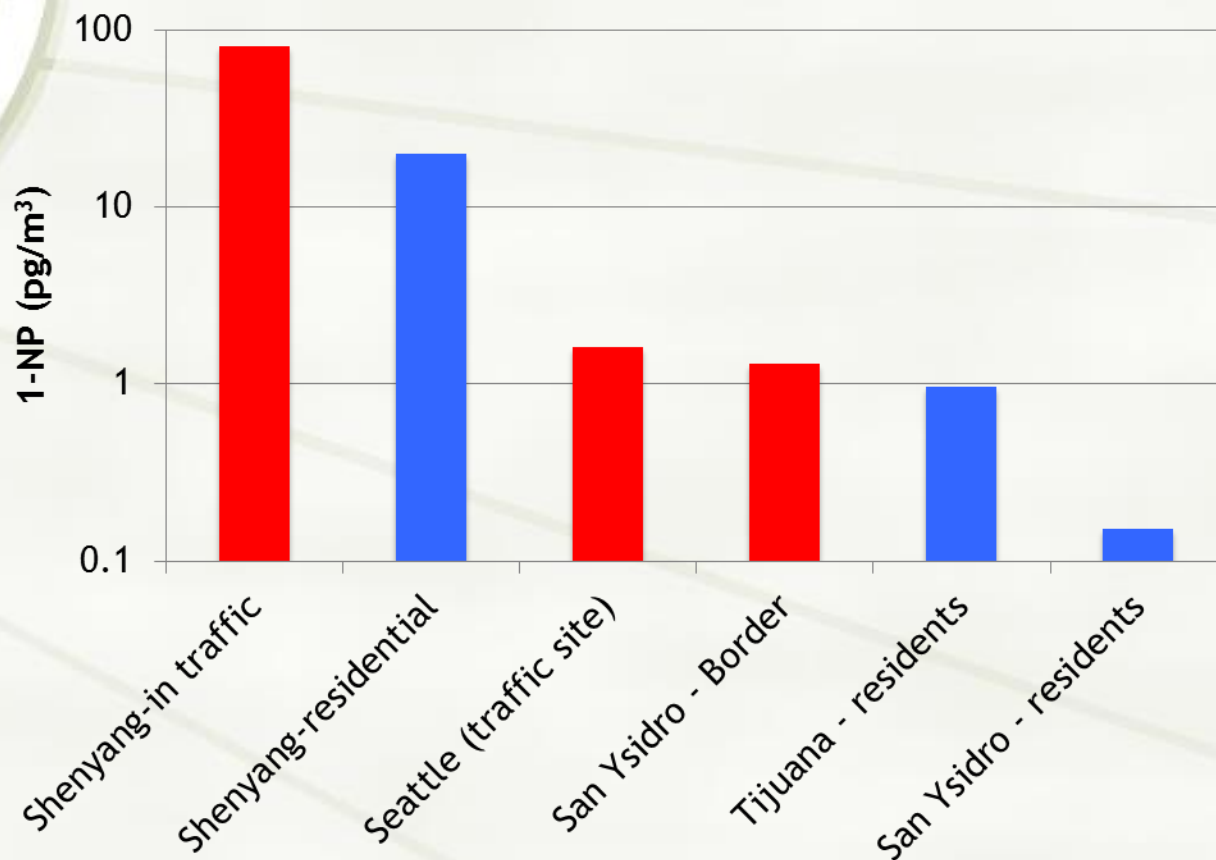


1-NP exposures in underground miners

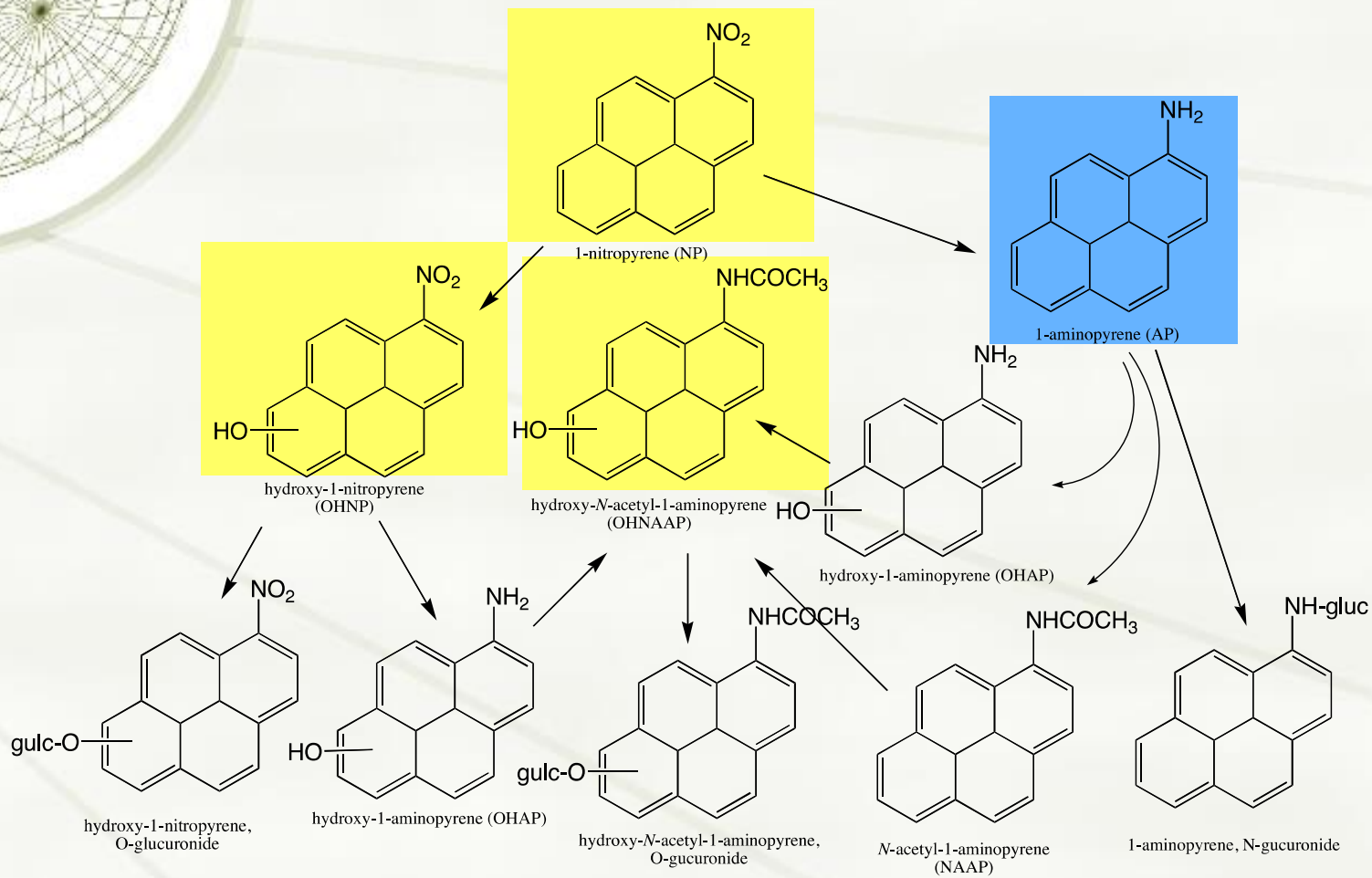




Air measurements

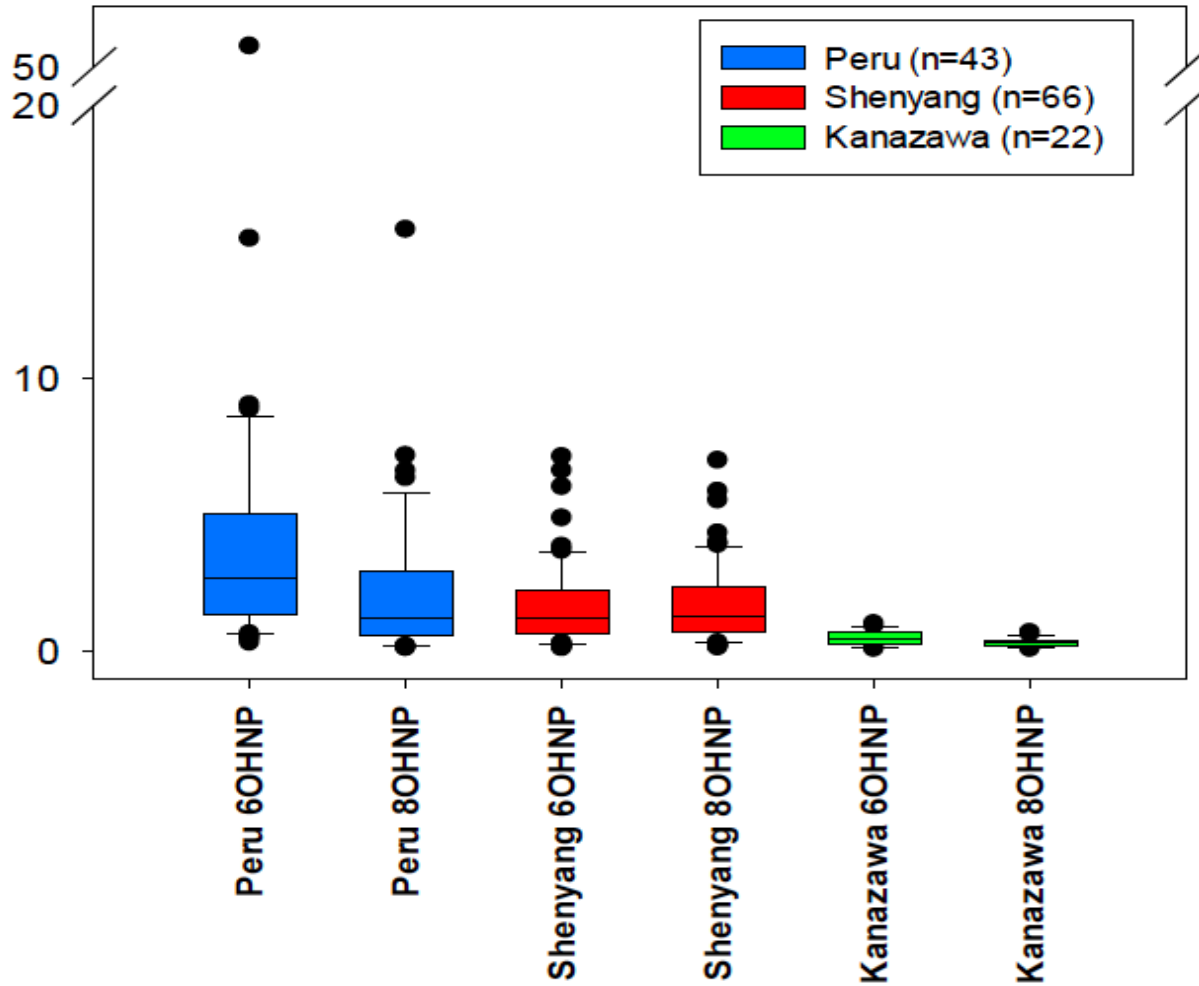


Biological monitoring of exposure to 1-NP



1-NP metabolite levels

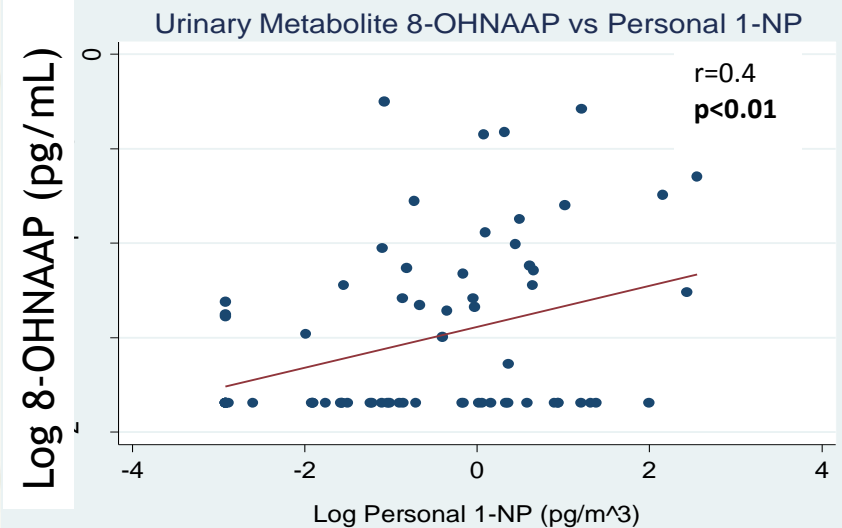
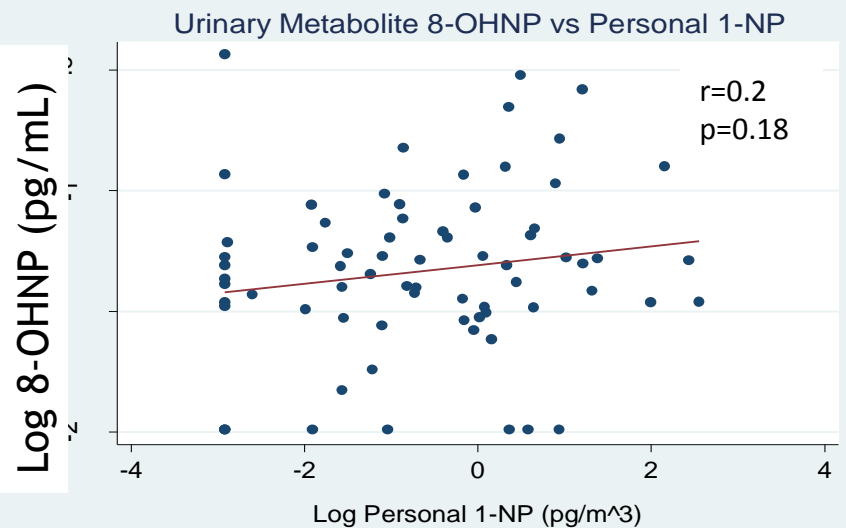
Hydroxy-Nitropyrene Metabolite Concentrations in Urine (pg Metabolite/mg Creatinine)





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 et al measured 2-200 ng of 1-AP in 24 hr urine specimens from underground miners. Corresponding 1-NP exposures $\sim 0.5\text{-}3 \text{ ng/m}^3$
- ★ Laumbach observed $\sim 10\text{x}$ 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 $\sim 1\text{-}3 \text{ ng/L}$
 - ★ Mass balance on Laumbach study indicates mass 1-NP inhaled 2.7 ng ; mass excreted/24hrs $\sim 1\text{-}3 \text{ ng}$

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

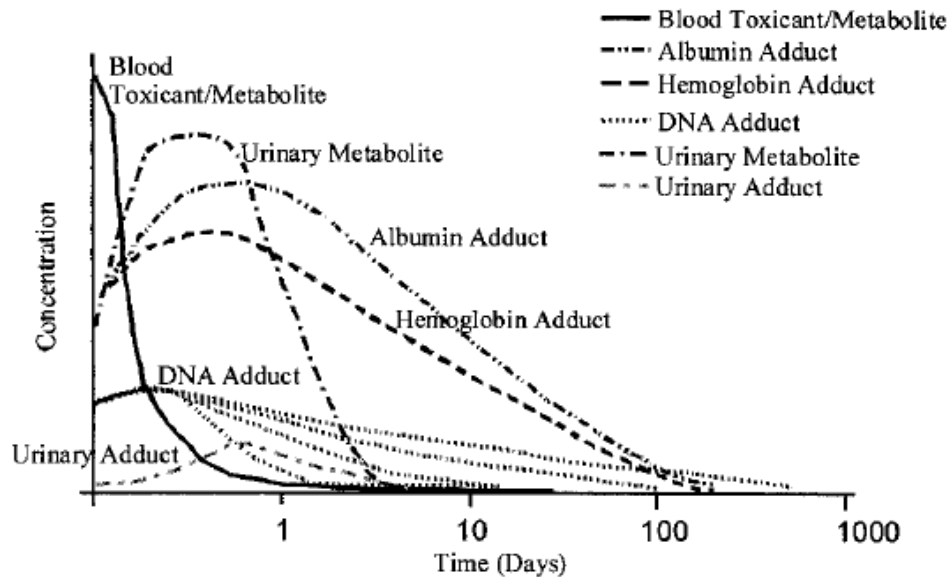


Figure 4. Post-exposure fate of a nonpersistent toxicant in blood and urine.



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.