A view at the interface between particle chemistry and toxicology

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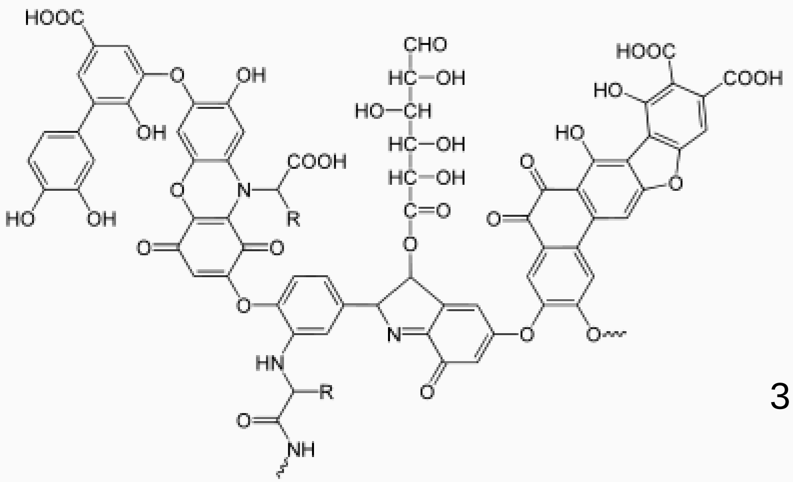
Introduction

I. Focus on primary (organic) aerosol particle composition
II. Provide a description of how bulk chemistry and individual molecules in PM have influenced toxicology
III. Examine how past and novel developments in analytical chemistry influence toxicology applications
IV. Possible new directions for health-related research including bioavailibility and thermodynamics based toxicology
V. Wrap-up

Aerosol chemical fractions

- organic carbon (OC); elemental carbon (EC); black carbon (BC); brown carbon (BrC);
- humic-like substances (HULIS);
- water-soluble organic carbon (WSOC);
- oxygenated organic aerosol (OOA) (Aerosol MS)
- molecular weight and size
- functional group-based chemistry (FT-IR)
- **volatility and thermal-chemical fractions**
- elemental and ionic (K^+ with some chloride, nitrate, and sulfate)
- water (hygroscopicity)

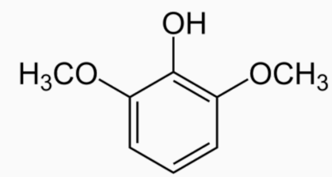


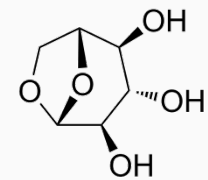
Bulk chemistry and toxicology

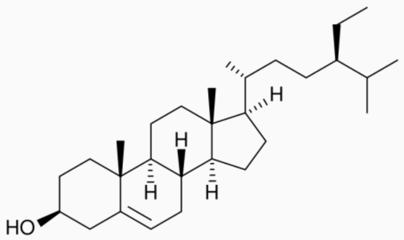
- Photochemical transformation of primary pollutants causes greater biological effect
  - Transcriptional changes in the RNA genome were observed *in-vitro* (qRT-PCR)
  - Rager et al. (2011) *Environ. Health Perspect.* 119 (11), p. 1583
- Volatility fraction of diesel emissions influences redox activity (SVOCs are potent)
  - Atmospheric dilution of emissions potentially governs PM toxicity (DTT assay)
  - Biswas et al. (2009) *ES&T* 43, p. 3905
- Both water-soluble and insoluble fractions of PM likely contribute to ROS toxicity
  - Wang et al. (2013) *Atmos. Environ.* 77, p. 301
- OC and EC (WSOC) levels influence biological effects (including cardiovascular)
  - Gilmour et al. (2015) *Anal. Bioanal. Chem.* DOI 10.1007/s00216-015-8797-9

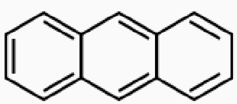
Examples of major organic compound classes

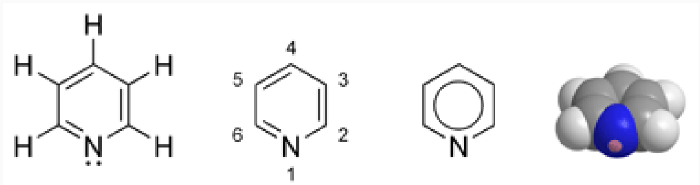
- carbohydrates and derivatives (anhydro-sugars)
- lignin derivatives (methoxyphenols)
- diterpenoids and triterpenoids
- phytosterols
- carboxylic acids
- alkanols, alkanals, and alkanoates
- alkanes and alkenes
- **polycyclic aromatic hydrocarbons (PAH)**
- **dioxins and furans**
- **organic nitrogen compounds (indoles, nitriles)**
- **heterocyclics (thiophenes, organometallics)**











- GC-MS identified compounds
- Relative proportions and class change with atmospheric conditions and combustion source

Medeiros and Simoneit, ES&T, **2008** (*42*) p. 8310

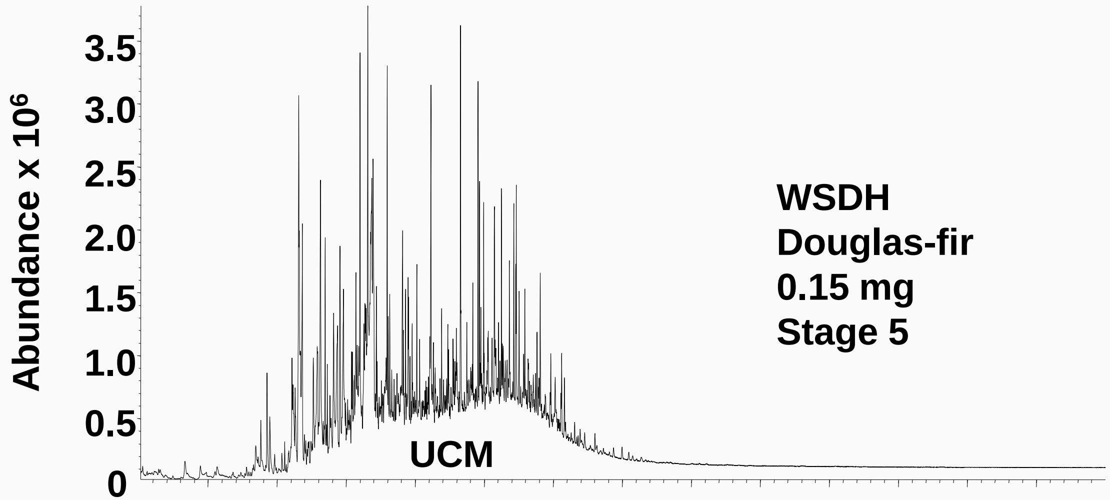
Molecular toxicology

- 1-NP and B[a]P mutagens detected in human lung tissue specimens
  - Proposed as tumor induction agents in female non-smokers inhaling coal burning emissions
  - Tokiwa et al. (1993) *Carcinogenesis*, Vol.14 p. 1933

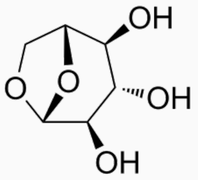
- Statistical analysis (PCA-PLS) show lung toxicity of motor vehicle emissions is closely associated with lubricating oil compounds
  - McDonald et al. (2004) *EHP, 112, p. 1527*

- Marker-based source apportionment shows urban sites impacted by vehicles and industry are most toxic.
  - Also done in combination with PCA-PLS (links chemicals, sources and health endpoints)
  - Acute cytotoxicity and inflammation
  - Seagrave et al. (2006) *EHP*,114, p. 1387

GC-MS (biomass burning example)



- SVOC chemistry grounded in GC-MS
- GC-MS limited by:
- temperature /volatility (300 °C)
  - thermal degradation
- polarity
  - derivatization
- resolution (column space)
  - –2-D GC methods



Resolution and temp. limits of GC-MS

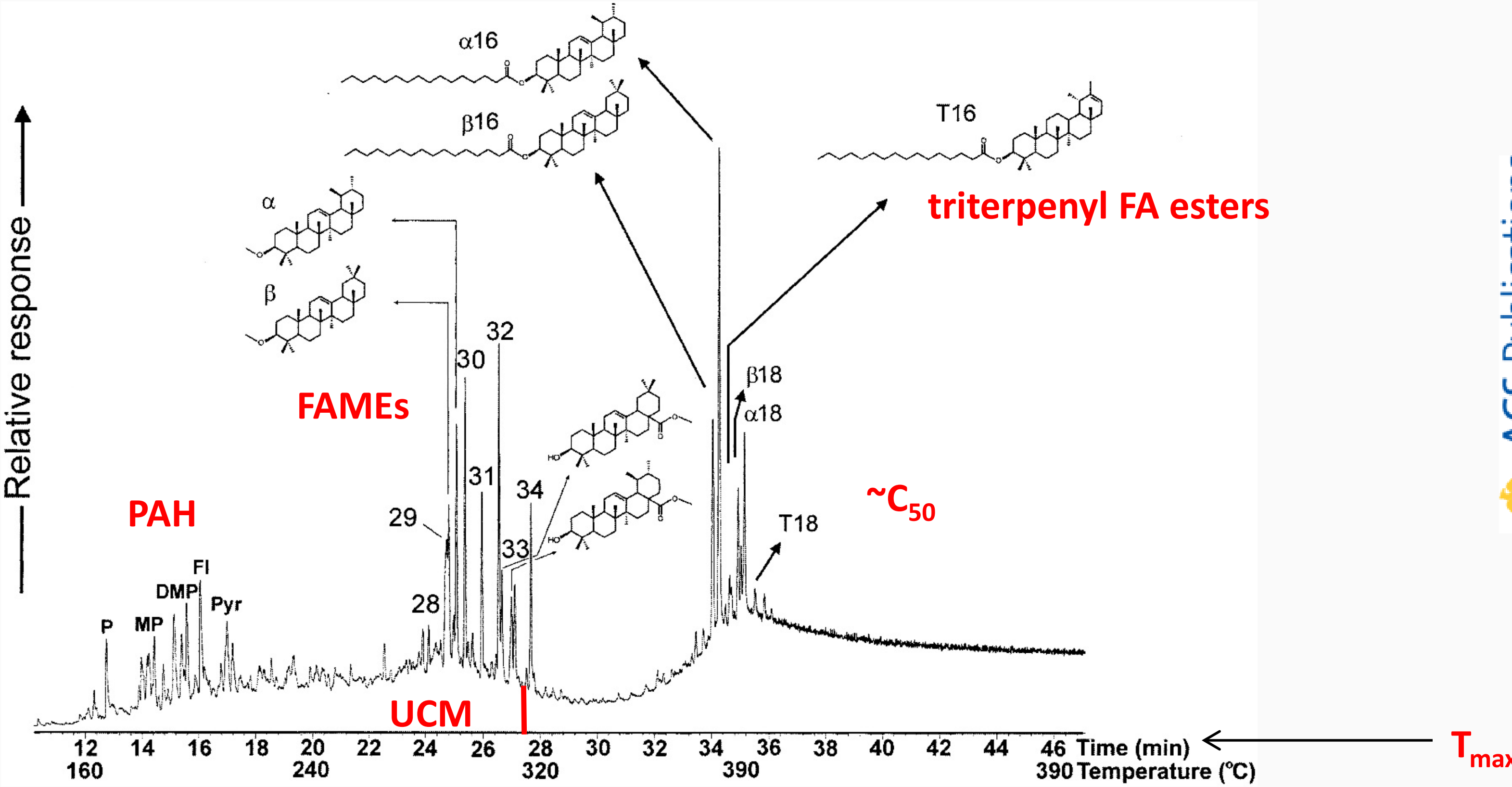
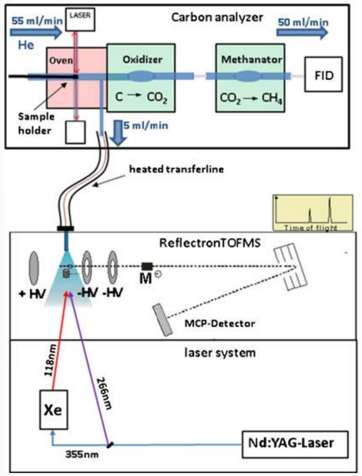


Figure 5. Representative total ion current trace (HTGC−MS) of the ester fraction from the smoke extract from burning of Castanha-do-Pará. Numbers refer to the carbon chain length of free fatty acids (analyzed as the methyl esters): P = phenanthrene; MP = methylphenanthrenes; DMP = dimethylphenanthrenes; Fl = fluoranthene, and Pyr = pyrene. α, β, and T are the esterified triterpenols α-amyrin, β-amyrin, and taraxasterol, respectively.

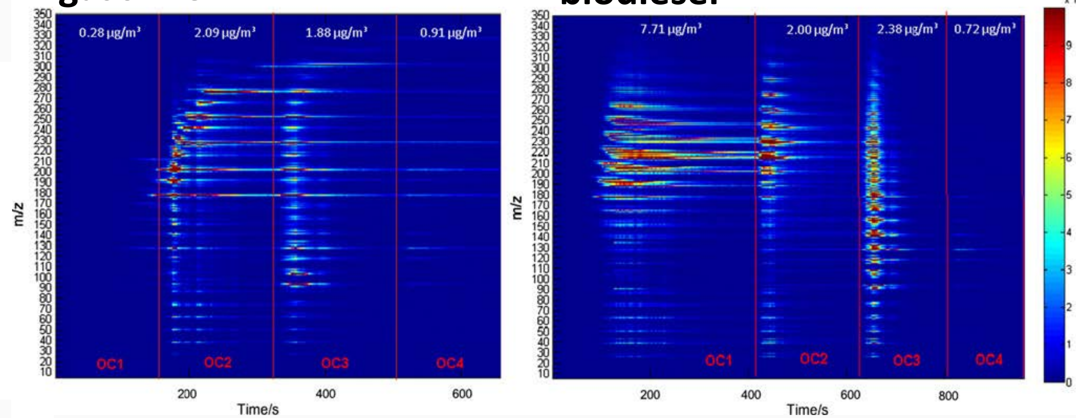
Carbon analyzer and PI-MS analysis

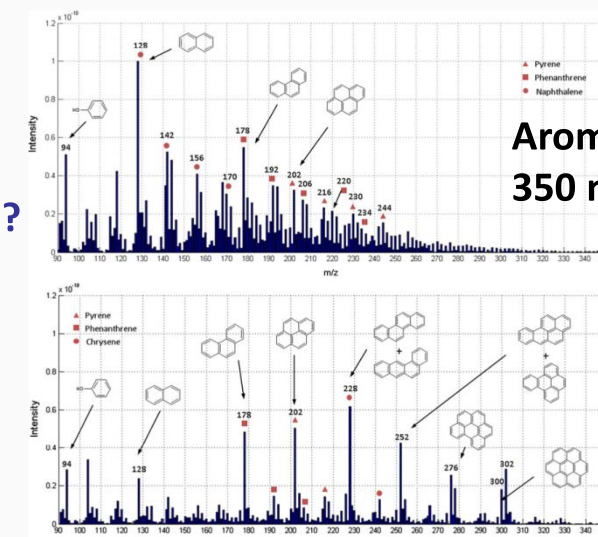
Chemistry changes with volatility:



Pure Helium		Helium / 2 % O_2	
OC1	120°C	EC1	550°C
OC2	250°C	EC2	700°C
OC3	450°C	EC3	800°C
OC4	550°C		

gasoline **biodiesel**





Aromatics 350 m/z

How do we further develop a volatility-based toxicology model?

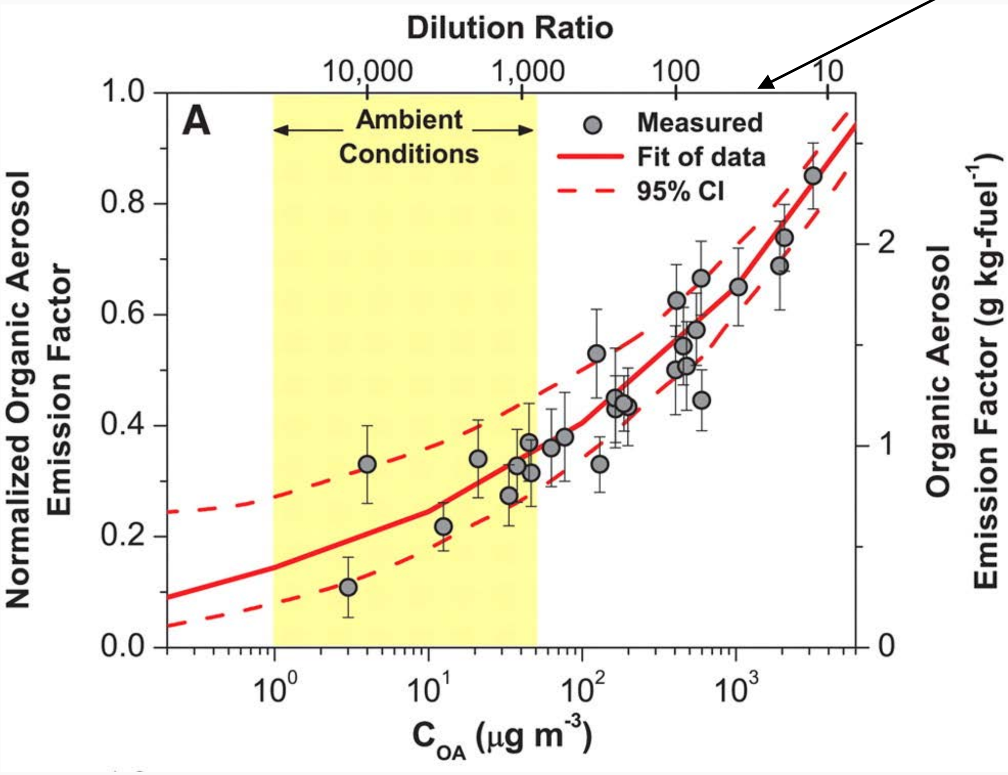
Higher temperature fractions contain PAH

Grabowsky et al., (**2011**), *Anal. Bioanal. Chem.*, 401, pp. 3153-3164

Why is volatility distribution important?

Diesel exhaust at 300 °K

typical emissions collection



- produce more realistic primary SVOC chemical exposure scenarios
  - considering phase
- there is more anthropogenic SOA than primary OA
  - reactive byproducts will be important

Robinson *et al.*, *Science*, **315** (5816): 1259-1262

Solvent extraction

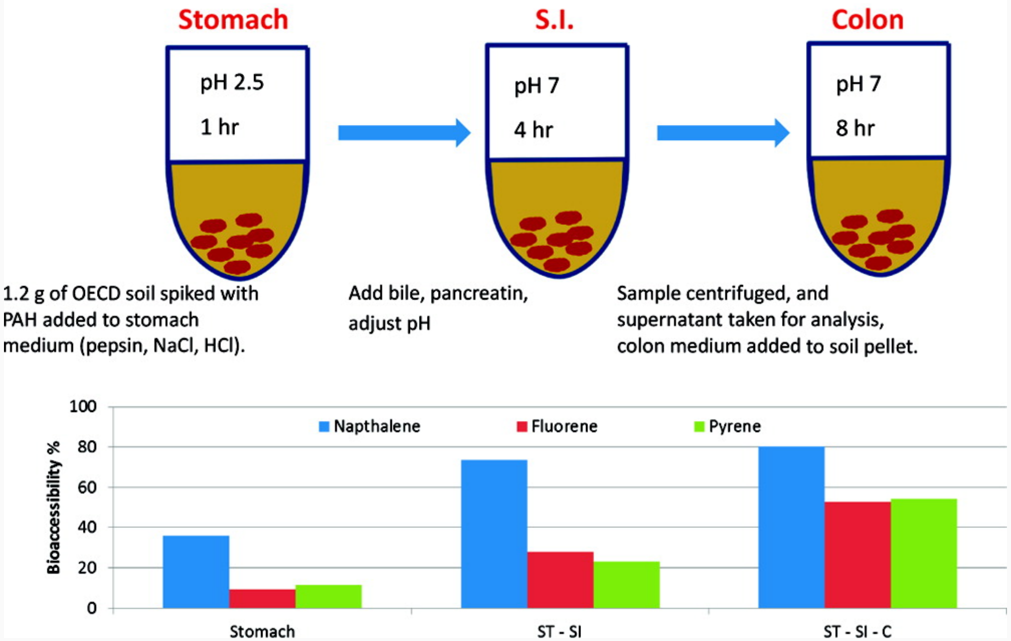
- goal is to extract as much and as many **organic** compounds as possible
- determine a maximum possible exposure
- **there can be organic solvent bias (dosimetry)**

What about bioavailability?

According to WEB OF SCIENCE™.

- since 1985, 518 papers have focused on “particulate matter” *AND* “bioavailability”
- more than half of those focused on “metals”
- minimal focus on organic compounds
- dissolution testing standards are generally ignored (Wiseman [2015] *Anal. Chim Acta*, 877 p. 9)
- cell response/expression was covered (e.g.; ascorbate oxidation, glutathione depletion)

Physiological-based fluid extractions



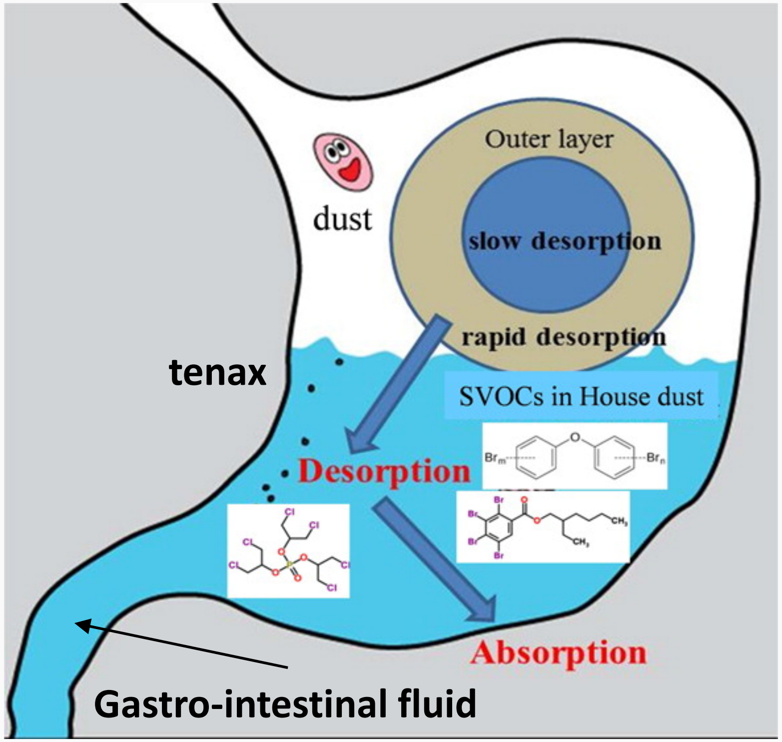
- Experiments
  - PAH in soil in the gastro-intestinal system
  - sequentially or in batch, time
  - differences in PAH bioaccessibility observed
  - GC-MS

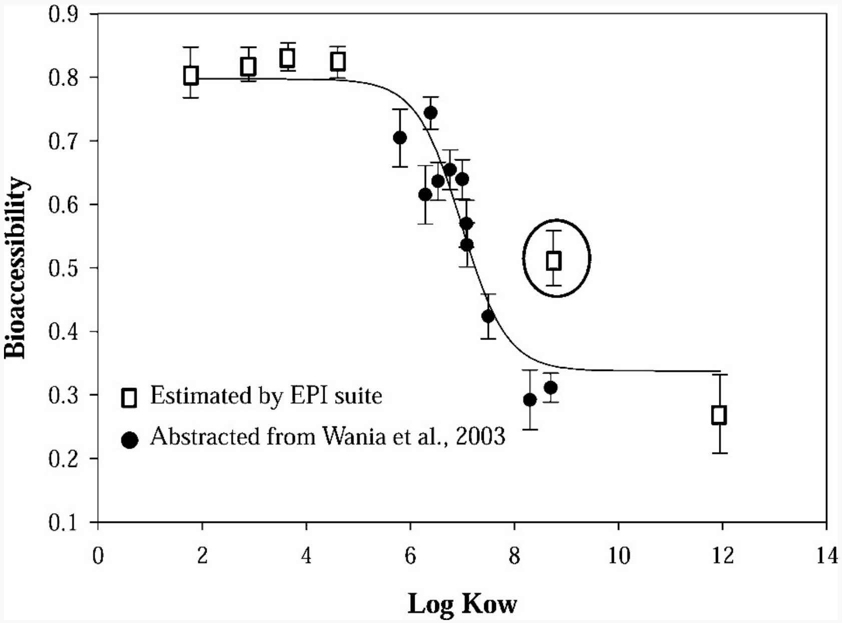
- Results
  - PBET underestimates [PAH] in soil
  - desorption of PAH is controlled by many factors
  - biological environment, K_{OW}
  - colon media aggressively desorbed PAH.

Precedent for particle extractions with lung fluid

E. L. Tilston; G. R. Gibson; C. D. Collins; *Environ. Sci. Technol.* **2011,** 45, 5301-5308.DOI: 10.1021/es2004705

Physiological-based fluid extractions





hydrophobic →

Flame retardants-PBDE and organophosphates

Published in: Mingliang Fang; Heather M. Stapleton; *Environ. Sci. Technol.* **2014,** 48, 13323-13330. DOI: 10.1021/es503918m

Simulated lung fluids

Table 11. Simulated Lung Fluid (SLF)

Composition	SLF1 ALF (g/L)	SLF1 Gamble's Solution (g/L)	SLF2 (mg/L)	SLF3 (g/L)	SLF4 (g/L)	SLF5 mMol/L
magnesium chloride	0.050	0.095	-	0.2033 (hexahydrate)	$MgCl_2$ hexahydrate 0.2033	-
sodium chloride	3.21	6.019	6800	6.0193	6.0193	116
potassium chloride	-	0.298	-	0.2982	0.2982	-
disodium hydrogen phosphate (Na_2HPO_4)	0.071	0.126	1700 (monohydrate)	-	-	-
sodium sulfate	0.039	0.063	-	0.0710 (anhydrous)	0.0710 (anhydrous)	-
calcium chloride dihydrate	0.128	0.368	290	0.3676	0.3676	0.2
sodium acetate	-	0.574	580	0.9526 (trihydrate)	0.9526 (trihydrate)	-
sodium hydrogen carbonate ($NaHCO_3$)	-	2.604	2300	2.6043	2.6043	27
sodium citrate dihydrate	0.077	0.097	-	0.0970	0.0970	0.2
sodium hydroxide	6.00	-	-	-	-	-
citric acid	20.8	-	420 (monohydrate)	-	-	-
glycine	0.059	-	450	-	-	5
sodium tartrate dihydrate	0.090	-	-	-	-	-
sodium lactate	0.085	-	-	-	-	-
sodium pyruvate	0.086	-	-	-	-	-
ammonium chloride	-	-	5300	-	-	10
phosphoric Acid	-	-	1200	-	-	-
sodium carbonate	-	-	630	-	-	-
potassium acid phthalate	-	-	200	-	-	-
sulfuric acid	-	-	510	-	-	0.5
sodium citrate dihydrate	-	-	590	-	-	-
sodium phosphate monobasic monohydrate	-	-	-	0.1420	0.1420	1.2
L-cystine hydrochloride	-	-	-	-	-	1.0
DPPC[a]	-	-	-	-	0.02% (w/v)	-
DTPA[b]	-	-	-	-	-	0.2
ABDCB[c]	-	-	-	-	-	50
Properties						
pH	4.5	7.4	7.4	7.4	7.4	-

[a] *DPPC: dipalmitoylphosphatidylcholine.*
[b] *DTPA: diethylenetriaminepentaacetic acid.*
[c] *ABDCB: alkylbenzyl dimethyl ammonium chloride 50% by volume.*

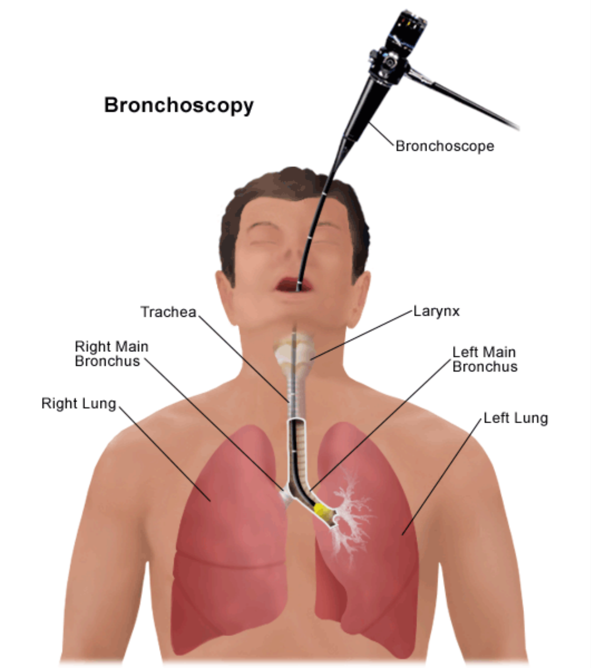
Gamble's solution - deep lung

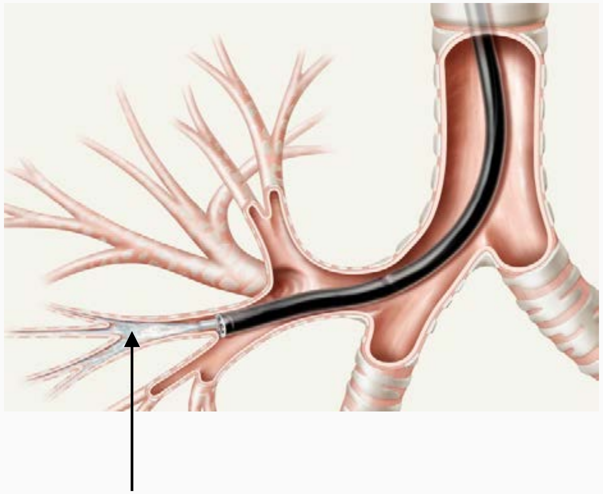
ALF – following macrophage phagocytosis

SLF2 – extracellular fluid interaction

- Respiratory mucous contains
  - Glycoproteins, proteins, and lipids.
  - Varies with disease states
- Lung is generally difficult to simulate
  - Due to surfactant and aqueous fluid
- Salts can precipitate
- Stability of organic compounds in fluids is unknown
- work-up is required to perform a chemical analysis

New research direction



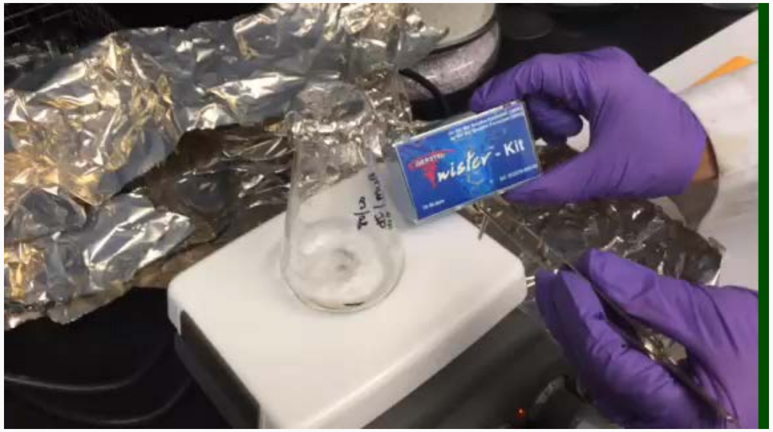


Bronchial lavage with saline wash

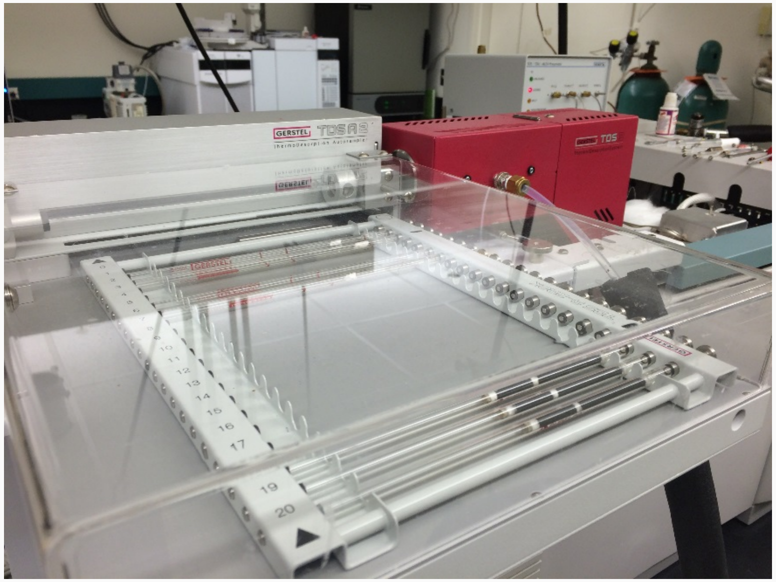
- Source exposed and unexposed patients and mice
- Lavage allows the collection of lung fluid, cells, and other materials inside the air sacs
- This fluid will be collected and used to perform PM extractions, assess bioavailability
- Potential to reduce animal use and save time compared with tissue measurements

Courtesy of Dr. Andy Ghio of the U.S. EPA

Stir-bar sorptive extraction



PDMS stir bar extraction



TD-GC-MS

Wrap-up

- Combustion and ambient aerosol is chemically complex,
  - requires multiple analytical approaches
- Different chemical entities are commonly associated (OC, HULIS, WSOC, etc.)
- links between POA and SOA need to be explored further using thermodynamics
  - generational chemistry
- thermodynamics-based toxicology will emerge and is important for source-to-effect research
- It is time for physiological-based extractions of PM using lung fluids
  - This will improve our understanding of bioavailability of specific PM components