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Non-targeted analysis methods: Tools for integrating rapid chemical assessments with exposome research

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Office of Research and Development

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA

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Why Study Exposures?

1) For understanding causes of human disease

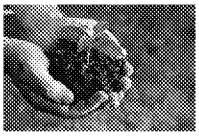
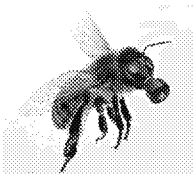
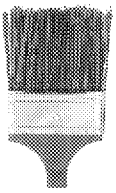
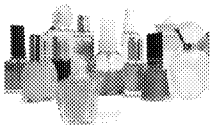
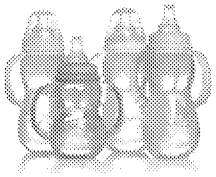
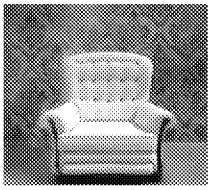
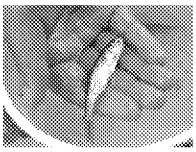
"…70-90% of disease risks are probably due to differences in environments"

DIMENSIONS

Environment and Disease Risks

Stephen M. Rappaport and Martyn T. Smith

2) For ensuring chemical safety and environmental/public health

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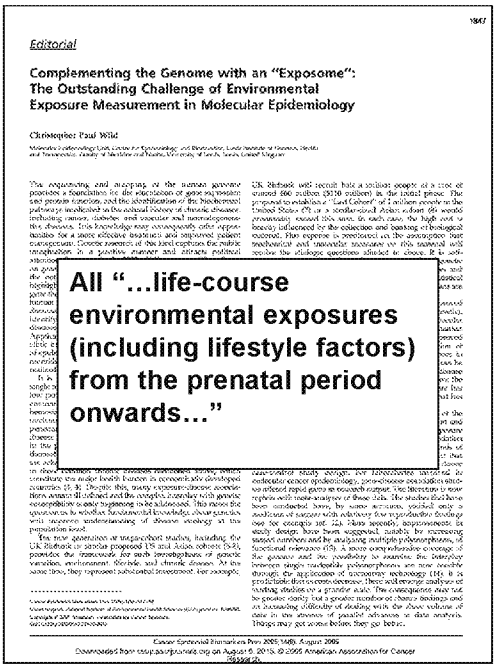
What is the "Exposome"?



1847

Editorial

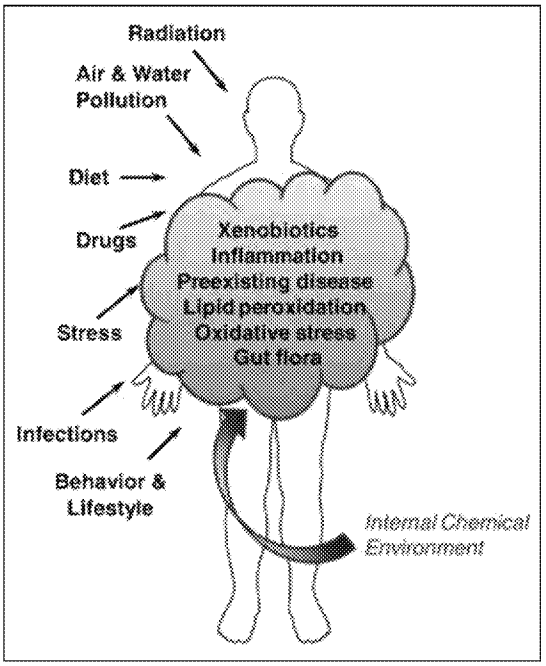
Complementing the Genome with an "Exposome": The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology

Christopher Paul Wild

Cancer Epidemiol Biomarkers Prev 2005;14(8). August 2005

Downloaded from cebp.aacrjournals.org on August 6, 2013. © 2005 American Association for Cancer Research.

All "…life-course environmental exposures (including lifestyle factors) from the prenatal period onwards…"



Rappaport SM. *J Expo Sci Environ Epidemiol.* 2011 Jan-Feb;21(1):5-9.

Workshops and Research Programs

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EMERGING SCIENCE FOR ENVIRONMENTAL HEALTH DECISIONS

The Exposome

The Exposome: A Powerful Approach for Evaluating Environmental Exposures and Their Influences on Human Disease

February 25-26, 2014

EMERGING SCIENCE FOR ENVIRONMENTAL HEALTH DECISIONS

Individual Exposomes

Emerging Technologies for Measuring Individual Exposomes

December 8-9, 2013

EMERGING SCIENCE FOR ENVIRONMENTAL HEALTH DECISIONS

Metabolomics as a Tool for Characterizing the Exposome

May 28 – 29, 2015

HEALS

http://www.heals-eu.eu/index.php/project/

HELIX BUILDING THE EARLY-LIFE EXPOSOME

http://www.projecthelix.eu/en

expos omics

http://www.exposomicsproject.eu/

HERCULES Exposome Research Center

http://emoryhercules.com/

the human exposome project

http://humanexposomeproject.com/

NIH National Institute of Environmental Health Sciences

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How is it Measured?
UVIS25 UV Index Sensor
Air Quality
20
MEAL SNAP
SEE YOURSELF.
5

Chemical Data Landscape

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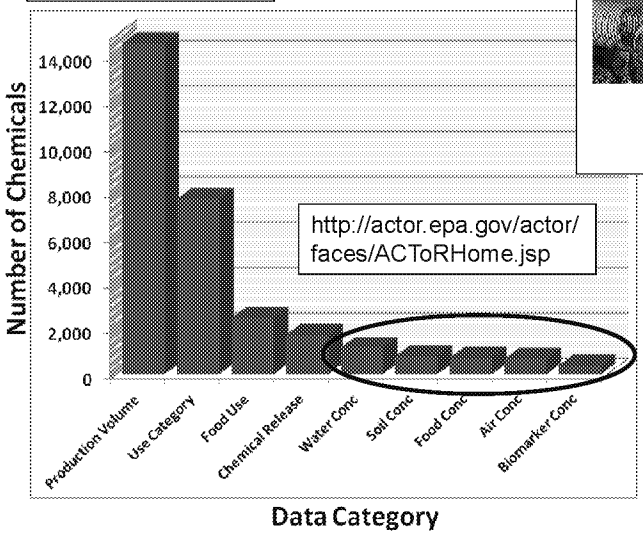
TSCA: > 84,000



http://actor.epa.gov/actor/faces/ACToRHome.jsp

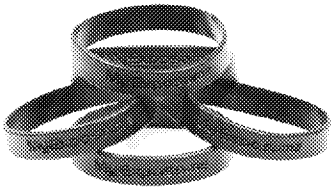
P.P. Egeghy et al. *Sci Total Environ.* 414 (2012) 159–166

~4000 chemical substances

http://www.t3db.ca/

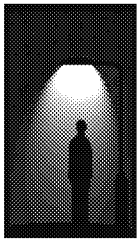
MyExposome

1400+ chemical substances

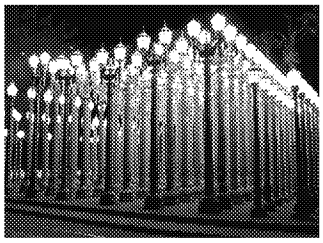


http://www.myexposome.com

Analytical Approaches for Chemicals



Targeted analysis:
Is the population exposed to chemical A?



Suspect screening analysis (SSA):
Is the population exposed to chemicals A - ZZZ?

Non-targeted analysis (NTA):
To what chemicals is the population exposed?

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Rapid Growth in NTA and SSA

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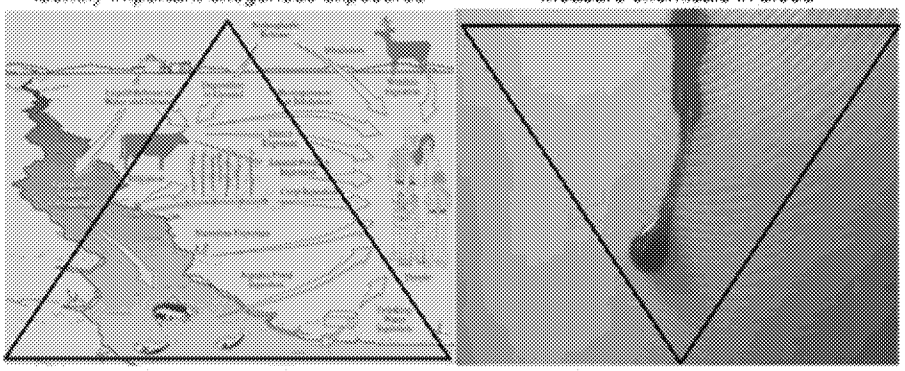
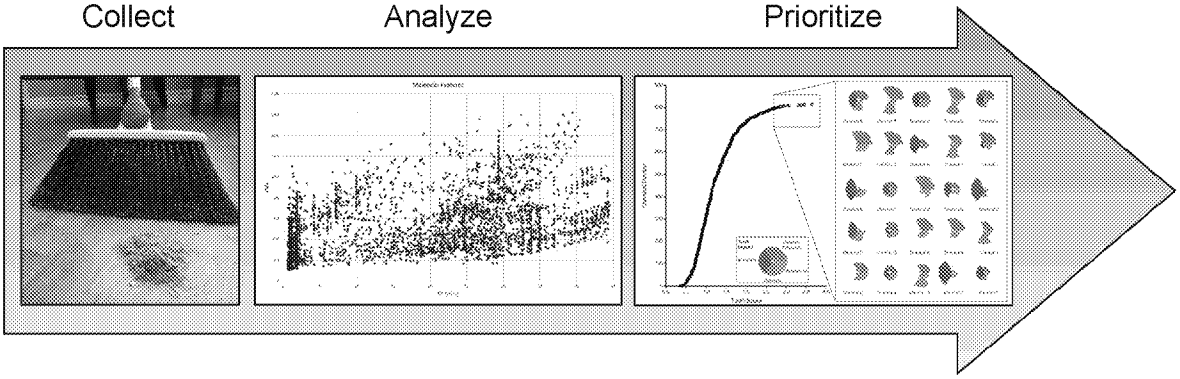
Characterization Approaches

Rappaport SM. *J Expo Sci Environ Epidemiol.* 2011 Jan-Feb;21(1):5-9.



Benefits:	1) Consideration for eco health	1) Integrated measures (dose)
	2) Mechanistic understanding	2) Exogenous & endogenous
	3) Allows for mitigation	3) Allows for treatment
Challenges:	1) Degradation/transformation	1) ADME
	2) Many media	2) Sensitivity

EPA Case Study Using House Dust

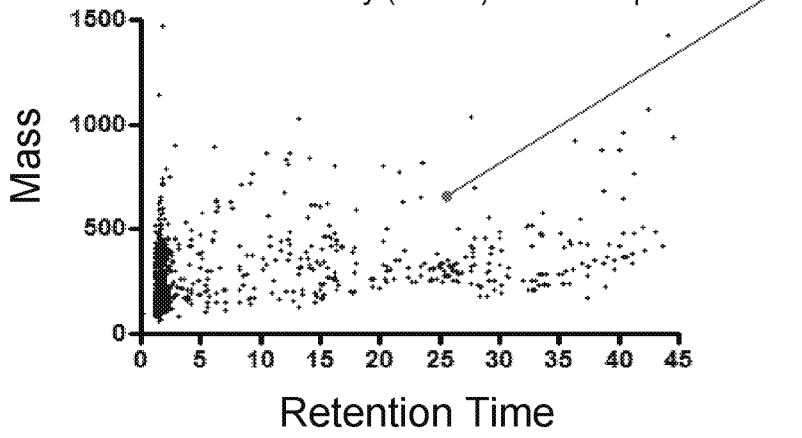


Method to prioritize "suspects" in dust for follow-up confirmation

(Rager *et al.*, submitted to *Environ. Int.)*

Suspect Screening Approach

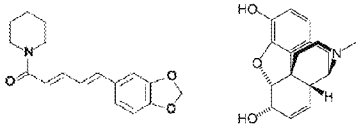
947 Peaks in an American Healthy Homes Survey (AHHS) Dust Sample



Each peak corresponds to a chemical with an accurate mass and predicted formula:

$C_{17}H_{19}NO_3$

Multiple chemicals can have the same mass and formula:



Is chemical A present, chemical B, or both?

We tested our analytical abilities using a known, but hidden mixture of 100 ToxCast chemicals

100 Chemical (ToxCast) Pilot

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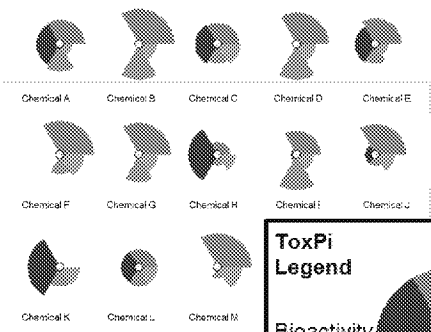
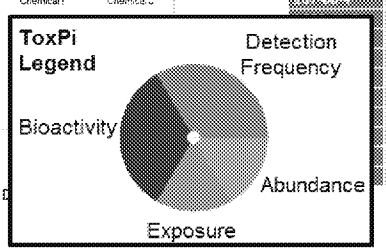
We use DSStox to tentatively identify chemicals, and ExpoCast and ToxCast/Tox21 data to prioritize chemicals for confirmatory analysis

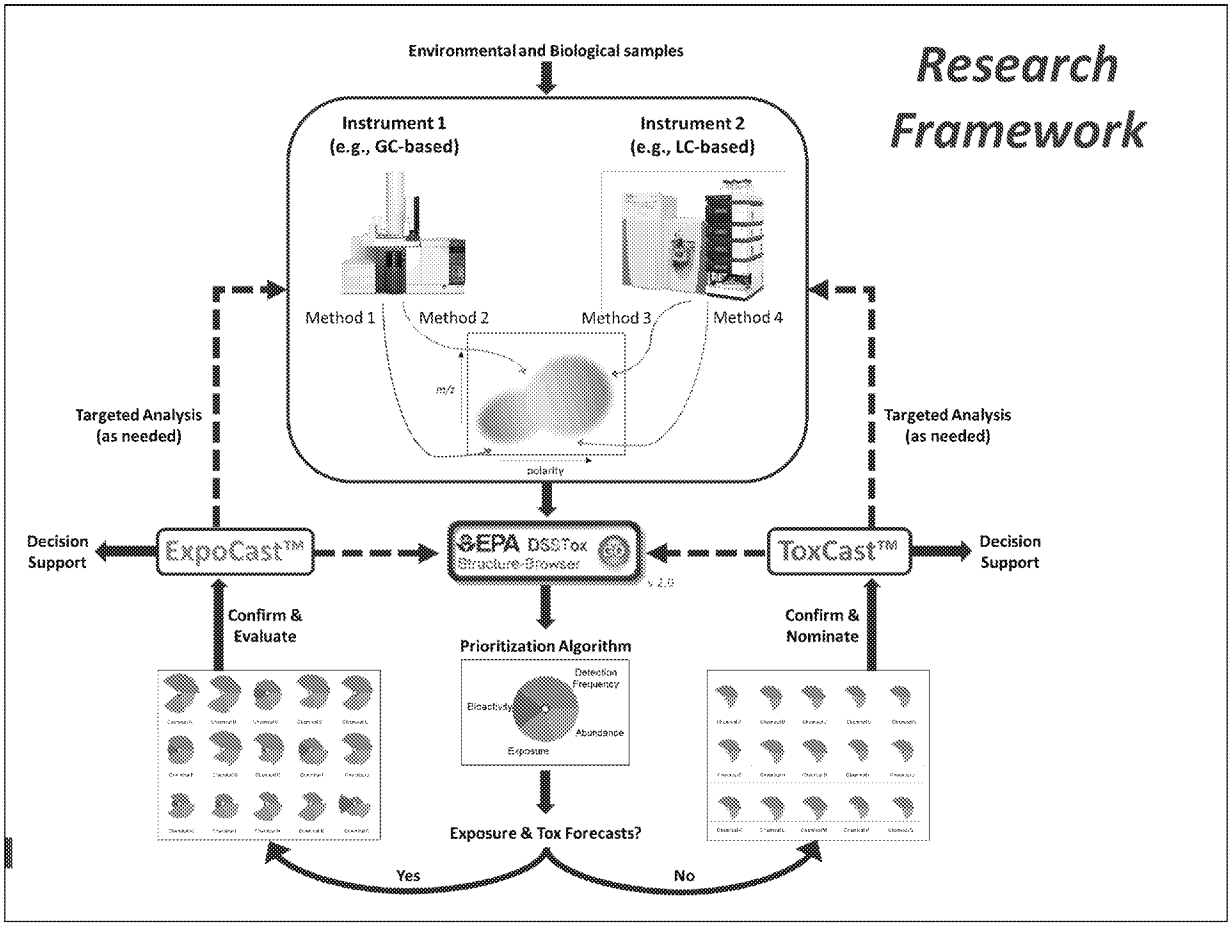
We can express these factors with ToxPI to identify the highest priority candidates (Rager *et al.*, under review)





CAS	Chemical Name	ToxPi Rank (%)	N_i	N_{tot}	PubMed hits
27138-31-4	Di(propylene glycol) dibenzoate	1.1%	32	4	0
94-62-2	Piperine	1.2%	42	42	0
101-20-2	Triclocarban	1.7%	21	21	0
134-62-3	N,N-diethyl-m-toluamide (DEET)	2.6%	33	33	15
84-66-2	Diethyl phthalate (DEP)	4.2%	23	23	24
94-13-3	Propylparaben	5.4%	19	19	0
1553-34-8	3,6,9,12-Tetraoxahexadecan-1-ol	5.7%	25	1	0
87-78-9	N-Dodecanoyl-N-methylglycine	6.0%	18.5	6	0
13674-87-8	Tris(1,3-dichloro-2-propyl) phosphate (TDCPP)	6.8%	18	15	14
99-76-3	Methylparaben	8.7%	12.5	16	0
298-46-4	Carbamazepine	12.0%	1	1	2
78-42-2	Tris(2-ethylhexyl) phosphate (TEHP)	12.4%	3.5	1	9
143-22-6	2-[2-(2-Butoxyethoxy)ethoxy]ethanol	15.5%	4.5	2	0
77-93-0	Triethyl citrate	16.8%	6	6	0
589-68-4	Tetradecanoic acid, 2,3-dihydroxypropyl ester	18.3%	3	1	0
120-32-1	Clorophene	25.1%	4	4	0
54-11-5	Nicotine	25.3%	6	10*	63
80-09-1	4,4'-Sulfonyldiphenol	33.5%	2.5	4	0
754-91-6	Perfluoroctylsulfonamide acid (PFOSA)	34.4%	1	1	0
86386-74-4	Fluconazole	34.8%	0.5	1	3
335-67-1	Perfluorooctanoic acid (PFOA)	38.0%	2	3	33
50-22-6	Corticosterone	39.9%	3	1	7
105-99-7	Dibutyl hexanedioate	48.9%	6.5	1	2
107-66-4	Phosphoric acid, dibutyl ester	51.0%	3.5	4	0
	C.I. Disperse Yellow 3	51.4%**	3	3	0
	Octyl beta-D-glucopyranoside	51.7%	1	1	0
	Perfluorodecanoic acid (PFDA)	54.2%	3	3	3
	Carbaryl	55.5%	2	2	13
	Rofecoxib	77.1%	0.5	1	0
	Primidone	78.6%	3	3	0
	2,4,5-Trichlorobenzenesulfonic acid	82.7%	2	2	0
	Lufenuron	89.7%	1	1	0
	Diphenyl phosphate	91.4%	3	6	0

Rager, Strynar, Liang, McMahen, Richard, Grulke, Wambaugh, Isaacs, Judson, Sobus


Research Framework
Environmental and Biological samples
Instrument 1 (e.g., GC-based)
Instrument 2 (e.g., LC-based)
Method 1
Method 2
Method 3
Method 4
m/z
polarity
Targeted Analysis (as needed)
Targeted Analysis (as needed)
Decision Support
ExpoCast™
EPA DSSTox Structure-Browser
ToxCast™
Decision Support
Confirm & Evaluate
Confirm & Nominate
Prioritization Algorithm
Detection Frequency
Bioactivity
Abundance
Exposure
Exposure & Tox Forecasts?
Yes
No

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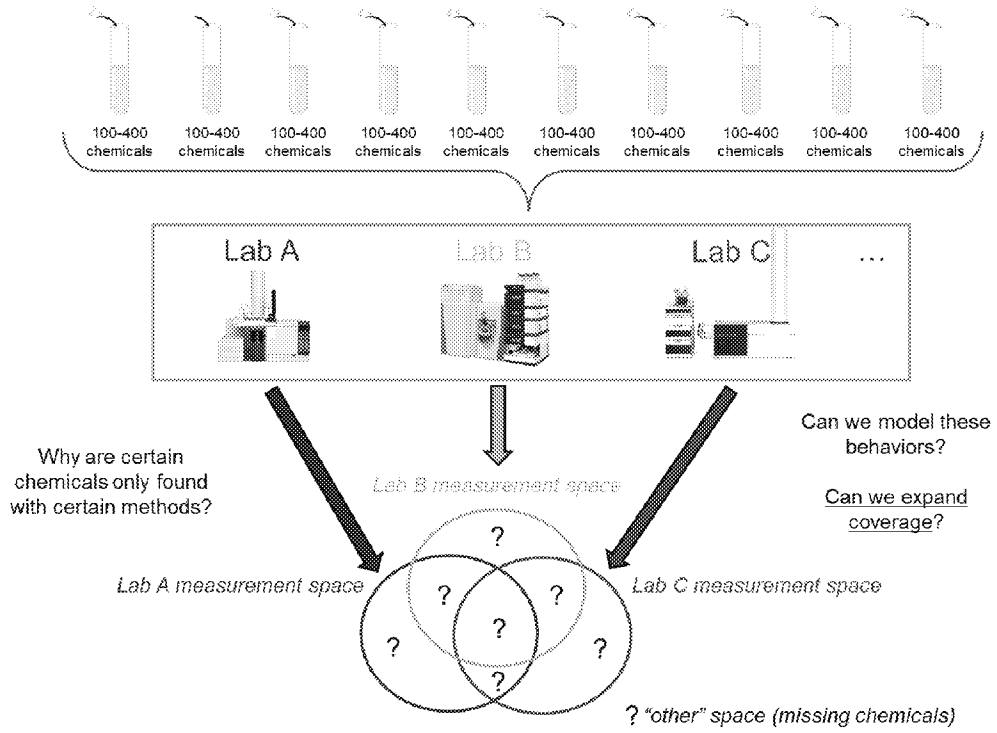
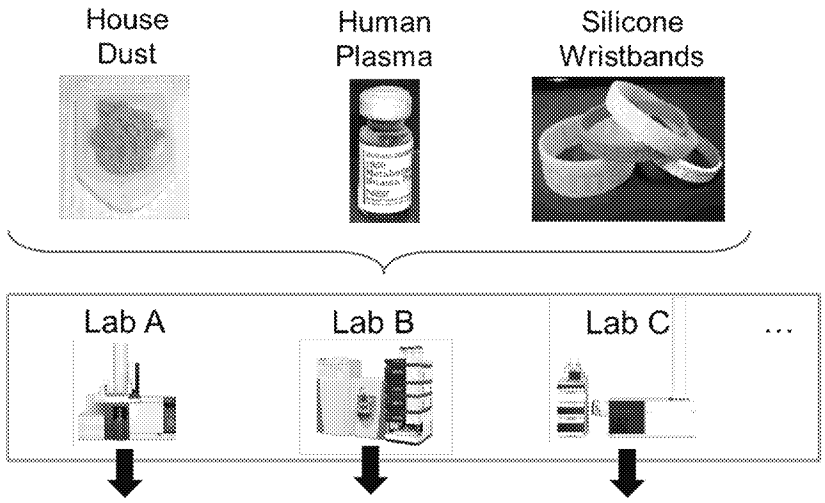
EPA Workshop on NTA and SSA

- Initiate dialogue amongst experts in NTA and SSA
- Discuss tools in common to envir. and biological analyses
- Identify “best” tools for data generation, analysis & storage
- Facilitate communication/collaboration
- Prioritize areas in greatest need of research & new tools
- Discuss need/potential for broad collaborative efforts
- <u>Plan collaboration to demonstrate the power of NTA/SSA</u>

Part 1: Synthetic Mixture Analysis



Part 2: "Real" Mixtures Analysis



How many chemicals?

Differences across methods?

Differences across media and methods?

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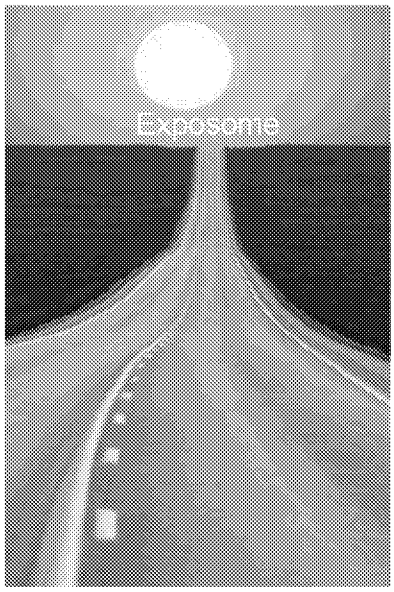
Research Goals



- **Sequence the human (or eco) exposome!**

- Establish performance benchmarks
- Integrate research communities
- Establish research consortia
- Collectively standardize methods
- Build open-source databases and workflows
- Share data and chemical standards

- **"Make non-targeted the new targeted"**
  - Dr. Thomas Burke

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Acknowledgements

- **EPA/ORD**:
  - Jennifer Orme-Zavaleta
  - Annette Guiseppi-Elie
  - Tina Bahadori
  - Mark Strynar
  - Elin Ulrich
  - Julia Rager (ORISE)
  - Ann Richard
  - Antony Williams
  - Chris Grulke (Lockheed Martin)
  - John Wambaugh
  - Kristin Isaacs

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Web links

Misc. Online Graphics:

- Bee: http://www.themarketbusiness.com/2015-04-25-bees-addiction-on-neonicotinoid-like-humans-on-nicotine
- Burning chair: http://www.environmentalleader.com/2013/11/26/fire-retardants-out-of-california-furniture/
- Cosmetics: http://www.justluxe.com/fine-living/health/feature-1591519.php
- Paint brush: http://oikos.com/library/green_materials/paints.html
- Plant: http://makecalgary.com/wp-content/upload/Biosolids-2.jpg
- Fish: http://www.thesmartmama.com/li-102/
- Health monitor: http://blog.aarp.org/2014/03/10/how-smart-phone-apps-help-doctors-track-your-health/
- UV sensor: http://www.st.com/web/en/press/p3655
- Air qualtiy app: http://news.discovery.com/tech/apps/pollution-level-check-at-your-fingertips-130104.htm
- Wristband sensor: http://www.angelsensor.com/
- Glasses: http://www.tokyotimes.com/glasses-help-track-eye-movements-will-tell-sleepy-tired/
- Meal Snap: http://blog.ziggytek.com/2011/04/06/app-of-the-day-meal-snap/
- Lamp post 1: http://sayra.deviantart.com/art/under-the-lamp-post-16921801
- Lamp post 2: https://beastandbean.wordpress.com/2008/11/24/urban-light-iaoma/
- Sun: http://cdn.playbuzz.com/cdn/5f9ab154-8aa4-4e79-9b7e-b41922e70fe0/d363275c-d231-4d1e-a474-e41165188b74.jpg
- Road and Sun: https://s-media-cache-ak0.pinimg.com/236x/9e/93/7d/9e937d445d95f1ff0629ce90deb6e470.jpg