www.exposomicsproject.eu

FACTSHEET N°2

April 2015

EXPOsOMICS has received founding from the European Union's Seventh Framework Program under grant agreement No. 308610

THE EXPOSOME refers to the totality of internal and external exposures which interact at a cellular and systems level to generate a metabolic/molecular signature which can be used to gain new understanding of the transition from health to disease.

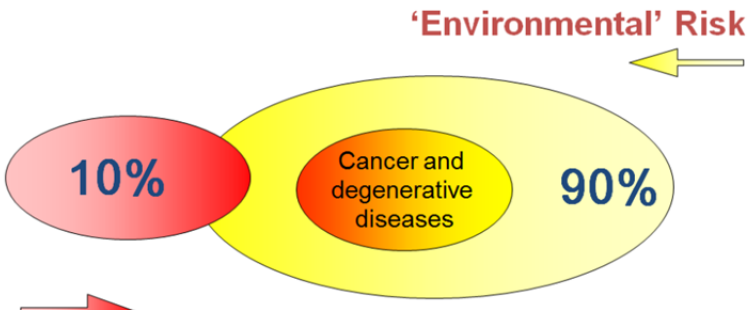
Such exposures come from a variety of sources including chemical and biological agents, gut microbial and psycho-social factors from pre-conception onwards, i.e., over the lifecourse. Assessment of the exposome at different stages of the lifecourse gives new insights into causal factors and mechanisms, which eventually may lead to new preventive strategies and treatments for chronic disease.

The exposome concept takes advantage of the rapid advances and availability in new technologies and the omics sciences. The external exposome can be measured with new more sensitive personal monitors and sensors. The internal exposome and the biological changes it induces in body molecules can be measured with high-throughput methods such as metabolomics, proteomics, transcriptomics, adductomics and epigenomics.

EXPOSOMICS has taken a lead in Europe in developing and applying these new technologies to epidemiological samples and cohorts. In this we have been working closely with the International Agency for Research on Cancer (IARC; Wild) and University of California, Berkeley (Rappaport, Smith) where the exposome concept was developed.

One of the premises of Exposomics work is that environmental exposures (E) or gene-environment interactions (GxE) are more important than genetic susceptibility (G) to explain disease occurrence (**Figure 1**). However, little is known on the causes of many chronic diseases, as the case of cancer exemplifies (**Figure 2**).

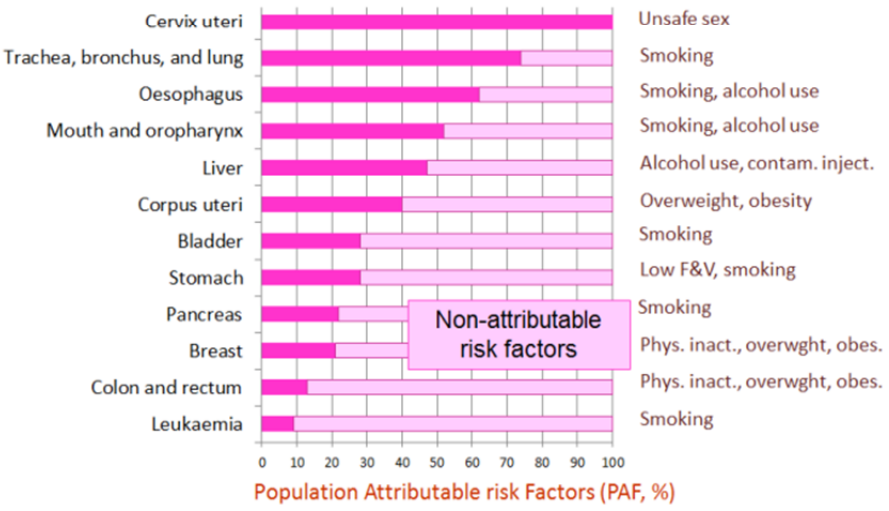
Figure 1 - Putting the E into GxE



M. T. Smith and S.M. Rappaport, "Building Exposure Biology Centers to Put the E into GxE Interaction Studies". Editorial in *Environ Health Perspect*, 117(8): A334-A335 (2009).

Figure 2

Known and unknown environmental causes of cancers



Established causes: infectious agents, smoking, alcohol, diet, lack of physical exercise

65% of cancer deaths unexplained

Danaei et al., 2005, *Lancet*

THE BLOOD EXPOSOME

To explore the "blood exposome" and its connection to disease, Rappaport et al (2014) sought human blood concentrations of many chemicals, along with their sources, evidence of chronic-disease risks, and numbers of metabolic pathways (Rappaport et al., 2014, Environ. Health Perspect).

From the literature they obtained human blood concentrations of 1,561 small molecules and metals derived from foods, drugs, pollutants, and endogenous processes. They mapped chemical similarities after weighting by blood concentrations, disease-risk citations, and numbers of human metabolic pathways.

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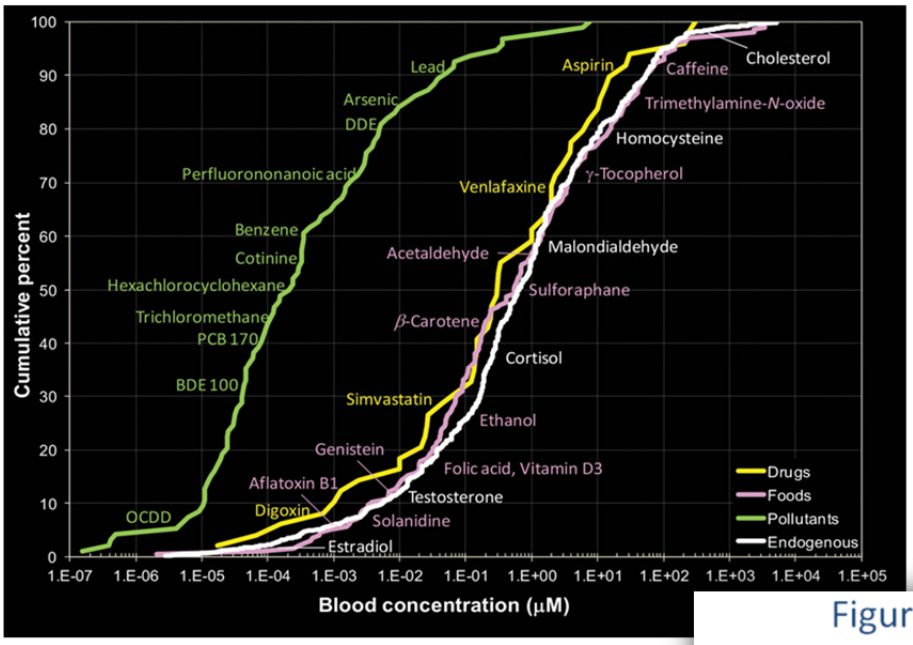
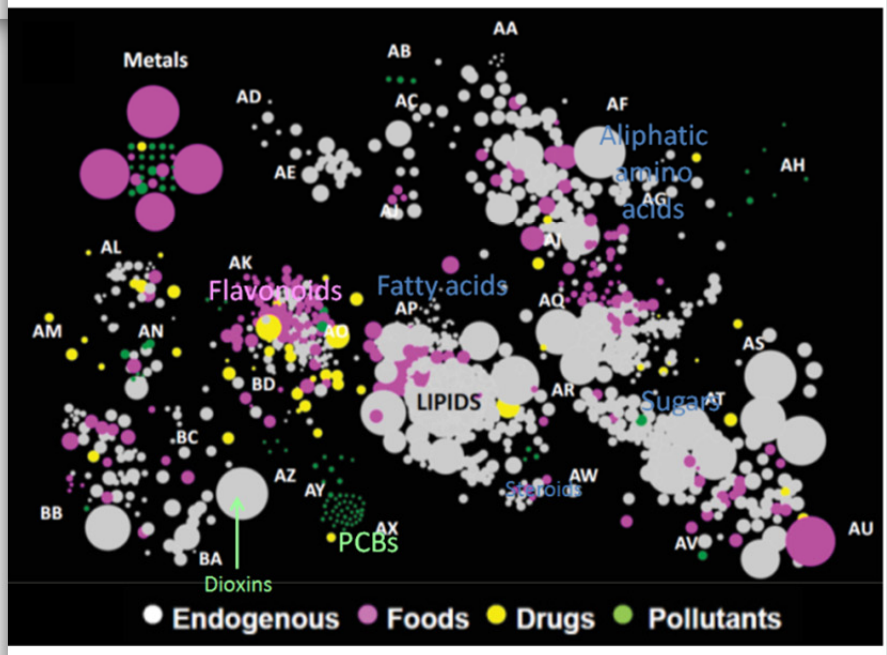
Figure 3 - Environmental pollutants present at (very) low concentrations in blood



Rappaport et al., 2014, *Environ. Health Perspect.*

Blood concentrations spanned 11 orders of magnitude and were indistinguishable for endogenous and food chemicals and drugs, whereas those of pollutants were 1,000 times lower (**Figures 3 and 4**). Chemical similarities mapped by disease risks were equally distributed by source categories, but those mapped by metabolic pathways were dominated by endogenous molecules and essential nutrients. Thus the exogenous exposome has much lower concentrations than the endogenous exposome and requires very sensitive methods to be measured.

Figure 4 - The blood exposome



Rappaport et al., 2014, *Environ. Health Perspect.*

THE EXPOSOME FOR RISK ASSESSMENT

Assessment of environmental hazards and risks is difficult with traditional tools, both for inaccurate characterization of exposures and for lack of knowledge on intermediate steps in diseases etiology and mechanisms. A key feature of risk assessment is the investigation of dose-response relationships, in addition to acquisition of knowledge on the mode of action of chemicals (e.g. genotoxicity).

We show here two examples of the type of research conducted within Exposomics:

- **The Piscina study**, in which exposure to (genotoxic) water contaminants in swimming pools is measured in volunteers before and after swimming, and metabolomic features are examined in relation to exposures.

- **The Epigenair study**, in which genome-wide methylation signals from Illumina 450K are related to estimated NOx and PM exposures (air pollution) causation.

In both cases the outputs will be:

(a) improved dose-response relationships (low dose effects)

(b) investigation of early signals of damage

(c) investigation of intermediate steps in disease

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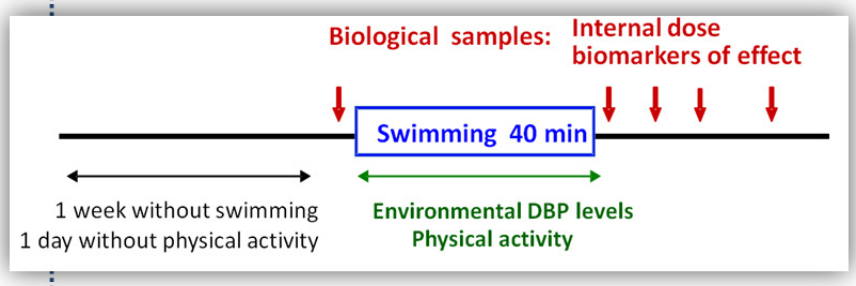
WATER CONTAMINATION: THE PISCINA STUDY

- ✓ Cross-over study – indoor chlorinated pool.
- ✓ Subjects: 120 volunteers (18-40y non-smokers, non-professional swimmers) swam for 40 minutes.
- ✓ 30 experimental days, 4 volunteers per day, 2 days per week.
- ✓ Untargeted metabolomics of blood samples (n=60) collected before and 2h after swimming was conducted using a UHPLC-QTOF mass spectrometer operated in ESI positive mode.

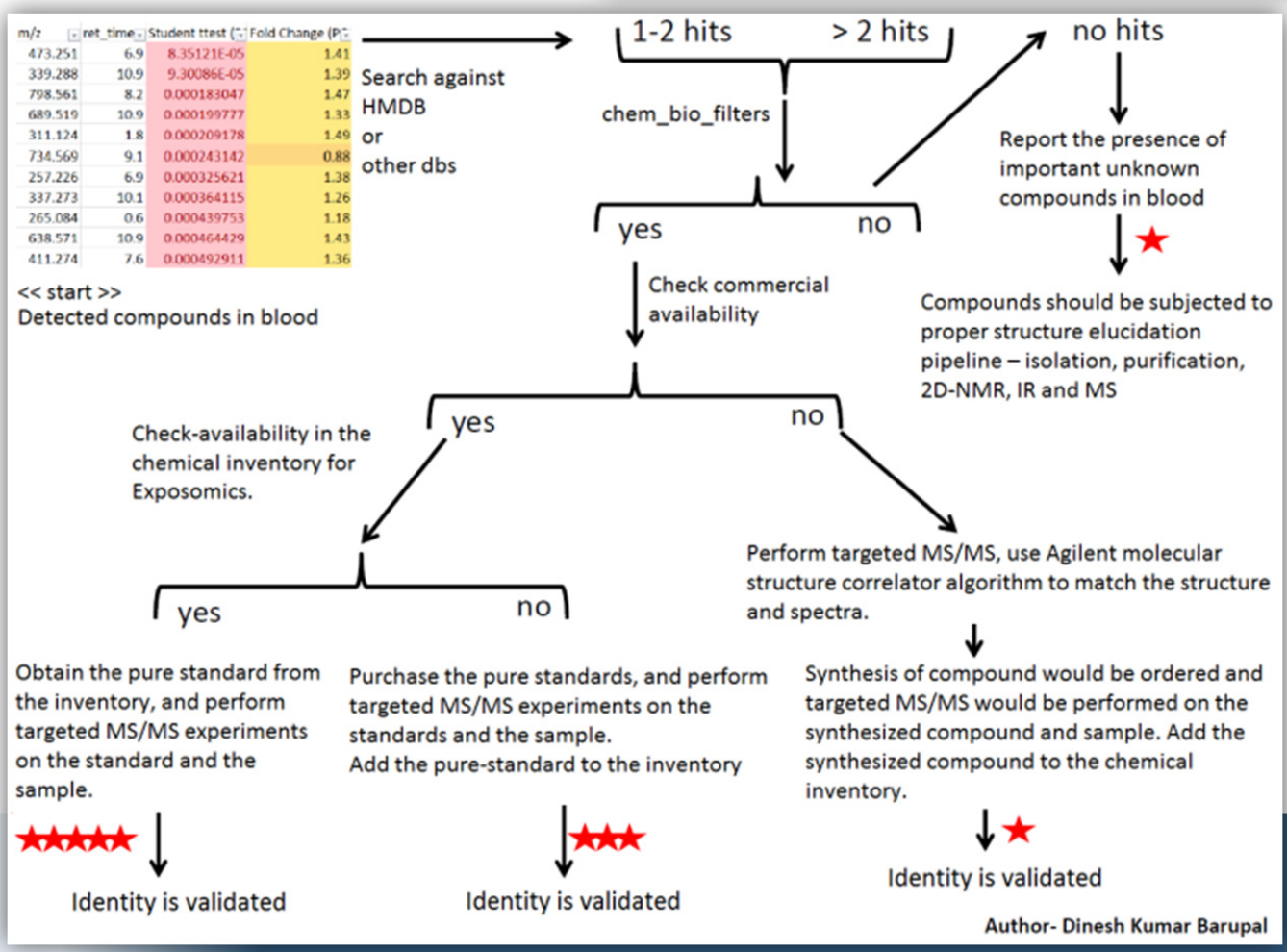


INTERNAL EXPOSURES

DBP measured in exhaled breath →

Trihalomethanes in exhaled breath - before and after swimming

Measurement	Difference POST - PRE swimming	P-value paired t-test
Chloroform (µg/m³)	11.10	< 2.2e-16
Bromodichloromethane (µg/m³)	2.42	< 2.2e-16
Dibromochloromethane (µg/m³)	0.52	< 2.2e-16
Bromoform(µg/m³)	0.09	1.875e-12
Total THMs (µg/m³)	**14.13**	**< 2.2e-16**



METABOLOMICS DATA IN PISCINA

N=3,608 compounds measured by IARC (UHPLC-QTOF)

← Scheme for annotation of compounds in untargeted metabolomics assays using UHPLC-QTOF

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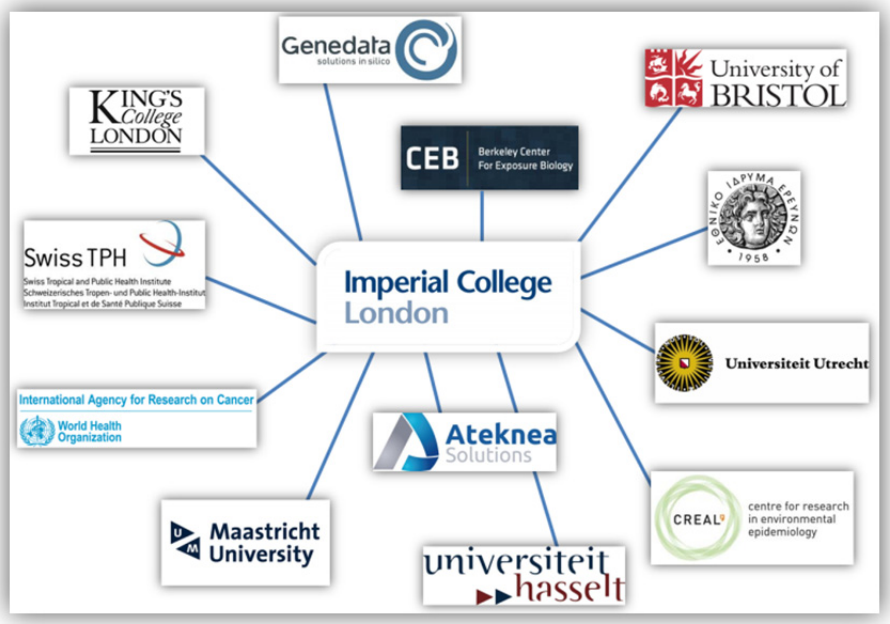
GENOME HYPOMETHYLATION IS RELATED TO AIR POLLUTION

- ✓ First data on air pollution suggest that exposure to NOx and NO2 can lead to global hypomethylation studied with the Illumina array.
- ✓ Altered methylation of several CpG sites was associated with air pollution measures.
- ✓ Future perspectives:
  - The study will be extended to differentially methylated regions
  - We will replicate the study in cord blood and children at age 7 in ALSPAC and in other Exposomics cohorts

EPIGENAIR

EPIGENomic markers for **AIR** pollution-induced health effects

	EPIC-Italy	EGM		EPIC-Netherlands
		Italy	*Sweden*	
Number of participants	457	79	406	169
Air pollution estimations (µg/m³)				
No_x	93.01 ± 30.01	85.12 ± 42.96	23.12 ± 5.86	29.62 ± 5.73
No_2	50.15 ± 14.27	43.8 ± 18.68	/	19.63 ± 3.48
$PM_{2.5}$	46.99 ± 4.59			24.48 ± 0.68
PM_{10}	30.10 ± 1.98			16.62 ± 0.39
$PM_{2.5absorbance}$	3.10 ± 0.44			1.04 ± 0.33
PM_{coarse}	16.8 ± 2.99			1.19 ±0.13



PROJECT PARTNERS

The collaborative activities of the EXPOsOMICS research have been divided amongst thirteen of the world's leading organisations in the field, each with extensive experience and expertise.

CONTACT US

Principal Investigator
Professor Paolo Vineis
Imperial College London
MRC-PHE Centre for Environment and Health
School of Public Health
St Mary's Campus, Norfolk Place
LONDON W2 1PG
Telephone: +44 (0)20 75943372
Email: p.vineis@imperial.ac.uk