

# Assessing the exposome in occupational cancer

Lode Godderis<sup>1,2</sup>, Steven Haenen<sup>1</sup>, Katrien Poels<sup>1</sup>, Jeroen Vanoirbeek<sup>1</sup>

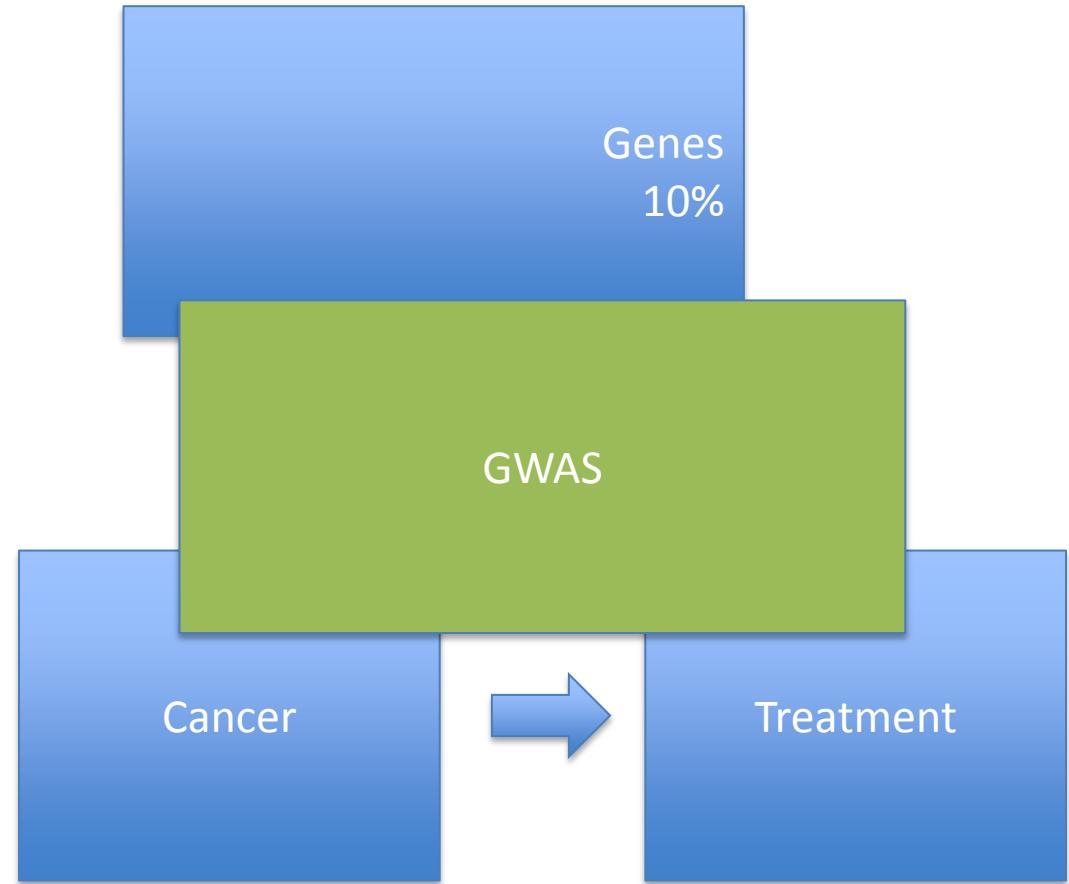
<sup>1</sup> KULeuven, Occupational, Environmental and Insurance Medicine  
Lab Occupational and Environmental Hygiene

<sup>2</sup> IDEWE, Knowledge, Information and Research

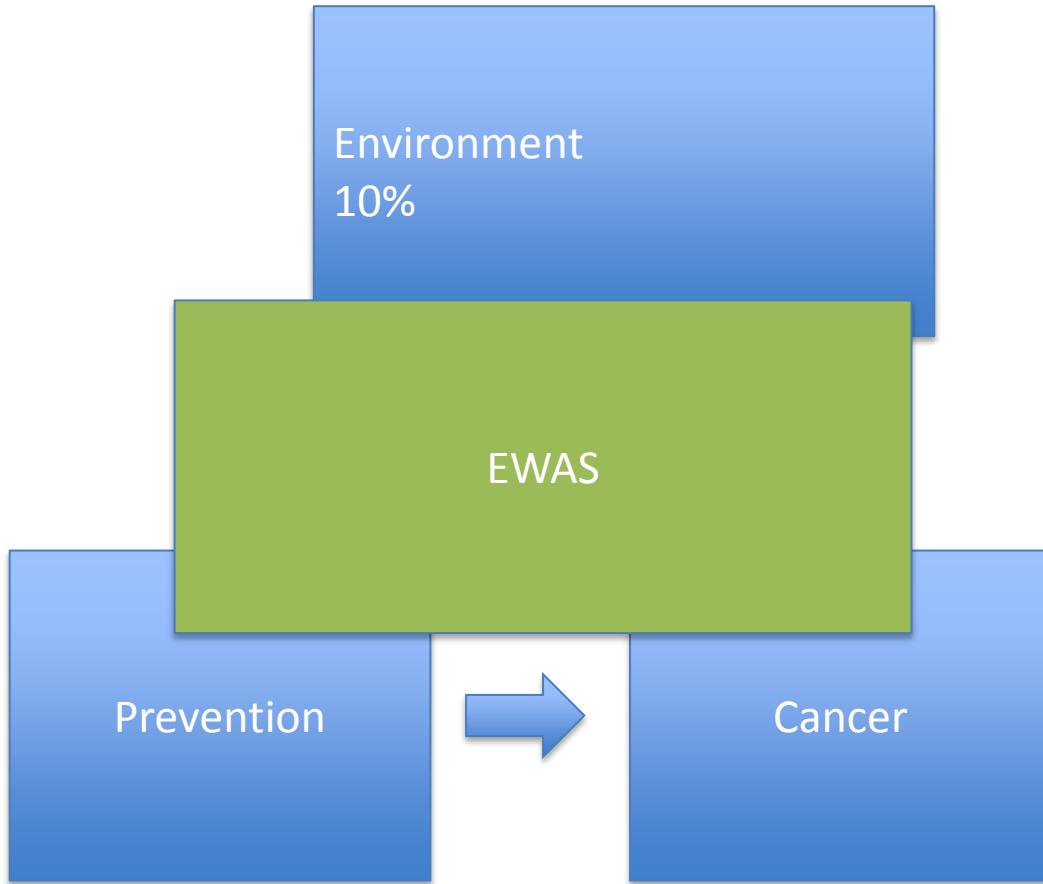
# Outline

- Introduction
- Omics → Exposomics
- Approaches
- Critical windows of exposure
- Conclusions

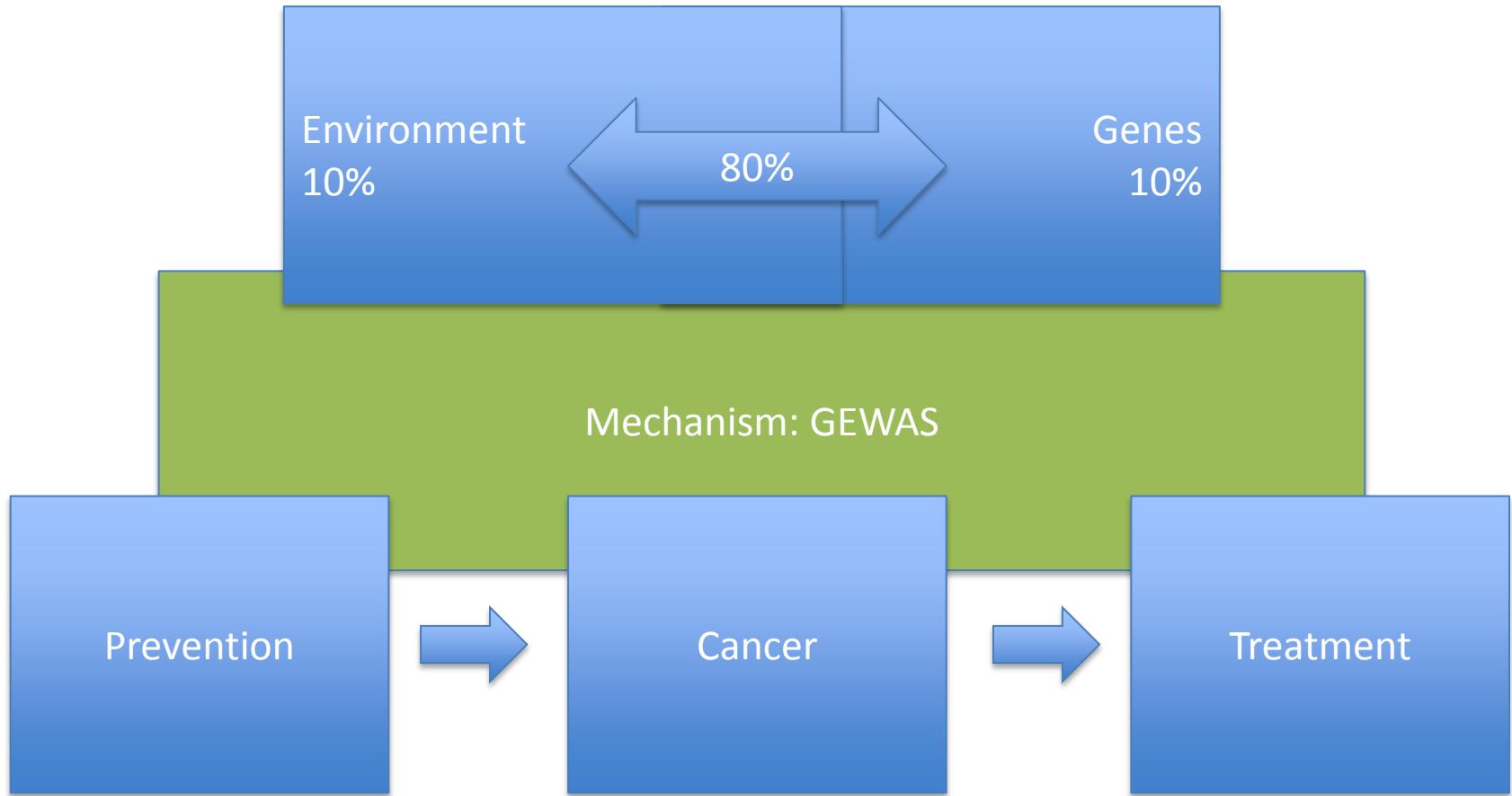
# Introduction



# Introduction



# Introduction



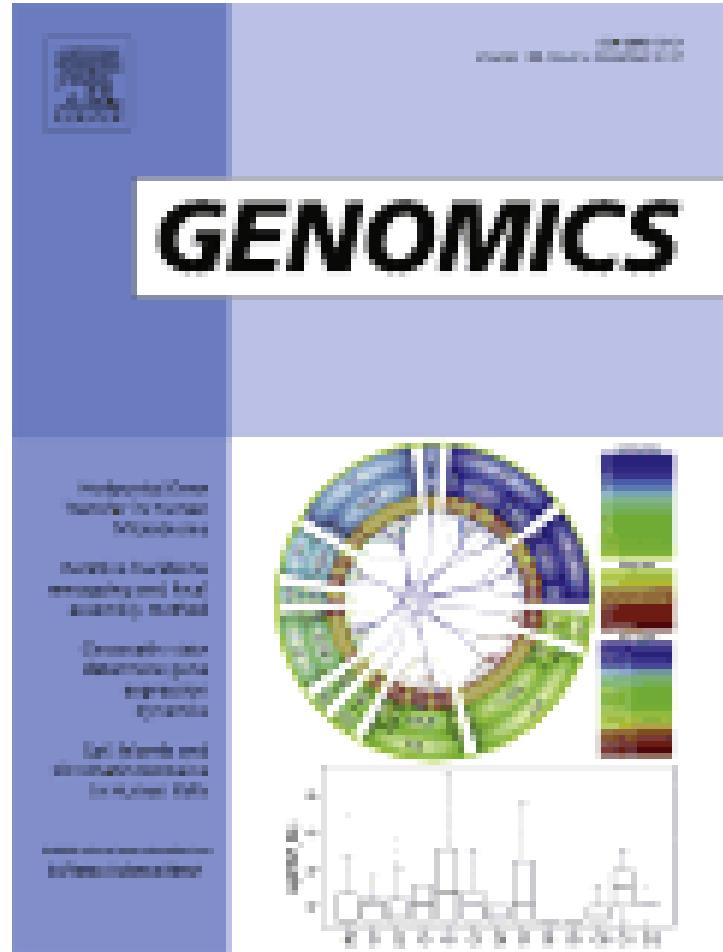
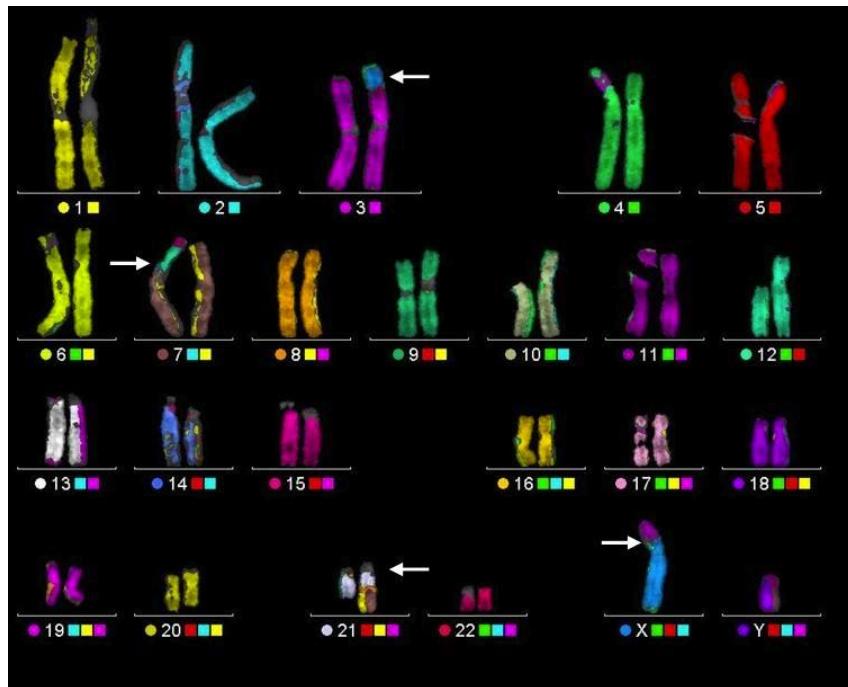
# Introduction



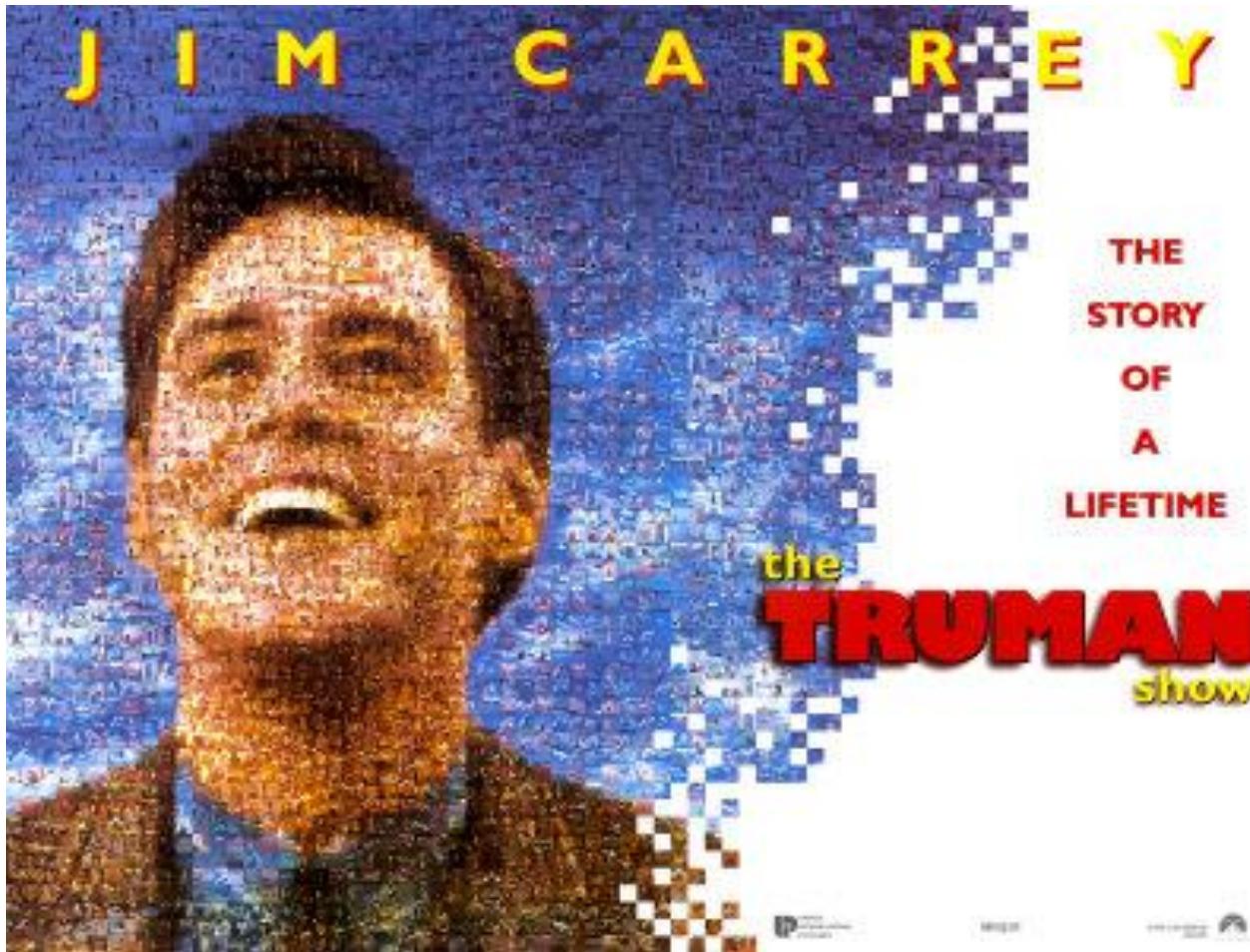
# Outline

- Introduction
- Omics → Exposomics
- Approaches
- Critical windows of exposure
- Conclusions

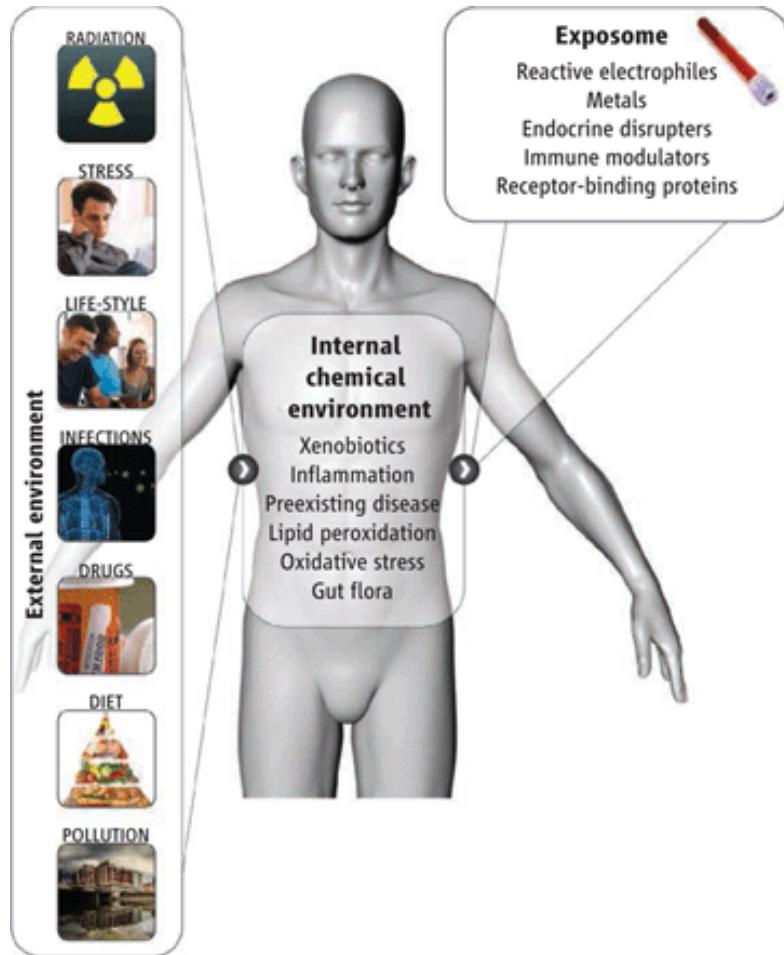
# Omics → Exposomics



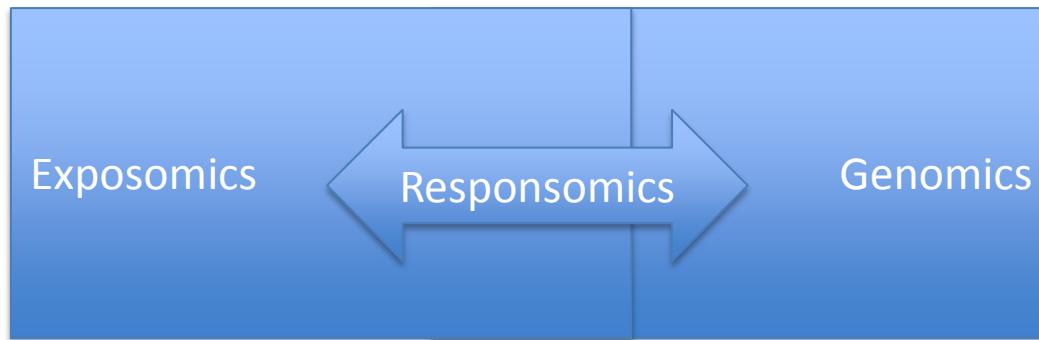
# Omics → Exposomics



# Omics → Exposomics



# Omics → Exposomics

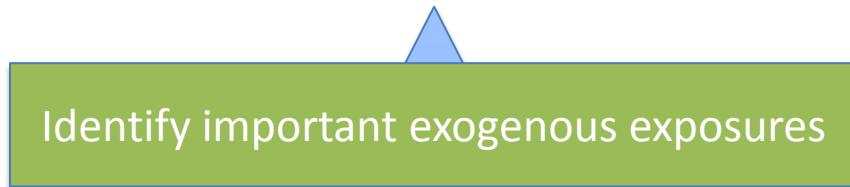


# Outline

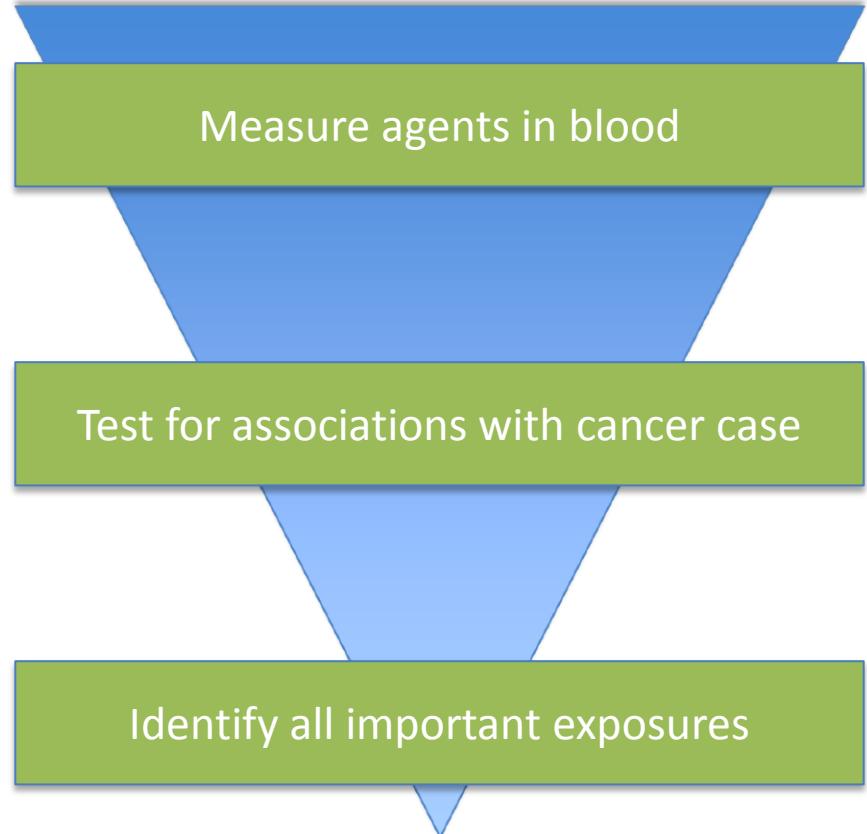
- Introduction
- Omics → Exposomics
- Approaches
- Critical windows of exposure
- Conclusions

# Approaches

## Bottom-up approach



## Top Down approach



Adapted from: Rappaport Journal of Exposure Science and Environmental Epidemiology 2011

# Approaches

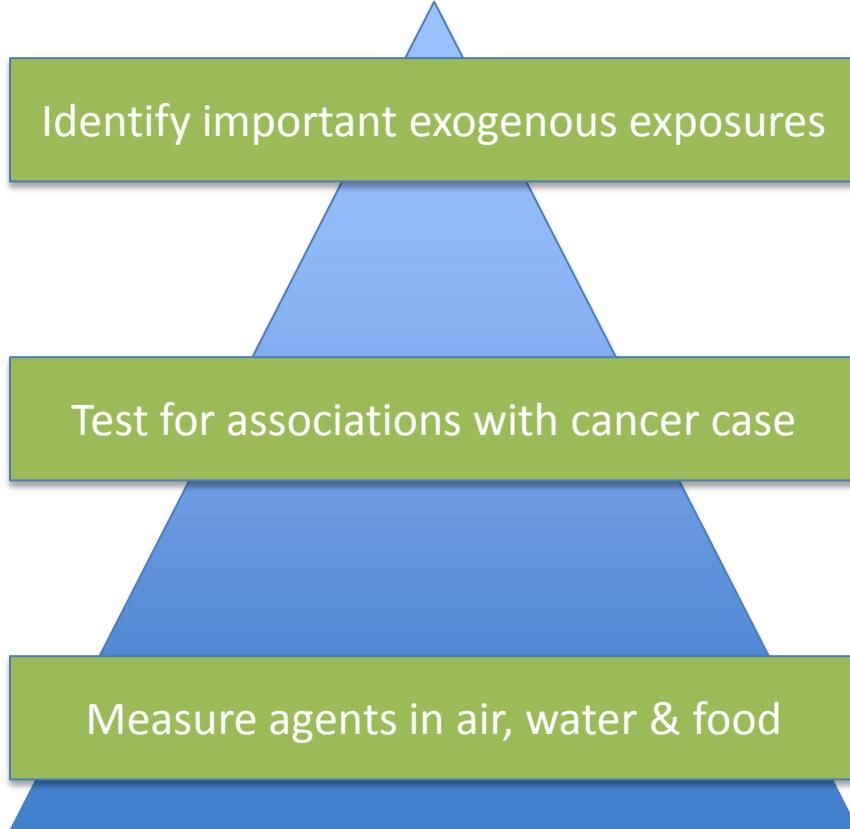
Solvent exposure

Genetic and epigenetic mechanisms

Cancer

# Approaches

## Bottom-up approach



# Bottom-up approach

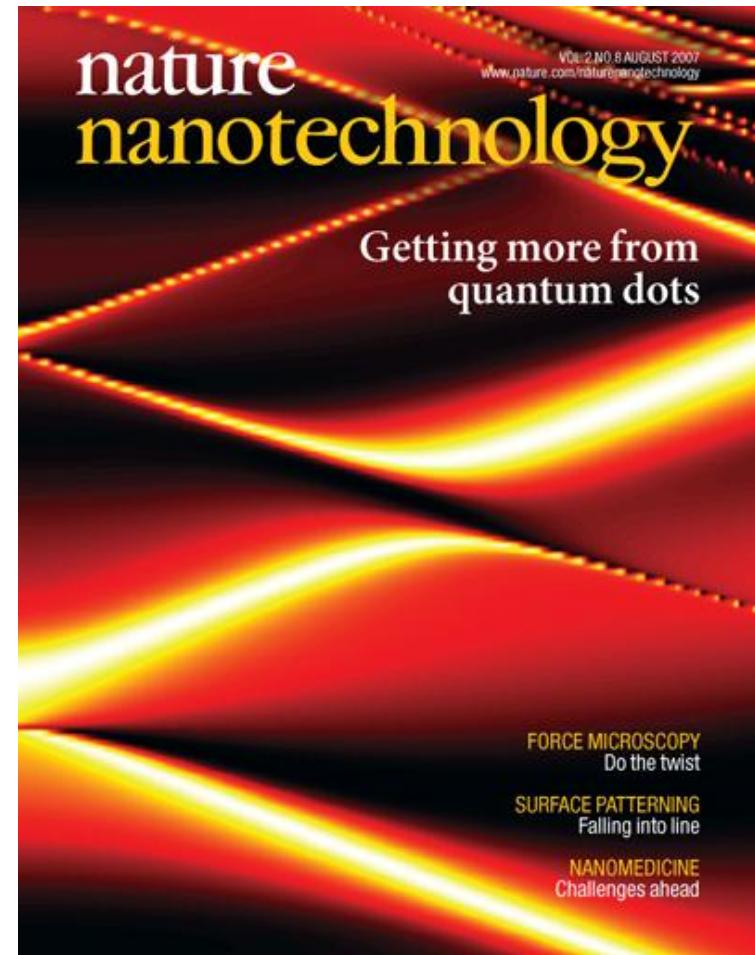
nber) determined in VOC-analysis

	<i>Chlorinated compounds</i>	<i>Miscellaneous</i>
benzene [71-43-2] *	methylene chloride [75-09-2] * **	tetrahydrofuran [109-99-9] *
chloroform [67-66-3] *	chloroform [67-66-3] *	1,4-dioxane [123-91-1] *
benzene [100-41-4] *	tetrachloromethane [56-23-5] *	acetonitrile [75-05-8] *
tolylbenzene [135-01-3]	1,1-dichloroethane [75-34-3]	acrylonitrile [107-13-1] *
tolylbenzene [141-93-5]	1,2-dichloroethane [107-06-2] *	gamma-butyrolactone [96-48-0]
[100-42-5] *	1,1,1-trichloroethane [71-55-6] *	1,2-dibromoethane [106-93-4]
benzene [103-65-1] *	1,1,2-trichloroethane [79-00-5]	methyliodide [74-88-4]
[98-82-8] *	1,1,2,2-tetrachloroethane [79-34-5]	
hydrostyrene [98-83-9]	pentachloroethane [76-01-7]	
enzen [104-51-8]	trichloroethylene [79-01-6] *	
benzene [538-93-2]	tetrachloroethylene [127-18-4] *	acetone [67-64-1] *
tolylbenzene [135-98-8]	iso-propylchloride [75-29-6]	methyl ethyl ketone [78-93-3] *
benzene [98-06-6]	1,2,3-trichloropropane [96-18-4]	methyl-n-butyl ketone [591-78-6] *
p [108-38-3] *	1-bromo-3-chloropropane [109-70-6]	methyl-iso-butyl ketone [108-10-1] *
[108-42-3] *	mono-chlorobenzene [108-90-7] *	methyl-iso-amyl ketone [110-12-3]
[95-47-6] *	benzylchloride [100-44-7]	ethyl-n-pentyl ketone [106-68-3]
toluene [611-14-3]	benzylidenechloride [98-87-3]	di-n-propyl ketone [123-19-3]
toluene [620-14-4]	trans-1,2-dichloroethene [156-60-5]	di-iso-propyl ketone [565-80-0]
toluene [622-96-8]	cis-1,2-dichloroethene [156-59-2]	di-iso-butyl ketone [108-83-8]
toluene [99-87-6]	p-dichlorobenzene [106-46-7] *	cyclohexanone [108-94-1] *
tolyltoluene [98-51-1]	o-dichlorobenzene [95-50-1]	isophorone [78-59-1] *
o-propylbenzene [99-62-7]	1,2,3-trichlorobenzene [87-61-6]	mesityl oxide [141-79-7] *
o-propylbenzene [100-18-5]		diacetone alcohol [123-42-2] *
ne [108-67-8]		acetophenone [98-86-2] *
methylbenzene [526-73-8]		1-methyl-2-pyrrolidone [872-50-4] *
methylbenzene [95-63-6] *		cyclopentanone [120-92-3] *
extra-methylbenzene [488-23-3]		2-methylcyclohexanone [583-60-8] *
extra-methylbenzene [527-53-7]		3-methylcyclohexanone [591-24-2] *
119-64-2] *		4-methylcyclohexanone [589-92-4] *
ne [91-20-3] *		
	<b>Alcohols</b>	
	ethanol [64-17-5] *	
	n-propanol [71-23-8]	
	iso-propanol [67-63-0] *	
	1-butanol [71-36-3] *	
	2-butanol [78-92-2] *	
	iso-butanol [78-83-1] *	
	tert-butanol [75-65-0] *	
	3-pentanol [584-02-1]	
	iso-amyl alcohol [123-51-3]	
	tert-amyl alcohol [75-85-4]	
	cyclohexanol [108-93-0] *	
	methyl-iso-butylcarbinol [108-11-2]	
	benzylalcohol [100-51-6] *	
	allylalcohol [107-18-6]	
	<b>Ethers</b>	
	diethylether [60-29-7] *	
	di-iso-propylether [108-20-3]	
	tert-butylmethylether [1634-04-4] *	
ethanol) [109-86-4] *		
oil) [110-80-5] *		
oxethanol) [109-59-1]		
anol) [2807-30-9]		
oil) [111-76-2] *		
110-71-4]		



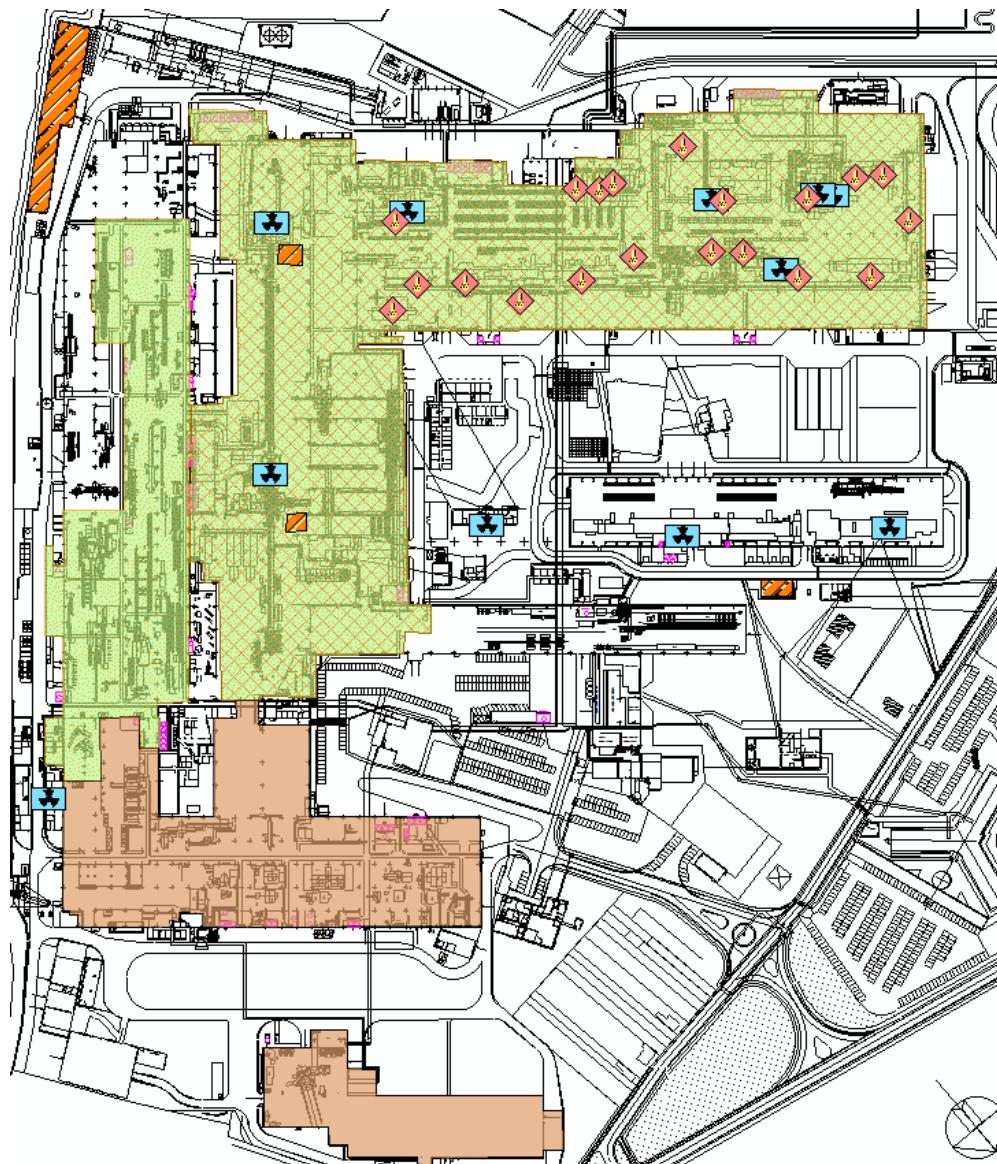
# Bottom-up approach

## Lab on a Chip

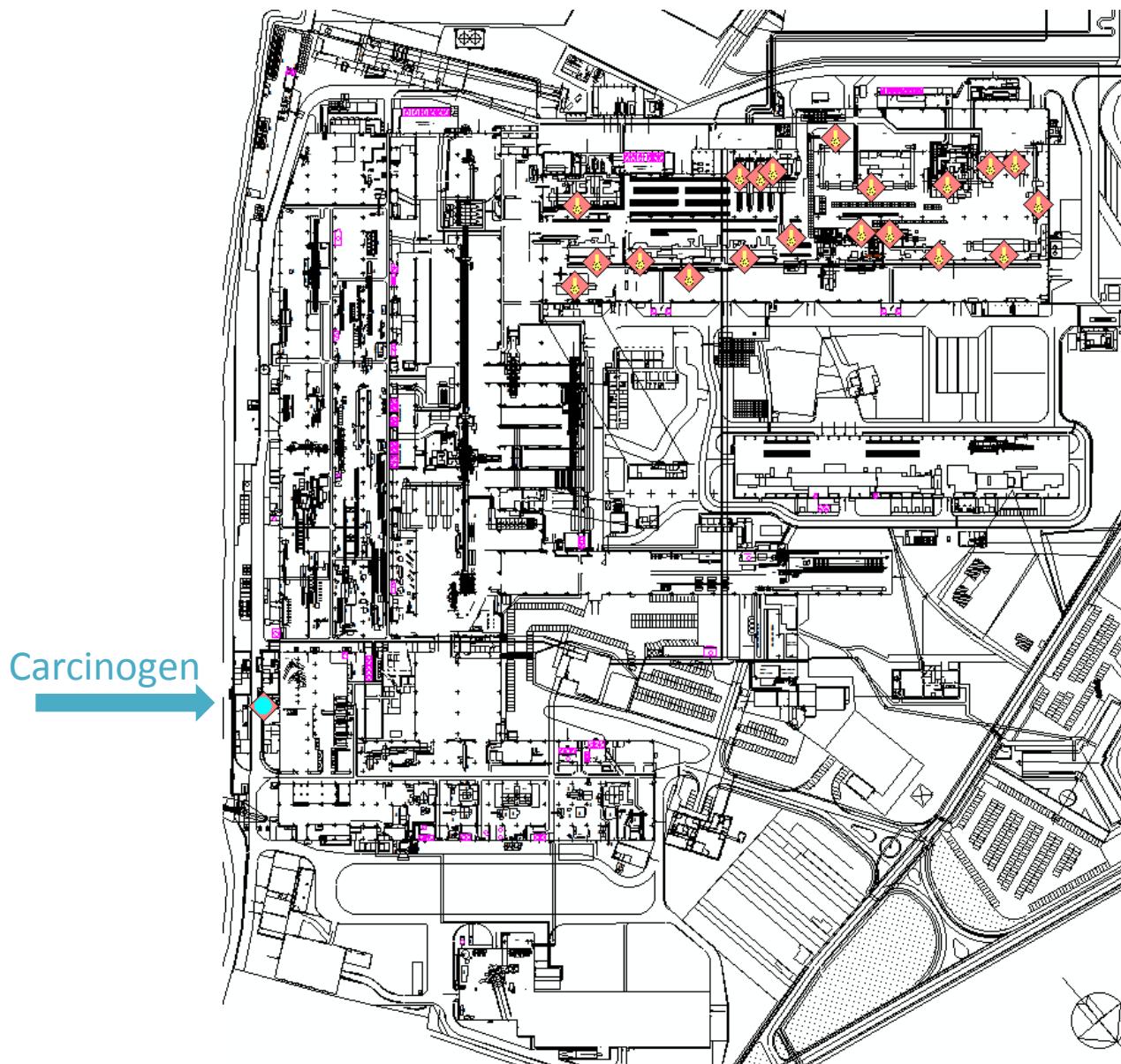


# Bottom-up approach

- Agents
- Chemicals
- 
- IonRadA
- 
- Biohazard
- 
- MetalFumes
- 
- Oilmists
- 
- Noisehaz
- 

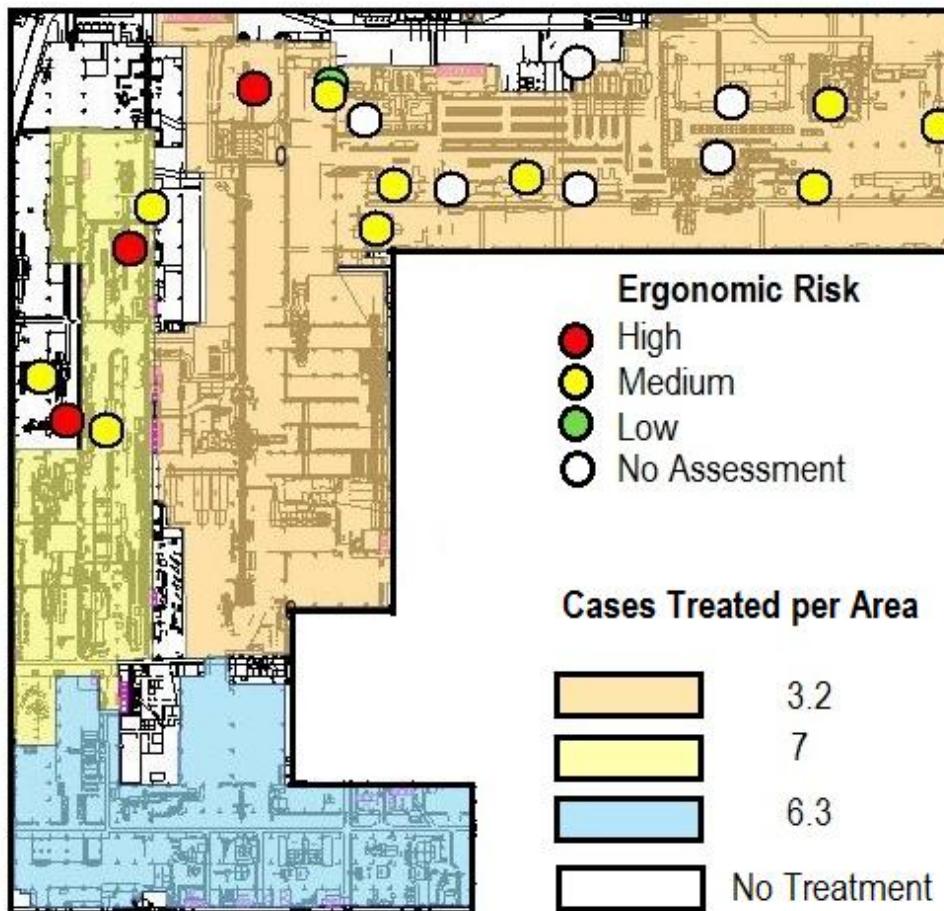


# Bottom-up approach



- Layer Chemical Agents
- Effective search Carcinogen

# Bottom-up approach



# Approaches

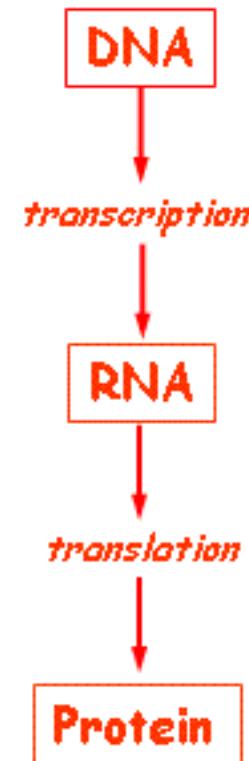
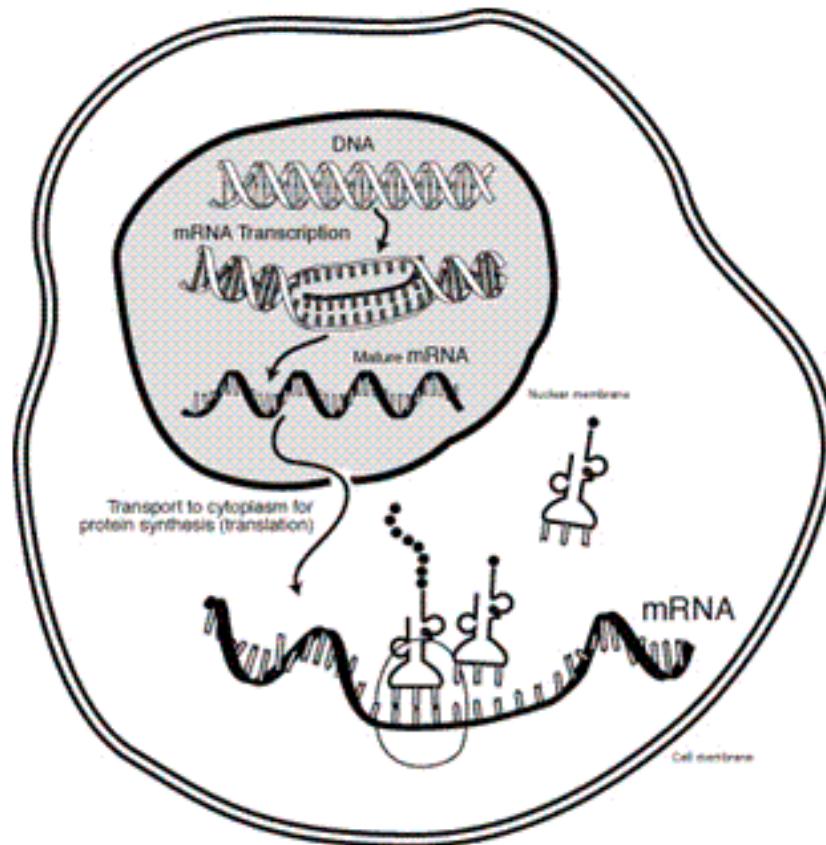
## Top Down approach

Measure agents in blood

Test for associations with cancer case

Identify all important exposures

# Top Down approach

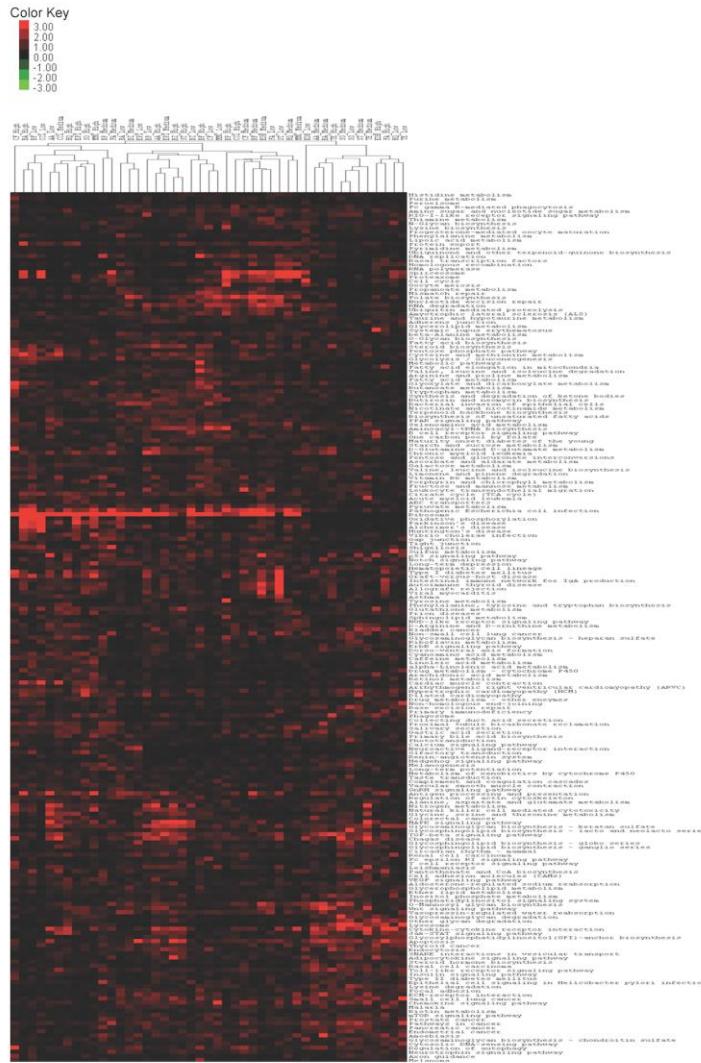


# Top Down approach

Agents	IARC	Category	Concentration ( $\mu\text{M}$ )		
			High	Medium	Low
Formaldehyde <sup>*,1,2</sup>	1	Aldehyde	100	10	1
Styrene <sup>**,1</sup>	2B	Aromatic hydrocarbon	5000	500	50
Styrene 7,8-oxide <sup>*,1</sup>	2A	Aromatic hydrocarbon	500	50	5
Benzene <sup>**,1</sup>	1	Aromatic hydrocarbon	100	10	1
Hydroquinone <sup>*,1</sup>	3	Aromatic hydrocarbon	0.5	0.05	0.005
Mitomycin C <sup>*,2</sup>	2B	Cytostaticum	0.5	0.05	0.005
Ethylenedibromide <sup>*,1,2</sup>	2A	Organobromide	1000	100	10
Epichlorohydrin <sup>*,1</sup>	2A	Organochloride	500	50	5
Acrylamide <sup>**,1</sup>	2A	Amide	500	50	5
Trichloroethylene <sup>**,1</sup>	2A	Chlorinated hydrocarbon	5000	500	50
Carbontetrachloride <sup>**,1</sup>	2B	Chlorinated hydrocarbon	1000	100	10
Cyclophosphamide <sup>**,1</sup>	1	Cytostaticum	50	5	0.5
Benzo[a]fluoranthene <sup>**,1</sup>	2B	Poly aromatic hydrocarbon	500	50	5
Benzo[a]pyrene <sup>**,1</sup>	1	Poly aromatic hydrocarbon	500	50	5
Benz[a]anthracene <sup>**,1</sup>	2B	Poly aromatic hydrocarbon	500	50	5

\*Direct acting agent; \*\*Indirect acting agent.  
 1: DNA adduct forming agent; 2: DNA Cross linking agent.  
[doi:10.1371/journal.pone.0039205.t001](https://doi.org/10.1371/journal.pone.0039205.t001)

# Results: Top Down approach



# Top Down approach

GO ID	GO Processes	Carcinogens*									
		AA	BA	BP	CCL	CP	FA	HQ	MMC	ST	TCE
GO:0009440	Cyanate catabolic process	✓	✓	✗	✗	✗	✗	✗	✓	✓	✗
GO:0019885	Antigen processing and presentation of endogenous peptide antigen via MHC class I	✓	✗	✗	✓	✗	✓	✓	✗	✓	✓
GO:0000085	G2 phase of mitotic cell cycle	✗	✓	✗	✓	✓	✓	✓	✓	✗	✓
GO:0006977	DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest	✗	✓	✗	✓	✓	✗	✗	✗	✗	✓
GO:0050823	Peptide antigen stabilization	✗	✗	✓	✓	✗	✓	✓	✗	✓	✓
GO:0001833	Inner cell mass cell proliferation	✗	✗	✗	✗	✓	✓	✓	✗	✓	✗

\* Carcinogens [AA:Acrylamide; BA:Benz[a]anthracene; BP:Benzo[a]pyrene; CCL:Carbontetrachloride; CP:Cyclophosphamide; FA:Formaldehyde; HQ:Hydroquinone; MMC:Mitomycin C; ST:Styrene; TCE:Trichloroethylene]

# Top Down approach

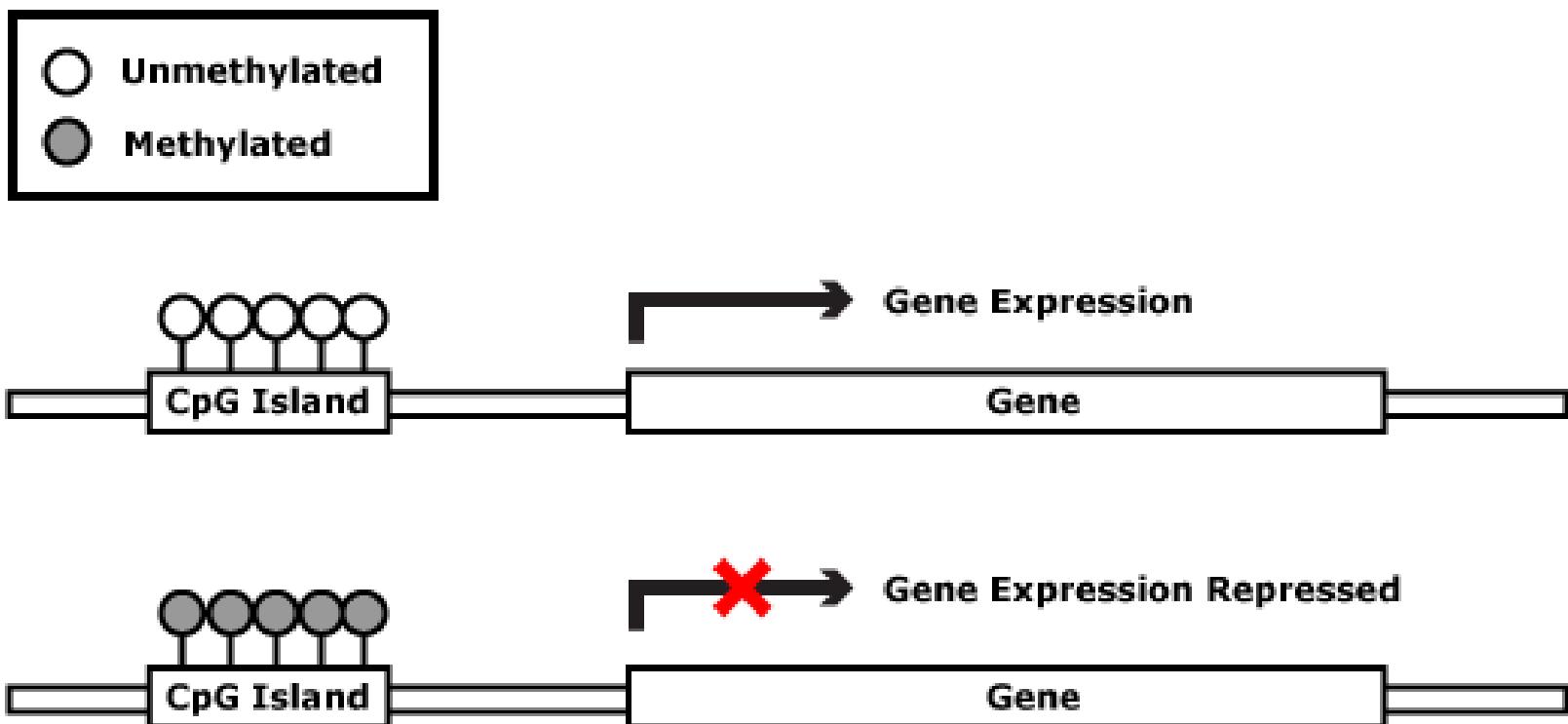
GO ID	GO Processes	Carcinogens*									
		AA	BA	BZ	EDB	EPI	HQ	SO	ST	TCE	
GO:0030503	Regulation of cell redox homeostasis	✓	✓	✗	✓	✗	✗	✗	✓	✗	
GO:0042789	mRNA transcription from RNA polymerase I	✓	✗	✓	✓	✓	✓	✗	✗	✗	
GO:0007050	Cell cycle arrest	✓	✗	✓	✗	✓	✓	✗	✓	✗	
GO:0032792	Inhibition of CREB transcription factor	✓	✗	✗	✓	✗	✓	✗	✓	✗	
GO:0043065	Positive regulation of apoptosis	✓	✗	✓	✗	✓	✗	✗	✓	✗	
GO:0001975	Response to amphetamine	✓	✗	✓	✗	✗	✓	✗	✓	✗	
GO:0001711	Endodermal cell fate commitment	✗	✓	✗	✗	✓	✓	✗	✗	✓	
GO:0006450	Regulation of translational fidelity	✗	✓	✗	✗	✓	✓	✗	✗	✓	
GO:0015855	Pyrimidine transport	✗	✓	✗	✗	✓	✗	✓	✗	✓	
GO:0030858	Positive regulation of epithelial cell differentiation	✗	✓	✗	✗	✓	✓	✗	✗	✓	

\* Carcinogens [AA:Acrylamide; BA:Benz[a]anthracene; BZ:Benzene; EDB:Ethylenedibromide; EPI:Epichlorohydrin; HQ:Hydroquinone; SO:Styrene 7,8-oxide; ST:Styrene; TCE:Trichloroethylene]

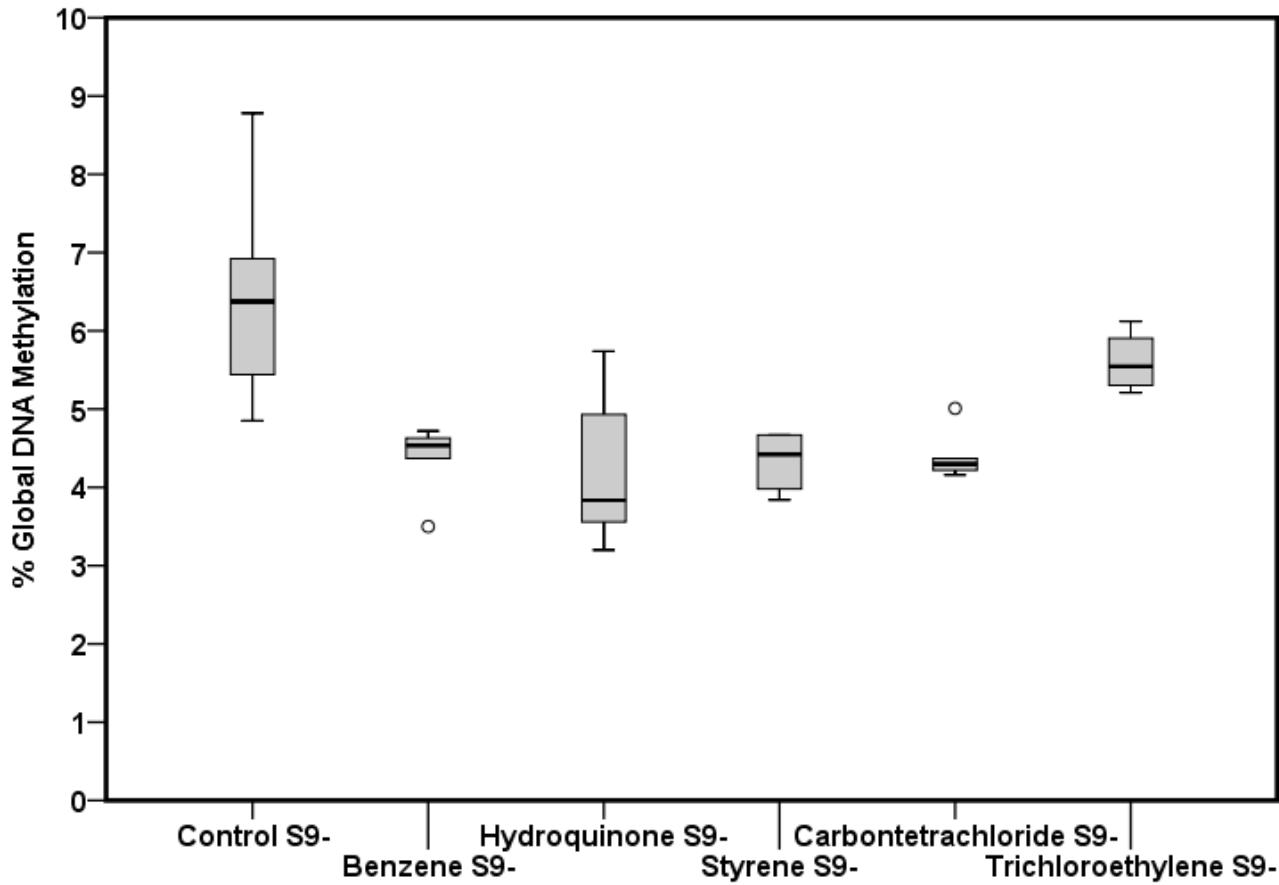
# Top Down approach

Chemical	No. Subjects	Tissue/cells	Omic Technology	No. Significant Targets	Reference
<b>Transcriptomics</b>					
			<b>Array</b>		
Air Pollution	47 <sup>a</sup>	PB	Agilent Human 22k	1727	Van Leeuwen et al. 2006 [57]
Air Pollution	24	PB	Agilent Human 22k	1698	Van Leeuwen et al. 2008 [58]
Arsenic	12	Liver	Clontech Atlas	60	Lu et al. 2001 [49]
Arsenic	24	PBL	cDNA array	62	Wu et al. 2003 [50]
Arsenic	40	PBL	Affymetrix HGU133A	468	Argos et al. 2006 [48]
Arsenic	32 <sup>b</sup>	CB	Affymetrix HGU133	9–170	Fry et al. 2007 [85]
Arsenic	21	PBL	Affymetrix HGU133	259	Andrew et al. 2008 [75]
Benzene	12	PBMC	Affymetrix HGU133 A/B	2129	Forrest et al. [45]
Benzene	16	PBMC	Affymetrix Human U133	2692	McHale et al. 2009 [46]
			Illumina HumanRef-8	1828	
Cigarette Smoke	85	PBL	Agilent Human 25k	36	Lampe et al. 2004 [52]
Cigarette Smoke	18	PB	Phase I Human Tox 600	34–76	Van Leeuwen et al. 2007 [53]
Cigarette Smoke	107	Airway Epithelium		175	Beane et al. 2007 [54]
Metal Fumes	28	PB	Affymetrix HGU133A	546	Wang et al. 2005 [51]
TCDD	26	PBMC	Affymetrix HGU133 A/B	135	McHale et al. 2007 [47]
Welding Fumes	40	PB/WBC	House spotted array	103	Rim et al. 2007 [175]
<b>Proteomics</b>					
			<b>Type of MS</b>		
Arsenic	91	Urine	SELDI-TOF MS	2	Hegedus et al. 2008 [94]
Arsenic	214	Plasma	SELDI-TOF MS	20	Harezlak et al. 2008 [95]
Arsenic and Lead	91	Serum	SELDI-TOF MS	5	Zhai et al. 2005 [96]
Benzene	88	Plasma	MALDI-TOF MS	18	Joo et al. 2004 [97]
Benzene	40	Serum	SELDI-TOF MS	3	Vermeulen et al. 2005 [93]
<b>Epigenomics</b>					
			<b>Array</b>		
<i>miRNA</i>					
Cigarette Smoke	20	Airway Epithelium	Invitrogen NCode Array	28	Schembri et al. 2009 [111]
<i>DNA Methylation</i>					
Benzene	10	PB	Illumina GoldenGate Cancer Panel I	>100	Zhang et al. 2009 [65]

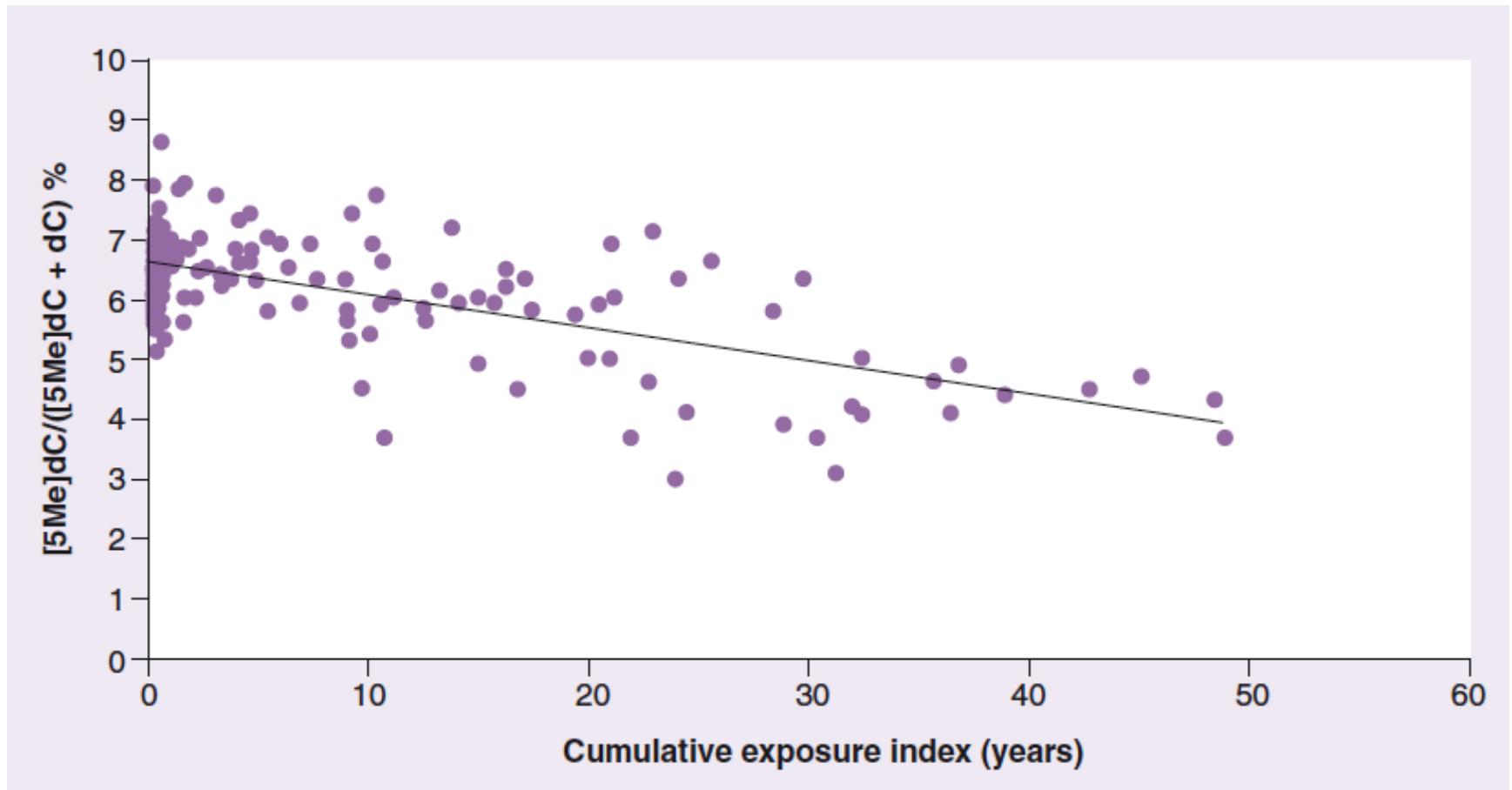
# Top Down approach



# Top Down approach



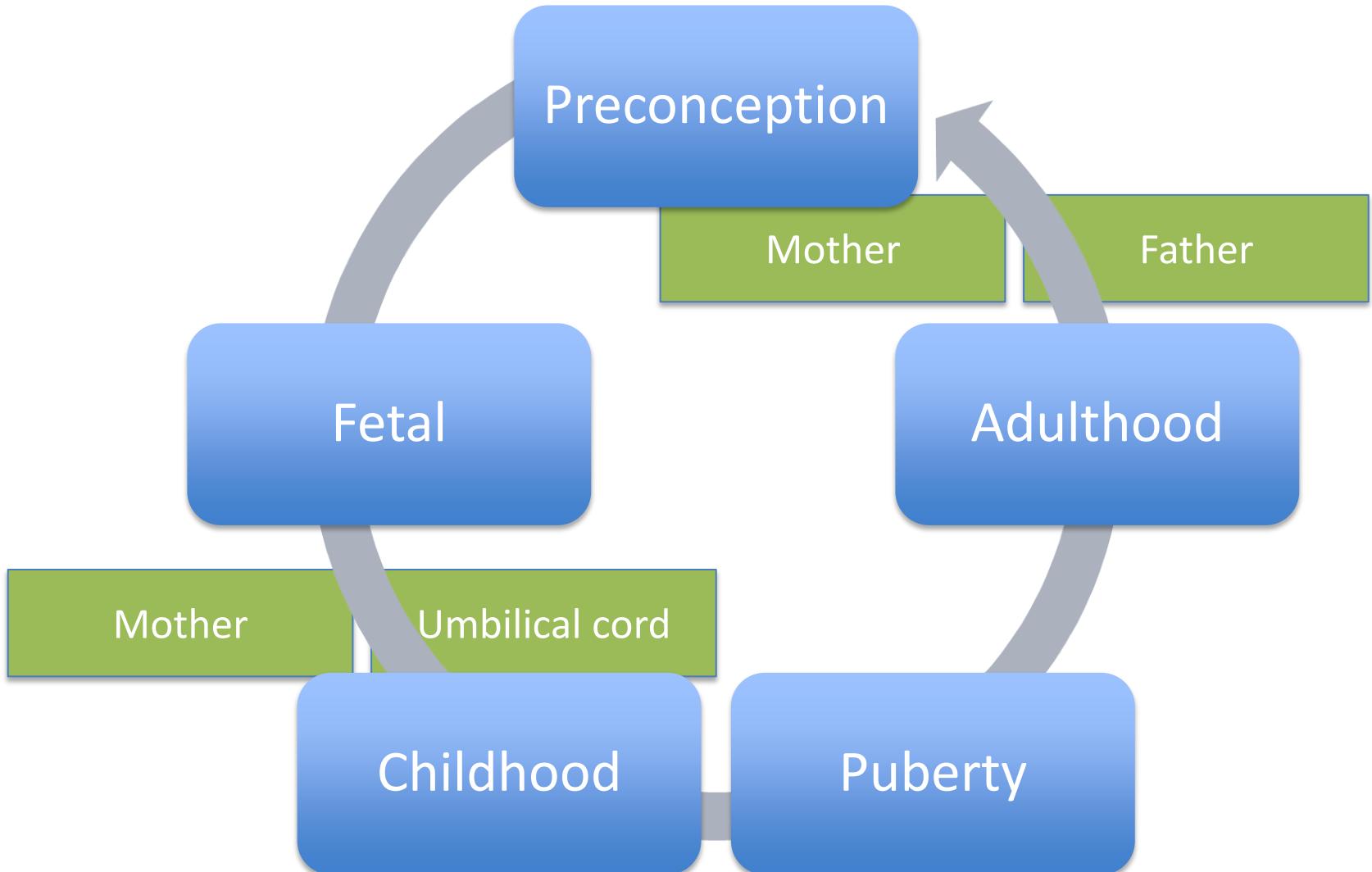
# Top Down approach



# Outline

- Introduction
- Omics → Exposomics
- Approaches
- Critical windows of exposure
- Conclusions

# Critical windows of exposure



# Outline

- Introduction
- Omics → Exposomics
- Approaches
- Critical windows of exposure
- Conclusions

# Conclusion

- Technological challenges
- Small volumes
- GIS
- “omic”s
  - “molecular signature”
  - mechanisms
- EWAS → GEWAS

# Conclusion

Thank you-  
omics

## Postdoctoral researcher

(Ref. BAP-2013-21)

Occupation : Full-time  
Period : Fixed-term contract  
Place : Leuven  
Apply before : May 13, 2013

For Occupational, Environmental and Insurance Medicine we are looking for a :

## Postdoctoral researcher

The research unit of occupational and environmental medicine studies the impact of work on health by unravelling the underlying mechanism. We aim to investigate the interaction of the human with his work environment through:

- Determination of occupational exposome; the complete exposure of workers throughout this working life; through the analysis of environmental (e.g. air) and biomonitoring (e.g. urine) samples
- Study of health (carcinogenic, neurological, respiratory, etc.) and biological (genetic, epigenetic, etc.) alterations in workers. The environment is not only limited to occupational exposure, but includes also pollution and nutrition.

Our ambition is to develop biomarkers for the evaluation of environmental exposure on health. Since 2008 we are investigating gene expression profiles in cells exposed to adduct-forming agents.

Considering the gene expression is controlled by miRNA, histone modification and DNA methylation among others, we are currently focussing our efforts towards the study of epigenetic changes induced by occupational agents.

<http://icts.kuleuven.be/apps/jobsite/vacatures/52411230?lang=en>