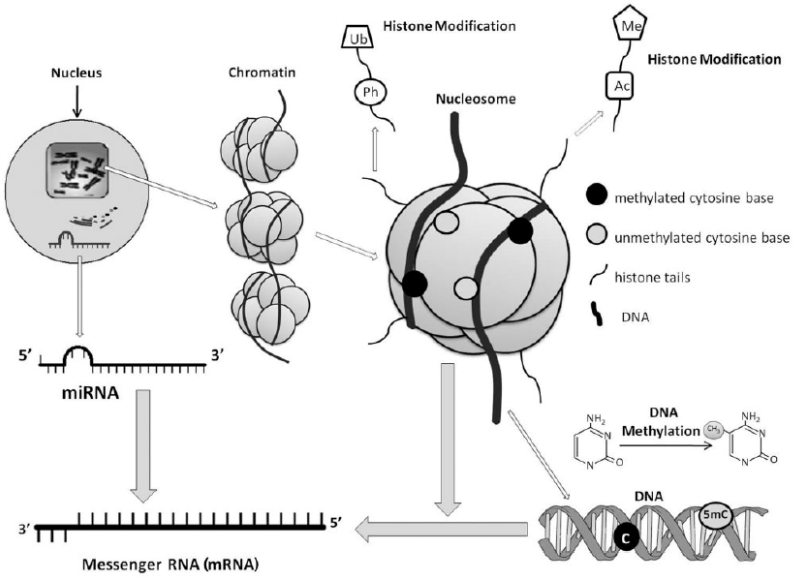
Epigenetics

- Stable changes in gene expression and chromatin organization that are independent of the DNA sequence itself and can mitotically inherited over cell divisions

- Epigenetic modifications include:
  - DNA methylation,
  - histone modifications (e.g. acetylation, methylation, ubiquitylation or sumoylation,),
  - non-coding RNAs (e.g. miRNA),
  - ……..

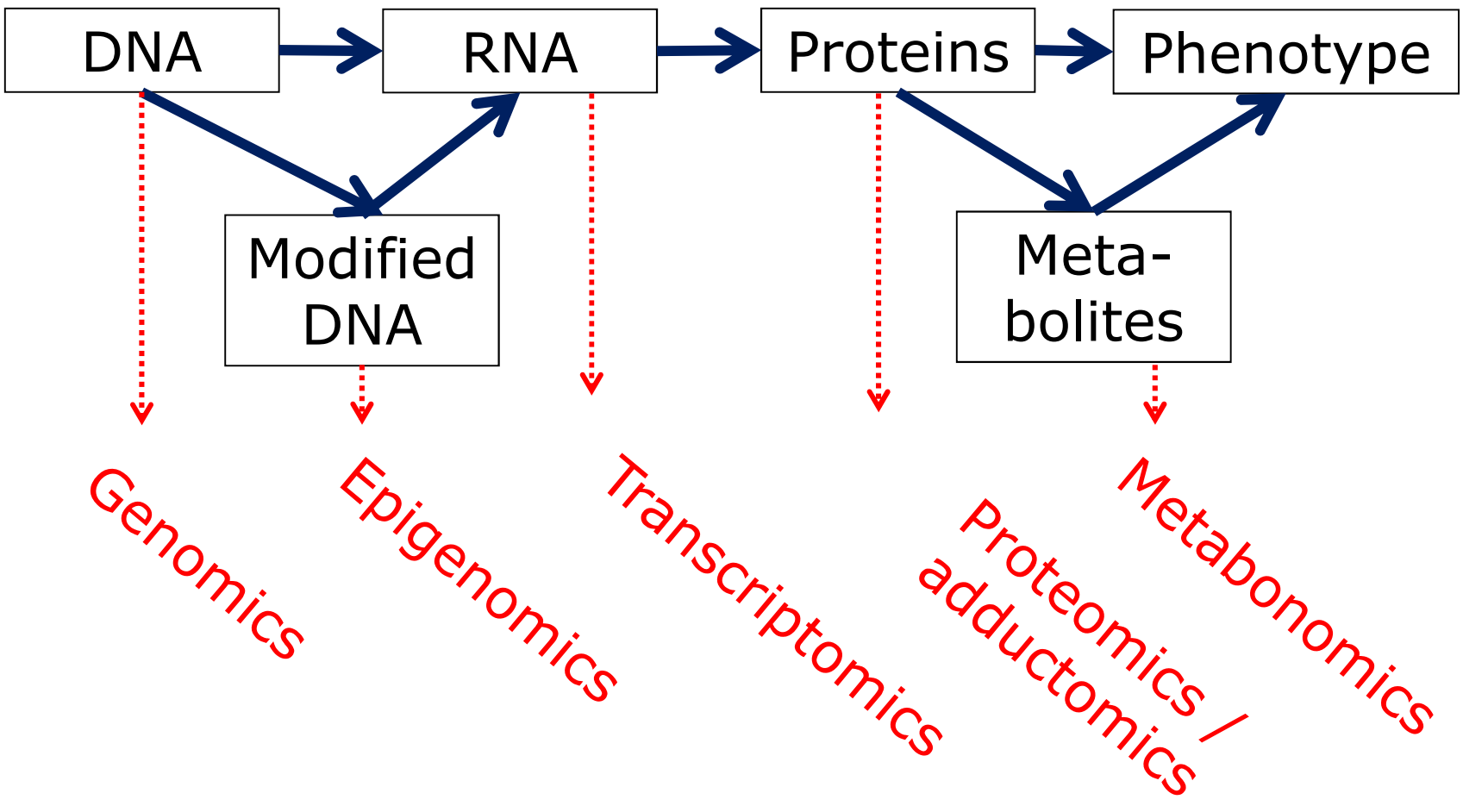
- Methylation
  - Transcriptional repression (CpG)
  - Genomic stability (telomeres)
  - Repress latent viral components
  - Transcriptional activation (gene body)

- *More stable then RNA, proteins*

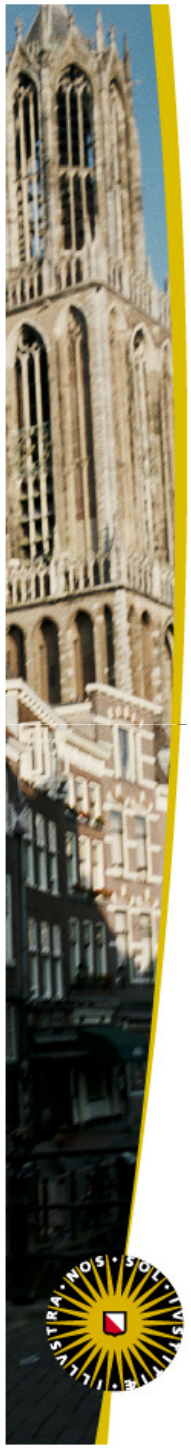


Universiteit Utrecht

Molecular Analyses

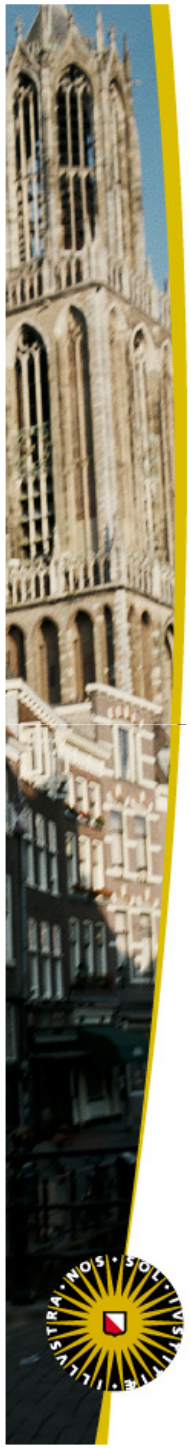


Increased relevance (closer to phenotype) but increased epidemiological and analytical challenges



Epigenetics - Methylation

- In recent years, momentum has also been building around the study of epigenetic events in the context of aging and other diseases
  - Autoimmune disorders
  - Cancer
  - Cardiovascular disease
  - Diabetes / metabolic syndrome
  - Neurodegenerative disorders,

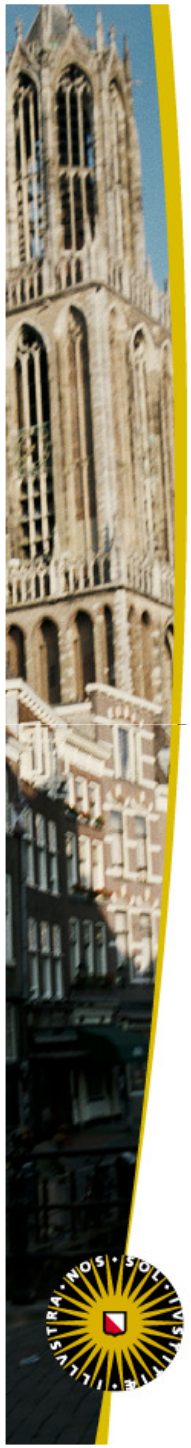


Plasticity of the epigenome

- Twin studies have demonstrated that epigenetic discordance between identical siblings increases over time; particularly as more time is spent apart [Fraga et al.,
  - Stochastic events that occur over time,
  - preprogrammed,
  - adaptive response to various exposures encountered,
  - during life (or a combination of these events).

- There is additional mounting evidence that environmental or dietary exposures or maternal signals such as stress that are sustained during the developmental stages, in particular during prenatal development, can result in epigenetic errors or modifications that propagate throughout somatic tissues

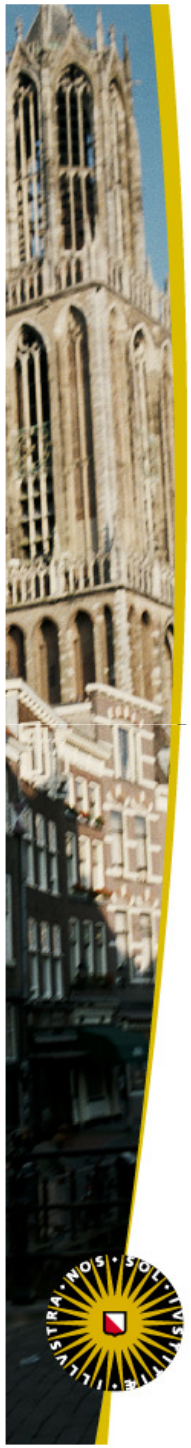
Langevin, 2013



Environmental factors related to epigenetic deregulation

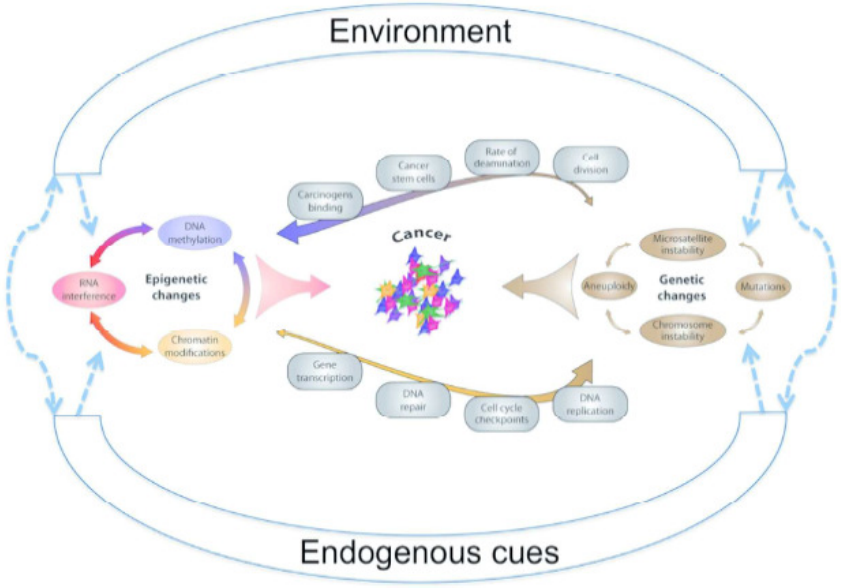
- Tobacco smoke
- Arsenic
- Cadmium
- Nickel
- Ionizing
- UV radiation
- Air polution

- Human hepatitis B virus
- Hepatitis C virus
- Human papillomavirus
- Helicobacter pylori



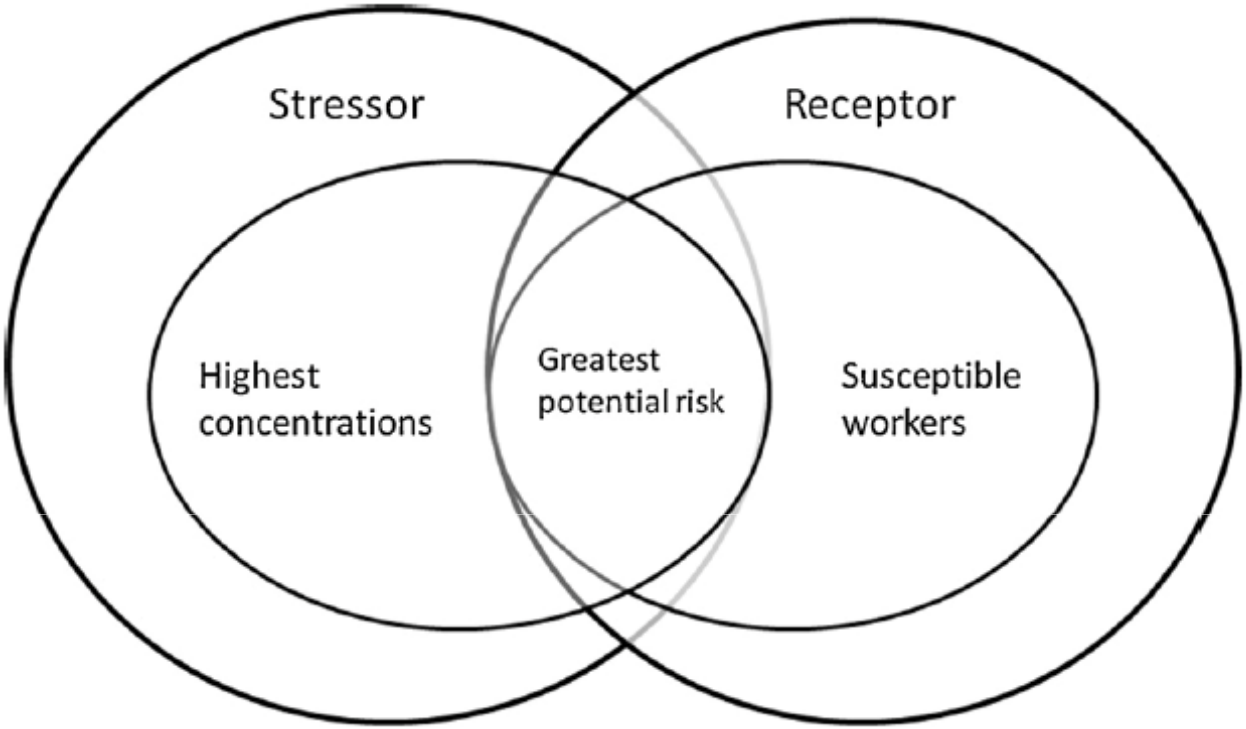
Epigenetics - Methylation

- Tissue heterogeneity
  - epigenetic signature varies by cell and tissue
- Reversed causality
- Platforms
  - Next generation sequencing
  - Array- based



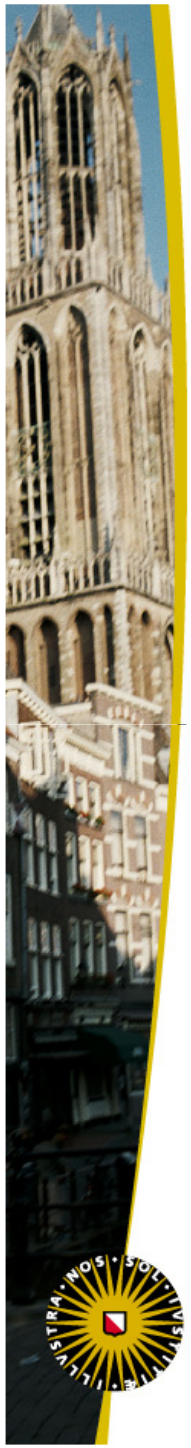
Universiteit Utrecht

Use of biomarkers in occupational health



Source: Adapted from Reiter [2009]

- Medical screening
- Diagnostic monitoring

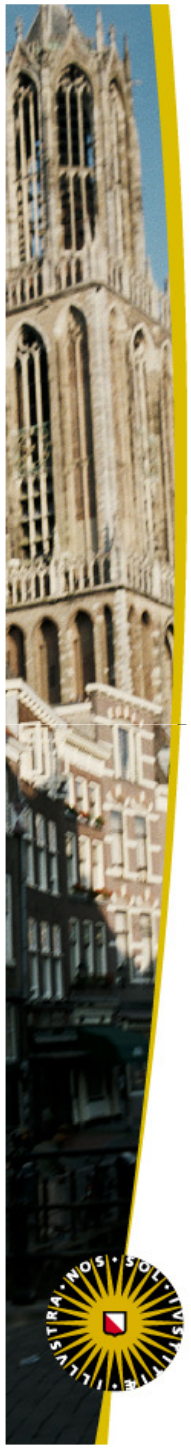


Use of Biomarkers in Occupational Health; Research

	Research	Practice
Exposure	• Identify mechanisms • Serve as independent and dependent variables • Assess exposure	• Biological monitoring • Genetic monitoring • Assess control effectiveness • Health surveillance
Effect	• Identify mechanisms • Serve as dependent variables • Useful in developing systems biology approaches	• Medical screening • Health surveillance • Early warning • Genetic monitoring • Fitness for duty
Susceptibility epimutations	• Identify mechanisms • Investigate new effect modifiers • Develop system biology approach	• Target high risk groups • Develop risk communication • Genetic screening

Universiteit Utrecht

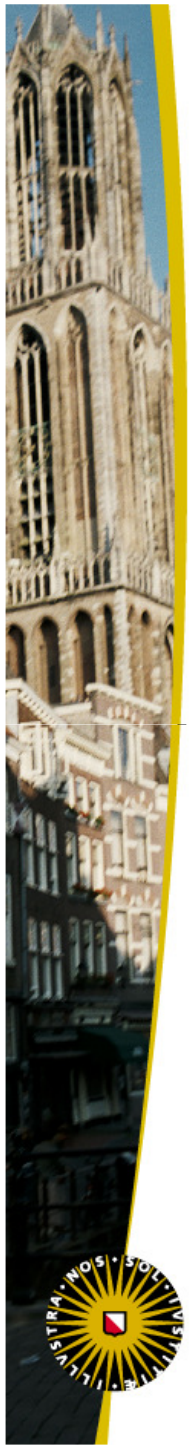
Schulte et al., 2012



Use of Biomarkers in Occupational Health; In practice

- Exposure assessment
  - Means to assure the effectiveness of risk management and prevention
- Health surveillance
  - Respiratory , cardiovascular conditions
- Identify high risk groups
  - Develop risk communication

Universiteit Utrecht

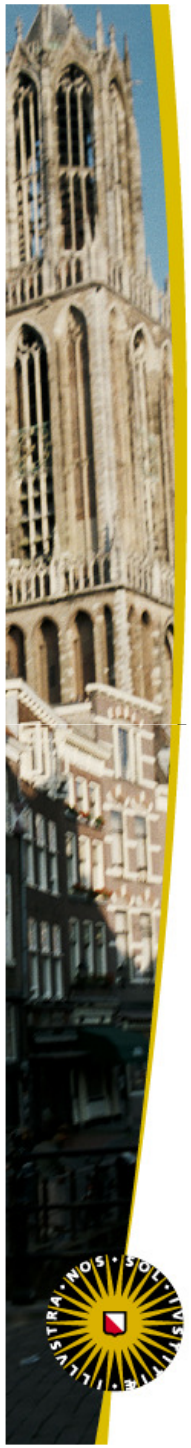


Use of Biomarkers in Occupational Health; Research

	Research	Practice
Exposure	• Identify mechanisms • Serve as independent and dependent variables • Assess exposure	• Biological monitoring • Genetic monitoring • Assess control effectiveness • Health surveillance
Effect	• Identify mechanisms • Serve as dependent variables • Useful in developing systems biology approaches	• Medical screening • Health surveillance • Early warning • Genetic monitoring • Fitness for duty
Susceptibility epimutations	• Identify mechanisms • Investigate new effect modifiers • Develop system biology approach	• Target high risk groups • Develop risk communication • Genetic screening

Universiteit Utrecht

Schulte et al., 2012



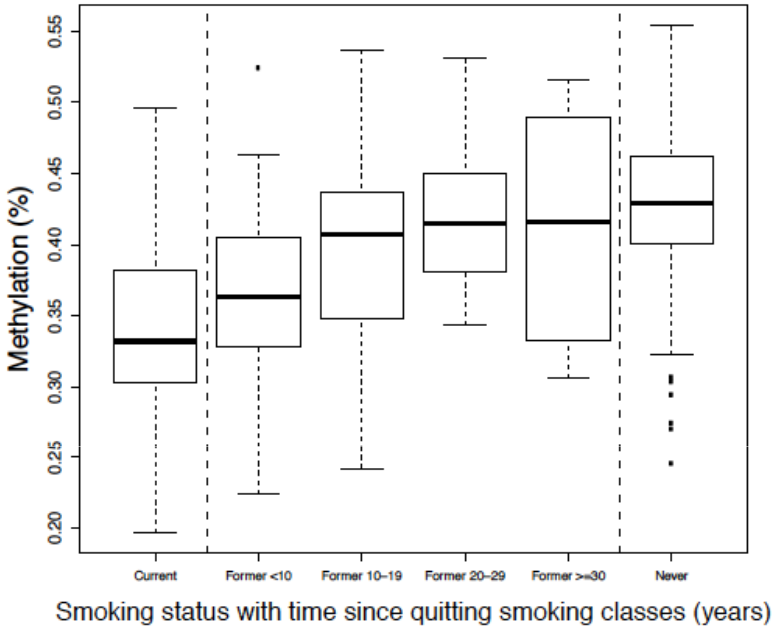
Epigenetics and exposure; Epigenetic changes and smoking

- Population
  - EPIC-Italy n=620
  - NOWAC n=343
- Detailed information on smoking
- PBMCs
- Methylation
  - Illumina Humanmethylation 450K chip

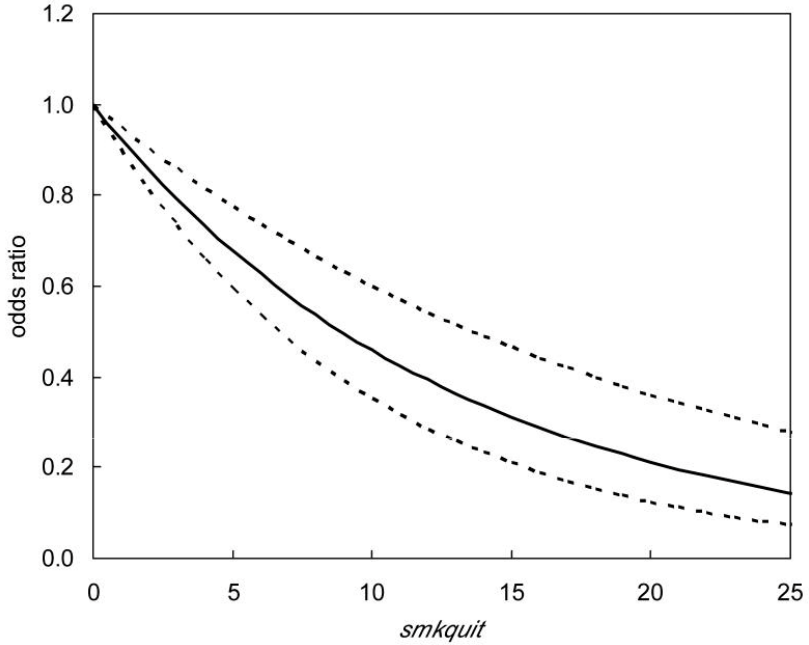
Universiteit Utrecht

Guida et al., 2013

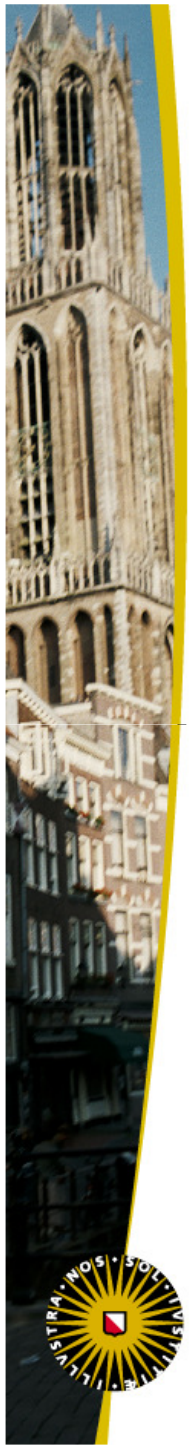
Biological effective dose?



Neuberger et al., 2007



Universiteit Utrecht



Use of Biomarkers in Occupational Health; Research

	Research	Practice
Exposure ✔ Sensitivity? Specificity?	• Identify mechanisms • Serve as independent and dependent variables • Assess exposure	• Biological monitoring • Genetic monitoring • Assess control effectiveness • Health surveillance
Effect	• Identify mechanisms • Serve as dependent variables • Useful in developing systems biology approaches	• Medical screening • Health surveillance • Early warning • Genetic monitoring • Fitness for duty
Susceptibility	• Identify mechanisms • Investigate new effect modifiers • Develop system biology approach	• Target high risk groups • Develop risk communication • Genetic screening

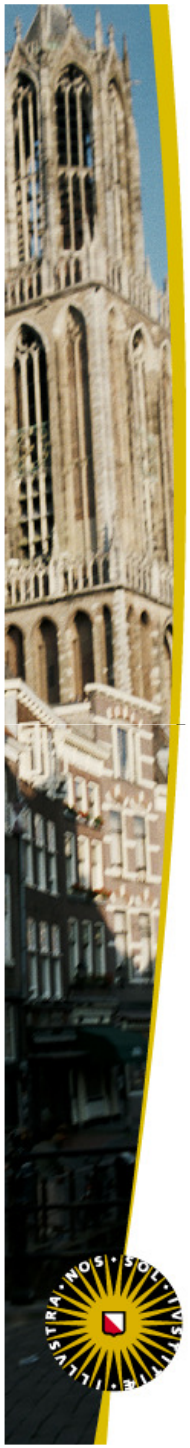
Universiteit Utrecht

Schulte et al., 2012

Effect markers – Epigenetic mechanisms of known carcinogens

Human carcinogen	Epigenetic mechanism	Model		
		Human samples	Cell lines	Animal model
Part C : Arsenic, Metals, Fibres, and Dusts and Part D: Radiation				
Arsenic				
	DNA methylation	*		
			*	
				*
	Histone marks		*	
	miRNA		*	
Cadmium				
	DNA methylation		*	
				*
	miRNA	*		
Nickel				
	DNA methylation		*	
				*
	Histone marks		*	
				*
Beryllium				
	DNA methylation			*

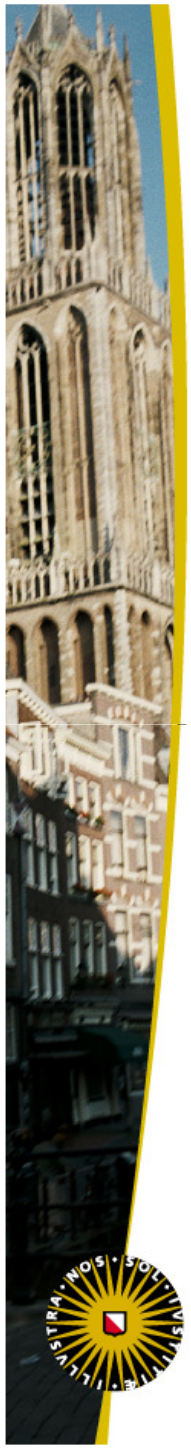
Zdenko et al., unpublished



Effect markers – Epigenetic mechanisms of known carcinogens

Human carcinogen	Epigenetic mechanism	Model		
		Human samples	Cell lines	Animal model
Asbestos				
	DNA methylation			*
	miRNA			*
X-radiation				
	DNA methylation	*		
				*
	miRNA	*		
			*	
				*
Gamma radiation				
	DNA methylation		*	
	miRNA			*
Smoky coal emissions (for cooking and heating)				
	DNA methylation	*		
Chromium VI compounds				
	Histone marks		*	
Air pollution	DNA methylation	*		
DEE	miRNA	*		

Zdenko et al. unpublished

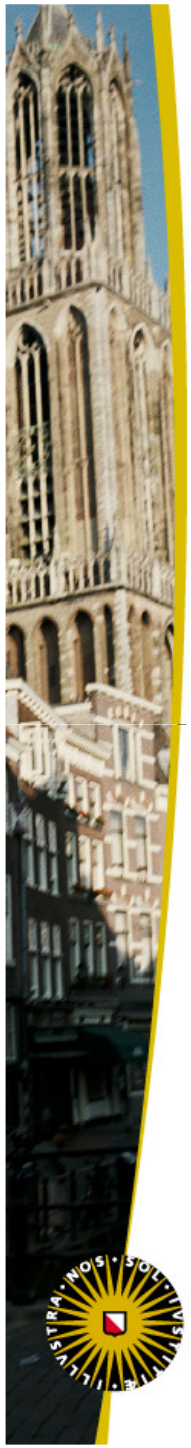


Use of Biomarkers in Occupational Health; Research

	Research	Practice
Exposure ✔ Sensitivity? Specificity?	• Identify mechanisms • Serve as independent and dependent variables • Assess exposure	• Biological monitoring • Genetic monitoring • Assess control effectiveness • Health surveillance
Effect ✔ Sensitivity? Specificity?	• Identify mechanisms • Serve as dependent variables • Useful in developing systems biology approaches	• Medical screening • Health surveillance • Early warning • Genetic monitoring • Fitness for duty
Susceptibility	• Identify mechanisms • Investigate new effect modifiers • Develop system biology approach	• Target high risk groups • Develop risk communication • Genetic screening

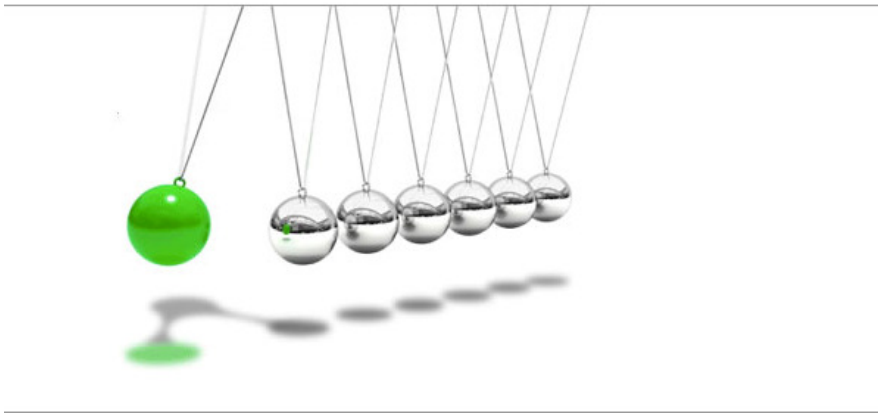
Universiteit Utrecht

Schulte et al., 2012



Cross Omics analyses

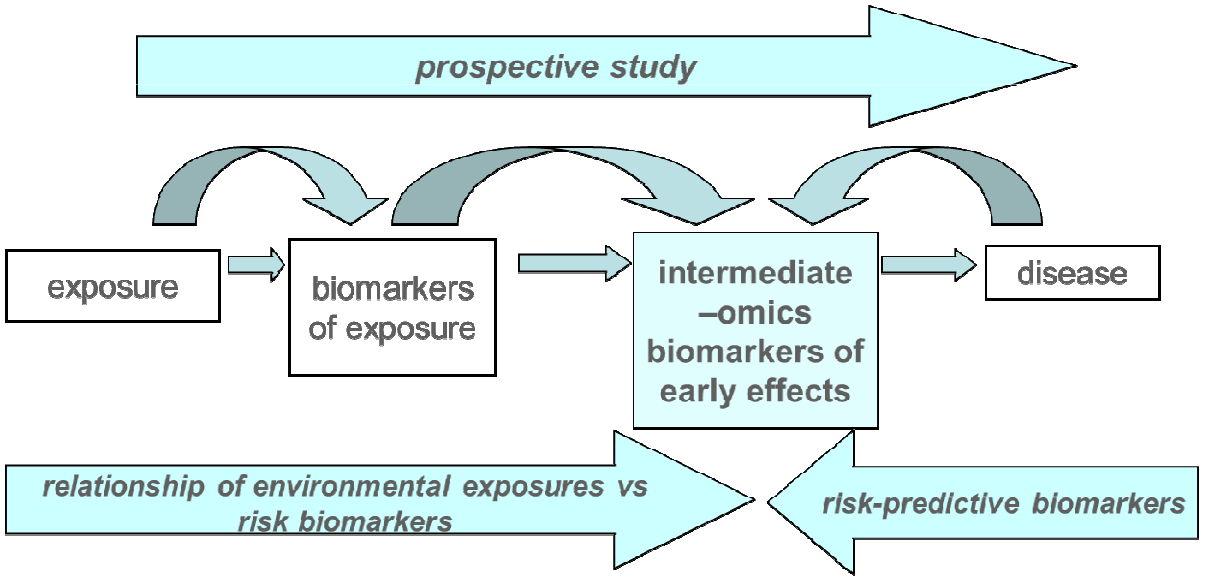
- Concatenating the methylation dataset on gene expression profiles
  - 558 gene expression probes significantly associated with 79 out of the 123 common CpG sites, using a Bonferroni 5% threshold.
  - Differentially significant expression probes were mapped to genes present in DAVID.

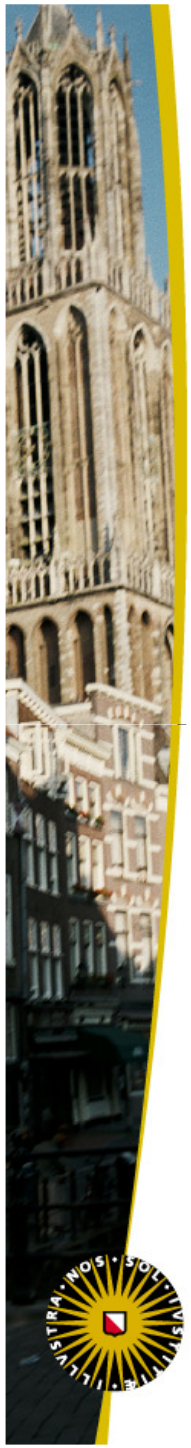


Universiteit Utrecht

OMICS based biomarkers – Epiphenomena?

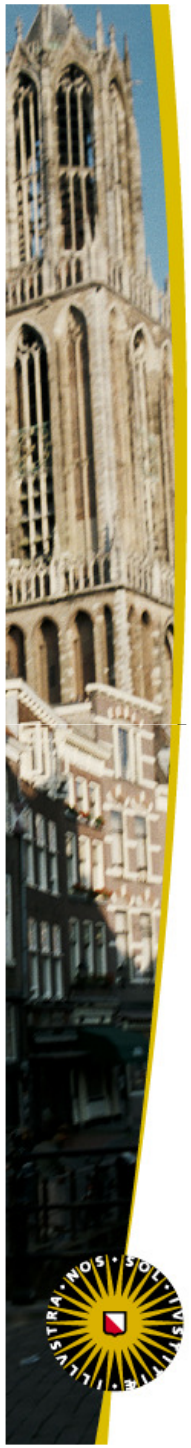
- Objectives
  - To identify exposure markers
  - To find disease classifiers (risk-predictive biomarkers)
  - To elucidate the etiology of the exposure – disease association (MITM biomarkers)





Use of Biomarkers in Occupational Health; Research

	Research	Practice
Exposure ✔ Sensitivity? Specificity?	• Identify mechanisms • Serve as independent and dependent variables • Assess exposure	• Biological monitoring • Genetic monitoring • Assess control effectiveness • Health surveillance
Effect ✔ Sensitivity? Specificity?	• Identify mechanisms • Serve as dependent variables • Useful in developing systems biology approaches	• Medical screening • Health surveillance • Early warning • Genetic monitoring • Fitness for duty
Susceptibility	• Identify mechanisms • Investigate new effect modifiers • Develop system biology approach	• Target high risk groups • Develop risk communication • Genetic screening



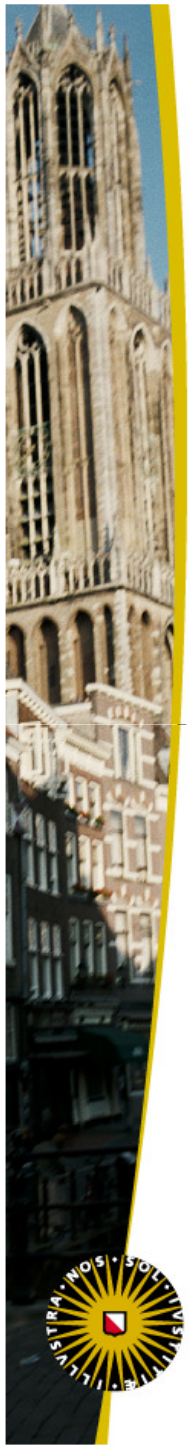
Susceptibility; Epigenetics adds another layer of complexity to individual variability

- Epigenome may be most vulnerable to environmental insults during periods of extensive epigenetic reprograming
  - Early stages of embryonic development
  - Childhood (oocyte, hyploid demethylated state)

  -> *Employment of fertile women*

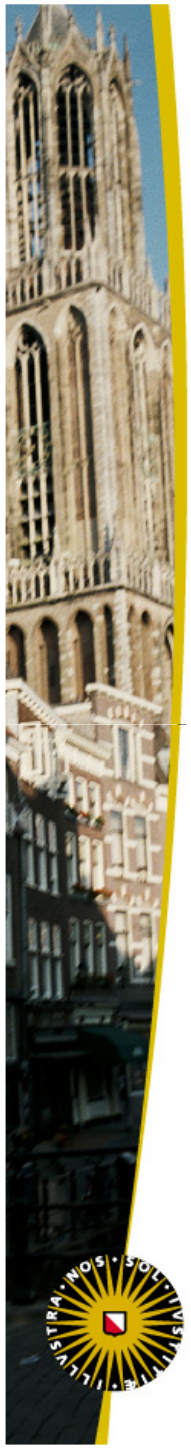
  -> *Intergenerational equity*

- Pre-exposure testing for individual susceptibility
  - Similar ethical issues as with genetic testing
    - *Privacy & confidentiality*
    - *Undermine individual autonomy*
    - *Create stigma*
    - *Psychological harm*



Use of Biomarkers in Occupational Health; Research

	Research	Practice
Exposure ✔ Sensitivity? Specificity?	• Identify mechanisms • Serve as independent and dependent variables • Assess exposure	• Biological monitoring • Genetic monitoring • Assess control effectiveness • Health surveillance
Effect ✔ Sensitivity? Specificity?	• Identify mechanisms • Serve as dependent variables • Useful in developing systems biology approaches	• Medical screening • Health surveillance • Early warning • Genetic monitoring • Fitness for duty
Susceptibility ✔ Ethics	• Identify mechanisms • Investigate new effect modifiers • Develop system biology approach	• Target high risk groups • Develop risk communication • Genetic screening



Epigenetica en blootstelling aan chemicaliën; Betekenis voor de bedrijfsgezondheidszorg

- *Epigenetics represents a new class of biological effects of harmful exposures and adds a multi-generational dimension to environmentally-caused adverse effects*
- Epigenetics holds promise for elucidating mechanisms of disease
  - Integral part of the systems biology approach
- May potentially lead to environmental fingerprints
  - Specificity, dynamics
- May potentially provide stable markers of early effect
  - Epiphenomena ~ validation
- May provide markers of susceptibility
  - Ethics

Universiteit Utrecht

Biomarkers are not a panacea for preventing all worker illnesses and injuries, but focused on particular issues, their use can contribute to improved protection

Schulte, 2012