Scene setting - the changing 'omics' landscape

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IGHRC Awareness Day Does progress in 'omics' help in human health risk assessment?

13th October 2017

The History of Ideas

- Development of NA array technology, proteomics and sensitive NMR led to suggestions that as well as understanding diseases these could be applied to toxicology and drug safety

- COT 2001 What do we want to achieve by the use of genomics proteomics, SNPs and bioinformatic analysis in risk assessment?

- RSC 2003 How useful will genomics, proteomics and metabonomics be to assess chemical risk in humans?

- Since then there has been explosion in omic technology, data acquisition and bioinformatics

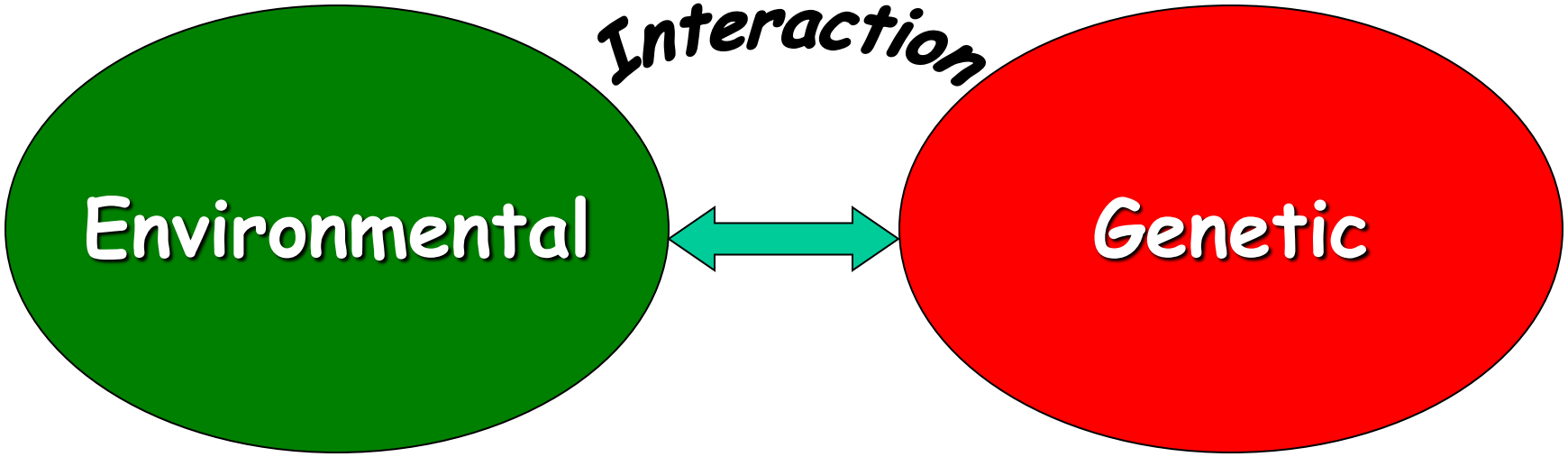
Overview of use of 'omics'
(Sanofi 2003)

Toxicogenomics transcript profiling	→	Hybridization of 'RNA' to cDNA or oligo arrays with fluorescence detection
Proteomics protein profiling	→	2D gel electrophoresis of protein source and mass spectrometry of peptides
Metabonomics metabolite profiling	→	^{1}H NMR (or MS) of *in vivo* samples (urine, plasma) for patterns of endogenous metabolites

Underlying these are complex technical and statistical manipulations all prone to variance and misinterpretation

Sources of natural variability (2003)

What is normal human and animal variation?



Even diet can significantly alter hundreds of gene expressions.

With 'omics' it may be difficult to detect polymorphisms with functional significance.

2003

Do 'omics' help to find a simple uniform mechanism and potential biomarkers?

One view

- Traditional biology shows a 'tree'.

  Omics shows 'forests and mountains'

Another view

- Can't see 'the wood for the trees'

Risk assessment even more difficult

Wikepedia

(2017)

'***Omics'***

- Genomics
- Lipidomics
- Proteomics
- Glycomics
- Foodomics
- Transcriptomics
- Metabonomics
- Epigenomics
- Exposomics
- Phenomics
- Pharmacogenomics
- Toxicogenomics
- Microbiomics
- Metallomics
- Others!

- ***Omic technology***
- Genomics (gene sequences etc)
- Transcriptomics (mRNA)
- Proteomics (protein gel/MS)
- Metabonomics(MS/NMR)
- Bioinformatic programmes

- Now thousands of papers and $100 millions spent
- Most are about hazard identification and mechanism
- Not risk evaluation

Proteomics

Although an important approach it does not seem to had the same impact for hazard and risk assessment as other technologies

Proteomics as the tool to search for lung disease markers in bronchoalveolar lavage

Isabelle Noël-Georis[a], A. Bernard[b], Paul Falmagne[a] and Ruddy Wattiez[a,*]

2001

Plasma Protein Level Changes in Waste Incineration Workers Exposed to 2,3,7,8-Tetrachlorodibenzo-p-dioxin

Mee Jeong Kang, Do-Youn Lee, Won-A Joo, and Chan-Wha Kim*

School of Life Sciences and Biotechnology, Korea University, Seoul, Korea

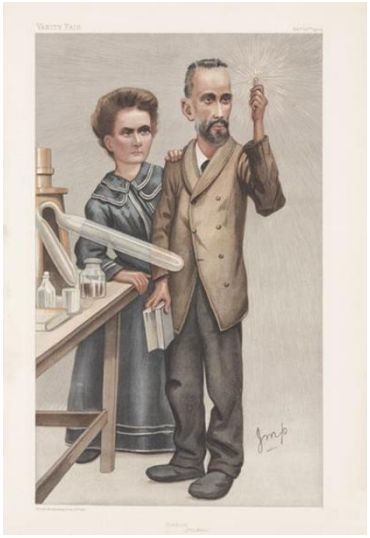
2005

Toxicoproteomics and its application to human health risk assessment

Yue Ge, R. Julian Preston and Russell D. Owen

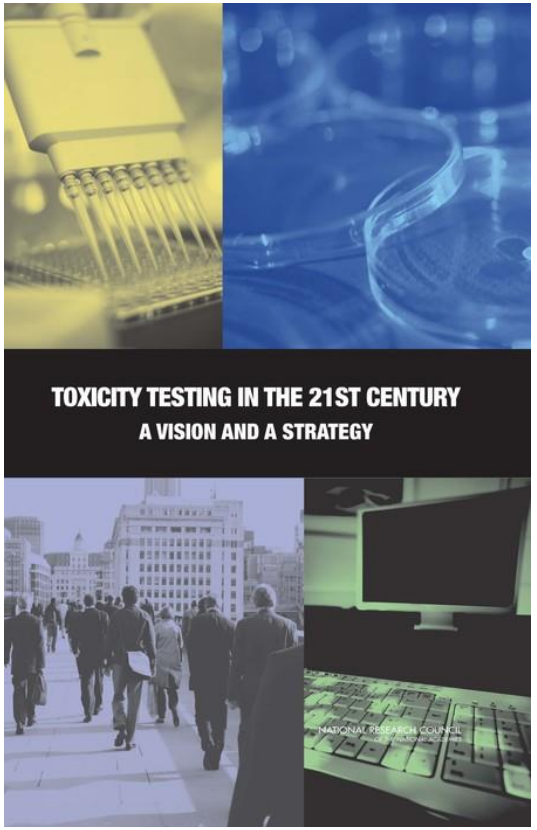
2007

The History of Ideas



- Risk assessment in the exposed human population would focus on avoiding perturbations in toxicity pathways.
- Computational systems to determine the dose-response models of perturbations of pathway function.
- Extrapolation of in vitro results to in vivo human blood and tissue levels to be based on pharmacokinetic models for a given exposure

US National Research Council

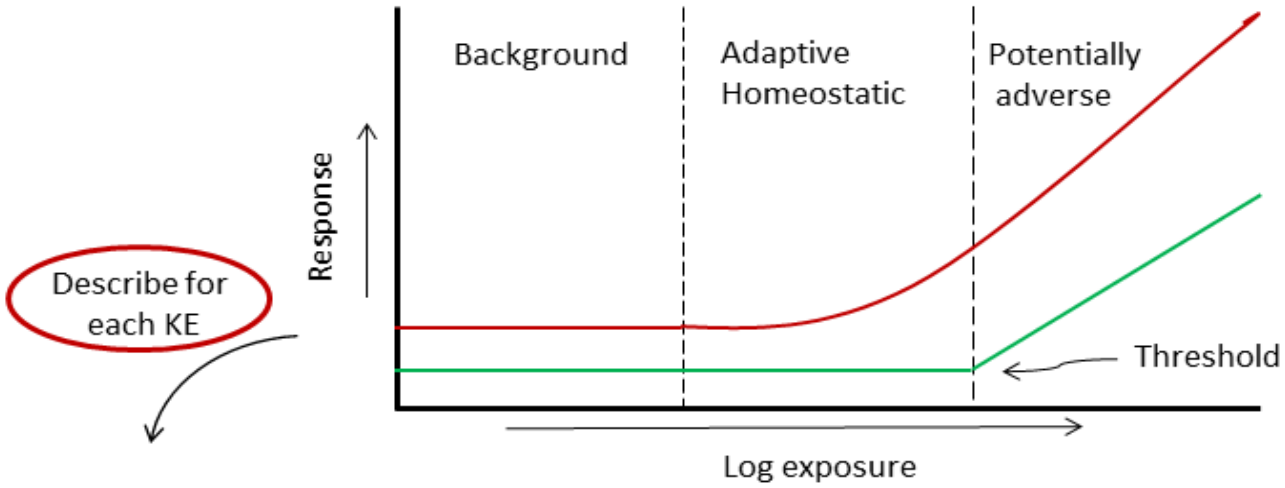


2010

What is an adverse effect rather than adaptive? NOAEL not NOEL

- With omics there can be hundreds of statistically significant changes- how to make sense. Depends on control ranges and on pathological opinion etc
- For instance, the problem of endocrine disruptors
- It may not be single 'biomarkers' that matter, but constellations of changes. cf. GCHQ.
- Bioformatic models especially important here
- Important to establish clear AOP relevant to humans and degree of exposure

Summary scheme for a non-monotonic dose response



Describe for each KE

Flutamide

AR interaction (antagonism)

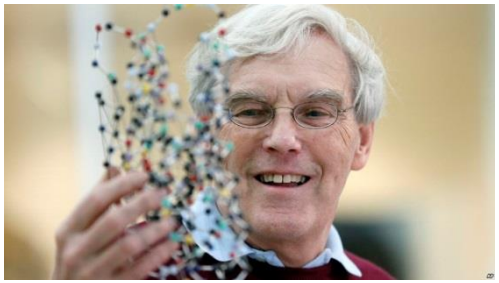
MIE

Altered gene expression
Hypothalamus
Pituitary
Gonads

Morphological consequences
- Decreased cell proliferation; AGD decrease
- Decreased apoptosis; nipple retention
- Changes in gubernaculum; testes descent
- Modelling changes; hypospadias
- Malformations of the prostate

Associated events
- Upregulation of AR
- Changes in enzymes, proteins, transcription factors
- Altered steroid /HPG profiles in blood, urine, tissues
- Differential stains for histopathology

The History of Ideas



R Henderson MRC
Nobel Prize 2017

2017>

Future challenges for human risk assessment

- Where population studies are available omic data can show small changes but must be compared with exposure data
- May be easier for drugs but environmental and occupational exposure much, much lower.
- Good robust epidemiological studies but large data sets with low variability
- Non human data may be very useful
- If in vitro data used, exposure and comparable AOP for humans must be available and secure for extrapolation to people
- Suitable to assess new chemicals in use and biologics