NORMAN WORKSHOP Emerging Chemicals, Oct. 2007

The pros and cons of using genomics to assess emerging chemicals

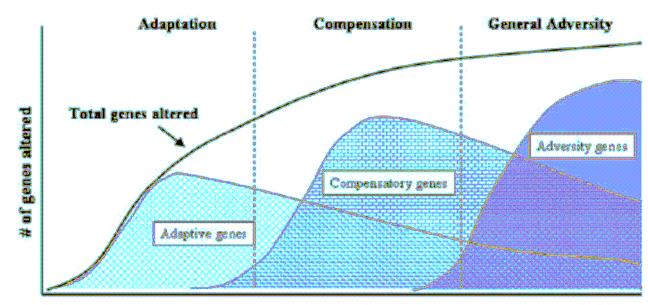
Juliette Legler

Institute for Environmental Studies (IVM), VU University Amsterdam



Genomics in toxicology

- Toxicogenomics: the "study of the relationship between the structure and activity of the genome and the adverse biological effects of exogenous agents"
- characterize changes in gene expression in cells or tissues after exposure to toxicants
- toxicologically relevant outcomes are based on differential gene expression

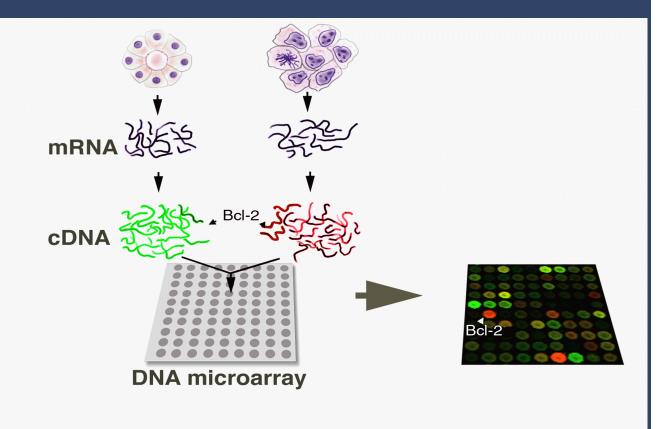


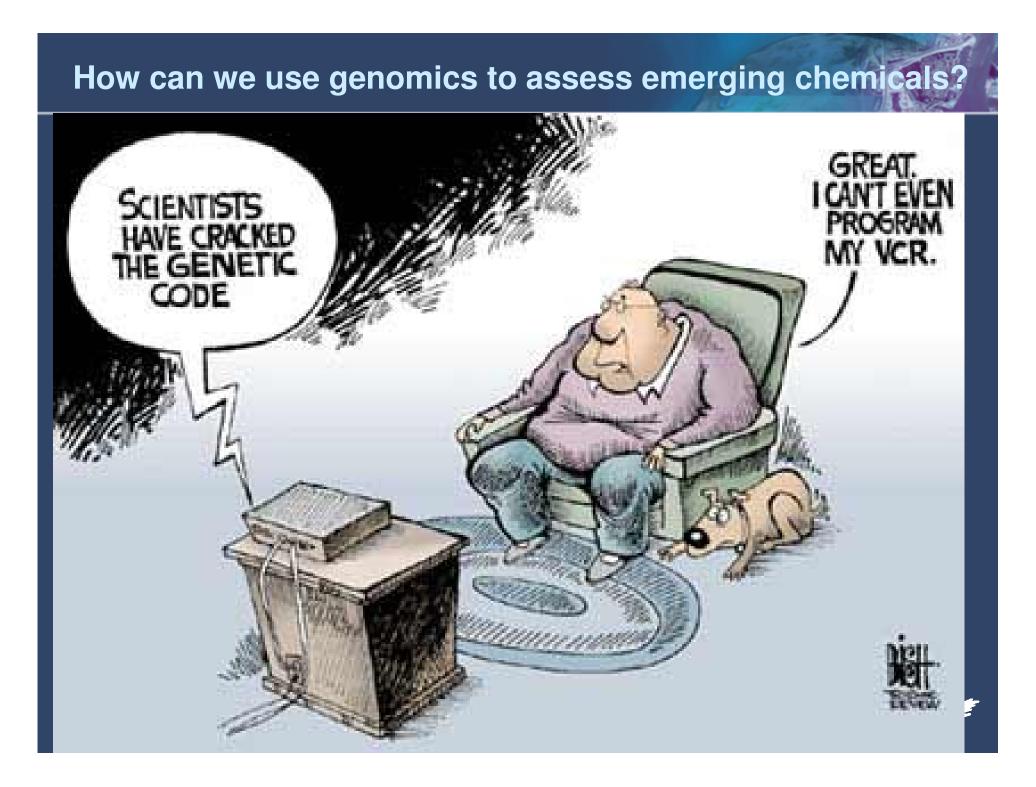
Concentration x Time

Genomics in toxicology: microarray technology

 instantaneous and simultaneous genome-wide detection of the expression of thousand of genes, even if the function of some of the genes is unknown.

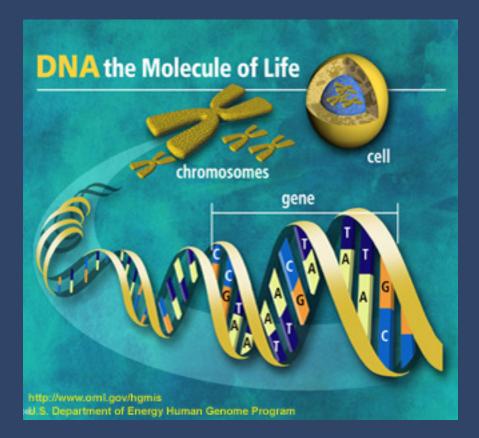
"a revolution in our ability to characterize simultaneously an unprecedented number of biological endpoints"





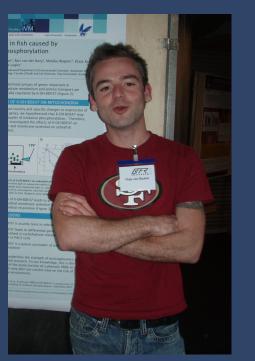
Genomics to assess emerging chemicals

PROS

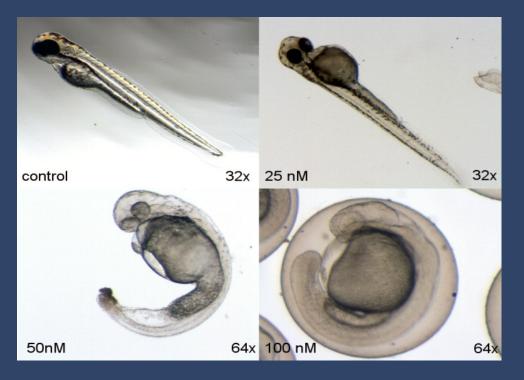




Genomics can help reveal mechanisms of action



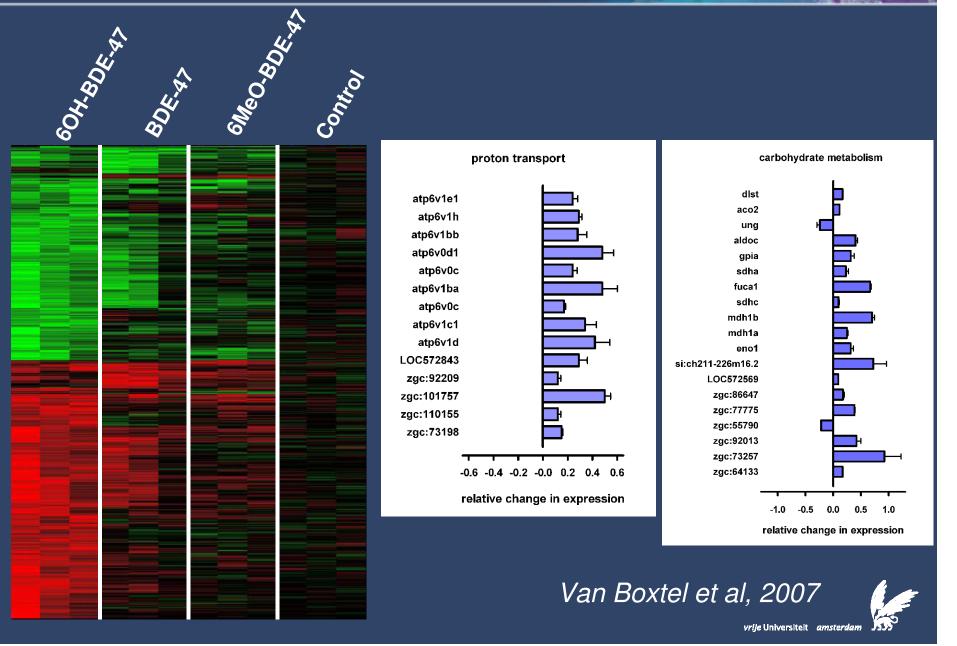
T. Van Boxtel et al, 2007



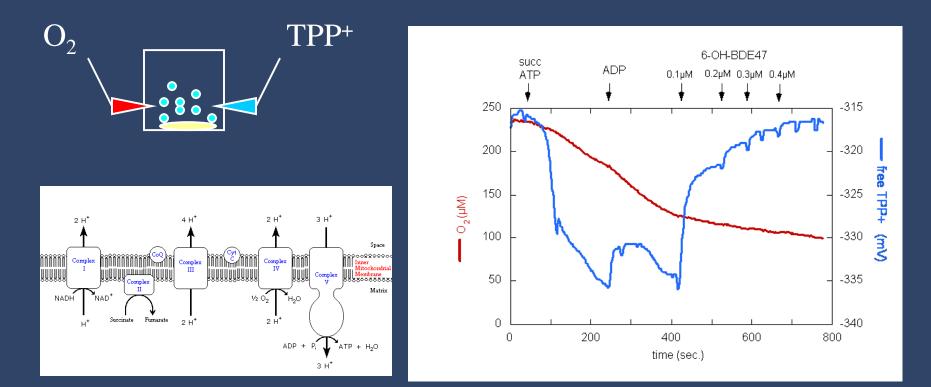
Environmentally relevant metabolite of BDE 47 (6-OH BDE 47) is toxic to developing zebrafish embryo



Genomics can help to reveal mechanisms of action



Genomics can help to reveal mechanisms of action



Van Boxtel et al, 2007

6-OH-BDE47 is an uncoupler of oxidative phosphorylaton



Genomics can reveal 'signatures' of toxicity

TOXICOLOGICAL SCIENCES 97(2), 595–613 (2007) doi:10.1093/toxsci/kfm065 Advance Access publication March 22, 2007

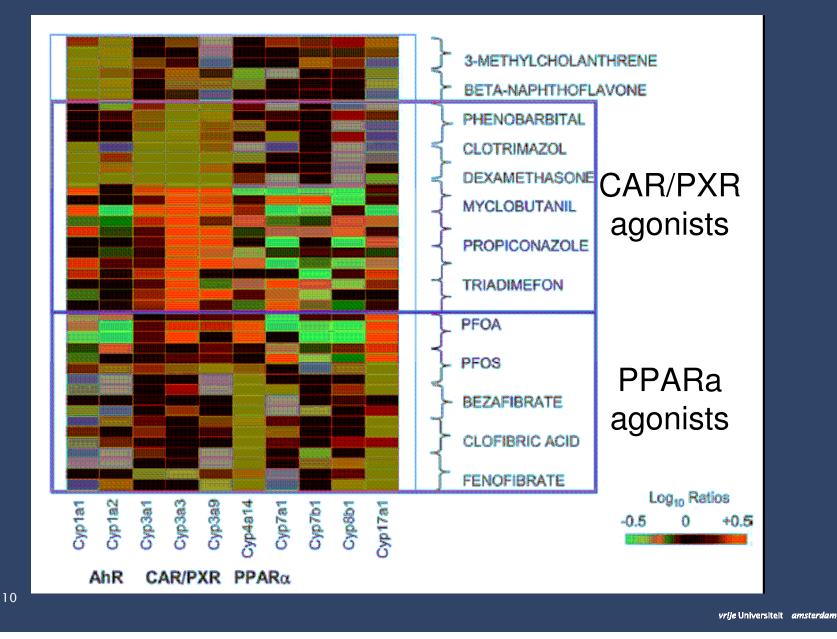
> Toxicogenomic Study of Triazole Fungicides and Perfluoroalkyl Acids in Rat Livers Predicts Toxicity and Categorizes Chemicals Based on Mechanisms of Toxicity

Matthew T. Martin,* Richard J. Brennan,‡ Wenyue Hu,‡ Eser Ayanoglu,‡ Christopher Lau,‡ Hongzu Ren,† Carmen R. Wood,† J. Christopher Corton,† Robert J. Kavlock,* and David J. Dix*^{,1}

- Gene expression profiles in rats exposed to three triazole antifungals (myclobutanil, propiconazole, and triadimeton) and two perfluorinated chemicals [perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS)]
- Compare gene expression profile to database of 630 chemicals



Genomics can reveal 'signatures' of toxicity



Genomics can identify biomarkers/classifiers of toxicity

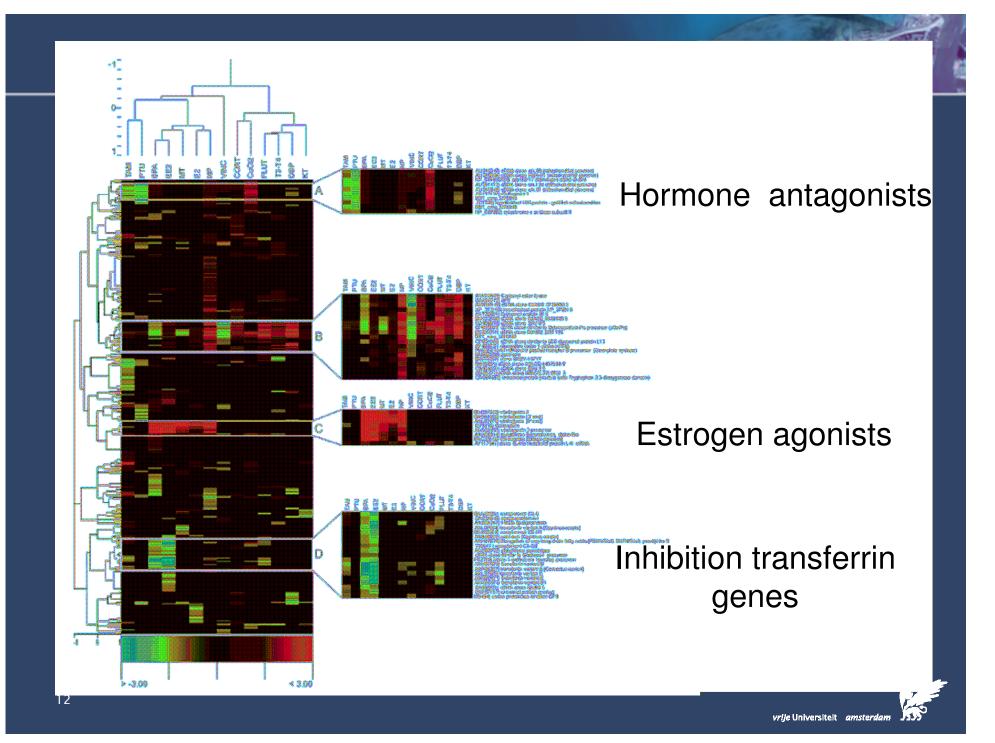
TOXICOLOGICAL SCIENCES **93(2)**, 298–310 (2006) doi:10.1093/toxsci/kfl057 Advance Access publication July 11, 2006

Expression Profiling of Endocrine-Disrupting Compounds Using a Customized *Cyprinus carpio* cDNA Microarray

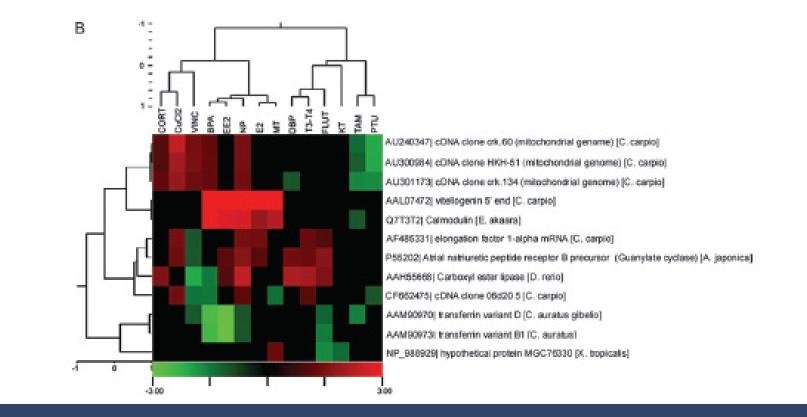
Lotte N. Moens,*¹ Karlijn van der Ven,* Piet Van Remortel,† Jurgen Del-Favero,‡ and Wim M. De Coen*

 17beta-estradiol, 17alpha-ethinylestradiol, 4-nonylphenol, bisphenol A, tamoxifen, 17alpha-methyltestosterone, 11ketotestosterone, dibutyl phthalate, flutamide, vinclozolin, hydrocortisone, CuCl2, propylthiouracil, and a mixture of Ltriiodothyronine and Lthyroxine





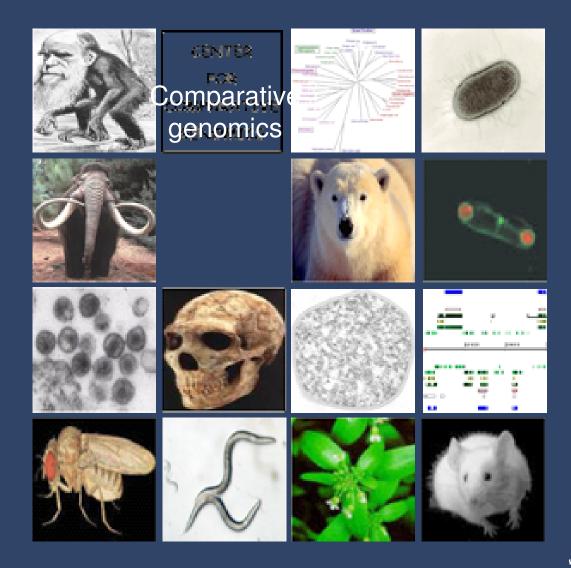
Genomics can identify biomarkers/classifiers of toxicity



Generational genetic algorithm: revealed a subset of genes that separated the compounds in an optimal way
Subset of 12 genes discriminates endocrine disrupting chemicals

Comparative genomics between species:

predicting toxicity in humans?



Comparative genomics between species:

predicting toxicity in humans?

TOXICOLOGICAL SCIENCES **94(1)**, 71–82 (2006) doi:10.1093/toxsci/kfl080 Advance Access publication August 17, 2006

Gene Expression Profiles in Fathead Minnow Exposed to 2,4-DNT: Correlation with Toxicity in Mammals

Henri Wintz,^{*,1} Leslie J. Yoo,[†] Alex Loguinov,^{*} Ying-Ying Wu,^{*} Jeffrey A. Steevens,[†] Ricky D. Holland,[‡] Richard D. Beger,[‡] Edward J. Perkins,[†] Owen Hughes,[§] and Chris D. Vulpe^{*}

*Department of Nutritional Sciences and Toxicology, Morgan Hall and Berkeley Institute of the Environment, University of California, Berkeley, California 94720; †US Army Corps of Engineer Research and Development Center, Environmental Laboratory, Vicksburg, Mississippi 39180; ‡Division of Systems Toxicology, National Center for Toxicological Research, Jefferson, Arkansas 72079; and §Eon Corporation, Davis, California 95616



Comparative genomics between species:

predicting toxicity

Fish and rodents: similar metabolic pathways affected by 2,4 DNT

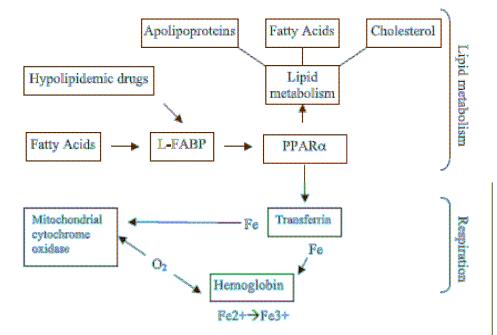


FIG. 2. Metabolic pathways affected by 2,4-DNT in fathead minnow liver. Genes affected by 2,4-DNT and how they relate to each other within known pathways are represented. Fatty acids or hypolipidemic drugs signals are relayed to the nucleus via the L-FABP, where it activates PPAR α , which controls expression of lipid metabolism genes (apolipoproteins and fatty acid metabolism genes) as well as Tf gene. Transferrin carries iron, which is an essential cofactor of hemoglobin and of the mitochondrial respiratory chain. Oxygen is a substrate of cytochrome oxidase and hemoglobin. 2,4-DNT is known to affect oxygen transport by oxidizing hemoglobin ferrous iron to its ferric state.

Application of genomics to "ecotox" species/models







Ecotoxicogenomics: gene expression in non-target organisms in response to environmental toxicant exposures ersitet ansterdam

Application of genomics to "ecotox"

Environ. Sci. Technol. 2007, 41, 1044-1050

Daphnia magna Ecotoxicogenomics Provides Mechanistic Insights into Metal Toxicity

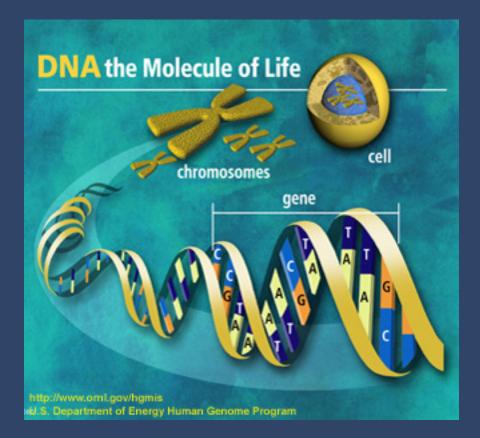
HELEN C. POYNTON,[†] JULIA R. VARSHAVSKY,[†] BONNIE CHANG,[†] GIORGIO CAVIGIOLIO,[‡] SARAH CHAN,[†] PATRICIA S. HOLMAN,[†] ALEXANDRE V. LOGUINOV,[†] DARREN J. BAUER,[§] KELLY KOMACHI,[⊥] ELIZABETH C. THEIL,[‡] EDWARD J. PERKINS,[‡] OWEN HUGHES,[⊥] AND CHRIS D. VULPE^{*,†}

Nutritional Sciences and Toxicology, University of California, Berkeley, California 94720, Center for BioIron at CHORI (Children's Hospital Oakland Research Institute), Oakland, California 94609, Hubbard Center for Genome Studies, University of New Hampshire, Durham, New Hampshire 03824, Eon/Terragenomics, Davis, California 95616, and Environmental Laboratory, U.S. Army Engineer Research and Development Center, Vicksburg, Mississippi 39180 TABLE 1. Predicted Function of Differentially Expressed Genes after Exposure to Copper, Cadmium, or Zinc at the 1/10 LC50

Exp. level Cu Cd Zn	Acc #	Predicted Protein Class
NETAL BINDING AND TRANSPORT		
	AJ292556	Featin
	OV437799	Metallothionein
	01/437828	Metallothonein
	DV437852 DV437849	remin suburd
	DV437835	Hoavy metal binding protein, Collagen a chain
DIGESTION		NT ABSORPTION
	DV437797	
		Endo-p-1.4-glucenese precureor
	DV437795 DV437794	Endo-6-1,4-mannanasa ar- amylase
	05407849	Cretita
	DV437815	Preamylase precursor
EXCONELET		D PROTEINS
	DV437807	Chills binding and metabolism
	DV/437809	Chinase
	DV437890 DV437850	Chits binding and metabolism Chits binding and metabolism
	DV437857	Chinase
	DV437858 DV437858	Chitnase precursor
		Cultie protein
CELL SION		
	DV437808 DV437805	Inceitel monephosphatese Leucine-rich protein phosphatese
	DV437828	Protein kinase
	07437832	Ras-related protein
IMMUNE FU	UCTION	
	DV437831	
	DV437813 DV437823	Lectin-like protein
	OV437848	Careballin procursor-like protein
OXIDATIVE	STRESS RES	
	DV437830	
	OV437833	Glutathione S-transforase Glutathione-S-transforase
	OV437829	Perexiredoxin V protein
NONCOYCE	NASES	
		Monoexygenese
3/////A		Dopernine §-hydroxylase
	DV437827	
	DV437820	Dopamine 6-hydrexylace
EFOTEASE	DV437820 DV437836	
PROTEASE	DV437820 DV437836	Dopomine p-Bydroxylace Cooper type II, assorbate-dependent monooxygenase
PROTEASE	DV437820 DV437838 DV437812 DV437812 DV437825	Dopamine p.bydroxytase Copper type II, assorbate-dependent monooxygenase Aminopepiidase Typpin precursor
PROTEASE	DV437820 DV437838 DV437812 DV437812 DV437855 DV437854	Dopamina p-hydroxytaae Copper yype II, ascorbate-dependent monooxygenase Aminopeptidase Toypsin precursor Carbaxyzeptidase Af procursor
PROTEASE	DV437820 DV437836 DV437812 DV437812 DV437855 DV437854 DV437853	Dopenine j-hydroxytabe Copper type II, assorbate-dependent monoorygenase Aminopeptidase Trypsin pracursor Carboxyceptidase AT procursor Trypsin
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PROTEASE	DV437820 DV437838 DV437838 DV437812 DV437852 DV437854 DV437853 DV437853 DV437803 DV437823	Dopamine 8-hydroxytabe Cooper type II, ascorbate-dependent monoorygenase Aminopeptidaso Typsin procursor Carboxypeptidaso M procursor Typsin Ohrmotrypain Bit procursor Zarc metalopeptidase Selfne collogenase precursor
PROTEASE	DV437820 DV437838 DV437832 DV437832 DV437855 DV437855 DV437853 DV437853 DV437826 DV437823 DV437823	Docemene j-hydroxytace Copper type II, ascorbate-dependent monooxygenase Arrinopeptidaso Toppin precursor Carboxycogidaso Al procursor Trypein Othernotypain Bil procursor Zino metisiopeptidee Berline collocenase precursor Citymotypesting precursor Citymotypesting precursor
PROTEASE	DV437820 DV437838 DV437838 DV437852 DV437854 DV437854 DV437853 DV437853 DV437842 DV437842 DV437842 DV437842 DV437842	Dopamine 8-hydroxytabe Cooper type II, ascorbate-dependent monoorygenase Aminopepiidaso Topsin precursor Carboxypepiidaso Al procursor Tripsin Chrmolrygain Bil precursor Zhin metatopepiitee Selfne colleguiase precursor Chymolrygein precursor Selfne processo Selfne colleguiase precursor Selfne processo
PROTEASES	DV437820 DV437830 DV437830 DV437852 DV437853 DV437853 DV437853 DV437853 DV437841 DV437841 DV437842 DV437843 DV437843 DV437843	Docemene 3-hydroxytace Copper type II, ascorbate-dependent monooxygenase Aminopeptidase Trypsin precursor Carboxygeptidase M precursor Trypsin Otwrrotrypsin Bit precursor Zano metalopeptidase Bedine collegenase precursor Cetymotrypsin precursor Serine protease Transmerthrane actine protease Transmerthrane serine protease
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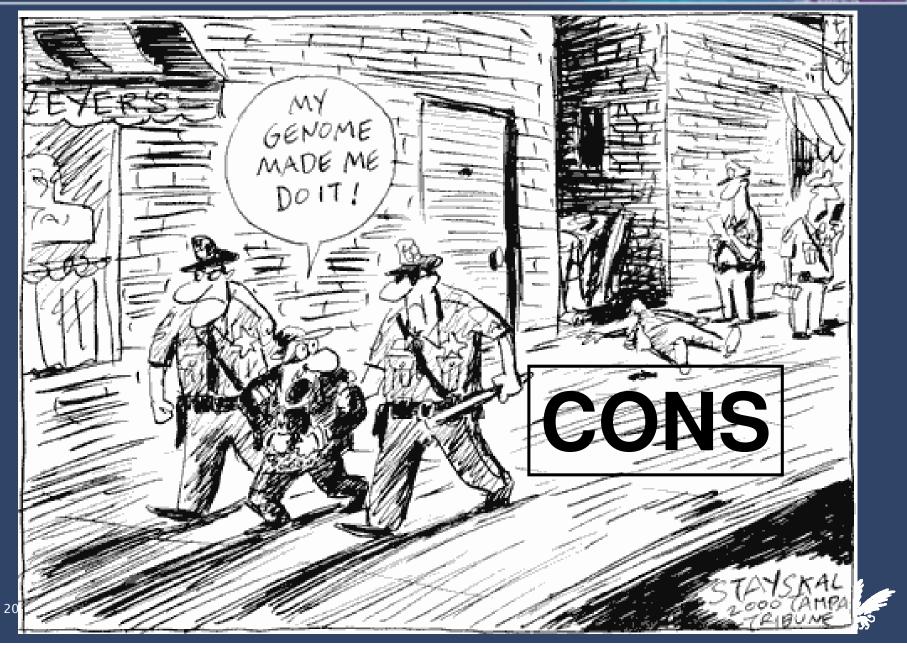
Genomics to assess emerging chemicals

PROS

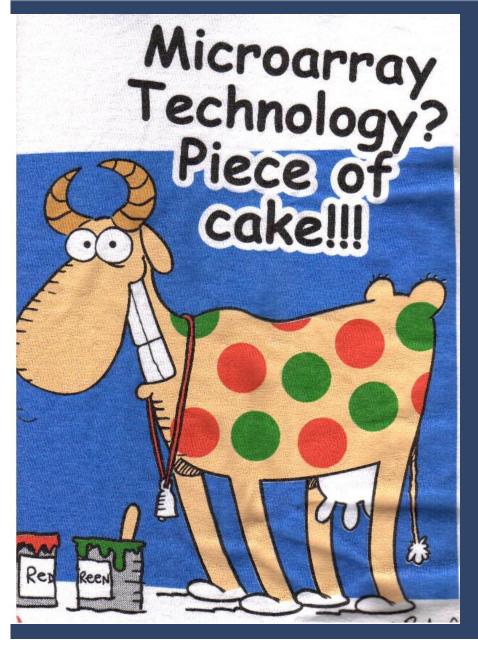




Genomics to assess emerging chemicals



Experimental design, data analysis and interpretation



- Experimental design
 - Number (biological) replicates
 - Dose response relationships
 - Temporal dynamics
- Sources of variation
 - Technical
 - Biological
 - Ecotoxicogenomics: internal and external environmental variables



Experimental design, data analysis and interpretation

Data analysis

- Huge numbers of data: multiple testing problem/false discovery
- Normalization
- Statistical analysis

Interpretation

- Gene function: many unknowns, differences in gene ontology allocations
- Comparison with existing gene expression databases
- Validation: RT-PCR sufficient?

Jan Kammenga: Genomics in ecotoxicology

At the Crossroads of Genomics and Ecology: The Promise of a Canary on a Chip Current microarray methods may lead to the misidentification of genes as "important"

rope 2007

"We are going too fast"

SETAC 2007 Porto

Can genomics be used to assess mixture effects



Aquatic Toxicology 81 (2007) 293-303



www.elsevier.com/locate/aquatox

Toxicogenomic responses in rainbow trout (*Oncorhynchus mykiss*) hepatocytes exposed to model chemicals and a synthetic mixture

E.F. Finne^{a,b,*}, G.A. Cooper^c, B.F. Koop^c, K. Hylland^{a,b}, K.E. Tollefsen^a

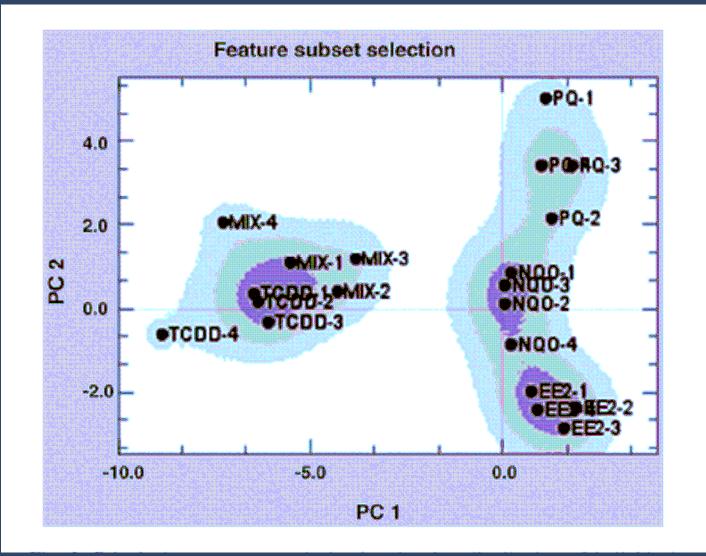
^a Norwegian Institute for Water Research, Gaustadallèen 21, N-0349 Oslo, Norway
 ^b University of Oslo, Department of Biology, P.O. Box 1066, Blindern, N-0316 Oslo, Norway
 ^c Centre for Biomedical Research, University of Victoria, BC V8P5C2, Canada

Received 11 September 2006; received in revised form 15 December 2006; accepted 18 December 2006

17-ethinylestradiol (EE2), 2,3,7,8-tetrachloro-dibenzodioxin (TCDD), paraquat (PQ) and 4-nitroquinoline-1-oxide (NQO)
Tested as individual chemicals and as mixtures



Can genomics be used to assess mixture effects?



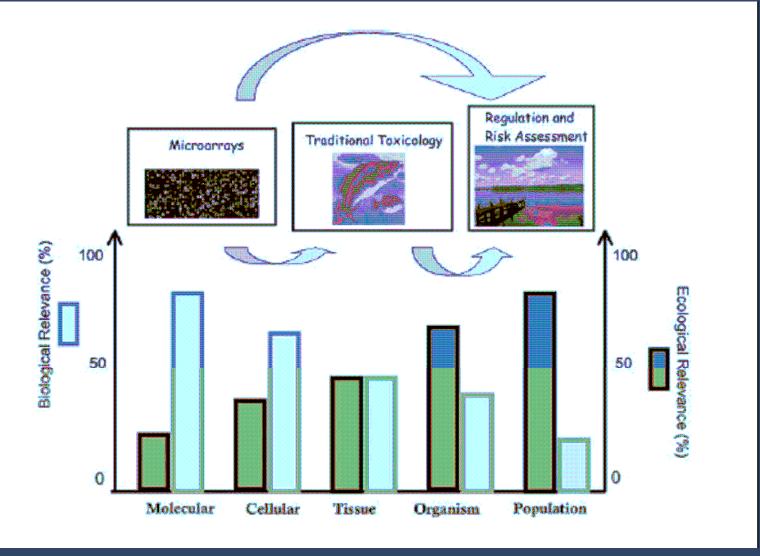
vrije Universiteit amsterdam

High costs



"No microarrays on a budget less that \$100,000" Expensive to repeat experiments \rightarrow limited experimental data available

Linking gene expression with ecological effects



Denslow et al., 2007, Mol. BioSyst., 2007, 3, 172 - 17

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Advantages

-elucidate mechanisms of action
-identify biomarkers/classifiers of toxicity
-identify signatures of gene expression
-comparative toxicogenomics
-apply to environmentally relevant species

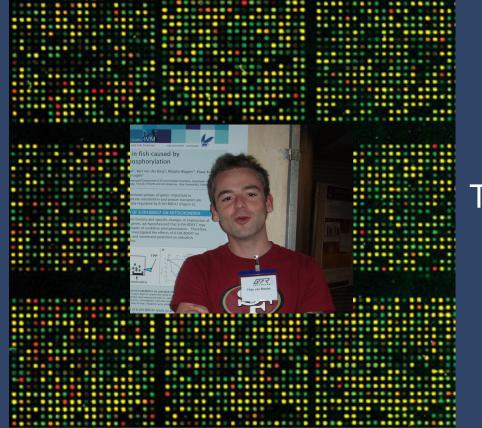
Limitations

-experimental design, analysis, interpretation, costs -identify signatures in mixtures and environmental samples?

-lack of commercial arrays for non-model species -linking effects at gene expression level to physiological and population effects

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