Når **komplekse** eksponeringer påvirker **komplekse** systemer:

Behov for **komplekse** metoder i effektovervåkning

Anders Goksøyr

Institutt for biologi

Universitetet i Bergen

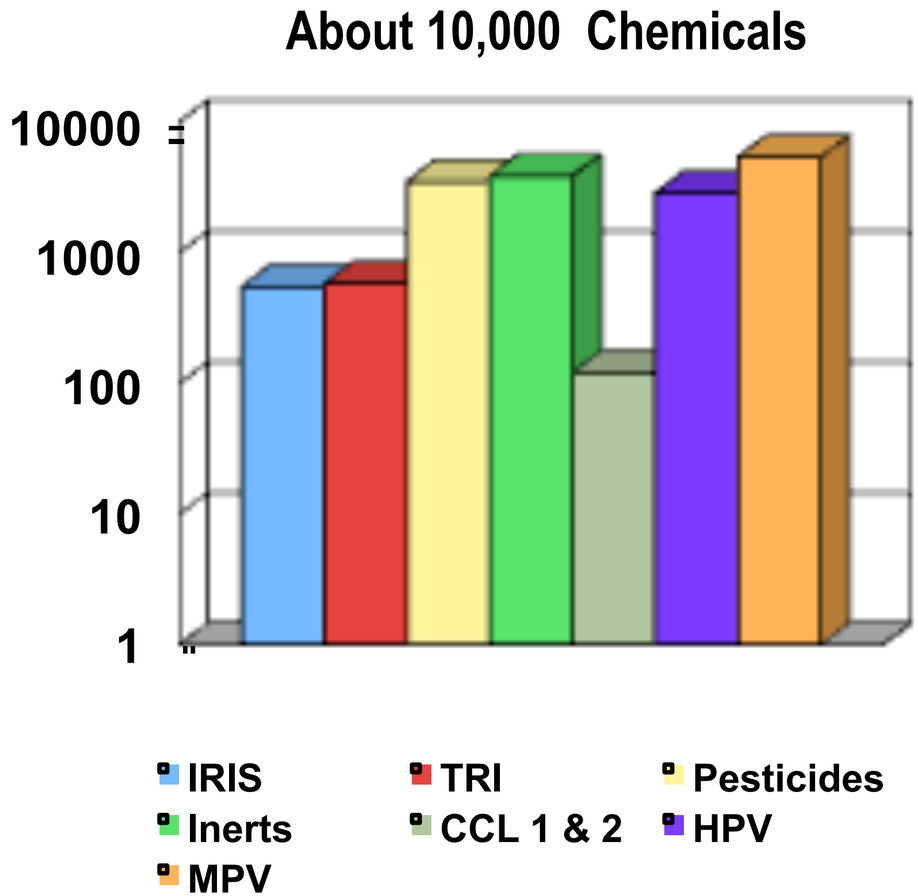
Miljøgiftkonferansen, KLIF/Oslo, 18.1.2012

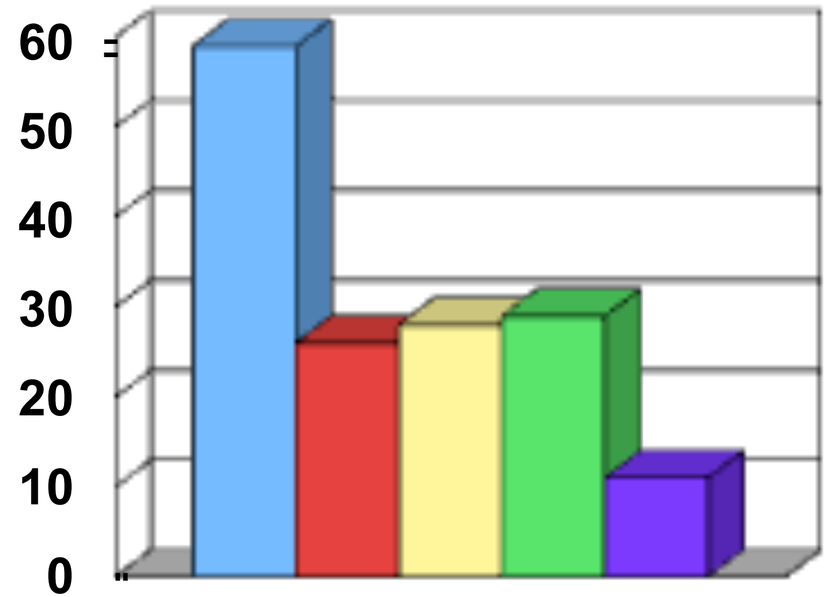
We're exposed to lots of chemicals but at very low concentrations over time. We need tools to help us understand how complex exposures perturb complex systems.

- William Suk

Spivey A.(2004) Systems biology: the big picture. Environ Health Perspect.

Too Many Chemicals, Too Little Data





Judson et al, EHP (2009)

Office of Research and Development

Kevin Teichman, US EPA,
at 2011 International Conference on Environmental Omics, Guangzhou, China

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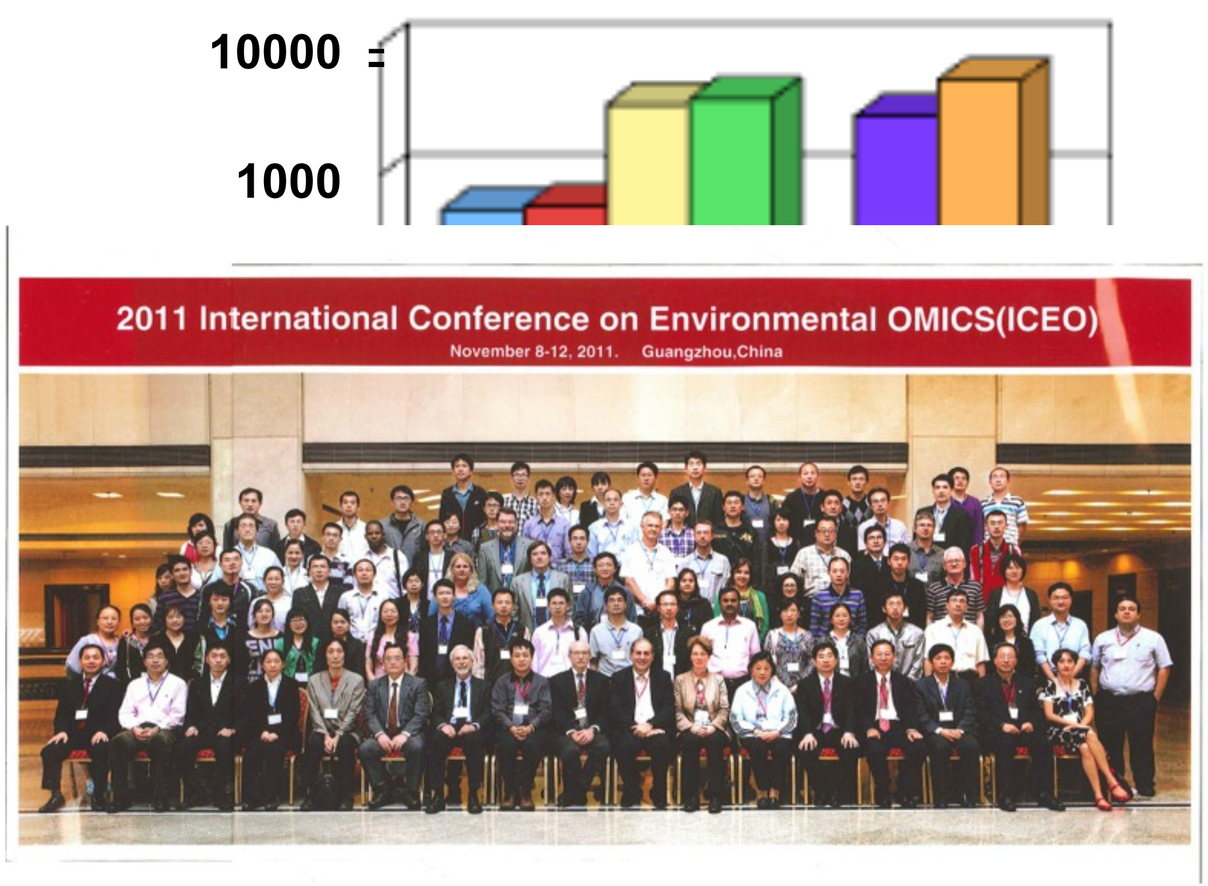

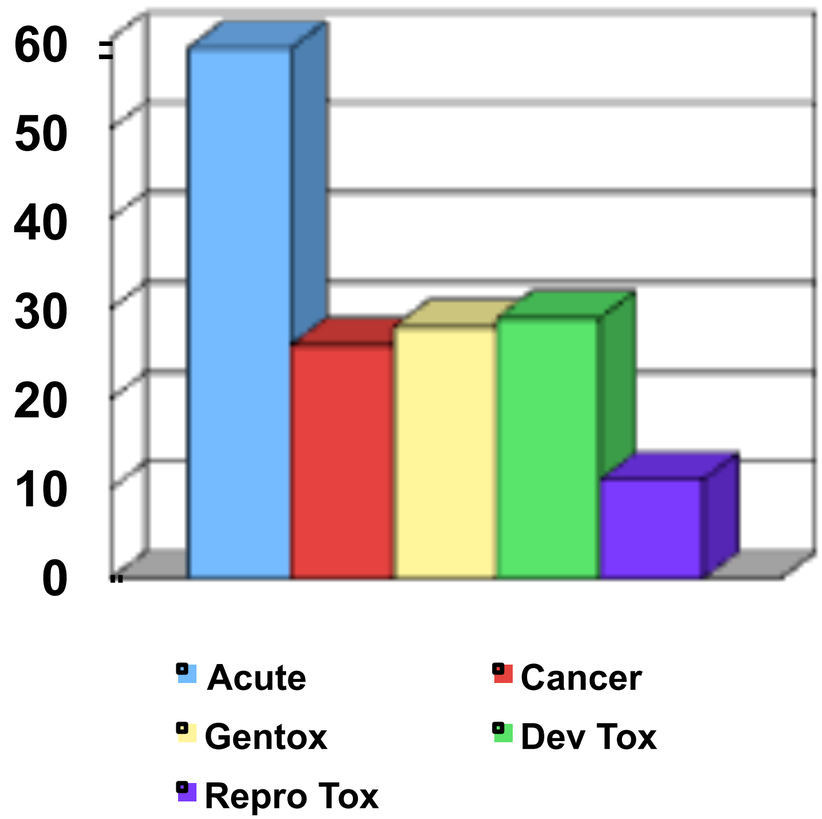

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Akutt toks. goodbye:

Et paradigmeskifte i toksikologien

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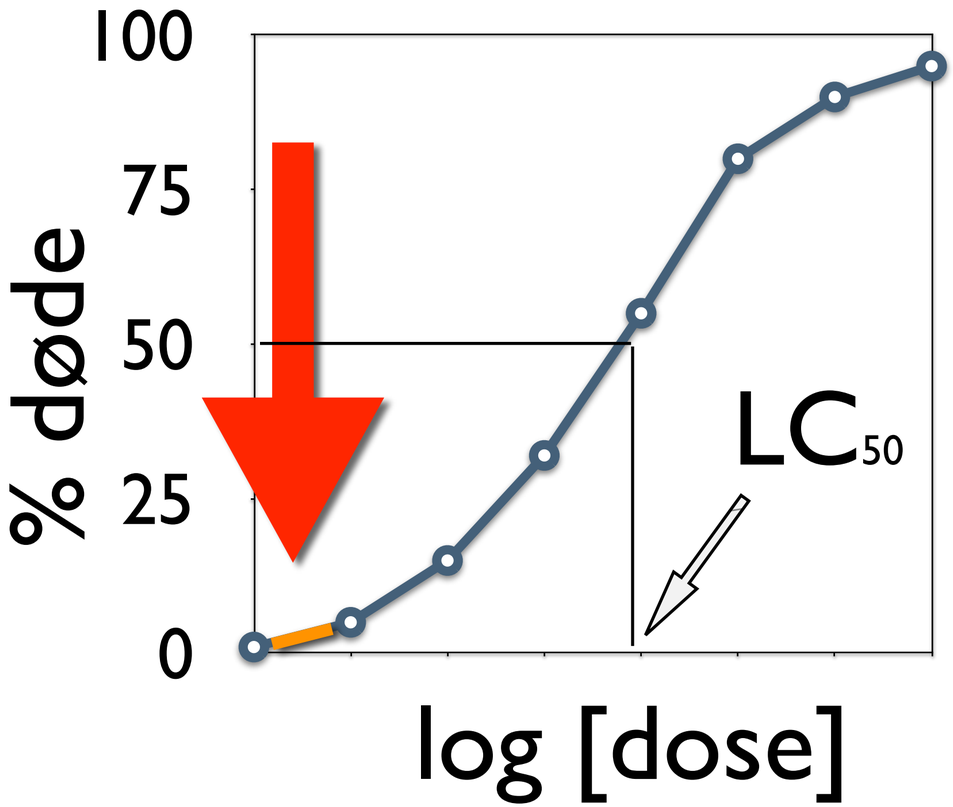
Et paradigmeskifte i toksikologien



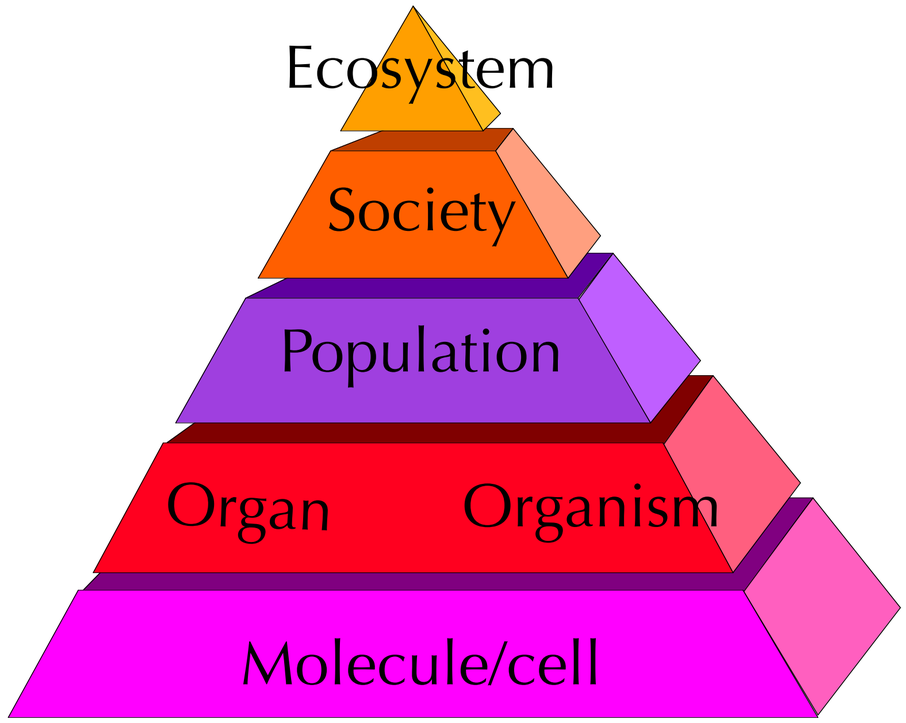
FRA:

- fokus på akutte effekter ved høye doser

TIL:

- fokus på stoffenes evne til å påvirke hormonsystem og metabolsk balanse ved lave doser

Effekter på det biologiske system



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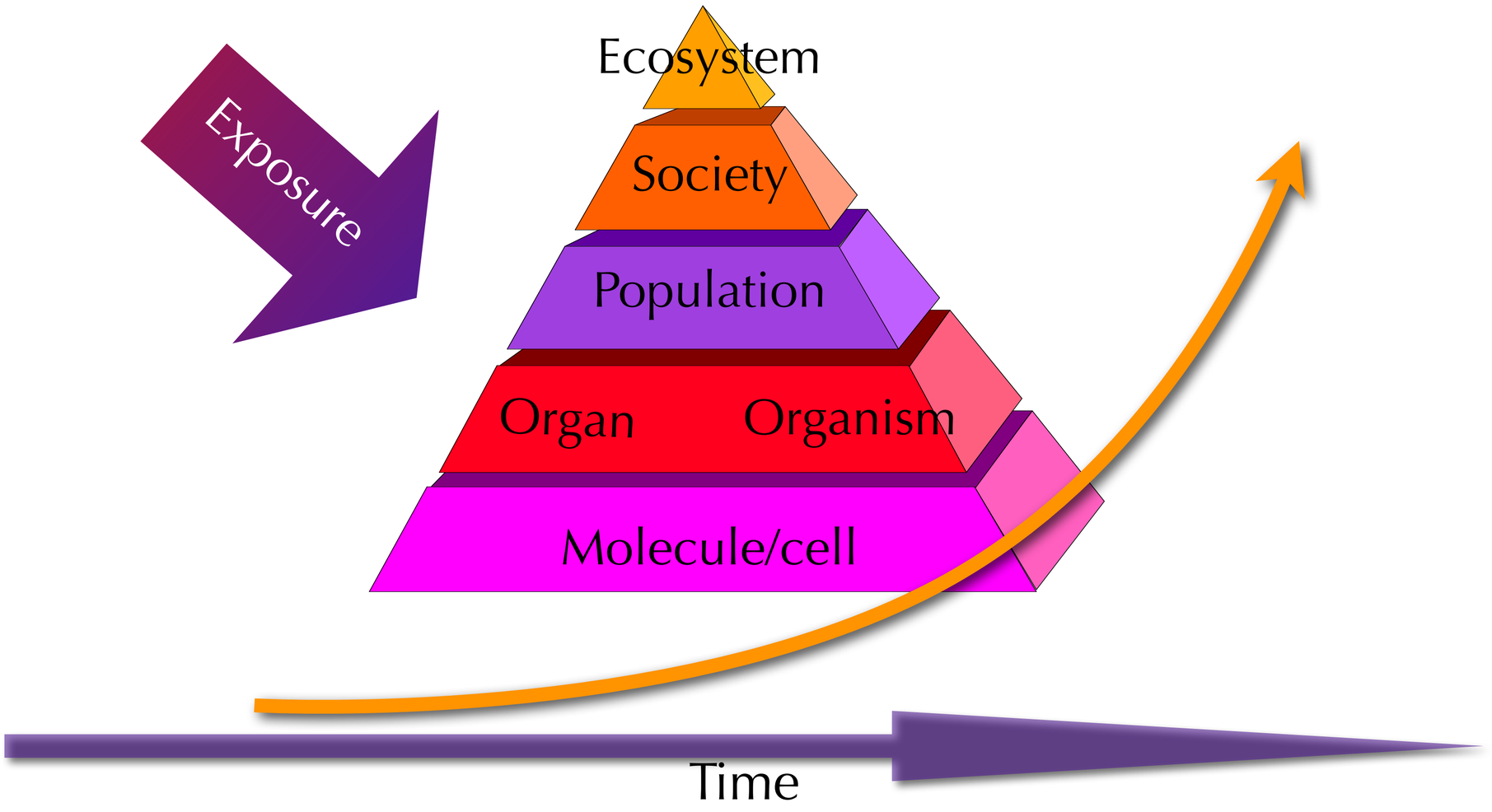

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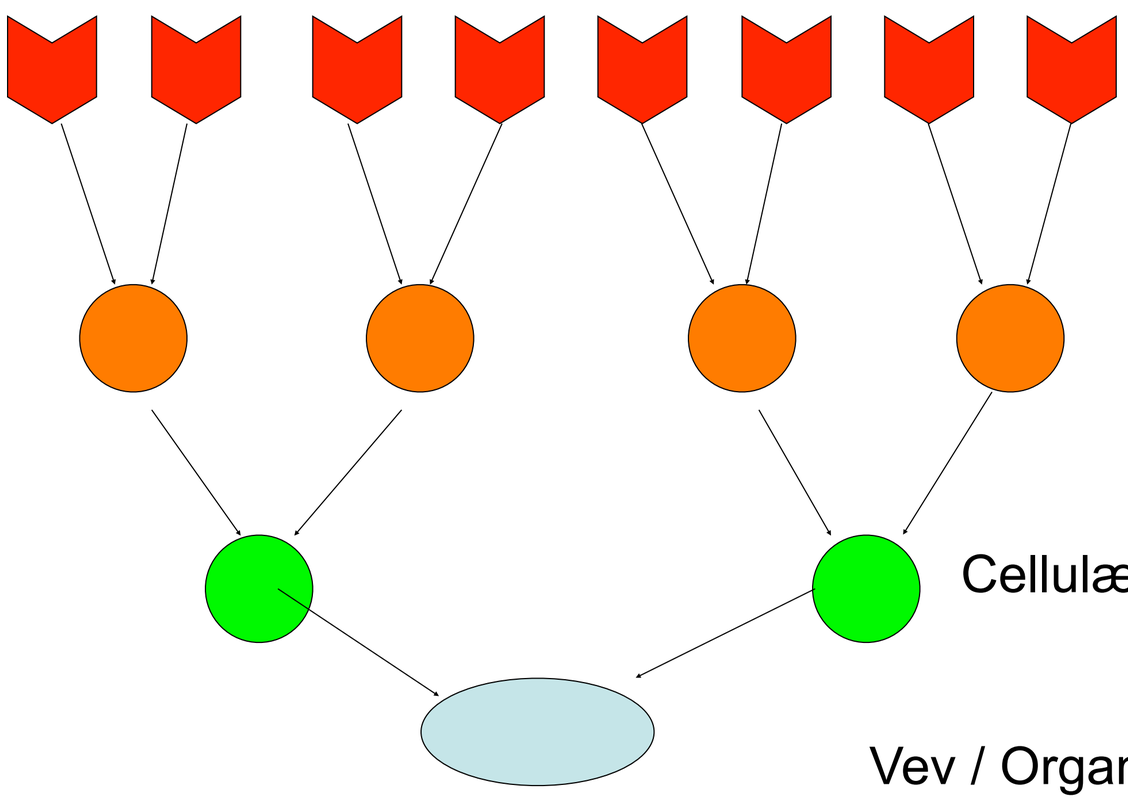


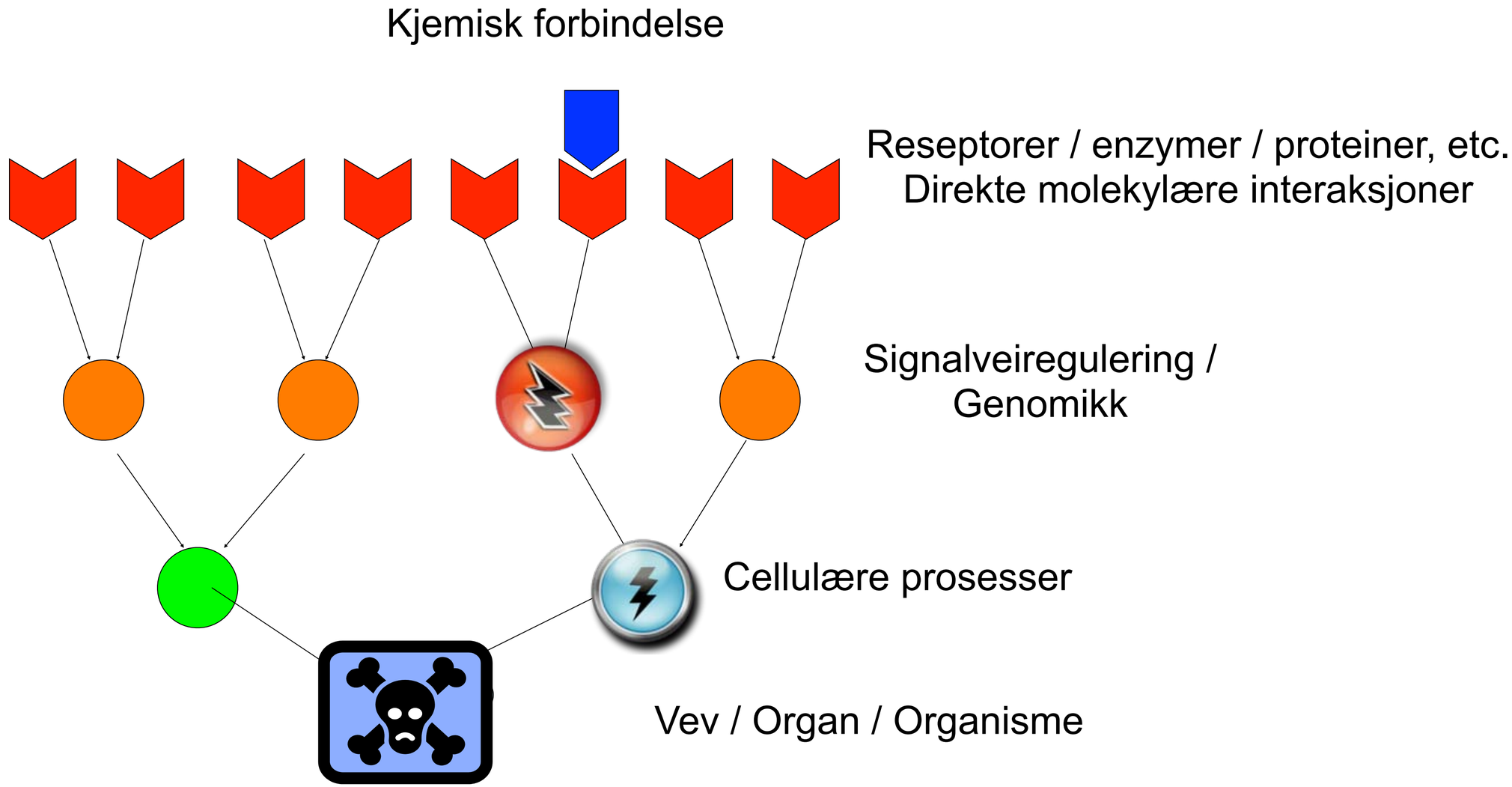
Reseptorer / enzymer / proteiner, etc.
Direkte molekylære interaksjoner

Signalveiregulering /
Genomikk

Cellulære prosesser

Vev / Organ / Organisme

Veier til giftighet



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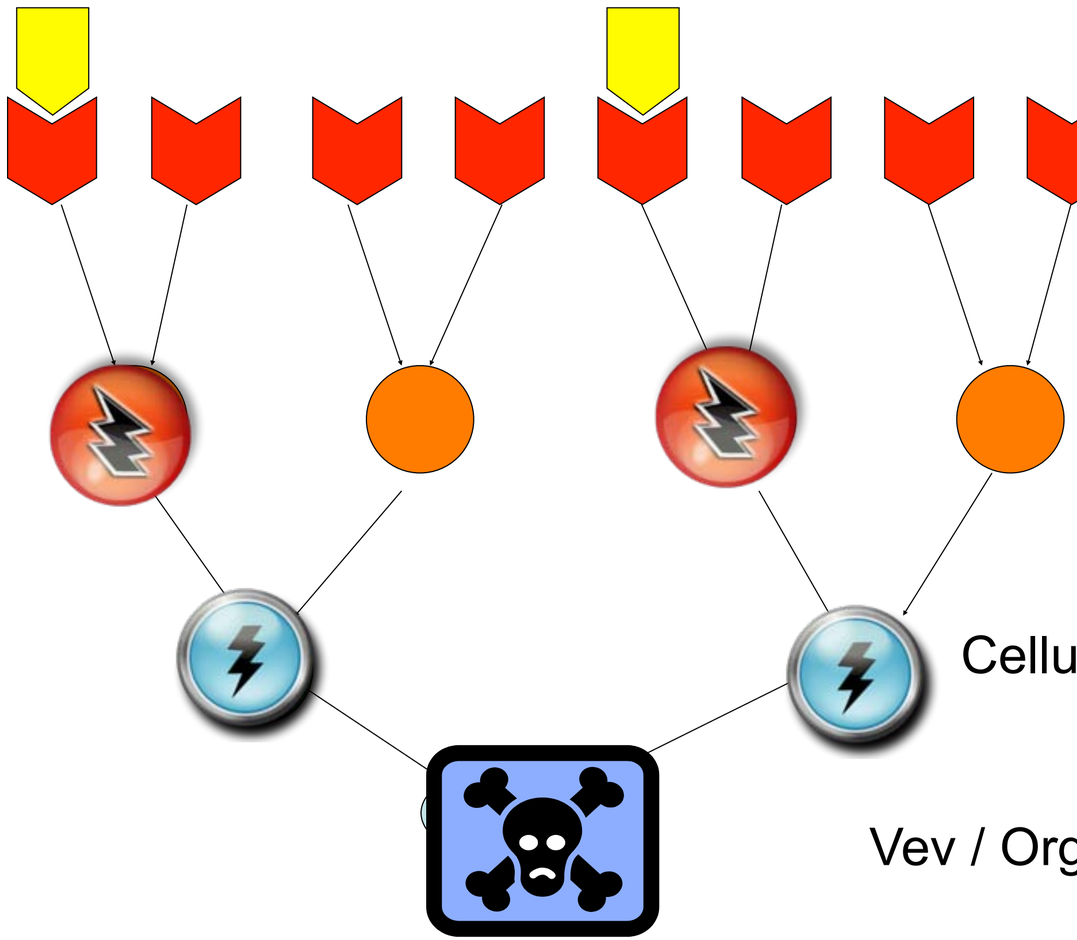

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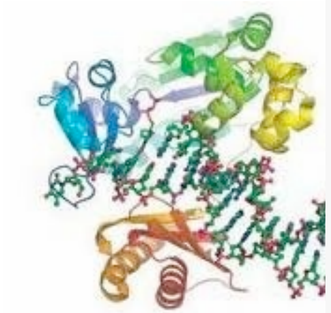
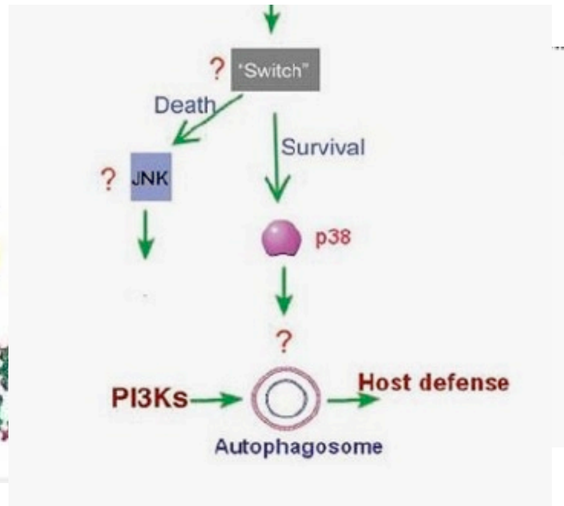
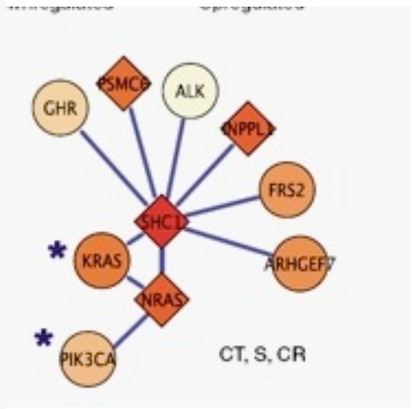
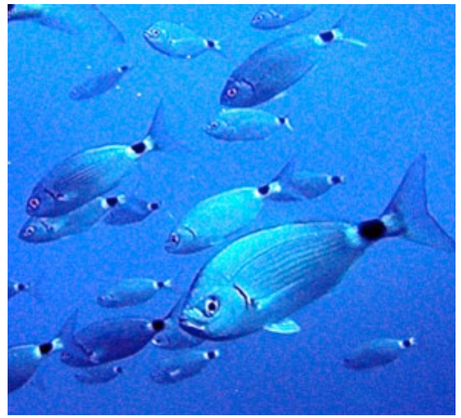
Alt henger sammen



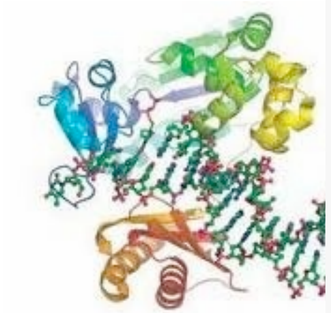


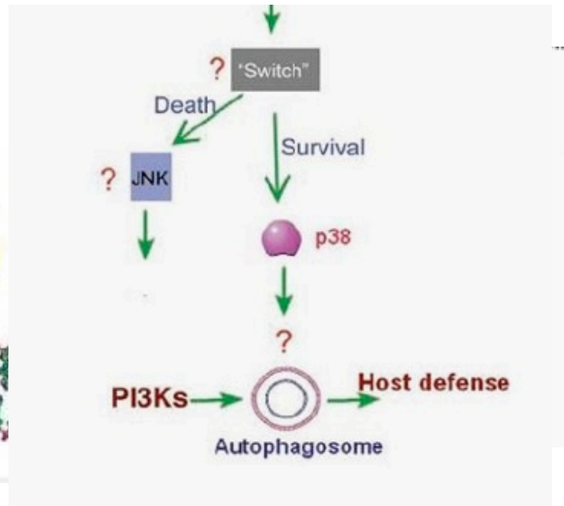


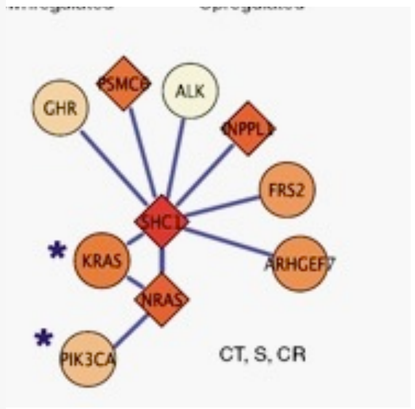


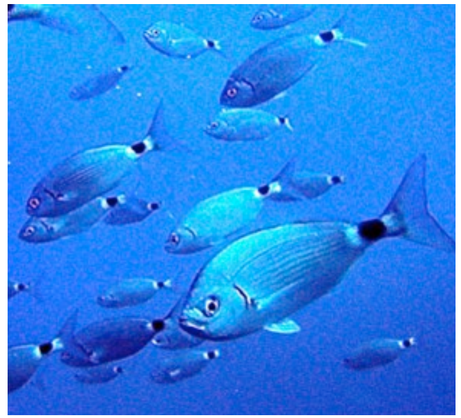
Single molecule → Cellular Pathways → Tissue Networks of interactions → Organism → Populations

Alt henger sammen







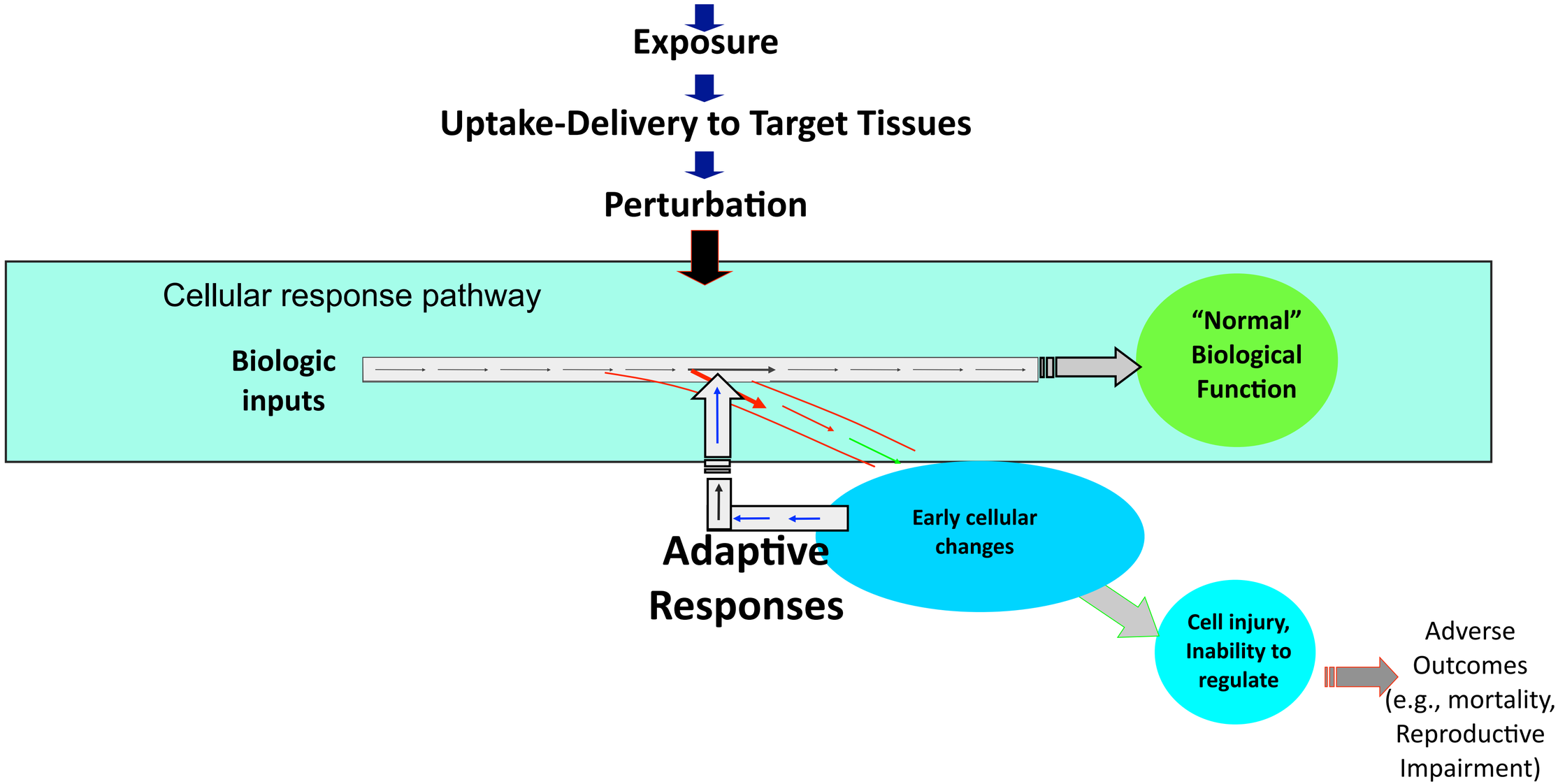


Single molecule → Cellular Pathways → Tissue Networks of interactions ⫽→ Organism → Populations

Complexity

Mechanistic

Tilpasning og kompensering i en toksisk respons



Adapted from Toxicity Testing in the 21st Century, NRC

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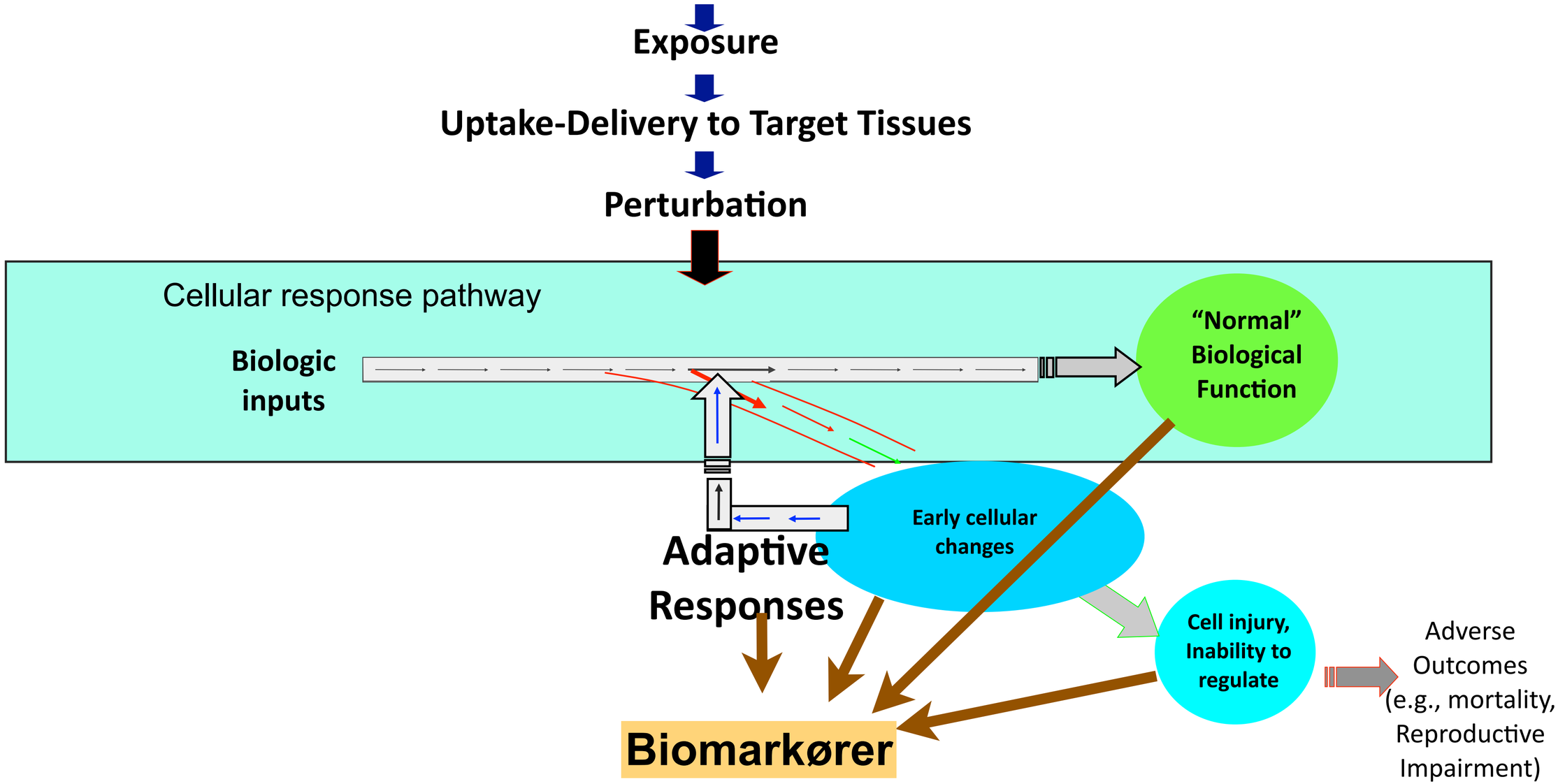

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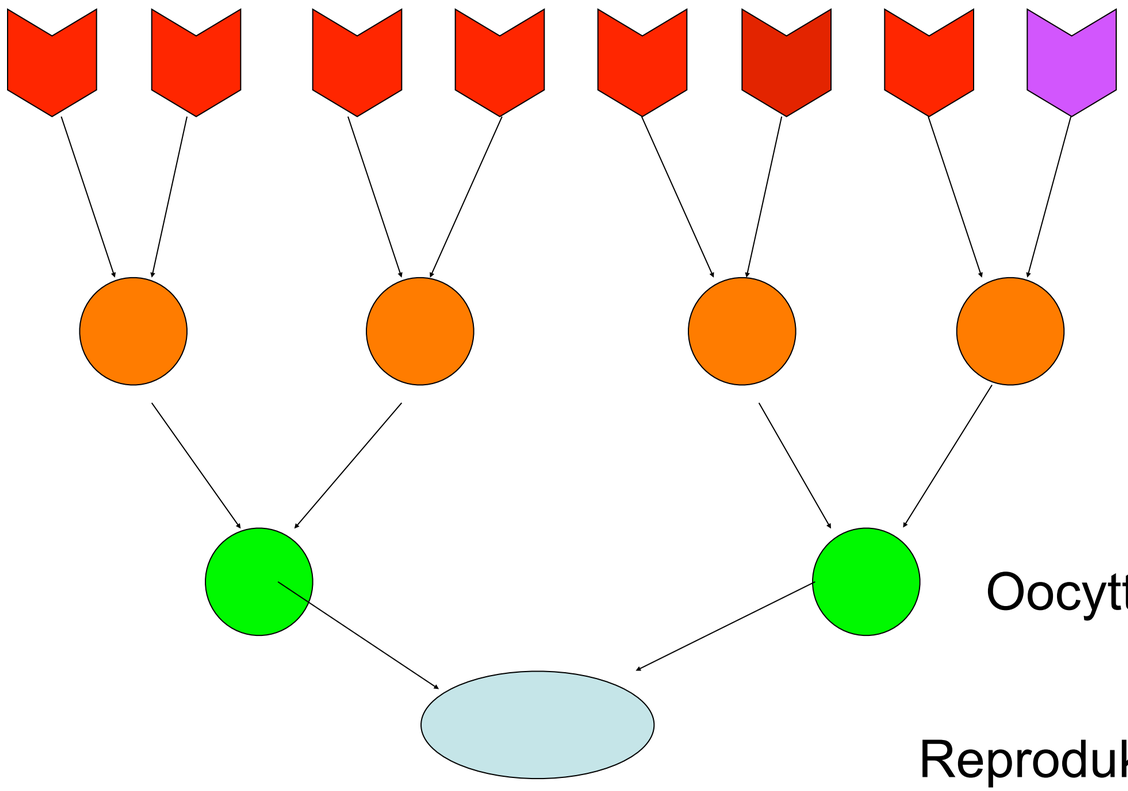
Vitellogenin (VTG) = biomarkør for hormonforstyrrende stoffer



Østrogen-reseptor

Vitellogenin

Oocytt-utvikling/ovotestis

Reproduksjonsevne/
Populasjonseffekter

Figurer fra Arukwe & Goksøyr Comp Hepatol (2003)

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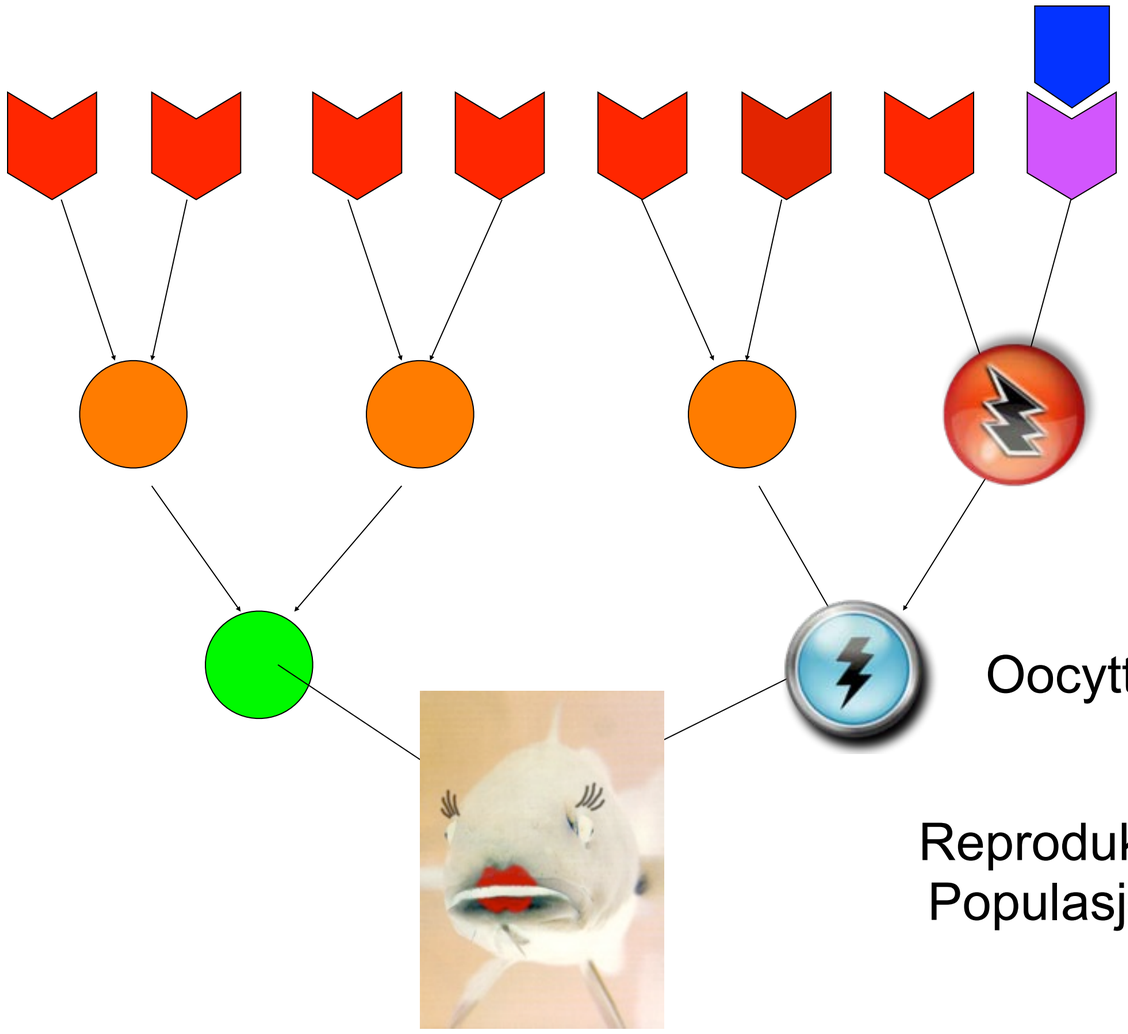


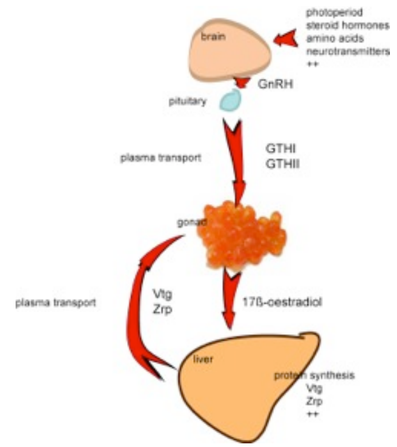
Hormonhermer

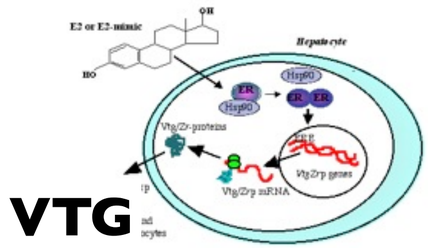
Østrogen-reseptor

Vitellogenin

Oocytt-utvikling/ovotestis

Reproduksjonsevne/
Populasjonseffekter





Histological section of a grossly intersex gonad of the gudgeon, Gobio gobio, containing testicular tissues and both primary and secondary (vitellogenic) oocytes. Picture is a kind donation from Ronny van Aerle and Charles Tyler.

Arukwe and Goksøyr Comparative Hepatology 2003 2:4 doi:10.1186/1476-5926-2-4

Figurer fra Arukwe & Goksøyr Comp Hepatol (2003)

PNAS

Collapse of a fish population after exposure to a synthetic estrogen

Karen A. Kidd*†, Paul J. Blanchfield*, Kenneth H. Mills*, Vince P. Palace*, Robert E. Evans*, James M. Lazorchak‡, and Robert W. Flick‡

*Fisheries and Oceans Canada, Freshwater Institute, 501 University Crescent, Winnipeg, Manitoba, Canada R3T 2N6; and ‡Molecular Indicators Research Branch, United States Environmental Protection Agency, 26 West Martin Luther King Drive, Cincinnati, OH 45268

Edited by Deborah Swackhamer, University of Minnesota, Minneapolis, MN, and accepted by the Editorial Board March 29, 2007 (received for review October 27, 2006)

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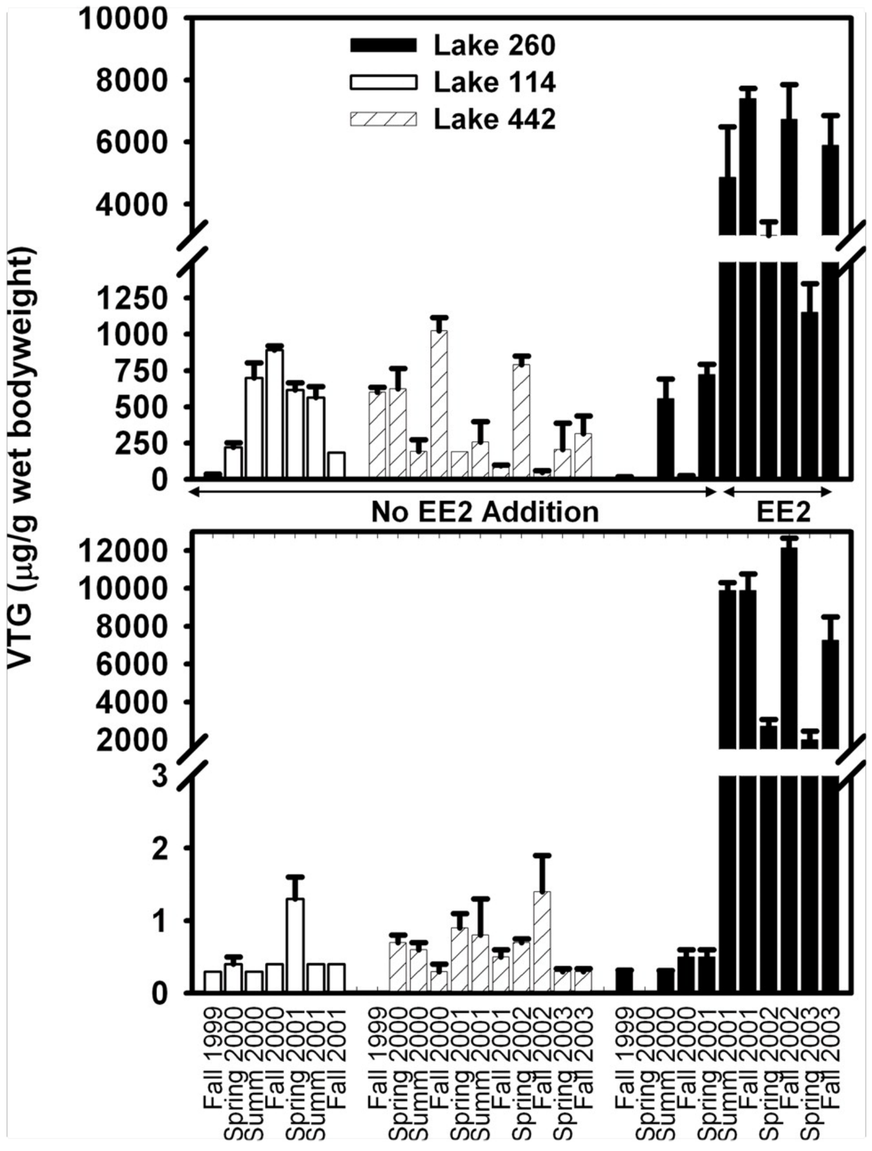

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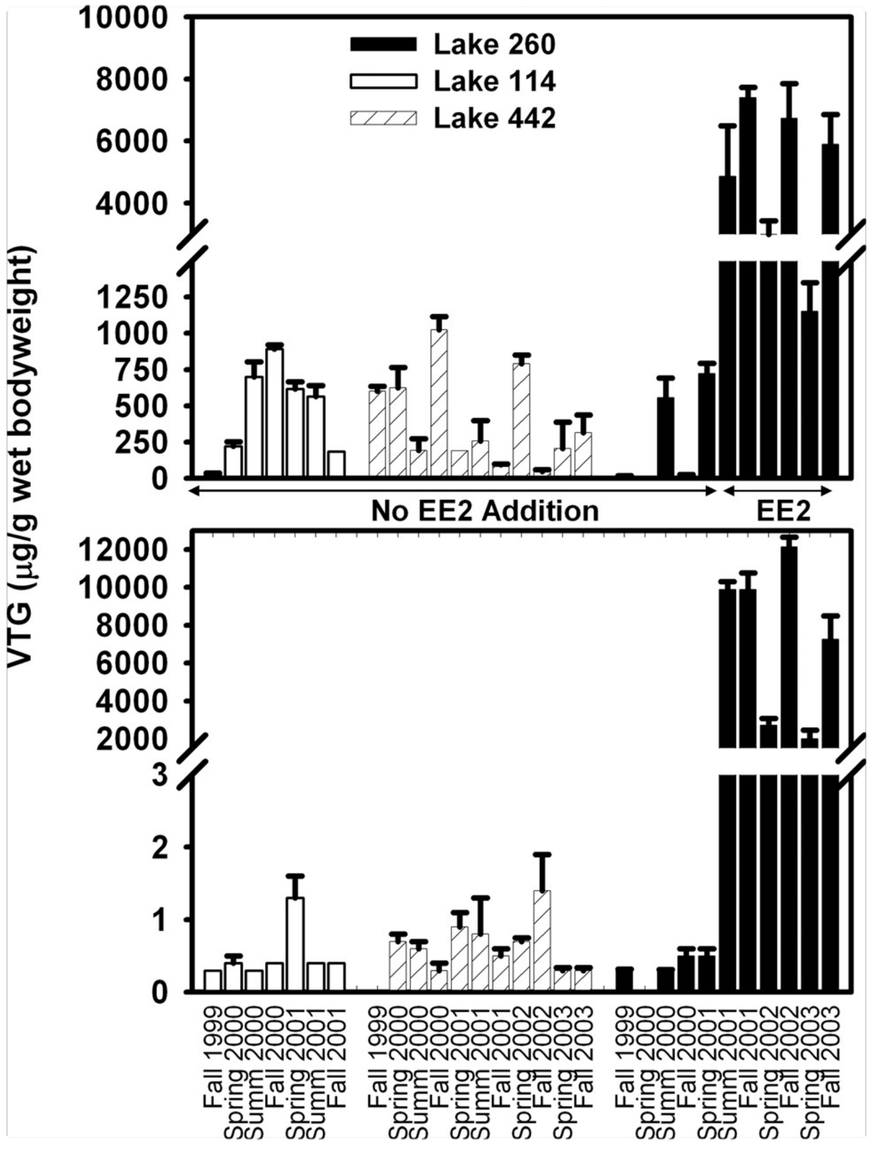
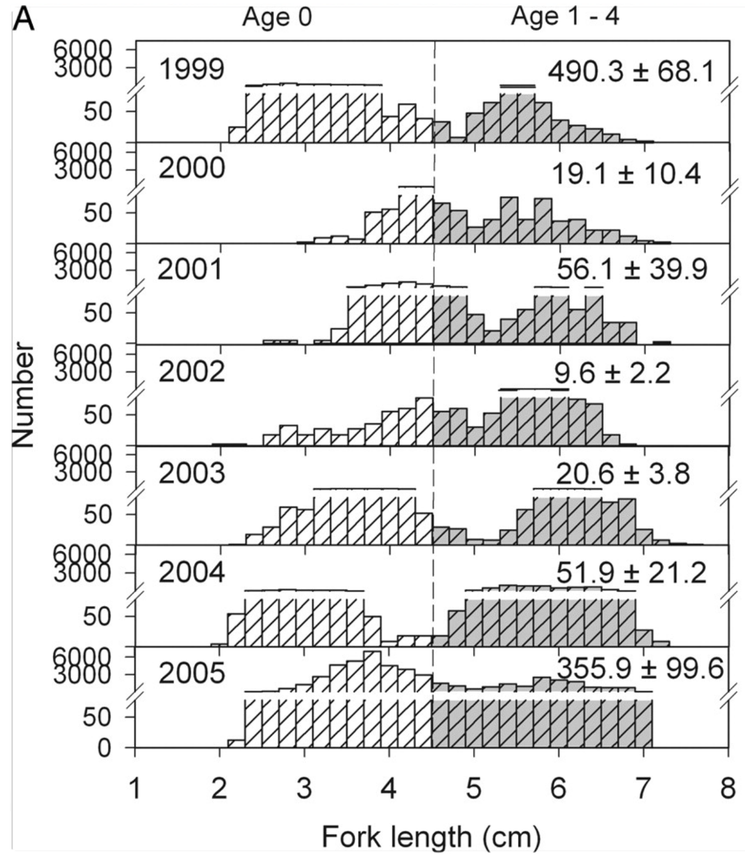
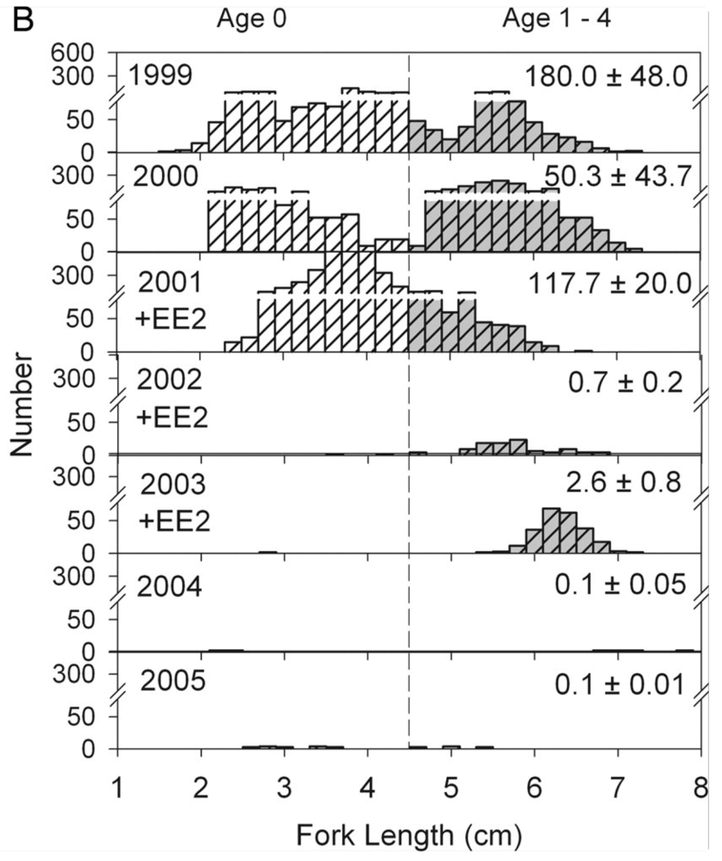




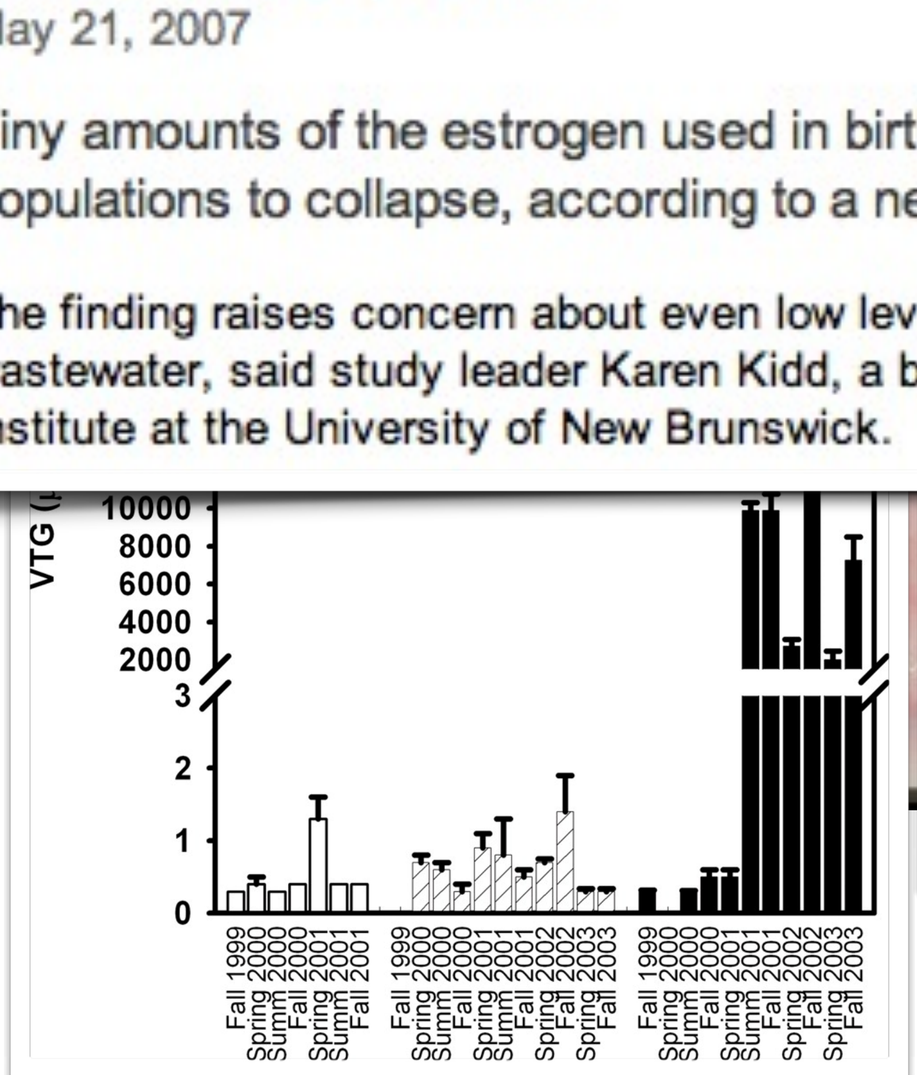


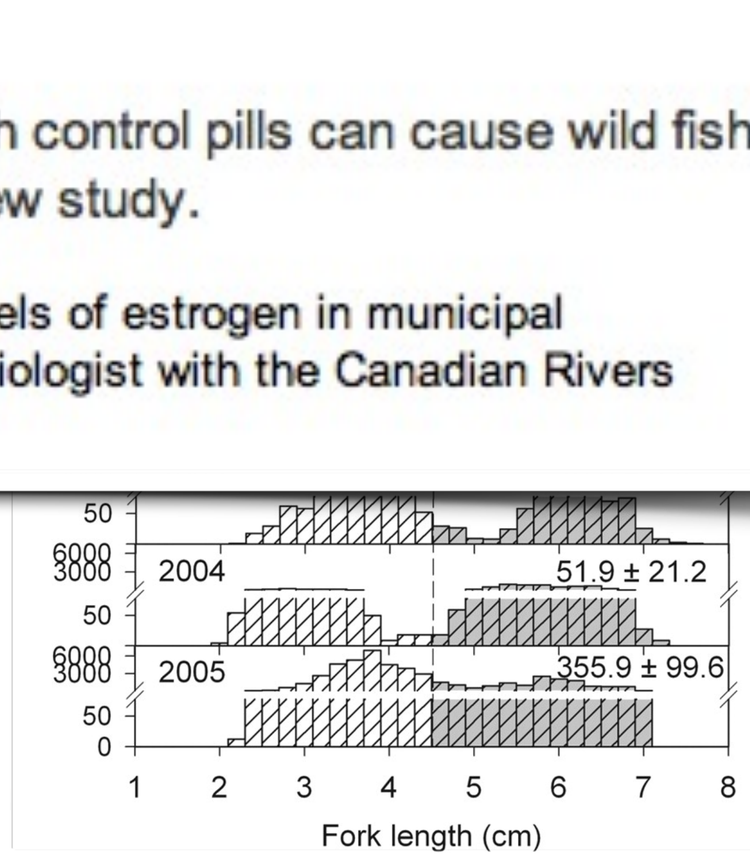
Sex-Changing Chemicals Can Wipe Out Fish, Study Shows

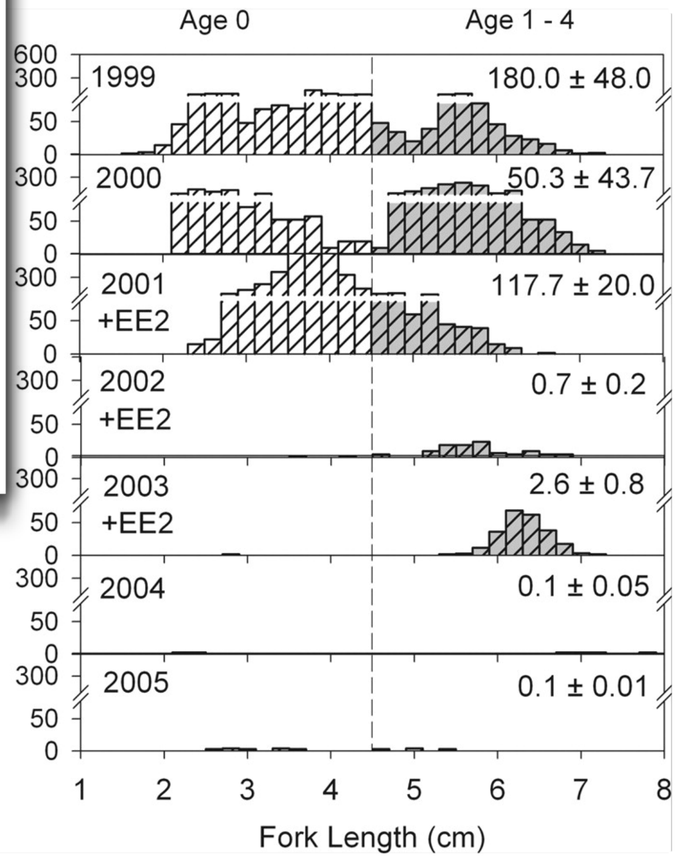
John Roach
for National Geographic News
May 21, 2007

Tiny amounts of the estrogen used in birth control pills can cause wild fish populations to collapse, according to a new study.

The finding raises concern about even low levels of estrogen in municipal wastewater, said study leader Karen Kidd, a biologist with the Canadian Rivers Institute at the University of New Brunswick.







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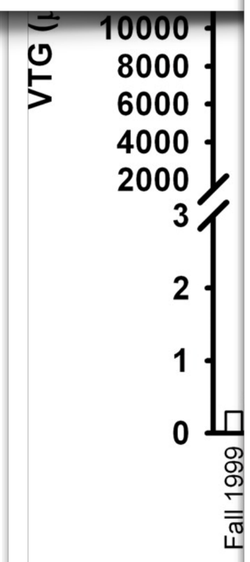

Environment

Estrogen Endangers Fish Populations

May 31, 2008 03:45 PM
by findingDulcinea Staff

Cite!

Sewage pollutes many waterways with the female hormone. Even tiny amounts could hurt wildlife and change the sex of some fish.

30-Second Summary

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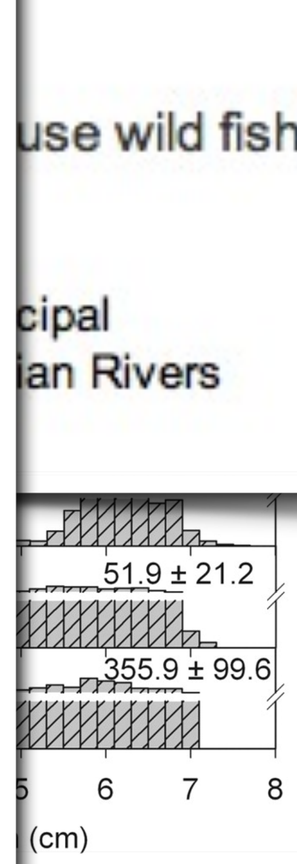
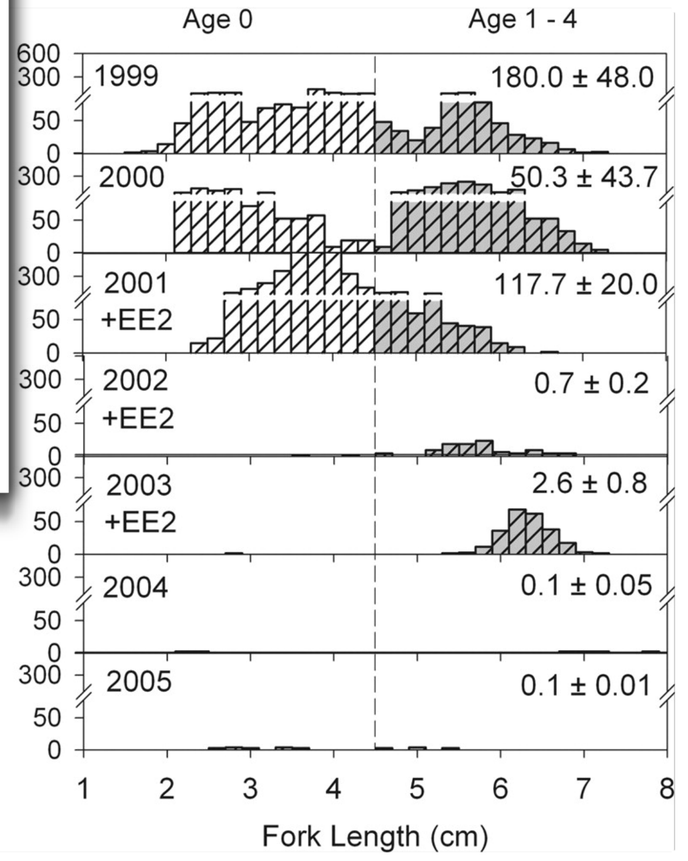
Scientist Karen Kidd added synthetic estrogen to an artificial lake in Ontario, Canada, for three summers to track its impact on wildlife.

The pollution killed many fish and disrupted reproduction in others. The sperm count of male minnows fell, with some even beginning to produce eggs in their testes.

"We've known for some time that estrogen can adversely affect the reproductive health of fish, but ours was the first study to show the long-term impact," Kidd said. "What we demonstrated is that estrogen can wipe out entire populations of small fish."





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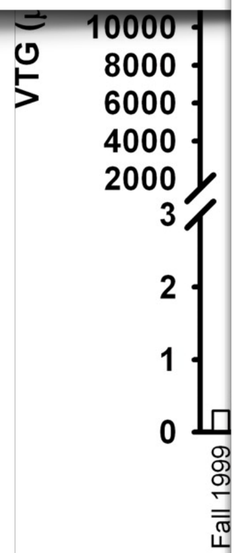

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Science NOW — UP TO THE MINUTE NEWS FROM SCIENCE

Feminized to Extinction

by Erik Stokstad on 21 May 2007, 12:00 AM | Permanent Link | 0 Comments

Email Print | +1 0 More PREVIOUS ARTICLE NEXT ARTICLE

All across the world, people are polluting waterways with estrogen. Excreted in urine, the hormone passes through most wastewater plants and ends up in streams and lakes, where some studies suggest it is feminizing male fish. Now a large experiment has shown that even a very low level of estrogen in a lake can cause enough reproductive harm to wipe out an entire population of minnows in 2 years.

Extra estrogen isn't good for male fish. Laboratory studies have shown that chronic exposure to low doses causes males to produce eggs in their testes and takes away their secondary sex characteristics, such as darker coloration and tubercules on their noses. The big question was what those levels mean for populations in the wild. To find out, researchers led by Karen Kidd of the University of New Brunswick, Canada, performed an experiment in a lake in western Ontario. Each summer for 3 years, they spiked the lake with a few parts per trillion of 17α-ethynylestradiol--the active ingredient in birth-control pills--in concentrations like those found in streams and lakes elsewhere. The experiment took place in a remote area set aside for research.

ENLARGE IMAGE

Empty nets.
Estrogen feminized male fathead minnows (*above*) and caused a population crash.

Credit: Karen Kidd (net) and Cheryl Podemski (minnow)

Within weeks of the first doses, male minnows started making vitellogenin, a protein that helps eggs mature in females. They wound up with levels 8000 to 10,000 times normal. (Females increased production to 8 to 80 times their usual levels, and the estrogen somehow slowed egg development.) Sexual development was delayed in the males, and fewer and fewer fish were found; apparently, the fish had stopped reproducing. After the second year, the researchers couldn't find any fathead minnow nests. "We didn't expect to see such a dramatic and quick response," Kidd says. It took more than 2 years after researchers stopped adding estrogen for the population to begin to recover.

Sex-Changing Chemicals Fish, Study Shows

John Roach
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May 21, 2007

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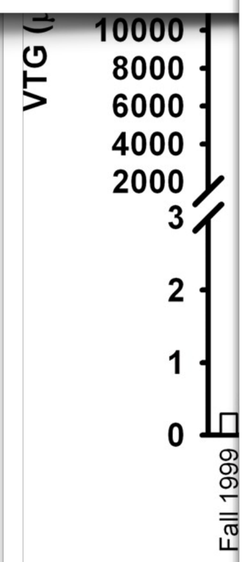

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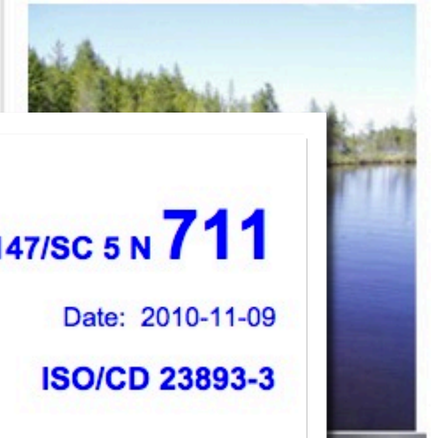

ISO/TC 147/SC 5 N 711

Date: 2010-11-09

ISO/CD 23893-3

ISO/TC 147/SC 5/WG 3 **N 184**

Secretariat: DIN

Water quality — Biochemical and physiological measurements on fish — Part 3: Determination of vitellogenin

Qualité de l'eau — Mesurages biochimiques et physiologiques sur poisson — Partie 3: Dosage de la vitellogénine

2011

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PLoS one

Biomarkers in Natural Fish Populations Indicate Adverse Biological Effects of Offshore Oil Production

Lennart Balk[1]*, Ketil Hylland[2,3], Tomas Hansson[1]*, Marc H. G. Berntssen[4], Jonny Beyer[5,6], Grete Jonsson[7], Alf Melbye[8], Merete Grung[3], Bente E. Torstensen[4], Jan Fredrik Børseth[5], Halldora Skarphedinsdottir[1], Jarle Klungsøyr[9]

1 Department of Applied Environmental Science (ITM), Stockholm University, Stockholm, Sweden, **2** Department of Biology, University of Oslo, Oslo, Norway, **3** Norwegian Institute for Water Research (NIVA), Oslo, Norway, **4** National Institute of Nutrition and Seafood Research (NIFES), Bergen, Norway, **5** International Research Institute of Stavanger (IRIS), Stavanger, Norway, **6** Department of Mathematics and Natural Science, University of Stavanger, Stavanger, Norway, **7** Department of Medical Biochemistry, Stavanger University Hospital, Stavanger, Norway, **8** Marine Environmental Technology, SINTEF Materials and Chemistry, Trondheim, Norway, **9** Institute of Marine Research (IMR), Bergen, Norway

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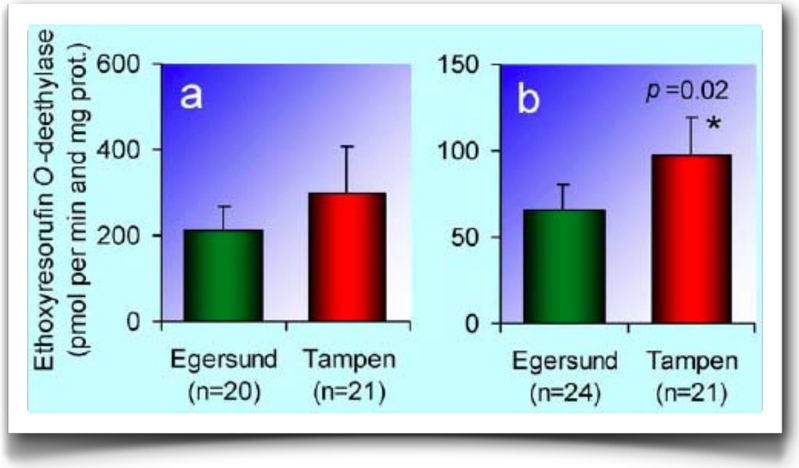
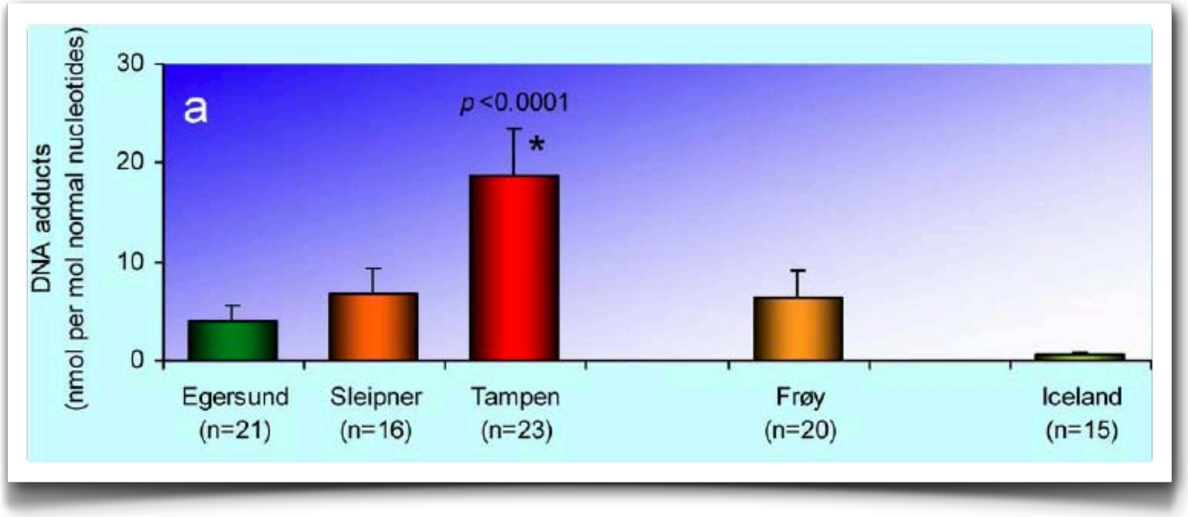


DNA-skade



Biomarkører kan identifiseres vha proteomikk
- reflekterer effekter av produsert vann med høy følsomhet

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/aquatox

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Photo: J. Skadal and I. Rønnestad

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Bohne-Kjersem et al., Aq Tox (2010); Meier et al., MER (2010)

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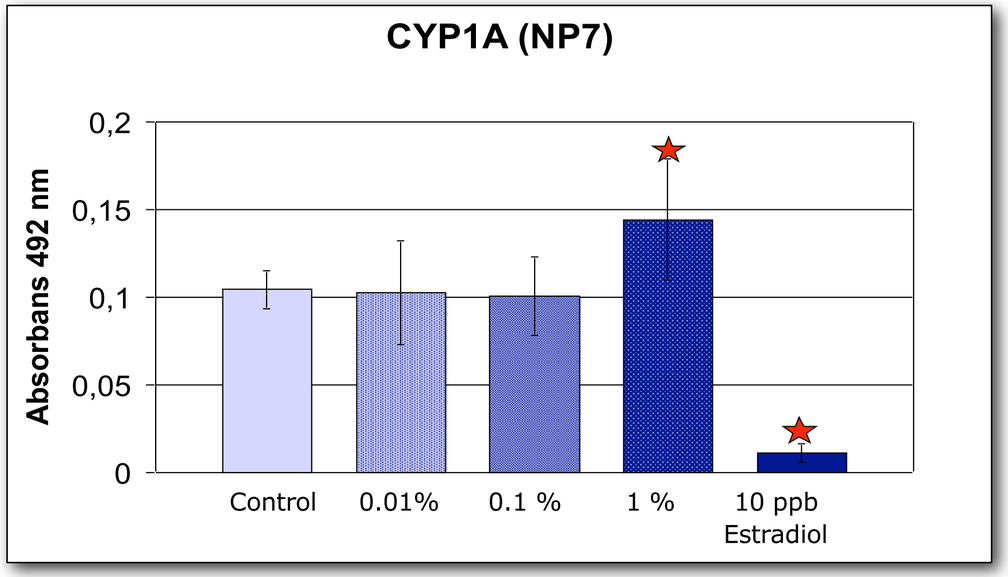

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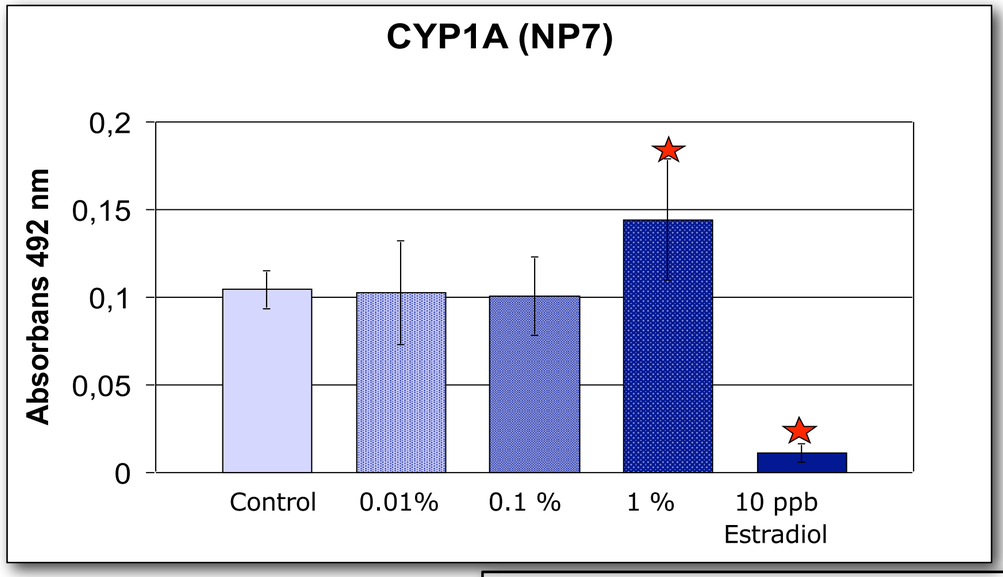

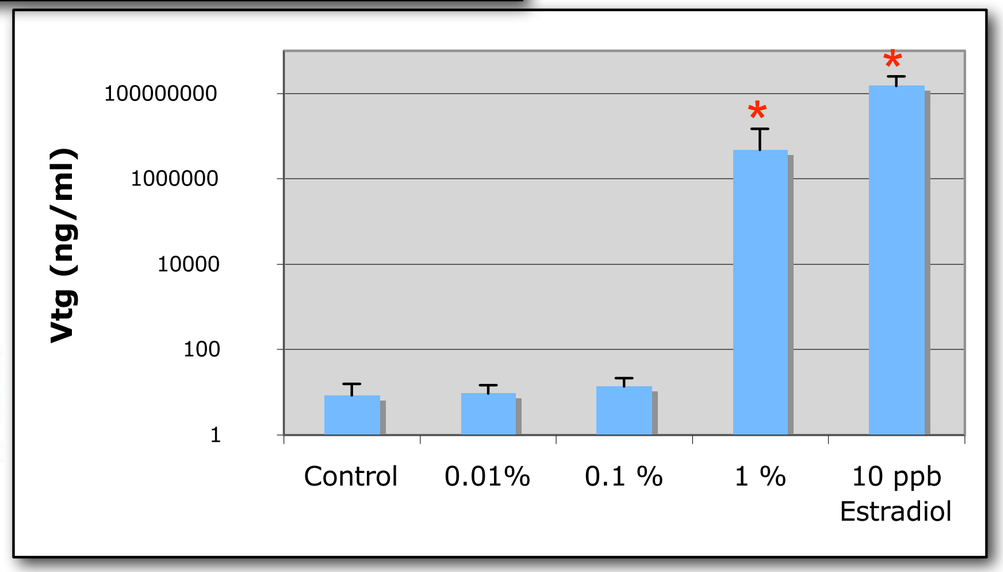

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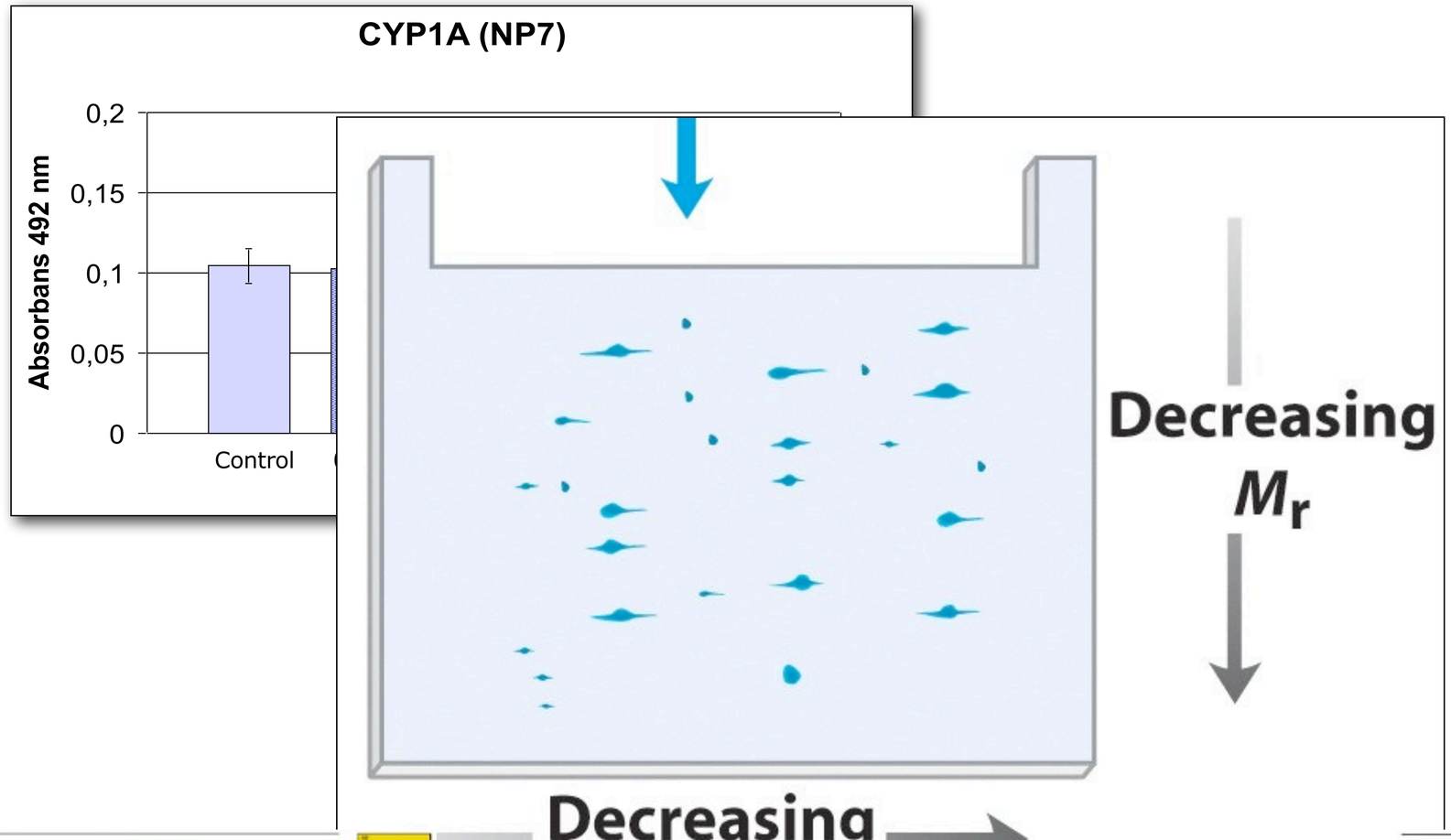

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Control	0.01%	0.1 %	1 %	10 ppb Estradiol

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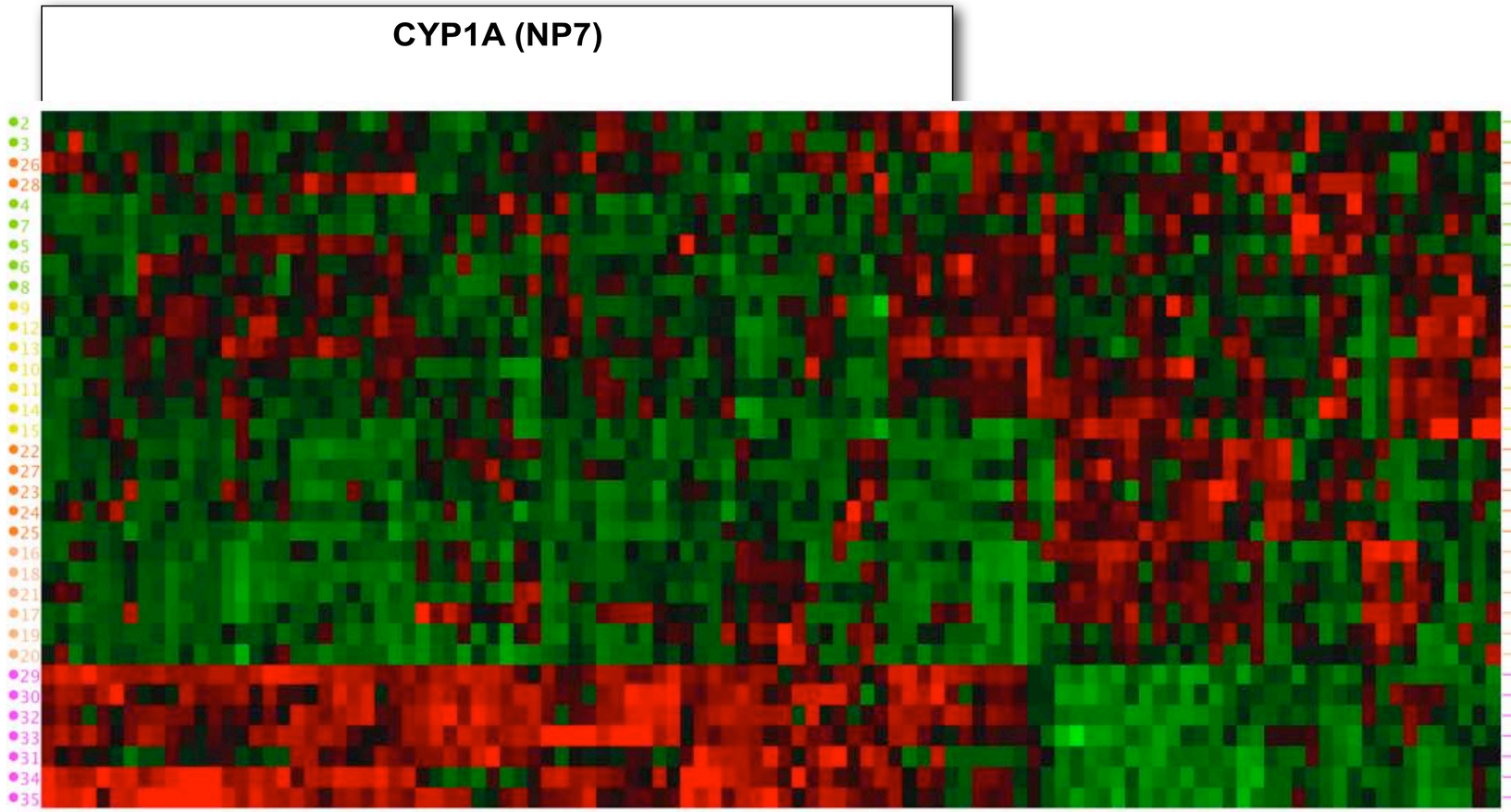

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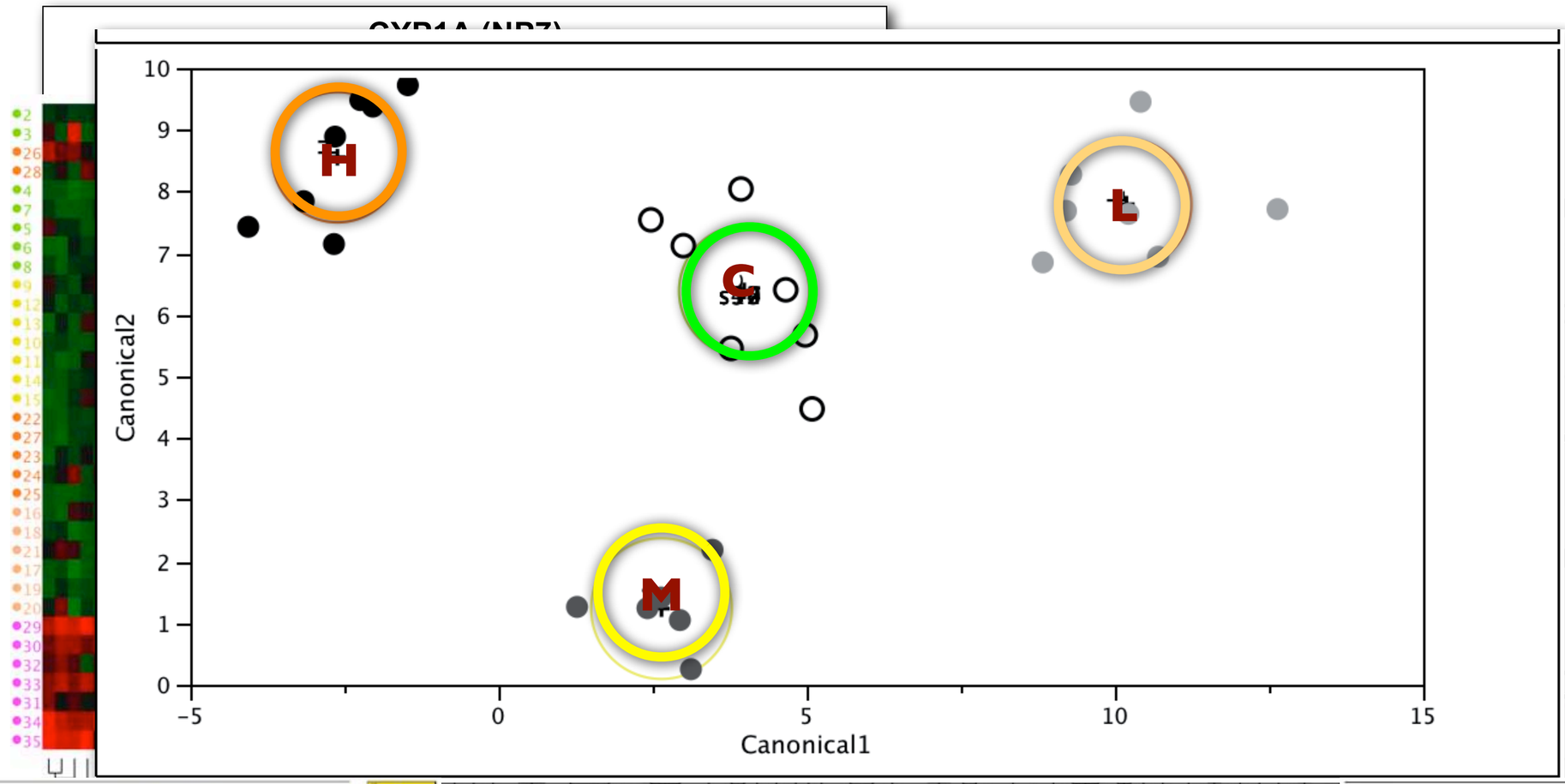

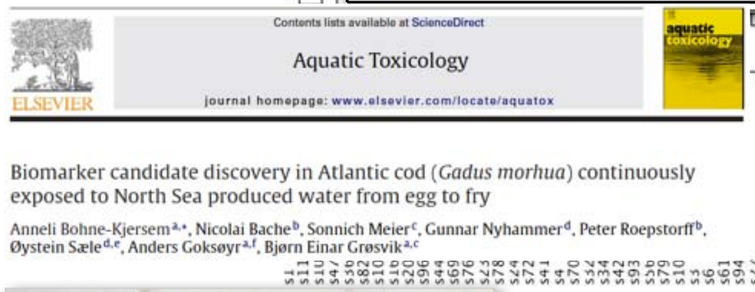

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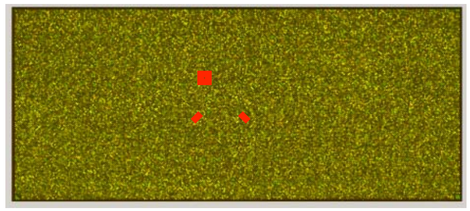
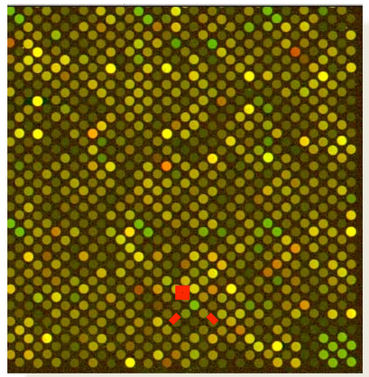
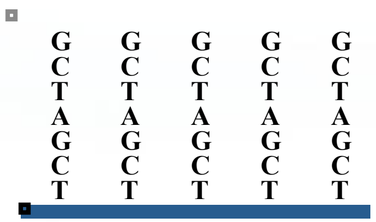
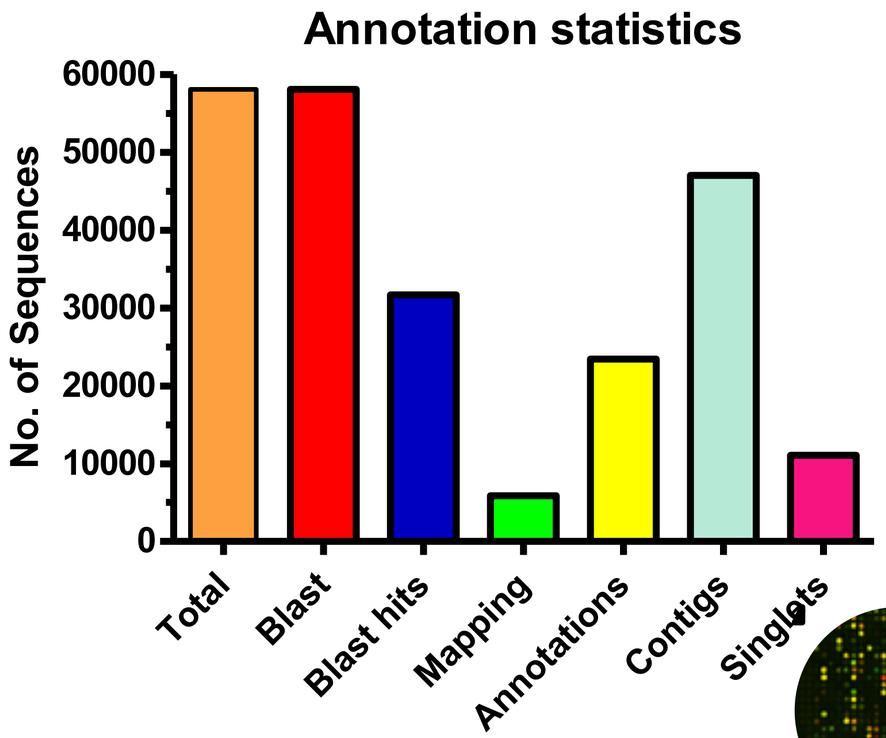
Transcriptomics

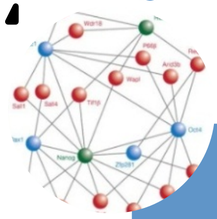




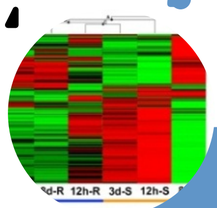




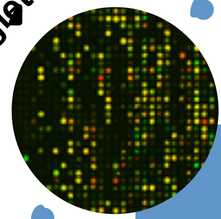
Results interpretation



Bioinformatics



Biostatistics



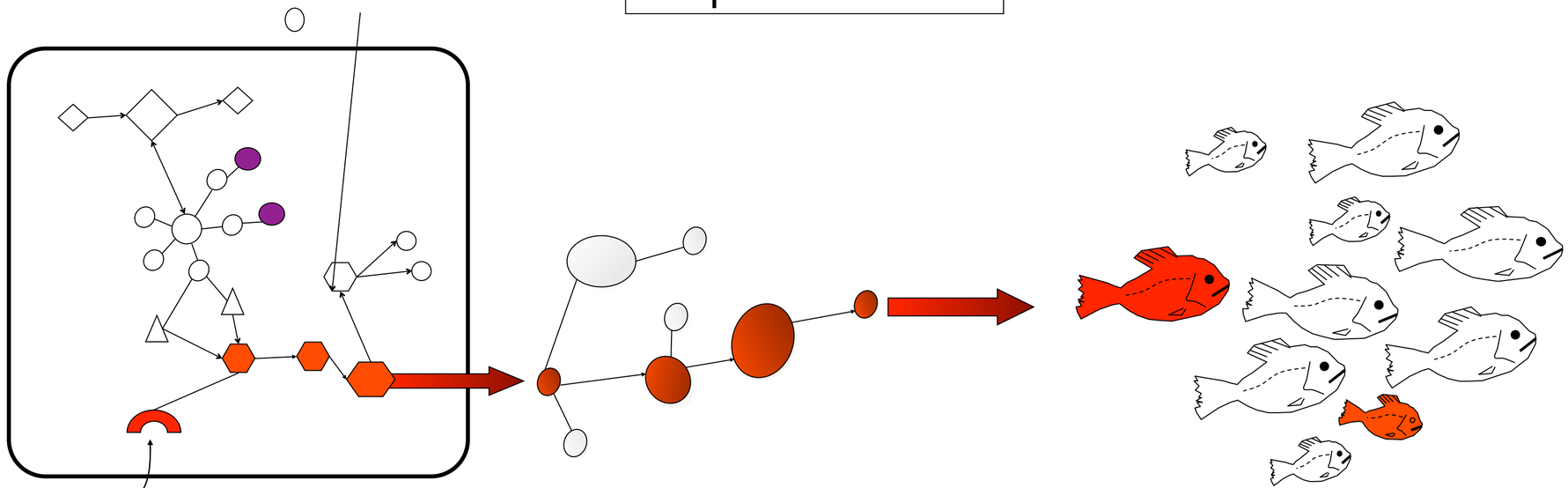
Microarray analysis

RNA extraction

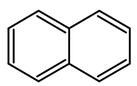
Exposure study

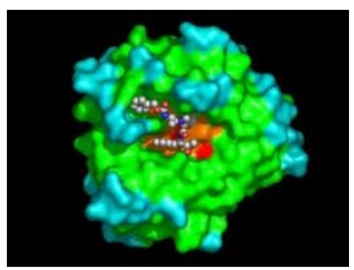
Komplekse responser på flere nivå

Initiating event → Response perturbation → Adverse effect



Exposure





Targets
Receptor,
Enzymes
Membranes
DNA

Toxicogenomics
Transcriptome
Proteome
Metabolome
Interactome

Effects
Growth
Development
Metamorphosis
Reproduction
Death

Komplekse metoder gir svar

Rager et al., EHP (2011)

Komplekse metoder gir svar

Research

A Toxicogenomic Comparison of Primary and Photochemically Altered Air Pollutant Mixtures

Julia E. Rager,[1] Kim Lichtveld,[1] Seth Ebersviller,[1] Lisa Smeester,[1] Ilona Jaspers,[2] Kenneth G. Sexton,[1] and Rebecca C. Fry[1]

[1]Department of Environmental Sciences and Engineering, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [2]Center for Environmental Medicine, Asthma, and Lung Biology, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

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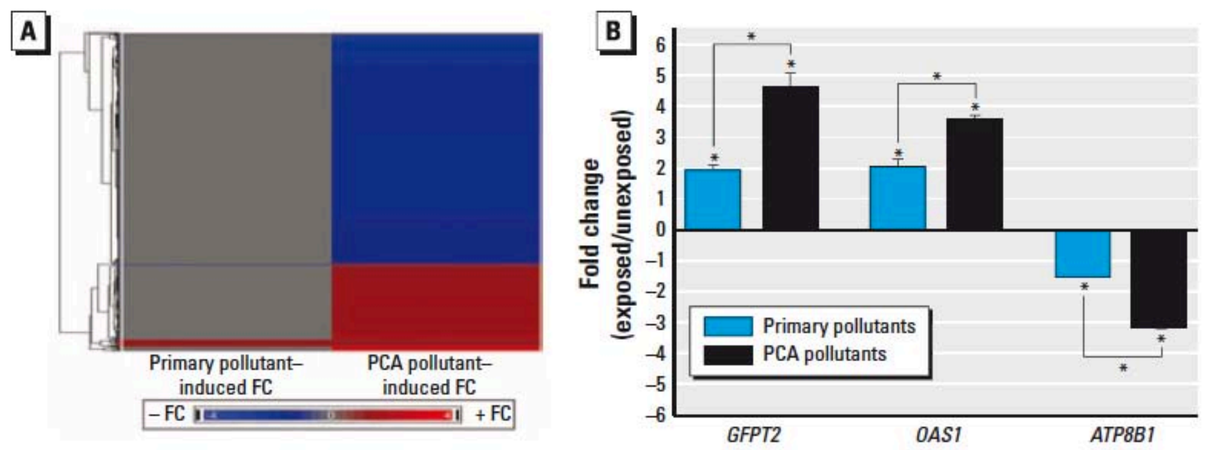

Figure 2. Air pollutant mixtures alter gene expression profiles in human lung cells. (*A*) Heat map showing average gene expression fold change (FC) of 714 total genes modulated by exposure to primary pollutant and/or PCA pollutant mixture. (*B*) qRT-PCR results displaying FC gene expression (mean ± SE).
*$p < 0.05$ compared with the control or the other exposure condition.

Rager et al., EHP (2011)

Komplekse metoder gir svar

A Toxicogenc
Air Pollutant

*Julia E. Rager,[1] Kim
and Rebecca C. Fry*

[1]Department of Environ
Hill, Chapel Hill, North
North Carolina at Chap

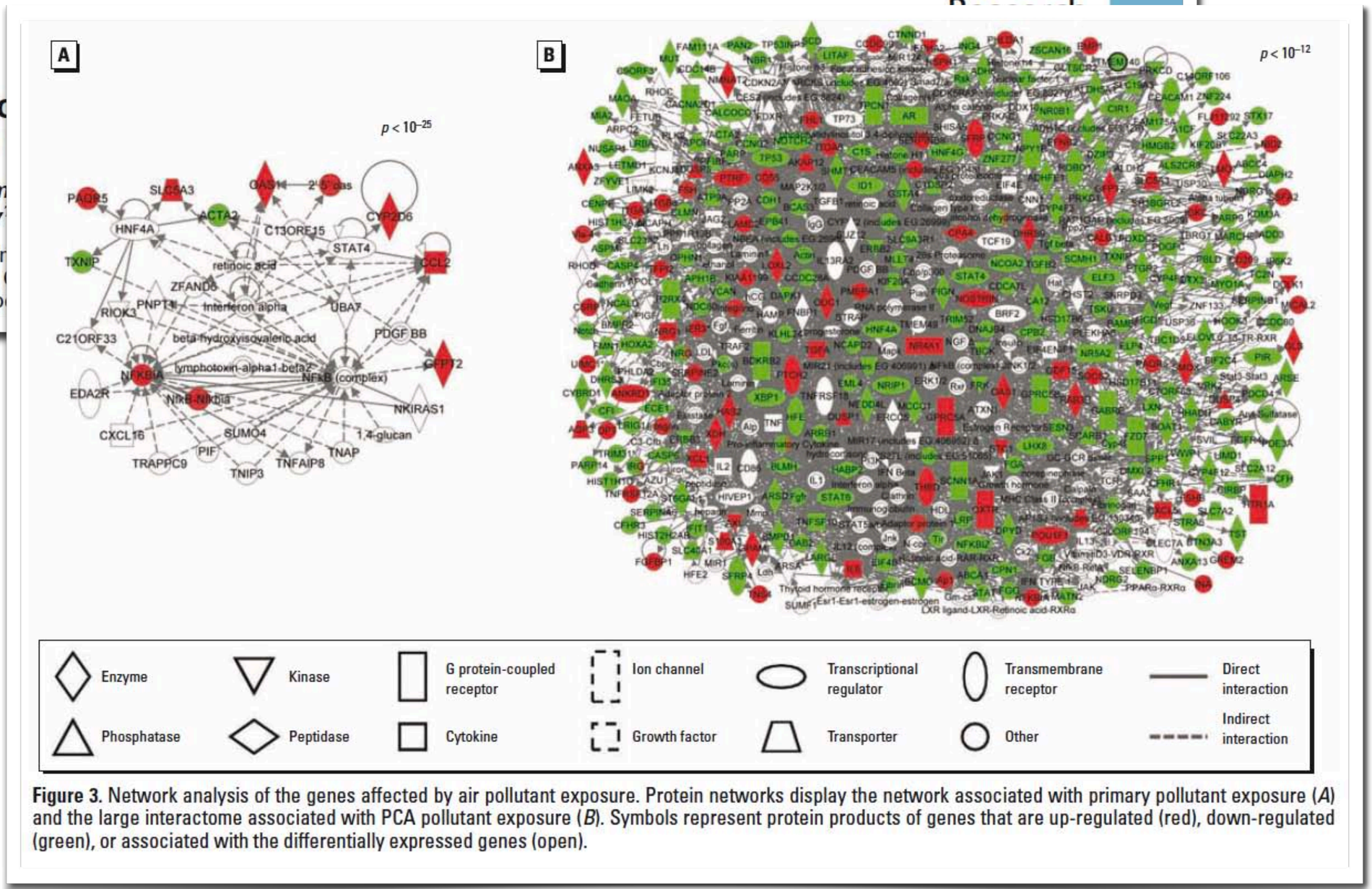

Figure 3. Network analysis of the genes affected by air pollutant exposure. Protein networks display the network associated with primary pollutant exposure (*A*) and the large interactome associated with PCA pollutant exposure (*B*). Symbols represent protein products of genes that are up-regulated (red), down-regulated (green), or associated with the differentially expressed genes (open).

Rager et al., EHP (2011)

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Air Pollutant

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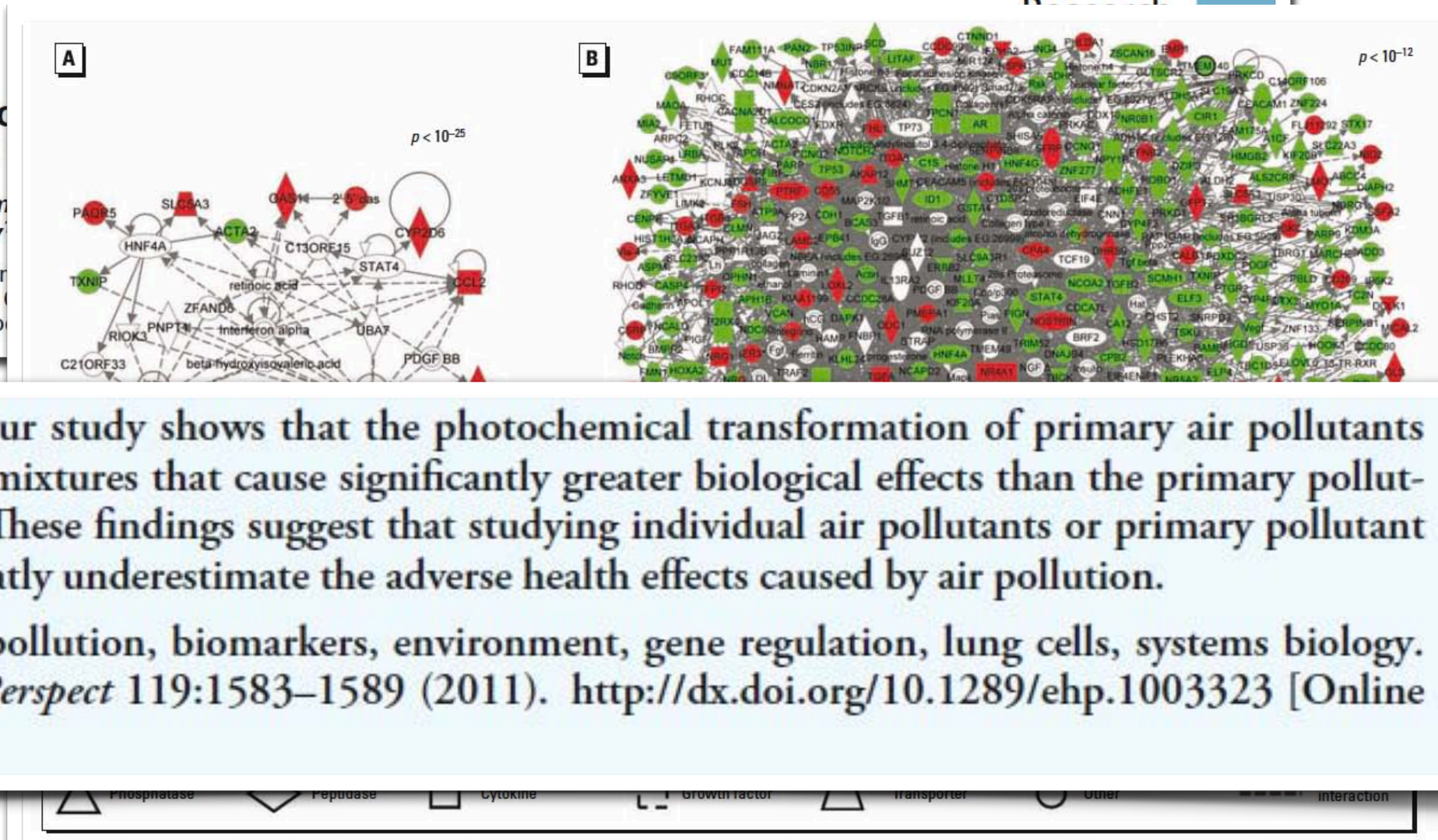

CONCLUSIONS: Our study shows that the photochemical transformation of primary air pollutants produces altered mixtures that cause significantly greater biological effects than the primary pollutants themselves. These findings suggest that studying individual air pollutants or primary pollutant mixtures may greatly underestimate the adverse health effects caused by air pollution.

KEY WORDS: air pollution, biomarkers, environment, gene regulation, lung cells, systems biology. *Environ Health Perspect* 119:1583–1589 (2011). http://dx.doi.org/10.1289/ehp.1003323 [Online 14 July 2011]

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Rager et al., EHP (2011)

Mekanismekunnskap gir koblinger mellom transkriptomdata og eksponering

Research

Bisphenol A Exposure Is Associated with *in Vivo* Estrogenic Gene Expression in Adults

David Melzer,[1] Lorna Harries,[2*] Riccardo Cipelli,[3] William Henley,[1] Cathryn Money,[4] Paul McCormack,[4] Anita Young,[4] Jack Guralnik,[5] Luigi Ferrucci,[6] Stefania Bandinelli,[7] Anna Maria Corsi,[7] and Tamara Galloway[3]*

[1]Epidemiology and Public Health, and [2]Institute of Biomedical and Clinical Sciences, Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, United Kingdom; [3]Biosciences, College of Life and Environmental Sciences, University of Exeter, Exeter, United Kingdom; [4]Brixham Environmental Laboratory, AstraZeneca UK Ltd., Brixham, United Kingdom; [5]Laboratory of Epidemiology, Demography, and Biometry, and [6]Clinical Research Branch, National Institute on Aging, Baltimore, Maryland, USA; [7]InCHIANTI Group, Piero Palagi Hospital, Florence, Italy

CONCLUSIONS: Because activation of nuclear-receptor–mediated pathways by BPA is consistently found in laboratory studies, such activation in humans provides evidence that BPA is likely to function as a xenoestrogen in this sample of adults.

KEY WORDS: bisphenol A, endocrine disruption, estrogen receptor-β, estrogen-related receptor-α, human biomonitoring, InCHIANTI, toxicogenomics. *Environ Health Perspect* 119:1788–1793 (2011). http://dx.doi.org/10.1289/ehp.1103809 [Online 10 August 2011]

Mekanismekunnskap gir koblinger mellom transkriptomdata og eksponering

Research

Bisphenol A Exposure in Adults

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Anita Young,[4] Jack Guralnik,[5] Lu

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University of Exeter, Exeter, United King
United Kingdom; [4]Brixham Environmer
Demography, and Biometry, and [6]Clinic
Group, Piero Palagi Hospital, Florence

CONCLUSIONS: Becaus
found in laboratory st
function as a xenoestro

KEY WORDS: bisphenol
human biomonitoring
(2011). http://dx.doi.o

Hormone Impact

BPA Linked to Altered Gene Expression in Humans

Urinary metabolites of bisphenol A (BPA), a widely used component of polycarbonate plastics and epoxy resins, serve as biomarkers for exposure to the chemical and are detectable in more than 90% of individuals tested in the United States and Europe. Studies to date suggest positive associations between BPA and cardiovascular disease, diabetes, and reproductive and developmental abnormalities in humans, although further research is needed to confirm these findings. Recent studies have shown links between BPA and changes in total testosterone concentrations and altered estradiol:testosterone ratio in men, but evidence for a mechanism behind such links has been lacking. A new study now links BPA exposure with altered expression of estrogen- and androgen-responsive genes in humans [*EHP* 119(12):1788–1793; Melzer et al.].

The InCHIANTI study—a prospective study of mid- and late-life morbidity risk factors among 1,453 participants in Chianti, Italy—provided the data for the current study. A subset of 96 men provided same-day blood and urine samples in 2008–2009. Urine samples were analyzed for concentrations of BPA, and blood leukocytes were used for transcript analysis of six estrogen- and androgen-responsive genes: *ESR1*, *ESR2*, *ESRRA*, *ESRRB*, *ESRRG*, and *AR*. These genes code nuclear hormone receptors involved in the control of developmental and physiological pathways shown to be activated by BPA in laboratory studies.

Urinary BPA concentrations ranged from 0.73 to 56.94 ng/mL and were positively associated with increased expression of *ESR2* and *ESRRA* based on models adjusted for potential confounding factors. Transcripts for other genes were either not detected (*ESRRG*) or were not associated with BPA concentrations (*ESR1*, *ESRRB*, and *AR*). Mean expression of *ESR2* and *ESRRA* increased by 65% and 38%, respectively, in the highest versus lowest BPA exposure tertile.

The implications of altered gene expression in blood leukocytes are unknown, and this measure has not been validated as a surrogate measure of effects on hormone-responsive gene expression. However, the results suggest that BPA is bioactive in humans, and the authors argue that the potential link between exposure, hormone signaling, and related disorders is biologically plausible. For example, estrogen receptor β, coded by *ESR2*, plays a significant role in maintaining the structure and function of tissues in the cardiovascular and central nervous systems.

The cross-sectional design, lack of distinction between free and conjugated BPA in urine samples, and possible unidentified confounding factors are limitations of the study. Additional research is needed to confirm the findings and further investigate gene expression changes and effects of BPA exposure in other estrogen-regulated target tissues.

Julia R. Barrett, MS, ELS, a Madison, WI–based science writer and editor, has written for *EHP* since 1996. She is a member of the National Association of Science Writers and the Board of Editors in the Life Sciences.

Mekanismekunnskap gir koblinger mellom transkriptomdata og eksponering

Research

Bisphenol A Exposure in Adults

David Melzer,[1] Lorna Harries,[2*] I*
Anita Young,[4] Jack Guralnik,[5] Lu

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dated as a surro-
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ays a significant
of tissues in the

on between free
ble unidentified
ditional research
investigate gene
other estrogen-

tor, has written for *EHP*
riters and the Board of

TOXICOLOGY

Transforming Environmental Health Protection

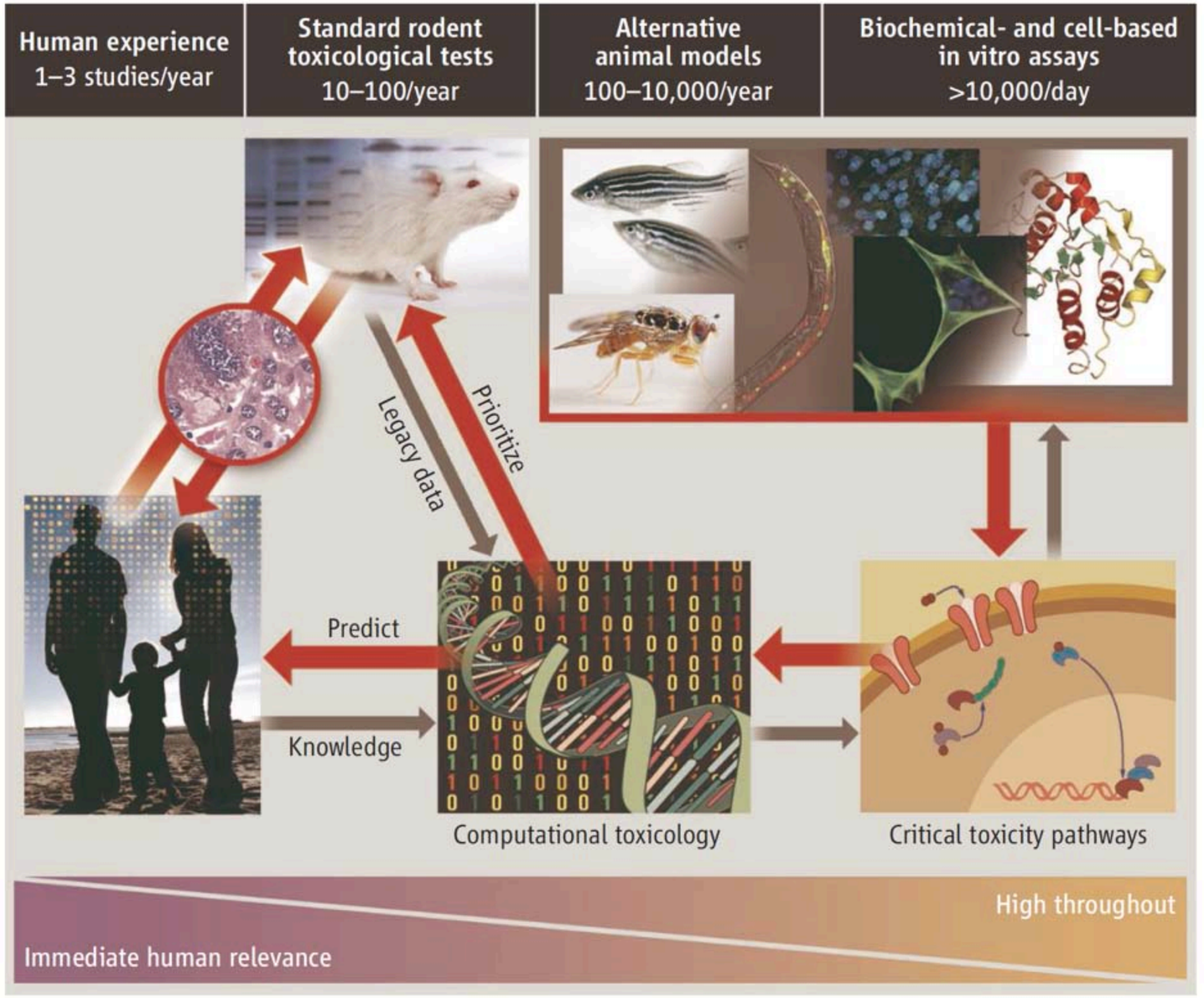
Francis S. Collins,[1*†] George M. Gray,[2*] John R. Bucher[3*]

Science (2008)

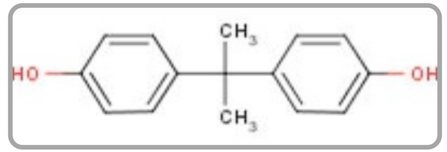
3R:

- reduction
- refinement
- replacement

We propose a shift from primarily in vivo animal studies to in vitro assays, in vivo assays with lower organisms, and computational modeling for toxicity assessments.



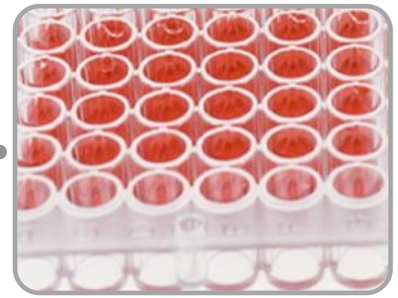
High Throughput Screening



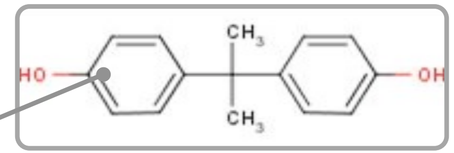
Chemical Exposure

High Throughput Screening

Robots

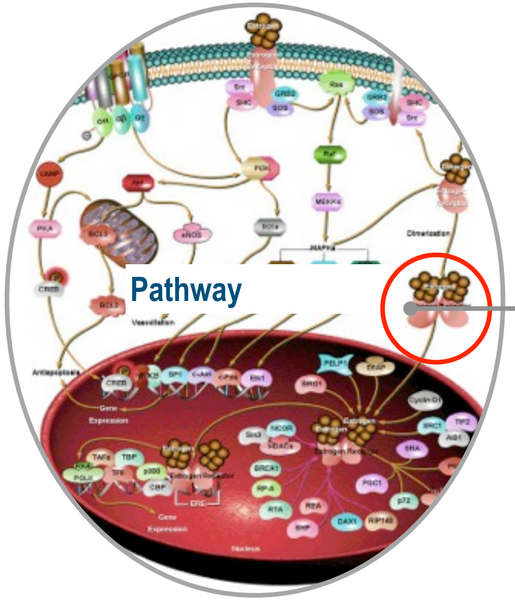


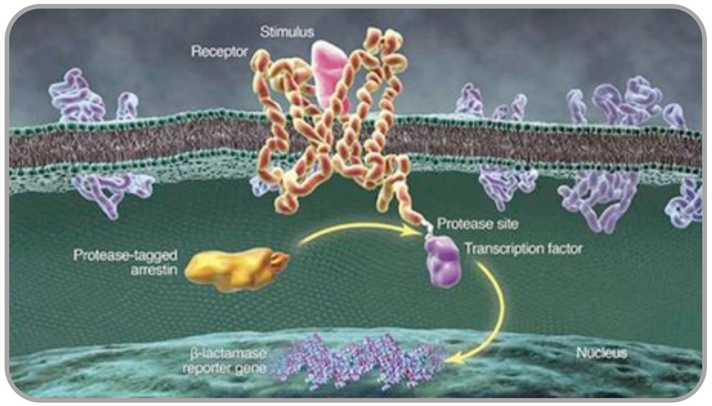
96-, 384-, 1536 Well Plates



Chemical Exposure

Cell Population

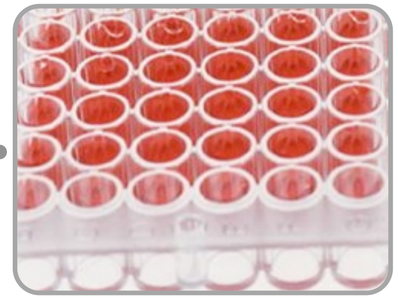




Target Biology
(e.g., Estrogen Receptor)

High Throughput Screening

Robots



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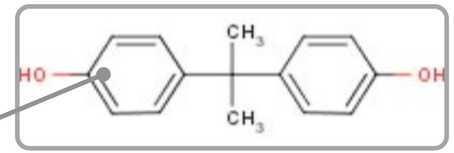

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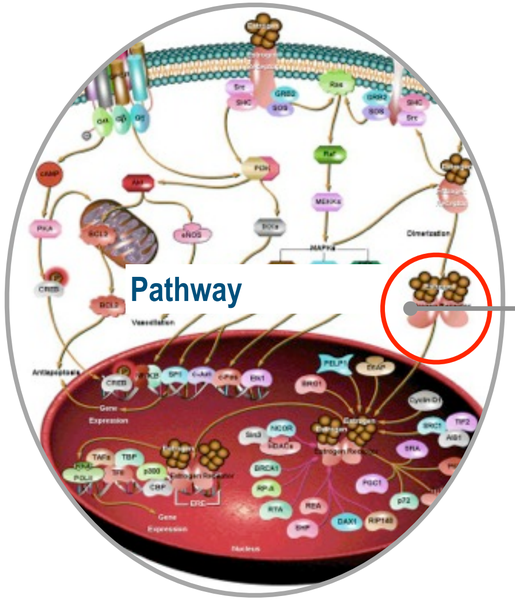

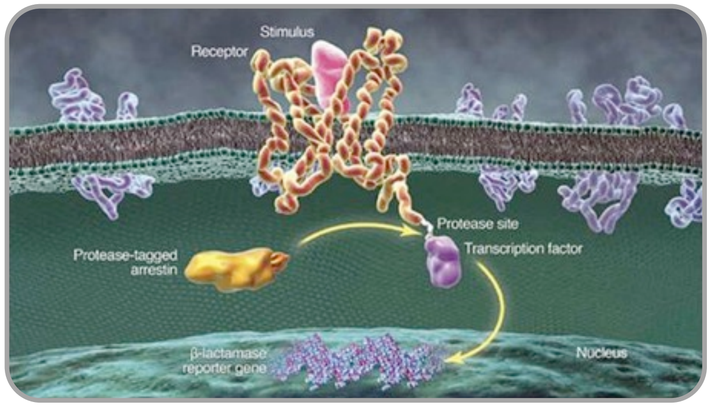

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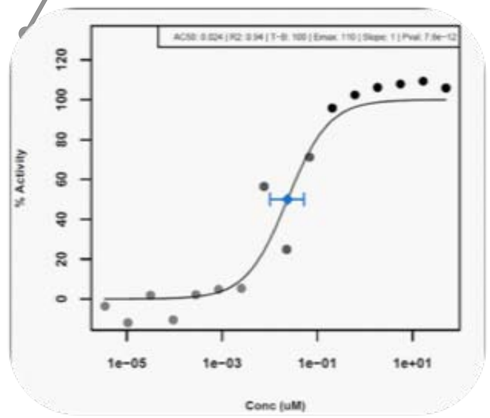
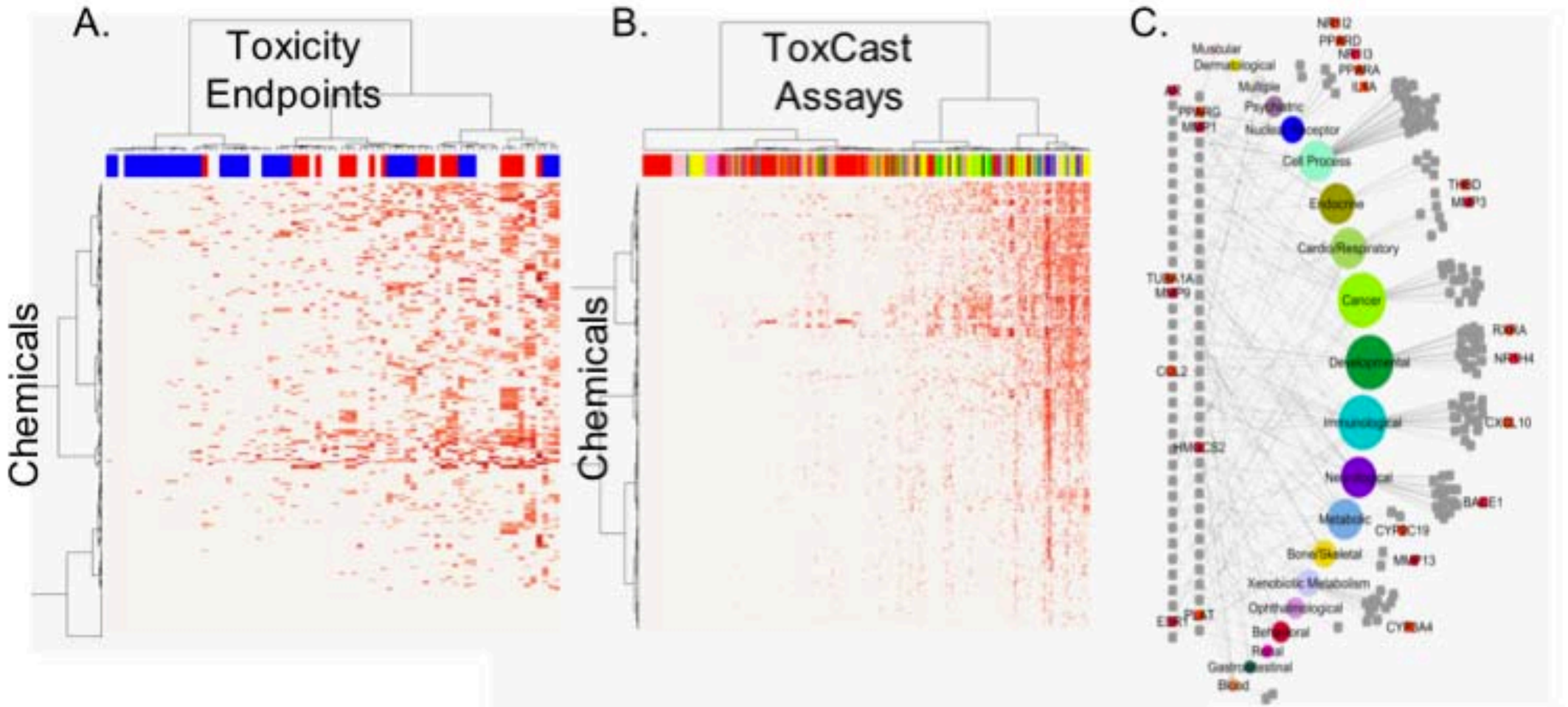
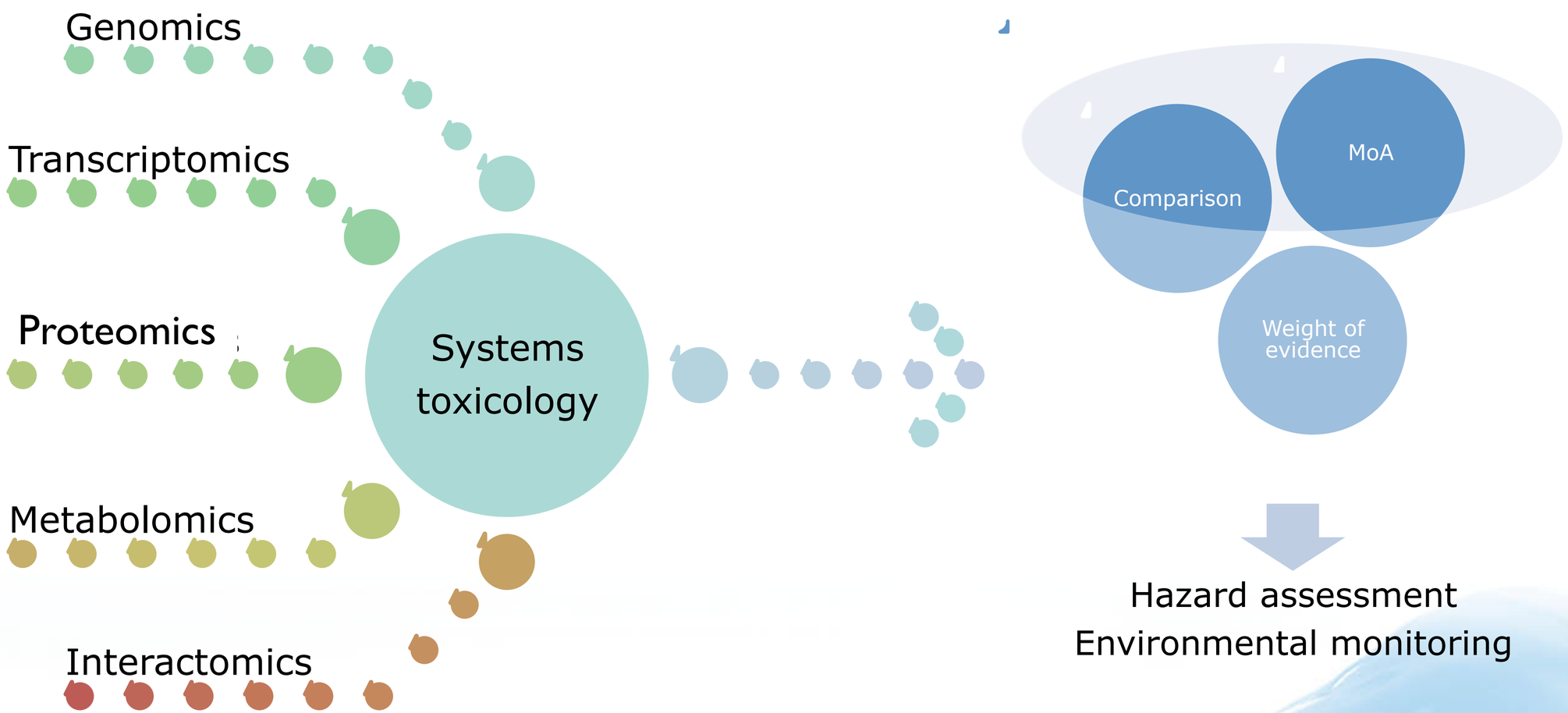


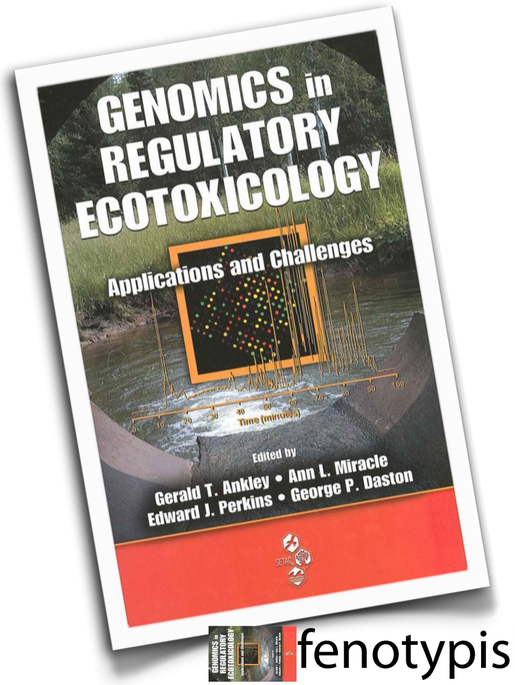
Predicting Toxicity and Disease

ToxRefDB ← ToxCast → Human Disease



Systems toxicology

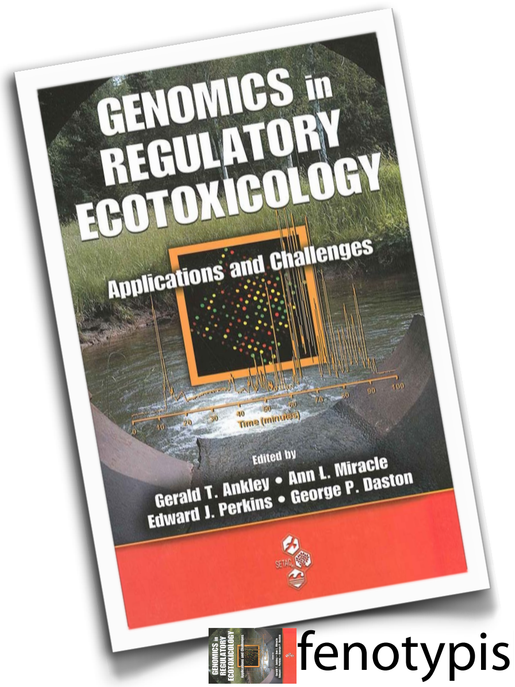




Fortsatte forskningsbehov

- fenotypisk forankring av genomiske endepunkt eller mønstre til skadelige effekter
- forbedret genomkunnskap om arter relevant for økologisk risikovurdering
- bedre kunnskap om hvordan ikke-kjemiske miljøvariable påvirker genomiske responser
- utvikling av alment tilgjengelige toksikogenomiske databaser
- standardisering og validering av prøveinnsamling, analyser og datafortolkningsverktøy for bruk i risikovurdering
- utvikling og kommersialisering av kostnadseffektive løsninger til bruk i lab og feltundersøkelser

Ankley et al., SETAC (2008)



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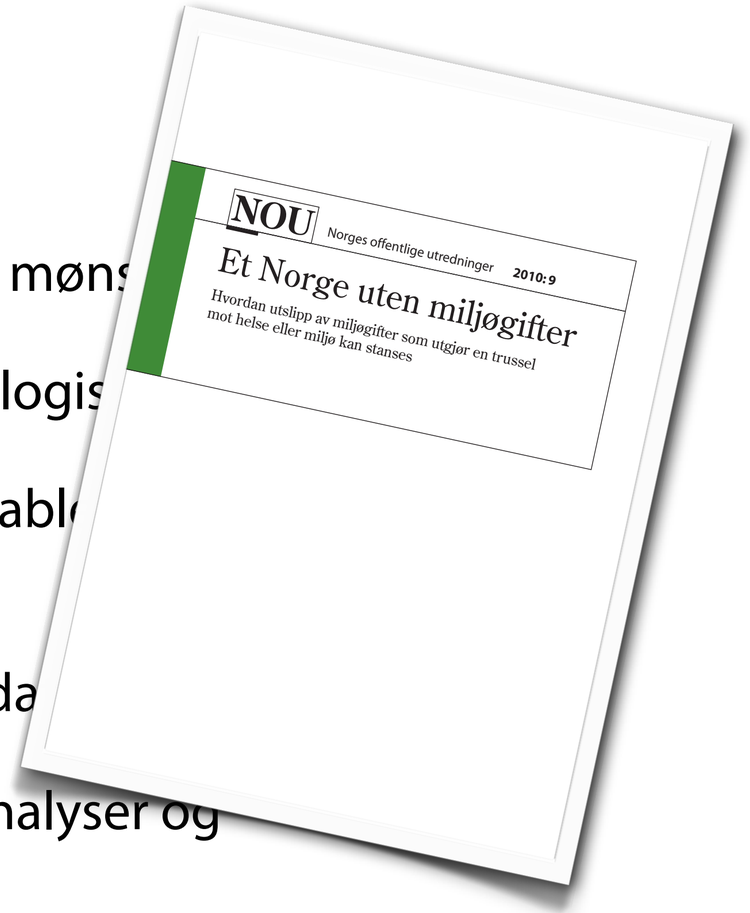

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Vi har:

- ☑ Forståelsen for hvordan komplekse systemer reagerer
- ☑ Kunnskap om komplekse metoder

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Hvem representerer «den bekymrete pasienten»?

- ○ Regulatoriske krav driver frem løsningene

Takk til

- For lysbilder:
  - Kevin Teichman, US EPA
  - Nancy Denslow, U Florida, Gainesville, USA
  - Knut-Erik Tollefsen, NIVA/UMB
- Finansiering: NFR, EU, Total, KLIF
- Studenter, stipendiater og kolleger ved UiB og andre steder