Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

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English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

WHO OECD ILSI/HESI International Workshop on Risk Assessment of Combined Exposures to Multiple Chemicals Annex 7 to the Workshop Report

Series on Testing & Assessment
No. 140

15-16 February 2011, Paris, France

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OECD Environment, Health and Safety Publications

Series on Testing and Assessment

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WHO OECD ILSI/HESI International Workshop on Risk Assessment of Combined Exposures to Multiple Chemicals: Annex 7

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among FAO, ILO, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

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No. 61, *Report of the Validation of the 21-Day Fish Screening Assay for the Detection of Endocrine Active Substances (Phase 1B) (2006)*

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No. 66, *OECD Report of the Validation of the Rodent Uterotrophic Bioassay: Phase 2. Testing of Potent and Weak Oestrogen Agonists by Multiple Laboratories (2006)*

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No. 69, *Guidance Document on the Validation of (Quantitative) Structure-Activity Relationship [(Q)SAR] Models (2007)*

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No. 71, *Guidance Document on the Uterotrophic Bioassay - Procedure to Test for Antioestrogenicity (2007)*

No. 72, *Guidance Document on Pesticide Residue Analytical Methods (2007)*

No. 73, *Report of the Validation of the Rat Hershberger Assay: Phase 3: Coded Testing of Androgen Agonists, Androgen Antagonists and Negative Reference*

Chemicals by Multiple Laboratories. Surgical Castrate Model Protocol (2007)

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No. 75, *Guidance Document on the Honey Bee (Apis Mellifera L.) Brood test Under Semi-field Conditions (2007)*

No. 76, *Final Report of the Validation of the Amphibian Metamorphosis Assay for the Detection of Thyroid Active Substances: Phase 1 - Optimisation of the Test Protocol (2007)*

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No. 84, *Report on the Workshop on the Application of the GHS Classification Criteria to HPV Chemicals, 5-6 July Bern Switzerland (2007)*

No. 85, *Report of the Validation Peer Review for the Hershberger Bioassay, and Agreement of the Working Group of the National Coordinators of the Test Guidelines Programme on the Follow-up of this Report (2007)*

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No.92, *Report of the Validation Peer Review for the Amphibian Metamorphosis Assay and Agreement of the Working Group of the National Coordinators of the Test Guidelines Programme on the Follow-Up of this Report (2008)*

No.93, *Report of the Validation of an Enhancement of OECD TG 211: Daphnia Magna Reproduction Test (2008)*

No.94, *Report of the Validation Peer Review for the 21-Day Fish Endocrine Screening Assay and Agreement of the Working Group of the National Coordinators of the Test Guidelines Programme on the Follow-up of this Report (2008)*

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No.101, *Report of the Workshop on Structural Alerts for the OECD (Q)SAR Application Toolbox, 15-16 May 2008, Utrecht, the Netherlands (2009)*

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No. 103, *Detailed Review Paper on Transgenic Rodent Mutation Assays (2009)*

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No. 105, *Report on Biostatistical Performance Assessment of the draft TG 436 Acute Toxic Class Testing Method for Acute Inhalation Toxicity (2009)*

No. 106, *Guidance Document for Histologic Evaluation of Endocrine and Reproductive Test in Rodents (2009)*

No. 107, *Preservative treated wood to the environment for wood held in storage after treatment and for wooden commodities that are not cover and are not in contact with ground. (2009)*

No. 108, *Report of the validation of the Hershberger Bioassay (weanling model) (2009)*

No. 109, *Literature review on the 21-Day Fish Assay and the Fish Short-Term Reproduction Assay (2009)*

No. 110, *Report of the validation peer review for the weanling Hershberger Bioassay and agreement of the working of national coordinators of the test guidelines programme on the follow-up of this report (2009)*

No. 111, *Report of the Expert Consultation to Evaluate an Estrogen Receptor Binding Affinity Model for Hazard Identification (2009)*

No. 112, *The 2007 OECD List of High Production Volume Chemicals (2009)*

No. 113, *Report of The Focus Session On Current And Forthcoming Approaches For Chemical Safety And Animal Welfare (2010)*

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No. 115, *Guidance Document on the Weanling Hershberger Bioassay in Rats: A Short-term Screening Assay for (Anti) Androgenic Properties (2009)*

No. 116, *Guidance Document on the Design and Conduct of Chronic Toxicity and Carcinogenicity Studies, Supporting TG 451, 452 and 453 (2010)*

No. 118, *Workshop Report on OECD Countries Activities Regarding Testing, Assessment and Management of Endocrine Disrupters Part I and Part II (2010)*

No. 119, *Classification and Labelling of chemicals according to the UN Globally Harmonized System: Outcome of the Analysis of Classification of Selected Chemicals listed in Annex III of the Rotterdam Convention (2010)*

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No. 123, *Guidance Document on the Diagnosis of Endocrine-related Histopathology in Fish Gonads (2010)*

No. 124, *Guidance for the Derivation of an Acute Reference Dose (2010)*

No. 125, *Guidance Document on Histopathology for Inhalation Toxicity Studies, Supporting TG 412 (Subacute Inhalation Toxicity: 28-Day) and TG 413 (Subchronic Inhalation Toxicity: 90-Day) (2010)*

No. 126, S*hort Guidance on the Threshold approach for Acute Fish Toxicity (2010)*

No. 127, *Peer review report of the validation of the 21-day androgenised female stickleback screening assay (2010)*

No. 128, *Validation Report of the 21-day Androgenised Female Stickleback Screening Assay (2010)*

No. 129, *Guidance Document on using Cytotoxicity Tests to Estimate Starting Doses for Acute Oral Systemic Toxicity Tests*

No. 130, *Guidance Document On Using Cytotoxicity Tests To Estimate Starting Doses For Acute Oral Systemic Toxicity Tests (2010)*

No. 131, *Report of the Test Method Validation of Avian Acute Oral Toxicity Test (OECD test guideline 223) (2010)*

No. 132, *Report of the Multi-Laboratory Validation of the H295R Steroidogenesis Assay to Identify Modulators (2010)*

No.133, *Peer Review Report for the H295R Cell-Based Assay for Steroidogenesis (2010)*

No.134, *Report of the Validation of a Soil Bioaccumulation Test with Terrestrial Oligochaetes by an International ring test (2010)*

No.135, *Detailed Review Paper on Environmental Endocrine Disruptor Screening: The use of Estrogen and Androgen Receptor Binding and Transactivation Assays in Fish (2010)*

No. 136, *Validation Report of The Chironomid Full Life-Cycle Toxicity Test (2010)*

No. 137, *Explanatory Background Document to the OECD Test Guideline On In Vitro Skin Irritation Testing (2010)*

No. 138, *Report of the Workshop on Using Mechanistic Information in Forming Chemical Categories (2011)*

No 139, *Report of the Expert Consultation on Scientific and Regulatory Evaluation of Organic Chemistry Mechanism Based Structural Alerts for the Identification of Protein-binding Chemicals (2011)*

ABOUT THE OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 34 industrialised countries in North and South America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised committees and working groups composed of member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's workshops and other meetings. Committees and working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

The Environment, Health and Safety Division publishes free-of-charge documents in ten different series: Testing and Assessment; Good Laboratory Practice and Compliance Monitoring; Pesticides and Biocides; Risk Management; Harmonisation of Regulatory Oversight in Biotechnology; Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents; and Safety of Manufactured Nanomaterials. More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (www.oecd.org/ehs/).

FOREWORD

This document is Annex 7 of a report of the WHO OECD ILSI/HESI International Workshop on Risk Assessment of Combined Exposures to Multiple Chemicals which was held on 15-16 February 2011 in Paris, France. The workshop was held following the proposal from the 45th OECD Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology in February 2010.

This document is published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology of the OECD.

ANNEX 7

SESSION B PRESENTATIONS

WHO OECD ILSI/HESI Workshop Paris 15-16 February 2011

Environmental Risk Assessment of Chemical Mixtures: UK Case Study

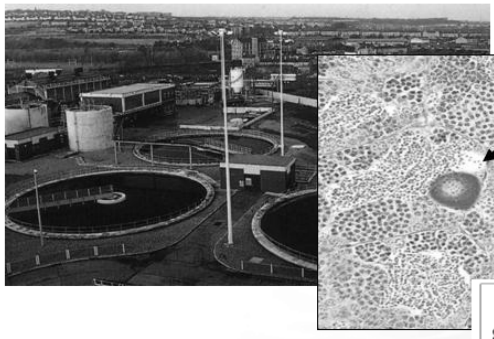
Tom Hutchinson
Centre for Environment Fisheries & Aquaculture Science
Weymouth, UK

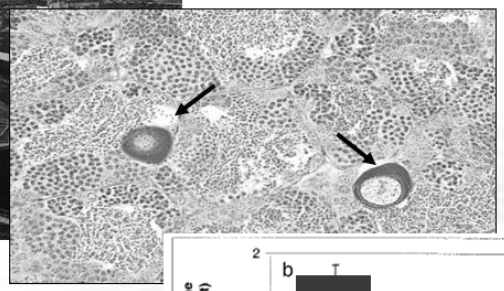
defra
Department for Environment Food and Rural Affairs

Cefas

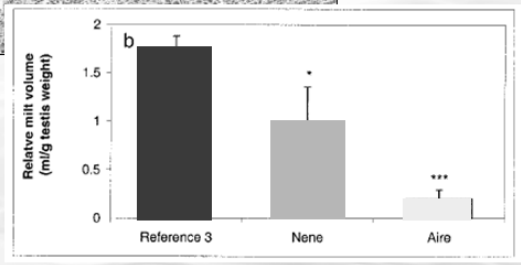
WHO OECD ILSI/HESI Workshop Paris 15-16 February 2011

Intersex fish & oestrogenic mixtures





UK research programme led by Brunel University plus Exeter University, Environment Agency and Cefas (funding from Defra, NERC & industry.



defra
Department for Environment Food and Rural Affairs

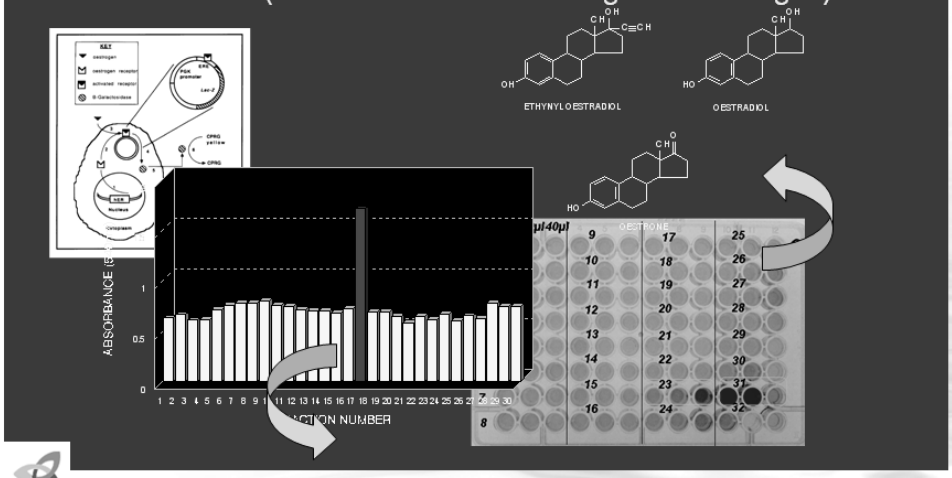
Jobling et al (2002) Biol Reproduction 66: 272-281

Cefas

WHO OECD ILSI/HESI Workshop Paris 15-16 February 2011

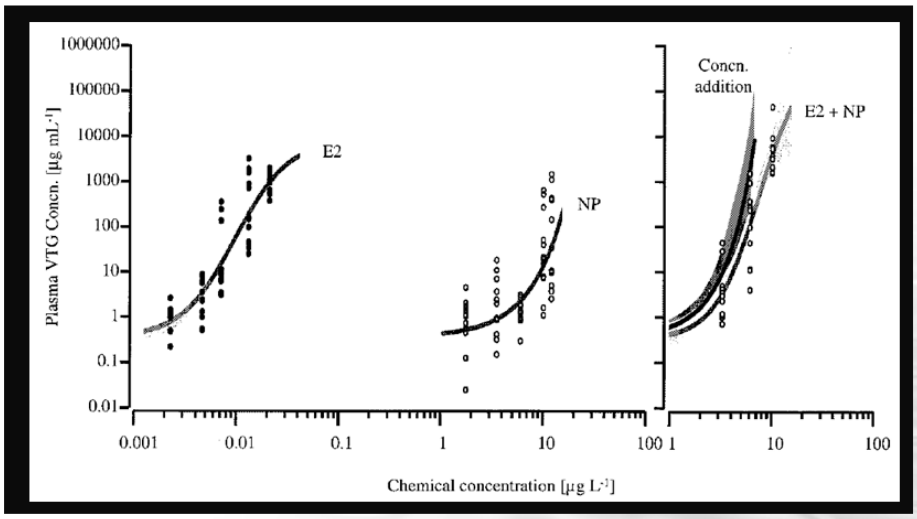
In vitro assays of effluents

Yeast Androgen Screen (YAS) & Yeast Estrogen Screen (YES) used to screen extracts (Waters Oasis HLB 200 mg 6 ml cartridges)



Ref: Desbrow et al (1998) Environ Sci Technol 32: 1549-1558

Oestrogenic mixtures *in vivo* 14d rainbow trout VTG assay



Model of concentration addition accurately predicted oestrogenic effects *in vivo* (Thorpe et al (2001) Environ Sci & Technol 35:2476-2481.

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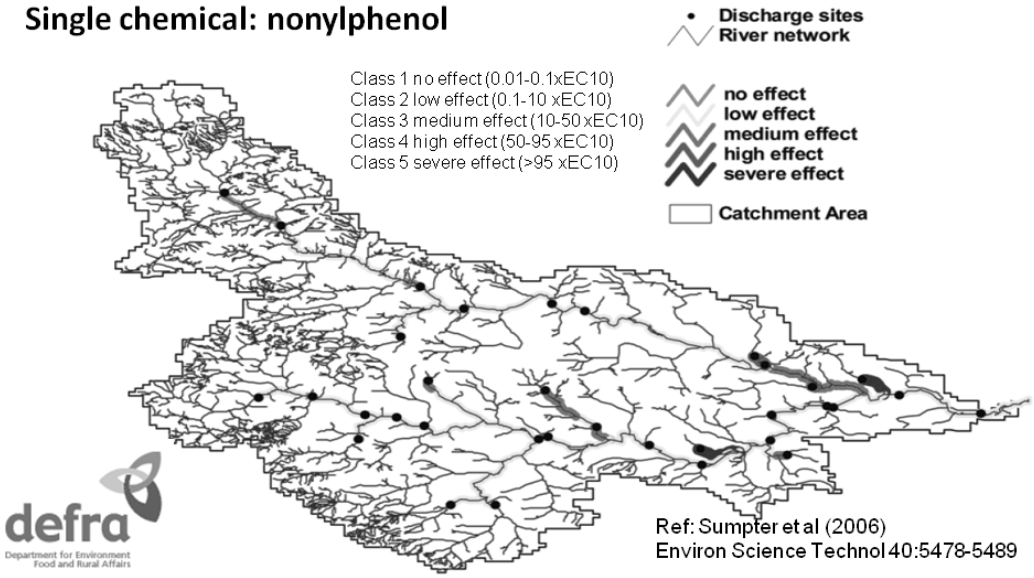
UK catchment modeling of the expected consequences of an oestrogen mimic



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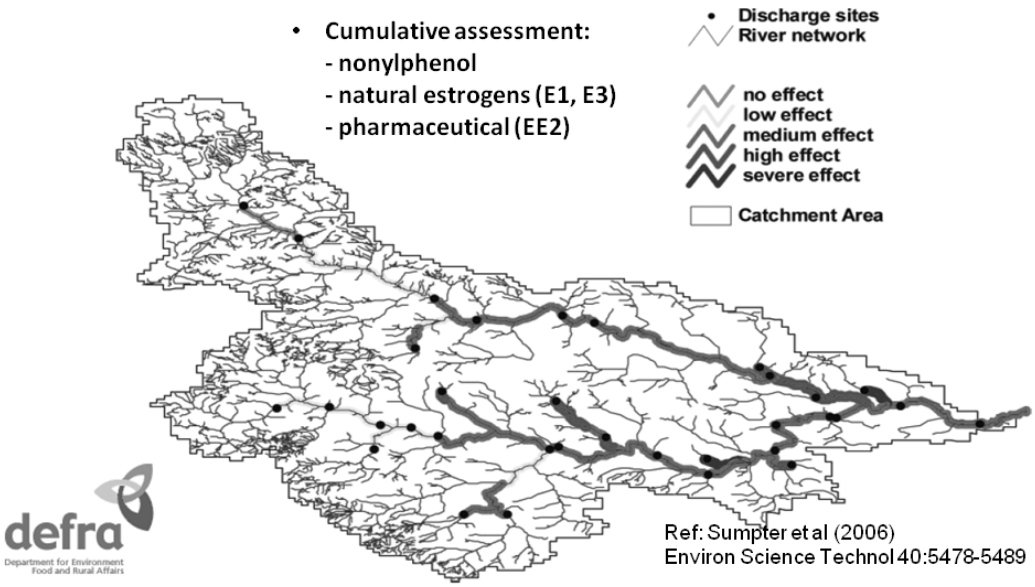
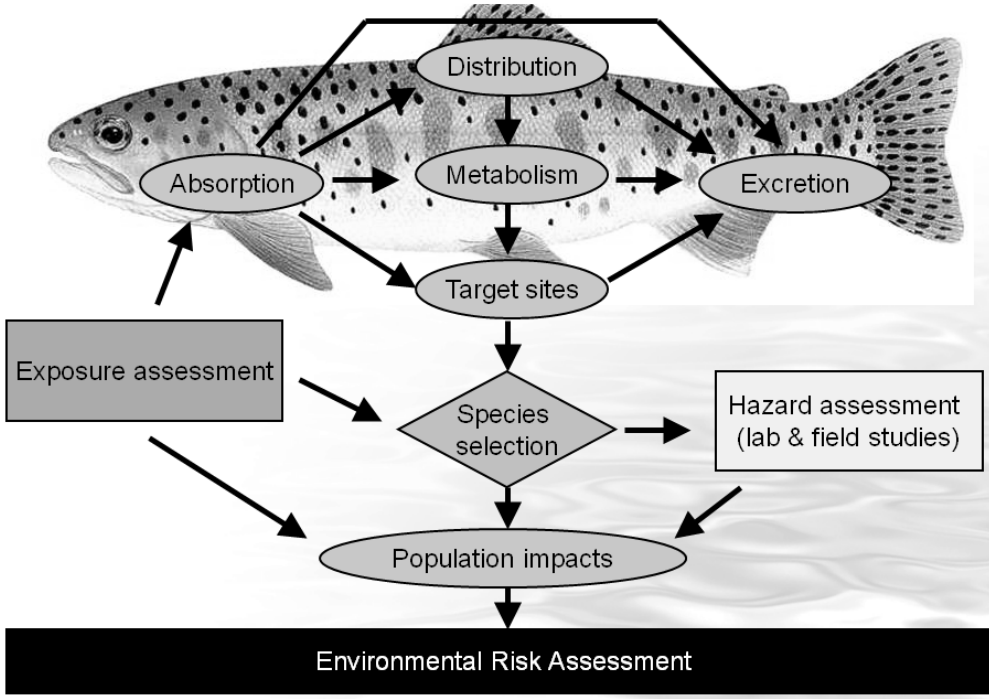
UK catchment modeling of expected effects of oestrogenic mixtures



MOA for Environmental Toxicology



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- Environment Agency
- NERC
- UKWIR
- University of Exeter
- University of London

Thank you for listening

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Department for Environment Food and Rural Affairs

Cefas

Exposure of 2-year olds to endocrine disrupters – an example of the use of dose addition

Shima Dobel
Chemicals Division
Danish EPA

Miljøministeriet
Miljøstyrelsen

BACKGROUND

- The Danish EPA had published app. 100 surveys on chemicals in consumer products before the survey on 2-years old.
- Surveys on chemicals in consumer products usually shows no risk for single substances in single products.
- Most of the conclusions are "there are no risk, but we do not know if there is a risk if we knew the total exposure of the substance from all sources".
- What is the conclusion when we look at the total exposure.

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BACKGROUND

- Reduced semen quality, increase in incidences of testicular cancer, malformations of male reproductive organs, early breast development in young girls in European countries.
- The effects observed in humans can be reproduced in animal studies
- Combined exposure to multiple EDs, in doses considered safe for the individual substances, cause serious reproductive effects in animals
- Exposure to pesticides (azolefungicides) during pregnancy caused endocrine disruptive effect (cryptorchidism) in sons born by mothers working in greenhouses

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Miljøstyrelsen

BACKGROUND

- Expert workshop on combination effects of chemicals. Special focus on endocrine disrupters and regulatory aspects
- International reputated experts from various fields working with the issues of endocrine disrupters and/or combination effects
- Conclusions:
  - Risk assessment of combined exposure is both necessary and feasible – can start immediately
  - Dose addition should be used as default method
  - Legal basis and/or guidance for risk assessment of combined exposure in EU needs to be enhanced

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OBJECTIVE

- Estimate the risk from combined exposure of the 2 year-old child to endocrine disrupting substances using the concept of Dose Addition

3 exposure scenarios:

- indoor environment
- food
- consumer products

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SUBSTANCES

- Known endocrine effects in animal studies and an anticipated exposure

  Anti-androgenic
  - Phthalates (DIBP, DEHP, DINP, DBP, BBP)
  - Pesticides (Prochloraz, Tebuconazole, Linuron, Vinclozolin, Procymidone)
  - PCBs
  - Dioxins and dioxin-like PCBs
  - DDT

  Estrogen-like
  - Parabens (Propyl-, Butyl-)
  - Bisphenol A

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RISK ASSESSMENT – SINGLE SUBSTANCES

Using a substance by substance approach:

- Immediate risk:
  Dioxins and dioxin-like PCB's
  Phthalates (DBP)
  Parabenes (butyl- og propyl-)

- Other substances found to cause limited exposure

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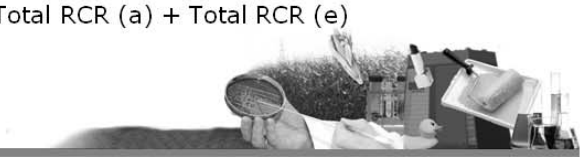
METHOD – RCRs AND COMBINED EXPOSURE

- DNEL = (N/L)OAEL / Assessment Factor
- Risk Characterisation Ratio (RCR) = Exposure/DNEL
- RCR > 1: uncontrolled risk
- Concept of dose addition
  - Total RCR (DBP) = RCR (consumer products)+ RCR (indoor env) + RCR (food)
  - Total RCR (antiandrogenic) = RCR (DBP) + RCR (DEHP) +...
  - Total RCR (estrogen-like) = RCR (BPA) + RCR (propylparaben) + RCR...
  - Total RCR (a+e) = Total RCR (a) + Total RCR (e)



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RISK ASSESSMENT – COMBINED EXPOSURE

- Total RCR for antiandrogenic substances (not including rubber clogs or phthalates in toys):
  - 3.37 - 9.96
- Total RCR for estrogen-like substances
  - 1.04 - 3.76
- Total RCRs for EDCs in total (not including rubber clogs or phthalates in toys):
  - 4.93-12.92

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CONCLUSION

- There is an immediate need to reduce exposure to endocrine disrupting chemcials from food and the indoor environment, but also from consumer products.
- The survey does not cover all exposure pathways and all endocrine disrupting chemicals
- There is a need for more information on exposure pathways and scenarios.

Miljøministeriet
Miljøstyrelsen

ACTIONS

- Extensive information campaign to parents and grandparents – with 8 pieces of advice

Miljøministeriet
Miljøstyrelsen

ACTIONS

- Denmark will submit a proposal to regulate 4 phthalates under REACH in order to protect vulnerable groups from the combined effects of phthalates.

- National ban on two parabenes in cosmetics for children

Miljøministeriet
Miljøstyrelsen

THANK YOU AND LINK`S

Study on 2-year olds: www.65000.dk, http://www2.mst.dk/udgiv/publications/2009/978-87-92548-81-8/pdf/978-87-92548-82-5.pdf

Expert Report – WS on combination effects: http://www.mim.dk/NR/rdonlyres/C59693B7-2421-4748-89F0-5937496E0A28/0/BILAG_2_Expertworkshop.pdf

Information campaign (pamphlet): http://images.netdoktor.com/dk/Emnecenter%20om%20Kemi/65.000_english.pdf

Miljøministeriet
Miljøstyrelsen

Cumulative Risk Assessment (CRA): Status of Activities at the US EPA

Louis (Gino) Scarano
U.S. EPA

WHO/OECD/ILSI-HESI International Workshop on Risk Assessment of Combined Exposures to Multiple Chemicals
Paris, France February 15-16, 2011

Overview

- Brief History of CRA in US
- The EPA Risk Assessment Forum (RAF)
- Examples of Spectrum of CRAs in US
- Policy Issues
- Current Activities

Brief (Recent)History of CRA in US

Landmark Reports

- National Academy of Sciences – multiple reports from 1983-2009
- Presidential/Congressional Commission on RA/RM - 1997
- U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry (ATSDR) – 2004
- International –
  - WHO 2007
  - 2009 EU Mixtures Report

U.S. EPA CRA Theory and Practice

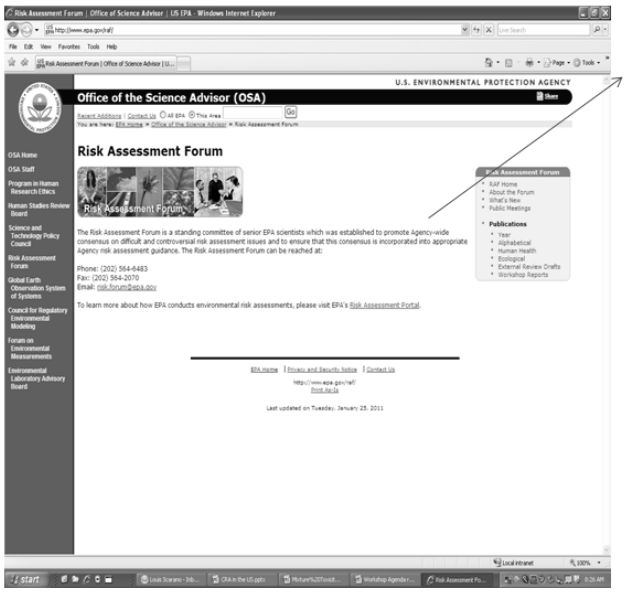
- Risk Assessment Guidance for Superfund (1989)
- Methodology for Multipathway Exposures to Combustor Emissions (1998)
- Guidance for Assessing Health Risks of Chemical Mixtures (1986, 2000)
- 4 CRA's & Guidance on Cumulative Risk of Pesticides (2002b;2006a,b,c;2007a)
- Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document (2007b)
- Planning & Scoping for Cumulative Risk Assessment (1997)
- Planning & Scoping Lessons Learned (2002a)
- Framework for Cumulative Risk Assessment (2003)
- 5 White Papers on CRA: Directions for CRA, Vulnerability, Combined Effects of Multiple Stressors, Environmental Mixtures, Biomarkers (2007c)
- Continuing Risk Assessment Forum CRA Efforts

Brief (Recent)History of CRA in US

Landmark Legislation/Activities

- 1980 - CERCLA (Superfund)
  (chemical-centric site evaluations including mixtures)
- 1996 – Food Quality Protection Act (FQPA) –
  (pesticides/cumulative risk/aggregate exposure)
- 1996 - Safe Drinking Water Act Amendments
  (chemical mixtures in drinking water)
- 1997 – Science Policy Council Guidance on Planning/Scoping CRA
- 1999 – Est. of Risk Assessment Forum Technical Panel on CRA
- 2008 - Consumer Product Safety Improvement Act
  (CRA of phthalate mixtures for children's products)
- *201? – TSCA reform? Both current proposed bills require consideration of CRA….*

US EPA Risk Assessment Forum (RAF)

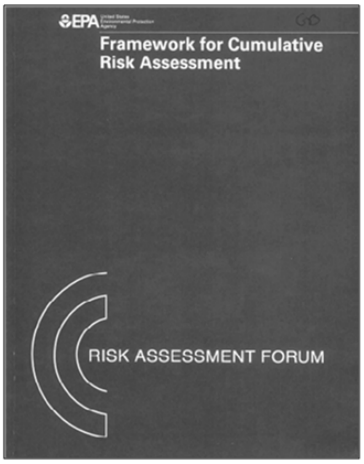


"The Risk Assessment Forum is a standing committee of senior EPA scientists which was established to promote Agency-wide consensus on difficult and controversial risk assessment issues and to ensure that this consensus is incorporated into appropriate Agency risk assessment guidance."

RAF – "Purple Books" (This is 2003 *Framework* Document)

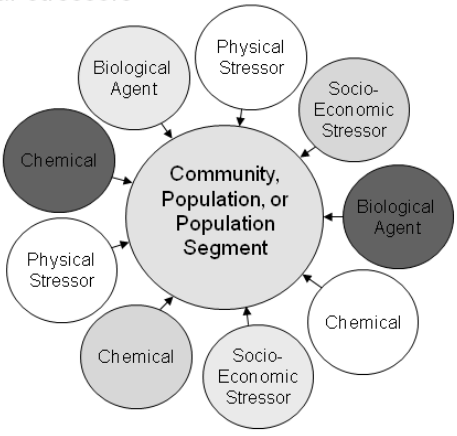
Cumulative Risk:
The combined risks from aggregate exposures to multiple agents or stressors.

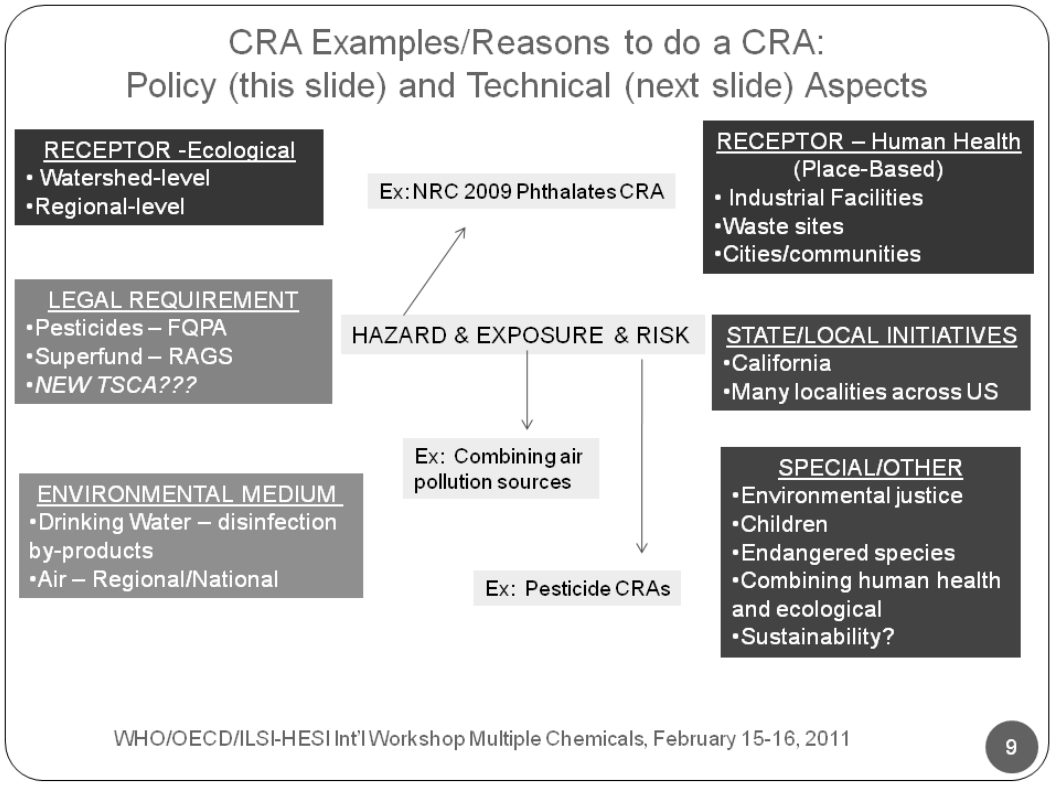
Cumulative Risk Assessment:
An analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors.



Features of CRA

- Multiple chemical, physical, biological stressors
- Complex, multiple-route exposures
- Stakeholder emphasis
- Human health and ecology
- Population vulnerabilities
- Benefits of healthy communities
- Benefits of healthy ecosystems
- Population focus




CRA Examples/Reasons to do a CRA:
Policy (this slide) and Technical (next slide) Aspects
RECEPTOR -Ecological
• Watershed-level
•Regional-level
Ex: NRC 2009 Phthalates CRA
RECEPTOR – Human Health
(Place-Based)
• Industrial Facilities
•Waste sites
•Cities/communities
LEGAL REQUIREMENT
•Pesticides – FQPA
•Superfund – RAGS
•NEW TSCA???
HAZARD & EXPOSURE & RISK
STATE/LOCAL INITIATIVES
•California
•Many localities across US
Ex: Combining air pollution sources
ENVIRONMENTAL MEDIUM
•Drinking Water – disinfection by-products
•Air – Regional/National
SPECIAL/OTHER
•Environmental justice
•Children
•Endangered species
•Combining human health and ecological
•Sustainability?
Ex: Pesticide CRAs
WHO/OECD/ILSI-HESI Int'l Workshop Multiple Chemicals, February 15-16, 2011
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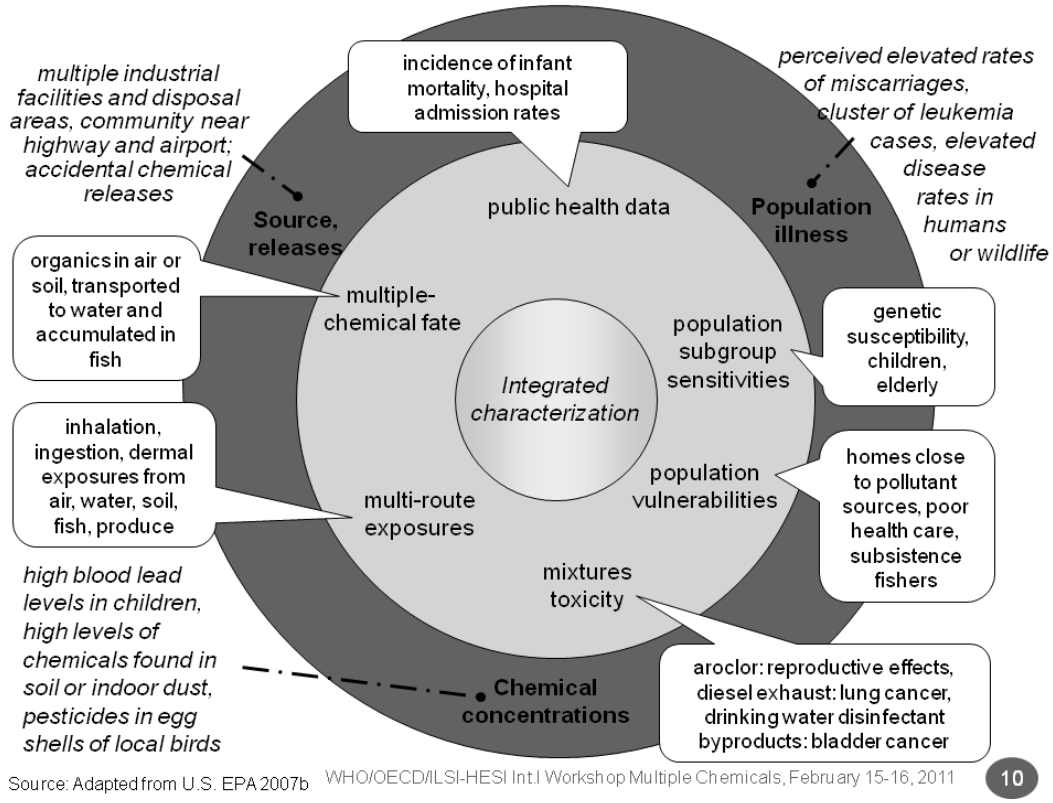
multiple industrial facilities and disposal areas, community near highway and airport; accidental chemical releases
incidence of infant mortality, hospital admission rates
perceived elevated rates of miscarriages, cluster of leukemia cases, elevated disease rates in humans or wildlife
Source, releases
public health data
Population illness
organics in air or soil, transported to water and accumulated in fish
multiple-chemical fate
population subgroup sensitivities
genetic susceptibility, children, elderly
Integrated characterization
inhalation, ingestion, dermal exposures from air, water, soil, fish, produce
population vulnerabilities
homes close to pollutant sources, poor health care, subsistence fishers
multi-route exposures
mixtures toxicity
high blood lead levels in children, high levels of chemicals found in soil or indoor dust, pesticides in egg shells of local birds
Chemical concentrations
aroclor: reproductive effects, diesel exhaust: lung cancer, drinking water disinfectant byproducts: bladder cancer
Source: Adapted from U.S. EPA 2007b
WHO/OECD/ILSI-HESI Int.l Workshop Multiple Chemicals, February 15-16, 2011
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Policy Issues

- Different U.S. Federal Agencies have purview/mission for related exposures (e.g., U.S. EPA, FDA, OSHA, ATSDR, CDC)
- U.S. EPA not well structured to conduct CRA
  - Does not jointly evaluate risks for multiple media and sources, e.g., indoor/outdoor air, food, pesticides
  - Does not routinely evaluate nonchemical stressors nor their joint impacts with chemical exposures
  - Does not evaluate vulnerability factors in chemical risk assessment with the exception of accounting for sensitive subpopulations (e.g., kids under FQPA, Uncertainty Factor for Human Variability in setting Toxicity Values on IRIS)
  - Program office structure "silos" risk assessment and risk management approaches
- No collaborative network with the medical community, industry or academia

Current/Recent Activities

- State of California
  - December, 2010 report (*Cumulative Impacts: Building a Scientific Foundation*)
- EPA Administrator Priority: Environmental Justice
  - March 2010 Workshop (***Strengthening Environmental Justice Research and Decision Making: A Symposium on the Science of Disproportionate Environmental Health Impacts)***
- EPA-funded research in 2009 (see references)
  - Dealing with non-chemical stressors and analytic tools for CRA
- National Academy of Sciences
  - Reports (2008 *Phthalates CRA*, 2009 *Science and Decisions in RA*)

….which led to

.....US EPA internal Colloquium in October, 2010 to evaluate the many issues raised in these reports

Science & Decisions Recommendations

- EPA should draw on other approaches to incorporate interactions between chemical and nonchemical stressors
  - Ecological Risk Assessment
  - Social Epidemiology
- Increase role of biomonitoring, epidemiologic, and surveillance data
- Develop guidelines and methods for simpler analytical tools

Phthalates & CRA Recommendations

- Focus on common health outcomes
- Group chemicals by common adverse outcomes
- (EPA IRIS program held expert workshop in December, 2010 on phthalate CRA)

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RAF Technical Panel on CRA

- Has been "re-invigorated" as of July, 2010
- Is ready to begin its task to develop agency-wide guidelines on CRA…

WHO/OECD/ILSI-HESI Int'l Workshop Multiple Chemicals, February 15-16, 2011 14

CRA Technical Panel Members 2011

Tri-Chairs

Charles Maurice	**ORD/OSP & Region 5**
Linda Teuschler	**ORD/NCEA**
Gino Scarano	**OCSPP/OPPT**

Tim Barzyk	**ORD/NERL**	**Devon Payne-Sturges**	**ORD/NCER**
Bob Benson	**Region 8**	**Elissa Reaves**	**OCSPP/OPP**
George Bollweg	**Region 5**	**Rita Schoeny**	**OW**
Carole Braverman	**Region 5**	**Brad Schultz**	**ORD/NERL**
Kevin Crofton	**ORD/NHEERL**	**Jane Simmons**	**ORD/NHEERL**
Stiven Foster	**OSWER**	**Betsy Smith**	**ORD/NERL**
Audrey Galizia	**ORD/NCEA**	**Mark Sprenger**	**OSWER**
Stephen Graham	**OAR/OAQPS**	**Cynthia Stahl**	**Region 3**
Roseanne Lorenzana	**Region 10**	**Winona Victery**	**Region 9**
Jayne Michaud	**OSA**	**Marjorie Wellman**	**OW**
Greg Miller	**OCHPEE**	**Lawrence Martin**	**Lead RAF Staff**
Ella Mulford	**Region 5**	**Julie Fitzpatrick**	**RAF Staff**
Marian Olsen	**Region 2**		

ORD = Office of Research Development
OSP = Office of Science Policy
Regions = EPA has 10 Regional Offices
NCEA = Nat'l Center for Environ. Assess.
OCSPP = Off. Chem. Safety Poll. Prev
OPPT = Off Poll. Prev. Toxics
NERL = Nat'l Exposure Res Lab
NHEERL = Nat'l Health/Env Eff Res Lab
OSWER = Off Solid Waste/Emerg Resp
OAR = Off Air and Radiation
OAQPS = Off Air Quality Planning/Stnds
OSA = Off Science Advisor
OCHPEE = Off Children's Health Prot
NCER = Nat'l Ctr Env Research
OPP = Off of Pesticide Programs
OW = Off of Water
RAF = Risk Assessment Forum

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WHO/OECD/ILSI-HESI Int'l Workshop Multiple Chemicals, February 15-16, 2011

Acknowledgements

- Linda Teuschler (RAF Tri-Chair)
- Chuck Maurice (RAF Tri-Chair)
- Lawrence Martin (RAF Staff)

WHO/OECD/ILSI-HESI Int'l Workshop Multiple Chemicals, February 15-16, 2011

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References (EPA)

- U.S. EPA. 1986. Guidelines for the Health Risk Assessment of Chemical Mixtures. U.S. EPA/ORD, Washington, DC. September. EPA/630/R-98/002.
- U.S. EPA. 1989. Risk Assessment Guidance for Superfund: Volume 1, Human Health Evaluation Manual (Part A). U.S. EPA/OERR, Washington, DC. EPA/540/1-89/002. (Also see Parts B-D.)
- U.S. EPA. 1997. Guidance on Cumulative Risk Assessment, Part 1. Planning and Scoping. U.S. EPA/SPC, Washington, DC. Attachment to memo dated July 3, 1997 from the Administrator, Carol Browner, and Deputy Administrator, Fred Hansen, titled "Cumulative Risk Assessment Guidance-Phase I Planning and Scoping." Available at: http://www.epa.gov/OSA/spc/2cumrisk.htm
- U.S. EPA. 1998. Methodology for Assessing Health Risks Associated with Multiple Pathways of Exposure to Combustor Emissions. U.S. EPA/ORD/NCEA, Cincinnati, OH. December. EPA/600/R-98/137.
- U.S. EPA. 2000. Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. U.S. EPA/RAF, Washington, DC. EPA/630/R-00/002. Available at: http://www.epa.gov/ncea/raf/pdfs/chem_mix/chem_mix_08_2001.pdf
- U.S. EPA. 2002a. Lessons Learned on Planning and Scoping of Environmental Risk Assessment. Memorandum from Science Policy Council. January. Available at: http://www.epa.gov/osp/spc/llmemo.htm
- U.S. EPA. 2002b. Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity. U.S.EPA/OPP, Washington, DC. Available at: http://www.epa.gov/oppfead1/trac/science/cumulative_guidance.pdf
- U.S. EPA. 2003. Framework for Cumulative Risk Assessment. U.S. EPA/ORD/NCEA, Washington, DC. EPA/600/P-02/001F. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54944
- U.S. EPA. 2006a. Organophosphorus Cumulative Risk Assessment 2006 Update. U.S. EPA/OPP, Washington, DC. Available at: http://www.epa.gov/oppsrrd1/cumulative/2006-op/op_cra_main.pdf
- U.S. EPA. 2006b. Cumulative Risk from Triazine Pesticides. U.S. EPA/OPP, Washington, DC. Available at: http://www.epa.gov/oppsrrd1/REDs/triazine_cumulative_risk.pdf
- U.S. EPA. 2006c. Cumulative Risk from Chloroacetanalide Pesticides. U.S. EPA/OPP, Washington, DC. Available at: http://www.epa.gov/pesticides/cumulative/chloro_cumulative_risk.pdf
- U.S. EPA. 2007a. Revised N-Methyl Carbamate Cumulative Risk Assessment. U.S. EPA/OPP, Washington, DC. Available at: http://www.epa.gov/oppsrrd1/REDs/nmc_revised_cra.pdf

References (EPA)

- U.S. EPA. 2007b. Concepts, Methods and Data Sources for Health Risk Assessment of Multiple Chemicals, Exposures and Effects. U.S. EPA/NCEA, Cincinnati, OH. EPA/600/R-06/013A. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=190187
- U.S. EPA. 2007c. U.S. EPA. Risk Assessment Forum White Papers on Cumulative Risk:
  - Callahan, M.A. and K. Sexton. 2007. If cumulative risk assessment is the answer, what is the question? *Environ Health Perspect* 115(5):799-806;
  - deFur, P.L. et al. 2007. Vulnerability as a function of individual and group resources in cumulative risk assessment. *Environ Health Perspect* 115(5):817-824;
  - Menzie, C.A. et al. 2007. A phased approach for assessing combined effects from multiple stressors. *Environ Health Perspect* 115(5):807-816;
  - Ryan, P.B. et al. 2007. Using biomarkers to inform cumulative risk assessment . *Environ Health Perspect* 115(5):833-840;
  - Sexton, K. and D. Hattis. 2007. Assessing cumulative health risks from exposure to environmental mixtures—Three fundamental questions. *Environ Health Perspect* 115(5):825-832.

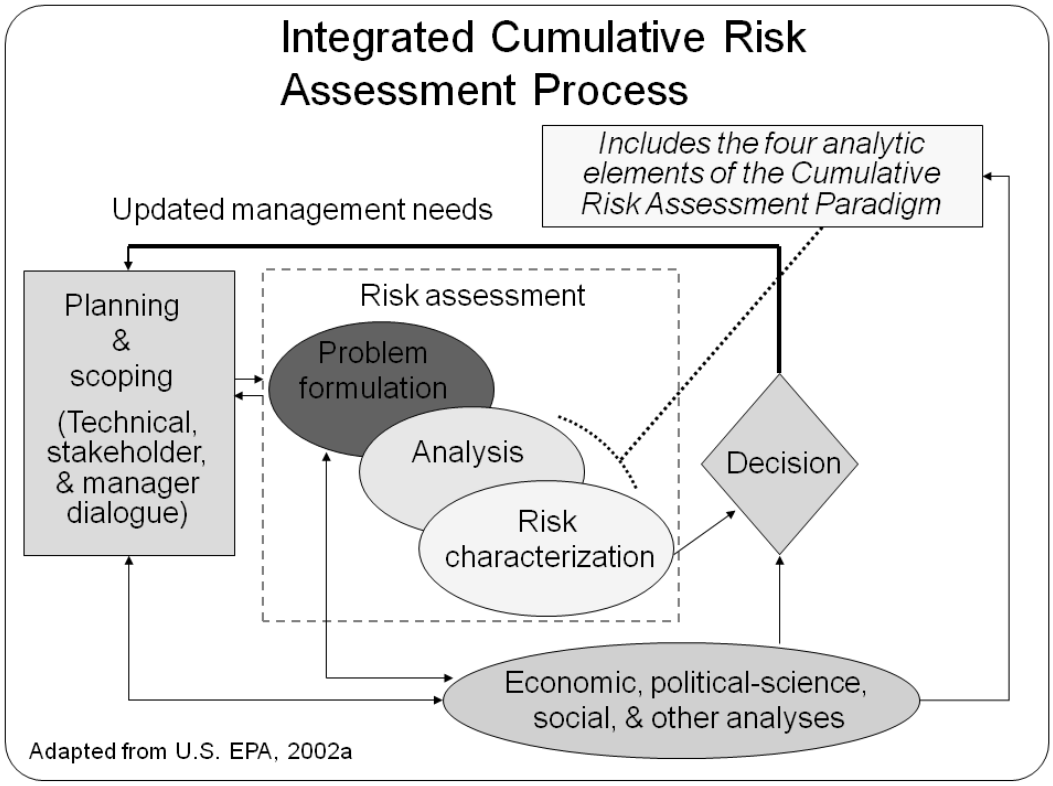
Other EPA Sources:

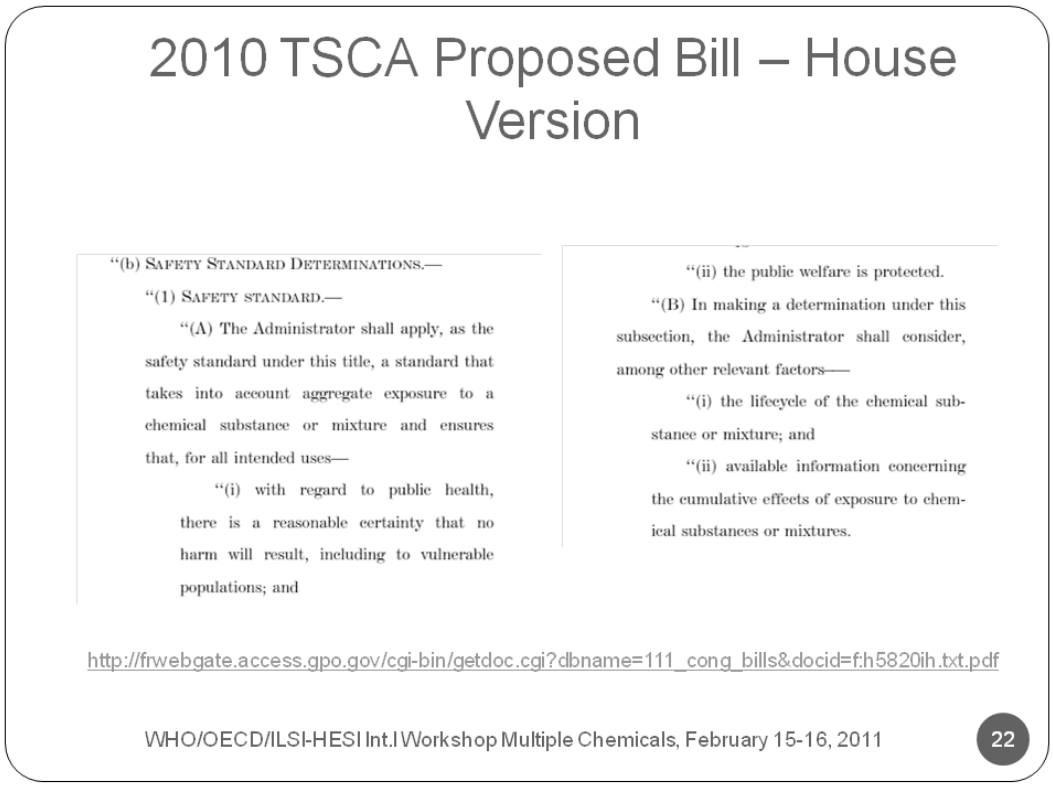
- March, 2010 Symposium on Environmental Justice: http://www.epa.gov/ncer/events/news/2010/03_17_10_calendar.html
- EPA Risk Assessment Forum: http://www.epa.gov/raf/
- **EPA-funded research for 2010-14 (through NCER):** http://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/recipients.display/rfa_id/515/records_per_page/ALL

References (Other, Non-EPA)

- Agency for Toxic Substances and Disease Registry (ATSDR). 2004. Guidance manual for the assessment of joint toxic actions of chemical mixtures. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.: http://www.atsdr.cdc.gov/interactionprofiles/ipga.html
- California 2010 report on Cumulative Impacts: http://www.oehha.org/ej/pdf/CIReport123110.pdf
- European Commission Mixtures report (2009): http://ec.europa.eu/environment/chemicals/pdf/report_Mixture%20toxicity.pdf
- NRC 1996. *Understanding Risk – Informing Decisions in a Democratic Society*. http://www.nap.edu/openbook.php?isbn=030905396X
- NRC. 2008 – *Phthalates and Cumulative Risk Assessment: The Tasks Ahead*. http://www.nap.edu/catalog.php?record_id=12528
- NRC. 2009 – *Science and Decisions: Advancing Risk Assessment*. http://www.nap.edu/catalog.php?record_id=12209
- Presidential/Congressional Commission on Risk Assessment and Risk Management, (PCCRARM). 1997. vols. 1-2. http://www.riskworld.com/riskcommission/default.html

EXTRA SLIDES


Integrated Cumulative Risk Assessment Process
Includes the four analytic elements of the Cumulative Risk Assessment Paradigm
Updated management needs
Planning & scoping (Technical, stakeholder, & manager dialogue)
Risk assessment
Problem formulation
Analysis
Risk characterization
Decision
Economic, political-science, social, & other analyses
Adapted from U.S. EPA, 2002a


2010 TSCA Proposed Bill – House Version
"(b) SAFETY STANDARD DETERMINATIONS.—
"(1) SAFETY STANDARD.—
"(A) The Administrator shall apply, as the safety standard under this title, a standard that takes into account aggregate exposure to a chemical substance or mixture and ensures that, for all intended uses—
"(i) with regard to public health, there is a reasonable certainty that no harm will result, including to vulnerable populations; and
"(ii) the public welfare is protected.
"(B) In making a determination under this subsection, the Administrator shall consider, among other relevant factors—
"(i) the lifecycle of the chemical substance or mixture; and
"(ii) available information concerning the cumulative effects of exposure to chemical substances or mixtures.
http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=111_cong_bills&docid=f:h5820ih.txt.pdf
WHO/OECD/ILSI-HESI Int.l Workshop Multiple Chemicals, February 15-16, 2011
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2010 TSCA Proposed Bill – Senate Version

Definitions Section

"(23) REASONABLE CERTAINTY OF NO HARM.—The term 'reasonable certainty of no harm' means, in establishing whether a chemical substance or mixture meets the safety standard under this subchapter, that aggregate exposure and cumulative exposure of the general population or of any vulnerable population to the chemical substance or mixture presents a negligible risk of any adverse effect on the general population or a vulnerable population.

"SEC. 4. MINIMUM DATA SET AND TESTING OF CHEMICAL SUBSTANCES AND MIXTURES.

"(A) IN GENERAL.—The types of health and environmental information for which standards for the development of test data may be prescribed include—

"(i) information pertaining to carcinogenesis, mutagenesis, teratogenesis, behavioral disorders, cumulative or synergistic effects, and any other effect which may be considered in a safety determination;

http://lautenberg.senate.gov/assets/SCA2010.pdf

Mixture Toxicity-Status Report EU Commission.

Patrick Murphy and Katarína Piršelová
European Commission – DG Environment

OECD Workshop, Paris, Feb 2011

environment

Background

- EU chemicals' legislation – assessment of individual substances
- Combination Effects in current chemicals'legislation:
  - **CLP Regulation**
  - **New PPP Regulation**
  - **New Biocides Regulation in adoption**
- Real life scenario – many different chemicals from different sources and pathways

  → ***Potential adverse combination effects***

environment

Combination Effects and Plant Protection Products (1)

- **Regulation (EC) No 396/2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC (Text with EEA relevance)**
- **Recital #6**

  "*It is also important to carry out further work to develop a methodology to take into account cumulative and synergistic effects. In view of human exposure to combinations of active substances and their cumulative and possible aggregate and synergistic effects on human health, MRLs should be set after consultation of the European Food Safety Authority ---"*

EUROPEAN COMMISSION

environment

Combination Effects and Biocides.

- **Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL concerning the placing on the market and use of biocidal products**
- ***Article 8*- Evaluation of applications**
- **"***Para 3. Where the evaluating competent authority considers that there are concerns with regard to the cumulative effects from the use of biocidal products containing the same active substance, it shall document its concerns----"*

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environment

Council Conclusions 17820/09 of 22 December 2009 - **Combination effects of chemicals**

Commission was invited:

- to assess **how** and **whether** relevant existing Community legislation adequately addresses risks from exposure to multiple chemicals from different sources and pathways, and on this basis to **consider appropriate modifications**, **guidelines and assessment methods**, and report back to the Council by early 2012 at the latest**,**

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DG ENV activities

- contract to gather and summarise knowledge (awarded end of 2007)
- Final report **State of the Art Report on Mixture Toxicity (**Febr 2010)
- Report dissemination
- DG ENV web-site ***Combination effects of chemicals***

  http://ec.europa.eu/environment/chemicals/effects.htm

- **consultations** - COM, MS and other stakeholders
- **a workshop** organised in June 2010

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DG ENV activities cont'd

- Request for opinion by the SANCO Scientific Committees
- Mandate – to advise the Commission on:
  - Scientific evidence - when organisms are exposed to different chemicals, substances may act jointly so that the overall toxicity level is affected; do the current assessment methods take proper account of these joint actions?
  - Analyse the existing approaches for mixture effect assessment – advantages/disadvantages
  - Effective way to target the combinations of chemicals with the highest risk for man and the environment
  - Where are major knowledge gaps, is the current knowledge sufficiently solid to address mixtures toxicity in a more systematic way (within the context of the EU legislation)
- a WG in place – draft opinion - summer 2011

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DG ENV activities cont'd

Preparatory work – Report to the Council

- Analysis of the existing EU ENV legislation *(REACH, CLP, WFD, IPPC, Marine Strategy Directive…)*
  - ***Gaps? Possible solutions?***
- *What is still missing ?* - research ? development ? methods?
- Increase integration of health and environmental monitoring data – *How it can be used for addressing combination effects?*

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Emerging Challenges

- **Definitions- number of chemicals, number of exposure routes and the time dimension;**
- **Low dose issue- definition and experimental evidence.**
- **Integrated assessments –are they needed? How to do them? How to do them effectively?**
- **Legislative compartmentalisation**
- **Liability**
- **Assessing combination effects in a regulatory context**

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Next steps

- Report to the Council due **early 2012**
- Form-Commission Communication
- Opinion of the Scientific Committee
- Analysis of the existing relevant EU legislation
  - **are risks adequately addresses?**
  - **ideas for possible modifications, guidelines and risk assessment methods**

EUROPEAN COMMISSION

environment

Thank you

European Commission

Katarina.Pirselova@ec.europa.eu
Patrick.Murphy@ec.europa.eu

http://ec.europa.eu/environment/

The control of chemical mixtures: the point of view of a scientific panel of the European Commission Environmental aspects

Marco Vighi
University of Milano Bicocca
Italy

The Terms of Reference

1) Is there scientific evidence that when organisms are exposed to different chemical substances, these may act jointly in a way that affects the overall level of toxicity?

2) Do the current assessment methods take proper account of these joint actions?

3) What are the advantages and disadvantages of the different approaches and is there any particular model sufficiently robust to be used as a default option?

4) What is the most effective way to target resources on those combinations of chemicals that constitute the highest risk for man and the environment?

5) Where are the major knowledge gaps?

6) Does current knowledge constitute a solid foundation upon which to address the toxicity of chemical mixtures in the context of EU legislations?

The general concepts

- The general concepts of mixture toxicity (CA, IA, synergism, etc) may be assumed to be the same for man and for the environment.
- However there are conceptual differences between human toxicology and ecotoxicology, which may affect the application of the CA and IA approaches.
- The most important difference is the objective of the protection. The goal of human toxicology is the protection of individuals. On the contrary, the goal of ecotoxicology is protecting structure and functions of biological communities and ecosystems.
- The death of individuals is accepted in the frame of natural selection processes.

The choice of endpoints

- **It follows that relevant end-points may be different in human toxicology and in ecotoxicology.**
- **Ecotoxicological end-points are related to relatively broad ecologically-relevant parameters such as massive mortality, reduction of fertility and any other effect affecting reproductive capability.**
- **Some effects extremely important for individuals but producing a moderate effect on population dynamics (e.g. cancerogenesis) are of negligible relevance in ecotoxicology.**
- **Therefore, precise end-points, that in human toxicology are often referred to a specific target organ, are meaningless in ecotoxicology.**

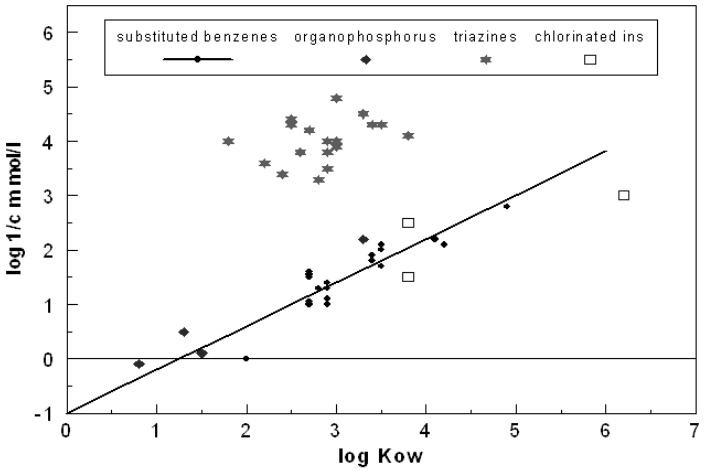
The availability of information

- Moreover, in ecotoxicology, knowledge on the toxicological mode of action on all the different types of organisms that may be present in an ecosystem is largely incomplete.
- Even for chemicals developed with the objective of a specific activity (e.g. pesticides) the toxicological mode of action is well known for target organisms but not for the non target ones.

The specificity of mode of action

Specific toxic chemicals exert their effect on particular functions that, usually, are not common to all living organisms present in a biologic community (photosynthesis inhibitors, ACHe inhibitors, etc.).

For non-target organisms, taxonomically far from the target ones, the effect of the chemical is likely to be narcotic-type (baseline toxicity).



Relationship between toxicity on algae and Log Kow for chemicals with specific and non-specific toxicological mode of action on algae

PNEC is not a toxicological endpoint

Ecosystems are exposed to a huge number of different substances at very low levels. Any assessment should start with the identification of the relevant components to be assessed.

For substances with specific mechanisms of actions, the sensitivity among tested species may differ by several orders of magnitude. So, the relevant components of a mixture assessment may differ for each species.

The general concepts of mixture toxicity (CA and IA) at levels close to the No Effect Level (NEL) are applicable to individuals/species, but difficult to implement when moving to the PNEC for community effects.

Environmental exposure

The different origin of environmental mixtures

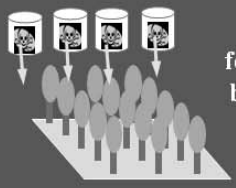
a. Chemicals used as technical mixtures.

b. Chemicals emitted by a human activity

c. Chemicals likely to be present in the environment as the result of multiple emissions

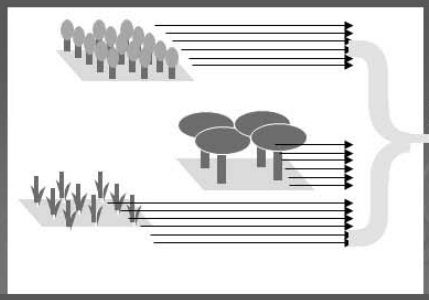
The example of pesticide mixtures

Many active ingredients may be present in the same formulation



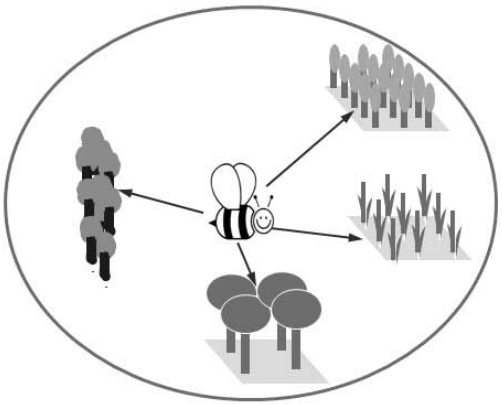
Many formulations may be applied on the same crop

Many crops may be present on the same agricultural area



Final mixture

The terrestrial ecosystem



The community potentially exposed is mouving within the area.

Exposure and mixture cpmposition is a function of the variable concentrations on different systems in the area (e.g.: treated crops, non crop vegetation, etc) as well as of the behaviour and the ecological role and niche of the organism.

Predicting mixture composition

Even for substances emitted simultaneously, the environmental fate (distribution and persistence) may be different for any individual component of the mixture.

Therefore, the composition of the mixture in the environment may by completely different from those of the originally emitted mixture and highly variable in space (particularly in different environmental compartments) and in time.

This prediction is generally made by modelling for individual substances. It is expected that, at concentrations present in the environment, distribution of each component of a mixture is not influenced by the other components.

Different objectives for different regulations

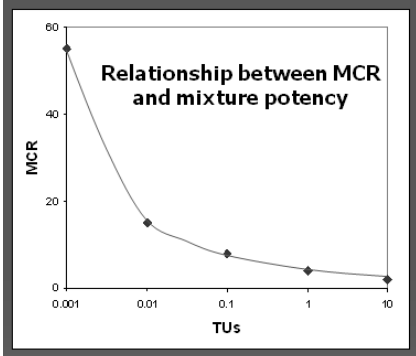
Approaches to assess mixture composition for regulatory purposes may be different as a function of the objective of the assessment.

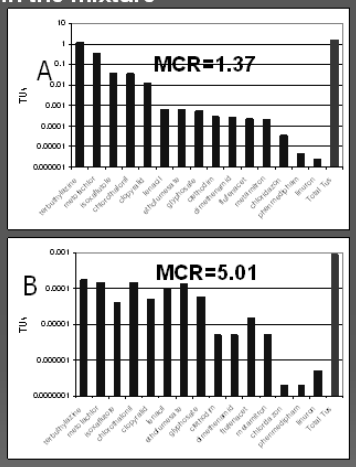
For hazardous chemical control (e.g. REACH) mixture exposure can be estimated as the result of a given process that would produce a specific emission into a generic environment assumed as representative of European conditions.

For the WFD, mixture assessment is the result of site specific measurements and the conditions that would produce effects on the real environment that must be taken into account case by case, for each individual water body.

The Concept of MCR
Maximum Cumulative Risk (Price, 2011)

MRC= Cumulative Toxicity/Maximum Toxicity from One Chemical
N<MCR<1 N=number of chemicals in the mixture





An experimental example:
Effects on algal toxicity of a mixture of the same pesticide assemblage in surface water of an agricultural basin in April (A) and in October (B).
Number of chemicals explaining 95%0f the total TUs:
A=2
B=8

This simplifies the management of the most dangerous mixtures

The knowledge needs

- **Improving knowledge on toxicological modes of action**
- **Improving knowledge on chemical interactions**
- **Improving knowledge on effects at biological community level (ecological interactions)**

The need for pragmatic proposals

The present knowledge on ecotoxicological effects of mixtures allows assuming the Concentration Addition (CA) approach as a default conservative model for environmental protection.

Thanks for your attention

"Cumulative risk assessment: How and when? Approaches for future strategies on mixtures" Outcomes of the December 2010 CEFIC Workshop

WHO OECD ILSI/HESI International Workshop on
Risk Assessment of Combined Exposures to Multiple Chemicals
Paris, February 15-16, 2011

Carlos Rodriguez
Procter & Gamble, Brussels

CEFIC MIAT

- **CEFIC: European industry association of chemicals producers**
- **CEFIC Mixtures Ad Hoc Team (MIAT) formed in Spring 2010**
- **Purpose: Develop strategies for addressing issues related to risk assessment and risk management of chemical mixtures (combined exposures to chemicals)**

CEFIC MIAT

Members

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Bausen Melanie BASF
Carney Edward W Dow
Corinna Weinz Bayer
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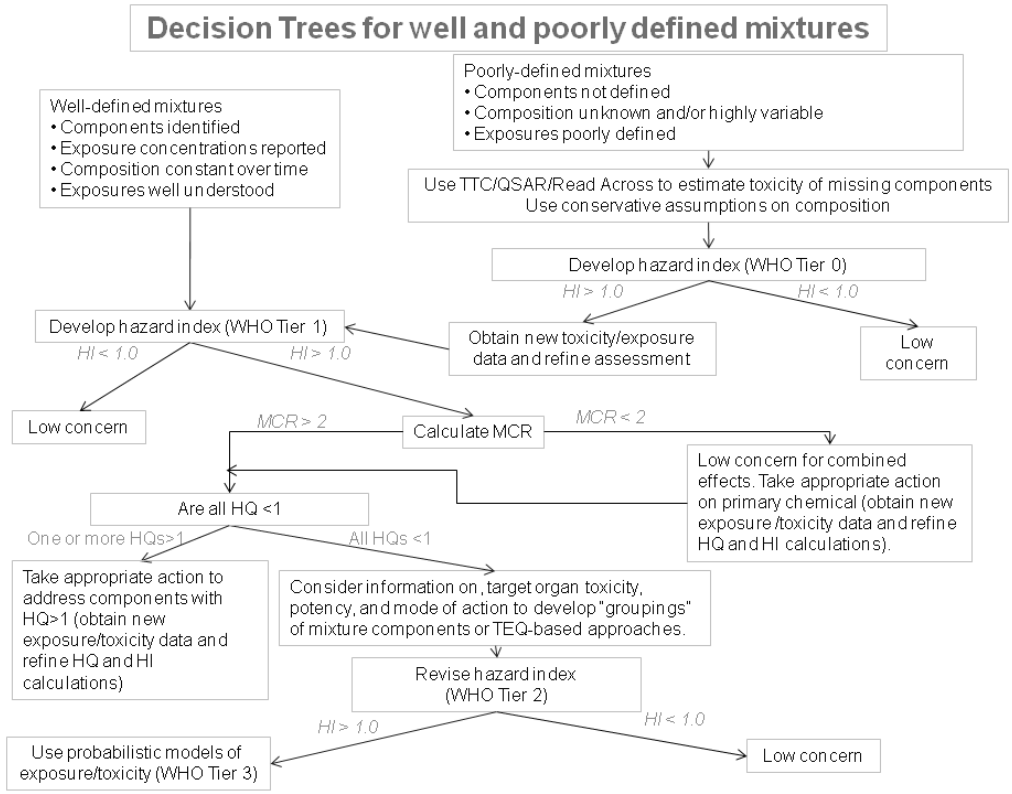
Rodriguez Carlos Procter & Gamble
Melching-Kollmuss Stephanie BASF
Stropp Gisela Bayer HealthCare
VAN WIJK Dolf CEFIC
Wheeler James Syngenta

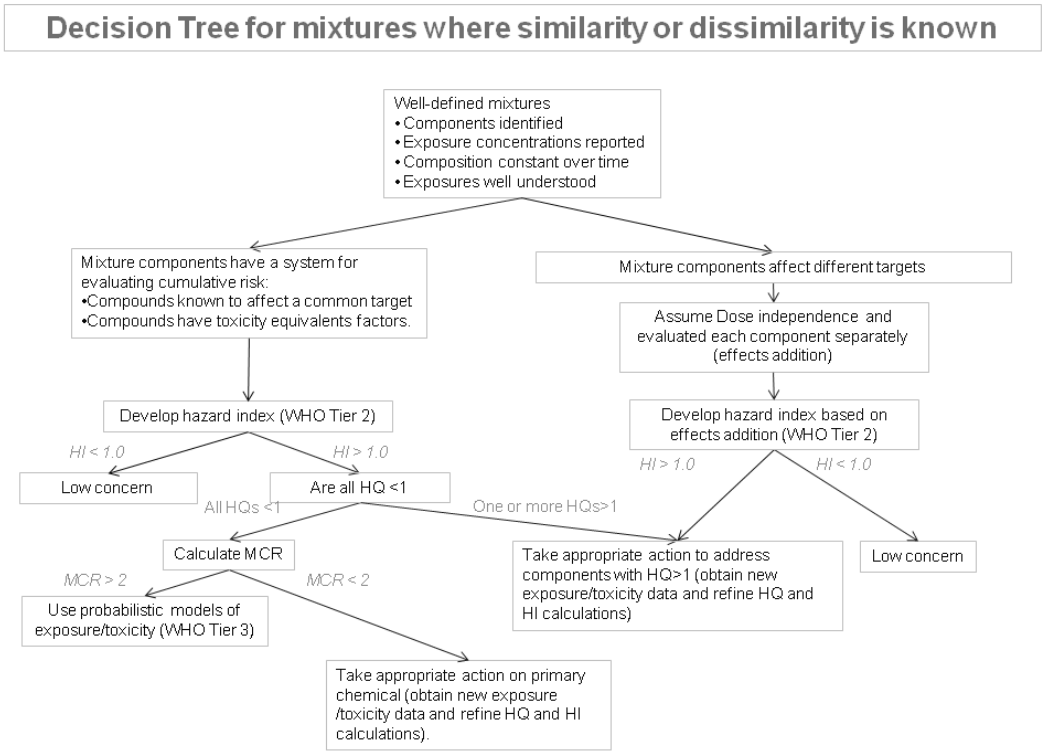
CEFIC MIAT

- Activities:
  - Comments to EC – commissioned "State of the Art Report on Mixture Toxicity"
  - Participation at CARACAL organised workshop (Brussels, June 2010)
  - Information for EC Scientific Committees opinion on toxicity and assessment of mixtures of chemicals
  - Development of prioritisation tool and approaches
  - Workshop (Brussels, December 2010)

CEFIC MIAT Workshop December 2010

- **Workshop: "Cumulative Risk Assessment: How and When? Approaches for future strategies on mixtures"**
- **Audience: EC Regulatory Community**
- **Speakers: Academic Experts and MIAC**
- **Discussion:**
  - **Human health and environmental aspects**
  - **Use of knowledge across sectors (e.g., pharmaceuticals)**
  - **Endorsement of WHO/IPCS general framework**
  - **Terminology (e.g., "low dose")**
  - **Proposal of "decision tree" tool for prioritisation**





Decision Tree

Compatible and consistent with WHO framework

Components on the decision tree include existing approaches:

- Tiered approach
- Hazard Indices and Hazard Quotients
- Additive and independence models of toxicity
- Refined additive models (MOA)

One new component is the concept of the Maximum Cumulative Ratio (MCR) - [P. Price, Dow]:

- MCR estimates "how much" of the mixture toxicity comes from the most toxic component

$$MCR = \frac{\text{Mixture Toxicity}}{\text{Toxicity from Most Toxic Component}}$$

- MCR is calculated using the same data that determines the Hazard Index

$$MCR = \frac{\text{Hazard Index}}{\text{Largest Hazard Quotient}}$$

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- **Discussion**
  - **One or a few components often drive toxicity in a mixture**
    - Environmental case studies (L. Posthuma, RIVM)
    - Human health case studies (P. Price, DOW)
  - **European data on combined exposures should be investigated using the prioritization tools**

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- Some key points to go forward
  - Common terminology
  - Avoid silos and integrate knowledge (regulations, industry sectors, scientific disciplines, regions)
  - Identification of relevant information gaps and evaluation of data quality
  - Integration of relevant existing regulations in an overall framework
  - Tiered and prioritisation approaches
  - Liability and responsibility

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THANK YOU