

9th Annual ECOPA Workshop

Improved REACH implementation using new science based tools? 29 November, 2008

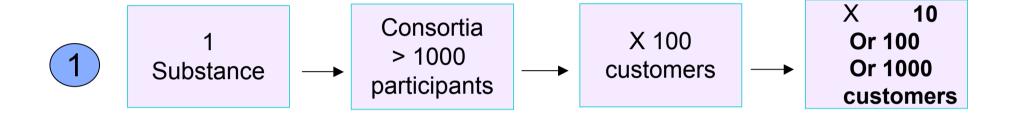
Bruessel



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The Challenges





2 REACH is about information, not testing!





Increased acceptance of high quality industry research as basis for policy making



New policy scenario - increased complexity; less animal tests =>diffuse results => increased precaution

- ease if data generation => lack of understanding => media attacks

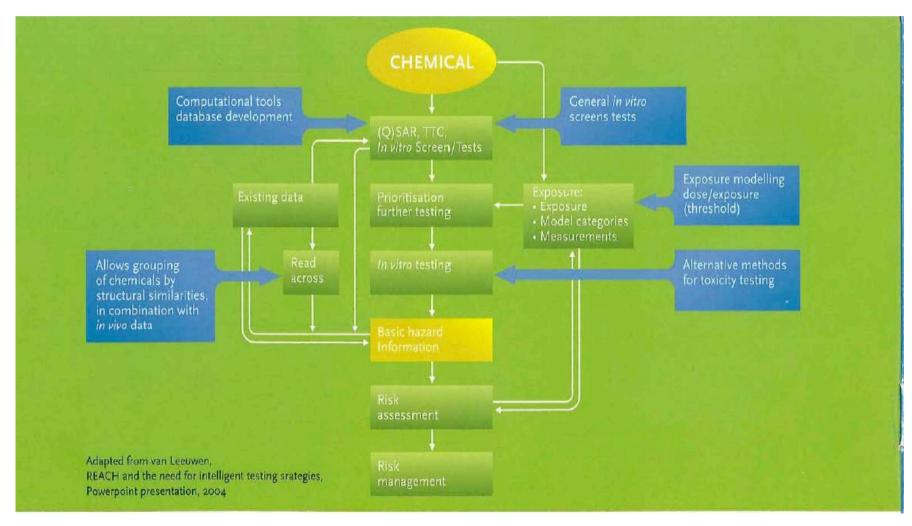
- bias in science today towards identifying additional adverse effects of chemicals

=> challenge to risk based decision making, impact on innovation

Refocus of LRI in 2007 **Health Impact Intelligent Testing and Societal Acceptance** of Complex of New **Assessment Environments Technologies and Products**

Map of LRI sponsored research on the Intelligent Testing flow chart







Cefic LRI projects 2007

Animal alternatives (3Rs)

Computational

tools Intelligent

Endocrine testing

disruption strategies

•New design for reproduction toxicty studies in mammals (replace standard 2-gen reprotox study –TG416

•Work with OECD on computational toolbox

•Contributions within OECD Endocrine disrupter Testing and Assessment framework (e.g. hershberger, uterotrophic, OECD 407))



Cefic LRI projects 2007

Animal alternatives (3Rs)

Computational

tools Intelligent testing

Endocrine disruption

strategies

- •Reduction on number of animals by means of innovative technologies and computational tools (AMBIT data management and OECD tool box)
- •Results used by the European Chemicals Bureau (ECB) to build tools such as ToxTree and ToxMatch.
- •New design for reproduction toxicty studies in mammals (replace standard 2-gen reprotox study –TG416
- •Through Cefic LRI, REACH Implementation Projects (RIPs) have integrated the 3Rs principle

Computational Tools



CEFIC LRI

- Validition criteria for (Q)SARs (Setubal, 2002)
- AMBIT Discovery (Joanna Jaworska & IdeaConsult)
- AMBIT XT (Joanna Jaworska & IdeaConsult)
- Gold-Standard bioconcentration database and repeat-dose toxicity database

ECB

- TC NES (Q)SAR Ad hoc Working Group
- (Q)SAR Work Programme (Andrew Worth)
 - e.g. ToxMatch & ToxTree (w/ IdeaConsult)
- Reporting formats: (Q)SARs and (Q)SAR predictions
- (Q)SAR database

OECD

- Existing Chemicals (Bob Diederich, Gill Veith)
- Validation criteria (Q)SARs
- Read Across and Categories guidance documents
- Proof of principle Toolbox



Cefic LRI strategic themes 2008

Outreach

Nanomaterial safety testing (human health, environment)

Acceptance of new technologies and products

- Nano safety evaluation of existing OECD guideline test and their value for risk assessment of nanomaterials
- Male reproductive health and toxicogenomics
- Develop harmonised, global standards for the assessment of NP in the environment
- Data from testing in toxicological framework and societal acceptance of risk assessments





- Requirement under REACH for higher tonnages
- New design of mammalian reprotoxicity studies, the « Extended 1-generational vs 2-generational study» was proposed:
 - Cooperation with EPAA, OECD and government bodies
 - Development of triggers/waivers by ECETOC Task Force (www.ecetoc.org)
 - Posibility of approximate reduction of 1500 animals per compound

Current Draft 5 inclusions



 Default of cohort 1, 2 and 3 for pesticides <u>and</u> for industrial chemicals are <u>mandatory</u>, ignoring tiered assessment approach.

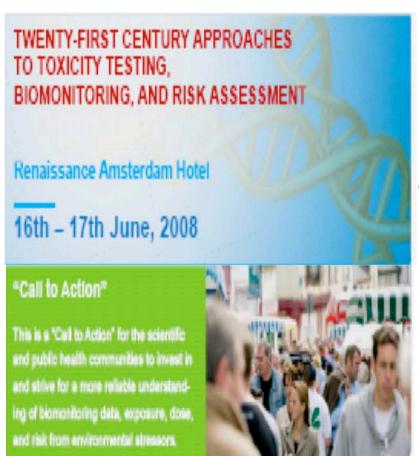
Draft 5 remains to be discussed at the WNT OECD.

Drawbacks of Draft 5:

- Inclusion of endpoints suggested would result in a complex design for routine evaluation of industrial chemicals (e.g. > 2800 tier 1 chemicals). Only a small number of laboratories would be capable of conducting such a study.
- It would increase the potential for additional animal usage in further studies
- It will increase the cost for Annex X reproductive testing (currently OECD 416) per substance from 350.000 Euro to approximately. 700.000 - 800.000 Euros

Twenty-first century approaches to toxicity testing, biomonitoring and risk assessment





ICCA-LRI Global Research Strategy

- Continuation and extension of biomonitoring conferences
- Refocus risk assessment framework to understanding of environmentally relevant doses, enabled by new technologies (e.g. toxicogenomics)

Outcomes

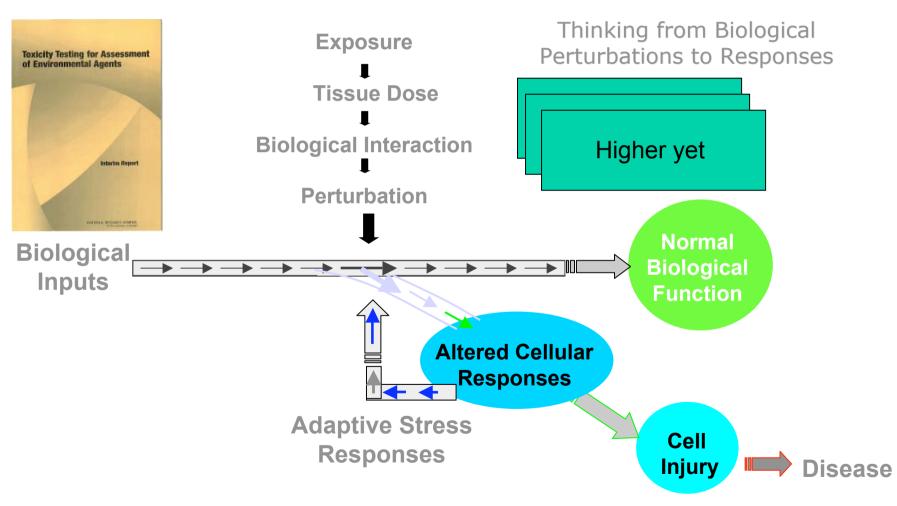
- Role of new molecular biology techniques on the assessment of impacts of various environmental stressors in relation to human health
- Awareness within the industry of innovations in toxicology testing

Message

 To engage academics, regulators, government and industry in the appropriate application of innovative toxicology

The Future Paradigm: Integrating Technology and Risk Assessment





Speakers affiliations



Government bodies

- Connecticut Department of Health, USA
- Environmental Protection Agency (EPA), USA
- European Commission, JRC, Italy
- Federal Environment Agency (UBA), DE
- National Institutes of Health, USA
- Centers for Disease Control and Prevention, USA
- The National Institute for Public Health and the Environment (RIVM), The Netherlands
- Flemish Institute for Technological Research (VITO), BE

Research Institutions

- University of Erlangen-Nürnberg, DE
- The Hamner Institutes for Health Sciences, USA
- University of Ottawa, CA
- University of Maastricht, NL
- Children's Hospital Osnabrück, DE



21st Century Approaches

Janus Challenge for risk assessment

opportunity to improve
Less testing through clustering of chemicals
activating similar pathways

threat of hazard-based decisions

More testing or by-pass of risk assessments by scare and media

Science has one question and one answer plus 2 new questions



Next requests for testing are around the corner beyond 2010

... next requests for testing are currently developed



→ WHO Children Environment & Health - 2009

Next 5-year cycle

EU Environment and Health Action Plan - 2010

Next 5-year cycle

Major points:

- Indoor air policy: focus on chemicals and products
- Human Biomonitoring, new risk assessment methods
- Precautionary principle extended
- Refocus on vulnerable population

Plus scientists are pushing for mixtures, late effects and low doses



Cefic LRI strategic themes 2008/2009

Animal alternatives (3Rs)

Assessment of PBTs

Computational tools

Intelligent testing strategies

Acceptance of new technologies and products

Nanomaterial safety testing (human health, environment)

Endocrine disruption

Developmental neurotoxicity

Health impact of complex environments

Human biomonitoring

Interpretation of 'omics' data

Outreach

OECD Conceptual Framework* for the Testing and Assessment of Endocrine Disrupting Chemicals Industry-sponsored development and validation activities

Level 1

Sorting & prioritization based upon existing information

- physical & chemical properties, e.g., MW, reactivity, volatility, biodegradability,
- human & environmental exposure, e.g., production volume, release, use patterns
- hazard, e.g., available toxicological data

Level 2

In vitro assays providing mechanistic data

- ER, AR, TR receptor binding affinity
- Transcriptional activation
- Aromatase and steroidogenesis in vitro
- Aryl hydrocarbon receptor recognition/binding
- QSARs

- -High Through Put Prescreens
- Thyroid function
- Fish hepatocyte VTG assay
- Others (as appropriate)

Level 3

In vivo assays providing data about single endocrine mechanisms and effects

- Uterotrophic assay (estrogenic related)
- Hershberger assay (androgenic related)
- Non -receptor mediated hormone function
- Others (e.g. thyroid)

- Fish screening assay

Level 4

In vivo assays providing data about <u>multiple</u> endocrine mechanisms and effects

- enhanced OECD 407 (endpoints based on endocrine mechanisms)
- male and female pubertal assays
- adult intact male assay

- Fish sexual development assay
- Frog metamorphosis assay

Level 5

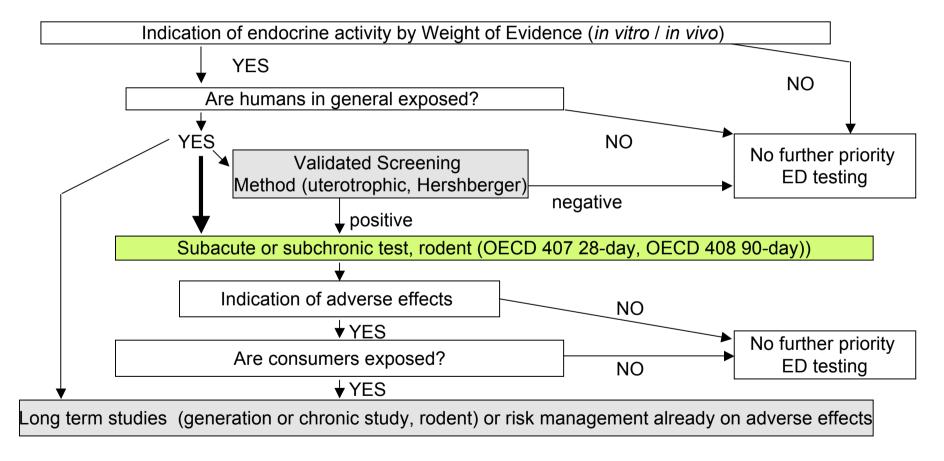
In vivo assays providing data on effects from endocrine & other mechanisms

- 1-generation assay (TG415 enhanced)¹
- 2-generation assay (TG416 enhanced)¹
- reproductive screening test (TG421 enhanced)¹
- combined 28 day/reproduction screening test (TG 422 enhanced)¹
- 1 Potential enhancements will be considered by VMG mamm

 Partial and full life cycle assays in fish, birds, amphibians & invertebrates (developmental and reproduction)

^{*} Framework based on 6th meeting of OECD EDTA Task Force, see www.oecd.org

Decision tree for toxicological testing of substances with indication of endocrine activity





Exact timing is part of the solution



