

LRI in Motion: ToolBox and new projects 2009-2010

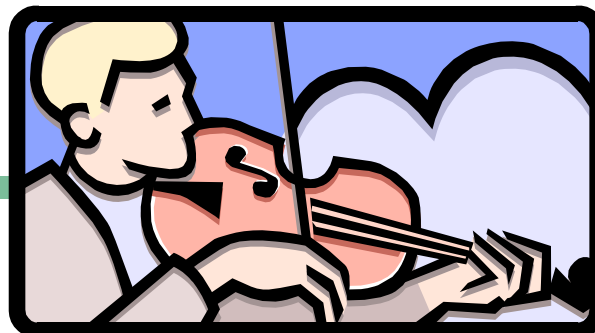
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Outline



LRI ToolBox

- **A selection of 12y. of research in a box**

2010-2011 projects

- **End 2010- early 2011: 6 new projects**
- **LRI strategy fit**
- **Key chemical policy issues focus**

LRI Toolbox



- **Repository of 14 tools (12y research)**
- **State-of-the-art, easy to use, QA**
- **Freely available to all (web based, downloads)**
- www.cefic-lri.org
- **Organized by areas (human, eco, databases, models)**
- **E.g. for RA and regulatory filing (REACH, GHS)**
- **Significant saving animal use + xxMio Eur testing**



LRI Toolbox

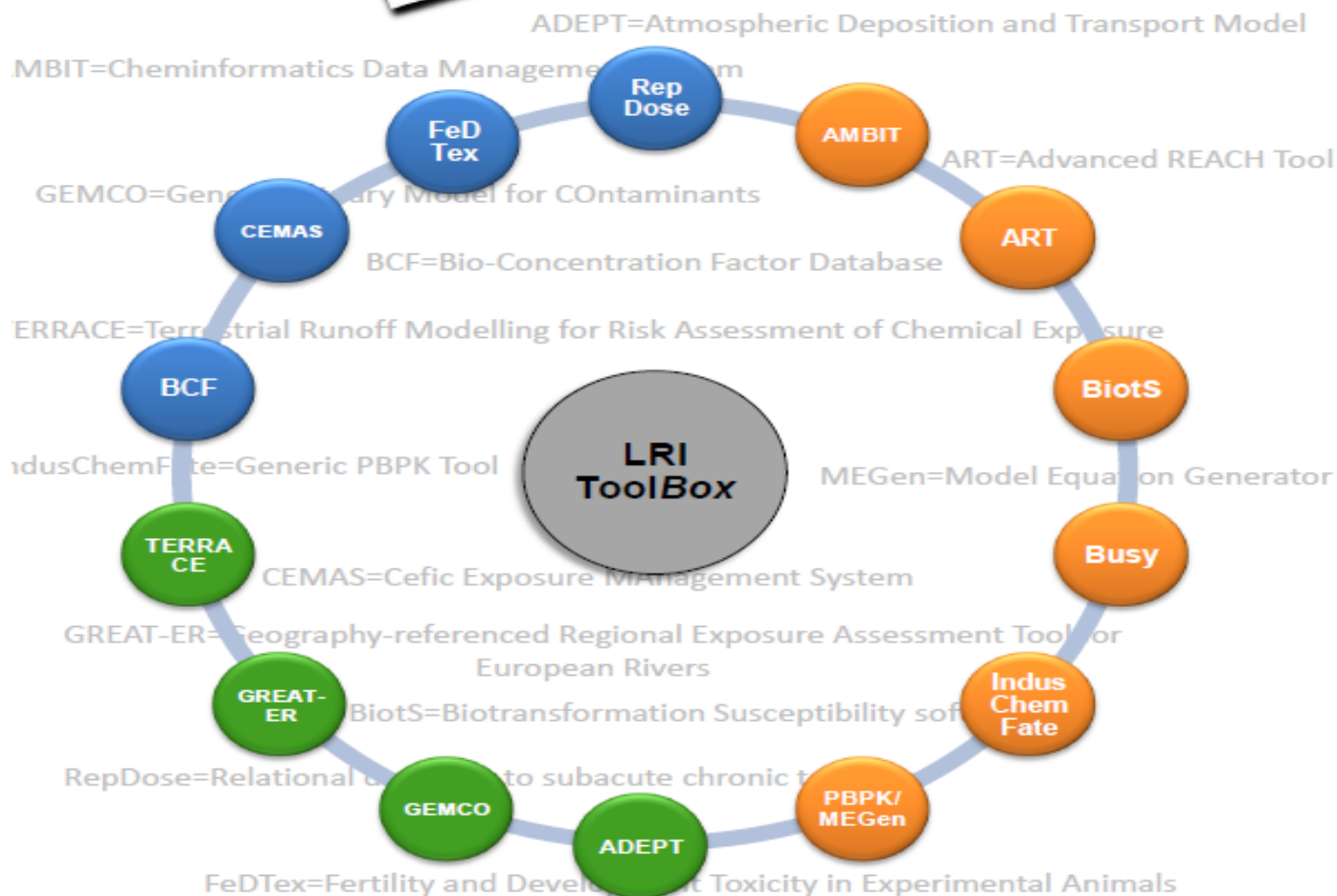
- **Human health databases**
- **Human health models**
- **Environmental models**



The LRI Toolbox



LRI ToolBox





Human health databases

- **BCF database**

Bio-Concentration Factor database

- **CEMAS database**

Cefic Exposure Management System

- **FeDTex**

Fertility and Developmental Toxicity in Experimental Animals

- **RepDose**

RepDose



LRI
*The Long-range
Research initiative*

“Need a quality relational database for repeated dose endpoints ?”



Example: RepDose

Tuesday, 16 February 2010



The database for the analysis of relationship between chemical function groups/categories and target organs in repeated dose studies.

[User guide](#)

[About Repdose](#)

[Contact](#)

[Impressum](#)

Project partner



Please enter your email and password.

Email

Password

Project

Ambit



[Password forgotten](#)

[New member](#)

RepDose



- **Relational database on subacute to chronic toxicity**
- **Developed by Cefic LRI and Fraunhofer ITEM**
- **A relational database on experimental NOEL/LOEL values**
- **Contains quality-assured data on subacute to chronic toxicity from nearly 2300 studies on 655 chemicals**
- **Useful in preparing dossiers and classifying compounds under REACH and GHS**
- **116 registered users only in 2010**
- **www.fraunhofer-repdose.de**

Main researcher: Dr. Inge Mangelsdorf (ITEM, DE)⁹



Human health models

- **BiotS:** Biotransformation Susceptibility software
- **Busy:** Bayesian Uncertainty SYstem
- **IndusChemFate:** Generic PBPK Tool
- **PBPK/ MEGen:** Physiologically-Based Pharmacokinetic Modelling / Model Equation Generator
- **AMBIT**
- **ART**

AMBIT



LRI
*The Long-range
Research initiative*

**“ Need quality support for your decisions
by chemical grouping and QSAR? ”**



AMBIT XT

A computational tool for data management



AMBIT

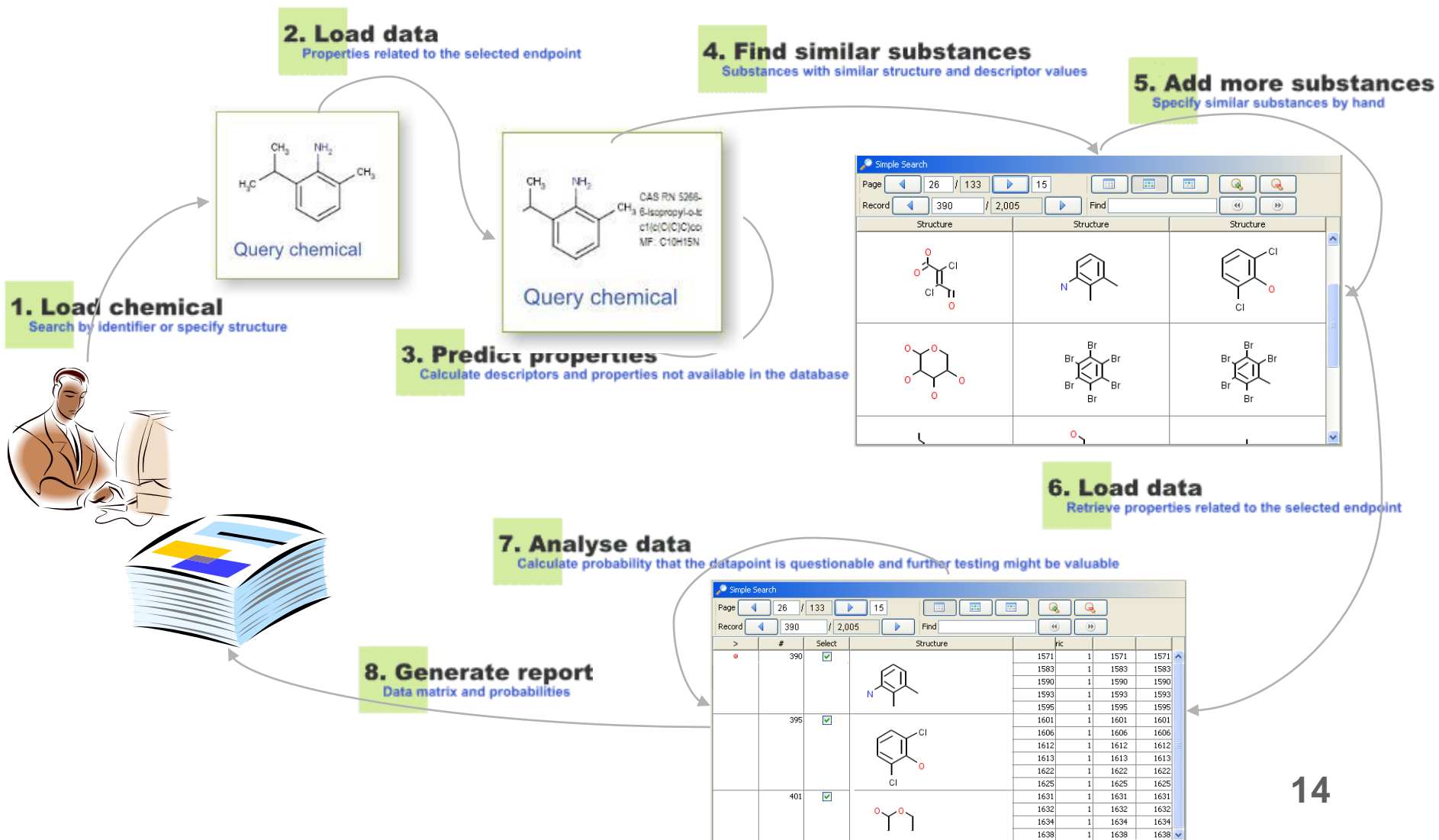


- **A software for chemoinformatic data management**
- **Developed by Cefic LRI, P&G, and IdeaConsult (BG)**
- **Stores more than 450.000 chemical structures and their identifiers such as CAS, Einecs, Inchi numbers.**
- **REACH applicable PBT and analogues assessment**
- **Results preformatted REACH**
- **<http://ambit.sourceforge.net/>**

Main researcher:

Dr. Joanna Jaworksa (Procter & Gamble, BE)

Datapoint evaluation workflow



ART



LRI
*The Long-range
Research initiative*

“Need an inhalation exposure estimation model?”

ART - Advanced REACH Tools



My Scenarios

Science

Support

Consortium

English | Deutsche | Francais | Nederlands

Welcome to the Advanced Reach Tool 1.0

Chemical Safety Assessments can be complex and time consuming. While Tier I models estimating exposure are available, should they be unable to show safe use, then refinement with more data or better assumptions is the only way forward. The Advanced REACH Tool (ART) version 1.0 incorporates a mechanistic model of inhalation exposure and a statistical facility to update the estimates with the user's own data. This combination of model estimates and data produces more refined estimates of exposure and reduced uncertainty.

The ART project has been conducted in close collaboration with a range of stakeholders from industry and member states. The use of ART for workers exposure assessment under REACH is described in ECHA' updated Guidance on [Information Requirements and chemical safety assessment](#).

ART can of course be used for exposure assessment in general, also beyond the REACH domain.

Existing users log in:

Email

Password

Log in

New user? [Register here](#).

Forgotten your password? Type in your email address above then [click here](#).

Latest News

History

First discussions on the need for a higher tier exposure model ... [\[more\]](#)

Future ART developments

ART is an evolving system that is anticipated to further develop in the future ... [\[more\]](#)

ART presentations

The basic concepts of ART and illustrative worked examples will be presented ... [\[more\]](#)

ART training

An ART training module is currently under development. It is anticipated ... [\[more\]](#)

Contributors to ART



ART



-
- **Advanced REACH Tool**
 - **Developed by Cefic LRI and TNO, HSL, IOM, BAuA, NRCWE and Utrecht University.**
 - **A mechanistic and Bayesian model of inhalation exposure**
 - **Facilitates higher tier exposure assessment under REACH guidance**
 - **Simple, easy-to-use, cost-effective**
 - **An ART training module is available**
 - **<http://www.advancedreachtool.com/>**

Main researcher: Dr. Erik Tielemans (TNO, NL) 17



Environmental models

- **ADEPT:** Atmospheric DEPosition and Transport model
- **GEMCO:** Generic Estuary Model for Contaminants
- **TERRACE:** Terrestrial Runoff Modelling for Risk Assessment of Chemical Exposure
- **GREAT-ER**

Example: GREAT-ER

GREAT-ER web directly from here. Webapplication hosted by **Intevation GmbH**'."/>

GREAT-ER
GEOGRAPHY - REFERENCED REGIONAL EXPOSURE ASSESSMENT TOOL FOR EUROPEAN RIVERS

A GIS Assisted Model For Environmental Risk Assessment and Management of Chemicals in River Basins.

Publically available scientific software. Subject to the included End User Licence Agreement.

Start [GREAT-ER web](#) directly from here.
Webapplication hosted by **Intevation GmbH**

***GREAT-ER 1.0 (1999)** was sponsored by the Environmental Risk Assessment Steering Committee (ERASM) of the Association Internationale de la Savonnerie, de la Détergence et des produits d'Entretien (AISE) and the Comité Européen des Agents de Surface et de leurs Intermédiaires Organiques (CESIO), in cooperation with the UK Environment Agency and*

GREAT-ER



- **Geography-referenced Regional Exposure Assessment Tool for European Rivers**
- **Developed by Cefic LRI, INTEVATION (DE) and Cranfield University**
- **A model for environmental risk assessment and management of chemicals in river basins**
- **Designed for use at a post-screening level under REACH and the EU Water Framework Directive (WFD)**
- **More than 8.000 visits in 2010!**
- **www.great-er.org**

Main researcher: Dr. Frank Koormann (Intevation, DE)



LRI Toolbox: What's next?

- **Be transparent on key drivers**
 - **QA**
 - **Ease of use/Support**
 - **Applicability domain**
 - **Regulatory acceptance**
- **Dissemination (ongoing)**



Levels of key drivers

Tools	Quality assurance	Applicability domain	User-friendliness	Support by regulators
Human health databases				
BCF database	Yellow	Yellow	Green	Yellow
CEMAS database	Orange	Yellow	Orange	White
FedTex	Green	Orange	Orange	Orange
RepDose	Green	Yellow	Green	Orange
Human health models				
AMBIT	Green	Yellow	Green	Yellow
ART	Yellow	Yellow	Yellow	Green
BiotS	Orange	Yellow	Orange	White
Busy	Yellow	Yellow	Orange	White
IndusChemFate	Yellow	Green	Yellow	Orange
PBPK/MEGen	White	Yellow	Yellow	Orange
Environmental Models				
ADEPT	Yellow	Orange	Green	White
GEMCO	White	White	White	White
GREAT-ER	Green	Yellow	Yellow	Yellow
TERRACE	White	White	White	White

Green	very good/ very broad
Yellow	good/ broad
Orange	satisfactory/ limited/ pending
White	not applicable

The LRI Toolbox: What is next?



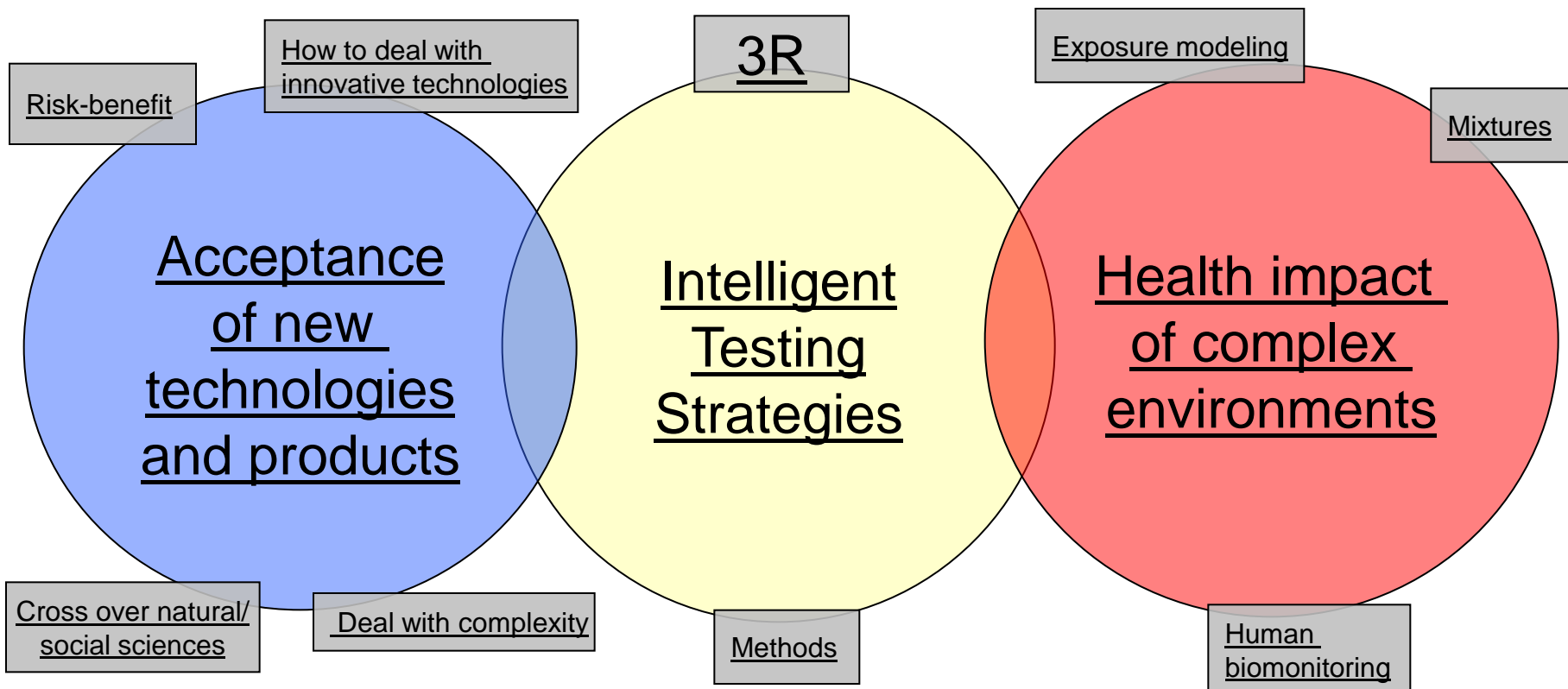
- **Beyond LRI: interlink + guidance**
 - OECD Environmental RA Toolkit**
 - OECD QSAR Application Toolbox**
 - WHO Human Health RA Toolkit**
 - OPENTOX**
 - ECHA Information Toolkit (eChem Portal)**
 - ECVAM *in-vitro* DB**
 - FP QSAR modeling tools: ORCHESTRA (box)**
(Ceasar, Osiris, Demetra, Scarlet, Rainbow,...)

LRI new projects 2010-2011





LRI Strategy Focus



Progress on 2010-2011 LRI Projects



4 critical issues addressed

Eco methodology (Intelligent testing)

New tools/'omics (Acceptance of new technologies)

**Mixtures in household, natural-synthetic, low dose
(Complex environments)**

Inhalation thresholds (ITS, Indoor Air Quality)

ECO17 – Evaluation of test methods for measuring toxicity to sediment organisms



Background

- Lack of methods for assessing potential effects on microorganisms, plants and animals from different taxonomic groups
- Development of acute and chronic sediment tests covering different trophic levels and exposure pathways are needed to better define the environmental risks posed by chemical in sediments

Why/Policy: relevant for REACH revision, ECHA impact

Objectives

- To improve scientific understanding of sediment toxicity
- To develop a guidance to assist regulators in selecting ecologically relevant endpoints to reflect the appropriate routes of exposure

Cost and Timing: 3 years / € 500,000

AIMT2 – Toxicogenomics as mechanistic readouts from in vitro studies



Background

- Toxicants elicit a characteristic pattern of gene expression which is dependent on mechanism of action
- *In vitro* models vs whole animal models may be able to provide comparable information

Why/Policy: both human/eco testing, reduction of animal testing

Objectives

- To investigate the use of toxicogenomic signatures as indicators of mechanisms of toxicity
- To demonstrate the utility of *in vitro* toxicogenomics in a predictive fashion

EMSG55 – Comparison of natural and synthetic endocrine active compounds



Background

- State-of-the-art Report on Mixtures Toxicity
- Little knowledge about the contribution of natural substances to environmental endocrine disruption
- Most available studies are only *in vitro* studies

Why/Policy?: exposure, future of RA/mixtures, REACH authorization

Objectives

- To identify potential endocrine activities of natural substances
- To suggest synthetic EAC for investigation
- To investigate the potential mixture effects with natural endocrine active substances on the reproduction and development of fish

EMSG56 – Combined low dose exposure to endocrine active chemicals



Background

- Current risk assessment methodologies insufficient to protect against combined exposure to endocrine active chemicals
- Hypothesis that the endocrine system is uniquely sensitive to low doses of exogenous hormonally active substances

Why/Policy?: addresses EU Council decision on mixtures issue, advocacy at EC level

Objectives

- To explore the ability of the endocrine system to compensate below the dose causing adverse changes and whether the response is the same between synthetic and natural chemicals
- To examine the effects of the simultaneous exposure to different endocrine active substances by using a whole mammalian model

B8 – Threshold of Toxicological Concern (TTC) for Inhalation Exposure



Background

- The TTC is based on the Threshold of Regulation
- Consideration of chemical structure in conjunction with toxicity data
- Systemic exposure following topical application of cosmetic products
- Application to inhalation exposure and risk assessment

Why/Policy?: indoor air policy, building guidance/advocacy for regulations, cy decisions on new products

Objectives

- To upgrade the RepDose databas on *in vivo* studies
- To address local and systemic effects
- Derivation of robust TTC values for inhalation exposure

B7 – Determining the nature of chemical substance additivity from household consumer products



Background

- Increasing realization of the need to consider the potential exposure to a substance as a consequence of its presence in multiple sources
- Different exposure routes, time scales and frequencies apply depending on the source

Why/Policy: mixtures high on SAICM/WHO/EU agenda

Objectives

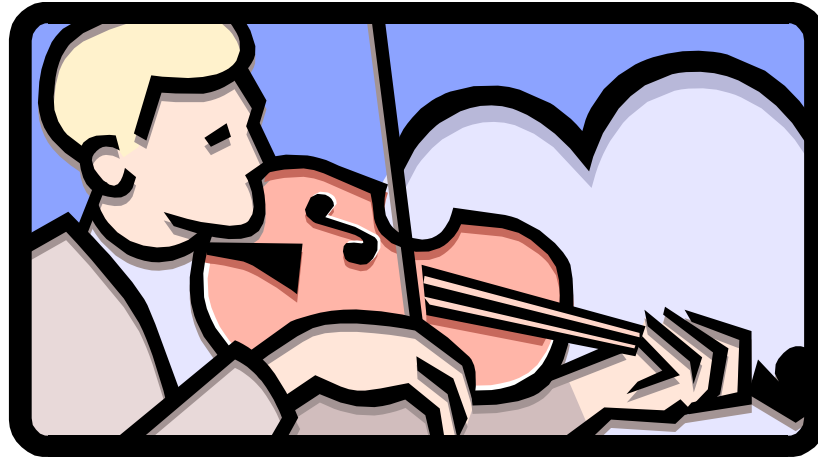
- To provide approaches which allow for quantitative estimations of aggregate exposure as realistic as possible
- To develop strategies to contrast the outcomes of exposure estimates with real exposures
- To identify key data gaps (including data quality issues) and parameters

2010-11 New Projects Summary



LRI area	Project title
Complex environments	<i>1A. Natural source and their combinatory effects with endocrine active chemicals</i>
	<i>1B. Combined low dose exposure to endocrine active chemicals</i>
Acceptance of new technologies	<i>2A. Determining the nature of chemical substance additivity from household consumer products</i>
	<i>2B. Genomics as mechanistic read-out from in-vitro systems</i>
Intelligent testing	<i>3A. Evaluation of test methods for measuring toxicity for measuring toxicity to sediment organisms</i>
	<i>3B. Inhalation Threshold of Toxicological Concerns (TTC)</i>

THE END



Thank you !

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