EUROPEAN COMMISSION

Community Research

SEVENTH FRAMEWORK PROGRAMME

RISKCYCLE

# Riskcycle – Aims and future impacts of the project

**Bernd Bilitewski**

**Veit Grundmann**

# RISKCYCLE
# Risk-Based Management of Chemicals and Products in a Circular Economy

A global network of information about the risk of chemicals and additives in products

Coordination Action, but not a Research Project!

# Content

- Issue of the project
- Objectives
- Why is the project necessary?
- Relevant key pieces of information
- How to gain the information?
- Where to find the information?
- Involved parties

# Involved parties and project partners

# Involved parties



- TUD: Dresden University of Technology. Prof. Bernd Bilitewski
- CSIC: Spanish Council for Scientific Research. Prof. Damià Barceló
- IRFMN: Istituto di Ricerche Farmacologiche Mario Negri. Prof. Emilio Benfenati

- UPC: Universitat Politècnica de Catalunya. Prof. Joaquim Casal
- CML: University of Leiden. Prof. Ester van der Voet
- IVL: Swedish Environmental Research Institute. Tomas Rydberg

- UCSC: Università Cattolica del Sacro Cuore. Prof. Ettore Capri
- URV: Universitat Rovira Virgili. Marta Schuhmacher
- HAW: Hamburg University of Applied Sciences Prof. Susanne Heise.

# Involved parties



- DTU: Technical University of Denmark. Henrik Fred Larsen
- BRGM: Orleans. Gael Bellenfant
- NORDEConsult Sweden: Stefan Rydin

- Institute of Clean Energy and Environmental Engineering, Shenyang, China, Prof. Li Rundong
- COPPETEC Rio de Janeiro, Brasil. Prof. Claudio Mahler
- Hanoi University of Science, Department of Chemistry, Vietnam. Prof. Nguyen Thi Diem Trang
- TERI. The Energy and Resources Institute. New Delhi, India. Col. Rakesh Johri

# Advisory Board

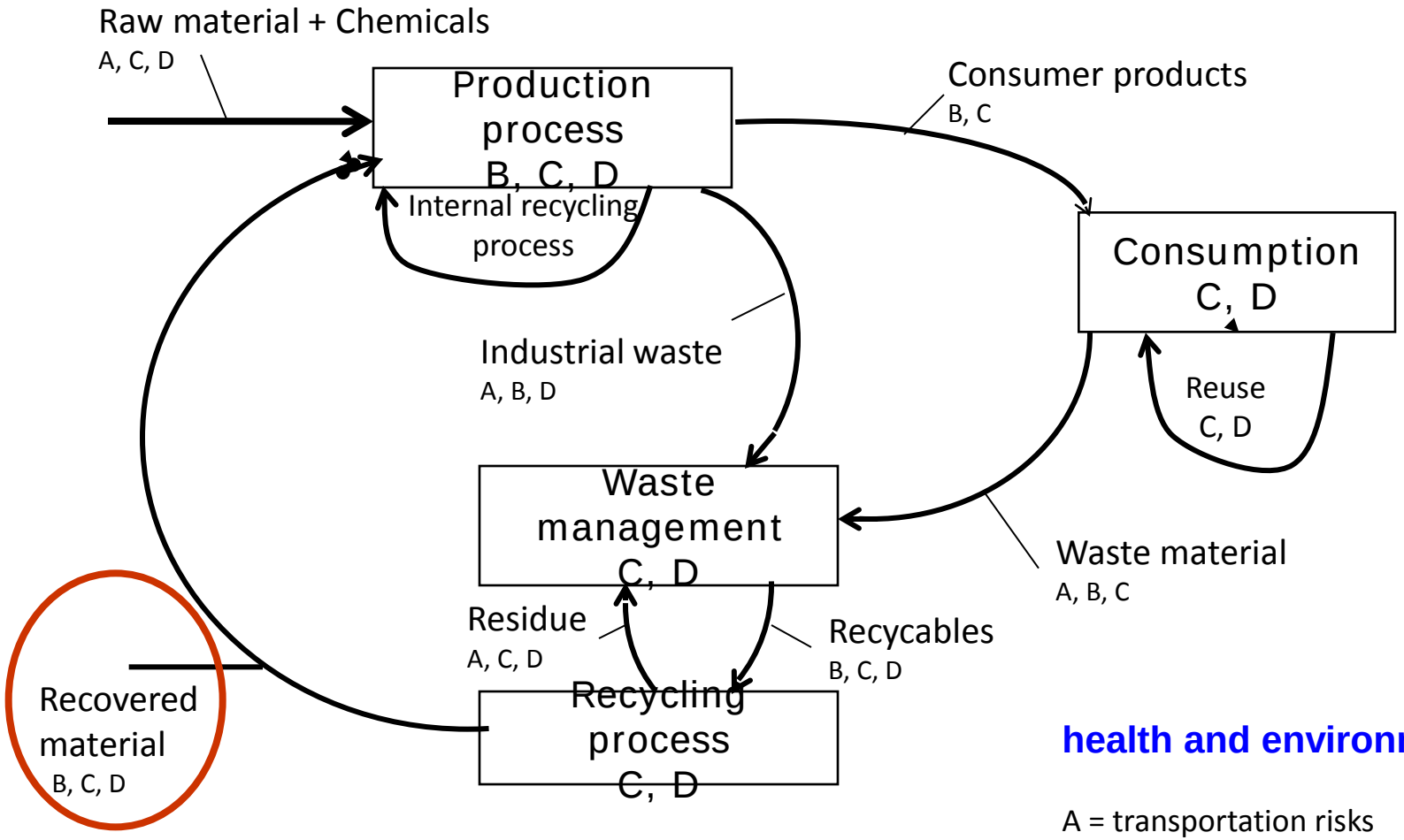


- Guarantee realism and quality of the action
- Consulting and advisory support

**Members: representatives from university, industry and administration**

- CEFIC
- OECD
- SCHER
- University of Wollongong (Australia)
- Chinese Academy of Social Science
- German Federal Agency for Environment
- TU Darmstadt
- Former Director General in the Federal Environment Ministry of Germany
- German Federal Institute of Risk Assessment

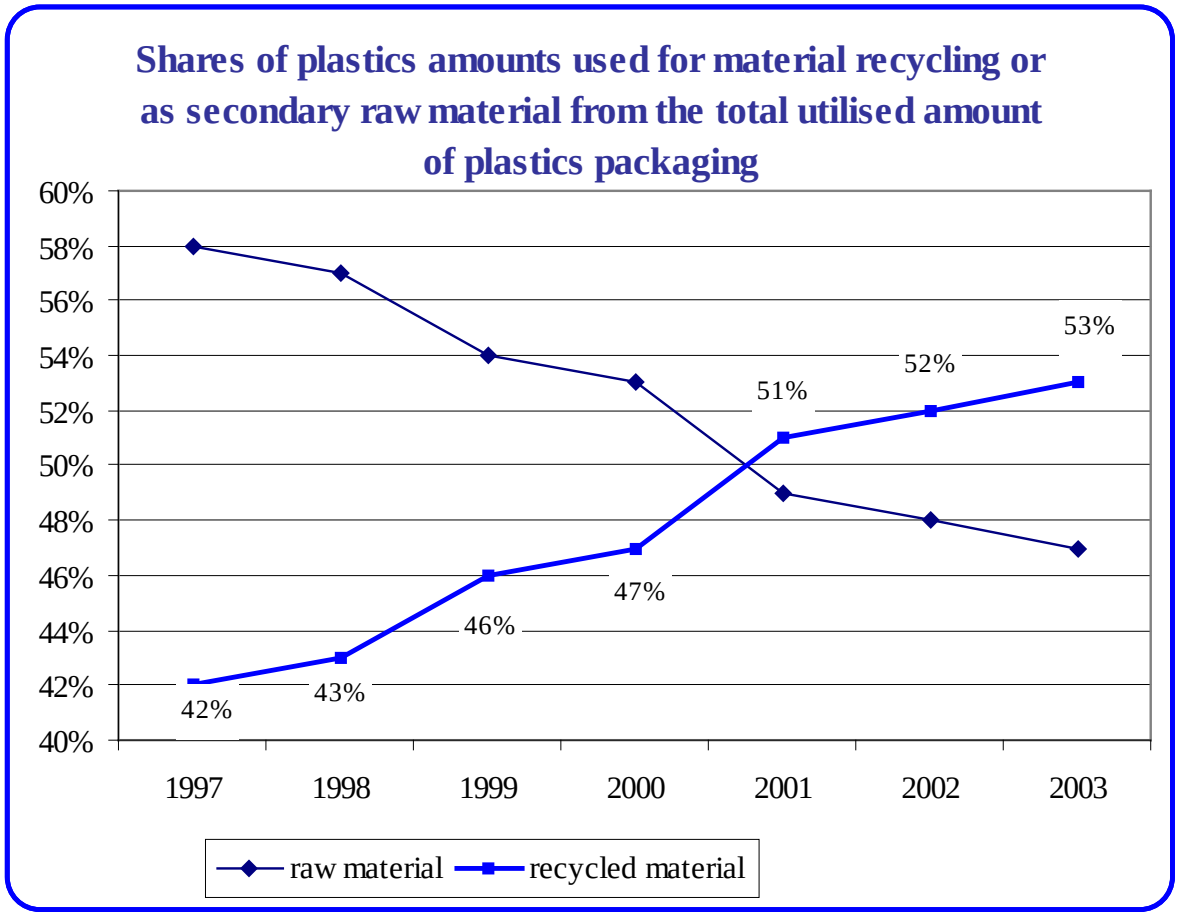
# Simplified material flow of a circular economy in a global scale




## health and environmental risks

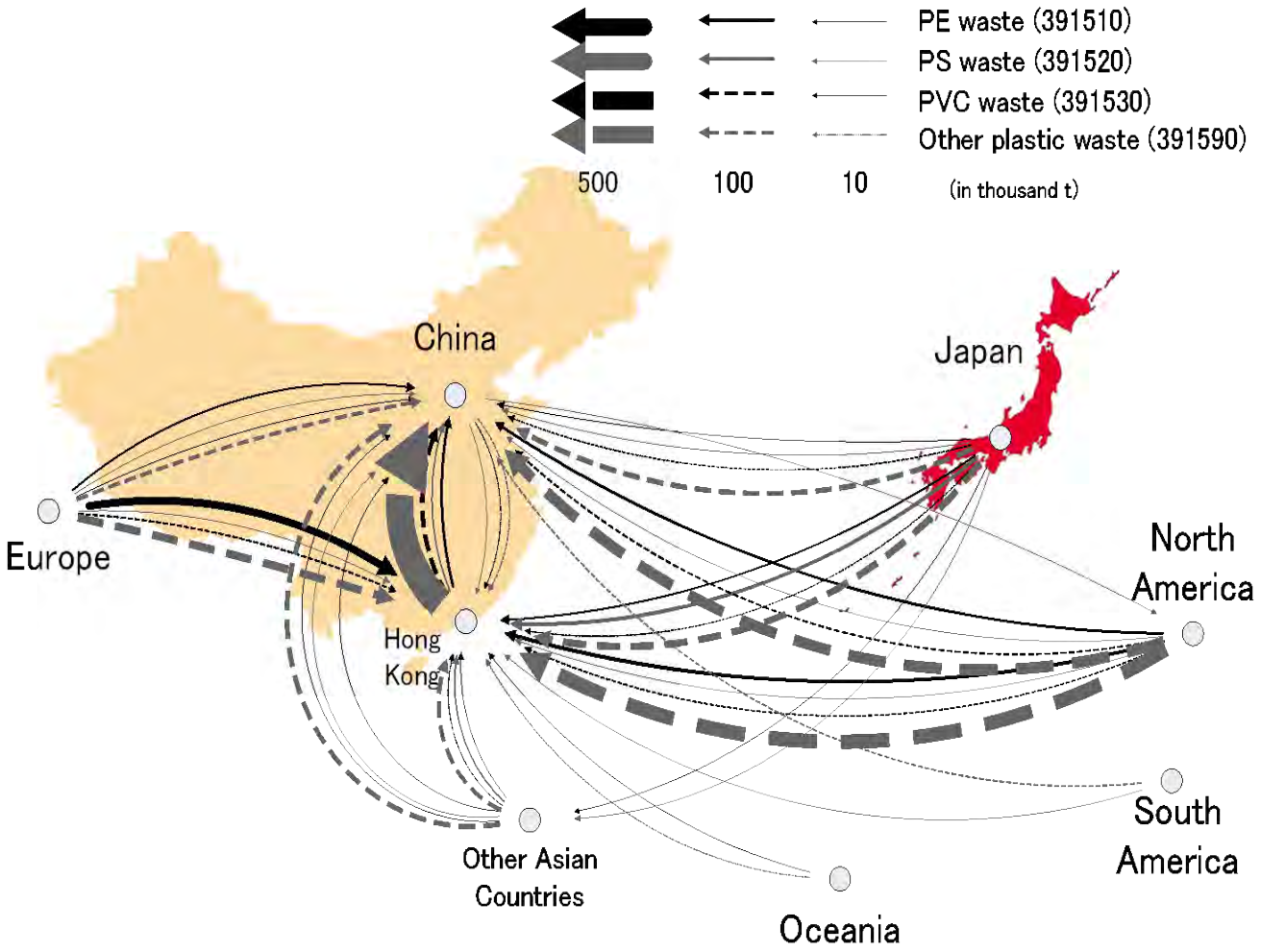
A = transportation risks
B = containing unidentified chemicals
C = unidentified health risks
D = environmental risks

# Plastics: recyclables become more important



# Paper: better known fluxes and behaviour of compounds

# Plastics: different types of plastics enormous amount of additives



**der spiegel 49/2009**


**Article illustrates WEEE „recycling conditions“ in Accra**

- worldwide trade
- dangerous circumstances
- wrong recycling technology
- unforseeable consequences

## Key pieces of information that were required and collected:

- Where are the critical points throughout the products life cycle for the release of chemical substances?
- Do methods or defined procedures find “critical points” or is there still the need to develop these methods?
- How hazardous and toxic is the material set free? Has an evaluation and control of the risk of the substances taken place?
- Has a development of strategies for limiting the environmental risks of these substances been done? If yes, for which substances?

## Key pieces of information that were required and collected:

- Do the effects caused by the chemicals have a global or only a regional meaning?
- Is the release of specific substances in the circular economy an actual risk or a perceived risk?
- Is the development of new "3R" methods (based on the principles of Refinement, Reduction and Replacement) as a modern alternative approach to the use of animals in safety assessment on a global scale known and supported by regulators?
- Is there a need to develop new safety assessment methods? Is there a need for 'global harmonisation' (GHS)? Is the 3Rs principle internationally sufficiently known and applied?

# The specific objectives of RISKCYCLE are:

- To exploit complementary elements needed with regard to the research objectives, methodologies and data of on-going as well as recently completed EU and international projects.

- To specify demands for tools for ecological design of consumer products, production, use and reuse of products and waste recycled to secondary material and products. Methods such as LCA, risk assessment and risk reduction strategies, environmental impact analysis, material flow analysis and economics related tools are considered to achieve socio-eco-efficient solutions.

- To create a powerful platform enabling discussion among all stakeholders on usage, risks, chemical properties of consumer products, labelling and the fate of certain chemicals in products traded, used and recycled in a global scale, identify problems and solutions.

# The specific objectives of RISKCYCLE are:

- To contribute to the UN Globally Harmonized System (GHS) for chemical substances and mixtures.
- To start with a conceptual development of a global strategy for a risk-based management of chemicals and additives in recycling and trade products.
- To identify alternative testing strategies and methods to avoid the enlargement and the outsource of animal tests to East and Southeast Asia
- To identify knowledge and research gaps for future research activities
- To consider the most effective way of ensuring continuing progress in this field involving EU and other partners at global scale including also international organisations.

# Where to find the information?

| | |
|---|---|
| Kick-off Meeting (Barcelona) | Month 10. 2009 done |
| Vietnam Workshop | Month 5. 2010 done |
| China Workshop | Month 11. 2010 done |
| Brazil Workshop | Month 5. 2011 done |
| India Workshop | Month 10. 2011 done |


**Final Conference (Dresden)** **8-9 May 2012**

**www.wadef.com**

# Publications



## Reports available on the project website:

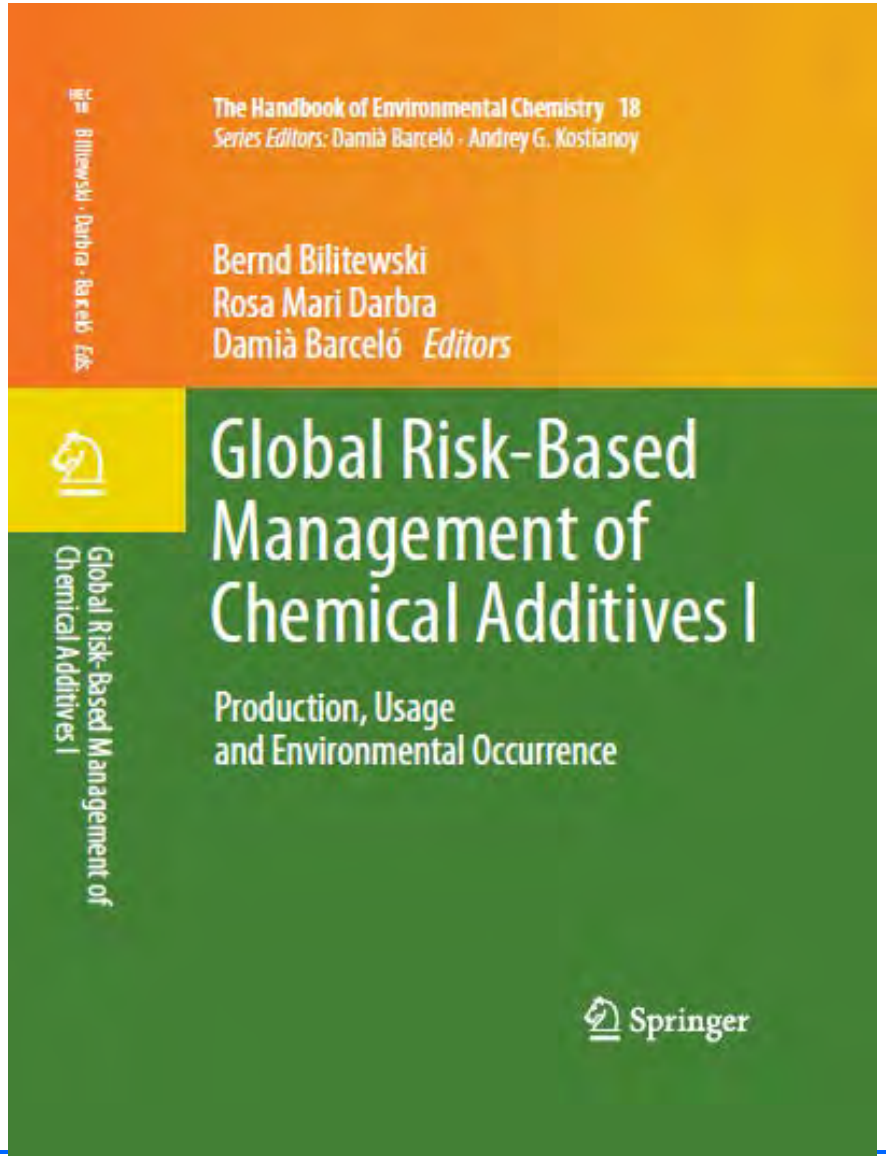
- Overview of environmental factor influence over additive exposure and release into the environment
- Review of models for predicting the concentration of chemicals in air, water and soil to human exposure, including mathematical and functional specification of the multimedia software
- Report containing a discussion on the identified criteria and their scores for alternative methods
- List of databases and meta-databases
- Report on the review of bioassays and biosensors and (Q)SAR models as candidate for the intended use
- Definition of risk scenarios and historical analysis
- Life Cycle Assessment of additives
- Meta-analysis of damage costs related to health, the built environment and the ecosystem

# Publications



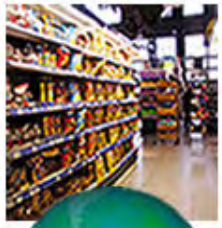
## Published books:

- The results of the investigations and the first project outcomes are published in the book: ***"Global Risk-Based Management of Chemical Additives I (Production, Usage and Environmental Occurrence)"***
- Additional results of the second project period will be published at the end of 2012 as part of the book, ***"Chemical Additives in selected industrial sectors at a global scale - Volume II (risk-based assessment and management strategies)".***



# Thank you for your attention!



Division of Technology, Industry and Economics

UNEP

# Chemicals in Products Project

**Kevin Munn**
Project Officer
UNEP/DTIE Chemicals Branch

RISKCYCLE Project
Dresden, 8 May 2012








# UNEP and chemicals

- Brief background on UNEP
  - UNEP's 6 subprogramme areas
- Multilateral environmental agreements and SAICM
- Chemicals in products activities under SAICM

# UNEP

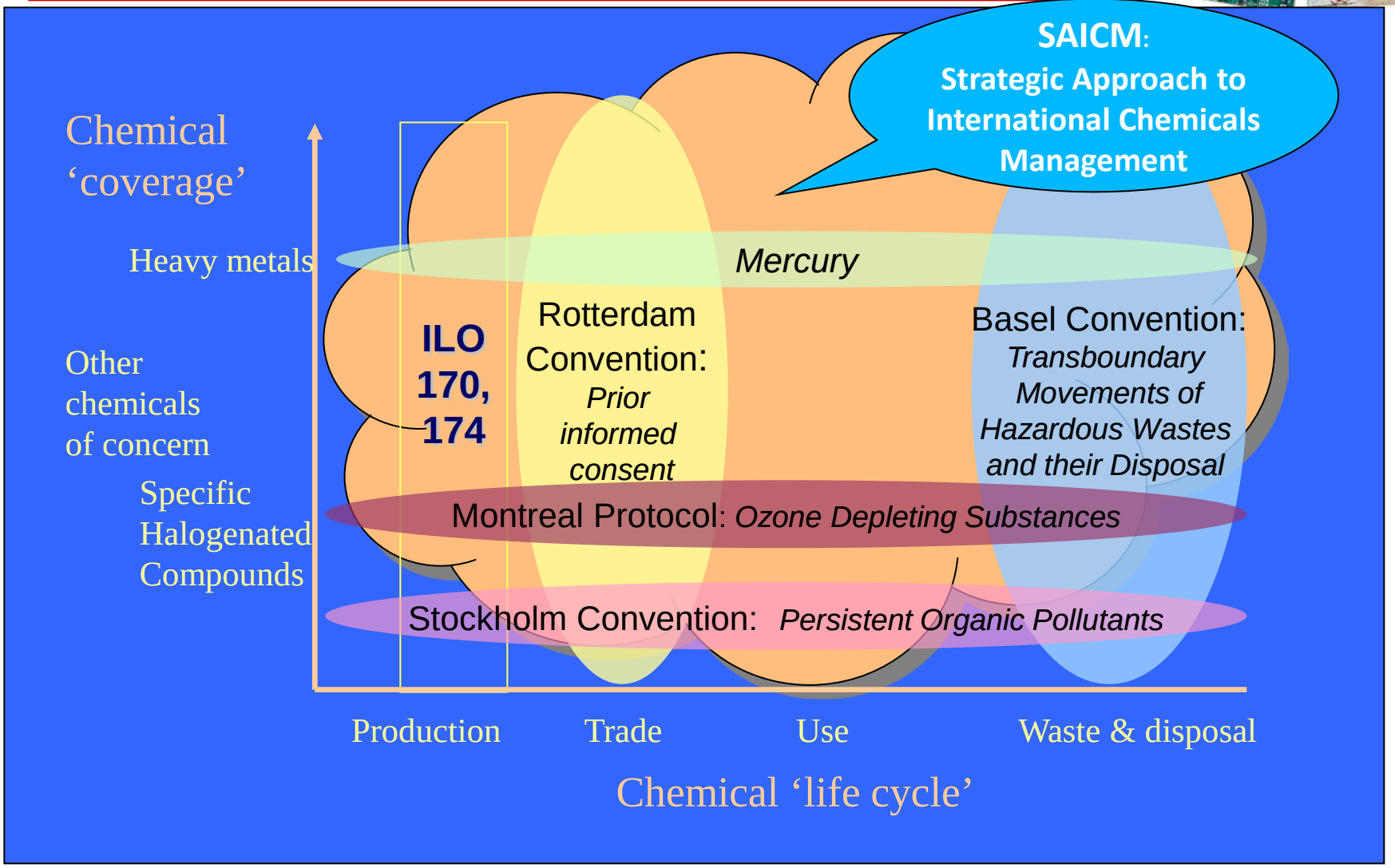
1972 – UN Director General directs UNEP to be the coordinator of environmental issues and the catalyst for environmental awareness and action in the UN system


2012 – UNEP subprogramme areas

Climate change
Resource efficiency
Environmental governance
Disasters and conflicts
Ecosystem management
Harmful substances and hazardous waste

**Includes Sustainable Production and Consumption**

# International governance in chemicals



# SAICM

## Strategic Approach to International Chemicals Management (SAICM)

- Established in 2006 at the first International Conference on Chemicals Management (ICCM)
- Overall objective: to achieve sound management of chemicals throughout their life-cycle so that “by 2020 chemicals are produced and used in ways that minimize significant adverse impacts on the environment and human health” (2002 World Summit goal)
- Voluntary, multi-sectoral and multi-stakeholder approach (governments, business and industry, civil society, labour)
- SAICM text: political declaration, policy strategy with specific objectives, plan of action
- ICCM (SAICM’s Governing body) meets ~ every 3 years

(http://www.saicm.org)

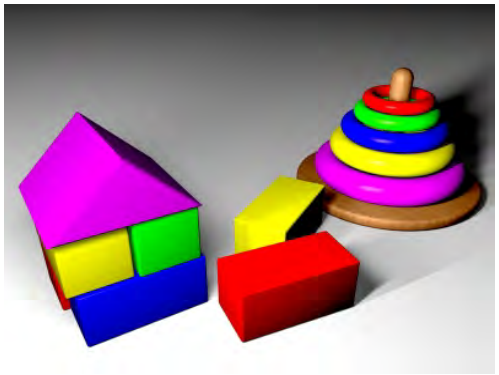
# Chemicals in Products project

- ICCM2 (2009) identified chemicals in products (CiP) as an emerging policy issue for cooperative action
  - CiP project responds to SAICM objective of Para 15b to ensure that **information on chemicals** throughout their life cycle, **incl. chemicals in products, is available, accessible and appropriate to the needs of all stakeholders**
- ICCM2 invited UNEP to lead the project to:
  - Investigate existing CiP information systems
  - Assess the systems and stakeholder information needs, and identify gaps
  - Recommend to OEWG and to ICCM3 actions to address the issue

# CiP project

Why a chemicals-in-products project?

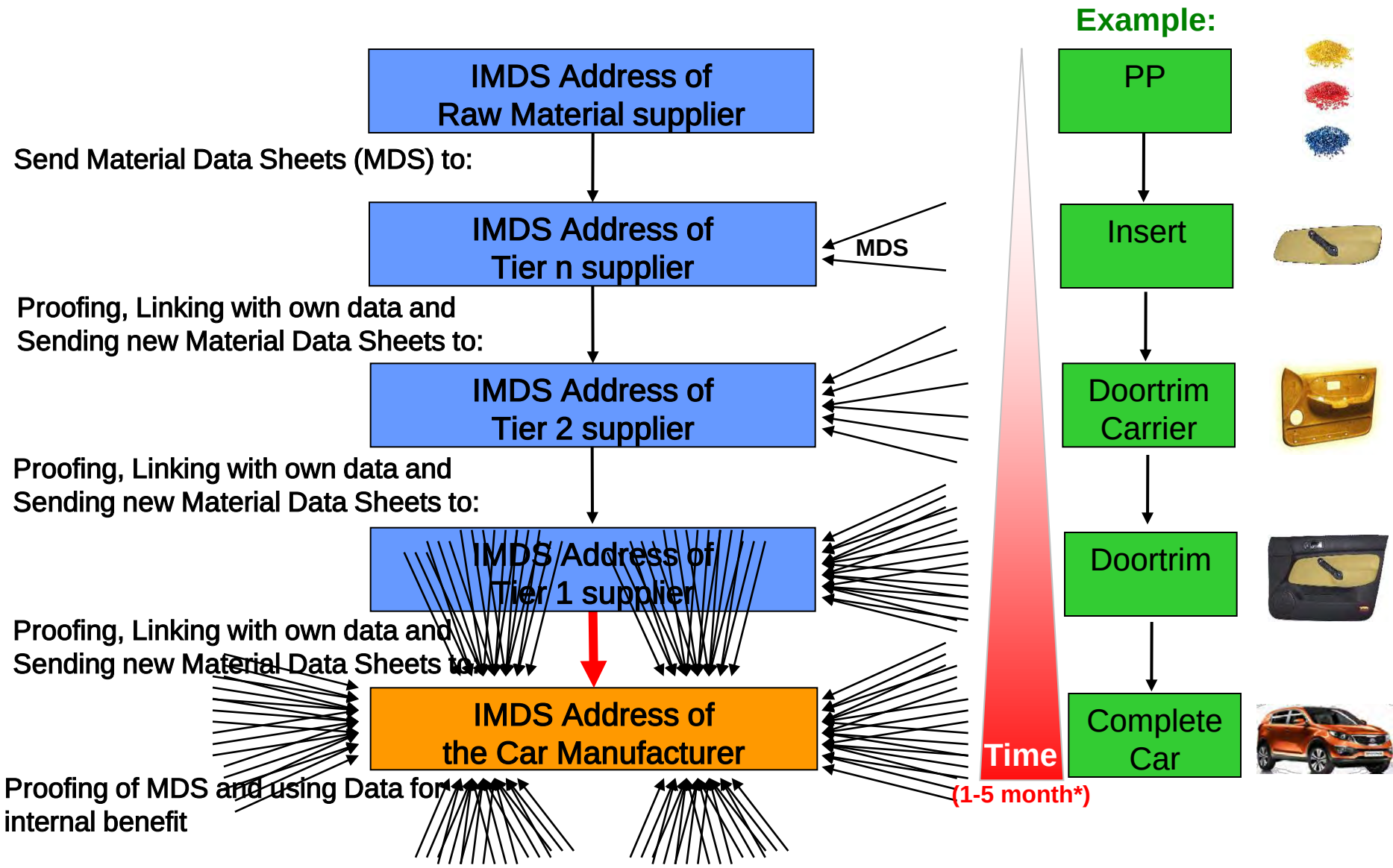
- Growing awareness of potential adverse effects of chemicals found in common products → increasing pressure for information on chemicals in products



# Examples of information systems?

- Product labels
- Databases, either publicly available or of limited access (i.e. when information is confidential or proprietary)
- Restricted substance lists (company driven)
- Safety data sheets (SDS)

# Data flow through the automotive supply-chain




* Estimate of a real data collection.
Depending on the complexity of the part & the strategy of the vehicle manufacturer (PPAP).

# CiP project – Major activities to date

Scoping phase

- Initial project scope defined (priority sectors: electronics, children's products, clothing, building products, cosmetics/personal care and food containers/packaging)

Analytical phase:

- Global report and in-depth studies of electronics, children's toys, textiles and building products sectors. Researched existing information exchange activities, stakeholder needs and gaps
- Extensive consultation (multi-stakeholder project Steering Group) to monitor activities and results, build awareness, gather input / feedback

# CiP project –
## results and conclusions

- Efforts already underway: GHS/SDS, sector / company specific
- developing countries → needs are largely unmet

- Harmonization would facilitate efforts

# CiP project –
## results and conclusions

Common drivers for chemicals information exchange:

- Need to meet legislative requirements (a major driver for most current chemicals in products information systems)
- Concerns among consumers and public interest groups regarding safety of products

# CiP project –
## results and conclusions

Common drivers for chemicals information exchange:

- Industry concern for product liability and brand and corporate image
- Corporate policies and actors regarding safety, health and environmental performance (some pushing for supportive legislation)

Sustainable Apparel Coalition

ICCA

BizNGO
FOR SAFER CHEMICALS AND SUSTAINABLE MATERIALS

- These drivers are generally present at a much higher level in developed countries.

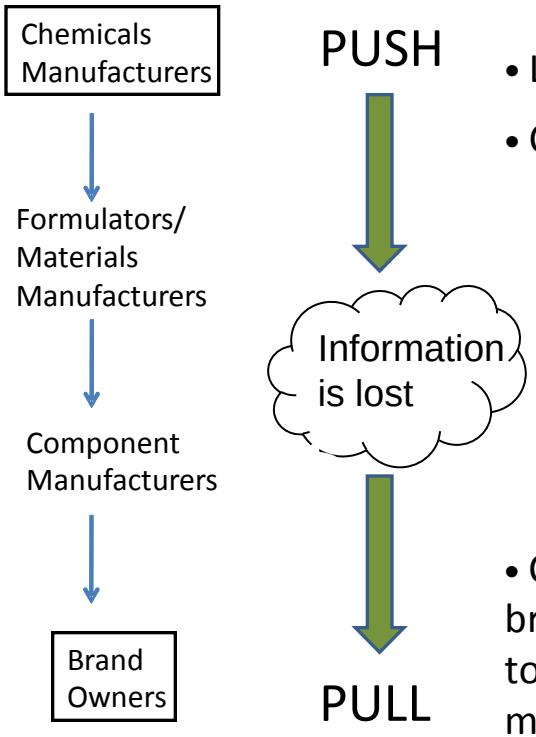
# CiP project –
## results and conclusions

Obstacles to information exchange:

- Complexity of the issue
- Lack of standardized systems
- Lack of defined roles and responsibilities
- Costs and other resource implications for gathering and processing the information
- Confidential nature of the information
- Has not been done in the past → a new activity which needs time and effort to establish

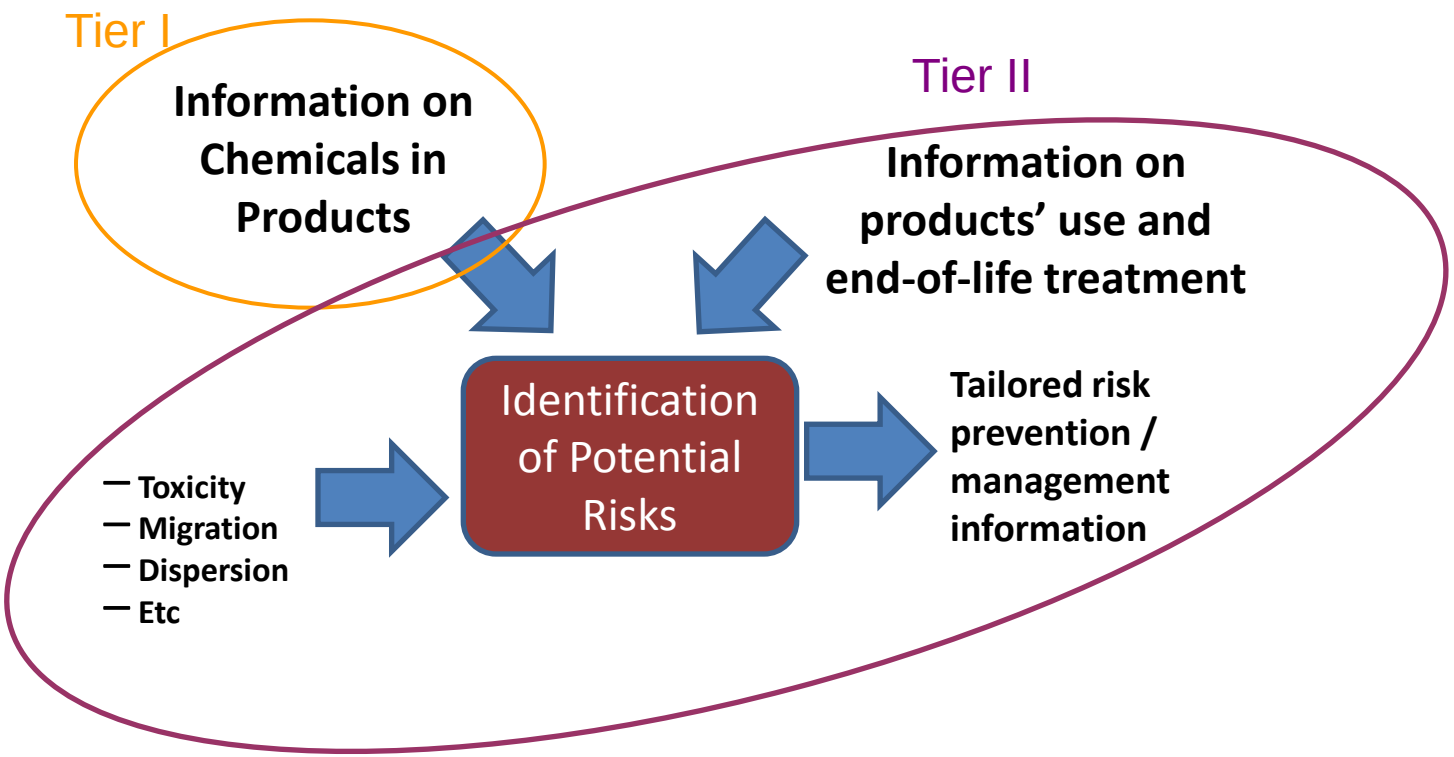
# Findings - Gaps in information exchange

Production chain “pull” and “push” of information access and provision



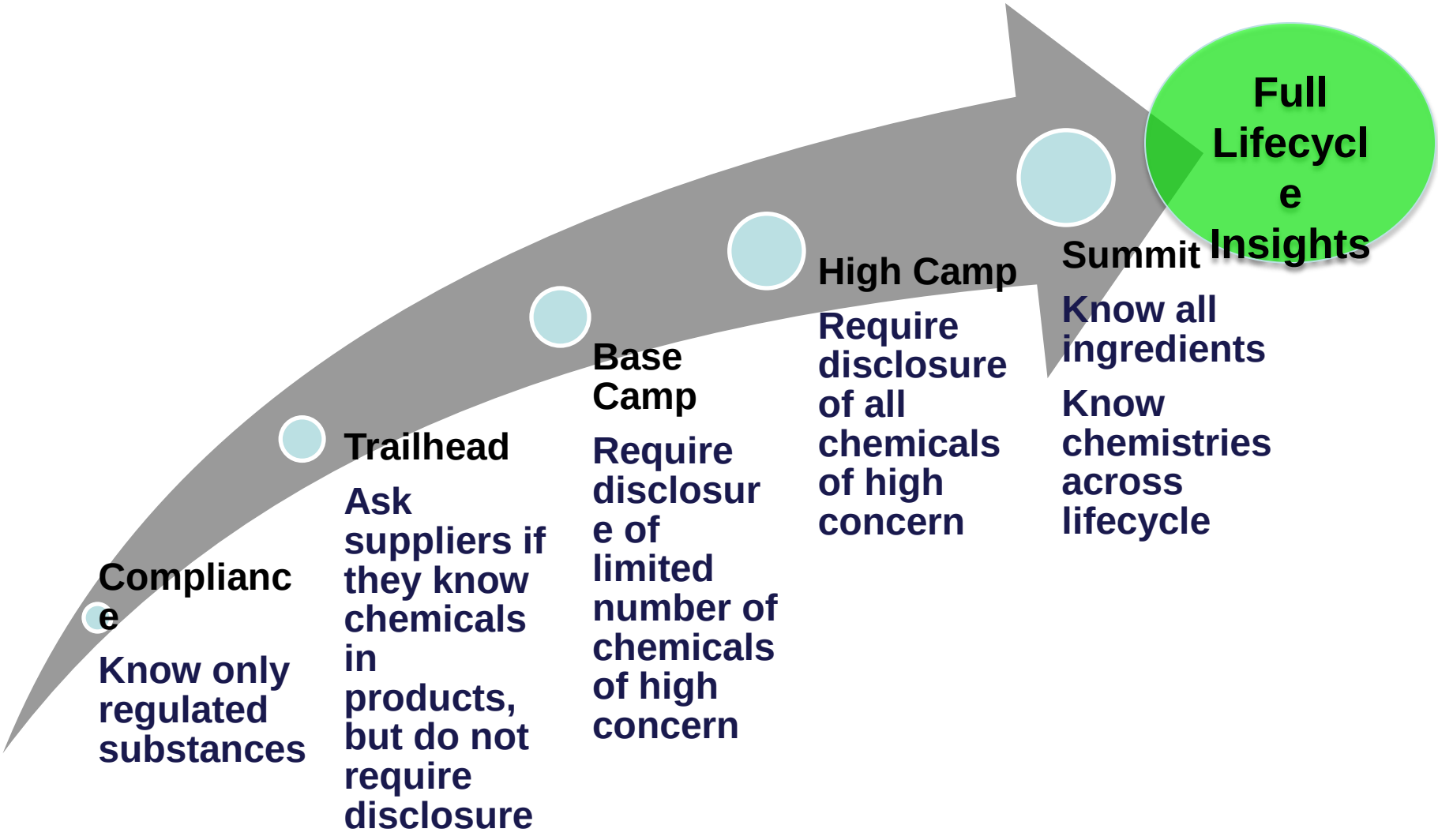

- Long supply chains with many tiers
- Complex networks with
  - a large number of materials/substances in each product
  - numerous applications for each chemical
  - many actors involved
- Chemicals manufacturers and brand owners feel the need to respond to consumer demand and regulatory drivers; mid-chain actors often do not

# A potential tiered approach to providing information



*BizNGO Guide to Safer Chemicals – Benchmarks*

# Principle #1a - Knowing Ingredients



# CiP project Workshop

International Workshop – March, 2011

- ~85 participants - all regions and major stakeholder groups represented
- Recommended the development of a CiP Programme to facilitate the exchange of information on chemicals in products
- Suggested pilot testing in one or more sectors
- Proposal for the Programme to be submitted to ICCM4 (2015)

# Recommendations to ICCM3

CiP Workshop recommended the development of a CiP Programme to facilitate the exchange of information on chemicals in products (WS report - Annex 2). The Programme could:

(a) Identify the roles and responsibilities of the major stakeholder groups

(b) Establish principles on what information could be transferred to different stakeholders and how that transfer could take place

(c) Build on existing experiences of best practices

Development of the CiP Programme could draw on the project global study and the sector case studies prepared for toys, electronics, construction materials and textiles and CiP project meetings / discussions

# Recommendations to ICCM3

Elements to address during the development of the CiP Programme:

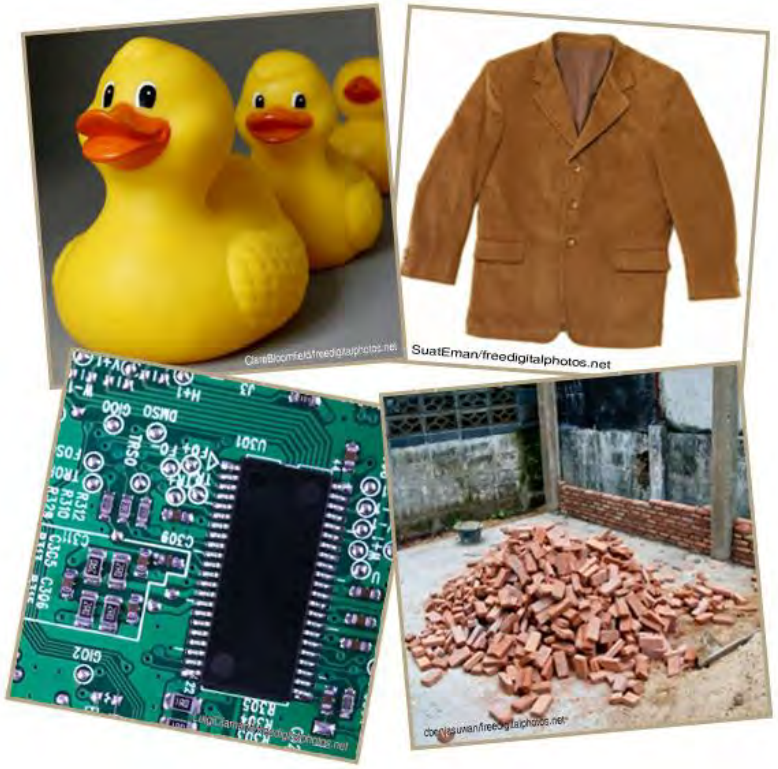
- Principles on what chemicals information could be transferred to different stakeholders → i.e. what information, for which chemicals and how transmitted
- The need to address differentiated needs of different stakeholders, sectors and regions
- Build on related activities (cost of inaction, capacity building, technical and financial assistance)
- Actions to gain buy-in by industry and other stakeholders
- Treatment of confidential business information
- Development of guidance documents – both general and sector specific – and including:
  - promotion of successful systems
  - use of standardized languages
  - policy guidelines
  - proposals for regulatory tools

# CiP project – Next steps

Report and recommendations to ICCM3

- Considered and generally approved at the SAICM Open-ended Working Group (Nov 2011)
- Outreach and awareness raising among stakeholders
  - Identify potential partners for eventual sector pilot test(s)

Decision point: ICCM3 in mid-2012 – will consider results and recommendations and decide on future actions




# THANK YOU!

Kevin Munn, Project Officer
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Geneva, Switzerland
kevin.munn@unep.org

CiP project: http://www.chem.unep.ch/unepsaicm/cip

European Commission

# HOW RISKCYCLE MAY INFLUENCE FUTURE EU RESEARCH ACTIVITIES

# RISKCYCLE Final Conference

**8-9 May 2012**
**Dresden**

Georges Deschamps
DG RTD – I2
Environment

Research and Innovation

# Risk assessment and alternative testing

> *Health*

> *Nanotechnology, Materials, Processes*

> *Environment*

# EU Research funding related to Alternative Testing Strategies

FP5 (1998-2002)

***Environment Programme*> 25 projects ~ 72 M€**

FP6 (2002-06) **+** FP7 (2007-11**)**

***Environment + Health + Nanotech.* >>>70 projects ~145 M€**

# WP2012 HEALTH: Call for Coordination action

>Protocol on the Protection and Welfare of Animals, and the use of animals in research and testing.
>Principle of the 3 Rs (reduction, refinement and replacement) to be applied where appropriate in research funded by the EU.

***CA for Preparing the future for health research and innovation*:**

In important and emerging areas of health research step up coordination efforts between European academia, industry, national programmes and other relevant organisations (including international ones)

European Commission

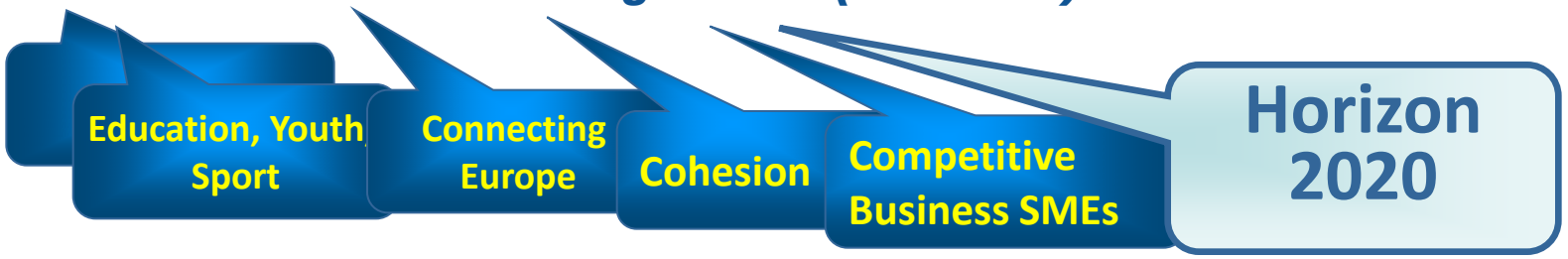
# *Towards the future EU Programme for Research and Innovation 2014-2020)*


*Research and Innovation*

# The Multiannual Financial Framework 2014-2020 ( Commission proposal 29/09/2011)

**Key challenge: to stabilise the financial and economic system while taking measures to create economic opportunities**

***1. Smart & inclusive growth (€491bn)***




***2. Sustainable growth, natural resources (€383bn)***

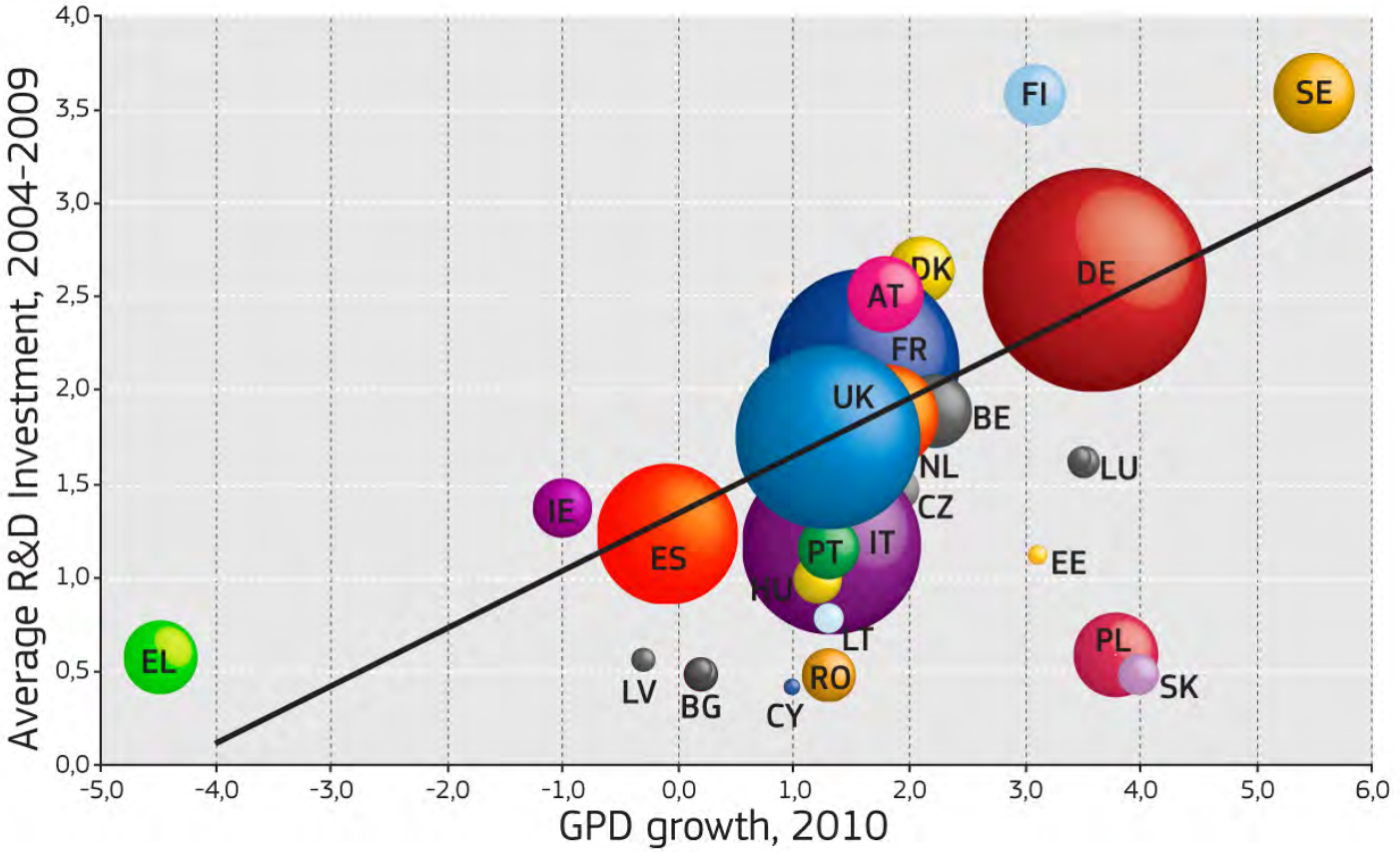
***3. Security and citizenship (€18.5bn)***

***4. Global Europe (€70bn)***

***5. Administration (€62.6bn)***

**Total: € 1,025bn**

# Investment in R&D (as % of GDP) against GDP growth in EU countries




Research and Innovation

# What is Horizon 2020

- **Commission proposal for a 80 billion euro research and innovation funding programme (2014-2020)**
- **A core part of Europe 2020, Innovation Union & European Research Area:**
  - **Responding to the economic crisis** to invest in future jobs and growth
  - **Addressing people's concerns** about their livelihoods, safety and environment
  - **Strengthening the EU's global position** in research, innovation and technology

# What's new

- **HORIZON2020** brings together three separate previous programmes/initiatives (FP7+CIP+EIT)
- **Couple research to innovation** – from research to retail via innovation
- **Focus on societal challenges** facing EU society, e.g. health, clean energy and transport
- **Simplified access** for all companies, universities, institutes in all EU countries and beyond

# Three priorities:

1. Excellence
2. Industrial leadership
3. Addressing societal challenges

# Priority 1. Excellent science

*Why:*

- World class science is the foundation of tomorrow's technologies, jobs and wellbeing
- Europe needs to develop, attract and retain research talent
- Researchers need access to the best infrastructures

# Proposed funding (million euro, 2014-2020)

| | |
|---|---|
| ***European Research Council***<br>Frontier research by the best individual teams | *13 268* |
| ***Future and Emerging Technologies***<br>Collaborative research to open new fields of innovation | *3 100* |
| ***Marie Curie actions***<br>Opportunities for training and career development | *5 572* |
| ***Research infrastructures*** *(including e-infrastructure)*<br>Ensuring access to world-class facilities | *2 478* |

# Priority 2. Industrial leadership

*Why:*

- Strategic investments in key technologies (e.g. advanced manufacturing, micro-electronics) underpin innovation across existing and emerging sectors
- Europe needs to attract more private investment in research and innovation
- Europe needs more innovative SMEs to create growth and jobs

# Proposed funding (million euro, 2014-20)

| | |
|---|---|
| ***Leadership in enabling and industrial technologies*** *(*ICT, nanotechnologies, materials, biotechnology, manufacturing, space) | *13 781* |
| ***Access to risk finance*** Leveraging private finance and venture capital for research and innovation | *3 538* |
| ***Innovation in SMEs*** Fostering all forms of innovation in all types of SMEs | *619 complemented by 6 829 (expected 15% of societal challenges + LEIT) and 'Access to risk finance' with strong SME focus* |

# Priority 3. Societal challenges

*Why:*

- Concerns of citizens and society/EU policy objectives (climate, environment, energy, transport etc) cannot be achieved without innovation
- Breakthrough solutions come from multi-disciplinary collaborations, including social sciences & humanities
- Promising solutions need to be tested, demonstrated and scaled up

# Proposed funding (million euro, 2014-2020)

| | |
|---|---|
| *Health, demographic change and wellbeing* | *8 033* |
| *Food security, sustainable agriculture, marine and maritime research & the bioeconomy* | *4 152* |
| *Secure, clean and efficient energy** | *5 782* |
| *Smart, green and integrated transport* | *6 802* |
| *Climate action, resource efficiency and raw materials* | *3 160* |
| *Inclusive, innovative and secure societies* | *3 819* |

***Additional €1 788m for nuclear safety and security from the Euratom Treaty activities (2014-2018). Does not include ITER.**

# Horizon 2020 and partnering

*Public private partnerships:*

- Trough Joint Technology Initiatives or other formal structures (Art. 187)
- Trough contractual agreements, which provide inputs for work programmes
- Only when criteria met, e.g. clear commitments from private partners

*Public public partnerships:*

- Trough « ERA-Nets » for topping up individual calls/actions (replacing current ERA-Net, ERA-Net Plus, Inco-Net, Inno-net)
- Trough participation in joint programmes between Member States (Art. 185)
- Supporting agendas of Joint Programming Initiatives when in line with Horizon 2020
- Only when criteria met, e.g. financial commitments of participating countries

*European Innovation Partnerships:*

- Not funding instruments, but for coordination with broader policies and programmes

# Role of the EIT and JRC in Horizon 2020

| | |
|---|---|
| ***European Institute Technology (EIT)***<br>Combining research, innovation & training in knowledge and Innovation Communities | ***1 360+***<br>***1 440****** |
| ***Joint Research Centre (JRC)*****<br>Providing a robust, evidence base for EU policies | ***1 962*** |

****Second tranche pro rata from LEIT and Societal challenges (subject to review)***

*****Additional €656 m for the JRC to be funded from the Euratom Treaty activities***

# Simplification: Rules for Participation

***1. A single set of rules***

- Adapted for the whole research and innovation cycle
- Covering all research programmes and funding bodies
- Aligned to the Financial Regulation, coherent with other new EU Programmes

***2. One project – one funding rate***

- Maximum of 100% of the total eligible costs (except for actions close to market, where a 70% maximum will apply)
- Indirect eligible costs: a flat rate of 20% of direct eligible costs

***3. Simple evaluation criteria***

- Excellence – Impact – Implementation (Excellence only, for the ERC)

***4. New forms of funding*** *aimed at innovation: pre-commercial procurement, inducement prizes, dedicated loan and equity instruments*

***5. International participation:*** *facilitated but better protecting EU interests*

# Simplification: Rules for Participation

6. ***Simpler rules for grants:*** *broader acceptance of participants accounting practices for direct costs, flat rate for indirect costs, no time-sheets for personnel working full time on a project, possibility of output-based grants*

7. ***Fewer, better targeted controls and audits***

- Lowest possible level of requirements for submission of audit certificates without undermining sound financial management
- Audit strategy focused on risk and fraud prevention

8. ***Improved rules on intellectual property***

- Balance between legal security and flexibility
- Tailor-made IPR provisions for new forms of funding
- A new emphasis on open access to research publications

***Beyond the Rules: further simplified provisions in the Grant Agreement and implementing procedures to facilitate access to Horizon 2020 (e.g. common IT platform).***

# Simplification: summary

- **Single set of** simpler and more coherent participation **rules**
- New **balance between trust and control**
- Moving from several **funding rates** for different beneficiaries and activities to just two
- Replacing the four methods to calculate overhead or «indirect costs» with a **single flat rate**
- Major simplification under the **forthcoming financial regulation**
- **Successful applicants to get working more quickly**: reduction of average time to grant by 100 days (current average of around 350 days under FP7)

# Contributing to the European Research Area (ERA)

- ERA framework proposal in 2012 to create a single market for knowledge research and innovation
- Complemented by Horizon 2020:
  - Boosting support to ERA priorities – mobility, infrastructures, knowledge transfer, policy learning
  - Stronger partnerships with Member States and private sector to invest more efficiently
  - Taking account of gender, ethical issues, researcher careers and open access to results

# Strong participation by SMEs

- **Integrated approach** - around 15% of the total budget for societal challenges and LEITs to go to SMEs.
- **Simplification** of particular benefit to SMEs (e.g. single entry point).
- A **new SME instrument**, building on the SBIR model, will be used across all societal challenges as well as for the LEITs
- A dedicated activity for research-intensive SMEs in **'Innovation in SMEs'.**
- **'Access to risk finance'** will have a strong SME focus (debt and equity facility)

# Links to COSME

***Horizon 2020 and COSME are complementary programmes to generate growth and jobs***

**Different focus:**

- Horizon 2020 = innovation driven growth
- COSME = support to create favourable business environment and competitiveness

**Closely coordinated, for instance:**

- Integrated financial instruments (debt and equity), with facilities in both programmes serving complementary objectives
- Enterprise Europe Network set up under COSME, but support to SMEs for EU funding

# Socio-economic sciences and humanities

- **Integrated approach**: SSH included as an integral part of the activities, working beyond 'silos' (*e.g. understanding the determinants of health and optimising the effectiveness of healthcare systems).*

- The **'Inclusive, Innovative and Secure Societies' challenge**: issues such as smart and sustainable growth, social transformations, social innovation and creativity, the position of Europe as a global actor as well as the social dimension of a secure society *(SSH have the tools to contribute to addressing security challenges, enhancing the societal dimension of security policy and research).*

- **Bottom-up funding**: ERC, MCA, Research Infrastructures.

# Widening participation

- **Principle of excellence**: continue to allocate funding on the basis of competitive calls, selecting only the best projects.
- **Clear division of labour** between cohesion policy and Horizon 2020.
  - Cohesion policy: support for regions in building up their research and innovation capacity.
  - Horizon 2020: widen participation, better coordination between the two Union funding programmes, support policy learning reforms.
- **Accompanying measures in Horizon 2020** to ensure that excellence prevails wherever it exists, including: twinning, ERA chairs, support for access to international networks, development of smart specialisation strategies.

# International cooperation

- **International cooperation is crucial** to address many Horizon 2020 objectives.
- **Principle of general openness**: the programme will remain to be the most open funding programme in the world.
- Horizon 2020 shall be open to the **association** of: acceding countries, candidate countries and potential candidates and selected third countries that fulfil the relevant criteria (capacity, track record, close economic and geographical links to the Union, etc.).
- Targeted actions to be implemented taking a **strategic approach to international cooperation** (dedicated measures in the 'Inclusive, innovative and secure societies' challenge).

# Next steps

| | |
|---|---|
| **Ongoing:** | Parliament and Council negotiations on the basis of the Commission proposals |
| **Ongoing:** | Parliament and Council negotiations on EU budget 2014-2020 (including overall budget for Horizon 2020) |
| **Mid 2012:** | Final calls under 7th Framework Programme for research to bridge gap towards Horizon 2020 |
| **Mid 2013:** | Adoption of legislative acts by Parliament and Council on Horizon 2020 |
| **1/1/2014:** | **Horizon 2020 starts, launch of first calls** |


# Thank you for your attention!

**Find out more:**

www.ec.europa.eu/research/horizon2020

*Research and Innovation*

# Status of the OECD Work on Alternative Testing (*in vitro* methods, new approaches)

*RISKCYCLE, Dresden, Germany, 8-9 May 2012*

*Laurence Musset*

Environment, Health and Safety Division

Environment Directorate

# Organisation for Economic Co-operation and Development

Intergovernmental organisation (34 members from Europe, America, Asia and Pacific regions) to:

- Discuss issues of mutual concern
- Work together and share the burden
- Co-ordinate and harmonise policies and tools (avoid duplication of work)
- Work towards regulatory acceptance of tools for chemicals management

All stakeholders are involved: members, selected non members, industry, trade unions, Environmental NGOs, Animal welfare NGOs

OECD is located in Paris (Approximately 2500 staff)

# OECD Member Countries

Intergovernmental Organisation grouping 34 industrialised countries

## EU

- Austria
- Belgium
- Czech Republic
- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- Ireland
- Italy
- Luxembourg
- The Netherlands
- Poland
- Portugal
- Slovak Republic
- Slovenia
- Spain
- Sweden
- United Kingdom

## EUROPEAN NON-EU

- Iceland
- Israel
- Norway
- Switzerland
- Turkey

## Americas

- Canada
- Chile
- Mexico
- United states

## ASIA - PACIFIC

- Australia
- Japan
- New Zealand
- South Korea

OECD 50

# Alternatives to *in vivo* testing
# OECD approaches for avoiding unnecessary animal testing

- Use of existing data & non-test information: eChemPortal, chemical categories, QSARs
- Test Guidelines for *in vitro* test methods (Mutual Acceptance of Data)
- Conceptual Frameworks, Testing strategies
- New approaches: Molecular screening, High throughput testing and toxicogenomics, Integrated approaches and Adverse Outcome Pathways

# Existing data: eChemPortal

- Internet gateway to information on the properties, hazards and risks of chemicals found in the environment, homes and workplaces, and in products used daily
- Users can simultaneously search data from multiple data sources
- Sources and quality of data are described

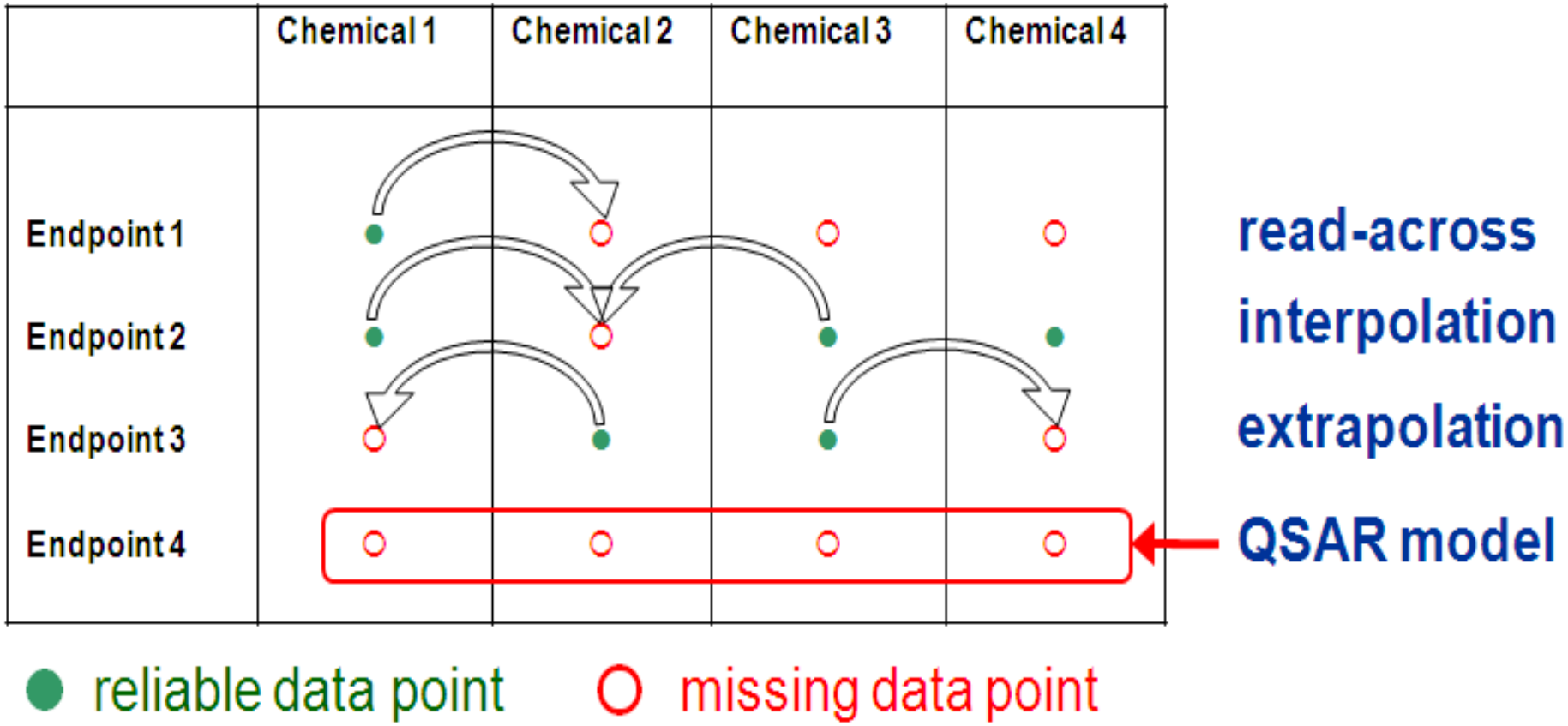
www.oecd.org/ehs/echemportal

# Non-test information: Chemical categories and (Q)SARs

Grouping / **Category Approach**: not every chemical needs to be tested for every endpoint

- OECD Principles for the Validation, for Regulatory Purposes, of (Q)SAR Models (2004)
- Case study report: overview of country uses of predictive methods (2006)
- Guidance Document on the Validation of (Q)SAR Models (2007)
- **(Q)SAR Application Toolbox** (implement the OECD Guidance Document N°80 on "Grouping of Substances" into a flexible computer programme).

# Chemical Categories



# (Q)SARs Application Toolbox

Decision system for governments and industry (mostly funded by the EC). The toolbox allows the user to built his own predictive model. It can be used to:

- Fill data gaps in a chemical category using read-across, trend analysis or QSAR models
- Explore a chemical list for possible analogues for each chemical
- Group chemicals based on molecular similarity and reactivity analysis
- Identify chemicals with specific metabolic pathways or toxicity mechanisms
- Group chemicals based on common metabolites

(Version 2.3)

www.oecd.org/env/hazard/qsar

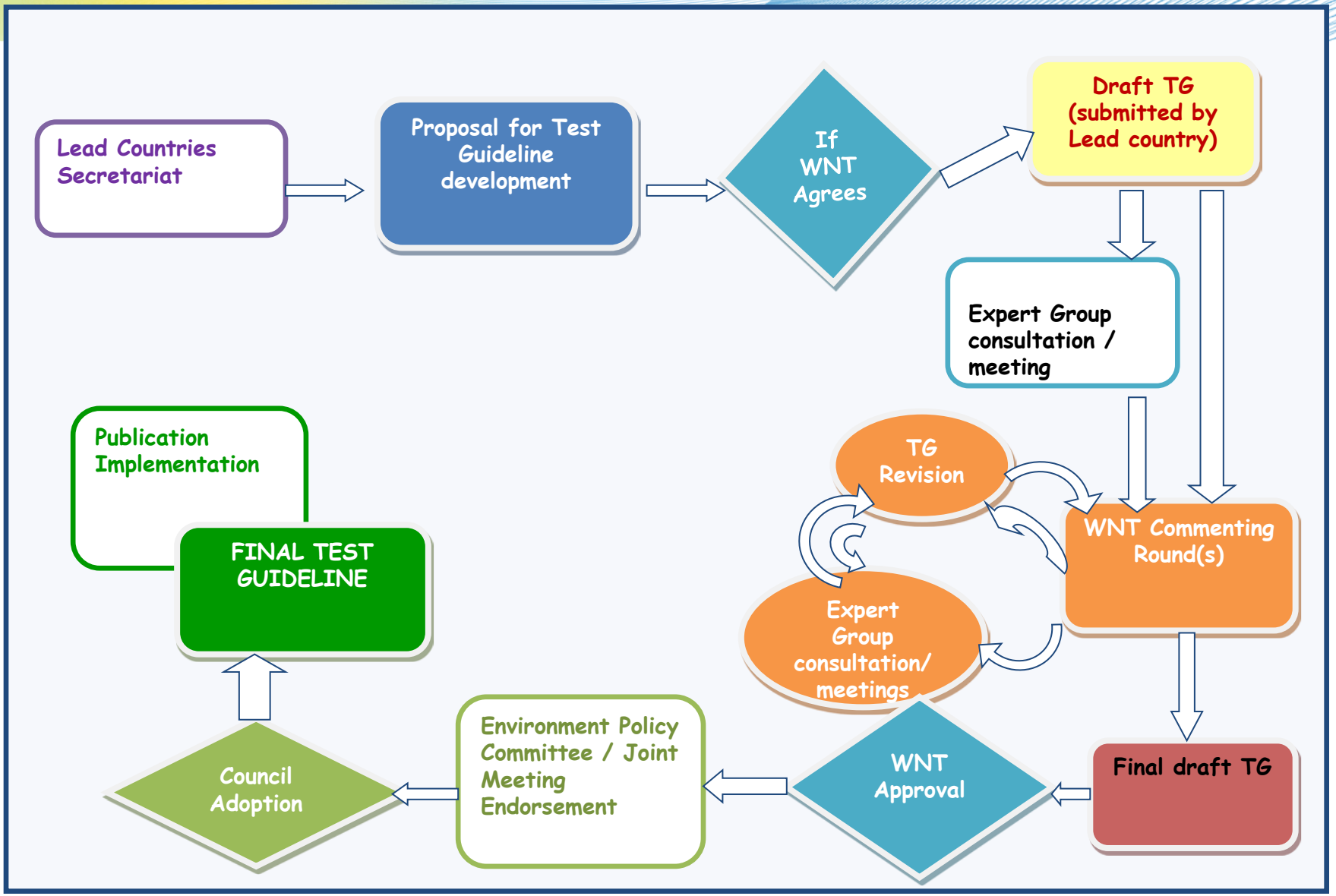
# Guidelines for the Testing of chemicals (TGs)

- Original publication: 1981; Last update: July 2011
- 140 new or updated Guidelines
- 45 new or updated TGs adopted in the 5 last years
- Test Guidelines for *in vivo* and *in vitro* test methods
- Regulatory acceptance: extended expert contribution and a Council Decision on the Mutual Acceptance of Data
- Available free of charge since January 2007

OECD Test Guidelines apply to all types of chemicals (e.g., industrial chemicals, pesticides, cosmetics, others) - substances (and mixtures) - non clinical health safety studies (For pharmaceutical, ICH methods are more currently used)

Working Group of National Coordinators of the Test Guidelines Programme (WNT)

# Procedures for Test Guidelines Development



# WNT Commenting Round

Lead country/EC/(Secretariat) formal proposal

Secretariat

- BIAC (representatives of chemicals industry)
- ICAPO (representative of animal welfare community)

Position Papers

National Coordinators
EU/JRC

National Experts
(Academia / Government)

National Coordinators
Position Papers
(responsibility of the
National Coordinators)

Other Partners:

- TUAC (representative of Trade Unions)
- EEB (representative of Environmental NGOs)
- ICH
- IOMC
- ISO
- ILSI
- Others (Public)

Position Papers
(as appropriate)

Secretariat

# 1981 and 1997 "MAD" Decisions

"The data generated in the testing of chemicals in an OECD Member country in accordance with OECD Test Guidelines and OECD Principles of Good Laboratory Practice shall be accepted in other Member countries for purposes of assessment and other uses relating to the protection of man and the environment."

- South Africa, Singapore, India, Brazil, and Argentina are now full adherents to the Council Acts on MAD with the same rights and obligations as member counties
- Malaysia and Thailand are provisional adherents
- Current Discussions with China, Chinese Taipei, Thailand and others

# Validation of (in vitro) test methods

- GD on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment (GD 34)

  includes 8 main principles/criteria for test method validation; however, it allows some flexibility (Introduction, Par.13)

- Validation is managed by OECD or by ECVAM / ICCVAM / JaCVAM
- Under discussion: Use of high throughput testing for the validation

# Existing Test Guidelines for *in vitro* test methods (1)

- *Genotoxicity* - TG 471, 473, 476, 479, 480, 481, 482 for (1997 or before); *In vitro* Micronucleus Test - TG 487 (2010)
- *Skin Absorption*: *In Vitro* Method - TG 428 (2004)
- *Skin Corrosion*
  - *In Vitro* Skin Corrosion: Transcutaneous Electrical Resistance Test - TG 430 (2004)
  - *In Vitro* Skin Corrosion: Human Skin Model Test -TG 431 (2004)
  - *In Vitro* Membrane Barrier Test Method for Skin Corrosion TG 435 (2006)
- *Skin irritation*: *In Vitro* Skin Irritation: Reconstructed Human Epidermis Test Method - TG 439 (2010)

# Existing Test Guidelines for *in vitro* test methods (2)

- *Phototoxicity*: *In vitro* 3T3 NRU Phototoxicity Test - TG 432 (2004)
- *Ocular Corrosion/Severe Irritation*
  - Bovine Corneal Opacity and Permeability Test Method, TG 437 (2009)
  - Isolated Chicken Eye Test Method, TG 438 (2009)
- *Endocrine disruption*:
  - Stably Transfected Human Estrogen Receptor-α Activation Assay for the Detection of Estrogenic Agonist-Activity of Chemicals Assay - TG 455 (2009)
  - H295R Steroidogenesis Assay - TG 456 (2011)

# Projects for new or updated Test Guidelines for *in vitro* test methods (1)

- *Skin irritation*: LabCyte24
- *Skin sensitisation*: Direct Peptide Reactivity Assay and KertinoSens assay
- *Ocular Corrosion/severe irritation*: Fluorescein Leakage test method and Cytosensor Microphysiometer test method
- *Carcinogenicity:* (HSE, Balb/c 3T3, Bhas 42 Cell line Cell Transformation Assays)
- *Genotoxicity*: *in vitro* Comet assay
- *Endocrine disruption*
  - MCF-7 Cell Proliferation Assay for the detection of Estrogen Receptor (Ant)Agonist
  - Chimpanzee Recombinant Androgen Receptor Binding Assay
  - STTA ER/AR Assays; ER Binding Assay

# Projects for new or updated Test Guidelines for test methods on Embryos/Larvae (2)

- *Ecotoxicity:*
  - Fish Embryo Toxicity Test
  - Xenopus Embryonic Thyroid Signalling Assay
  - Honey bee (Apis mellifera L.) Brood test

# Draft updated Conceptual Framework for Testing and Assessment of Endocrine Disrupters

- Level 1: Existing data and non-test information
- Level 2: *In vitro* assays providing data about selected endocrine mechanism(s)/pathways
- Level 3: *In vivo* assays providing data about selected endocrine mechanism(s)/pathway(s)
- Level 4: *In vivo* assays providing data on adverse effects on endocrine relevant endpoints
- Level 5: *In vivo* assays providing more comprehensive data on adverse effects on endocrine relevant endpoints over more extensive parts of the life cycle of the organism

# Testing Strategies

- Draft recommended revised testing strategy for eye irritation/corrosion (updated TG 405)
  (*publication expected in 2012*)

- Development of a Guidance Document on Integrated Testing Strategy and weight of evidence approach Skin irritation/corrosion

- Draft Generic Testing Strategy for Fish toxicity
  (*publication expected in 2012*)

# High Throughput Screening and Toxicogenomics

Extended Advisory Group on Molecular Screening and Toxicogenomics

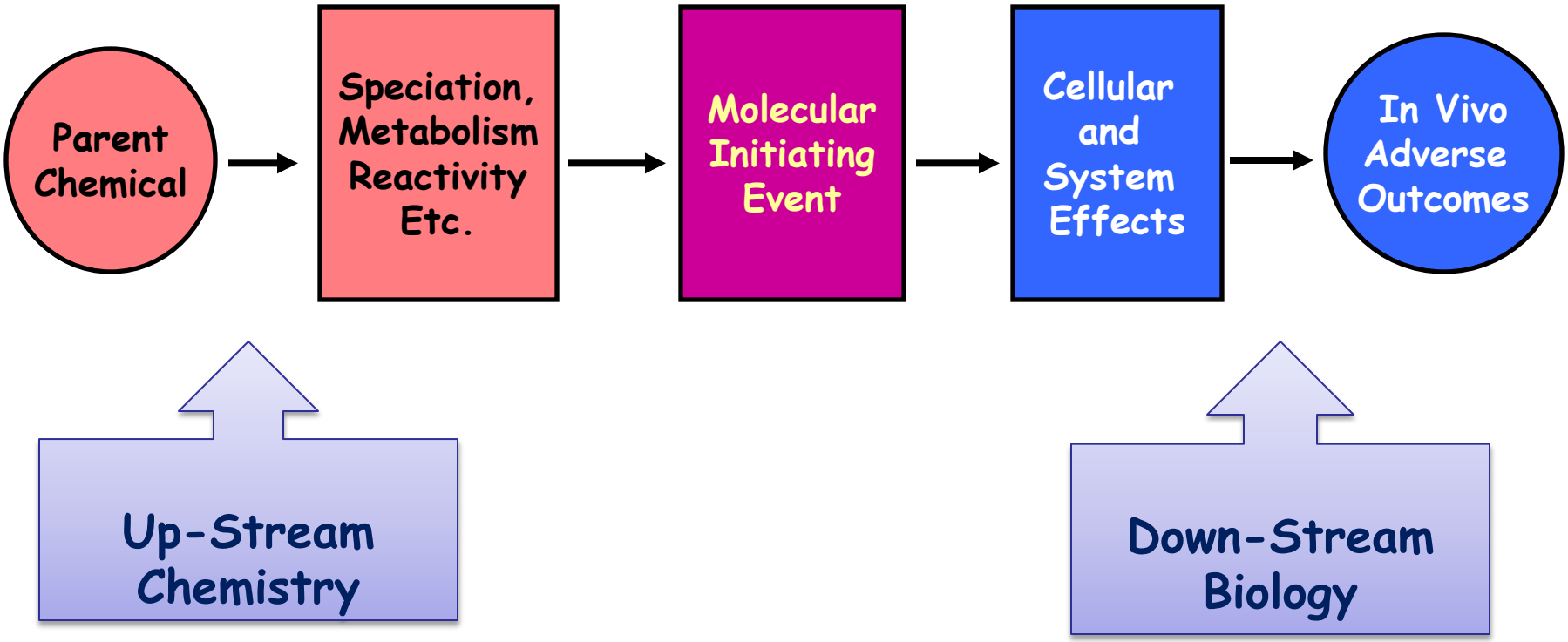
- Exchange of information on EU/US/Japan projects for new approaches to testing, in particular high throughput *in vitro* assays (Activity based on the US ToxCast Program)
- Subgroups work on pathways/mechanisms of action (Thyroid signalling, PPAR alpha associated pathways, Cancer Epigenetics, sensitisation, neutotoxicity,…)

# Adverse Outcome Pathways (AOPs)

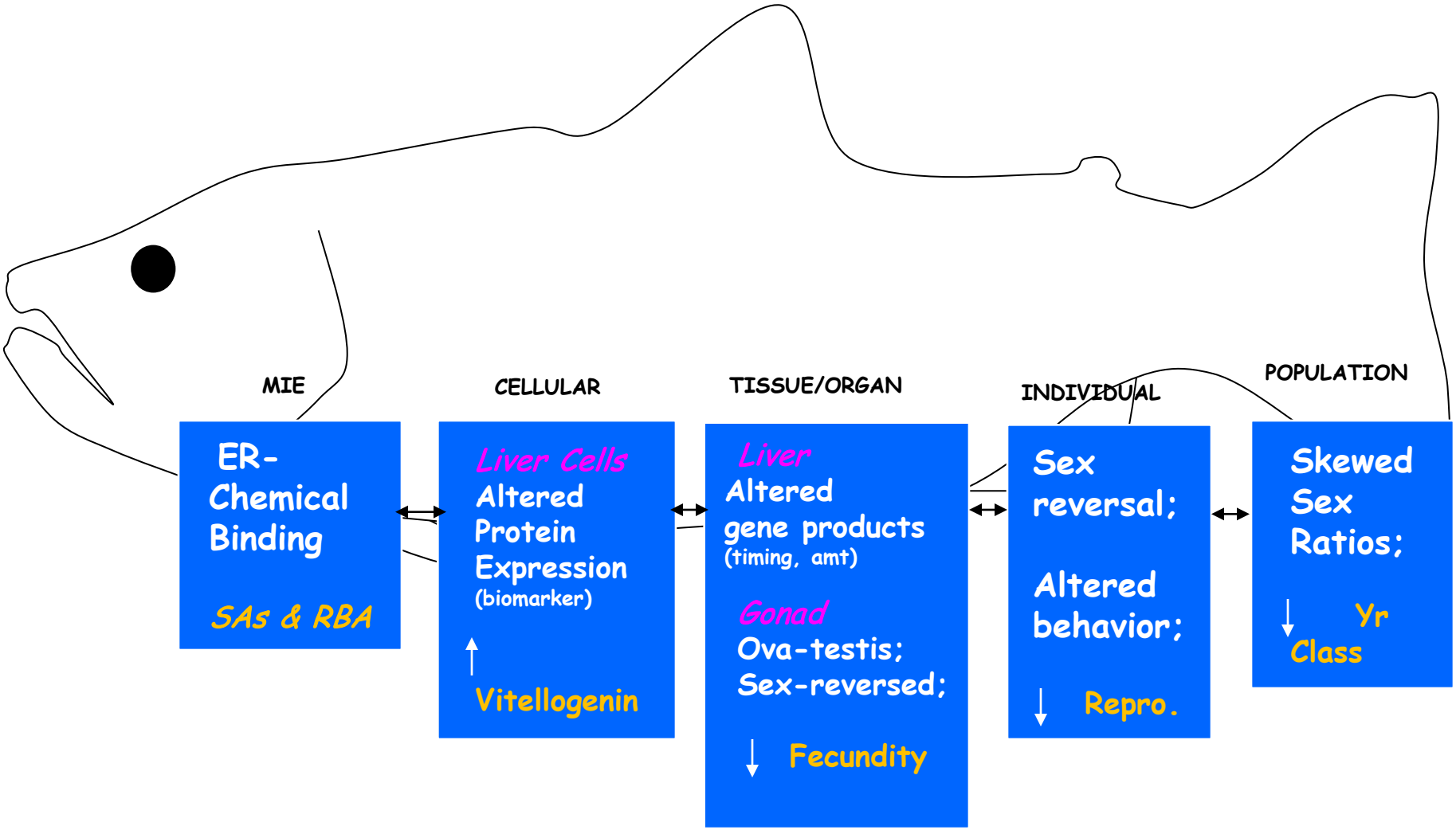
Information on the plausible mode of toxic action, organised as key events and processes within adverse outcome pathways (AOPs).

- Draft Guidance document including working definitions
- Format for submitting AOPs
- Example AOP on skin sensitisation initiated by covalent binding to proteins
- Draft AOPs for the cell signalling pathways associated with proliferation and differentiation that are conserved across species
- Draft AOPs for mitochondrial toxicity.

# Generic Linear AOP



# AOP for ER-mediated Reproductive Impairment



# Integrated Approaches to Testing and Assessment

The development of science-based and transparent integrated approaches for testing and assessment that are globally accepted for regulatory decision making is supported by OECD as a long-term goal. The development of an OECD framework should

- facilitate interpretation of test and non-test results
- facilitate the building and access of knowledge bases for regulatory decision-making
- be adaptive to new scientific developments.

It could be based on Current activities on Mode of Action and Adverse Outcome Pathways. Given the complexity of new approaches, communication is important to inform the public and regulators.

# New Approaches / Regulatory Acceptance Main issues and challenges

- Need for flexibility: Test Guidelines and other methods need to be updated/deleted more frequently than in the past
- Need for clear applicability domain and limitations of the methods
- Comparability of the (test) methods, given their increasing number for assessing the same endpoint
- « Me-too tests » - Performance Standards – Proprietary elements
- Use of methods as part of a testing stategy & weight of evidence approach
- Improved knowledge of mechanisms of action and AOPs
- International Harmonisation of Integrated Testing Strategies

# For more information on the Environment, Health and Safety Programme

www.oecd.org/ehs

Laurence.musset@oecd.org


***Istituto di Ricerche Farmacologiche "Mario Negri" Milano***

*Environmental Chemistry and Toxicology Lab.*

**Nazanin GOLBAMAKI B.**

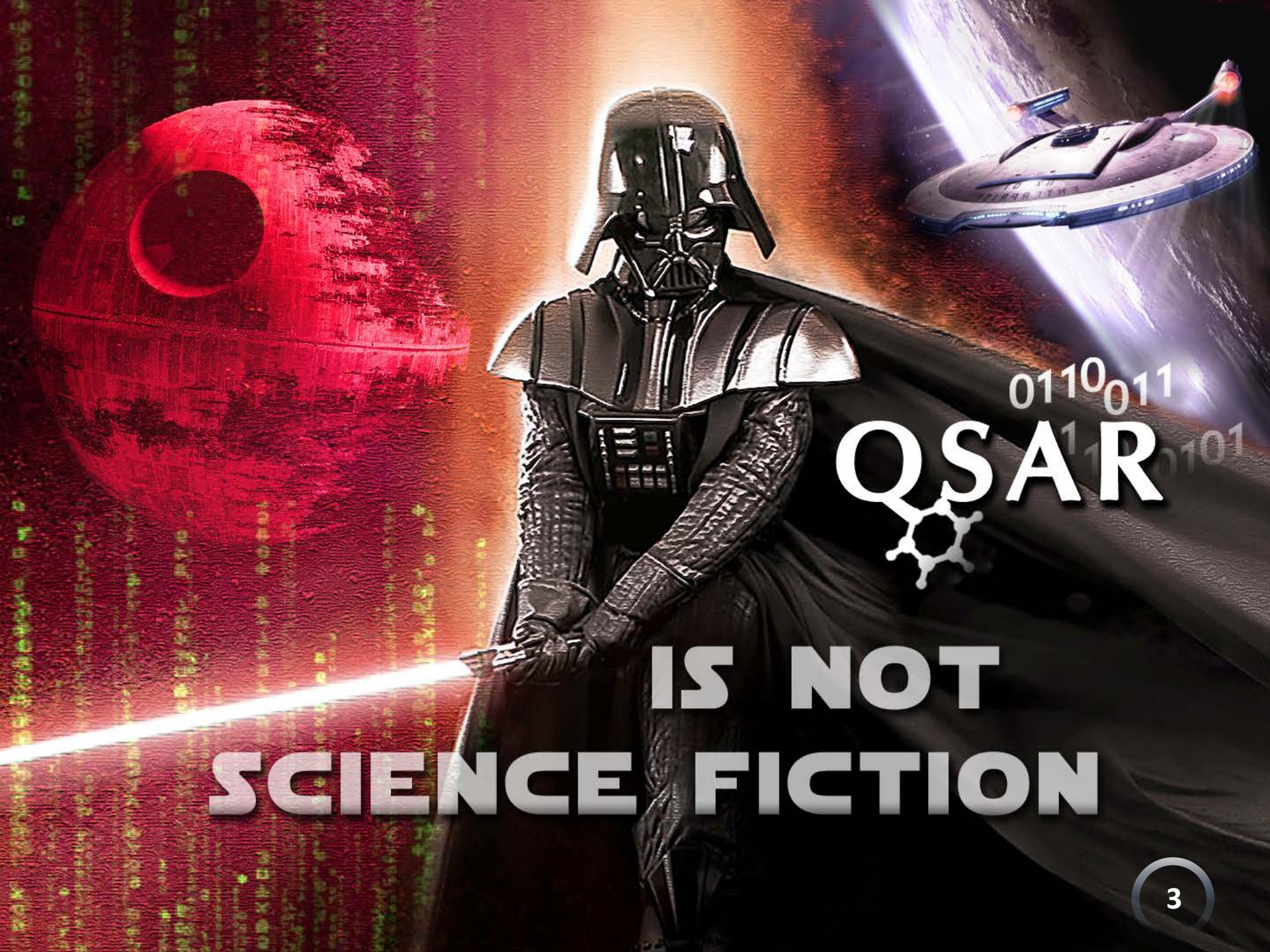
E-mail nazanin.golbamaki@marionegri.it

# (Q)SAR

=

## (Quantitative) Structure-Activity Relationship

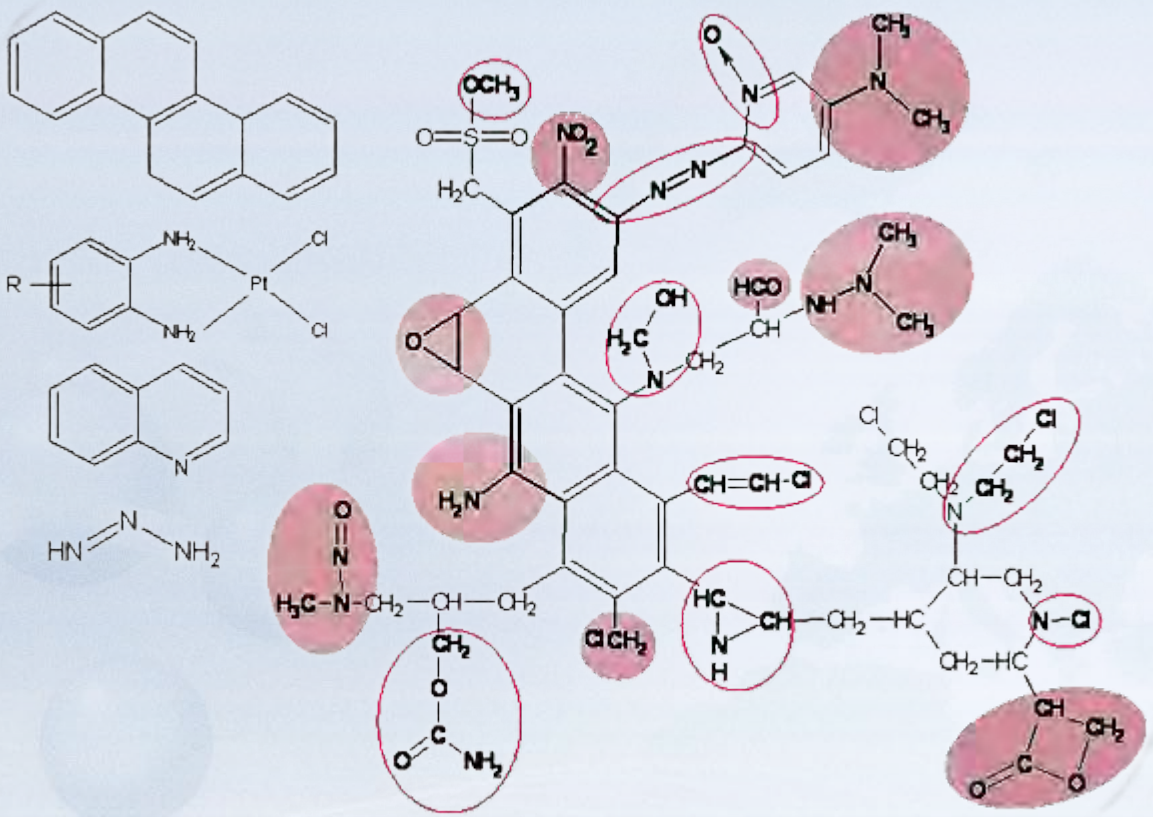
## IN SILICO


0110011
QSAR
IS NOT
SCIENCE FICTION

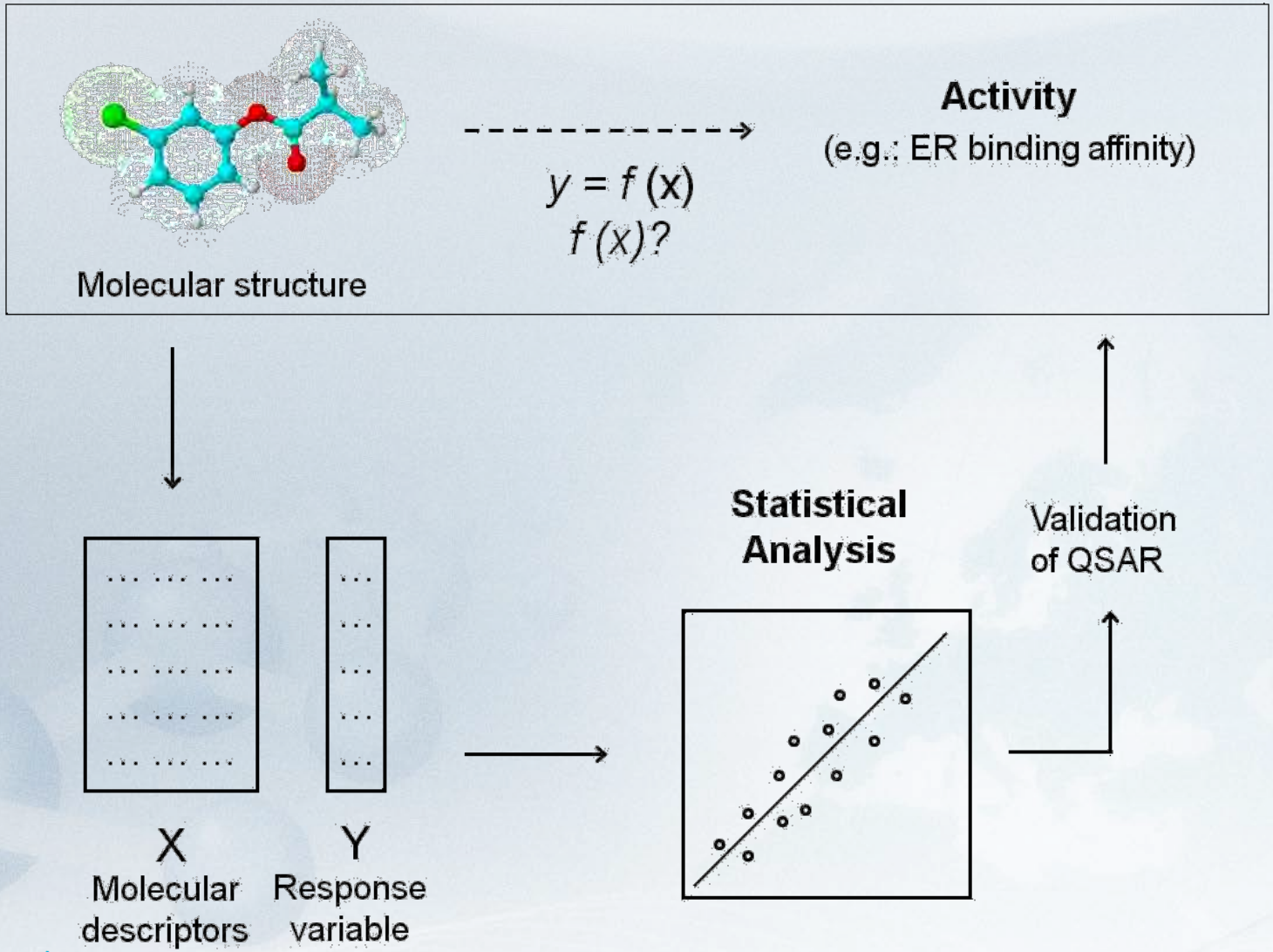

QSAR
is not
a magic

# HUMAN EXPERTS HAVE IDENTIFIED LINKS BETWEEN STRUCTURE AND TOXICITY

## *ASHBY* identified a list of RESIDUES for GENOTOXIC EFFECT



# BUILDING UP QSAR



# FROM CHEMICAL COMPOUNDS TO DESCRIPTORS

**Chemical compound**
**(real)**

↓

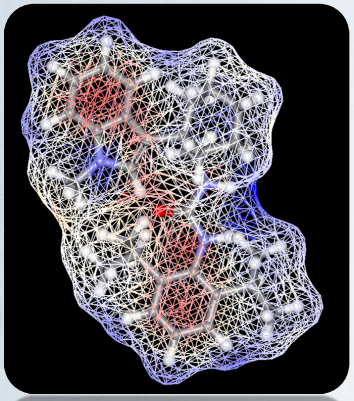
**Structural representation**
**(model)**

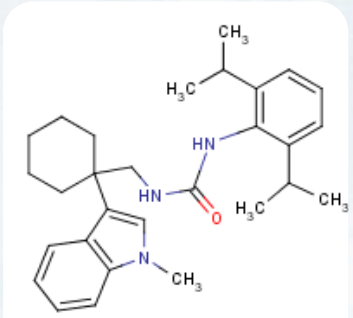
↓

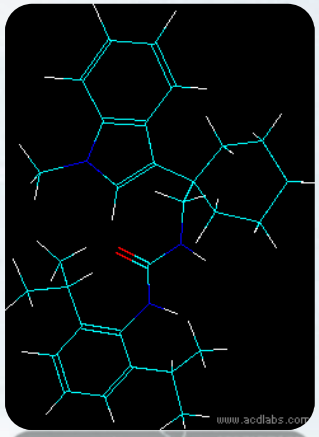
**Chemical descriptors**

**CAS RN. 145131-25-5**
N-(2,6-Bis(1-methylethyl)phenyl)-N'-((1-(1-methyl-1H-indol-3-yl)cyclohexyl)methyl)urea

CC(C)C1=CC=CC(C(C)C)=C1NC(=O)NCC2(CCCCC2)C3=CN(C)C4=C3C=CC=C4

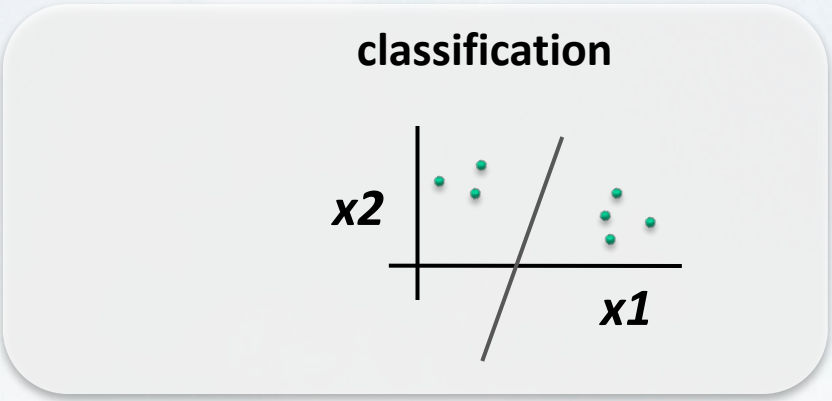




# ALGORITHMS

- Discriminant Analysis
- CART
- KNN
- Fuzzy logic
- Multi Variate Analysis (MVA)
- Self Organizing Map (SOM)
- Support Vector Machine (SVM)

# UNITED STATES / 1

## US EPA

### New Chemicals Program
### Industrial Chemicals

Section 5 of **TSCA** (**Toxic Substance Control Act**) requires a **manufacturer and/or importer** of a **new chemical substance** to submit a **premanufacture notice** (**PMN**) to US EPA ***90 days before*** commencing manufacture or import of the new chemical

# UNITED STATES / 2

## US EPA

- Decisions often made in the **absence** of any **experimental data**
- **SAR methods** and **(Q)SAR developed** to help **reviews**
- US EPA evaluates approximately **1500-2000 PMN cases** a year

# TARGET is *Environment / Man*

target

*in vivo* model

*in silico* model

# Seven Reasons

## to use QSAR

1. ***Innovation*** *(also in view of thousands of new data - ToxCast)*
2. ***Time for experiments***
3. ***Occurrence of enough laboratories/resources***
4. ***Reduction of costs***
5. ***Use of animals***
6. ***Prioritization needs***
7. ***Pro-active approach for greener chemicals***

MARIO NEGRI ISTITUTO DI RICERCHE FARMACOLOGICHE

ECT Environment Chemistry Toxicology

# REACH and QSAR

**According to *REACH regulation* (Annex XI)**

**a (Q)SAR is VALID if:**

- **the model is recognized *scientifically valid*;**
- **the substance is included in the *applicability domain* of the model;**
- **results are *adequate* for *classification and labelling and for risk assessment*;**
- ***adequate documentation* of the methods provided.**

# different performances for different endpoints

- ***Physico-chemical properties have low experimental variability and many data***

- ***Chronic human toxicity has high variability and low number of data***

# endpoint specificity

- *Refer to the uncertainty of the experimental original data: if it is high, it is legitimate to accept lower performance for QSAR*
- *Use high quality data*
- *Refer to the data cardinality: models based on higher number of compounds are more general*

**250 QSAR models listed**

**for 38 endpoints**

**70 free QSAR models**

www.antares-life.eu

CAESAR ORCHESTRA antares Ministero della Salute CAESAR ORCHES

Use QSAR/read across

About QSAR/read across

QSAR Regulation & Research

## News & Updates

**February 03th 2011**
MUTAGENICITY v 2.0 Standalone Version for download

**October 19th 2010**
The new version of CAESAR website online

Contributors

## On site

**February 03th 2011**
MUTAGENICITY v 2.0 Standalone Version for download

**October 19th 2010**
The new version of CAESAR website online

fera The Food and Environment Research Agency

POLITECNICO DI MILANO

MARIO NEGRI ISTITUTO DI RICERCHE FARMACOLOGICHE

KnowledgeMiner Software

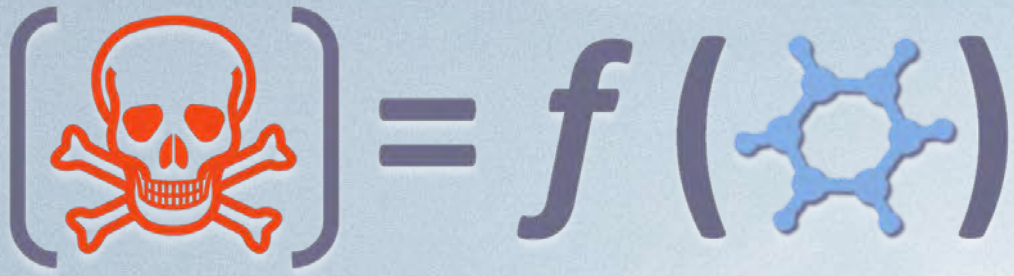


WebDesign AGDesigner

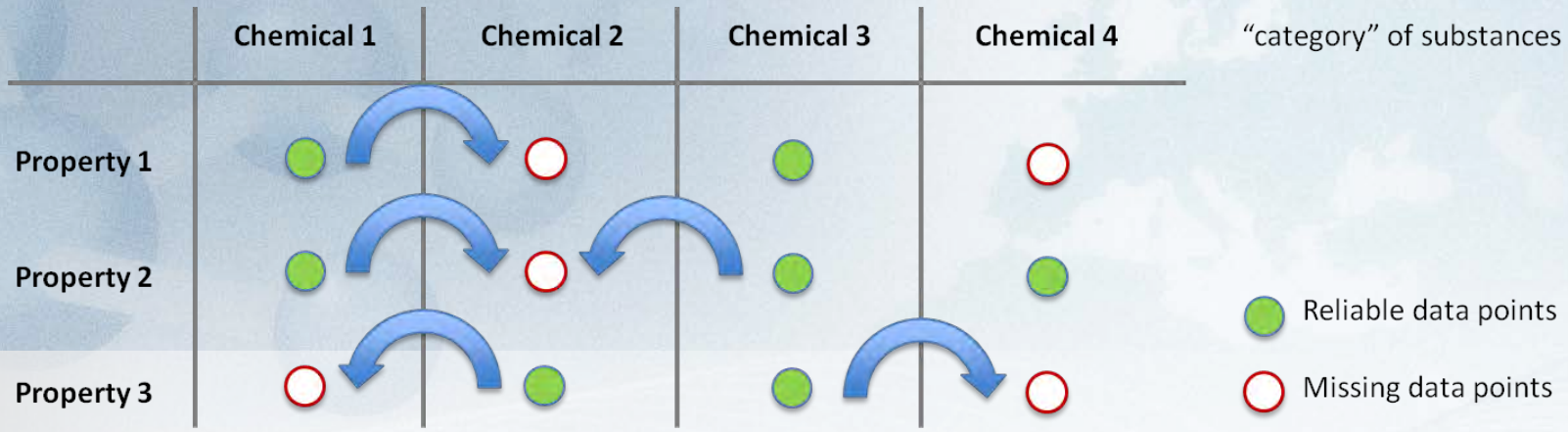
# VEGA MODELS


All
Prioritize
PBT
vPvB
CMR
Tox
Carcinogenicity
Mutagenicity
Developmental tox
Skin sensitisation
Ecotox
Fish
Daphnia
Environ
Bio concentration
Persistence
Phys-Chem
LogP
INSERT

# VEGA combines QSAR and read-across



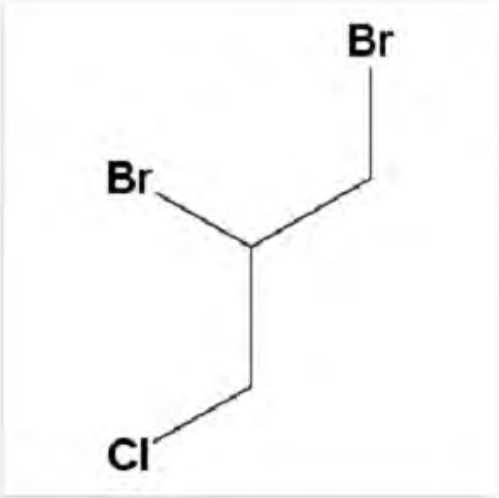
## READ-ACROSS



# VEGA: QSAR + read across

- *VEGA combines QSAR and read across*
- *QSAR and read across are based on independent software*
- *VEGA automatically evaluates the prediction reliability*
- *Effort  to make objective some evidences*
- *The user should always use its/her experience*
- *VEGA assists the human expert*
- *VEGA = collaboration between computer and expert*
- *Expert can override QSAR using read across*

# the Applicability Domain Index




Compound: 138
Compound SMILES: C(C(CBr)Br)Cl
Prediction: 1.649 [log units]
Prediction: 45 [L/Kg]
Prediction from model 1 (HM): 1.754 [log units]
Prediction from model 2 (GA): 1.614 [log units]
Structural Alerts: -
Calculated LogP: 2.957 [log units]
Experimental value: -
Reliability: Compound could be out of model AD
Remarks for the prediction:

**Global AD Index**
AD Index = 0.7
Explanation: predicted substance could be out of the Applicability Domain of the model.

**Similar molecules with known experimental value**
Similarity index = 0.753
Explanation: strongly similar compounds with known experimental value in the training set have been found.

**Accuracy (average error) of prediction for similar molecules**
Accuracy index = 0.295
Explanation: accuracy of prediction for similar molecules found in the training set is good.

**Concordance with similar molecules (average difference between target compound prediction and experimental values of similar molecules)**
Concordance index = 1.025
Explanation: similar molecules found in the training set have experimental values that completely disagree with the target compound predicted value.

**Maximum error of prediction among similar molecules**
Max error index = 0.33
Explanation: the maximum error in prediction of similar molecules found in the training set has a low value.

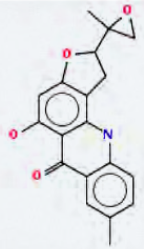
**Atom Centered Fragments similarity check**
ACF matching index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

**Descriptors noise sensitivity analysis**
Noise Sensitivity = 0.922
Explanation: predictions has a good response to noise scrambling, thus shows a good reliability.

**Model descriptors range check**
Descriptors range check = true
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

# adi: similarity search

Prediction for the compound no. 1: Cc1ccc2Nc3c4CC(Oc4cc(O)c3C(=O)c2c1)C1(C)CO1

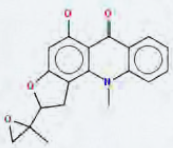


Activity: Mutagen

Remarks for the prediction:

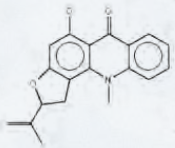
**VISUALIZATION OF SIMILAR SUBSTANCES**

The following chemicals similar to the query compound have been identified in the CAESAR database:



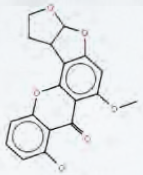
Dataset id: 10
SMILES: O=C5c1ccccc1N(c3c5(c(O)cc2OC(Cc23)C4(OC4)(C)))C
Similarity: 0.99

Experimental class: Mutagen
Predicted class: Mutagen



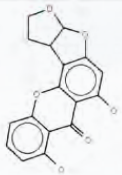
Dataset id: 772
SMILES: O=C2c1ccccc1N(c4c2c(O)cc3OC(C(=C)C)Cc34)C
Similarity: 0.922

Experimental class: Mutagen
Predicted class: Mutagen



Dataset id: 1963
SMILES: O=C1c5c(O)cccc5(Oc3c1c(OC)cc2OC4OCCC4(c23))
Similarity: 0.828

Experimental class: NON-Mutagen
Predicted class: NON-Mutagen

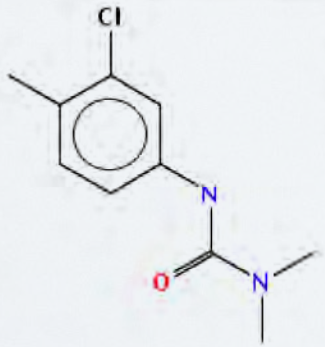


Dataset id: 3769
SMILES: O=C4c5c(O)cccc5(Oc2c4(c(O)cc1OC3OCCC3(c12)))
Similarity: 0.825

Experimental class: NON-Mutagen
Predicted class: NON-Mutagen

# adi: accuracy of prediction for similar molecules

Prediction for the compound no. 1: CN(C)C(=O)NC1=CC(Cl)=C(C)C=C1

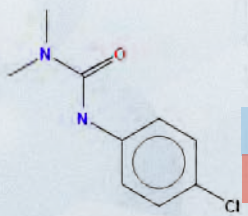



Carcinogenic: Non-Positive

Class indices: Positive=0.079, Non-Positive=0.921

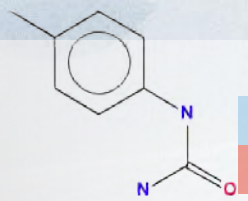
Remarks for the prediction:

The following chemicals similar to the query compound have been identified in the CAESAR database:




Dataset id: 162
SMILES: Clc1ccc(cc1)NC(=O)N(C)C
Similarity: 0.884

Experimental class: Positive
Predicted class: Non-Positive




Dataset id: 754
SMILES: O=C(Nc1ccc(cc1)C)N
Similarity: 0.857

Experimental class: Non-Positive
Predicted class: Positive

# RISKCYCLE PROJECT AND IN VITRO

***Perfluorinated compounds (PFCs) are a family of fluorine-containing chemicals used in different applications to make materials oil and water resistant.***

***Using in vitro and computational predictive models for the carcinogenicity endpoint, SETAC Berlin 2012.***

# Riskcycle project and in silico

***Freely available software for hazard estimation;***
***EPA models: T.E.S.T., ECOSAR, Episuite,..***
***VEGA: CAESAR, CORAL and SARpy***
***Toxtree***
***LAZAR***

***Commercial models and databases***

***Used for the prediction of tens of additives within Riskcycle project.***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Azadi Golbamaki
Antonio Cassano
Alla Toropova
Andrei Toropov
Thank you for your time and valuable inputs!
GRAZIE!

# ERICA approach to assess the risk of recycled products (Ecotoxicological Risk Index for a Chemical Assessment)

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# (**E**nvironmental **R**isk **I**ndex for a **C**hemical **A**ssessment)


- Physico-chemical Properties
- Toxicological Properties
- Ecotoxicological Properties
- Environmental Fate and Transport
- Uncertainty (missing data – unreliable data)
- …

**ERICA UNIQUE VALUE**

E. Boriani, A. Mariani, D. Baderna, C. Moretti, E. Benfenati.
"**ERICA: a multiparametric toxicological risk index for the assessment of environmental healthiness.**". Environmental International, 36 (2010) 665–674
E. Boriani. **"Assessing the environmental risks associated with contaminated sites"**, PhD thesis, The Open University, Milton Keynes, UK, 2010

# WHAT IS ERICA ?

- Multiparametric eco/toxicological risk index
- Risk assessment and prioritization strategy
- A condensed information in an unique value

# SOME SIMPLE QUESTIONS IN FEW MINUTES:

- WHY A UNIQUE NUMBER?
- HOW IS ERICA CALCULATED?
- WHO WILL APPLY ERICA?

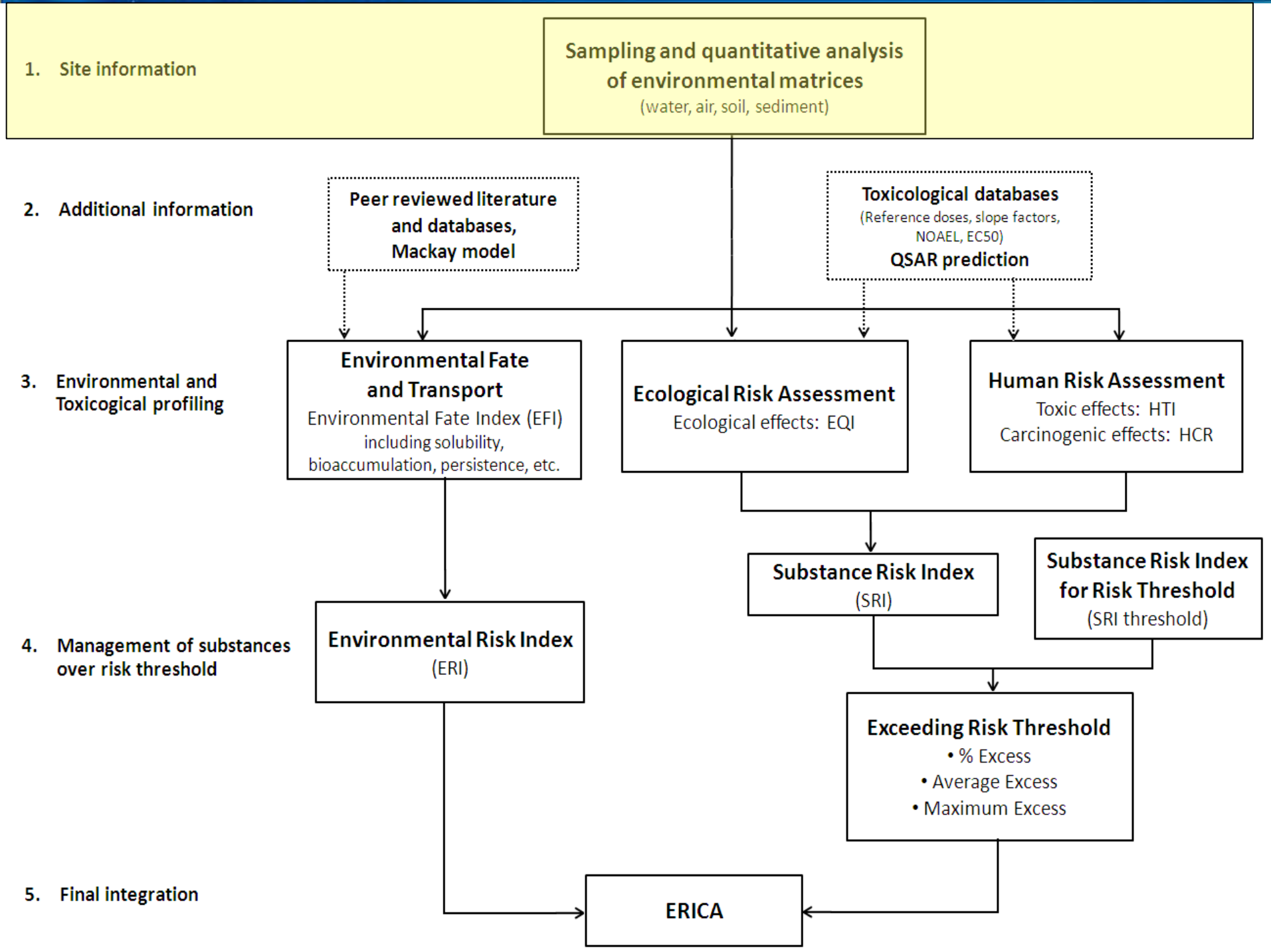
# A UNIQUE NUMBER

ERICA CONDENSED INFORMATION:

- Simple but reproducible approach
- Considers the impact of chemicals present or released
- Classification of health status of a territory /situation (space and time dimensions)
- Tool for environmental management
- Strong scientific basis
- Possible to analyze the detailed assessment

| Environmental and health status | |
|---|---|
| Environmental Quality | ERICA |
| VERY GOOD | < 25 |
| GOOD | 25-49 |
| MODERATE | 50-99 |
| UNHEALTHY FOR SENSITIVE GROUPS | 100-149 |
| UNHEALTHY | 150-199 |
| VERY UNHEALTHY | 200-299 |
| DANGEROUS | 300-399 |
| EXTREMELY DANGEROUS | > 400 |

# HOW IS ERICA CALCULATED ?


1. Site information
Sampling and quantitative analysis of environmental matrices
(water, air, soil, sediment)
2. Additional information
Peer reviewed literature and databases, Mackay model
Toxicological databases
(Reference doses, slope factors, NOAEL, EC50)
QSAR prediction
3. Environmental and Toxicogical profiling
Environmental Fate and Transport
Environmental Fate Index (EFI) including solubility, bioaccumulation, persistence, etc.
Ecological Risk Assessment
Ecological effects: EQI
Human Risk Assessment
Toxic effects: HTI
Carcinogenic effects: HCR
Substance Risk Index
(SRI)
Substance Risk Index for Risk Threshold
(SRI threshold)
4. Management of substances over risk threshold
Environmental Risk Index
(ERI)
Exceeding Risk Threshold
• % Excess
• Average Excess
• Maximum Excess
5. Final integration
ERICA

| | |
|---|---|
| **ERICA = [(ERIE x 100) / ERIE $_{\text{risk threshold}}$] x ITE** | **ITE = 1+ (AE x ME)**<br>AE= average exceeding<br>ME= max exceeding |
| ERIE = (1+**E%**) x <ERI> | |
| <ERI>= ($ERI_1$+ $ERI_2$ $ERI_3$ + …+ $ERI_x$)/$x$ | **%E** = (NEP / NIC) x 100<br>NEP=number of pollutants exceeding the risk threshold, with PI>1<br>NIC=number of investigated priority compounds |
| **PI** = $SRI_{toxicant}$ / $SRI_{threshold}$ | PI >1 exceeding risk threshold |
| EFI = 1 + [($EF_{compound}$ – $EF_{min}$) / $EF_{max}$] | $EF_{compound}$ = (S + M) / V + BCF+P<br>S=solubility, M=motility, V=volatility, BCF=bioconcentration factor, P=persistency |
| **SRI** = (0.5 x **EQI**) + (0.25 x **HTI**) + (0.25 x **HCR**) | |
| **HCR** = ($sCR_{soil}$ x $D_{soil}$) + ($sCR_{water+sediment}$ x $D_{water+sediment}$) + ($sCR_{air}$ x $D_{air}$) | CR = CDI x SF<br>SF=slope factor [ $mg^{-1}$ kg d] |
| **HTI** = ($sHQ_{soil}$ x $D_{soil}$) + ($sHQ_{water+sediment}$ x $D_{water+sediment}$) + ($sHQ_{air}$ x $D_{air}$) | HQ = CDI/RfD<br>RfD= reference dose [mg $(kg\ d)^{-1}$] |
| **EQI** = ($sEQ_{soil}$ x $D_{soil}$) + ($sEQ_{water+sediment}$ x $D_{water+sediment}$) + ($sEQ_{air}$ x $D_{air}$) | D = 1+[(9.5*distribution %) / 100] |

# WHO WILL APPLY ERICA?

- **ASSESSORS, POPULATION, MAYORS, REGULATORS, INDUSTRY, SCIENTISTS**

**WHY?**

- **concise, transparent, clear parametres**
- **to get a comprehensive picture of the general situation of a critical compound/area**
- **prioritization**
- **functional for an in depth risk analysis of potentially dangerous compounds also along both time and space dimensions**

# ERICA APPLIED TO RECYCLED PRODUCTS

Data of environment toxicity, human toxicity, human carcinogenicity, physico-chemical properties

- For each chemical
- For main exposure scenario

→**Purposes:**

1) **Prioritization**
2) **environmental fate**

# HAZARD LIMIT

- the limit when an adverse effect starts to occur to any endpoint

- different from the legislative limit that is a compromise related to the risk management process.

# DATA REQUIRED

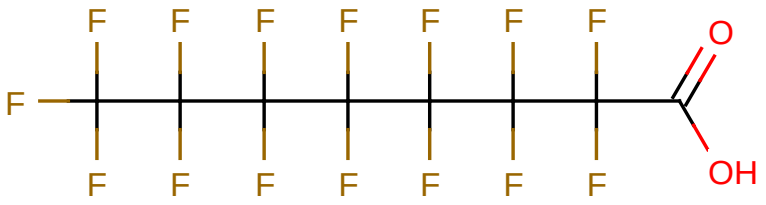
-physico-chemical and eco/toxicological properties, fate and transport properties

-these data can be derived from

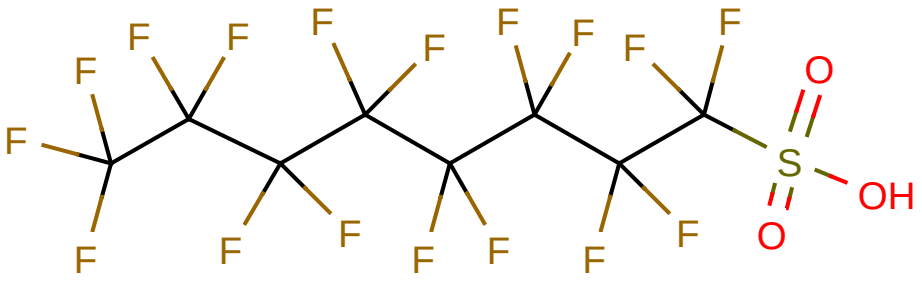
- peer-reviewed literature,
- international databases,
- experimental values or
- predicted using quantitative structure–activity relationship (QSAR) models.

| Identifier | Physico-Chemical properties | Environ. parameters | Ecotoxicological data | Toxicological data |
|---|---|---|---|---|
| Chemical ID, Name, CAS number, SMILES | MW, Solubility, Koa, Kow, Kaw, Koc, Vapor Pressure | Biodegrad., BCF, BAF Mackay Model Level I, Level III – Fugacity model | Acute inhalatory toxicity, acute oral toxicity, acute water toxicity | Class of carcinogenicity, slope factor for ingestion, slope factor for inhalation, reference dose for ingestion |

Perfluorooctanoic acid (PFOA) is a synthetic, stable perfluorinated carboxylic acid and fluorosurfactant. It's a water and oil repellant. FOA can form as a breakdown product from a variety of precursor molecules such as PTFE and fluorotelomer-based polymers (i.e. fluorotelomer alcohols)

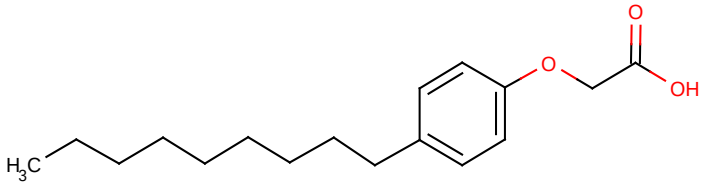



Perfluorooctanesulfonic acid (PFOS) is a man-made fluorosurfactant.
It was added to Annex B of the Stockholm Convention on Persistent Organic Pollutants in May 2009.PFOS can form from the degradation of precursors (about 50) in addition to industrial production.




Both compounds are considered as global pollutants.

(p-Nonylphenoxy)acetic acid (NPAA),
also known as (4-Nonylphenoxy)acetic acid,
is a biodisel fuel additive.
It can be also found in wastewater as a biodegradation product of Alkylphenol polyethoxylates, a non-ionic surfactants used in household cleaning products.



# MAIN INFORMATION ABOUT LUBRICANTS(1)

PFOA Perfluorooctanoic acid :

2010- DRAFT SCREENING ASSESSMENT by CANADIAN EA
http://www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&n=705376A7-1&offset=10&toc=show

2010- PROPOSAL FOR CLASSIFICATION AND LABELLING Ammonium pentadecafluorooctanoate, (APFO), a salt of Perfluorooctanic acid(PFOA) by Climate and Pollution Agency (Norway)

PFOS Perfluorooctane sulfonate:

2002- HAZARD ASSESSMENT OF PERFLUOROOCTANE SULFONATE (PFOS) AND ITS SALTS by OECD

# MAIN INFORMATION ABOUT LUBRICANTS (2)

NPAA(4-Nonylphenoxy)acetic acid:

2002 Reports and risk assessment data about 4-Nonylphenol (branched) and Nonylphenol

Few data about (4-Nonylphenoxy)acetic acid, REACH-SIEF report similarities and possibilities to use QSARs model to assess main eco/tox charactheristics

# Modelling resources

## PHYSICO-CHEMICAL DATA


```
SMILES : O=C(C=C)OCCCCCCCC(C)C
CHEM   : 2-Propenoic acid, isodecyl ester
CAS NUM: 001330-61-6
MOL FOR: C13 H24 O2
MOL WT : 212.34
---------- EPI SUMMARY (v3.12) ----------
Physical Property Inputs:
   Water Solubility (mg/L):   ------
   Vapor Pressure (mm Hg) :   ------
   Henry LC (atm-m3/mole) :   ------
   Log Kow (octanol-water):   ------
   Boiling Point (deg C)  :   ------
   Melting Point (deg C)  :   -100.00

Log Octanol-Water Partition Coef (SRC):
   Log Kow (KOWWIN v1.67 estimate) =  5.07

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVIN v1.41):
   Boiling Pt (deg C):  258.36  (Adapted Stein & Brown method)
   Melting Pt (deg C):  11.48  (Mean or Weighted MP)
   VP(mm Hg,25 deg C):  0.0227  (Mean VP of Antoine & Grain methods)
   MP  (exp database):  -100 deg C
   BP  (exp database):  158 @ 50 mm Hg deg C

Water Solubility Estimate from Log Kow (WSKOW v1.41):
   Water Solubility at 25 deg C (mg/L):  3.034
      log Kow used: 5.07 (estimated)
      melt pt used: -100.00 deg C

Water Sol Estimate from Fragments:
   Wat Sol (v1.01 est) =  2.3895 mg/L
```

## Validated QSAR models from

**EPISUITE (v 4.00)[1],**

**CAESAR EU Project[2]**

**VEGA platform[3]**

[1]http://www.epa.gov/oppt/exposure/pubs/episuite.htm

[2] www.caesar-project.eu

[3]www.vega-qsar.eu

# PROBLEMS / UNCERTAINTY

-log $K_{ow}$ is a problematic parameter for ionized surfactants because of their tendency to aggregate at the interface of a liquid–liquid system.

- Other effects to be considered (Endocrine Disruptors)

- Quantity of compounds in the environment

# Ecotoxicological Profile

- Predicted No-Effect Concentration ecotoxicological values (PNECs) using toxicity values for the most sensitive species.
- information about aquatic, oral and inhalation toxicity.
- data sources: experimental standard tests, international databases, peer-reviewed literature, official papers and QSAR models.

PNECs values can be derived from LC50, EC50 or NOEL values using dedicated safety factors:

- = 1000 in case of data of acute toxicity (short-term, e.g. 4 days for fish);
- = 100 sub-acute toxicity data or No Observed Effect Level (medium term, e.g. 21 days for fish);
- = 10 for chronic data (Chronic = long term, e.g. 30 days for fish).

# Toxicological Profile

Human health effects are described by:

- Inhalation and Ingestion Reference Doses (RfD) for toxic, non-carcinogenic effects.
- Inhalation and Ingestion Slope Factors (SF) for carcinogenic effects.

Data sources: experimental standard tests, international databases, peer-reviewed literature, official papers and QSAR models.

In the case of missing previous risk assessment, values can be also derived from experimental or predicted values (EC50, LC50, NOEL) from animal in vivo studies (rat or mouse) using appropriated uncertainty factors:

- = 10000 in case of data of acute toxicity;
- = 1000 sub-acute toxicity data or No Observed Effect Level;
- = 100 for chronic data.

# **Example** of use for PRIORITIZATION:

## ENVIRONMENTAL FATE AND TRANSPORT INDEX

Solubility, Kow, Koc, BCF

Distribution in environmental compartment

Persistency

| | |
|---|---|
| PFOA | 12 |
| PFOS | 11.5 |
| NPAA | 8.5 |

# ERICA IMPROVEMENTS

Future perspectives

- Degradation
- Refinements
- Synergies

# ACKNOWLEDGMENTS

- Environmental and Industrial Hygiene Unit Mario Negri Institute
- Environmental Chemistry and Toxicology Lab Mario Negri Institute
- RISKCYCLE PROJECT

**THANK YOU**
**FOR YOUR ATTENTION**

# Towards QSAR based USEtox™ characterisation factors for assessing ecotoxicological impacts of emissions from plastic additives

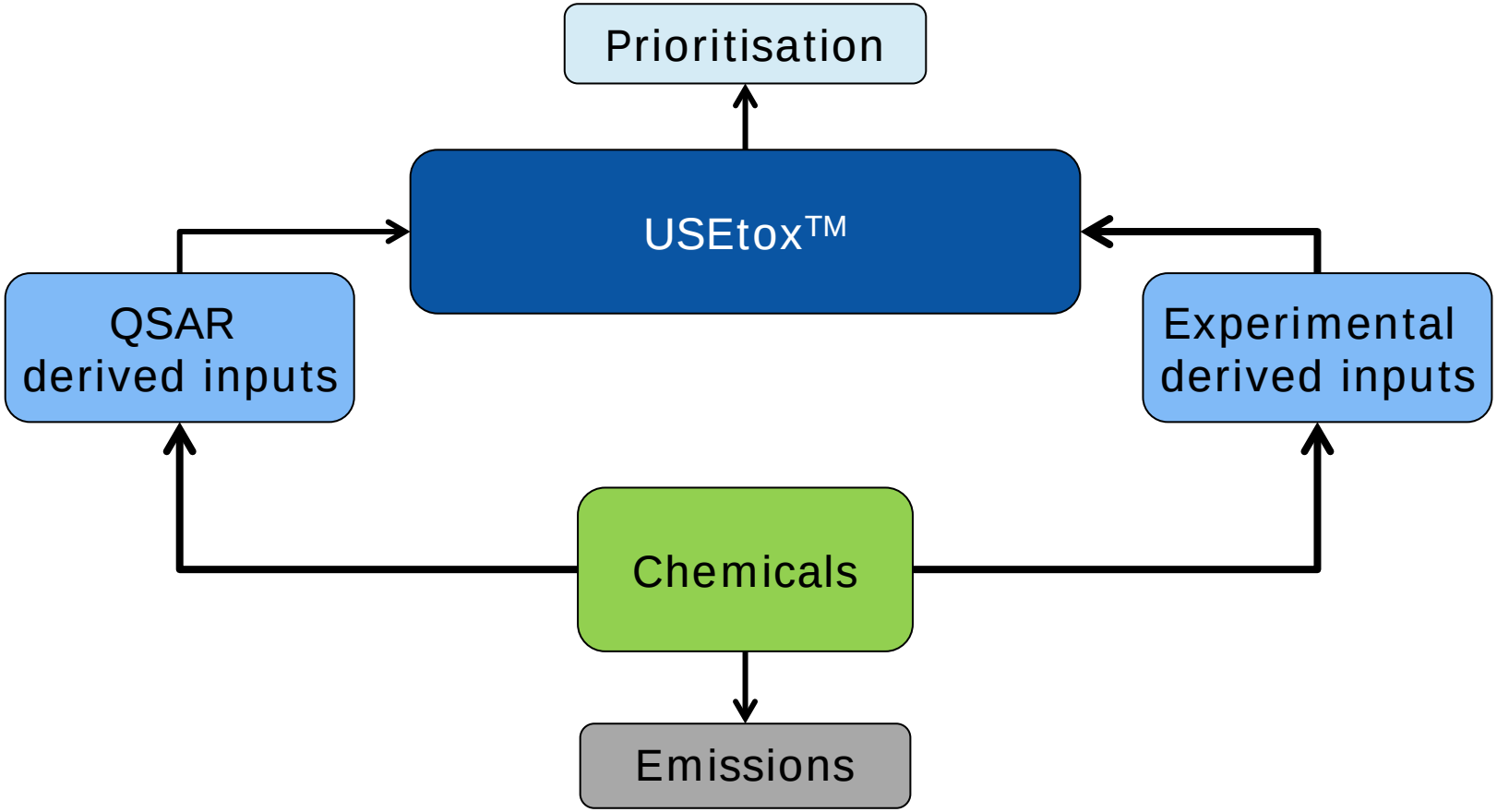
**Magnus Rahmberg**

**IVL Swedish Environmental Research institute**

# Introduction

- Every day a wide variety of chemicals are emitted into the environment.
- These emissions may pose a risk to the ecosystem and human health.
- To efficiently reduce this risk by implementing reduction measures or substitution, it is necessary to identify chemical emissions of concern.
- There is a need for a fast and easy-to-use screening tool to be able to do a first prioritisation.
- The use of QSAR models can speed up the screening process.

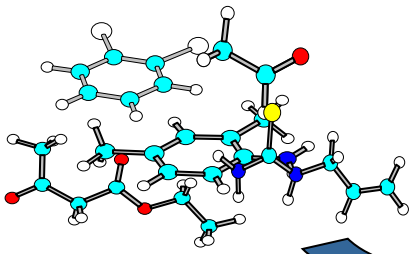
# Outline of study



# USEtox™

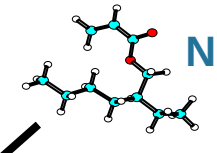
- USEtox™ model is an environmental model for characterisation of human and ecotoxicological impacts in Life Cycle Impact Assessment (LCIA).
- Focus in this study on ecotoxicological impacts.
- Calculates Characterisation Factor, CF.
- CF = FF × XF × EF, were FF= fate factor, XF= exposure factor and EF= effect factor.
- EF based on toxicity data.

# QSAR- Quantitative Structure-Activity Relationships

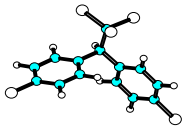


| | Microtox | Daphnia | Leuciscus | Alga |
|---|---|---|---|---|
| | pEC-50 | pEC-50 | pLC50 | pEC-50 |
| aceton | -2.23 | -2.17 | -2.29 | |
| Acrolein | | | 1.35 | |
| AcryCOOH | | -0.21 | -0.64 | |
| Am-TA | | -1.31 | | 0.32 |
| aniline | 0.13 | 0.31 | 0.18 | 0.69 |
| Balk | 0.23 | 0.29 | | |
| bensen | 0 | 0.45 | 0.37 | |
| DCP23 | 1.53 | 1.5 | | 1.51 |
| DCP24 | 2.14 | 1.78 | 1.51 | 1.07 |

(Model not valid)



New chemical



New chemical

QSAR model

pEC50, pLC50...

# QSAR – OECD principles

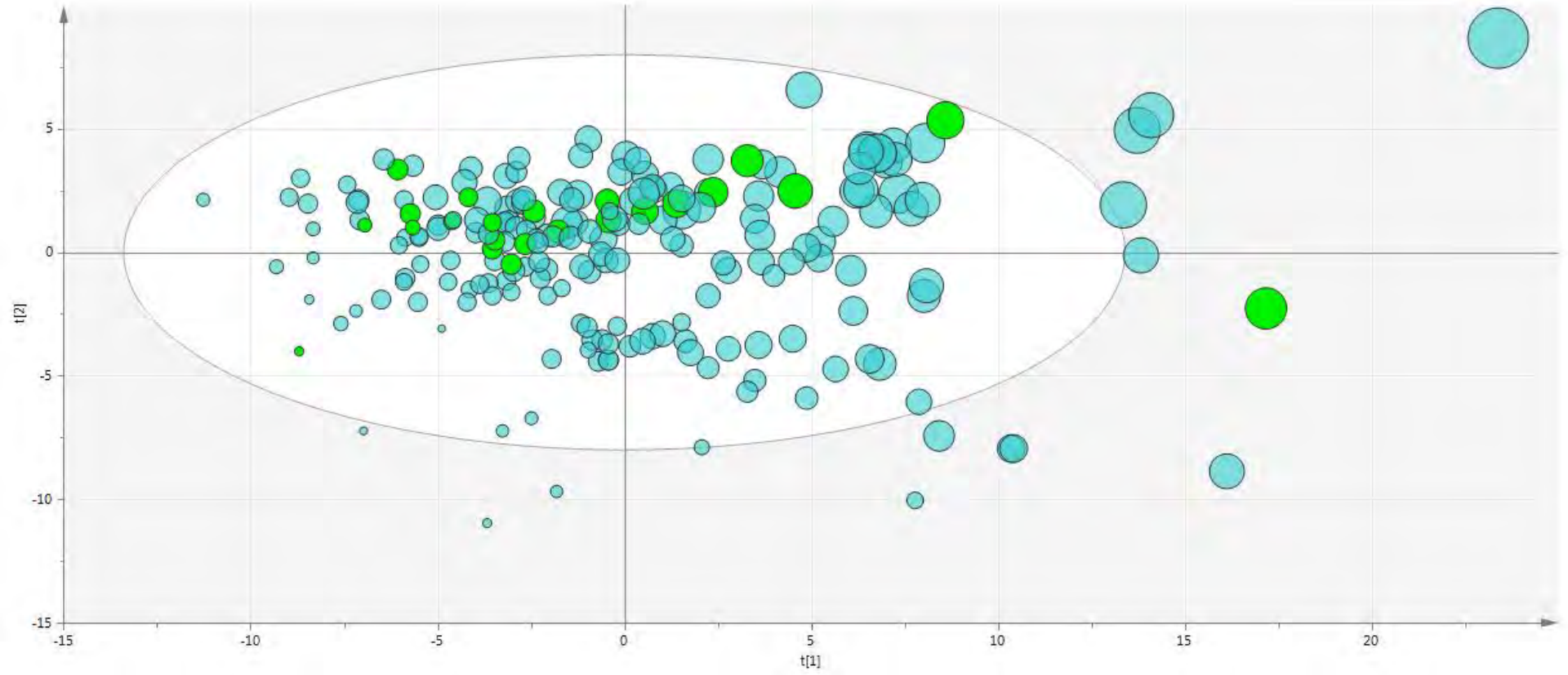
- A defined endpoint
- An unambiguous algorithm
- A defined domain of applicability
- Appropriate measures of goodness-of-fit, robustness and predictivity
- A mechanistic interpretation, if possible

# QSAR – Calculation

T.E.S.T. software, Toxicity Estimation Software Tool, from US EPA, (version 4.0).

- Fathead minnow $LC_{50}$ (96 hour)
- Daphnia magna $LC_{50}$ (48 hour)

# Chemicals - Plastic additives



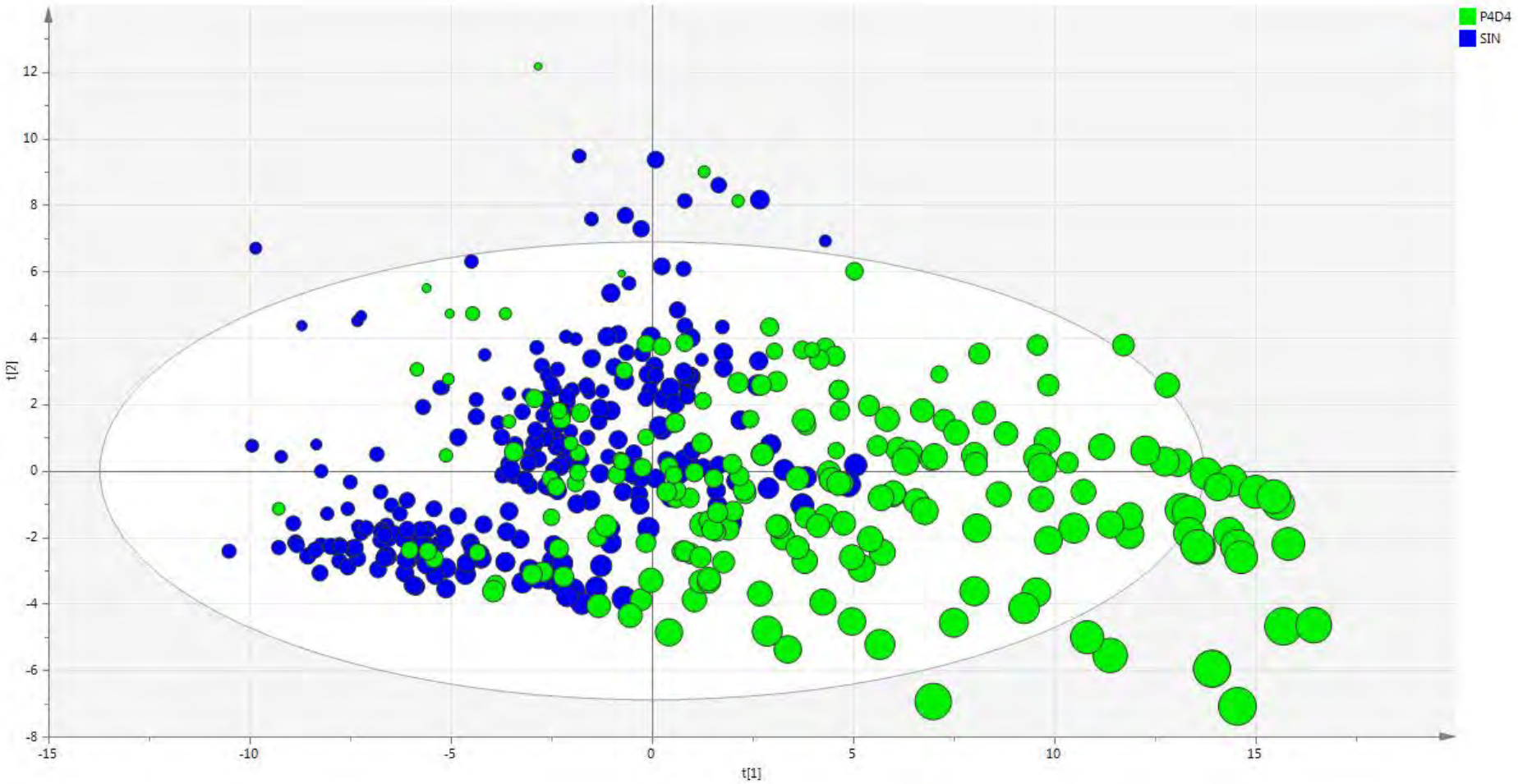
# Results plastic additives

- Characterisation factors calculated for 196 chemicals out of 211.
- For comparison of CF calculated data from USEtox™ with QSAR based data 39 substances with data for both sets were available.
- 13 reported in USEtox™ as interim.
- 3 substances only QSAR toxicity data for 1 species.
- Correlations not significant between the two sets.
- Overestimate of the CF based on toxicity QSAR models.

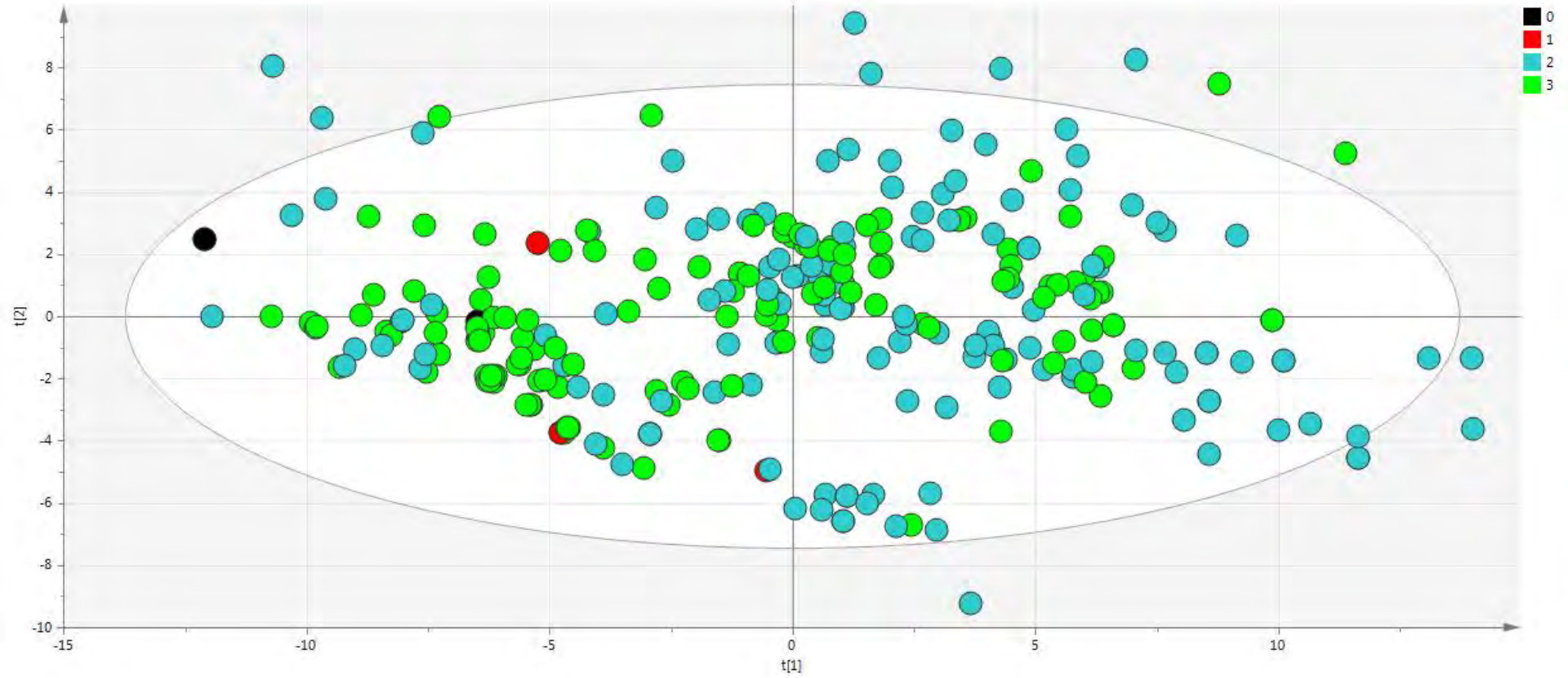
# Improvements

- Extended dataset for comparison and evaluation.
  – SIN (Substitute It Now!) List
- Add QSAR derived ecotoxicity for another trophic level.
  – QSAR toolbox used for Algae
  Danish EPA QSAR model for
  Pseudokirchneriella subcapitata $LC_{50}$ (48h)

# SIN List vs. plastic additives



# SIN List



# Results SIN List

- 138 substances could be calculated for 3 species.
- Comparing the ecotoxicity values between USEtox™ and QSAR derived values there were a underestimated for large concentrations but for small concentration there were an overestimate instead.
- With this approach the risk for underestimate the CF were almost eliminated.
- Ranking the chemicals based on QSAR derived inputs will give an indication of the potential risk.

# Further research

For more reliable estimation that are comparable to CF calculated in USEtox™ based on experimental data improvements are needed.

- Include uncertainty estimations for QSAR.
- Develop local/specific QSAR models for the data set in question.
- Specie to specie interpolation.

# Acknowledgment


- Tomas Rydberg, Jenny Westerdahl, Hanna Andersson
- Patrik Andersson, Umeå University