REACH
Cost Saving Potential by Alternative Testing Approaches

4th REACH Registration Expo
27 – 28 May 2008, Seoul/Korea

Dr. Dieter Drohmann

Managing Director

Chemservice S.A.

51, Route de Mondorf, L-5552 Remich, Luxemburg

Tel.:+352-2666-4923 Fax:+352-2666-4924

d.drohmann@chemservice-group.com www.chemservice-group.com

CHEMSERVICE

Why do we need Data on Chemicals?

- Data on intrinsic properties determine hazard
- Hazard information is pre-requisite for determining most appropriate and cost-effective risk management measures ensuring safe use
- No hazard information
  - Uncertain and/or insufficient protection level
  - Over-protection to be on the safe side (precautionary principle)

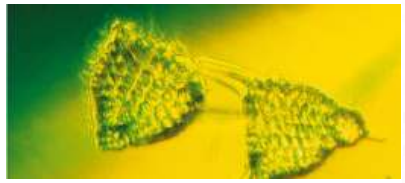
CHEMSERVICE

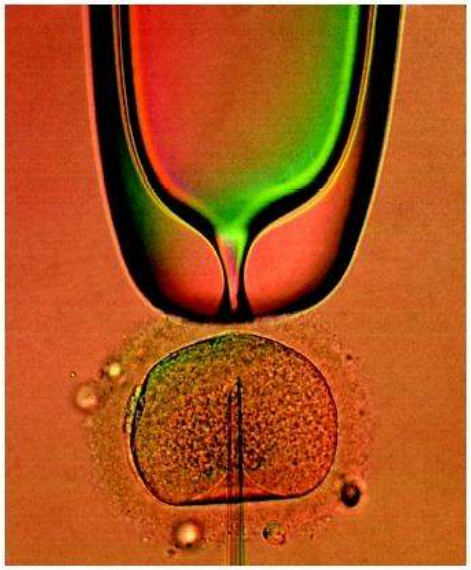
What data do we need?

- Physico-chemical properties, e.g.
  - Flammability, explosivity
  - Vapour pressure
- Health properties, e.g.
  - Acute and chronic effects
  - Carcinogenicity
- Environmental properties, e.g.
  - Degradation
  - Short and long term effects on aquatic species

CHEMSERVICE

How to obtain data?





- Laboratory tests
  - *In vivo* tests (animal tests)
  - *In vitro* tests (cell cultures)
  - Other tests (e.g. fate studies)
- Epidemiology
- Estimation methods – Computational Toxicology (*In silico*)
  - Qualitative [Structure-Activity Relationships (SAR), Read-Across, Grouping]
  - Quantitative Structure-Activity Relationships (QSAR)
- Waiving [abandonment]
  - Testing is technically difficult or impossible
  - Testing makes no sense
  - Low exposure

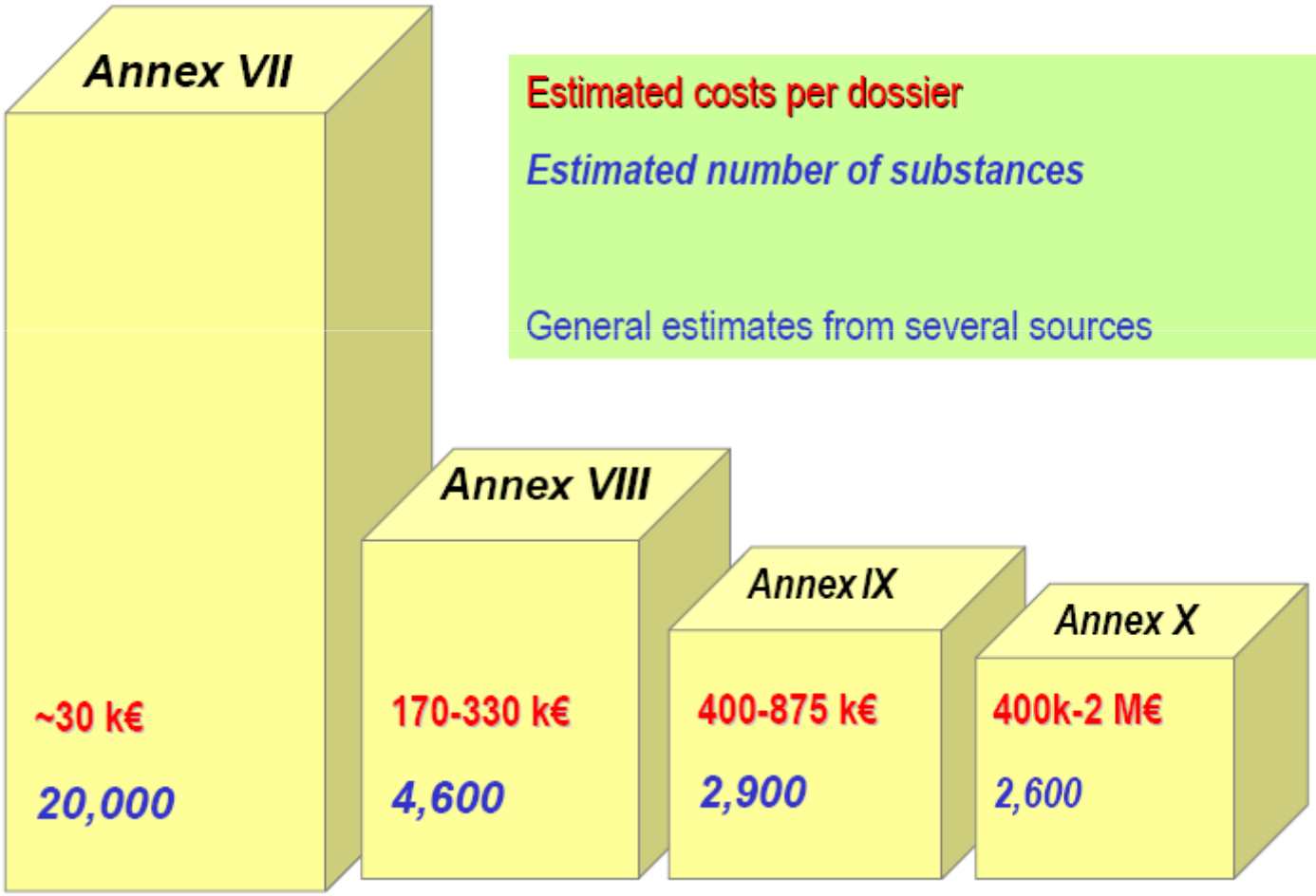
CHEMSERVICE

REACH Data Requirements

- **Annex VII (≥ 1 tonne per year)**
  - Physicochemical properties
  - Human health: in vitro irritation, sensitization, mutagenicity, acute toxicity (one route)
  - Environmental: acute aquatic toxicity (daphnia, algae), biodegradation
- **Annex VIII (≥ 10 tonnes per year)**
  - Human health: including in vivo irritation, and 28-day repeat dose studies
  - Environmental: acute toxicity fish, fate studies (hydrolysis, adsorption / desorption)
- **Annex IX (≥ 100 tonnes per year)**
  - Long term, repeat dose, chronic toxicity, fate etc
- **Annex X (≥ 1000 tonnes per year = HPV)**
  - Further long term, repeat dose, chronic toxicity, fate etc

CHEMSERVICE

REACH Data Costs



Source: Van Leeuwen et al.

CHEMSERVICE

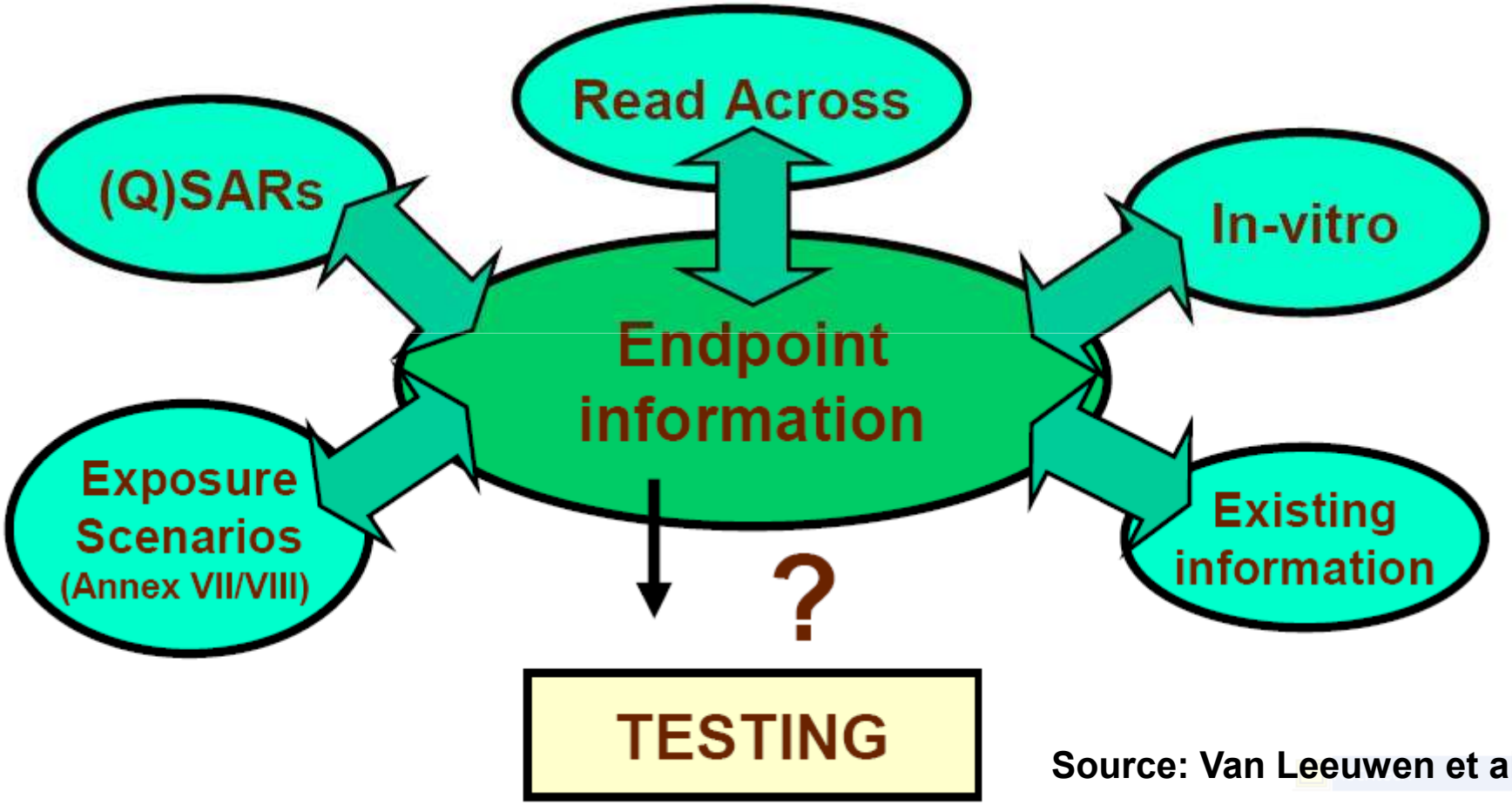
Availability of Data on HPV-Chemicals

- 14% - Base Set Data available
- 65% - Less than Base Set
- 21% - No Data

86%

Source: Hansen et al.

Intelligent Testing Strategies (ITS)



Source: Van Leeuwen et al.

CHEMSERVICE

In-silico-Testing / Computational Toxicology

- **Structure-activity relationship (SAR)**

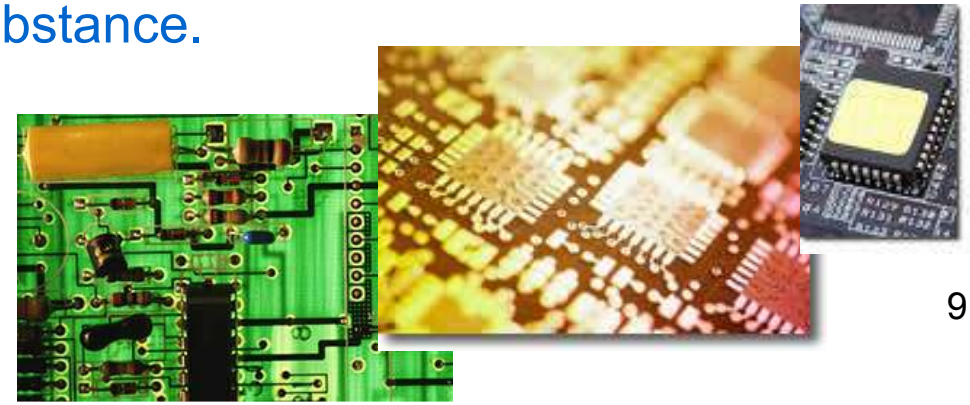
  A qualitative relationship between a (sub)structure and presence or absence of a property of interest is calculated.

- **Quantitative structure-activity relationship (QSAR)**

  A mathematical model is used for the relationship between quantitative chemical structure parameters and a property or activity of interest.

- **Quantitative structure-property relationship (QSPR)**

  Mathematical models will be used for the prediction of physico-chemical properties of a substance.



CHEMSERVICE

What is QSAR?

- Chemical structure determines properties of substances
- Structure characterised by molecular or physicochemical descriptors
- Quantitative structure-activity relationship is the process by which chemical structure is quantitatively correlated with a well defined process, such as biological activity or chemical reactivity.
- For example:
  - biological activity can be expressed quantitatively as concentration of a substance required to give a certain biological response. Additionally, when physiochemical properties or structures are expressed by numbers, one can form a mathematical relationship, or quantitative structure-activity relationship, between the two. The mathematical expression can then be used to predict the biological response of other chemical structures.
- QSAR's most general mathematical form is:
  - **Activity = *f*(physiochemical properties and/or structural properties)**

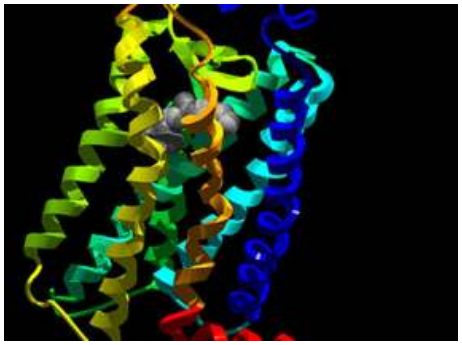
CHEMSERVICE

What is SAR?

- **Structure-activity relationship**s (**SAR**) are the traditional practices of medicinal chemistry which try to modify the effect or the potency (i.e. activity) of bioactive chemical compounds by modifying their chemical structure.
- Medical chemists use the chemical techniques of synthesis to insert new chemical groups into the biomedical compound and test the modifications in their biological effect.
- This enables the identification and determination of the chemical groups responsible for evoking a target biological effect in the organism. This method was later refined to build mathematical relationships between a chemical structure and its biological activity, known as (Q)SAR.

CHEMSERVICE

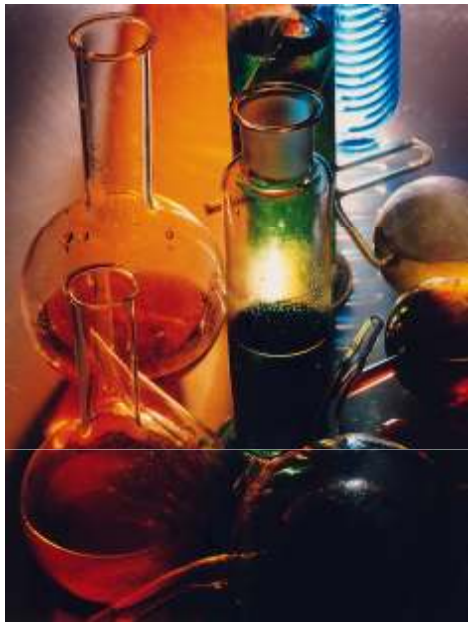
SAR Paradoxon



- The basic assumption for all molecule based hypotheses is that similar molecules have similar activities. This principle is also called **S**tructure-**A**ctivity **R**elationship (SAR). The underlying problem is therefore how to define a *small* difference on a molecular level, since each kind of activity, e.g. reaction ability, biotransformation ability, solubility, target activity, and so on, might depend on another difference.
- In general, one is more interested in finding strong trends. Created hypotheses usually rely on a finite number of chemical data. Thus, the induction principle should be respected to avoid overfitted hypotheses and deriving overfitted and useless interpretations on structural/molecular data.
- The SAR paradox refers to the fact that it is not the case that all similar molecules have similar activities.

CHEMSERVICE

Applications of (Q)SAR / QSPR



- Generation of information on
  - Physicochemical properties
  - (Eco)toxic potential and potency
  - Environmental distribution and fate
  - Biokinetic processes

- Regulatory processes
  - Assessment of available data to prioritise chemicals
  - Reduce testing, especially avoidance of animal testing
  - Ranking and grouping of chemicals for authorisation
  - Assessing membership of existing categories (“cross-reading”)
  - Quick identification of hazardous properties of chemicals

CHEMSERVICE

(Q)SAR Software

- More than 200 software's of (Q)SAR concern are available for free, free-online or by purchase.
- Software is available for 3-D-QSAR, Properties/Parameters, Toxicity prediction, Metabolism prediction, Data-analysis and modelling and ... and ... and ....
- For REACH, the relevant software solutions are used for toxicity prediction (e.g. skin sensitization and eye irritation), determination of physico-chemical properties and PBT and vPvB assessment.
- The choice of an appropriate software should be based on the applicability of the (Q)SAR domain, the validity of the evaluation, the training data set and the parameters (molecular descriptors) used.

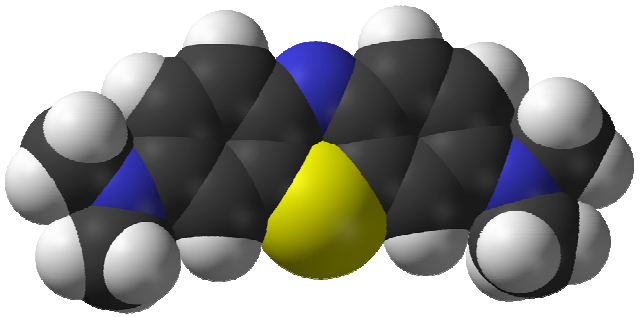
CHEMSERVICE

(Q)SAR Software - Examples

- Toxtree
- Toxmatch
- DART (Decision Analysis by Ranking Techniques)
- Danish QSAR Database

  → these softwares can be downloaded from the ECB website
- OECD (Q)SAR Application Toolbox

  → this software can be downloaded from the OECD website
- CASE/M-CASE
- HazardExpert
- OASIS
- SuCCSES
- OncoLogic



CHEMSERVICE

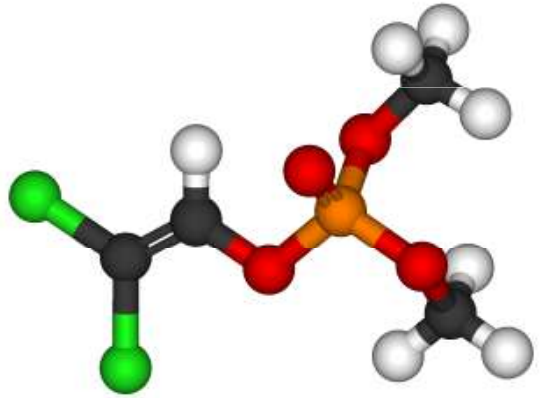
(Q)SAR Software - Examples

- **DSS BfR Toxtree**
- **MultiCASE Inc. (MC4PC), MDL®-QSAR, and TOPKAT®** (combine human expert decisions with statistical and correlative approaches)
- **DEREK® and OncoLogic®** (programs designed to capture and automate rules and decision trees based on human expertise)
- **PBT Profiler®** (screening for chemicals that potentially persist, bioaccumulate and be toxic to aquatic life
- **EPI Suite®** (suite of physico-chemical property and environmental fate estimation model)
- **ECOSAR®** (Ecological Structure Activity Relationships, is used to estimate the toxicity of chemicals used in industry and discharged into water)

These are not the only QSAR programs available!

(Q)SAR for E-fate Modelling

- The fate and behaviour of chemical in the environment in the regulatory context often uses modelling programs.
- E-fate depends on the biodegradability, volatilization, adsorption and dilution.
- Basic inputs are:
  - Molecular weight/structure
  - Water solubility
  - log P_{OW} (Octanol-Water partition coefficient)
  - Vapour pressure
  - k_{OC} (Organic carbon partition coefficient
  - Henry's law coefficient (air/water partition)
  - Biodegradability
- Based on a basic data set, the fate in the environment can be predicted.



CHEMSERVICE

(Q)SAR for E-fate Modelling

- The knowledge on the e-fate behaviour is basically for the PBT assessment.
- For chemicals regulation, modelling systems usually are used for the rapid screening of PBT substances.
- One example for PBT screening tool is the PBT Profiler, free accessible on the US EPA website.
- An example for an e-fate assessment tool is the Estimation Program Interface (EPI) Suite, free downloadable from the US EPA website.
- Different estimation models will be used to estimate the e-fate (e.g. KOWWIN, BIOWIN, BCFWIN).

CHEMSERVICE

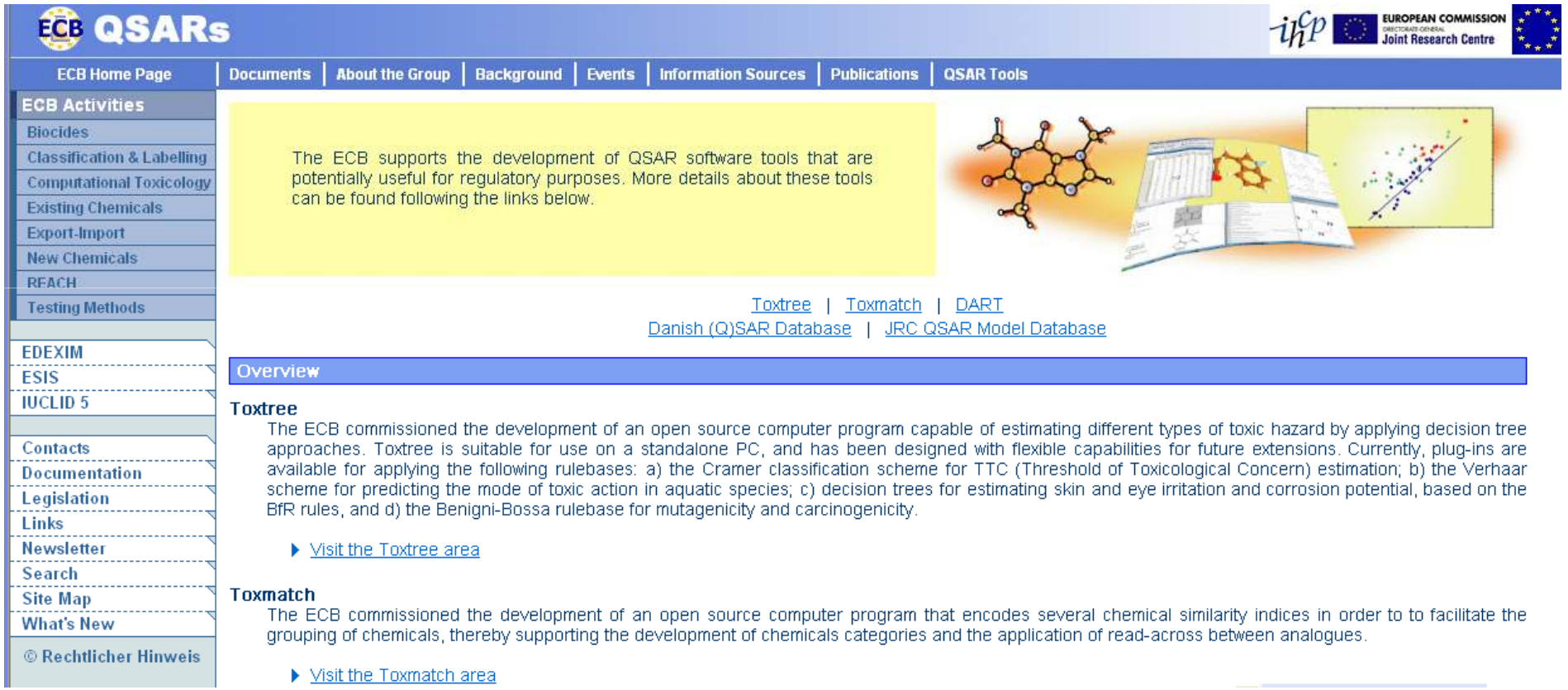
(Q)SAR Software - Links

Prediction of physico-chemical properties

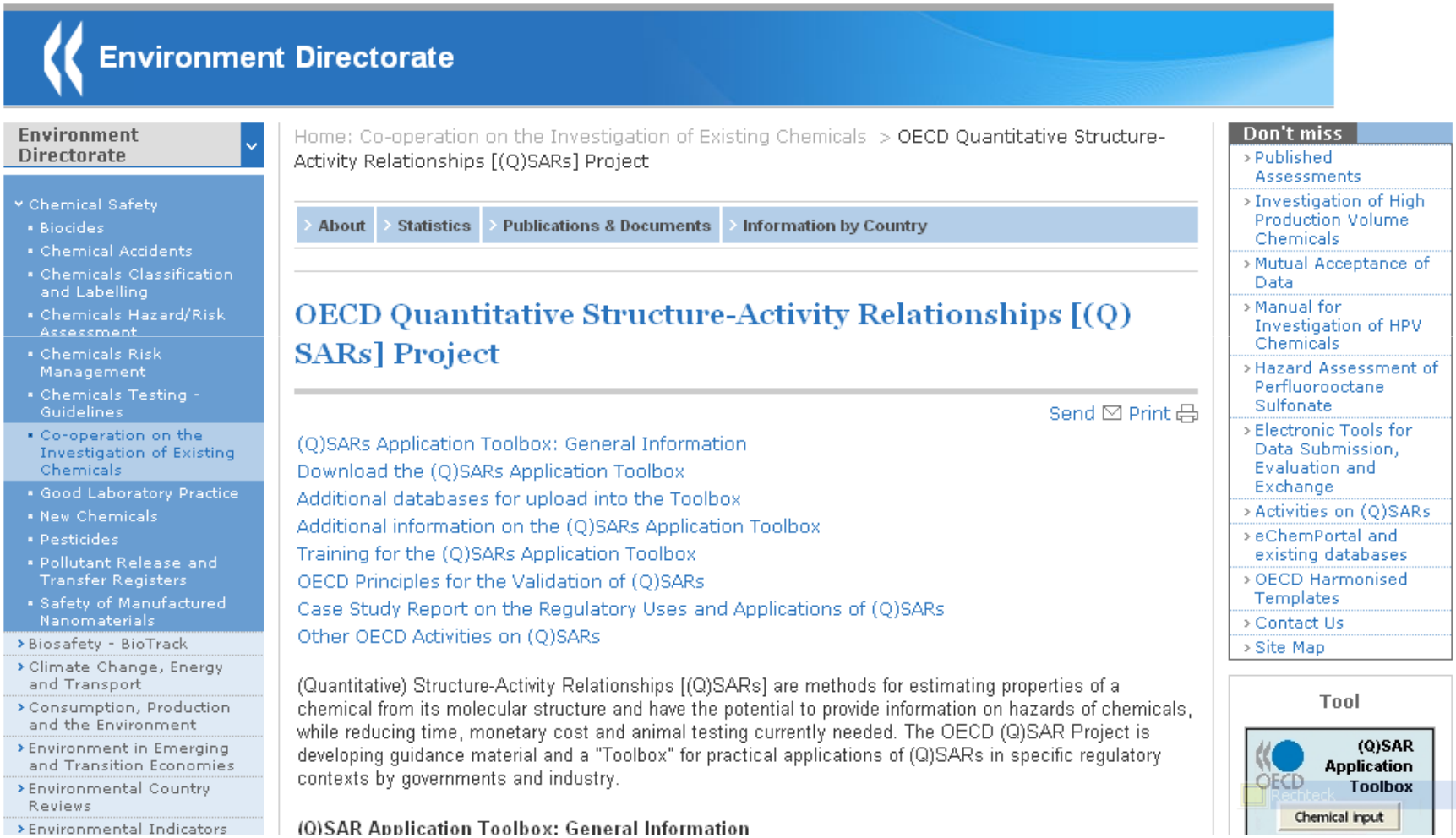
Software	Availability	Website address
ACD/Labs[a]	Purchase	www.acdlabs.com
ChemAxon	Purchase	www.chemaxon.com
ChemOffice	Purchase	www.cambridgesoft.com
ChemSilico	Purchase	www.chemsilico.com
ClogP	Purchase	www.daylight.com
Episuite	Freely downloadable	www.epa.gov/oppt/exposure/pubs/episuitedl.htm
Molecular Modeling Pro	Purchase	www.chemsw.com
PREDICT	Purchase	mwsoftware.com/dragon/
QikProp	Purchase	www.schrodinger.com
SPARC[d]	Free on-line	ibmlc2.chem.uga.edu/sparc
TSAR	Purchase	www.accelrys.com
VCCLAB	Free on-line	www.vcclab.org

CHEMSERVICE

QSAR at the ECB Website



QSAR at the OECD Website



CHEMSERVICE

QSAR at the US EPA Website

U.S. ENVIRONM

New Chemicals Program

Contact Us Search: All EPA This Area Go

You are here: EPA Home » Prevention, Pesticides & Toxic Substances » Pollution, Prevention & Toxics » New Chemicals Program » ECOSAR

- New Chemicals Home
- PMN Forms and Information
- Premanufacture Notice Status
- New Chemicals Policies
- Guidance Materials
- Chemical Categories Report
- Consent Orders and Significant New Use Rules
- ECOSAR: Ecological Structural Activity Relationships
- Importing and Exporting New Chemicals

Ecological Structure Activity Relationships

v. 0.99g, January, 2000

What is ECOSAR?

ECOSAR (Ecological Structure Activity Relationships) is a personal computer software program that is used to estimate the to discharged into water. The program predicts the toxicity of industrial chemicals to aquatic organisms such as fish, invertebrat Activity Relationships (SARs). The program estimates a chemical's acute (short-term) toxicity and, when available, chronic (lor

What is a Structure Activity Relationship (SAR)?

PBT-Profiler

PBT Profiler

A Component of OPPT's P2 Framework

Assessing Chemicals in the Absence of Data

Methodology · Criteria · Definitions · Chemicals That Should Not be Profiled

Home · Start a New Profile · Results · Terms of Use · Security

Results

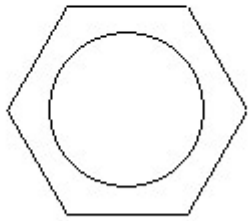
Orange or red highlights indicate that the EPA criteria have been exceeded.
Black-and-white version

Persistence | Bioaccumulation | Toxicity

71-43-2 Benzene

PBT Profiler Estimate = PBT

Media	Half-Life (days)	Percent in Each Medium	BCF	Fish ChV (mg/l)
Water	38	47%	8.7	7.6
Soil	75	14%		
Sediment	340	0%		
Air	13	40%		



P2 Considerations and more information

Start a New Profile | Add More Chemicals to Your Profile

(Q)SAR – Summary (1)

General

- Allowed under OECD SIDS and in US HPV Programme
- Computer assisted programs for quantitative/qualitative predictions
- Optimize efficiency of chemical/animal testing
- Assist in defining categories for testing
- Identify endpoints within categories for testing
- Interpolate/extrapolate effects across products
- Justify "read-across" based on toxicological principles

Concepts for Read-across

- Based on expert judgement & consideration of all available data
- Knowledge on production process, especially for streams/mixtures
- Appropriate use depends on chemical class and endpoint
- Considers similar chemicals/products and QSAR models
- Focus on interpolation *vs* extrapolation.

(Q)SAR – Summary (2)

Appropriate Use of (Q)SAR - Chemical Class

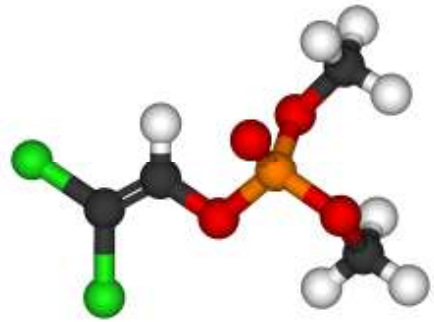
- Isomers with comparable structure activity profiles
- Related homologues
- Knowledge on relevant precursors and breakdown products
- Similar production process
- Knowledge on mixture components or related mixtures (e.g., petroleum streams)
- Similar metabolism and/or degradation profiles

Appropriate Use of (Q)SAR – Endpoint

- Physical/chemical properties
- Environmental fate
- Ecotoxicity
- Mammalian toxicity

CHEMSERVICE

(Q)SAR – Summary (3)



Recommendations

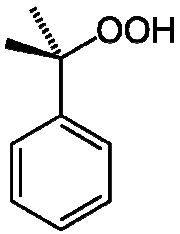
- Apply expert judgement and (Q)SAR to streamline category and testing selection
- Encourage appropriate use of (Q)SAR
- Support reduced chemical/animal testing, when appropriate
- Document rationale for "read-across"
- Consider all data including (Q)SAR and exposure potential for testing exemptions

CHEMSERVICE

Waiving

Waiving

- The exemption from conducting individual tests is termed **„waiving“** in REACH. Of importance is:
  - the theoretically generally anticipatable possibility, not to conduct tests when this is scientifically not necessary or technically not feasible, corresponding to Annex IX;
  - consideration in Annex IX of the REACH-Regulation of general provisions for deviations from the standard testing programmes according to Annexes V to VIII, in particular the customized testing according to Chapter 3. According to Annex IX the tests according to Annexes VII and VIII can be waived, if in the chemical safety report corresponding exposure scenarios were developed;
  - special waiving-conditions for individual tests (example: according to Annex VI.6.6.1: Exemption from the 28-day-test for non-relevant exposure of humans), as specified in Annexes VI to VIII (Column 2).



Waiving

are studies dispensable with consideration of known intrinsic properties?

➔ industry approach:

studies are dispensable, if no additional risk measures can result

→ example:

substance is acutely very toxic or carcinogenic: no additional sub-acute study necessary

Source: Prof. Bender, 2006

CHEMSERVICE

Waiving - Examples

- From a toxicological point of view the flexibility described in the Annexes (especially Annexes VII - IX) is sufficient to allow waiving of unnecessary tests, in particular animal studies.
- The **90-day toxicity study** does not need to be conducted if a reliable short-term toxicity study (28 days) is available showing severe toxicity effects according to the criteria for classifying the substance as R48, for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor, allows the extrapolation towards the NOAEL-90 days for the same route of exposure.
- Or a reliable chronic toxicity study is available; or the substance is non-reactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day “limit test”, particularly if such a pattern is coupled with limited human exposure.
- The **tests on reproductive toxicity** may be waived if the substance is a known genotoxic carcinogen or a germ cell mutagen and appropriate risk management measures are implemented.

CHEMSERVICE

Waiving - Examples

Water solubility - study does not need to be conducted if:

- the substance is hydrolytically unstable at pH 4, 7 and 9 (half-life less than 12 hours); or
- the substance is readily oxidisable in water.
- If the substance appears "insoluble" in water, a limit test up to the detection limit of the analytical method shall be performed

Partition coefficient n-octanol/water - study does not need to be conducted if:

- substance is inorganic.
- test cannot be performed (e.g. the substance decomposes, has high surface activity, reacts violently during performance of test, does not dissolve in water or in octanol),
- a calculated value for log Pow as well as details of the calculation method shall be provided.

CHEMSERVICE

Waiving - Examples

Granulometry - study does not need to be conducted if the substance is marketed or used in a non-solid or granular form

In-vivo eye-irritation - study does not need to be conducted if:

- the substance is classified as irritating to eyes with risk of serious damage to eyes; or
- the substance is classified as corrosive to the skin and provided that the registrant classified the substance as eye irritant; or
- the substance is a strong acid (pH < 2,0) or base (pH > 11,5); or
- the substance is flammable in air at room temperature

Inhalation route - testing is appropriate

- if exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size.

CHEMSERVICE

Waiving - Examples

Hydrolysis as a function of pH - study does not need to be conducted if:

- the substance is readily biodegradable; or
- the substance is highly insoluble in water.

Dissociation constant - the study does not need to be conducted if:

- the substance is hydrolytically unstable (half-life less than 12 hours) or is
- readily oxidisable in water; or
- it is scientifically not possible to perform the test for instance if the analytical method is not sensitive enough.

Stability in organic solvents and identity of relevant degradation products

- Only required if stability of the substance is considered to be critical.
- The study does not need to be conducted if the substance is inorganic.

CHEMSERVICE

Exposure-Based Waiving

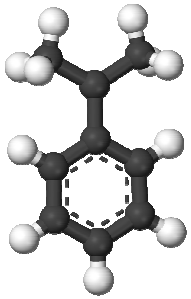
- **„Exposure-based“** waiving“ means exemption from conducting studies according to Annex VI, when the justification for waiving is based on the fact that there is no relevant exposure of humans and environment to the substance to be registered.
- Exposure based waiving: in general justification difficult but simple criteria also problematic.
- Up until now there is no legally certain definition or criteria, as to what is meant concretely for the condition „no relevant exposure“.

Exposure-Based Waiving

Examples:

Activated sludge respiration inhibition testing - study does not need to be conducted if:

- **there is no emission to a sewage treatment plant**; or
- there are **mitigating factors** indicating that microbial toxicity is unlikely to occur,
  - **for instance the substance is highly insoluble in water**; or
  - the substance is found to be readily biodegradable and the applied test concentrations are in the range of concentrations that can be expected in the influent of a sewage treatment plant.
  - The study may be replaced by a nitrification inhibition test if available data show that the substance is likely to be an inhibitor of microbial growth or function, in particular nitrifying bacteria.



CHEMSERVICE

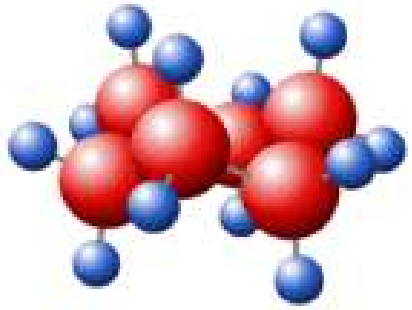
Grouping & Read-Across

Grouping – Functional Groups

- In organic chemistry, **functional groups** (or **moieties**) are specific groups of atoms within molecules that are responsible for the characteristic chemical reactions of those molecules. The same functional group will undergo the same or similar chemical reaction(s) regardless of the size of the molecule it is a part of.
- However, its relative reactivity can be modified by nearby functional groups.

Read-Across

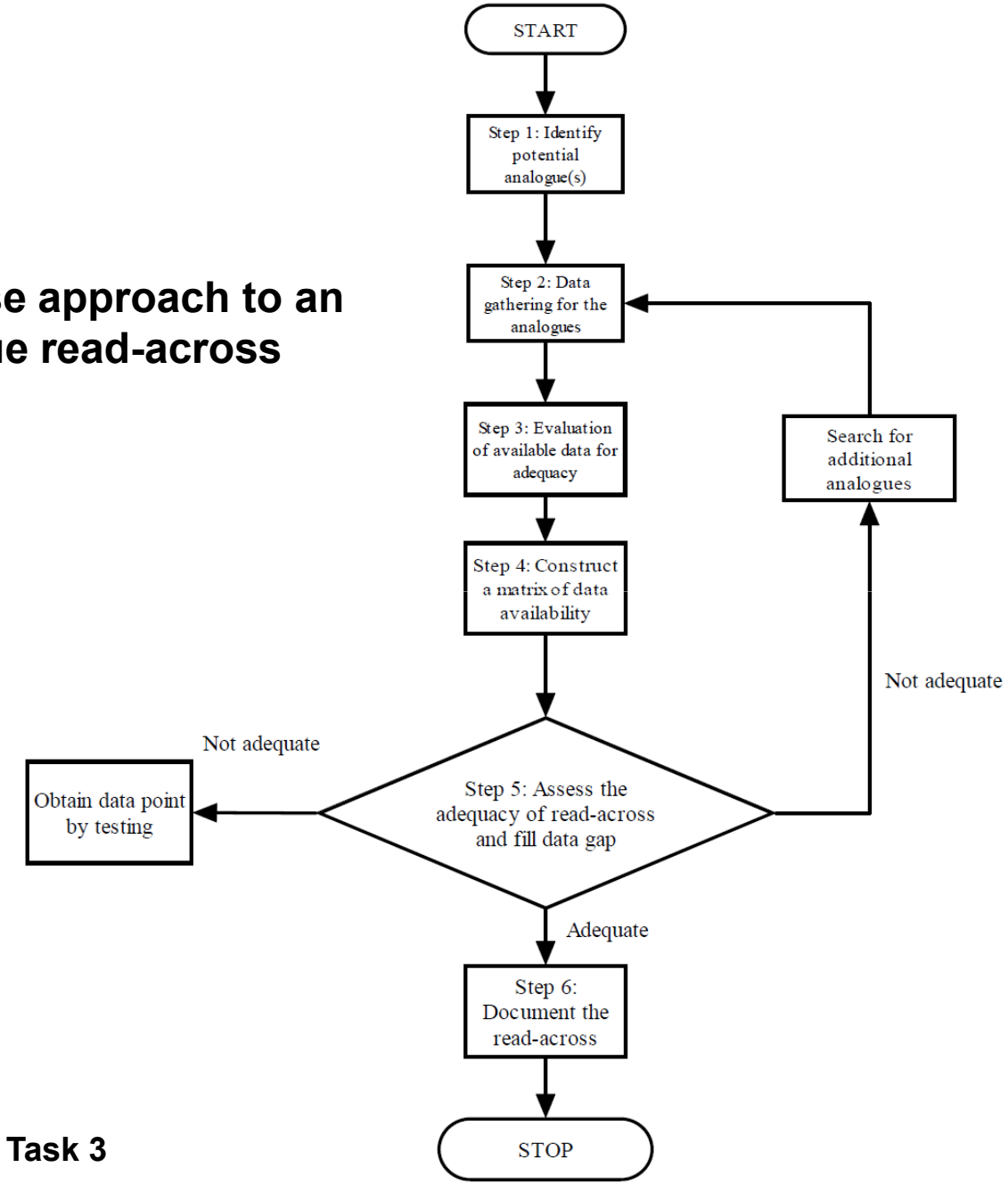
- In the Read-Across (analogue) approach, endpoint information for one chemical is used to make a prediction of the endpoint for another chemical, which is considered to be “similar” in some way.
- A chemical category is a “family” of chemicals that have been grouped together because they share similar chemical structures or physicochemical properties, and are consequently considered to share similar environmental, ecotoxicological or toxicological properties.



Grouping and Read-Across Approach

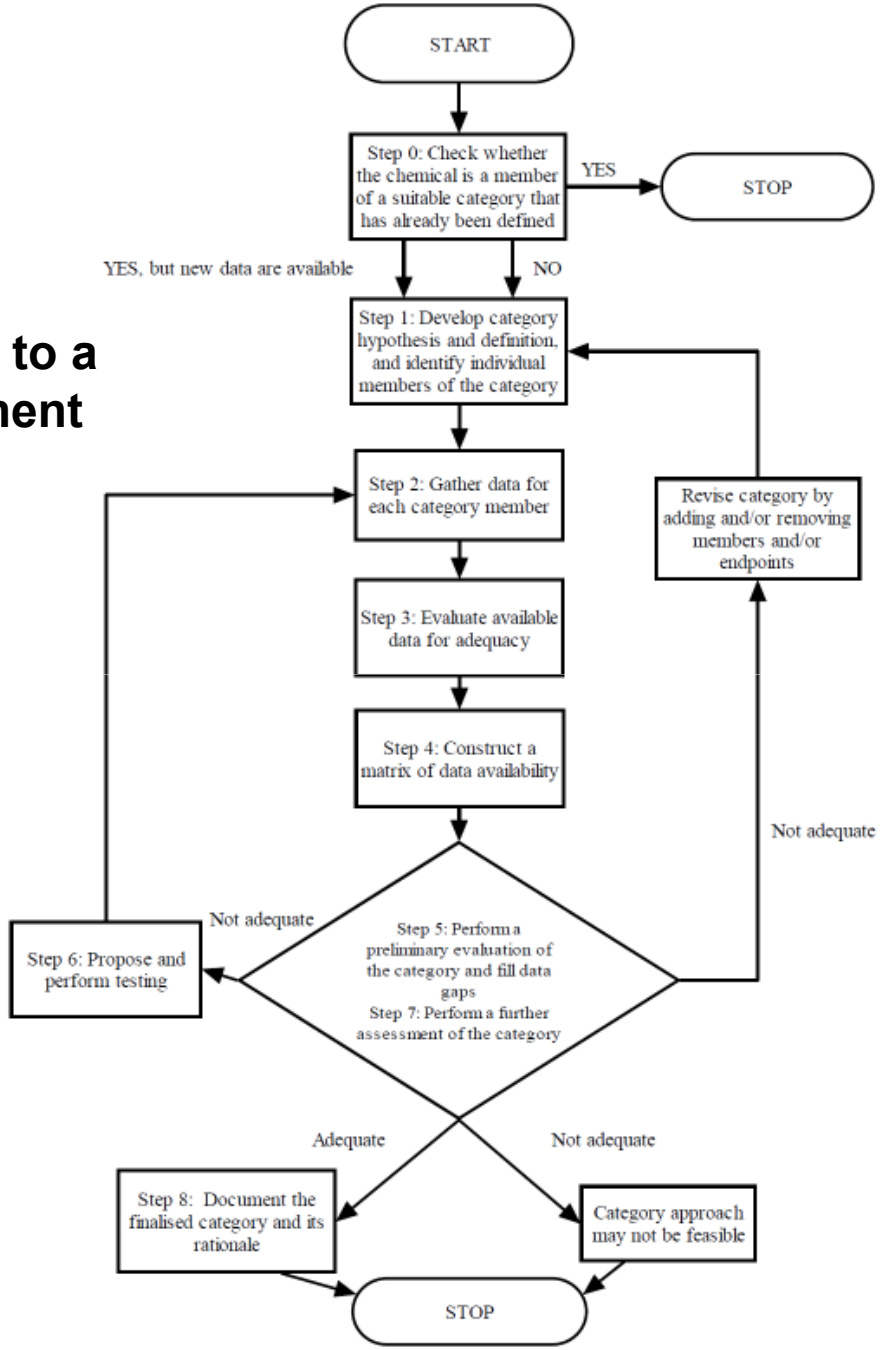
- Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or "category" of substances.
- Application of the group concept requires that physico-chemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).
- Avoids the need to test every substance for every endpoint.
- The Agency, after consulting with relevant stakeholders and other interested parties, shall issue guidance on technically and scientifically justified methodology for the grouping of substances sufficiently in advance of the first registration deadline for phase-in substances.

Stepwise approach to an analogue read-across



Source: RIP 3.3-2 Task 3

Stepwise approach to a Category Development



Source: RIP 3.3-2 Task 3

Chemical category and approach for filling data gaps

	Chemical 1	Chemical 2	Chemical 3	Chemical 4	
Structure	xxxxxxxxx	xxxxxxxxx	xxxxxxxxx	xxxxxxxxx	
Property 1	● →	○	● →	○	SAR/Read-across
Property 2	● →	○	○ ←	●	Interpolation
Property 3	○ ←	●	● →	○	Extrapolation
Activity 1	● →	○	● →	○	SAR/Read-across
Activity 2	● →	○	○ ←	●	Interpolation
Activity 3	○ ←	●	● →	○	Extrapolation

● Existing data point ○ Missing data point

Source: RIP 3.3-2 Task 3

CHEMSERVICE

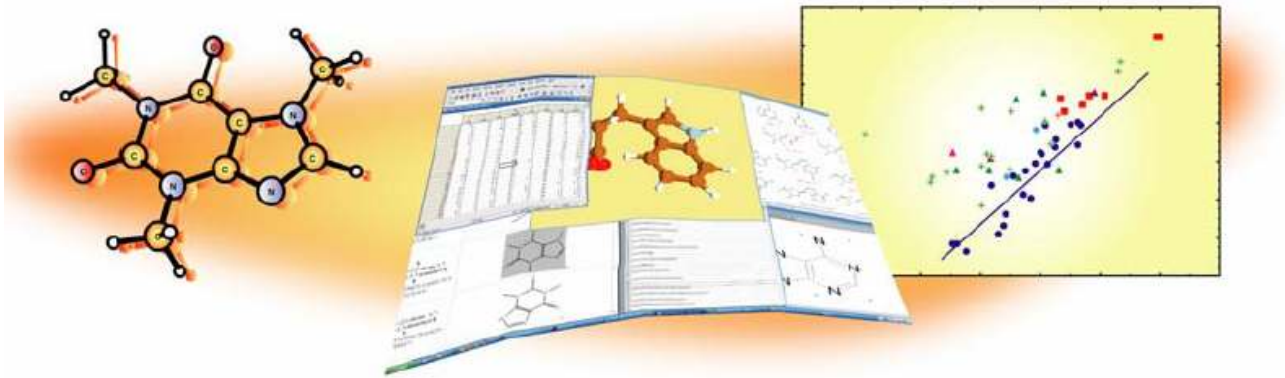
(Q)SAR in Practice

Current Regulatory use of (Q)SARs

- USA
  - Pre-manufacturing assessment of new substances
  - HPV-Challenge Program
- Canada
  - Screening and priority setting of Domestic Substance List
- EU
  - DK: Advisory list for self-classification
  - DK: Identification of PBT and vPvB substances
  - D: Decision support to assessment of new substances
  - NL: Ecotoxicity of HPV Chemicals
  - COM: Priority setting of existing chemicals
- OECD
  - Aquatic effects of HPV Chemicals
  - SIDS Endpoints
- Lower acceptance of (Q)SAR results in EU than in USA for SIDS endpoints

Experience from the US HPV Challenge Program (Auer, 2004)

	Human health	Environmental effects
Adequate studies	50 %	58 %
Estimation	44 %	35 %
Testing	6 %	7 %



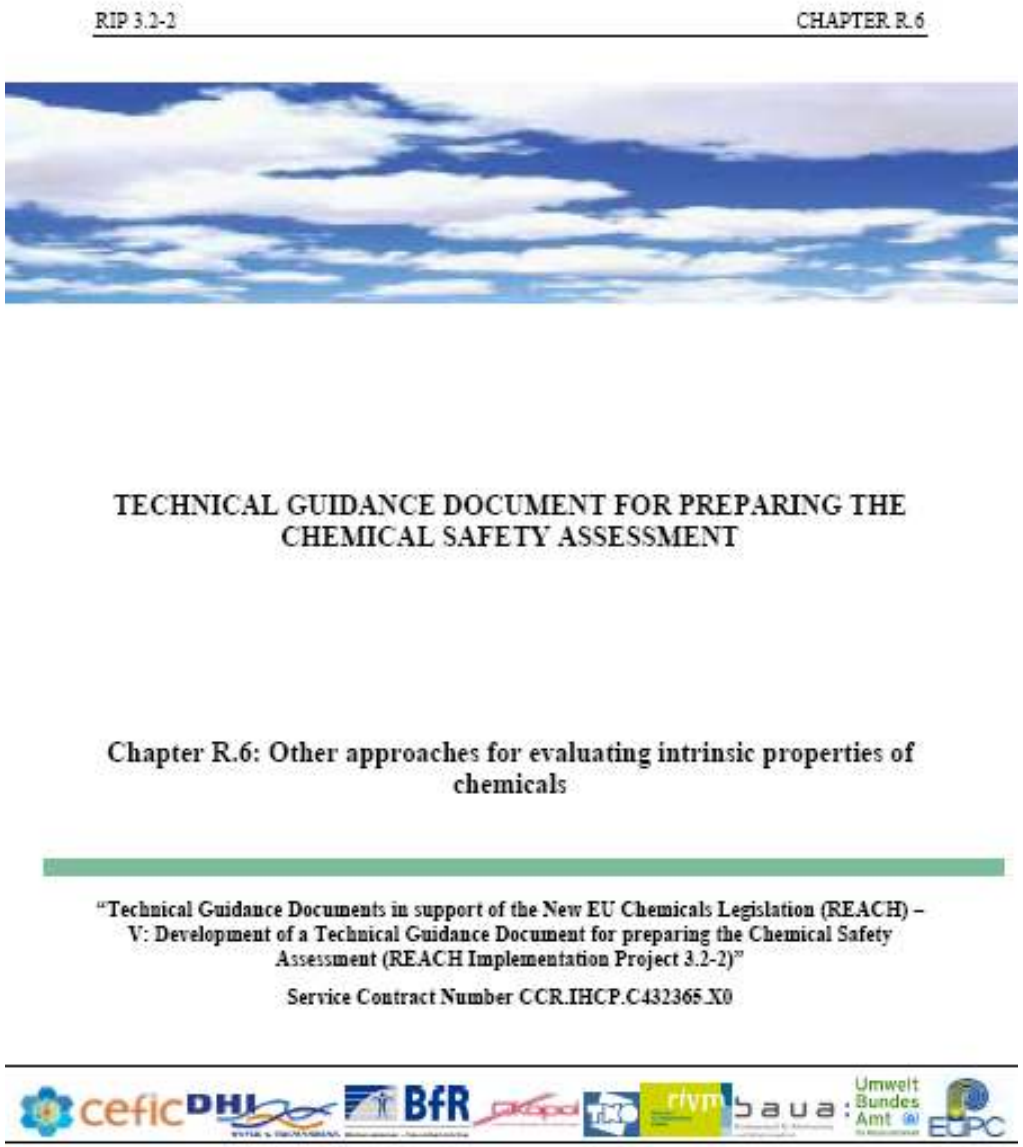
REACH Article 13

- General requirements for generation of information on intrinsic properties of substances
  - Information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out are met.
  - In particular for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, for example, in vitro methods or qualitative or quantitative structure-activity relationship models or from information from structurally related substances (grouping or read-across).
  - Testing may be omitted where justified by information on exposure and implemented risk management measures.

Use of QSAR under REACH?

- Information may be generated by other means than tests, in particular through *in vitro* methods, (Q)SARs and read-across (Art. 13)
- Tests on vertebrate animals shall only be conducted as a last alternative
- (Q)SARs may replace tests under certain conditions:
  - Scientific validity has been established
  - Results adequate for C&L and RA
  - Method is adequately documented
- (Q)SAR estimates may be used to guide testing
  - Selection of tests and/or test set-up
- Conclusions:
  - Regulatory use of (Q)SARs is encouraged
  - Development and validation of (Q)SARs are needed
  - But: Expectations to replace animal tests with *in vitro* and (Q)SAR seems to be running ahead of scientific reality

Technical Guidance



RIP 3.2-2 CHAPTER R.6

TECHNICAL GUIDANCE DOCUMENT FOR PREPARING THE CHEMICAL SAFETY ASSESSMENT

Chapter R.6: Other approaches for evaluating intrinsic properties of chemicals

"Technical Guidance Documents in support of the New EU Chemicals Legislation (REACH) – V: Development of a Technical Guidance Document for preparing the Chemical Safety Assessment (REACH Implementation Project 3.2-2)"

Service Contract Number CCR.IHCP.C432365.X0

CHEMSERVICE

Technical Guidance

RIP 3.3-2 Task 3 report draft 01 October 06

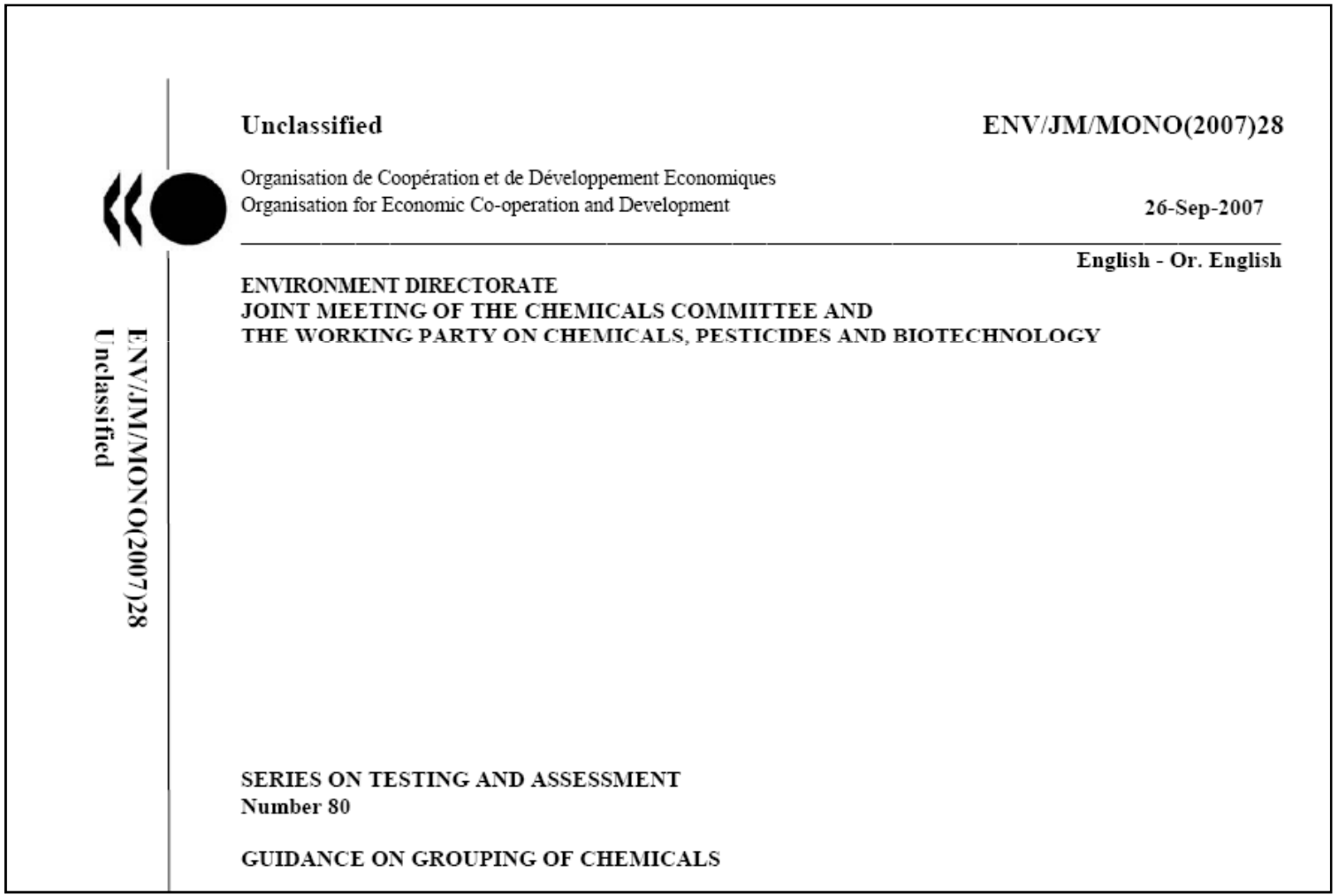
DRAFT GUIDANCE ON THE GROUPING OF CHEMICALS (INCLUDING BY READ-ACROSS AND CHEMICAL CATEGORIES)

This report is a draft version of the Task 3 report, submitted for the first PMG review and for the information of the SEG.

The document reflects the broad consensus of the Task 3 Drafting Group but due to time constraints it does not necessarily reflect consensus on all details.

A number of comments were raised by Drafting Group members in the days preceding submission but these have not been addressed in this draft. The Drafting Group will try to address those comments in the next draft.

Technical Guidance



Unclassified ENV/JM/MONO(2007)28

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

26-Sep-2007

English - Or. English

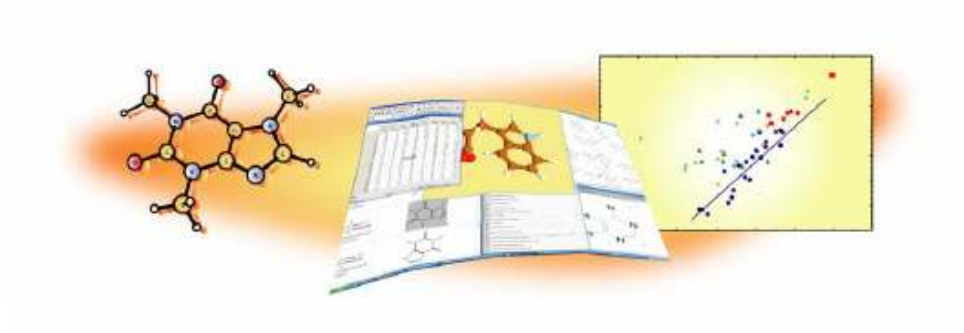
ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ENV/JM/MONO(2007)28
Unclassified

SERIES ON TESTING AND ASSESSMENT
Number 80

GUIDANCE ON GROUPING OF CHEMICALS

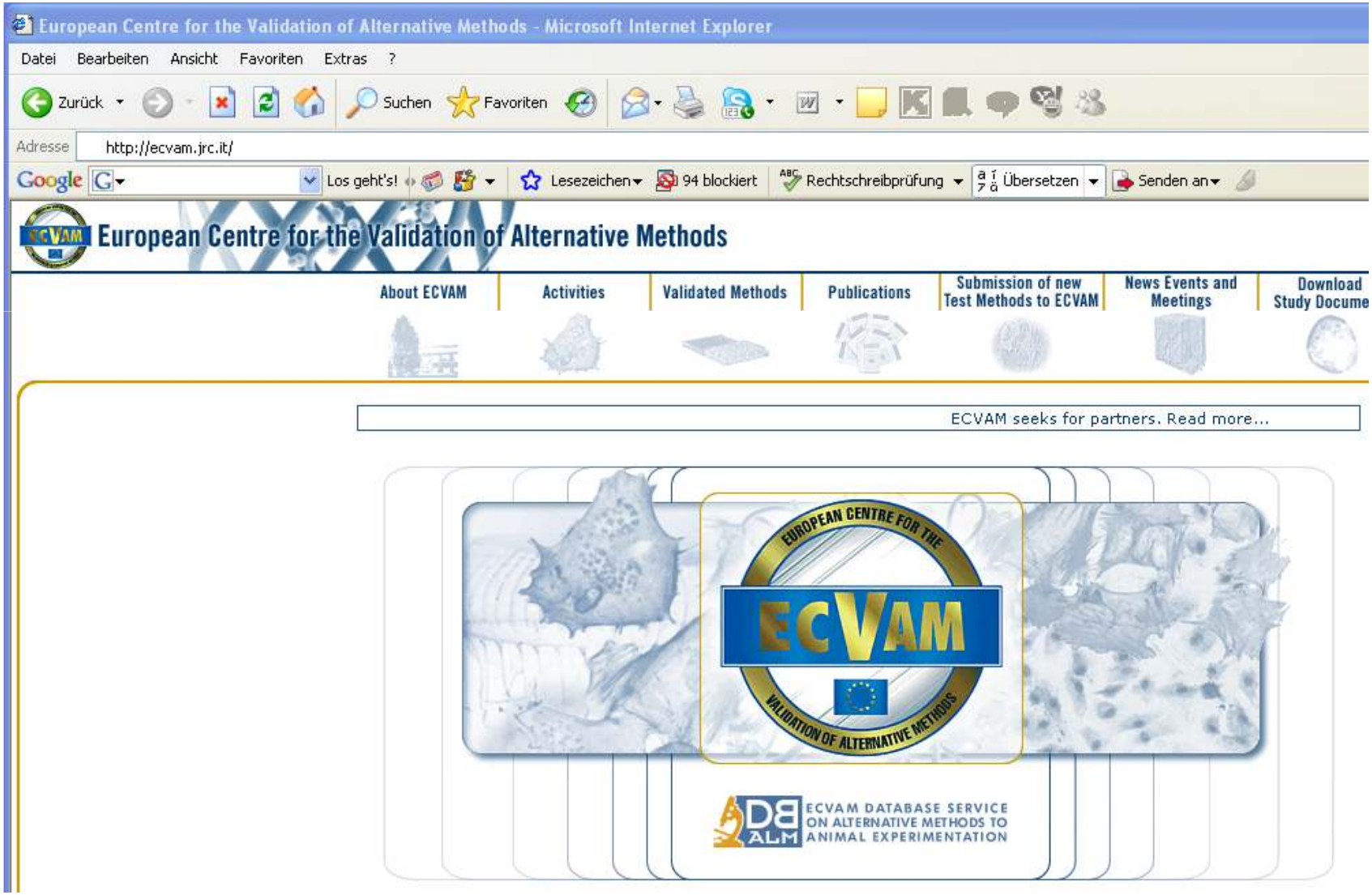
Technical Guidance



Comparative Assessment of QSAR Models for Aquatic Toxicity

Manuela Pavan, Andrew P. Worth and Tatiana I. Netzeva

Technical Guidance



CHEMSERVICE

(Q)SAR and Costs

Cost-saving Aspects

- The most efficient way to carry out hazard and risk assessments of large numbers of chemicals, while reducing costs to industry and minimising animal testing, is to obtain the necessary information by means of intelligent testing strategies (ITS).
- Intelligent testing strategies are integrated approaches comprising of
  - multiple elements aimed at speeding up the risk assessment process
  - while reducing costs and animal tests

(Source: Bradbury, Feytel and Van Leeuwen, 2004)

(Q)SAR - Resources & Strategy

- During the preparation phase for REACH, (Q)SARs can be used as tools for grouping.
- Results of (Q)SAR evaluation will document rationale for "read-across“.
- (Q)SAR evaluation may give reasons for testing exemptions
- Dangerous substances will be determined in an early stage. This may influence the REACH strategy of a company.
- The *in-silico* testing **can save time** (e.g. test for carcinogenicity takes 2 years). On an appropriate data base, the (Q)SAR evaluation can be done shortly.
- *In-silico* testing **can save costs**: (Q)SAR costs are assumed to be ca. < 10% of regular testing, depending on the endpoint.

Cost Saving Potential by (Q)SAR

- Average QSAR: Based on current models, but need validation and regulatory implementation
- Max. QSAR: Requires further development, followed by validation and implementation
- Cost-saving potential: 700 – 940 Mill. EURO in REACH
- Mainly on Annex VIII & IV tests (10 – 1000 tpa)
- (Q)SARs have a big potential for
  - Saving test animals
  - Saving money
  - Saving time

CHEMSERVICE

Cost Saving Potential by (Q)SAR

Test costs	Tonnage band (tpa)				Total
(M EURO)	1-10	10-100	100-1000	>1000	
No QSAR	230	690	510	710	2130
Average QSAR	150	350	330	610	1430
Max QSAR	130	260	260	540	1190

Source: Van Leeuwen et al.

Conclusions

- Paradigm shift is needed from extensive animal testing to efficient, focussed animal testing applying **Intelligent Testing Strategies** – including (Q)SARs, Read-Across, Waiving
- Alternative approaches can significantly reduce animals killed, costs spent and time needed to fill data gaps
- REACH Article 13 requires and promotes „alternative testing“
- REACH Registration Dossier – filling data gaps:
  - Documentation of rationale and justification for "read-across"
  - Consider all data including (Q)SAR and exposure potential for testing exemptions (Weight of Evidence)
  - ECHA will come back if they disagree after evaluation of dossier

CHEMSERVICE

Thank you very much for your highly respected Attention !

Any remaining Questions ?

Any Comments or Responses ?