Willie Peijnenburg
RIVM – Laboratory for Ecological Risk Assessment

Summer School "Towards new ideas" – Kiev: 11 August 2009

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RIVM: a centre of expertise serving the public

Public health, nutrition, environment and safety

rivm

Core facts

- Established in 1909
- Employs 1500 men and women
- Has a budget of € 180 million
- Consists of 30 labs/centres, 4 divisions
- Carries out independent research (laid down in the RIVM Act)
- Boasts 300 projects annually

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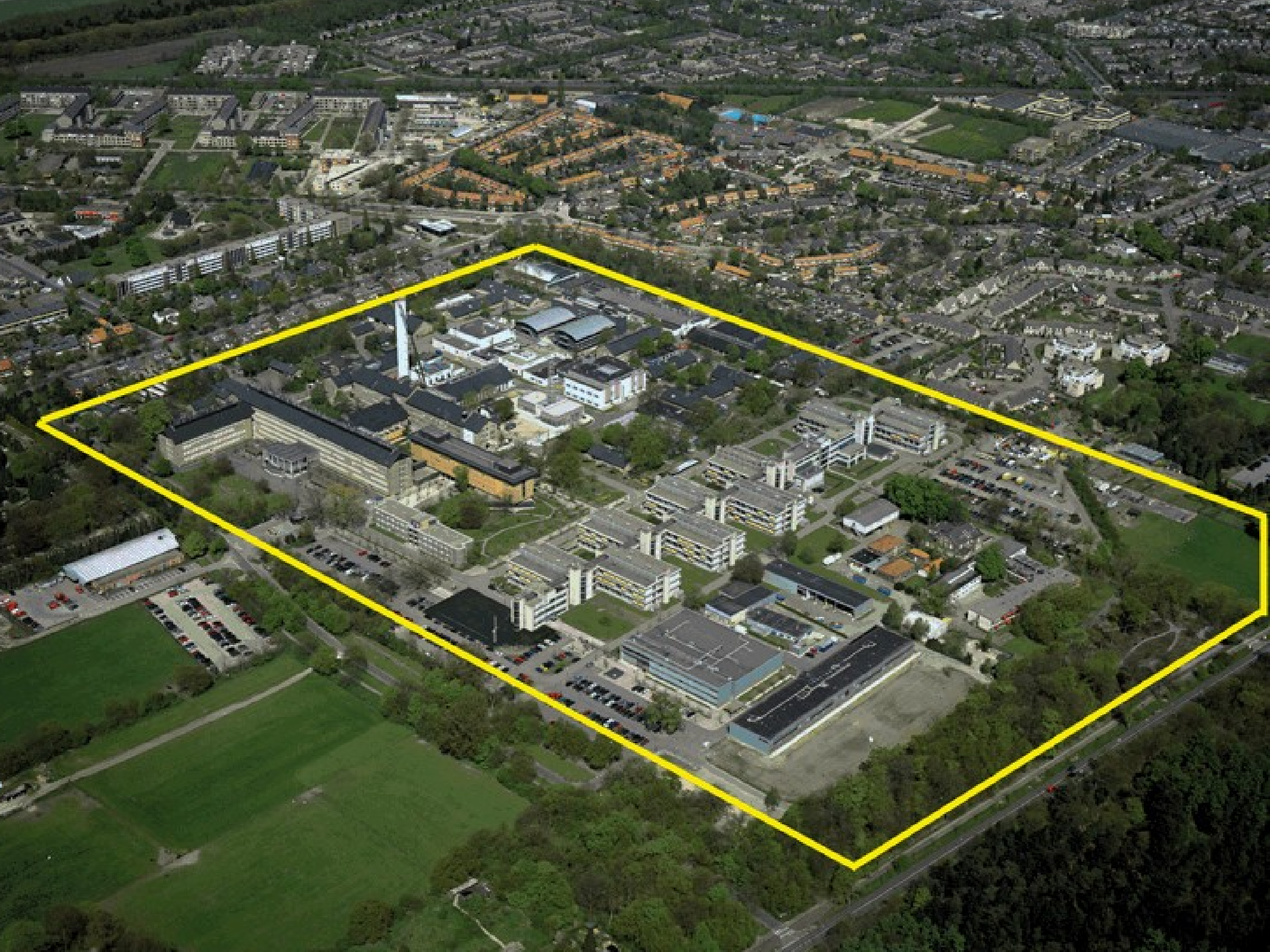

RIVM's position

- RIVM is an agency of the Dutch government (Ministry of Health, Welfare and Sports -VWS)
- RIVM works mainly for VWS, VROM (environment) and LNV (nature conservation, food & consumer safety)

Has a responsibility in policy-making

Conducts independent research and implements initiatives

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Public authorities responsible for public health

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Public authorities responsible for protection and improvement of the environment

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RIVM's core tasks

Public Health

Nutrition

Environment

Safety

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RIVM's added value

- Offers scientifically sound and independent advice
- Offers continuous monitoring and rapid detection of threats
- Offers integrated risk assessment
- Plays a role internationally through scientific fora and networks

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Risks to public health and the environment

Independent advice following a disaster

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Environmental threats

Risk assessment following an incident

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All environmental risks

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Chemical Similarity

Willie Peijnenburg

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Similarity : philosophers' view

- exploiting the similarity concept is a sign of immature science (Quine)
- "it is ill defined to say "*A is similar to B*" and it is only meaningful to say "*A is similar to B with respect to C*"

A chemical "A" cannot be similar to a chemical "B"
in absdute terms
but only with respect to some measurable key feature

Similarity : chemists' view

- Intuitively, based on expert judgment

  A chemist would describe "similar" compounds in terms of "approximately similar backbone and almost the same functional groups".

- Chemists have different views on similarity

  Experience, context

  Lajiness et al. (2004). Assessment of the Consistency of Medicinal Chemists in Reviewing Sets of Compounds, J. Med. Chem., 47(20), 4891-4896.

Chemical similarity

- Computerized similarity assessment needs unambiguous definitions
- Structurally similar molecules have similar biological activities
  - The basic tenet of chemical similarity
  - Long supporting experience
  - Many exceptions ***Exceptions are important!***
- Identification of the most informative representation of molecular structures ***Avoiding information loss is important!***
- Similarity measures

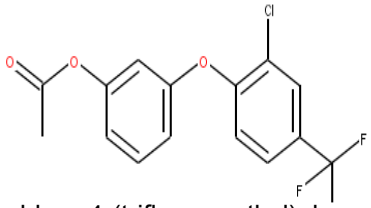
Chemical similarity quantified

- Numerical representation of chemical structure
  - Structural similarity
  - Descriptor –based similarity
  - 3D similarity
  - Field –based
  - Spectral
  - Quantum mechanics
  - More…
- Comparison between numerical representations
  - Distance-like
  - Association,
  - Correlation

Structural similarity

- Substructure searching
- Maximum Common Substructure
- Fragment approach
  - Atom, bond or ring counts, degree of connectivity
  - Atom-centred, bond-centred, ring-centred fragments
  - Fingerprints, molecular holograms, atom environments
- Topological descriptors
  - Hosoya' Z, Wiener number, Randic index, indices on distance matrices of graph (Bonchev & Trinajstic), bonding connectivity indices (Basak), Balaban J indices, etc.
  - Initially designed to account for branching, linearity, presence of cycles and other topological features
  - Attempts to include 3D information (e.g. distance matrices instead of adjacency matrices)

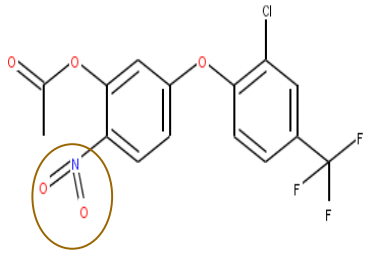
Structural similarity



3-(2-chloro-4-(trifluoromethyl)phenoxy-) phenyl acetate,

CAS# 50594-77-9

- Oral LD_{50} for male rats = 2.5g/kg
- Dermal LD_{50} for male rats = 3.54g/kg
- Not irritating to eyes of rabbits
- Slightly irritating to skin of rabbits



5-(2-chloro-4-(trifluoromethyl)phenoxy)-2-nitrophenyl acetate,

CAS# 50594-44-0

- ***Not mutagenic in Salmonella strains***
- ***Higher potential binding affinity to the estrogen receptor than the nitrophenyl acetate***
- ***Higher potential to cause cancer than the phenyl acetate***

Walker . J. (2003) ,QSARs for pollution prevention, Toxicity Screening, Risk Assessment and Web Applications, SETAC Press

So: A single group makes difference …but…

Isosteric replacements of groups

- Substituents:
  - F, Cl, Br, I, CF_3,NO_2
  - Methyl,Ethyl, Isoprpyl, Cyclopropyl, t-Butyl,-OH,-SH,-NH_2,-OMe,-$N(Me)_2$
- Atoms and groups in rings:
  - -CH=,-N=
  - -CH_2-,-NH-,-O-,-S-
- More …

Depends on the endpoint!

(e.g. lipophilicity, receptor binding)

Structural similarity

- Rosenkranz H.S., Cunningham A.R. (2001) Chemical Categories for Health Hazard Identification: A feasibility Study, Regulatory Toxicology and Pharmacology 33, 313-318.
- Examined the reliability of using chemical categories to classify HPV chemicals as toxic or nontoxic
- Found: ***"most often only a proportion of chemicals in a category were toxic"***
- Conclusion: ***"traditional organic chemical categories do not encompass groups of chemical that are predominately either toxic or nontoxic across a number of toxicological endpoints or even for specific toxic activities"***

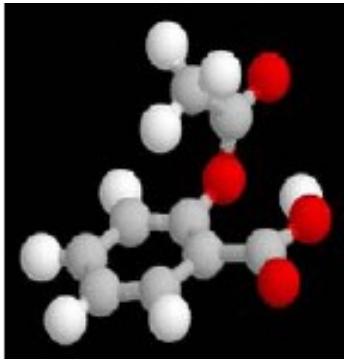
Distribution of Toxicants Containing Carbonyls and Alcohols

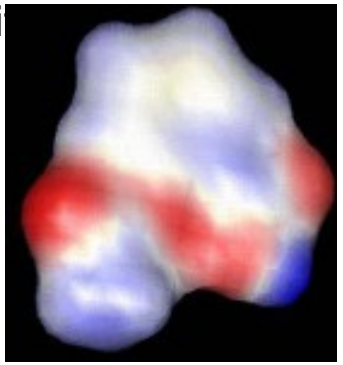
Category	EyI	LD_{50}	Dev	CA	Mnt	SAI	MLA
 aldehyde	3/9 33%	2/76 3%	2/6 33%	2/2 100%	0/2 0%	7/33 21%	11/19 58%
 primary ketone	1/16 8%	15/160 13%	17/33 52%	15/29 52%	14/21 67%	22/75 29%	24/42 57%
 secondary ketone	ND	5/17 29%	3/7 43%	0/3 0%	1/1 100%	2/8 25%	4/6 67%
 secondary ketone	ND	3/21 14%	7/14 50%	0/1 0%	4/4 100%	3/14 21%	3/5 60%
 tertiary ketone	0/1 0%	2/4 50%	1/1 100%	0/1 0%	ND	0/1 0%	ND
 primary alcohol	25/49 51%	4/79 5%	17/28 61%	7/14 50%	9/22 41%	28/75 37%	25/76 33%
 secondary alcohol	8/31 26%	8/70 11%	19/42 45%	5/18 28%	15/32 47%	13/49 27%	20/80 23%
 tertiary alcohol	2/4 50%	3/36 8%	8/16 50%	2/6 33%	5/6 83%	4/21 19%	7/12 58%

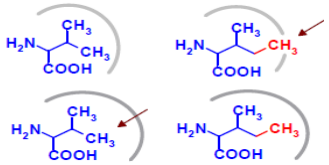
The bold portion of the chemical in the Category column defined the fragment used to query each data set. Abbreviations: EyI,eye irritation;LD50, rat LD50; Dev, developmental toxicity;CA, rodent carcinogenesis; Mnt, *in vivo* induction of micronuclei; Sal, *Salmonella* mutagenesis; MLA, mutagenesis in cultured mouse lymphoma cells.

3D Similarity

- Distance-based and angle-based descriptors (e.g. inter-atomic distance)
- Field similarity (not exhaustive list)
  - Comparative Molecular Field Analysis (CoMFA), CoMSIA
  - Electrostatic potential
  - Shape
  - Electron density
  - Test probe
  - Any grid-based structural property
- Molecular multi-pole moments (CoMMA)
- Shape descriptors (not exhaustive list)
  - van der Waals volume and surface (reflect the size of substi
  - Taft steric parameter
  - STERIMOL
  - Molecular Shape Analysis
  - 4D QSAR
  - WHIM descriptors
- Receptor binding

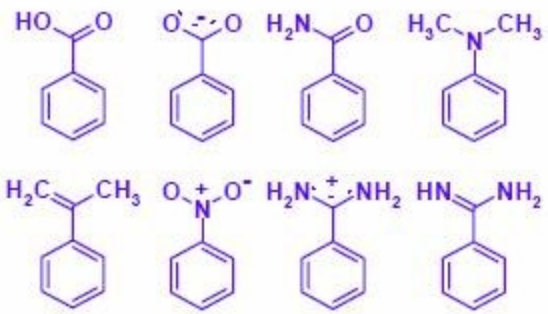




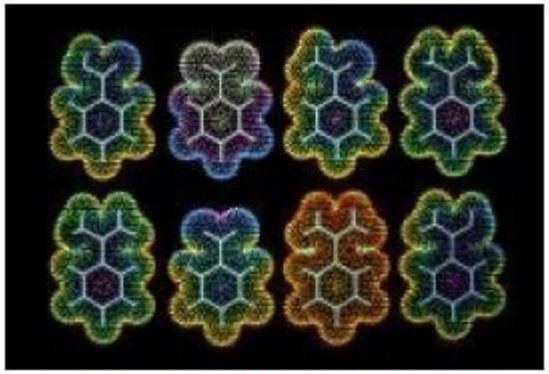


Structurally similar compounds can have very different 3D properties

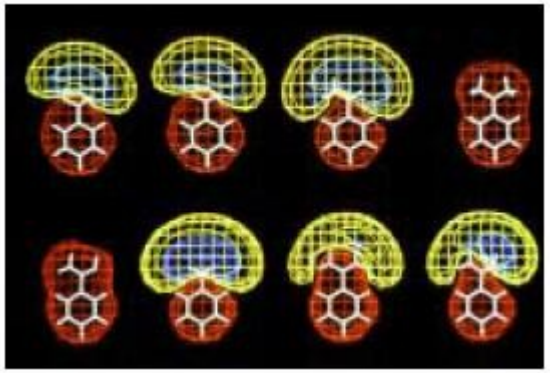
Similarity and Diversity



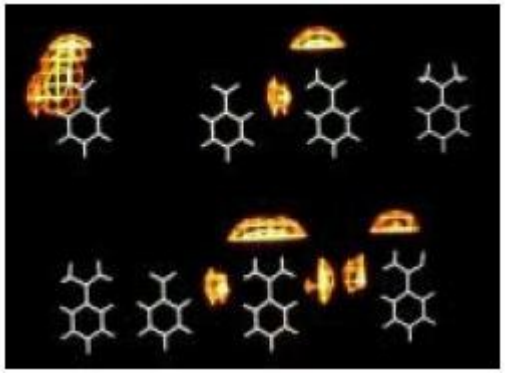
Volumes and Surface Potentials



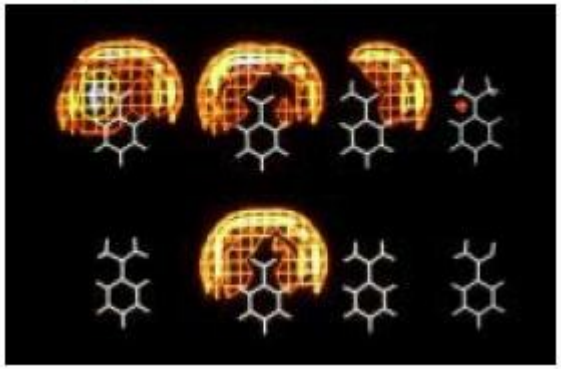
Hydrophobic and Polar Regions



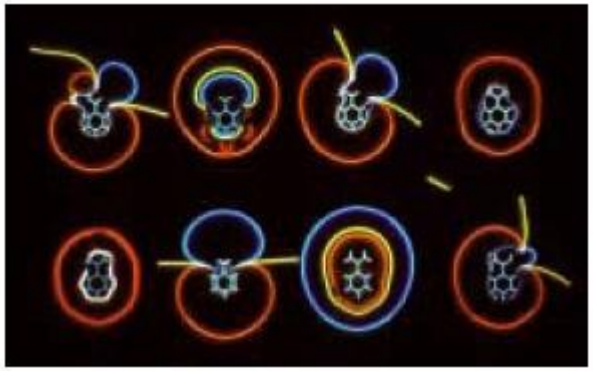
Hydrogen Bond Donor Potentials



Hydrogen Bond Acceptor Potentials



Molecular Electrostatic Potentials (MEP)



Kubinyi, H., Chemical Similarity and Biological activity

Physicochemical properties

- Molecular weight
- Octanol - water partition coefficient
- Total energy
- Heat of formation
- Ionization potential
- Molar refractivity
- More…

Quantum chemistry approaches

- The wave function and the density function contain all the information of a system.
  - All the information about any molecule could be extracted from the electron density. Bond creation and bond breaking in chemical reactions, as well as the shape changes in conformational processes, are expressed by changes in the electronic density of molecules. The electronic density fully determines the nuclear distribution, hence the electronic density and its changes account for all the relevant chemical information about the molecule.
  - ***In principle, quantum-chemical theory should be able to provide precise quantitative descriptions of molecular structures and their chemical properties.***

Quantum chemistry approaches

- Quantum chemical descriptors - characterize the reactivity, shape and binding properties of a complete molecule or molecular fragments and substituents:

  HOMO and LUMO energies, total energy, number of filled orbitals, standard deviation of partial atomic charges and electron densities, dipole moment, partial atomic charges
- Approaches from The Theory of Atom in Molecules – BCP space, TAE/RECON, MEDLA, QShAR (additive density fragments)
- Quantum chemistry calculations depend on several levels of approximation
- Computationally intensive

Reactivity

- Similarity between reactions
- Similarity of chemical structures assessed by generalized reaction types and by gross structural features. Two structures are considered similar if they can be converted by reactions belonging to the same predefined groups (for example oxidation or substitution reactions).

Similarity indices

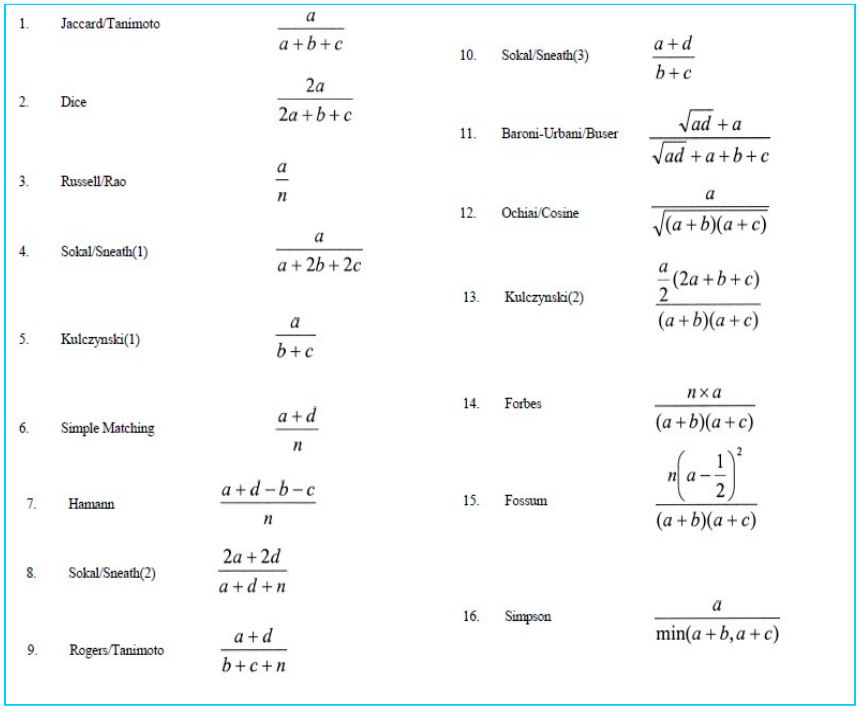
- Association, correlation, distance coefficients
- Most popular :
  - Tanimoto distance (fingerprints)
  - Euclidean distance (descriptors)
  - Carbo index (fields)

$$T_{AB} = \frac{N_{AB}}{N_A + N_B - N_{AB}}$$

$$C_{AB} = \frac{Z_{AB}}{\sqrt{Z_{AA} Z_{BB}}}$$

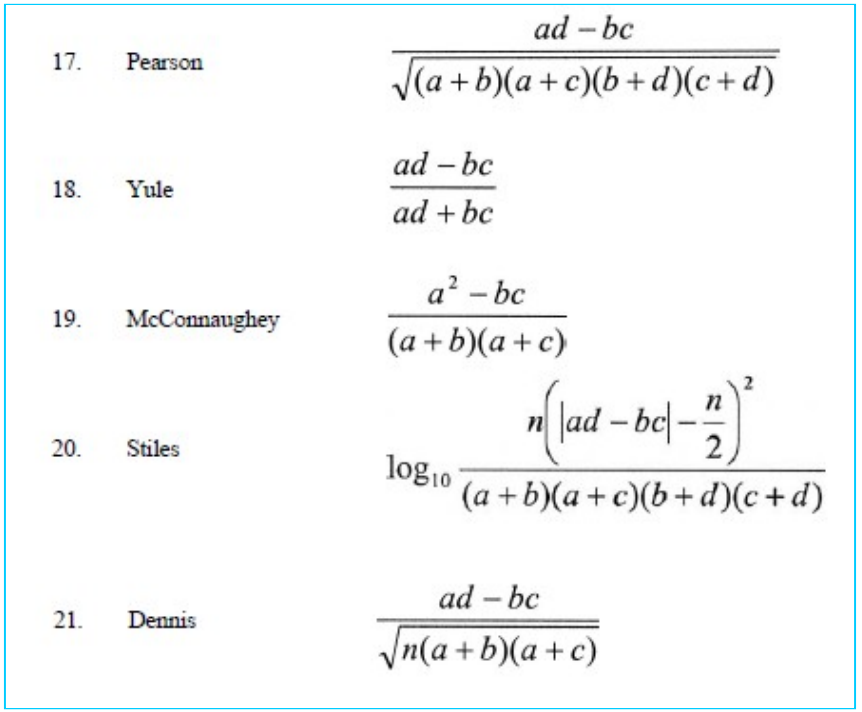
- Essentially a classification problem has to be solved (decide if a query compound is closer to one or another set of compounds)
  - Many methods available (Discriminant Analysis, Neural networks, SVM, Bayesian classification, etc.)
  - Statistical assumptions and statistical error is involved

Similarity indices



1.	Jaccard/Tanimoto	$\frac{a}{a+b+c}$
2.	Dice	$\frac{2a}{2a+b+c}$
3.	Russell/Rao	$\frac{a}{n}$
4.	Sokal/Sneath(1)	$\frac{a}{a+2b+2c}$
5.	Kulczynski(1)	$\frac{a}{b+c}$
6.	Simple Matching	$\frac{a+d}{n}$
7.	Hamann	$\frac{a+d-b-c}{n}$
8.	Sokal/Sneath(2)	$\frac{2a+2d}{a+d+n}$
9.	Rogers/Tanimoto	$\frac{a+d}{b+c+n}$
10.	Sokal/Sneath(3)	$\frac{a+d}{b+c}$
11.	Baroni-Urbani/Buser	$\frac{\sqrt{ad}+a}{\sqrt{ad}+a+b+c}$
12.	Ochiai/Cosine	$\frac{a}{\sqrt{(a+b)(a+c)}}$
13.	Kulczynski(2)	$\frac{\frac{a}{2}(2a+b+c)}{(a+b)(a+c)}$
14.	Forbes	$\frac{n\times a}{(a+b)(a+c)}$
15.	Fossum	$\frac{n\left(a-\frac{1}{2}\right)^2}{(a+b)(a+c)}$
16.	Simpson	$\frac{a}{\min(a+b,a+c)}$

Association indices

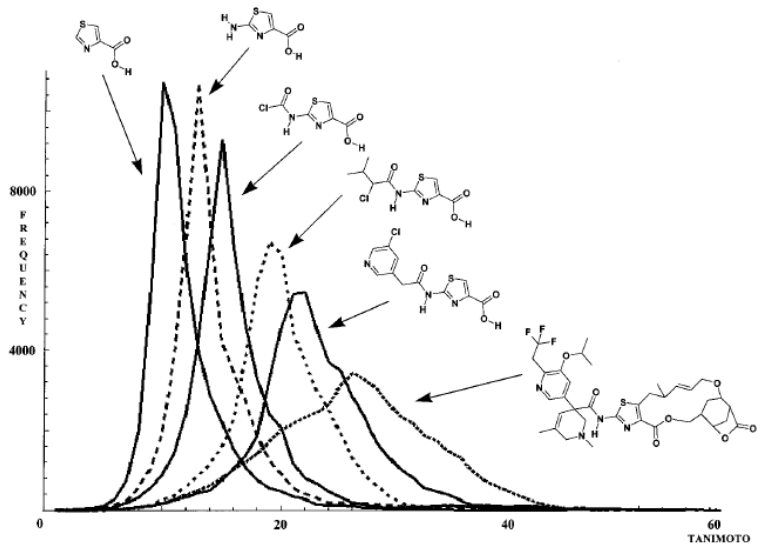


17.	Pearson	$\frac{ad-bc}{\sqrt{(a+b)(a+c)(b+d)(c+d)}}$
18.	Yule	$\frac{ad-bc}{ad+bc}$
19.	McConnaughey	$\frac{a^2-bc}{(a+b)(a+c)}$
20.	Stiles	$\log_{10}\frac{n\left(\lvert ad-bc\rvert-\frac{n}{2}\right)^2}{(a+b)(a+c)(b+d)(c+d)}$
21.	Dennis	$\frac{ad-bc}{\sqrt{n(a+b)(a+c)}}$

Correlation indices

J. D. Holliday, C-Y. Hu† and P. Willett,(2002) Grouping of Coefficients for the Calculation of Inter-Molecular Similarity and Dissimilarity using 2D Fragment Bit-Strings, Combinatorial Chemistry & High Throughput Screening,5, 155-166 155

Fingerprint similarity

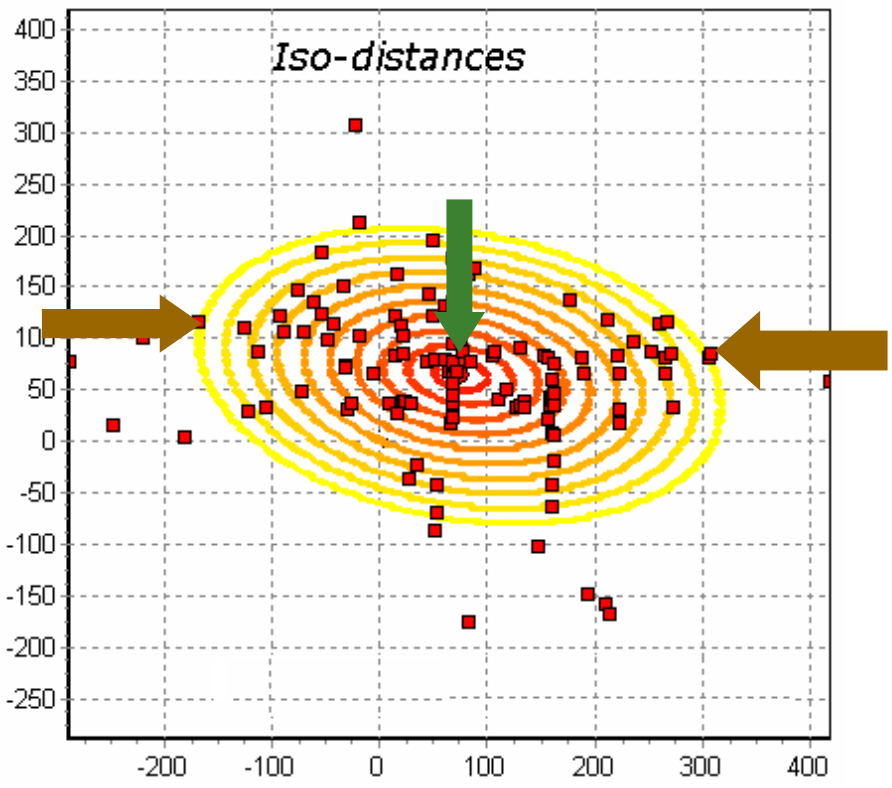


The distribution of Tanimoto values found in database searches with a range of query molecules

Flower D., On the Properties of Bit String-Based Measures of Chemical Similarity, *J. Chem. Inf. Comput. Sci., Vol. 38, No. 3, 1998*

- Information loss – fragments presence and absence instead of counts
- Bit string saturation – within a large database almost all bits are set
- Can give nonintuitive results
- The average similarity appears to increase with the complexity of the query compound
- Larger queries are more discriminating (flatter curve, Tanimoto values spread wider)
- Smaller queries have sharp peak, unable to distinguish between molecules

Distance indices



Equidistant contours = Points on the equal distance from the query point

- Euclidean distance

$$\delta = \|\mathbf{x}_i - \mathbf{x}_j\| = \sqrt{\sum_{k=1}^{K} (x_{ik} - x_{jk})^2}$$

- City-block distance

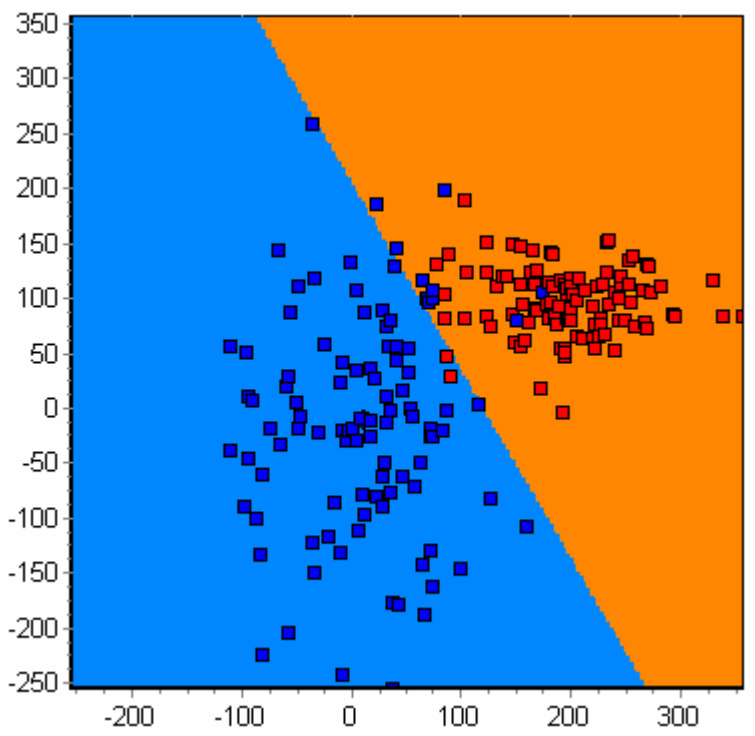
$$\delta = \sum_{k=1}^{K} |x_{ik} - x_{jk}|$$

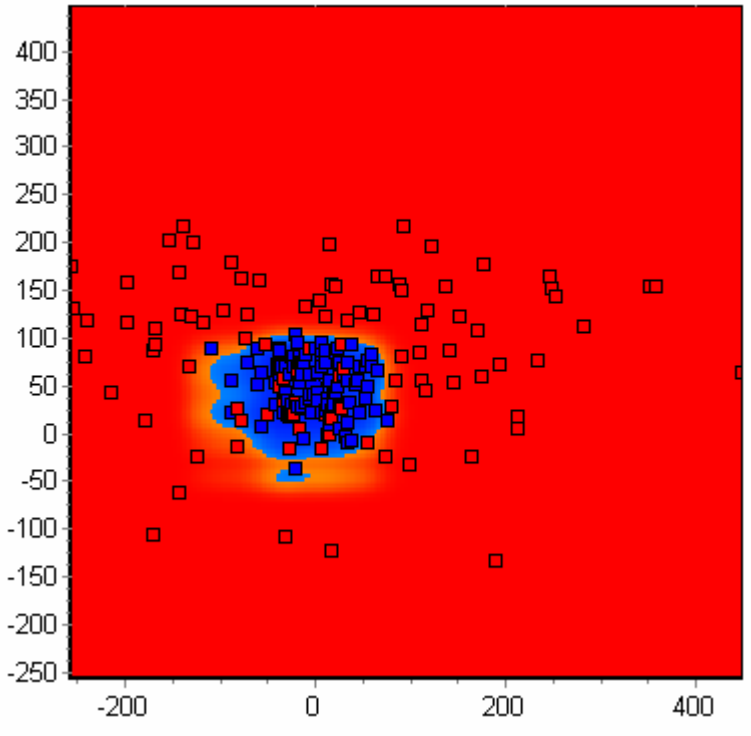
- Mahalanobis distance

$$\delta = (\mathbf{x}_i - \mathbf{x}_j)^T \Sigma^{-1} (\mathbf{x}_i - \mathbf{x}_j)$$

Distances obey triangle inequality

Similarity in descriptor space

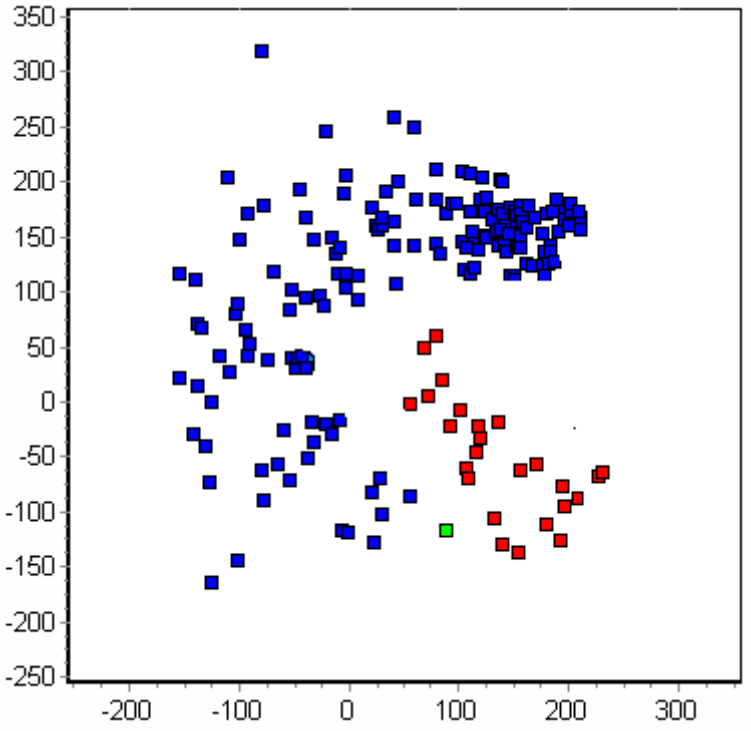




Comparison between a point and groups of points is a classification problem. Euclidean distance performs very well if groups are separable (left). Other classification methods help in other cases.

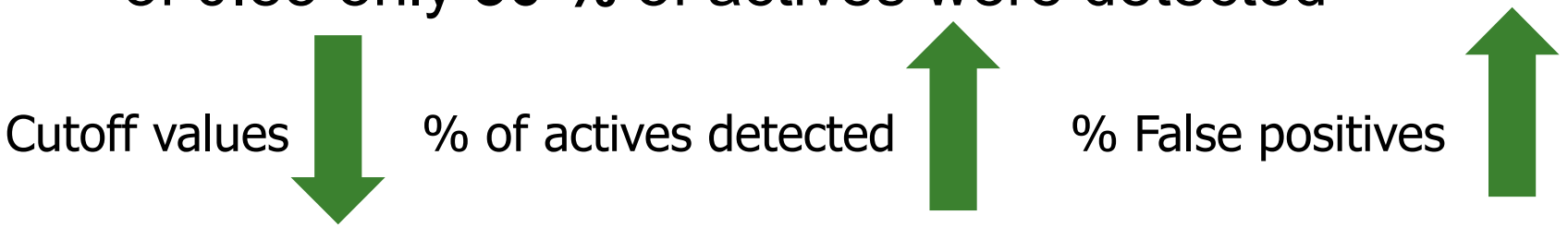
What do we measure

- We compare numerical representations of chemical compounds
  - The numerical representation is not unique
  - The numerical representation includes only part of all the information about the compound
  - A distance measure reflects “closeness” only if the data holds specific assumptions



Example: Y. Martin et al (2002) Do structurally similar molecules have similar biological activity ?

- Set of 1645 chemicals with IC50s for monoamine oxidase inhibition
- Daylight fingerprints 1024 bits long (0-7 bonds)
- When using Tanimoto coefficient with a cut off value of 0.85 only **30 %** of actives were detected



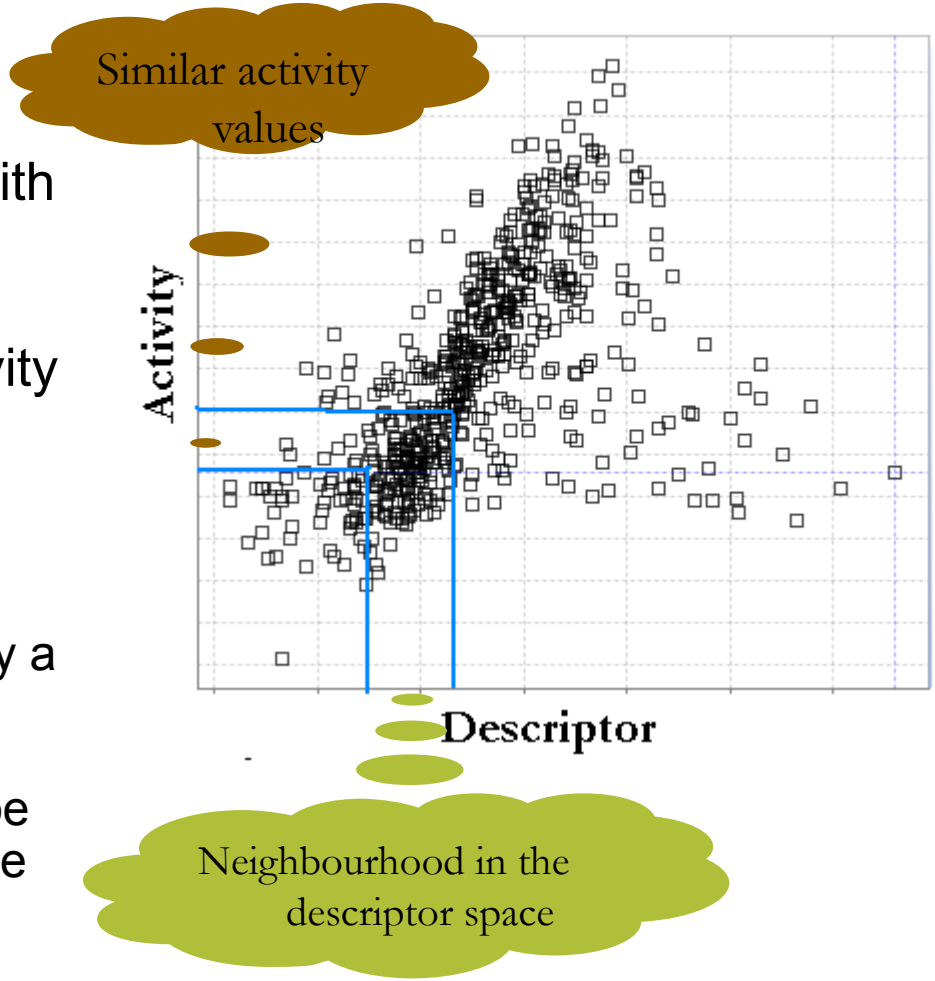
J. Med. Chem. 2002,45,4350-4358

Chemical similarity caveats

- The similarity computation may not correctly represent the intuitive similarity between two chemical structures
  - The properties of a chemical might not be implicit in its molecular structure
  - Molecular structure might not be fully measured and represented by a set of numbers (information loss)
  - Comparison by similarity indices may be counterintuitive
- Intuitively similar chemical structures may not have similar biological activity
  - Bioisosteric compounds
  - Structurally similar molecules may have different mechanisms of action

Similarity and Activity "Neighbourhood principle"

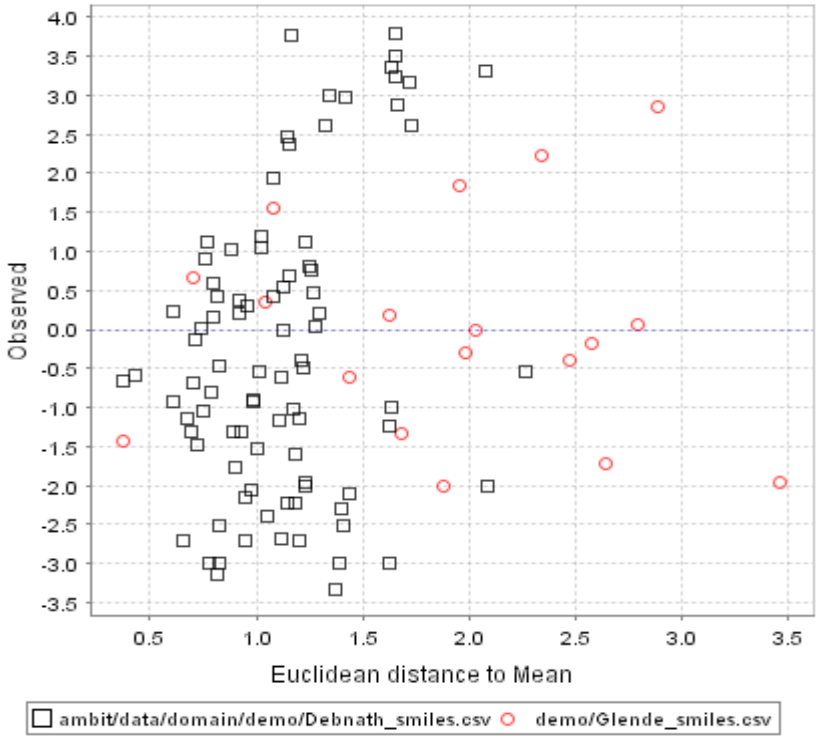
- Proximity with respect to descriptors does not necessary mean proximity with respect to the activity
- Depends on the relationship between descriptor and activity
  - True if a continuous & monotonous (e.g. linear,…) relationship holds between descriptors and activity
  - The linear relationship is only a special case, given the complexity of biochemical interactions. Its use should be justified in every specific case and/or used only locally

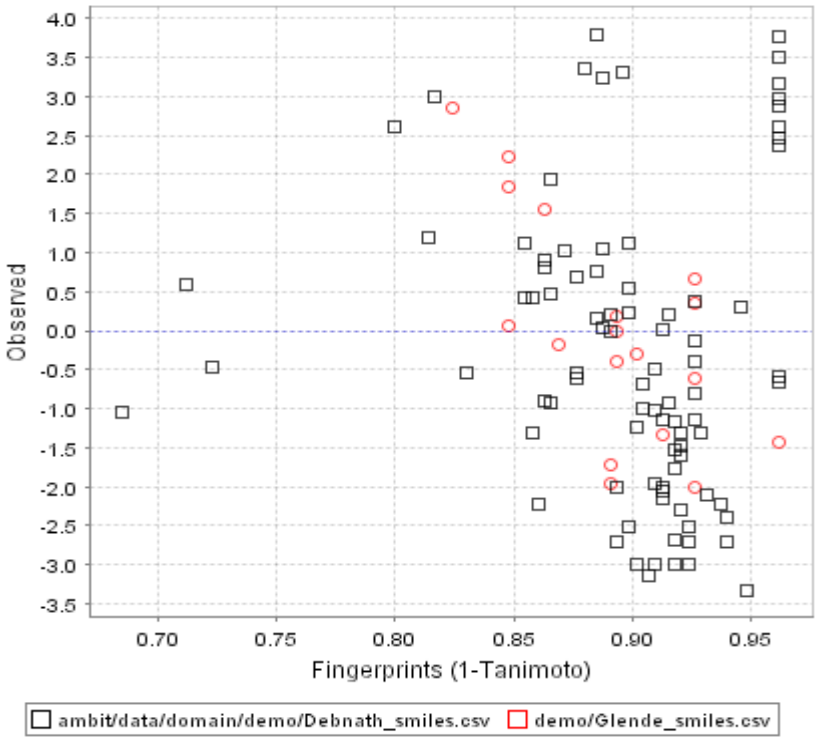


Similarity vs. Activity

Black square: Salmonella mutagenicity of aromatic amines [Debnath et al. 1992] (log TA98)

Red circle: Glende et al. 2001 set: alkyl-substituted (*ortho* to the amino function) derivatives not included in original Debnath data set

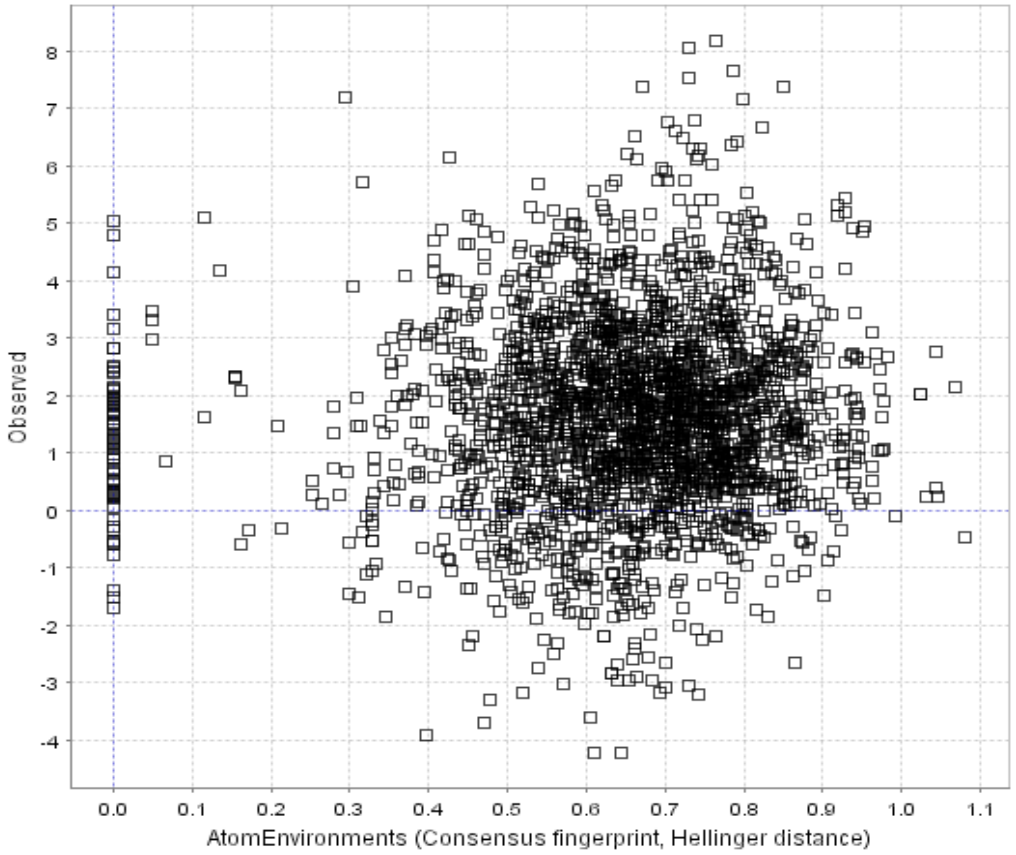




logP, E_{homo}, E_{lumo}

Similar compounds, Relatively small data set

Similarity by atom environments vs. logP



Syracuse Research KOWWin training set, 2400 compounds

(diverse compounds, large data set)

Molecular representation requirements

- Information preserving or allowing only controlled loss of information
- Feature selection
  - By domain knowledge (e.g. receptor binding, any knowledge of mechanism of action)
  - By verification of the « neighbourhood » assumption
  - By feature selection methods
    - Examples: PCA, Entropy, Gini index, Kullback-Leibler distance, filter and wrapper methods
    - Compounds should cluster tightly within a class and be far apart for different classes
- Combining different measures (consensus approach)

Structure is not the sole factor for biological activity

- Interactions with environment
  - Solvation effects
  - Metabolism
  - Time dependence
  - More...
- Biological activity in different species

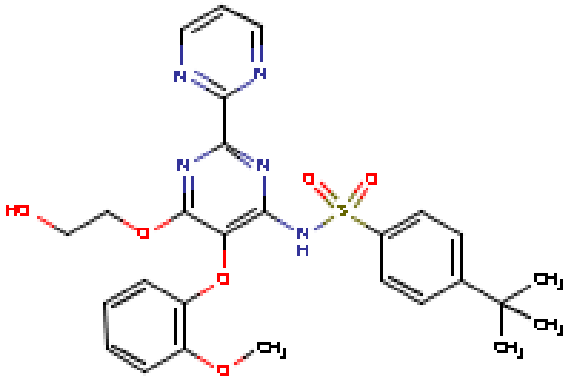
Conclusions

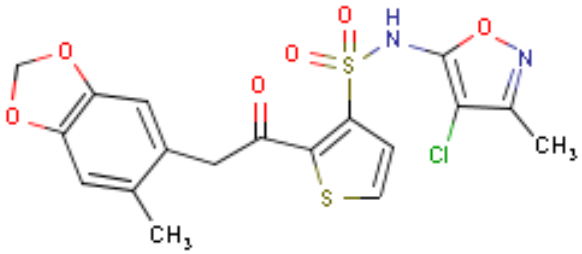
- Molecular similarity is relative
- Molecular representation and similarity index have to account for the underlying bio-chemistry
- Validation of the similarity formulation and its algorithmic solution is essential
  - "Neighbourhood" assumption has to be proven case by case

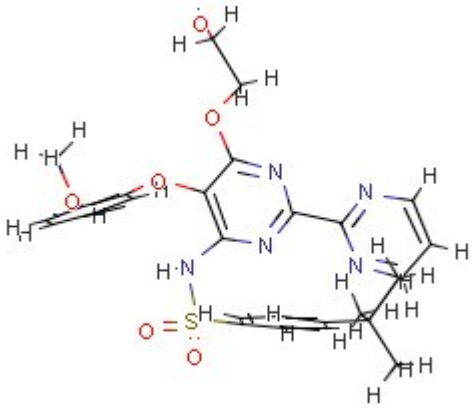
"As understanding of the chemistry and biology of drug action improves and a greater ability to model the underlying mechanisms appears, the need for 'similarity' approaches will diminish."

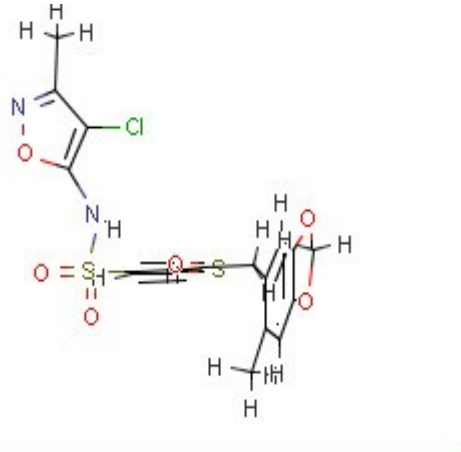
Bender, A.; Glen, R. C. (2004)
Molecular similarity: a key technique in molecular informatics.
Org. Biomol. Chem., 2(22), 3204-3218

Case study









Case study

- Tanimoto coefficient: 0.51 (i.e. < 0.80 border):
- Chemist' view:
- Type of effects:

- DISSIMILAR, although sulphonamide-moieties share similarities!

Nikolova N., Jaworska J., Approaches to Measure Chemical Similarity - a Review, QSAR Comb. Sci. 22 (2003) pp.1006-1024

REACH - Current status

rivm

Aim of the presentation

- Provide overview on main processes in REACH
  - Short overview
  - Information requirements and Integrated Testing Strategies
- Provide overview of main topics on Integrated Testing Strategies in OSIRIS (FP 6)

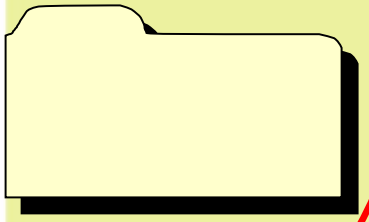
Most relevant titles

REACH= Registration, Evaluation, Authorisation and restriction of CHemicals

EU Regulation 1907/2006

Registration

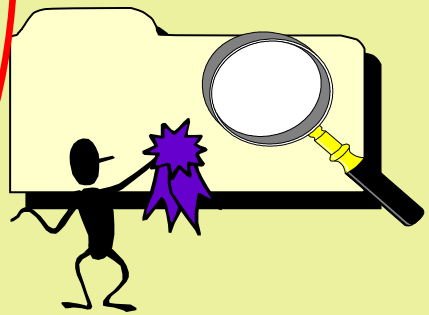
> 1 tonne/yr



Evaluation

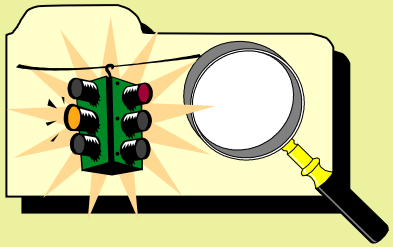
> 10 tonnes/yr

+ substances of concern



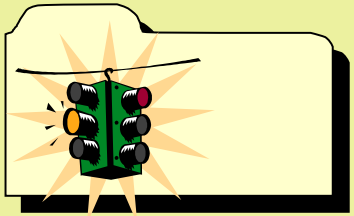
Authorisation

CMR & PBT & equivalent concern



Restrictions

Substances of concern



Industry and registration

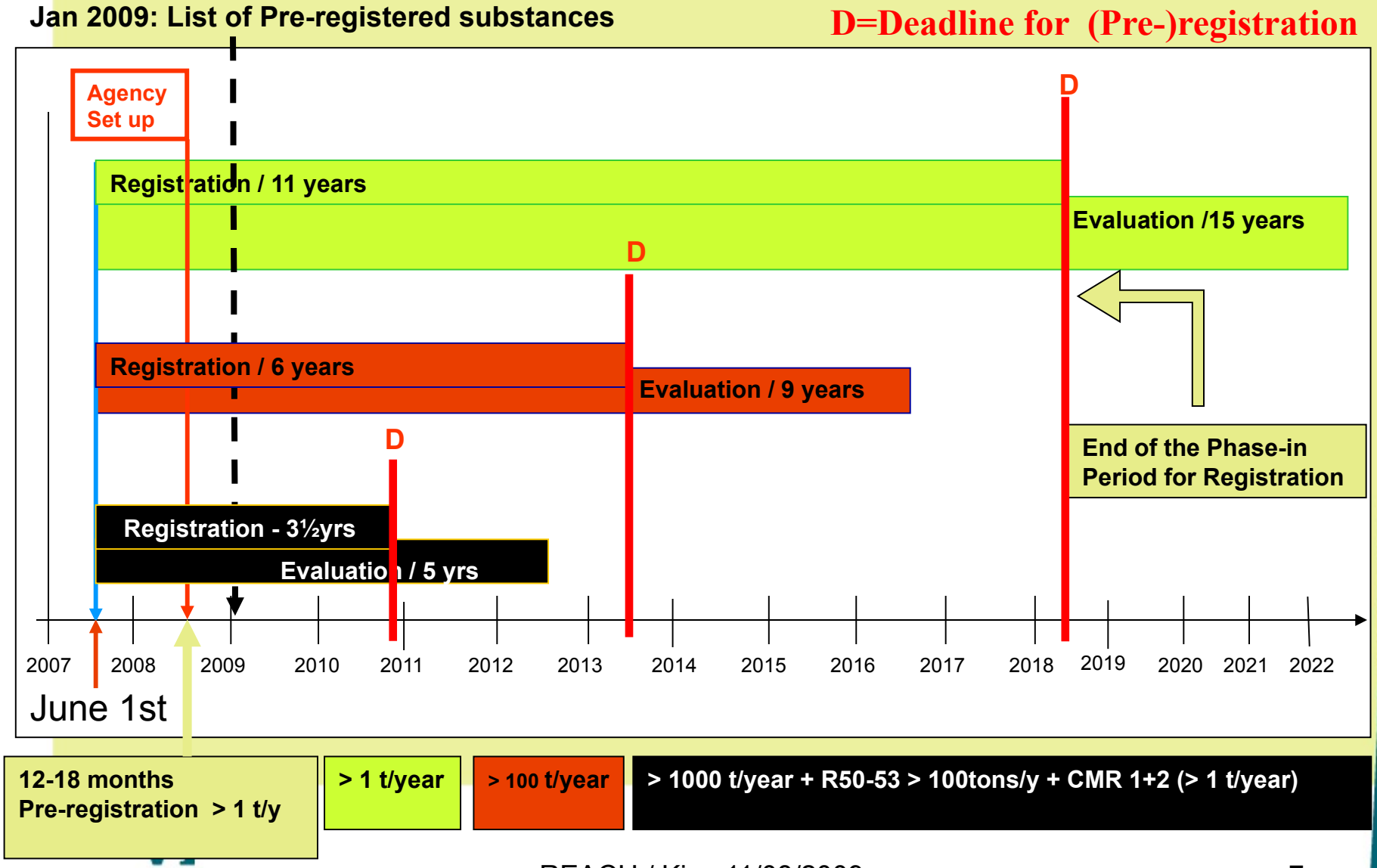
- First pre-registration (of phase-in substances)
- Then: registration
- Or: registration (of non phase-in substances)

PRE-REGISTRATION …. and THEN?

- ***January 2009:***
  - ECHA published list of pre-registered substances
    - Names of substances
    - EINECS and CAS number or other ID-code
    - First envisaged registration deadline
  - No names of Companies

- ***Substance Information Exchange Forum (SIEF):***
  - Companies are informed of other pre-registrants of the same substance
    - Aim: to stimulate data sharing for registration

Deadlines registration and pre-registration

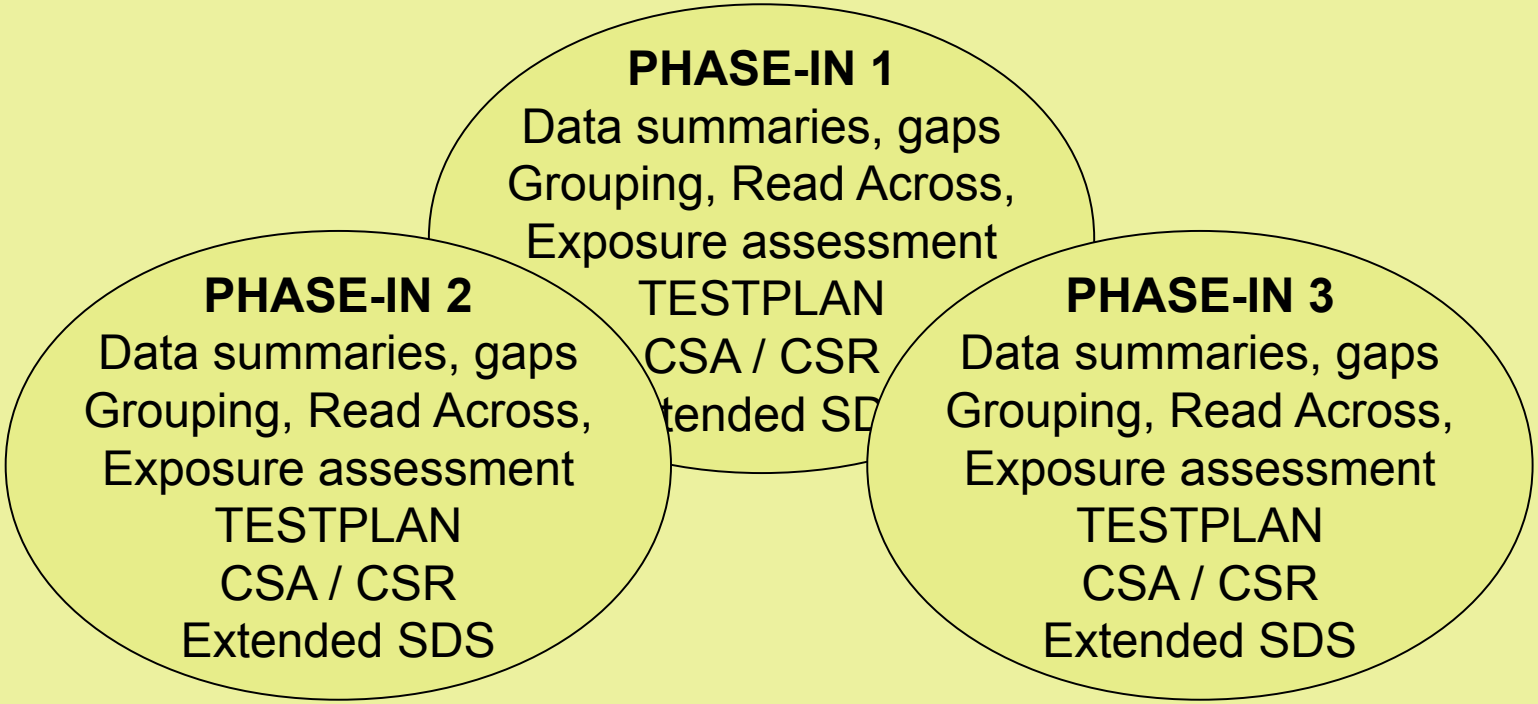


REGISTRATION: IS NEXT STEP

PUBLICATION PRE-REGISTERED SUBSTANCES (Jan. 2009)

SIEF formation and data sharing

- DOSSIER PREPARATION:



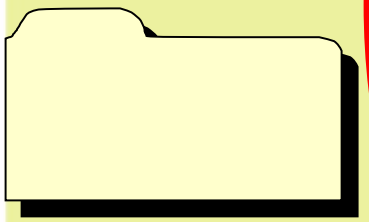
- **DOSSIER COMPLETION & SUBMISSION**

REACH= Registration, Evaluation, Authorisation and restriction of CHemicals

EU Regulation 1907/2006

Registration

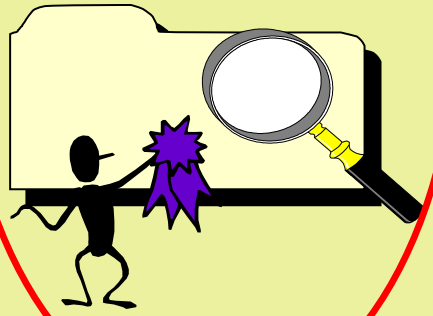
> 1 tonne/yr



Evaluation

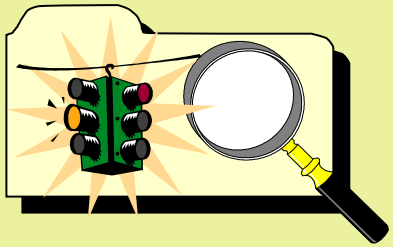
> 10 tonnes/yr

+ substances of concern



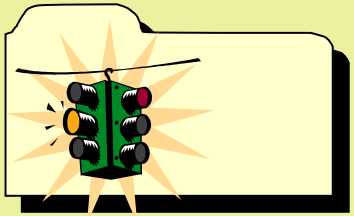
Authorisation

CMR & PBT & equivalent concern

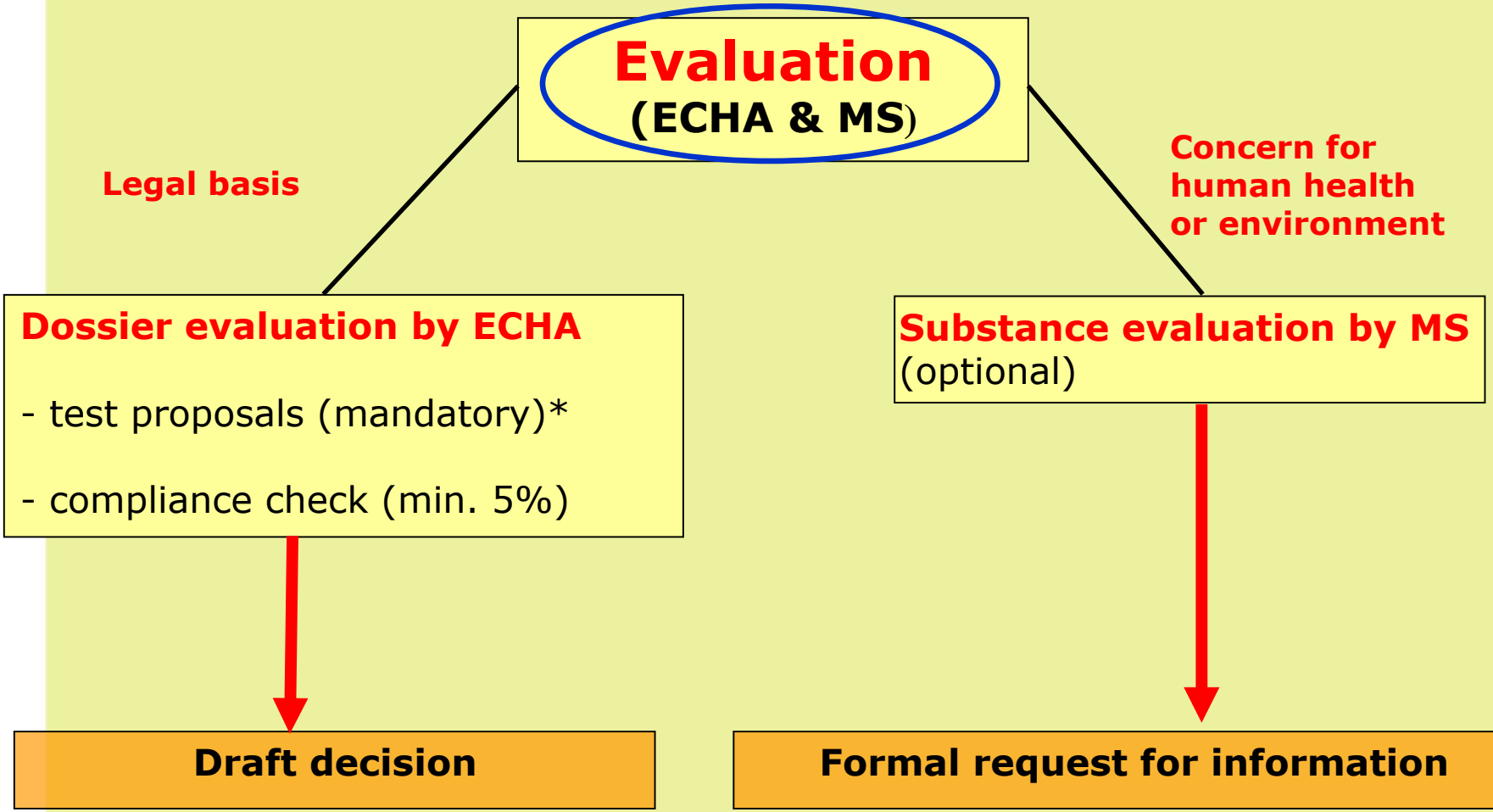


Restrictions

Substances of concern



Title VI. Evaluation



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* Prevention of unnecessary animal tests

Testing proposals

- Two main aspects in relation to examination of testing proposals
  - Does the proposal comply with the standard testing requirements.
  - Are the reasons for proposing additional testing for endpoints over and above the standard testing requirements appropriate

    (aim: avoid unnecessary testing).

- Relevant issues:
  - Several (different) testing proposals
  - Proposal justified and adequate? (RIP3.2/3.3)
  - Priority also to substances subject on Community Rolling Action Plan (CRAP) for substance evaluation

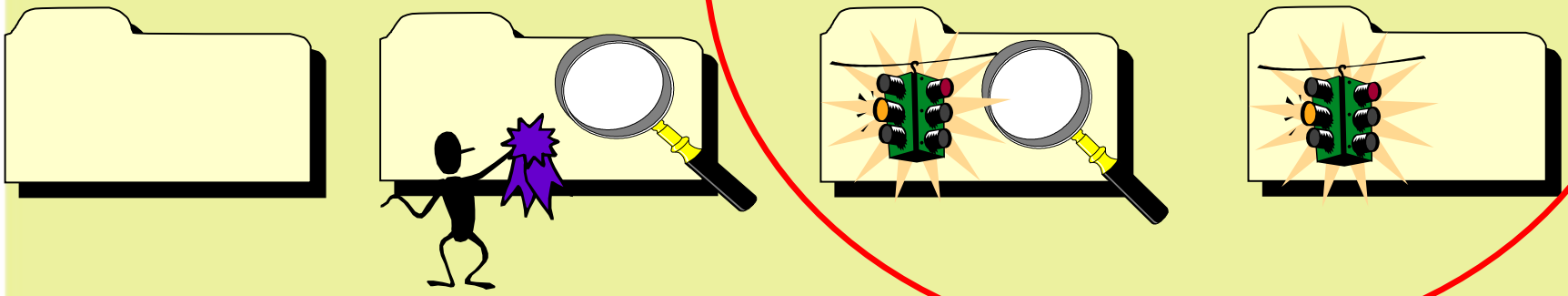
Compliance check

- Quality check! (risk irrelevant)
  - Technical dossier (information/adaptations)
  - Chemical Substance Register
  - Explanation for separate submissions
- Focus
  - Random *vs* non-random selection of dossiers, Targeting, Joint submissions, Read-across/category approach, Timing in relation to substance evaluation, Drafting decisions
- Actor
  - ECHA

REACH= Registration, Evaluation, Authorisation and restriction of CHemicals

EU Regulation 1907/2006

Registration	Evaluation	Authorisation	Restrictions
> 1 tonne/yr	> 10 tonnes/yr + substances of concern	CMR & PBT & equivalent concern	Substances of concern



Free circulation of substances on the internal market

Chemical safety

is responsibility of

manufacturer, importer and downstream user

Interference in the internal market

Community-wide action

is responsibility of

authorities

Registration
Chemical Safety Report
Risk adequately controlled

Evaluation
← Dossier evaluation
Substance evaluation →

Restrictions
Annex XV dossier
Unacceptable risk

Annex XVII

Derogations

Authorisation
Substances of Very High Concern

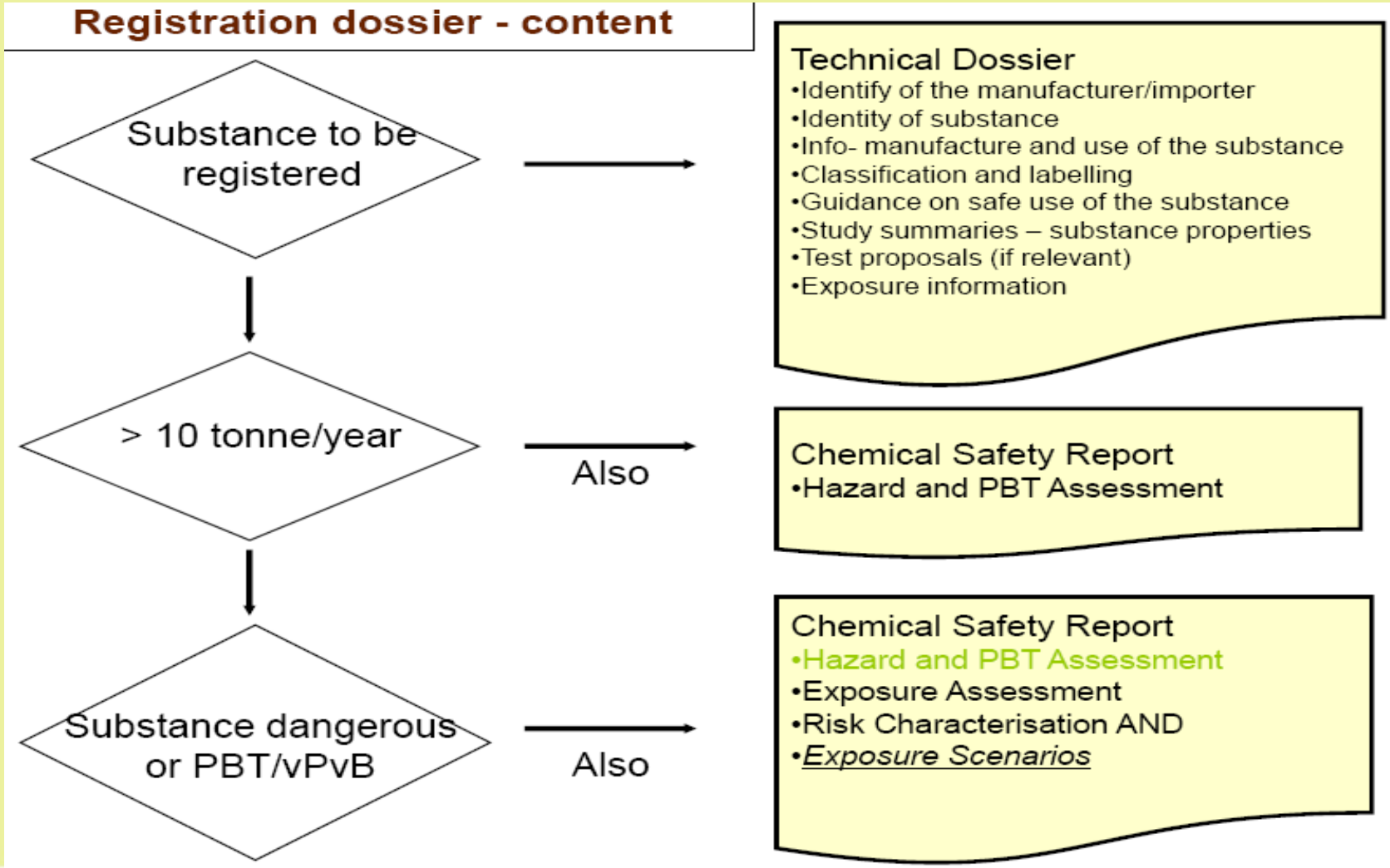
Annex XIV

Exemptions

Authorisation

Pt. II: information requirements in REACH

Overview of registration requirements



Steps in data gathering process

- Gather and share existing information
- Consider Information needs (Annex VII-XI in REACH)
- Identify information gaps
- Generate new data/ propose test

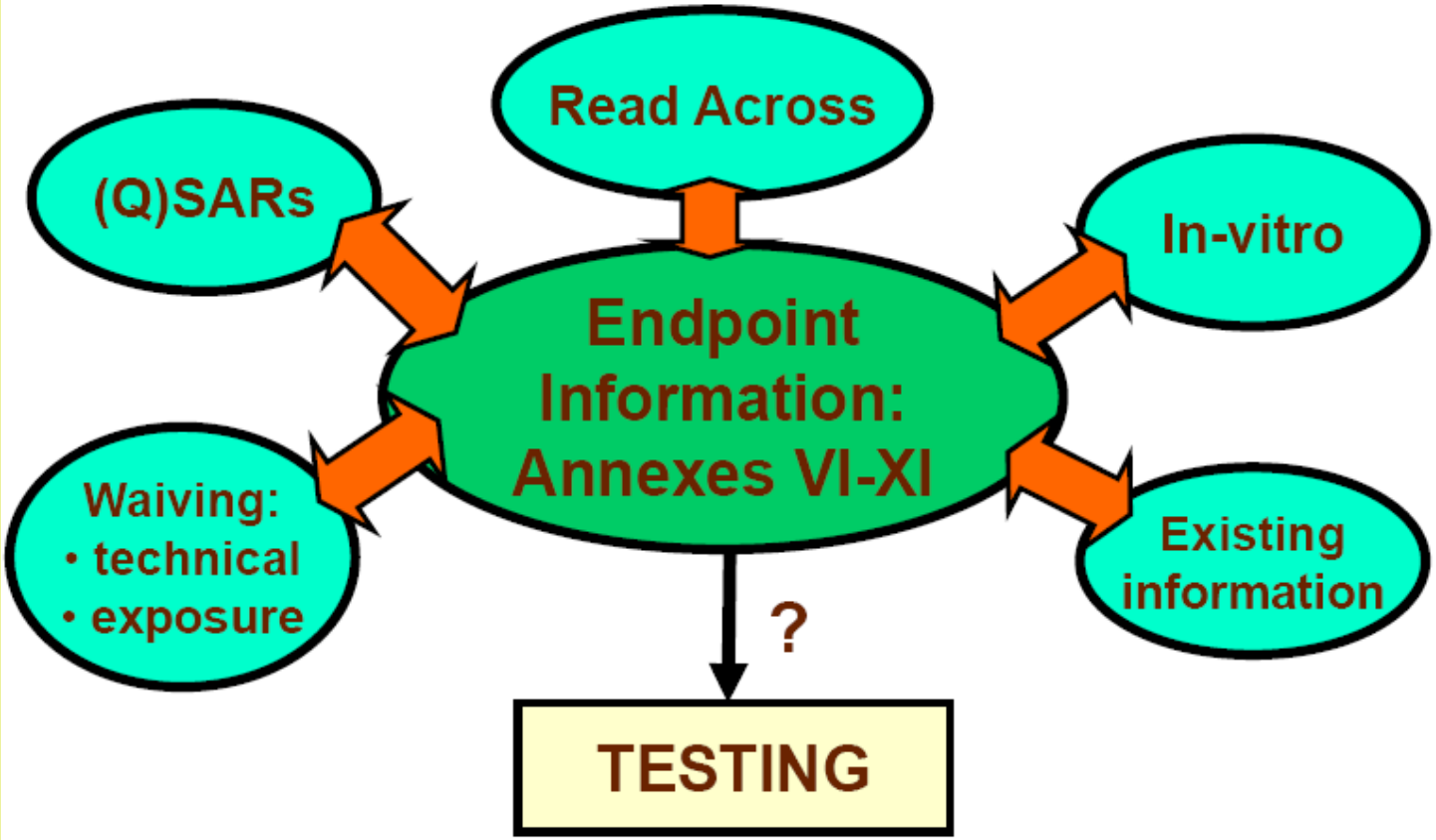
- *Animal testing as a last resort!*

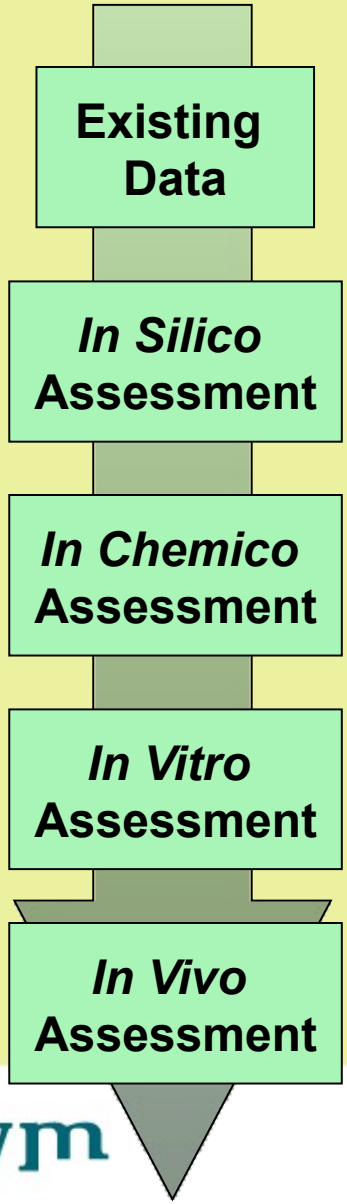
- An efficient hazard assessment is needed while reducing costs and reducing animal use in toxicity testing.
- The alternatives should allow for use in
  - Chemical Safety Assessment
  - Classification and Labelling
  - PBT assessment

Why Integrated testing strategies?

- To get the “right information” to adequately identify and manage the risks
- To limit the number of animal tests
- To reduce the costs for industry
- To speed up the assessment process

Elements of Integrated testing strategies

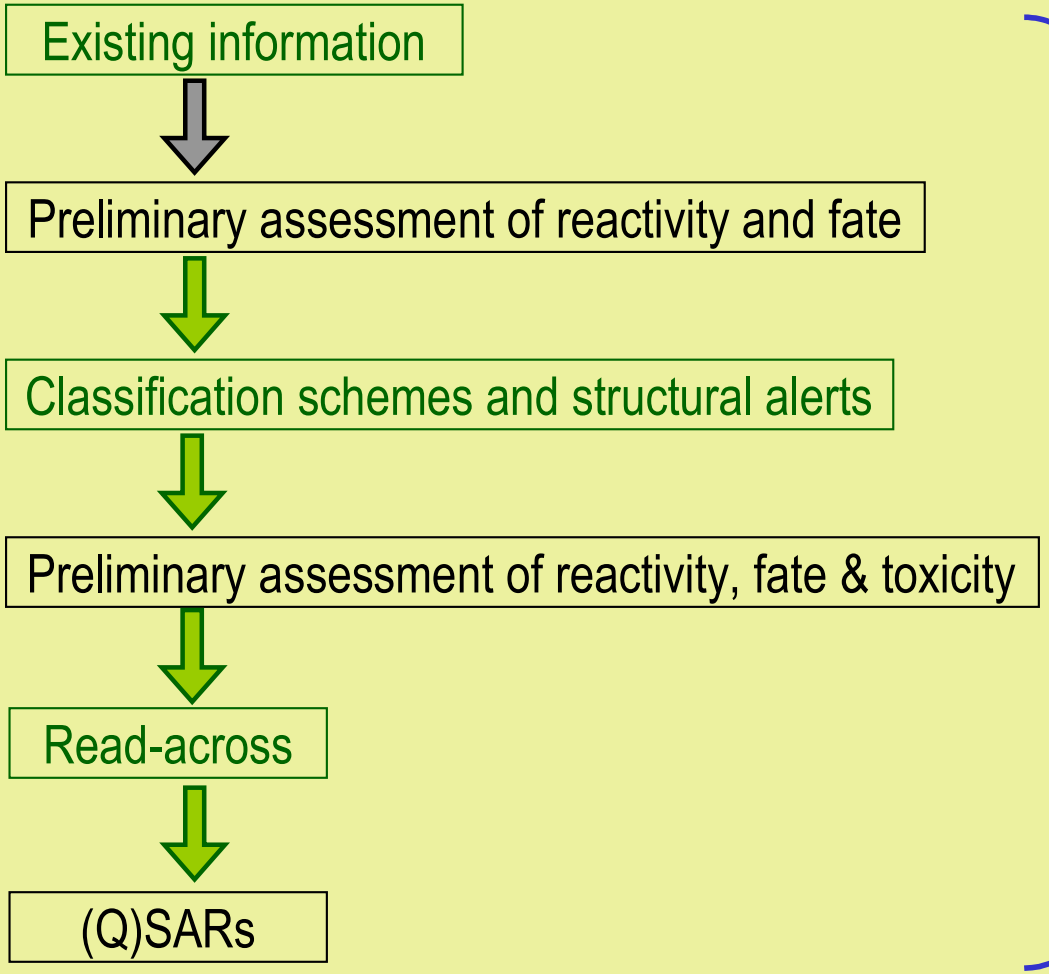




- Existing data
- Category formation
  - Developing groups of similar compounds
  - Obtaining toxicological data and information
  - Performing read-across
- Filling data gaps

[source: OSIRIS, Mark Cronin]

A non-testing strategy (Worth, SETAC oct. 2008)



Working Matrix

	A	B	C
Chemical			
Metabolite 1			
Metabolite 2			

Assess adequacy

Conclusion or targeted testing

Pt III. Projects supporting ITS in REACH

- Many international scientific programs and efforts aim to improve the knowledge base for toxicity testing, testing strategies and hazard assessment; e.g.

  - ***CADASTER (FP7)***
  - ***OPENTOX (FP7)***
  - ***OSIRIS (FP6)***
  - ***REPROTECT (FP6)***
  - ***SENS-IT-IV (FP6)***

  - ***OECD activities***
  - ***JRC activities***
  - ***ECHA activities***
  - ***Etc.***

OSIRIS

Integrated Project (IP), FP6

Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of non-Test and Test Information

Sub-Priority: 1.1.6.3 (Global change and ecosystems), Complementary Research, Development of advances methodologies for risk assessment

Date of Preparation: 10 August 2006

Coordinator:

Professor Gerrit Schüürmann, UFZ Centre for Environmental Research, Leipzig, Germany

Tel +49-341-235-2309, Fax +49-341-235-2401, E-mail gerrit.schuurmann@ufz.de

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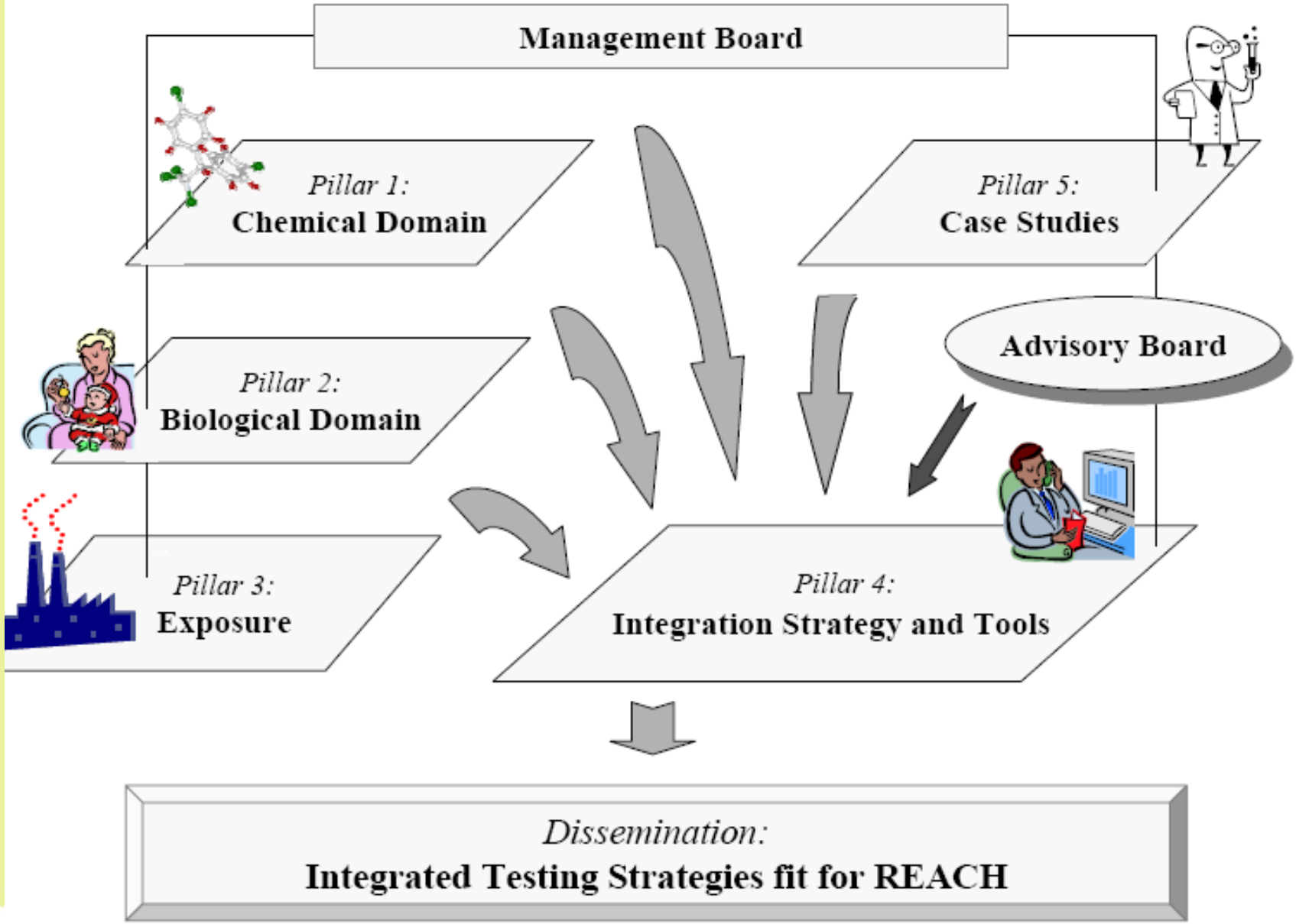
Intelligent  (Integrated) Testing Strategy

decision analysis - WOE

- (Q)SAR
- omics
- read across
- categories
- *in vitro*
- exposure
- optimized *in vivo*, TTC

Goals

- The goal of OSIRIS is to develop **Integrated Testing Strategies** (ITS) **fit for REACH** that make it possible to significantly **increase** the **use** of **non-testing information** for **regulatory decision making,** and to effectively **reduce animal testing** to the **level needed** from a **risk perspective**.
- To this end, **operational procedures** will be developed, tested and disseminated that **guide** a transparent and scientifically sound **evaluation** of chemical substances in a **risk-driven**, **context specific** and **substance-tailored** (RCS) manner, and allow decision making to be built on **information-rich combinations** of **novel non-testing** and **optimized experimental information**.
- In this context, a major scientific challenge is to identify, reduce and manage the level of uncertainty. Accordingly, the envisaged **decision-theory based framework** will be designed to **handle uncertainty explicitly**, covering data, methods, models and decision making.


Management Board
Pillar 1:
Chemical Domain
Pillar 5:
Case Studies
Advisory Board
Pillar 2:
Biological Domain
Pillar 3:
Exposure
Pillar 4:
Integration Strategy and Tools
Dissemination:
Integrated Testing Strategies fit for REACH

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Major objectives

Objective 1 (Pillar 1: Chemical Domain)
To develop methods and guidance for transparent and scientifically sound use of chemistry driven information in ITS.

Objective 2 (Pillar 2: Biological Domain)

- To provide efficient strategies and guidance for exploitation of all types of biological information on toxic effects of chemicals in ITS, focusing on reduced animal use and informed extrapolation across human and environmental toxicology, species, endpoints and time scales.

Objective 3 (Pillar 3: Exposure)
To develop criteria for exposure informed testing as foreseen in the future REACH regulation,
and to refine relevant exposure assessment methods accordingly.

Objective 4 (Pillar 4: Integration Strategies and Tools)
To develop weight-of-evidence approaches for ITS based on a computerized decision theory framework ready for web access, optimizing the use of existing data and non-test information,
and minimizing the need for new testing in risk assessment procedures.

Objective 5 (Pillar 5: Case Studies)
To evaluate the feasibility and effectiveness of the new ITS methodologies and to provide
guidance for their use in concrete form, covering major human and environmental endpoints.

Conclusions

- You may want to familiarise yourself with the guidance on information requirements and QSAR/ read-across / Weight of evidence in REACH
- REACH needs the information for taking decisions on
  - Chemical Safety Assessment (risk assessment)
  - Classification and Labelling
  - PBT assessment
- The new models may contribute in a weight of evidence approach: can the improved prediction power of your model be quantified and can it be combined with other information /data?
- Given the number of research projects on ITS, good dessimination, collaboration and integration towards REACH is needed to optimise the effort

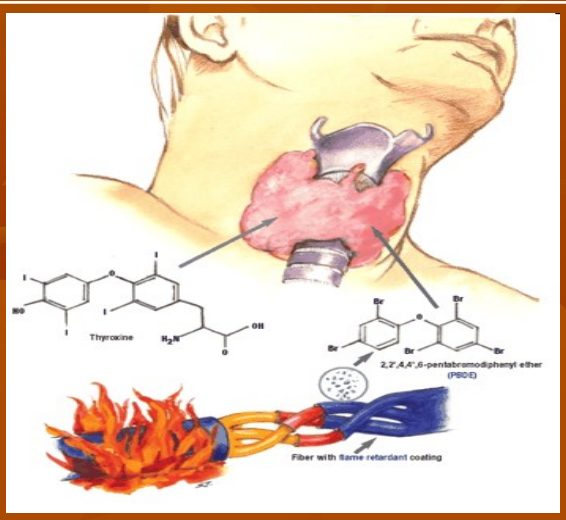
CAse studies on the Development and Application of *in-Silico* Techniques for Environmental hazard and Risk assessment

Willie Peijnenburg

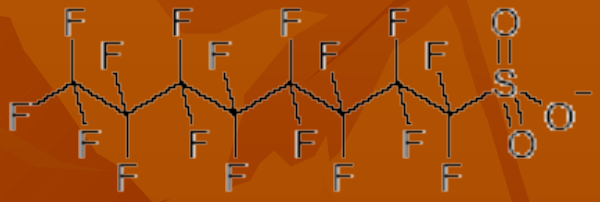
RIVM – Laboratory for Ecological Risk Assessment

willie.peijnenburg@rivm.nl

CADASTER



PBDE: "The PCB's of the future"

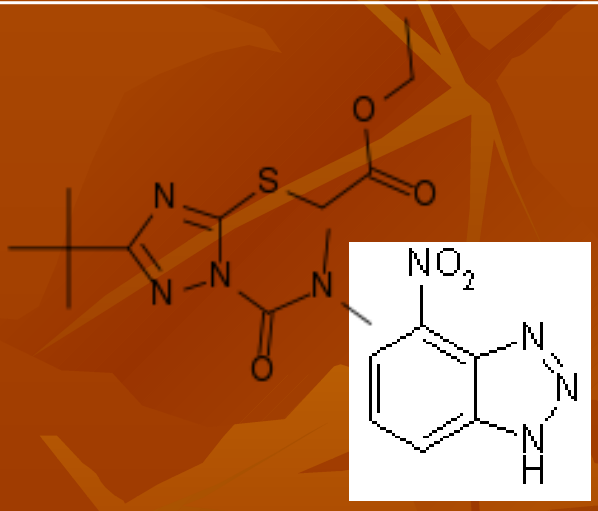


Classification of PFOS-compounds in 22 categories according to OECD

Table 3. Personal care products produced in Germany (1993).

Product category	Tons produced
Bath additives	162,300
Shampoos, hair tonic	103,900
Skin care products	75,500
Hair sprays, setting lotions, hair dyes	71,000
Oral hygiene products	69,300
Soaps	62,600
Sun screens	7,900
Perfumes, aftershaves	6,600
Total	559,100

Personal Care Products in the Environment: Agents of Subtle Change?



Microbicidal benzotriazoles

REACH

Registration, Evaluation, Authorisation and Restriction of Chemicals

- REACH requires demonstration of safe manufacture and use of chemicals
- REACH based on precautionary principle, aims at achieving proper balance between social, economic and environmental objectives
- REACH aims to optimise the use of scarce and scattered info on substances
- REACH aims to minimise animal testing by optimal use of info on “related” compounds

REACH

Minimised animal use:

1 – Use of validated *in silico* techniques: (Q)SAR/(Q)SPR

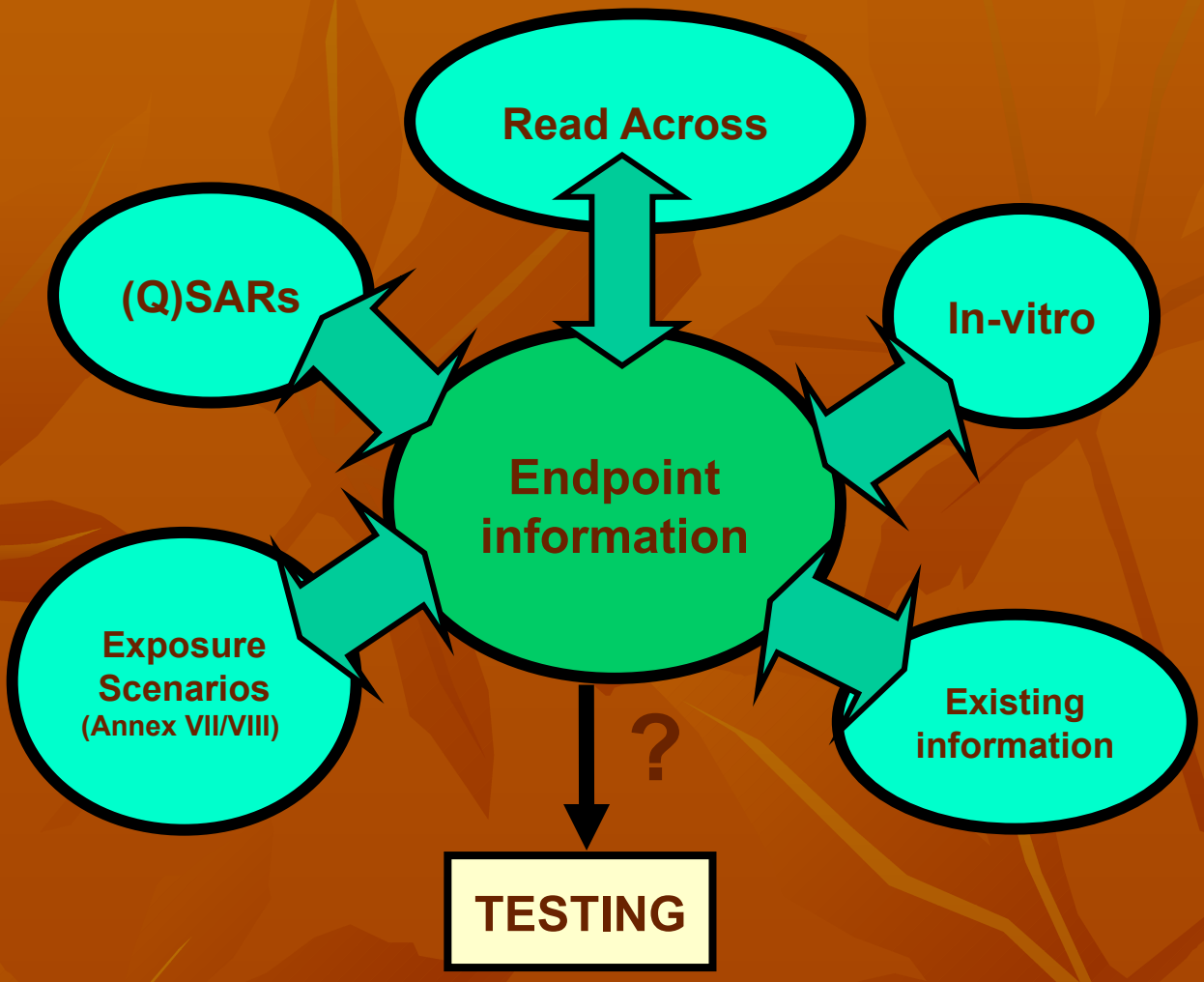
2 – New *in vitro* test methods, *in vivo* info analogues

3 – Minimization actual numbers of animals used, and replacement of animal tests by alternative methods

4 – Substance Information Exchange Forums (SIEFs) for obligatory provision of data and cost sharing

5 - Requirement of official sanctioning of proposals for tests for compounds with production volumes of above 100 tonnes to minimize animal testing

Intelligent Testing Strategies (ITS)



Constituents of an Intelligent (or Integrated) Testing Strategy (ITS).

Taken from a presentation of K. van Leeuwen and S. Bradbury: "REGULATORY RISK ASSESSMENT: Trends and paradigm shifts are needed" - European Commission & USEPA.

CADASTER

Goals:

Exemplify the integration of information, models, strategies for safety-, hazard-, risk assessment for large numbers of substances

Carry out “real” risk assessment for large numbers of substances according to the basic philosophy of REACH: < costs, animal testing, time

Exemplify how to increase non-testing information whilst quantifying and reducing uncertainty

CADASTER

Aim:

Provide full environmental hazard and risk assessment according to the REACH philosophy for chemicals belonging to 4 classes of emerging chemicals:

- 1 – Polybrominated diphenylethers (PBDE), typically class of hydrophobic chemicals that pose a threat to man and the environment.
- 2 - Perfluoroalkylated substances and their transformation products, like perfluoroalkylated sulfonamides, alkanoic acids, sulfonates. Persistent hydrophilic compounds that may be toxic for man and environment.
- 3 – Substituted musks/fragrances; a heterogenic group of chemicals of varying composition like substituted benzophenones, polycyclic musks, terpene derivatives. Common emission pattern in the environment.
- 4 - Triazoles/benzotriazoles: increasingly used as pesticides and anti-corrosives.

CADASTER

Outcome:

DSS – regularly updated for new compound classes:

- New testing strategies
- New testing data
- New models
- Actual integrated evaluations, including uncertainty and variability

- On-line and stand-alone tool

PARTNERS

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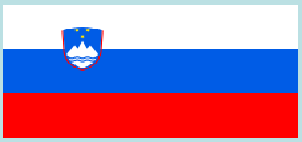
A. Woldegiorgis

T. Öberg

I. Tetko

N. Jeliazkova

M. Comber



Beneficiary Number *	Beneficiary name	Beneficiary short name	Country
1 (coordinator)	Rijksinstituut voor Volksgezondheid en Milieu (RIVM)	RIVM	Nl
2	Public Health Institute Maribor	PHI	Si
3	University of Insubria (Varese)	UI	Italy
4	IVL Swedish Environmental Research Institute	IVL	S
5	University of Kalmar	HIK	S
6	Helmholtz Zentrum München - German Research Center for Environmental Health (GmbH)	HMGU	Ge
7	Ideaconsult Ltd.	IDEA	Bu
8	Radboud University Nijmegen	RUN	Nl
9	Mike Comber Consulting	MCC	Be

Objectives - Work packages

1: Collection of data and models

- Experimental data intrinsic hazards – Screening Initial Data Set Dossier (SIDS)
- Models – Screening Initial Data Set Dossier (SIDS)

- Generation new data essential for validation and proper hazard/risk assessment
- Database data/models: dissemination purposes

Objectives - Work packages

2: Development/validation QSAR models

- Evaluate performance
- Similarity analysis and multivariate ranking methods for identification of priority chemicals to orient the experimental testing
- Develop new QSARs where gaps are identified due to lack of existing models or due to models of insufficient quality.
- Documentation of the performance of the (final) models selected and developed.

Objectives - Work packages

3: Integration of QSARs within hazard and risk assessment

- Integration in probabilistic risk assessment framework: characterize variability/ uncertainty, sensitivity analyses with regard to contributions in overall risk assessment framework, modelling of variability with regard to application in SSDs
- Evaluate ECETOC TRA screening risk assessment tool
- Evaluate methods and decision points for establishing scientific validity and applicability domains for QSAR models
- Explore possibilities for economic valuation of substitution of chemicals from within chemical classes

Objectives - Work packages

3 (cont.): Integration of QSARs within hazard and risk assessment

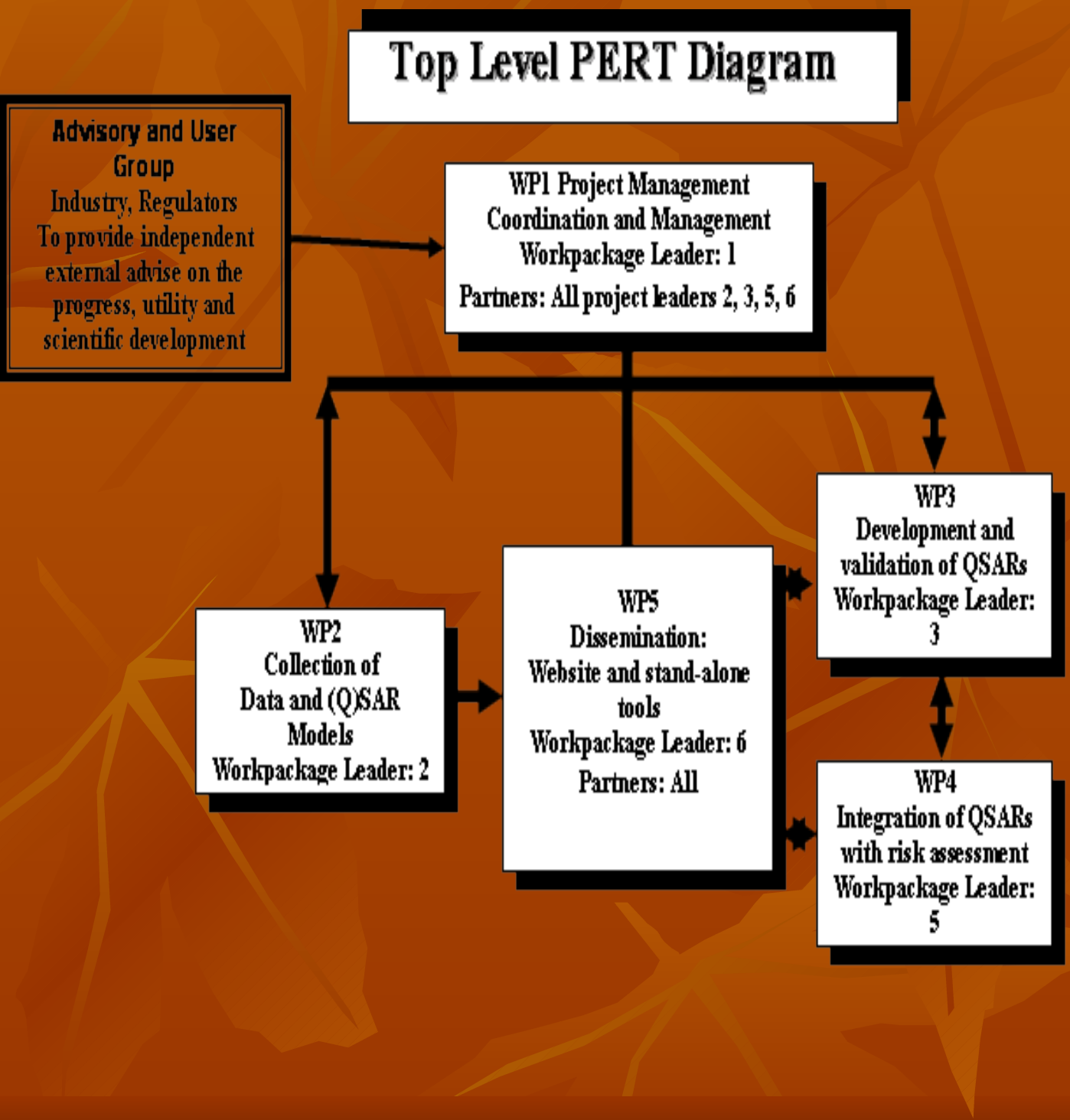
- Policy and management: provision of recommendations on a viable management strategy for optimized testing and in-silico modelling of hazardous organic substances.

Objectives - Work packages

4: Outreach: website, newsletters/ workshops, stand-alone tools for dissemination of project results

- Development of on-line, stand-alone DSS: develop, publish, use QSAR/QSPR models for REACH
- Integration of the developed models with the QSAR Application Toolbox developed by OECD: establish the com-patibility of the models with the (Q)SAR Model Reporting Format (QMRF) format
- Provision of a sustainable dissemination of project results by the WWW and as stand-alone tools
- Communication including newsletters and workshop(s).

Management


Top Level PERT Diagram
Advisory and User Group
Industry, Regulators
To provide independent external advise on the progress, utility and scientific development
WP1 Project Management
Coordination and Management
Workpackage Leader: 1
Partners: All project leaders 2, 3, 5, 6
WP2
Collection of Data and (Q)SAR Models
Workpackage Leader: 2
WP5
Dissemination:
Website and stand-alone tools
Workpackage Leader: 6
Partners: All
WP3
Development and validation of QSARs
Workpackage Leader: 3
WP4
Integration of QSARs with risk assessment
Workpackage Leader: 5