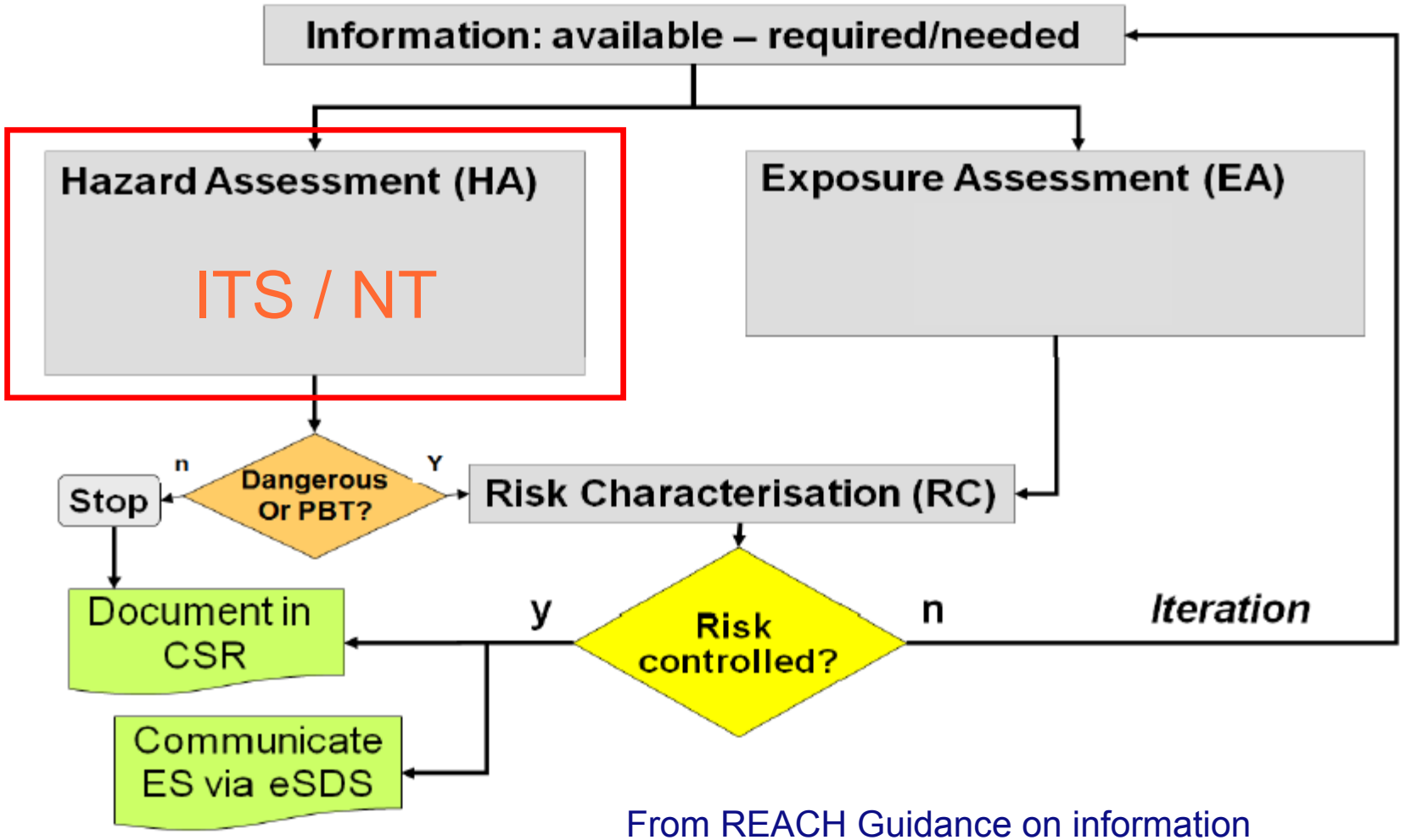
Non-testing / ITS

Dinant Kroese

TNO| knowledge for business

Chemical Safety assessment scheme



From REACH Guidance on information requirements and CSA – Part D

CONTENTS

1. ITS & Non-testing data

CSA steps (Annex VI)

1. Gather and share available information
2. Consider information needs
3. Identify information gaps
4. Generate new data / propose testing strategy

ITS:
“Efficient Information Gathering Strategy”

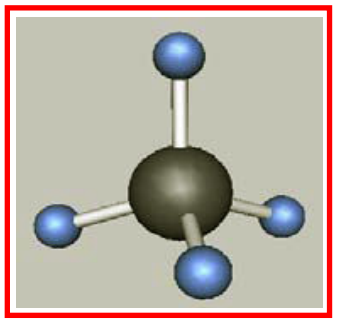
Step 1: Gather all available Testing and Non-Testing information

All available Testing and Non-Testing information

Non-Testing information

Human data

(Q)SAR models



In vitro

Grouping & read across

Exposure

General rules for adaptation of Standard (test) Requirements

Annex XI

1. Testing does not appear scientifically necessary
    - Use of existing data: PC, non-GLP etc, Historical human data
    - Weight of evidence
    - *In vitro* methods
    - Quantitative or Qualitative Structure Activity Relationships ((Q)SAR)
    - Grouping of substances and read-across approach

2. Testing is technically not possible

3. Substance-tailored exposure-driven testing

ITS: Information Gathering Strategy

Step 1: Gather all available Testing and Non-Testing information

If not sufficient ↓ *(for C&L and RA)*

(*Is Testing technically possible?*)

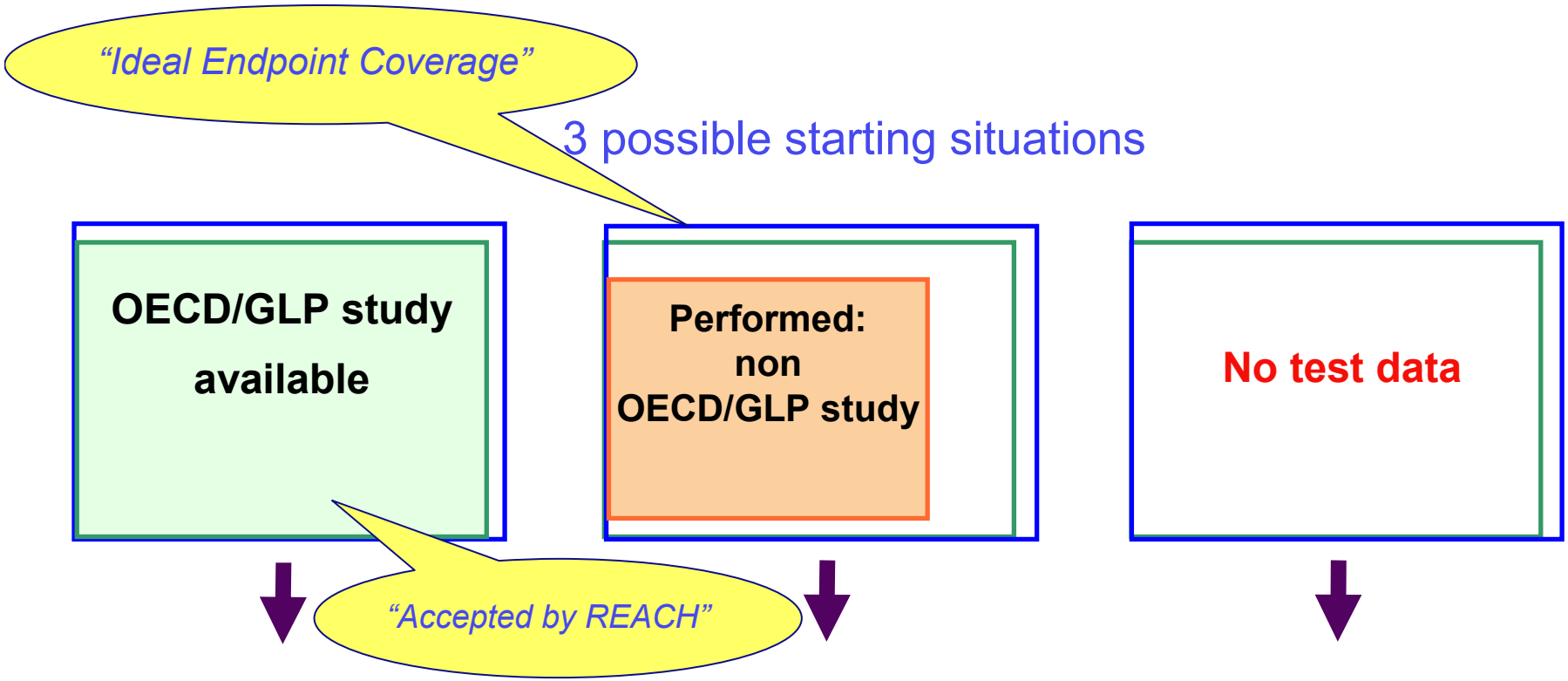
Step 2: Is Exposure-Based Waiving an option?

If not possible ↓

Step 3: Perform / Propose Testing as last resort!!

Testing in REACH very last resort: (a.o. in *art*.13, 25 & in Annex XI)

When assessing hazards

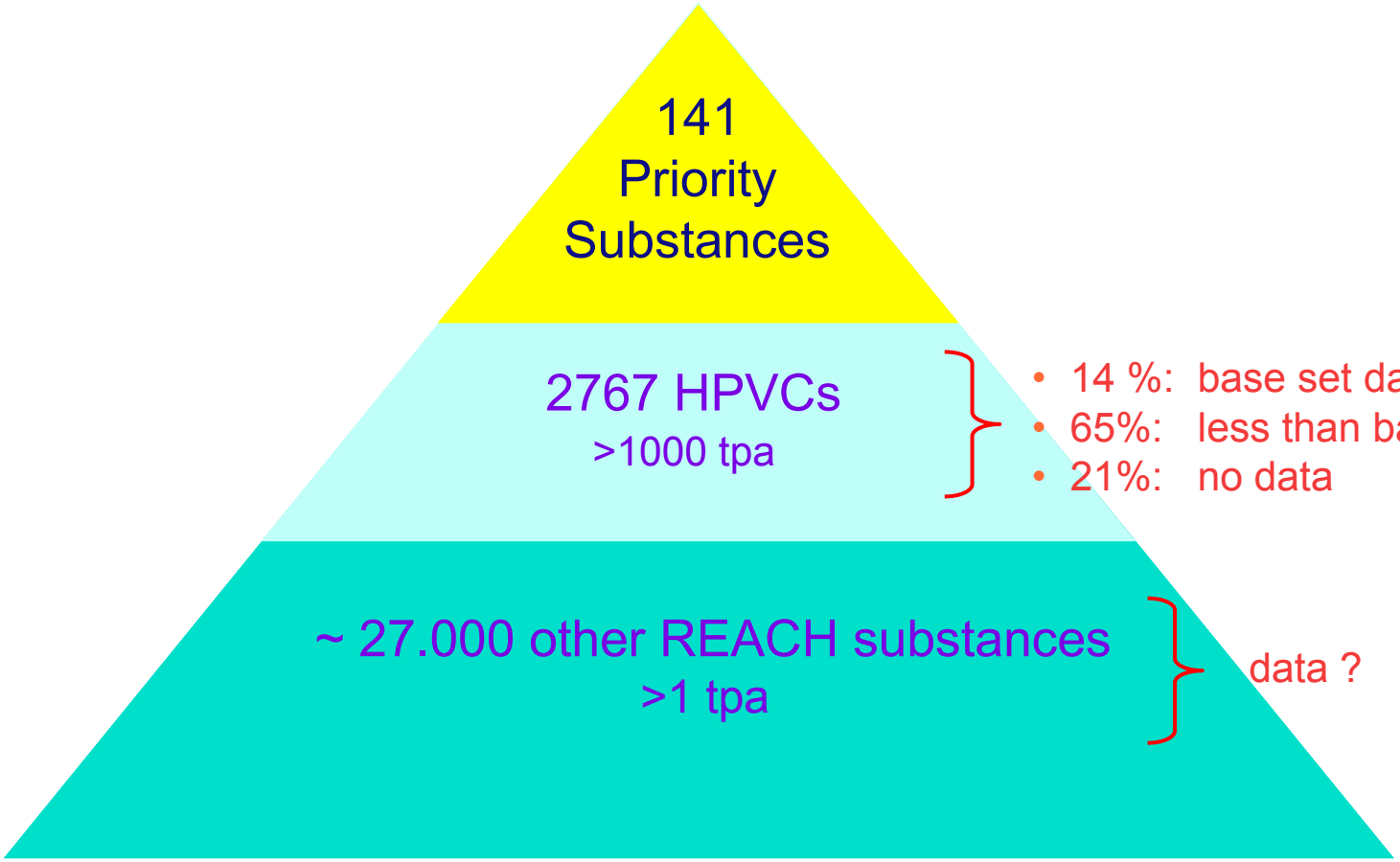


EBW ‘opties’:

Als geen NT data, dan is er ook geen category-specific TTC afleidbaar….. en vervallen we dus naar de heel lage Munro of evt. Cramer TTC…

The current situation on available testing data

for about 30.000 (?!) REACH chemicals > 1 tpa

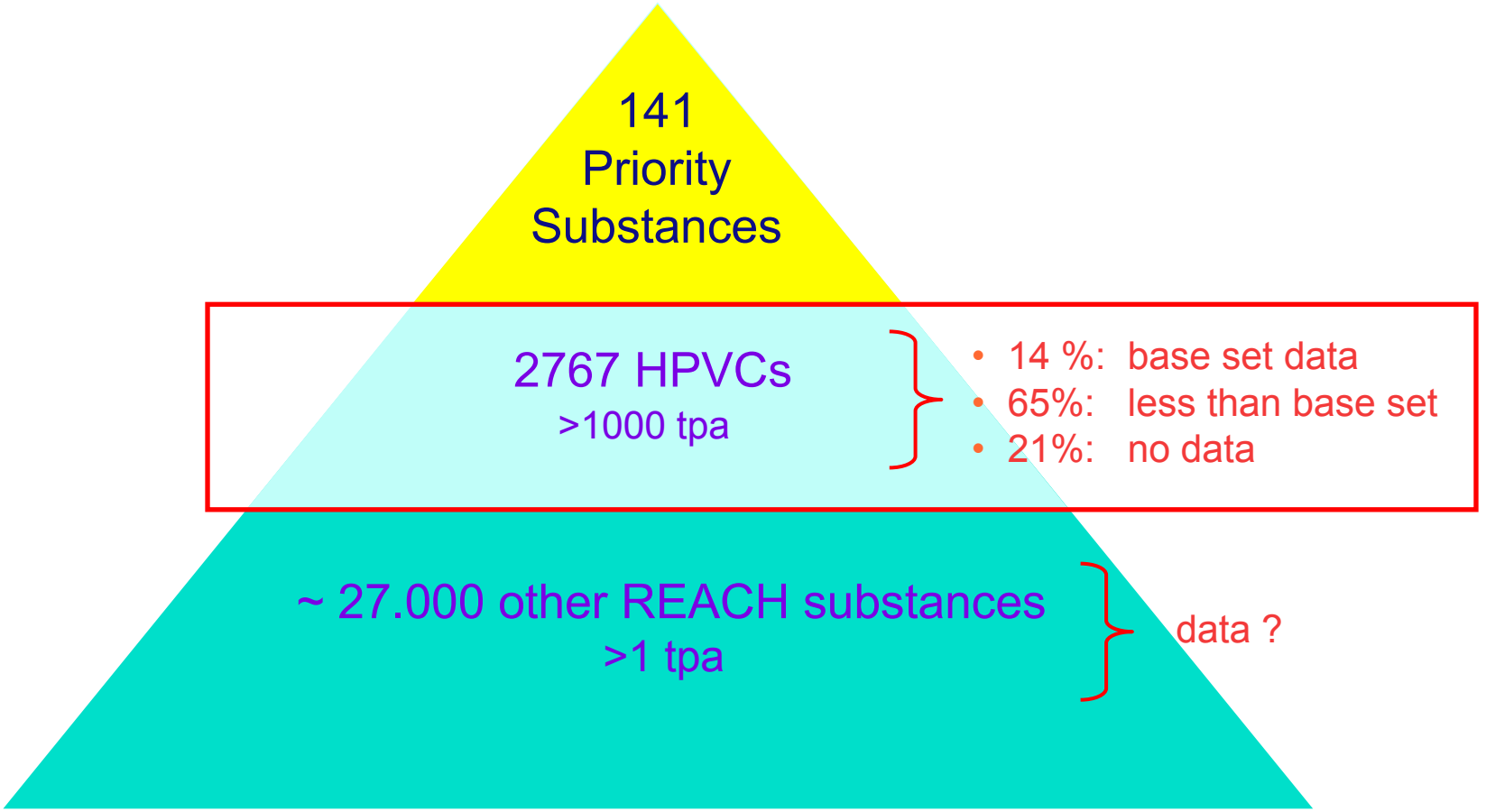


(> 100.000 EINECS substances)

Allanou, Hansen and van Der Bilt, 1999

The current situation on available testing data

for about 30.000 (?!) REACH chemicals > 1 tpa

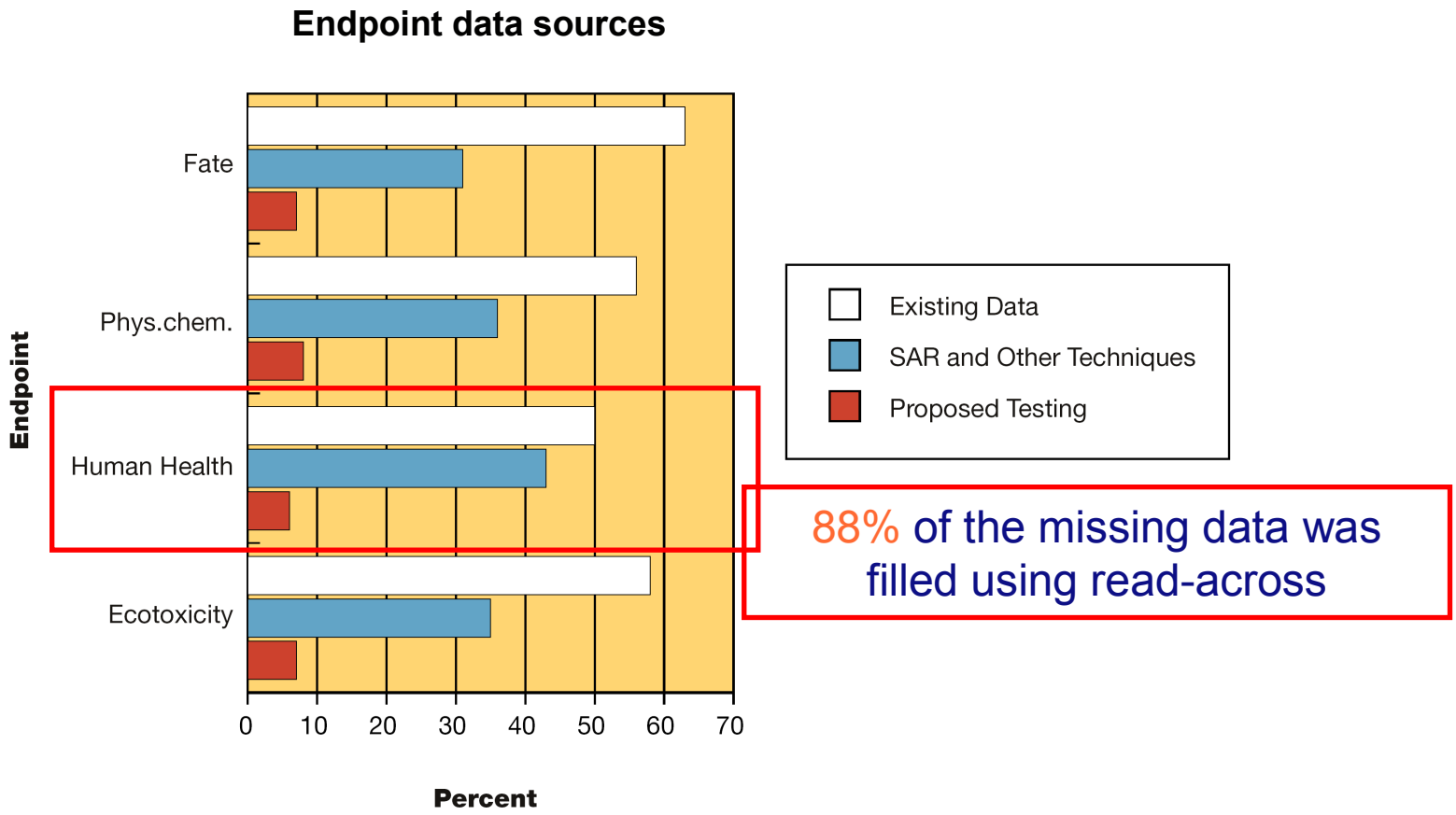


(> 100.000 EINECS substances)

Allanou, Hansen and van Der Bilt, 1999

Potential Impact of NT data

HPV Challenge Program (US.EPA, 2004)



88% of the missing data was filled using read-across

Expected savings of NT in ITS under REACH

Van der Jagt *et al.*, 2004

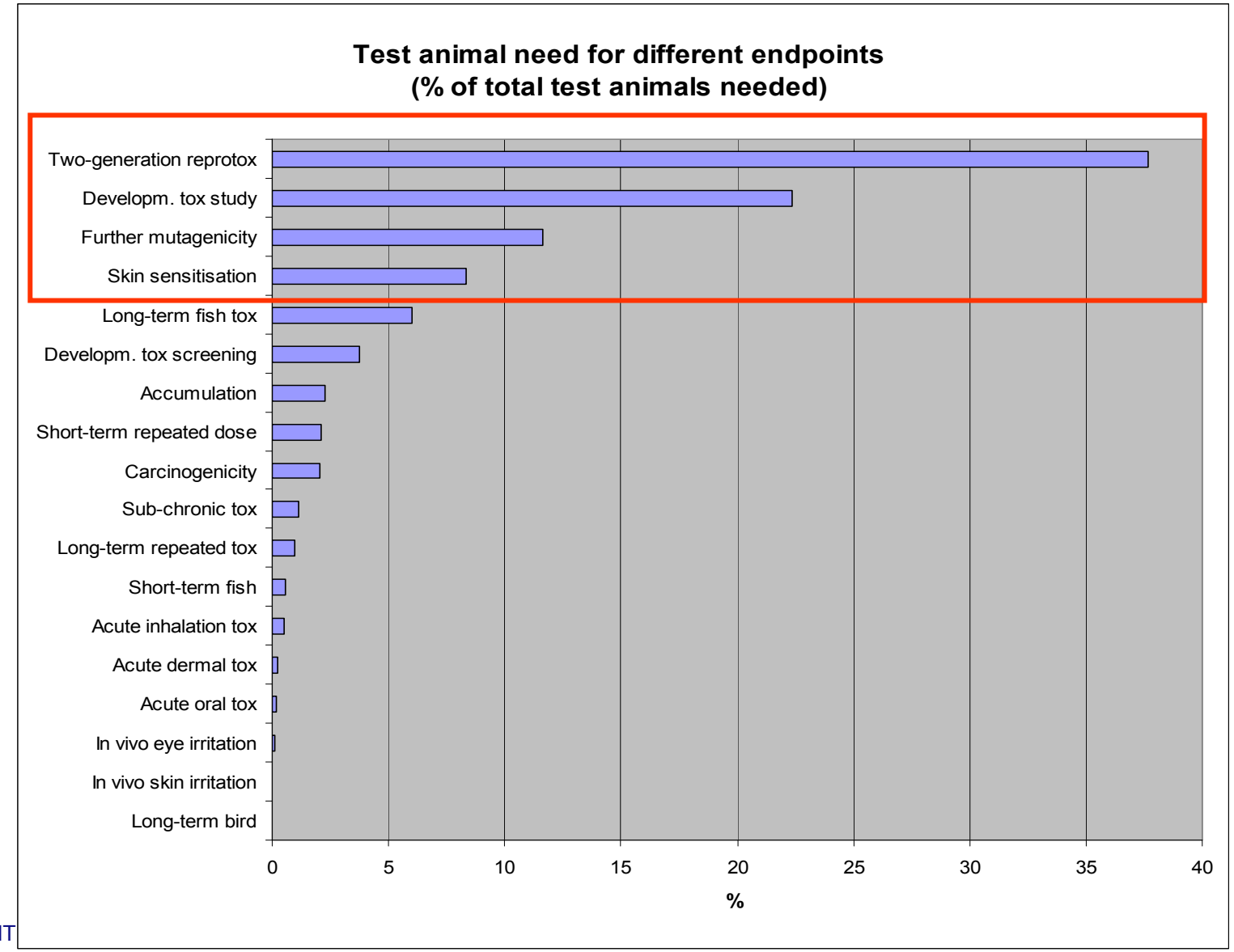
- ⇨ Testing costs: € 800-1130 million
- ⇨ Number of animals: 1.3-1.9 million

EUR report, 2005 (http://ecb.jrc.it)

- ⇨ Testing costs: € 1.500 million
- ⇨ Number of animals: 2.6 million

Estimated test animal need under REACH

(van der Jagt et al., 2004)



2. Existing Guidance & Tools for generating NT data

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

JT03232745

Document complet disponible sur OLIS dans son format d'origine
Complete document available on OLIS in its original format

English - Or. English

ECHA

Guidance on information requirements and chemical safety assessment

Chapter R.6: QSARs and grouping of chemicals

May 2008

Guidance for the implementation of REACH

Definitions

Structure Activity Relationship (SAR)

a qualitative relationship that relates a (sub)structure to the presence or absence of a property or activity of interest

Quantitative Structure Activity Relationship (QSAR)

a mathematical model relating one or more quantitative parameters derived from chemical structure to a quantitative measure of a property or activity of interest

Definitions (2)

category approach & *analogue approach*

describe techniques for grouping chemicals

read-across

a technique of filling data gaps in either approach

Definitions (3)

chemical category

a group of chemicals whose properties

i.e. phys-chem, human health *and/or* environmental toxicological and/or environmental fate

are likely to be similar or follow a regular pattern

as a result of *structural similarity*

In principle, the number of members generally present enables the detection of trends across endpoints

(and robustness of conclusions)

Definitions (4)

analogue approach

a *limited* number of chemicals whose properties

i.e. phys-chem, human health *and/or* environmental toxicological and/or environmental fate

are likely to be similar

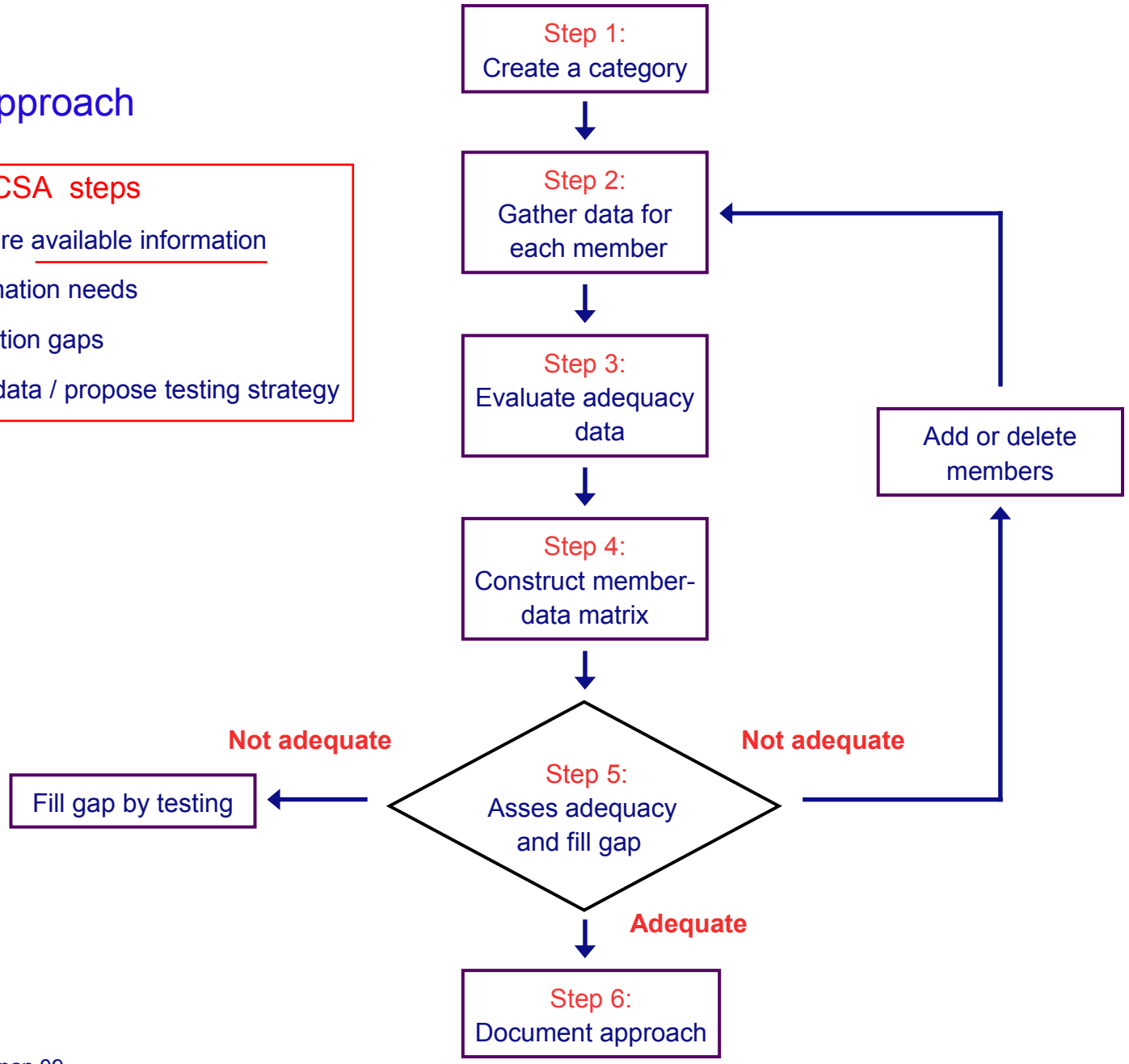
as a result of *structural similarity*

In principle, the *limited* number of chemicals do not allow identification of trends in these properties

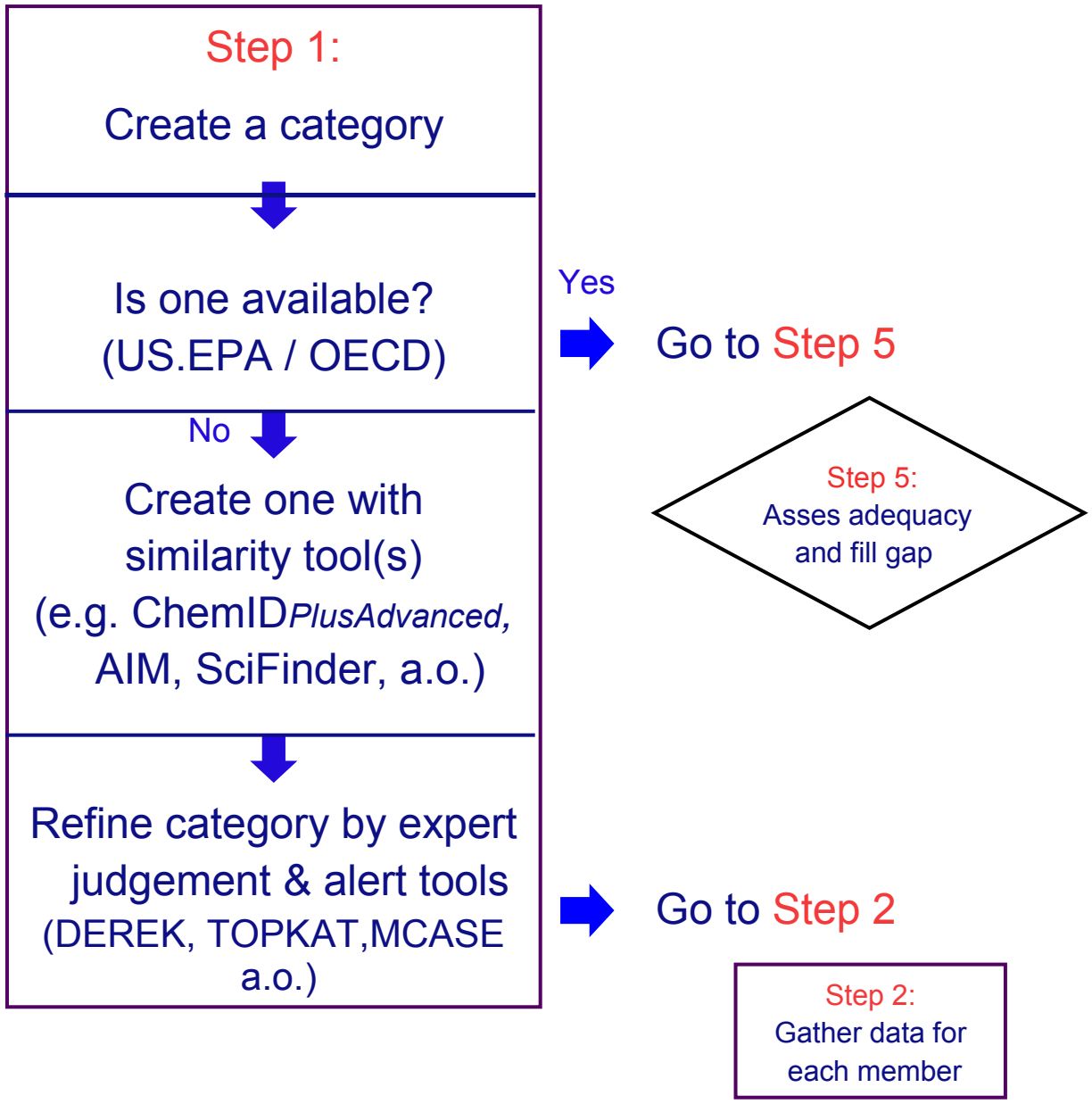
Category approach

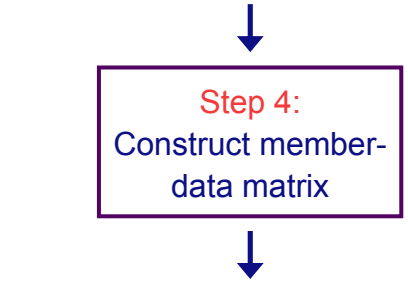
CSA steps

1. Gather and share available information
2. Consider information needs
3. Identify information gaps
4. Generate new data / propose testing strategy



Category approach





Similar effects / observable trend

	Member 1	**Member X**	Member 3	Member n..	……..
Endpoint 1	……		……		
Endpoint 2				……	……
Endpoint X	……	⁉		……	……
Endpoint n..	……		……		
……		……	……		

How identify category members or analogues in Step 1?

ChemID (*Plus Advanced*)

AIM

SciFinder

OECD QSAR Toolbox

DSSTox

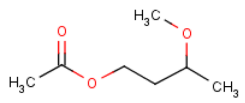
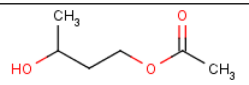
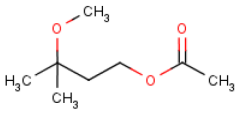
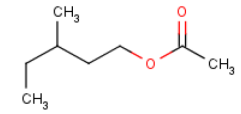
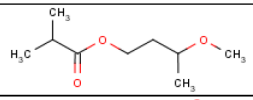
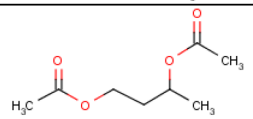
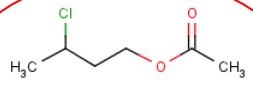
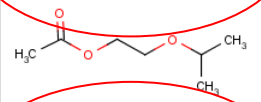
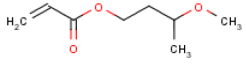
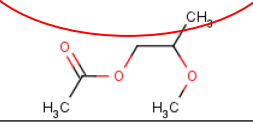
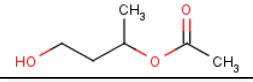
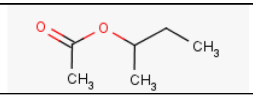
a.o.

How identify category members or analogues in Step 1?

By applying similarity principles:

- common functional group(s) related to a specific activity (e.g. aldehyde, epoxide, ester, specific metal ion)
- the likelihood of common precursors and/or breakdown products
- an incremental and constant change across the category (e.g. a chain-length category with differences in methylene groups)
- common constituents or chemical classes, similar carbon range numbers (UVCB substances)

ChemID
(*Plus Advanced*)

Substance	CAS number	Molecular structure	Structural similarity (%)
1-Butanol, 3-methoxy-, 1-acetate	4435-53-4		100
3-Hydroxybutyl acetate	1851-86-1		76
1-Butanol, 3-methoxy-3-methyl-, acetate	103429-90-9		70
3-Methylpentyl acetate	35897-13-3		69
Propionic acid, 2-methyl-, 3-methoxybutyl ester	72785-13-8		67
1,3-Butanediol, 1,3-diacetate	1117-31-3		65
Acetic acid, 3-chlorobutyl ester	2203-36-3		64
Ethanol, 2-(1-methylethoxy)-, 1-acetate	19234-20-9		63
3-Methoxybutyl acrylate	2768-07-2		62
2-Methoxypropyl-1-acetate	70657-70-4		62
3-Hydroxy-1-methylpropyl acetate	75355-65-6		61
sec-Butyl acetate	105-46-4		60

?

?

Read across: qualitative and quantitative

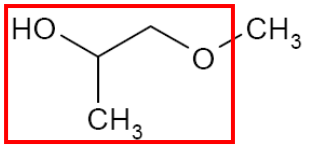
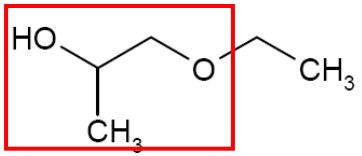
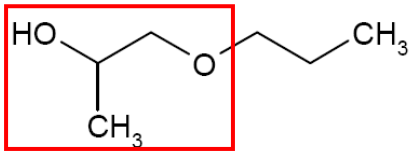
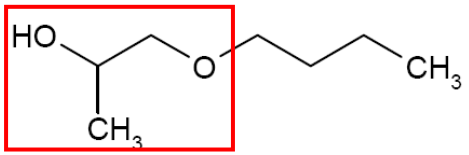
Qualitative: categorial similar responses (mut, sens, irrit..)

Quantitative: finding surrogate ‘DNEL’ → *next slide*

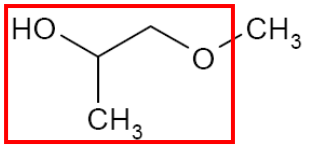
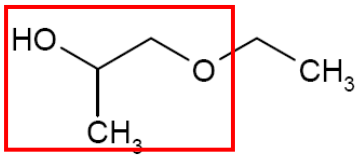
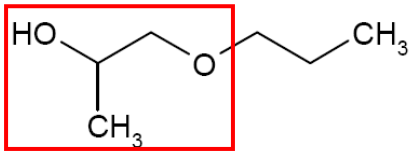
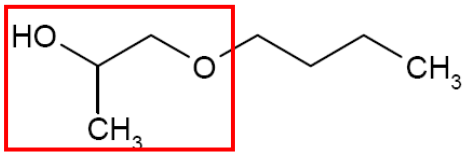
Quantitative read across:

target

source

Substance	DNEL
 Methoxypropan-2-ol (PGME)	
 2-propanol, 1-ethoxy- (PGEE)	22.2 mg/m^3
 1-Propoxy-2-propanol	22.1 mg/m^3
 propylene glycol n-butyl ether (PnB)	14.8 mg/m^3

Quantitative read across:

	Substance	DNEL	
target	 Methoxypropan-2-ol (PGME)	11.0 mg/m^3 45.1 mg/m^3	Based on AF of 2 for read across Based on own testing data
source	 2-propanol, 1-ethoxy- (PGEE)	22.2 mg/m^3	
	 1-Propoxy-2-propanol	22.1 mg/m^3	
	 propylene glycol n-butyl ether (PnB)	14.8 mg/m^3	

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

OECD

Organization for Economic Co-operation and Development

"QSAR Application Toolbox"

-filling data gaps using available NT data-

TNO

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

OECD

What is the key feature of the Toolbox ?

to systematically group chemicals according to the presence or modulation of a particular effect for all members of the category based on the presumption of a common chemical or toxicological mechanism or mode of action.

to quickly evaluate all members of a category for common toxicological behaviour or consistent trends among important regulatory endpoint data.

TNO

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

OECD

What tools are in the Toolbox ?

The Toolbox estimates missing values by:

Read-Across, that extrapolates for an untested chemical from tested chemicals within a category

Trend Analysis, that estimates for an untested chemical from a "trend" (increasing, decreasing or constant) in effect within a category

(Q)SAR Models that estimate missing values from a statistical model for a category

TNO

Structure of the QSAR Toolbox

Logical sequence of components usage

Use of components via:

- **“rigid tract”**
- **“flexible tract”**

3. Our experience

On identifying similar structures

- All tools appear to have different similarity algorithms
- Basis of similarity algorithms is obscure (for toxicologists)
- Similarity outcome appears not always toxicologically-funded
- Additional expert judgement is needed

3. Our experience

OECD QSAR Toolbox

- User friendly (once familiar to its structure)
- Data very well organised
- Toxicological and chemistry expertise is required
- Reliability depends on structure complexity, data availability and experience user
- Transparency high (reporting module)
- At present limited to human health endpoints mutagenicity & sensitisation only

3. Our experience

Using NT data

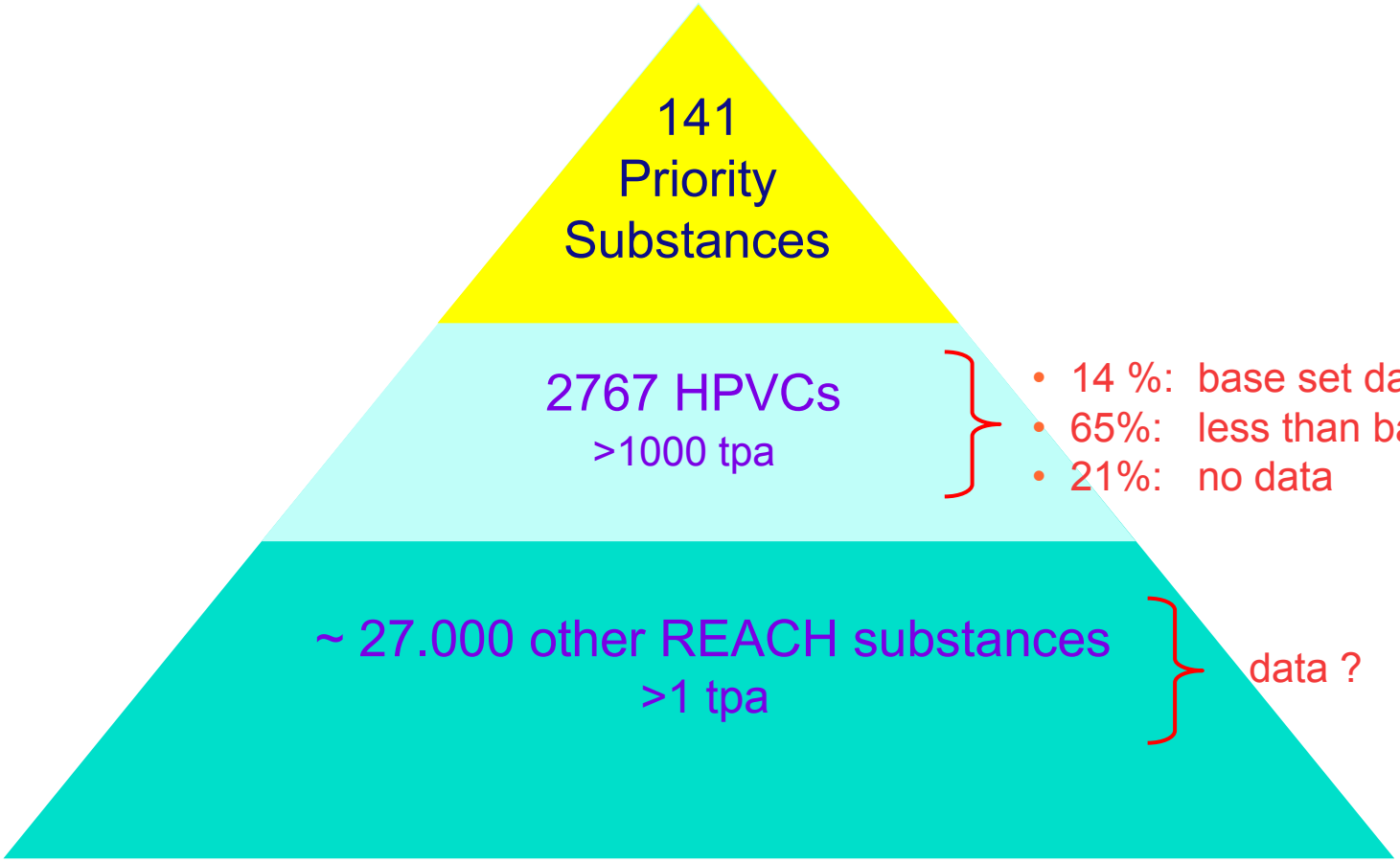
- One should start with concrete cases and apply available tools; to built capacity & expertise
- It is not be learned, like from a cookbook
- Toxicological and chemistry expertise needed (or hired)

How will ECHA respond, what will it accept??

4. Developments for generating NT data

The current situation on available testing data

for about 30.000 (?!) REACH chemicals > 1 tpa



- 14 %: base set data
- 65%: less than base set
- 21%: no data

data ?

Allanou, Hansen and van Der Bilt, 1999

The current situation on available testing data

Non-Testing data need Testing data!!

Existing data should be made (publicly) available!

New data should be generated in an intelligent way!

Toxicology Mechanisms and Methods, 18:103–118, 2008

ISSN: 1537-6516 print; 1537-6524 online
DOI: 10.1080/15376510701857452

informa
healthcare

Existing data should be made (publicly) available!

REVIEW

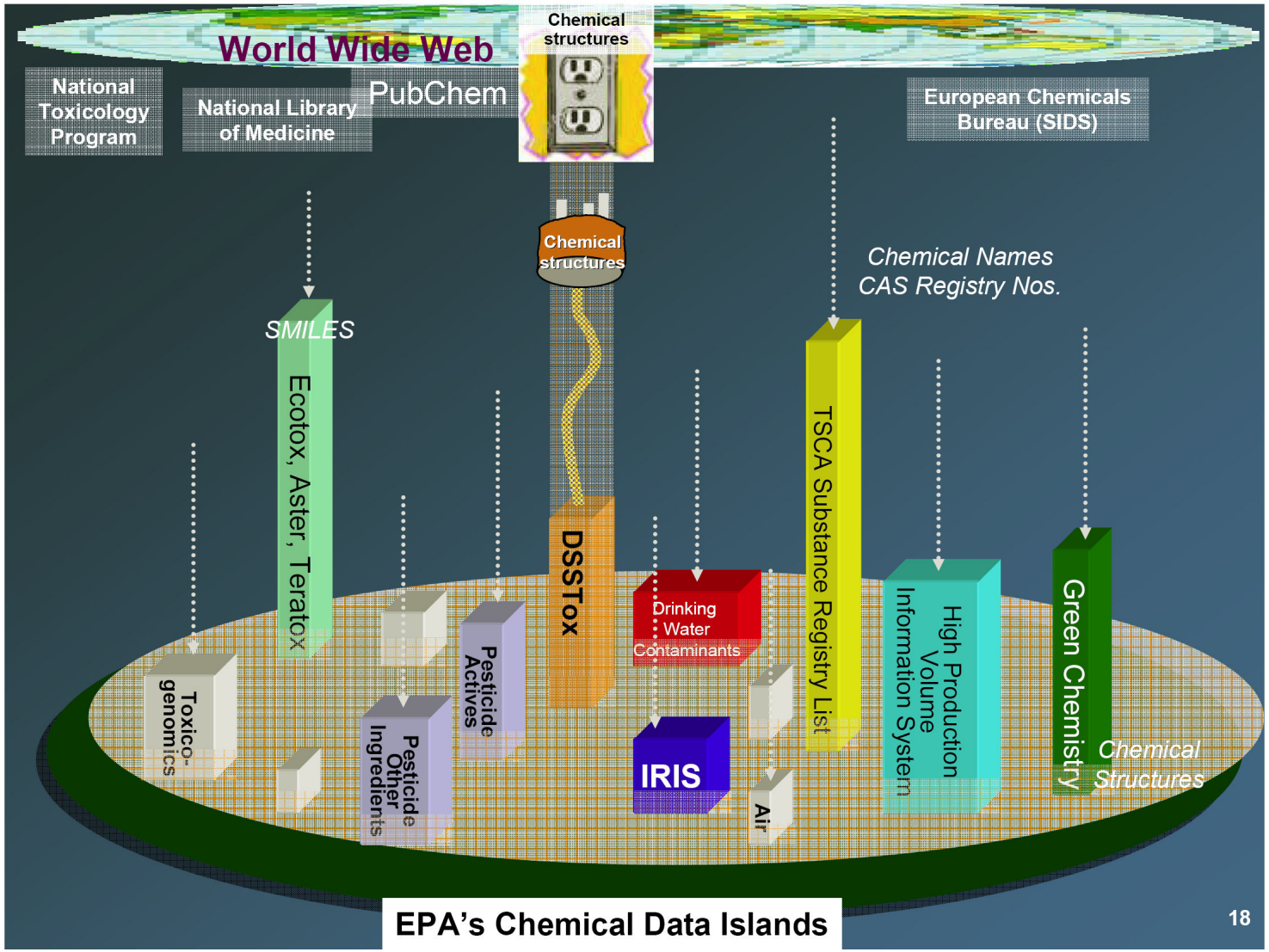
Toxicity Data Informatics: Supporting a New Paradigm for Toxicity Prediction

Ann M. Richard
National Center for Computational Toxicology, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Chihae Yang
Leadscope, Inc., Columbus, OH 43235

Richard S. Judson
National Center for Computational Toxicology, U.S. Environmental Protection AgencyResearch Triangle Park, NC 27711

DSSTox databases: Concept



NAMEID	version #records date	Expanded DSSTox Data File Title & Description
CPDBAS	v5b 1547 10Feb2008	**Carcinogenic Potency Database Summary Tables - All Species:** Tumor target site incidence, TD50 potencies, summary activity calls for rat, mouse, hamster, dog, and/or non-human primate; data reviewed and compiled from literature and NTP studies.
DBPCAN	v4b 209 15Feb2008	**EPA Water Disinfection By-Products with Carcinogenicity Estimates Database:** Carcinogenicity estimates (high, moderate, low concern) by EPA experts using a mechanism-based analog SAR approach on a set of 209 water disinfection by-products, mostly small halogenated organics.
EPAFHM	v4b 617 15Feb2008	**EPA Fathead Minnow Acute Toxicity Database:** Acute toxicities of 617 chemicals tested in common assay, with mode-of-action assessments and confirmatory measures.
FDAMDD	v3b 1216 15Feb2008	**FDA Center for Drug Evaluation & Research - Maximum (Recommended) Daily Dose Database:** Maximum (recommended) daily dose (MRDD) s extracted from
HPVCSI	v2c 3548 15Feb2008	d on EPA HPV
HPVISD	v1b 1006 15Feb2008	chemical inventory of erties and toxicity
IRISTR	v1b 544 15Feb2008	hemical-specific URLs
NCTRER	v4b 232 15Feb2008	binding affinities
NTPBSI	v2b 2293 15Feb2008	**National Toxicology Program (NTP) On-line Chemical Bioassay Database** Structure-Index Locator File: Compiled structures for the NTP On-line Database with chemical-specific URLs linking to NTP study summary pages; file includes fields for each of 4 main bioassay study areas with indicator values specifying presence or absence of study data for the chemical substance record.
NTPHTS	v2b 1408 15Feb2008	**National Toxicology Program (NTP) High-Throughput Screening Project** Structure-Index File: Compiled structures for set of 1408 NTP chemical substances provided to the NIH Chemical Genomics Center for HTS bioassay testing and to PubChem (PubChem_CIDs and PubChem_SIDs included in NTPHTS_v2a file); NCGC HTS bioassay data are being deposited into PubChem and can be retrieved with these PubChem chemical CID and SID record listings.
TOXCST	v2b 320 08Feb2008	**Research Chemical Inventory for EPA's ToxCast™ Program** Structure-Index File: Compiled structures for 320 chemical substances that are candidates for Phase I High-Throughput screening (HTS) within the EPA ToxCast™ program. File will be updated with links to PubChem CIDs and SIDs for retrieving assay data, and with updates to chemical inventory as Program moves to Phase II and beyond.

DSSTox currently with 9 databases operational and accessable by internet for identifying structural analogues and retrieving associated toxicological profiles

New data should be generated in an intelligent way!

Strategy to efficiently fill
'inadequately filled' and 'empty'
chemical categories
(chemical domains)
!!

Once a datagap is ‘filled’ with NT data….

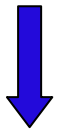
is that information sufficient to replace Testing data??

or

How to ‘weight’ NT data

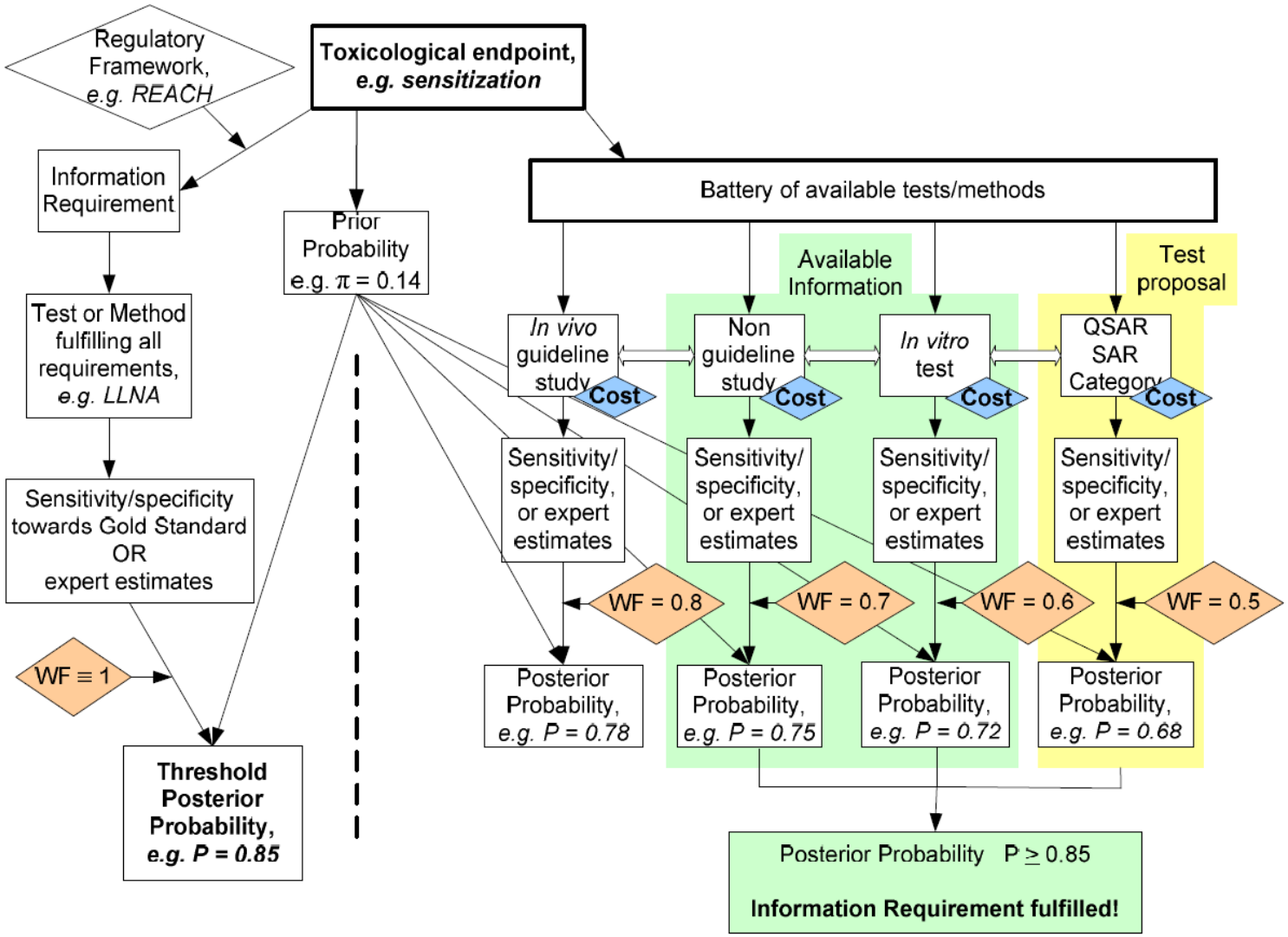
and

How to ‘add’ NT data to Testing data…?



By Expert judgement or …… more formalized WoE…?

Add different types of information in an ITS



5. Exposure-based Waiving (EBW)

General rules for adaptation of Standard Requirements

Annex XI

1. Testing does not appear scientifically necessary
    - Use of existing data: PC, non-GLP etc, Historical human data
    - Weight of evidence
    - *In vitro* methods
    - Quantitative or Qualitative Structure Activity Relationships ((Q)SAR)
    - Grouping of substances and read-across approach

2. Testing is technically not possible

3. Substance-tailored exposure-driven testing

ITS: Information Gathering Strategy

Step 1: Gather all available Testing and Non-Testing information

If not sufficient ↓ *(for C&L and RA)*

(*Is Testing technically possible?*)

Step 2: Is Exposure-Based Waiving an option?

If not possible ↓

Step 3: Perform / Propose Testing as last resort!!

EBW: General rules Annex XI

Tonnage	Health Information requirements
1 – 10 tpa	• *In vitro* skin and eye irritation • Skin sensitization • *In vitro* mutagenicity • Acute toxicity (one route)
10 – 100 tpa	• *In vivo* skin and eye irritation • Further *in vitro* mutagenicity • Acute toxicity (2nd route) • Sub acute toxicity (28d) • Reproductive toxicity screen
100 – 1000 tpa	• Further mutagenicity tests • Sub-chronic toxicity (90d)* • Reproductive toxicity tests
>1000 tpa	• Further mutagenicity tests • *Chronic toxicity (>12 m)* may* • Further reproductive toxicity tests • *Carcinogenicity may*

Tests may be omitted based on the exposure scenarios developed.

In all cases, adequate justification and documentation shall be provided of the exposure estimate derived.

• * *Sub acute toxicity (28d) is available*

EBW: Specific rules

Tonnage	Health Information requirements	Specific rules of adaptation 'on exposure' (column 2 of Annexes VIII-X)
1 – 10 tpa	• *In vitro* skin and eye irritation • Skin sensitization • *In vitro* mutagenicity • Acute toxicity (one route)	• None
10 – 100 tpa	• *In vivo* skin and eye irritation • Further *in vitro* mutagenicity • Acute toxicity (2nd route) • Sub acute toxicity (28d) • Reproductive toxicity screen	• No • NA • No (route specifics) • Relevant human exposure can be excluded...*cf* Annex XI.3 • Relevant human exposure can be excluded...*cf* Annex XI.3
100 – 1000 tpa	• Further mutagenicity tests • Sub-chronic toxicity (90d) * • Reproductive toxicity tests	• NA • unreactive, insoluble, and not inhalable, and no evidence of absorption & toxicity, coupled with limited human exposure. • ….low tox, and no systemic absorption, and no or no significant human exposure.
>1000 tpa	• Further mutagenicity tests • *Chronic toxicity (>12 m)* may* • Further reproductive toxicity tests • *Carcinogenicity may*	• NA • ….low tox, and no systemic absorption, and no or no significant human exposure. • NA

• * *Sub acute toxicity (28d) is available*

Guidance?

Presently under construction:

Qualitative approach & Quantitative approach

Document by RIVM

EBW, qualitative approach

Situations for EBW	Explanation
Specific use or limited emissions	Certain uses excluded: - no consumer exposure - no professional application Emissions to certain env compartments are excluded (e.g. air emissions irrelevant as substance is solid and forms no dust).
Specific operational or use conditions	Use in (semi)closed systems, leading to limited or negligible exposure Use in strictly controlled systems with extensive PPE due to the toxicity of the substance
Intensity of use (duration, frequency)	Infrequent use due to function of substance, e.g. specialty products for highly specific occupational situations with a low frequency and duration
Substance properties	Phys-chem properties of preparation or article, e.g. when substance is locked in or covalently bound to matrix

EBW, quantitative approach

When a qualitative justification is not preferred, not possible or not allowed:

A quantitative approach *cf* Annex XI can be submitted:
adequate justification and documentation of waiving, based on an exposure assessment *cf* Annex I.5: description of development of an ES, and of the exposure estimation

This exposure estimate will be compared with a 'DNEL' or if this is not available it may be possible to use a TTC (**T**hreshold of **T**oxicological **C**oncern).

If this is not possible: additional hazard data need to be collected.

EBW, quantitative approach

If ‘DNEL’ or TTC available:

Risk Characterisation Ratio (RCR)

$$RCR = \frac{\text{Exposure estimate of ES}}{\text{‘DNEL’ or TTC}}$$ is determined

If RCR ≤ 1, then ‘control of risk’;
document and communicate in CSR and SDS+

If RCR > 1, then ‘no control of risk’
assessment needs to be refined

REACH & TTC value

present situation

Based on route-specific database for food chemicals

route	workers	consumers	man-v-env
oral mg/kg bw,day		TTC	?
inhalation mg/m^3	?	?	?
dermal mg/kg bw,day; mg/cm^2	?	?	?

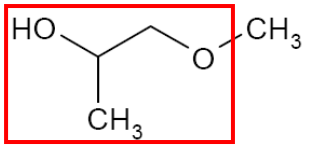
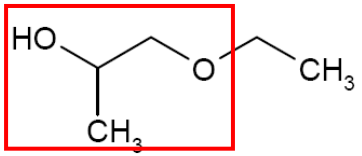
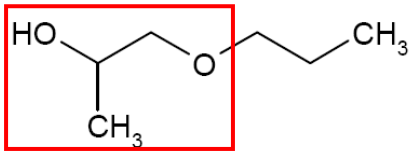
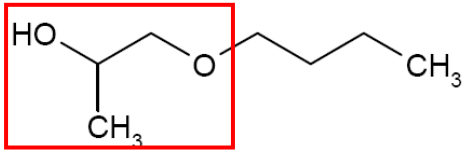
REACH & 'DNEL' values

present situation

route	workers	consumers	man-v-env
oral mg/kg bw,day		'DNEL'	?
inhalation mg/m^3	?	?	?
dermal mg/kg bw,day; mg/cm^2	?	?	?

i.e. = 'chemical category specific TTC'

What is ‘significant’ or ‘relevant’ exposure ?

	Substance	DNEL
target	 Methoxypropan-2-ol (PGME)	11.0 mg/m^3 45.1 mg/m^3
source	 2-propanol, 1-ethoxy- (PGEE)	22.2 mg/m^3
	 1-Propoxy-2-propanol	22.1 mg/m^3
	 propylene glycol n-butyl ether (PnB)	14.8 mg/m^3

Based on AF of 2 for read across

Based on own testing data

If RWC exposure estimates for ES would give:
1 or 5 mg/m^3…..

REACH & TTC values

present situation

TTC for oral route:

- large database available (some identified exceptions)
- but coverage REACH substances domain unclear

TTC for inhalation and dermal routes urgently needed:

Preferably route-specific, but:

- number of useful studies limited, and consequently
- applicability to REACH substances domain limited

If obtained via appropriate route-to-route extrapolation:

- larger database, higher coverage REACH substances domain,
- but uncertainty on potential local effects

There is a need for tools to derive chemical category confined TTCs

EBW: promising…….?

Guidance on Qualitative approach & Quantitative approach under construction ….

3 EU SC developed an Opinion Document on TTC.. quite critical on this tool…

CIE recently published revised legal section 3 Annex XI: more stringent criteria…

5. Final Conclusions

Additional chemistry & toxicological expertise clearly is needed to generate and assess NT data.

The NT data area is a rapidly developing field: many new tools and options (note potential overlap when using more than one)

The QSAR Toolbox is helpful and user-friendly tool but critically dependent on more testdata input: DSSTox, ToxCast, Fraunhofer and a Japanese databases on complex human endpoints will be incorporated

EBW appears to become a difficult route……

5. Final Conclusions (2)

There are no worked-out examples

How will ECHA respond to any NT approaches?

Will REACH be achievable, then a ‘mind-set’ is needed!

Thank you for your attention!