1

REACH information requirements and compliances with the GLP principles

Annual GLP meeting Scientific Institute of Public Health
16 October 2008

Maarten Roggeman
Risk Management Service
DG Environment
FPS Health, Food Chain Safety and Environment

federal public service
HEALTH, FOOD CHAIN SAFETY AND ENVIRONMENT

.be

FPS Health, Food Chain Safety and Environment

2

Important principles in REACH

- Reversal burden of proof
- No data, no market (and no manufacturing)
- Duty of care/precautionary principle:

  « This Regulation is based on the principle that it is for manufacturers, importers and downstream users to ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment. Its provisions are underpinned by the precautionary principle. » **(art 1.3)**
- Central Agency with lot of power: European CHemicals Agency in Helsinki (ECHA)
- RIPs

FPS Health, Food Chain Safety and Environment

3

Aims of REACH

Art 1 (1): The purpose of this Regulation is to ensure a high level of protection of *human health* and the *environment*, including the promotion of *alternative methods* for assessment of hazards of substances, as well as the free circulation of substances on the *internal market* while enhancing *competitiveness* and *innovation*.

-> 3 main goals, 2 secondary goals

-> explicit reference to promotion of alternative methods, also reference in art 13(1), recital 38, 40 & 47; Annex VI step 1

FPS Health, Food Chain Safety and Environment

4

Actors

- **Manufacturers of substances**
- **Producers of articles**
- **Importers (of substances and articles)**: Importing means the physical introduction into the customs territory of the European Union.
- **Downstream Users** (industrial users or professional users)
- **Distributors**: only store & place on market (if refilling: DU)

More than 1 role is possible at the same time

FPS Health, Food Chain Safety and Environment

5

Substances, preparations & articles

substance: means a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition;

preparation (GHS « mixture »): means a mixture or solution composed of two or more substances;

article: means an object which during production is given a special shape, surface or design which determines its function to a greater degree than does its chemical composition;

FPS Health, Food Chain Safety and Environment

6

Pre-registration

- For phase-in substances
- 1 June 2008 – 1 December 2008
- Objective = datasharing in SIEFs (Substance Information Exchange Forum)
- If not pre-registered: no use of deadlines, and no market 'til registration: no continuity in production!

Required data for pre-registration

- name/EINECS/CAS
- his name and address
- envisaged deadline & tonnage band
- the name of substance(s) for which the available information is relevant for QSAR or grouping/read-across

FPS Health, Food Chain Safety and Environment

7

Registration

No data, no market

- **-> M/I has to register all substances >1t/y**
- **-> exemptions for certain substances & certain uses**
- **-> Special regime for articles: notification or registration, independant tonnages**
- **-> polymers: no registration, no evaluation (but monomer registration!)**
- **-> PPORD notification : exemption to registration**
  - 5 + 5 years extension with justification (R&D programme) ; or
  - 5 + 10 years extension for exclusive use in medicinal products or if not placed on market

FPS Health, Food Chain Safety and Environment

8

Registration dossier

Technical dossier

- **identity of M/I**
- **identity of the substance**
- **identified uses (relevant use and exposure categories)**
- **C&L**
- **guidance on safe use**
- **study summaries/if needed robust study summaries**
- **indication if information on study summaries/robust study summaries/C&L/identified uses has been reviewed by an assessor**
- **proposals for testing (Annexes IX and X)**
- **for substances 1-10 t/y exposure information (section 6 of Annex VI)**
- **confidentiality request including a justification (degree purity, tonnage band, study summaries, SDS,...)**

Chemical Safety Assessment (>10t/y)

FPS Health, Food Chain Safety and Environment

9

Registration dossier

Chemical Safety Assessment (>10t/y)

Steps of CSA:

(a) human health hazard assessment (C&L and DNEL)
(b) physicochemical hazard assessment (C&L)
(c) environmental hazard assessment (C&L and PNEC)
(d) PBT and vPvB assessment (compare to criteria -> emission characterisation)

If substance is classified or PBT/vPvB, additional steps:

(e) exposure assessment (ESs & exposure estimation)
(f) risk characterisation (exposure vs DNEL/PNEC, likelihood/severity event)

FPS Health, Food Chain Safety and Environment

10

Registration deadlines

Class	Quantity	Deadline
non phase-in substances	> 1 t/y	1 June 2008
phase-in substances		
phase-in substances	> 1 000 t/y	30 November 2010
phase-in substances classified CMR cat 1 or 2	> 1 t/y	
phase-in substances classified as R50-53 (very toxic to aquatic organisms and may cause long-term adverse effects in the aquatic environment)	> 100 t/y	
phase-in substances	> 100 t/y	31 May 2013
phase-in substances	> 1 t/y	31 May 2018

FPS Health, Food Chain Safety and Environment

11

Information requirements

Standard info requirements REACH vs 67/548: approximate comparison

reduced notification		Base Set	Level 1	Level 2
Annex VII C	Annex VII B	Annex VII A	Annex VIII Level 1	Annex VIII Level 2
0,01-0,1 t/y	0,1-1t/y	1-100 t/y	100-1000 t/y	>1000 t/y

Annex VII 1-10 t/y REACH

Annex VIII 10-100 t/y REACH

Annex IX 100-1000 t/y REACH

Annex X >1000 t/y REACH

Standard requirements!
Remember REACH has lot of waivers!

FPS Health, Food Chain Safety and Environment

12

Information requirements

PHYSCHEM PROPERTIES		Annex VII 1-10 t/y	Annex VIII 10-100 t/y	Annex IX 100-1000 t/y	Annex X >1000 t/y
7.1	State of the substance at 20oC and 101,3 kPa				
7.2	Melting/freezing point				
7.3	Boiling point				
7.4	Relative density				
7.5	Vapour pressure				
7.6	Surface tension				
7.7	Water solubility				
7.8	Partition coefficient n-octanol/water				
7.9	Flash-point				
7.10	Flammability				
7.11	Explosive properties				
7.12	Self-ignition temperature				
7.13	Oxidising properties				
7.14	Granulometry				
7.15	Stability in organic solvents and identity of relevant degradation products				
7.16	Dissociation constant				
7.17	Viscosity				

FPS Health, Food Chain Safety and Environment

13

Information requirements

TOXICOLOGICAL INFORMATION		Annex VII 1-10 t/y	Annex VIII 10-100 t/y	Annex IX 100-1000 t/y	Annex X >1000 t/y
8.1	Skin irritation or skin corrosion	in vitro			
8.1.1	In vivo skin irritation		in vivo		
8.2	Eye irritation	in vitro			
8.2.1	In vivo eye irritation		in vivo		
8.3	Skin sensitisation	in vivo			
8.4	Mutagenicity				
8.4.1	In vitro gene mutation study in bacteria	in vitro			
8.4.2	In vitro cytogenicity study in mammalian cells or in vitro micronucleus study		in vitro		
8.4.3	In vitro gene mutation study in mammalian cells, if - result in 8.4.1. and section 8.4.2.		in vitro		
	Mutagenicity (in vivo) consider if + results	(possibly)	possibly	possibly	possibly
8.5	Acute toxicity				
8.5.1	By oral route	in vivo			
8.5.2	By inhalation		in vivo		
8.5.3	By dermal route		in vivo		
8.6	Repeated dose toxicity				
8.6.1	Short-term repeated dose toxicity study (28 days)		in vivo		
8.6.2	Sub-chronic toxicity study (90-day)			in vivo	
8.6.3	Long-term repeated toxicity study (≥ 12 months)				in vivo
8.7	Reproductive toxicity				
8.7.1	Screening for reproductive/developmental toxicity (OECD 421 or 422)		in vivo		
8.7.2	Pre-natal developmental toxicity study (B.31 or OECD 414), potential 2nd species		possibly	in vivo	
8.7.3	Two-generation reproductive toxicity study		possibly	in vivo	
8.8	Toxicokinetics				
8.8.1	Assessment of the toxicokinetic behaviour based on relevant available information		any info		
8.9	Carcinogenicity study				in vivo

FPS Health, Food Chain Safety and Environment

14

Information requirements

ECOTOXICOLOGICAL INFORMATION		Annex VII 1-10 t/y	Annex VIII 10-100 t/y	Annex IX 100-1000 t/y	Annex X >1000 t/y
9.1	Aquatic toxicity				
9.1.1	Short-term toxicity testing on invertebrates (Daphnia preferred)				
9.1.2	Growth inhibition study aquatic plants (algae preferred)				
9.1.3	Short-term toxicity testing on fish				
9.1.4	Activated sludge respiration inhibition testing				
9.1.5	Long-term toxicity testing on invertebrates (Daphnia preferred)				
9.1.6	Long-term toxicity testing on fish (FELS, embryo and sac-fry, or Fish juvenile growth test)				
9.2	Degradation				
9.2.1	Biotic				
9.2.1.1	Ready biodegradability				
9.2.1.2	Simulation testing on ultimate degradation in surface water				
9.2.1.3	Soil simulation testing				
9.2.1.4	Sediment simulation testing				
9.2.2	Abiotic				
9.2.2.1	Hydrolysis as a function of pH				
9.2.3	Identification of degradation products				
9.3	Fate and behaviour in the environment				
9.3.1	Adsorption/desorption screening				
9.3.2	Bioaccumulation in aquatic species, preferably fish				
9.3.3	Further information on adsorption/desorption depending on the results of the study required in Annex VIII				
9.3.4	Further information on the environmental fate and behaviour of the substance and/ore degradation products				
9.4	Effects on terrestrial organisms				
9.4.1	Short-term toxicity to invertebrates				
9.4.2	Effects on soil micro-organisms				
9.4.3	Short-term toxicity to plants				
9.4.4	Long-term toxicity testing on invertebrates				
9.4.6	Long-term toxicity testing on plants				
9.5.1	Long-term toxicity to sediment organisms				
9.6.1	Long-term or reproductive toxicity to birds				

Attention This is a very simplified representation of the standard testing requirements!

FPS Health, Food Chain Safety and Environment

15

Information requirements

All *new* testing according to test guidelines!

- → **Test Method Regulation or other accepted guidelines (OECD)**
- → **Regulation (EC) No 440/2008 of 30 May 2008, OJ L142**
- → **consolidated version of Annex V of 67/548 (reductionistic approach because of timepressure: 1 June 2008 repeal of Annex V of 67/548)**
- → **1st ATP under way with 5 adaptations + Episkin?**

OECD Test guideline + GLP

↓

Mutual Acceptance of Data (MAD)
Accepted in all 30 OECD member countries

FPS Health, Food Chain Safety and Environment

16

Test Method Regulation (TMR)

New streamlined procedure for approval of test methods

Stage 1: Member States' National Coordinators comments (2 months)

↓

Stage 2: EU Coordinator redrafts, meeting NC if needed (3 weeks). *All difficult issues should be resolved at this stage of the procedure: in reality stage 2 can be > 3 weeks*

↓

Stage 3: MSCAs "silent consent" written procedure (3 weeks)

↓

Stage 4: ATP to TMR comitology regulatory procedure with scrutiny

FPS Health, Food Chain Safety and Environment

17

Good Laboratory Practice (GLP)

Directive 2004/10/EC (adopted from OECD)

Good Laboratory Practice (GLP) is a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. *(OECD)*

Goal
promote quality and validity of data
in order to facilitate recognition

FPS Health, Food Chain Safety and Environment

18

Good Laboratory Practice (GLP)

→ **NEW Tox/ecotox testing**

- GLP or « *other international standards recognised as being equivalent by COM or ECHA* » legally required
- In line with protection of laboratory animals (Directive 86/609/EEC)

→ **NEW Physchem testing**

GLP not legally required, but strongly advised in the general testing strategy for physchem:

« As far as the quality is concerned, new studies for substances that have been conducted under GLP standards will enable the registrant to prove that the study uses a Study Director, study plans, Quality Assurance Programme and well-defined archiving policies and procedures. Methods and practices conform to GLP standards will therefore promote the transparency and credibility of the submitted data by ensuring their quality and integrity. » (Guidance on Information Requirements)

FPS Health, Food Chain Safety and Environment

19

Good Laboratory Practice (GLP)

In vitro methods GLP?

→ New tests: YES!

- Art 13.4 of REACH
- OECD No 14 "The Application of the Principles of GLP to in vitro Studies"

  "*Unless specifically exempted by national legislation, the Principles of Good Laboratory Practice apply to all non-clinical health and environmental safety studies required by regulations for the purpose of …, and for the regulation of industrial chemicals.*"

- ECVAM

  "ECVAM has taken a leading role in safeguarding quality control for in vitro *studies including the application of the principles of OECD Good Laboratory Practice (GLP) to* in vitro *toxicological studies."*

  (ECVAM website http://ecvam.jrc.it/)

FPS Health, Food Chain Safety and Environment

20

Good Cell Culture Practice (GCCP)

Aim

Reduce uncertainty in the development and application of *in vitro* procedures

- greater international harmonisation
- rationalisation and standardisation of cellcultures

ECVAM taskforce report

ECVAM Good Cell Culture Practice Task Force Report 2. Coecke, S. *et al* (2005). *ATLA 33*, 261-287.

FPS Health, Food Chain Safety and Environment

21

Information requirements

- Standard information requirements: column 1 of Annexes VII to X
- Adaptation to standard requirements:
  - **A) Specific adaptations: Column 2 of Annexes VII to X**
  - **B) General adaptations: Annex XI**
    - 1) Testing does not appear scientifically necessary
      - · Use of existing data
        - → might be non-GLP or 'non-guideline' studies, historical human data
      - · Weight of evidence
      - · QSAR
      - · *in vitro*
      - · grouping & read-across
    - 2) Testen is technically not possible
    - 3) Exposure Based Waiving (EBW)

Note: substance ID needs testing but not on intrinsic properties (Annex VI)

FPS Health, Food Chain Safety and Environment

22

Information requirements

COLUMN 1 STANDARD INFORMATION REQUIRED		COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
8.1.	Skin irritation	
8.1.1.	*In vivo* skin irritation	8.1.1. The study does not need to be conducted if: — the substance is classified as corrosive to the skin or as a skin 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, or — the substance is classified as very toxic in contact with skin, or — an acute toxicity study by the dermal route does not indicate skin irritation up to the limit dose level (2 000 mg/kg body weight).

FPS Health, Food Chain Safety and Environment

23

Information requirements

7. INFORMATION ON THE PHYSICOCHEMICAL PROPERTIES OF THE SUBSTANCE

COLUMN 1 STANDARD INFORMATION REQUIRED		COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1	
7.1.	State of the substance at 20 °C and 101,3 kPa		
7.2.	Melting/freezing point	7.2.	The study does not need to be conducted below a lower limit of - 20 °C.
7.3.	Boiling point	7.3.	The study does not need to be conducted: — for gases, or — for solids which either melt above 300 °C or decompose before boiling. In such cases the boiling point under reduced pressure may be estimated or measured, or — for substances which decompose before boiling (e.g. auto-oxidation, rearrangement, degradation, decomposition, etc.).
7.4.	Relative density	7.4.	The study does not need to be conducted if: — the substance is only stable in solution in a particular solvent and the solution density is similar to that of the solvent. In such cases, an indication of whether the solution density is higher or lower than the solvent density is sufficient, or — the substance is a gas. In this case, an estimation based on calculation shall be made from its molecular weight and the Ideal Gas Laws.

FPS Health, Food Chain Safety and Environment

24

Integrated testing strategies

Endpoints

- physico-chemical endpoints (17)
  - **melting/freezing point**
  - **water solubility**
  - **partition coefficient n-octanol/water**
  - **flammability**
  - **viscosity**
  - **…**
- toxicological endpoints
  - **1) skin irritation/corrosion**
  - **2) eye irritation**
  - **3) skin sensitisation**
  - **4) mutagenicity**
  - **5) acute toxicity**
  - **6) repeated dose toxicity**
  - **7) reproductive toxicity**
  - **8) toxicokinetics**
  - **9) carcinogenicity**

ITS for every endpoint

- ecotoxicological endpoints
  - **1) aquatic toxicity**
  - **2) degradation**
  - **3) fate and behaviour**
  - **4) effects on terrestrial organisms**
  - **5) long-term toxicity to sediment organisms**
  - **6) long term or reproductive toxicity to birds**

FPS Health, Food Chain Safety and Environment

25

Integrated testing strategies

- Specific for every endpoint
- ITS characterised by flexibility and case specificity
- Case-by-case decision will always be necessary
- Focus on decision making criteria and underlying considerations rather than on ready-to-use procedures

FPS Health, Food Chain Safety and Environment

26

Integrated testing strategies

⇨ **Annex VI contains the 4 steps to take**

Step 1: Gather and share existing information
Step 2: Consider information needs
Step 3: Identify information gaps
Step 4: Generate new information or propose a testing strategy

2 General Decision Making Frameworks (GDMFs)
And for every endpoint an ITS (specific guidance)

FPS Health, Food Chain Safety and Environment

27

Key study

A key study is the study that has been identified as the most suitable to describe an endpoint from the perspective of quality (relevance & reliability), completeness and representativity of data.

Study highest concern = key study
(taking into acount data quality)

FPS Health, Food Chain Safety and Environment

28

Key study

- Normally the most sensitive species used
- Method with highest sinsitivity
- Might be needed to consider several studies as key study
- Key study concept from OECD manual for investigation of HPV chemicals, chapter 2

FPS Health, Food Chain Safety and Environment

29

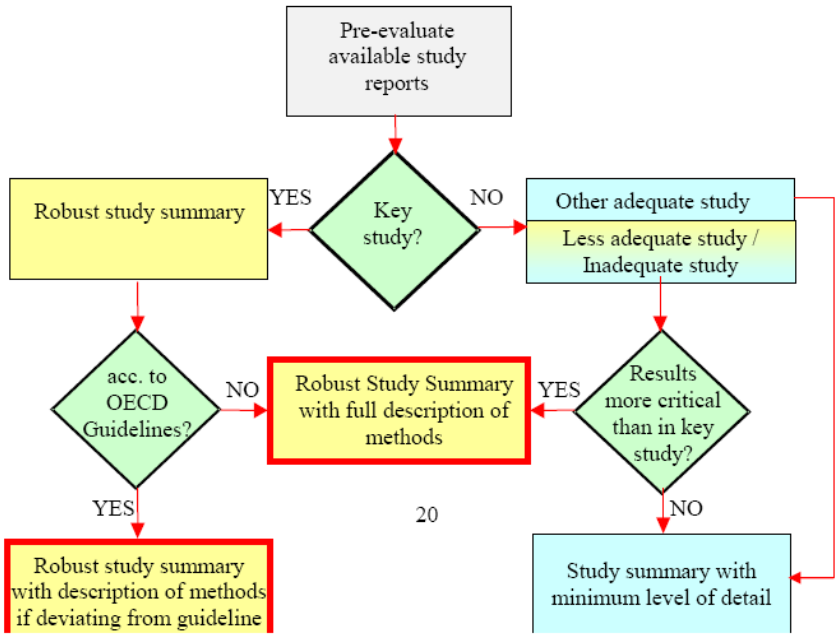
Reporting of studies

Full study report: means a complete and comprehensive description of the activity performed to generate the information. This covers the complete scientific paper as published in the literature describing the study performed or the full report prepared by the test house describing the study performed;

Robust study summary: means a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report;

Study summary: means a summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an assessment of the relevance of the study;

Fig. 2.1.-Decision tree for defining the level of detail for reporting of key and non-key studies



20

FPS Health, Food Chain Safety and Environment

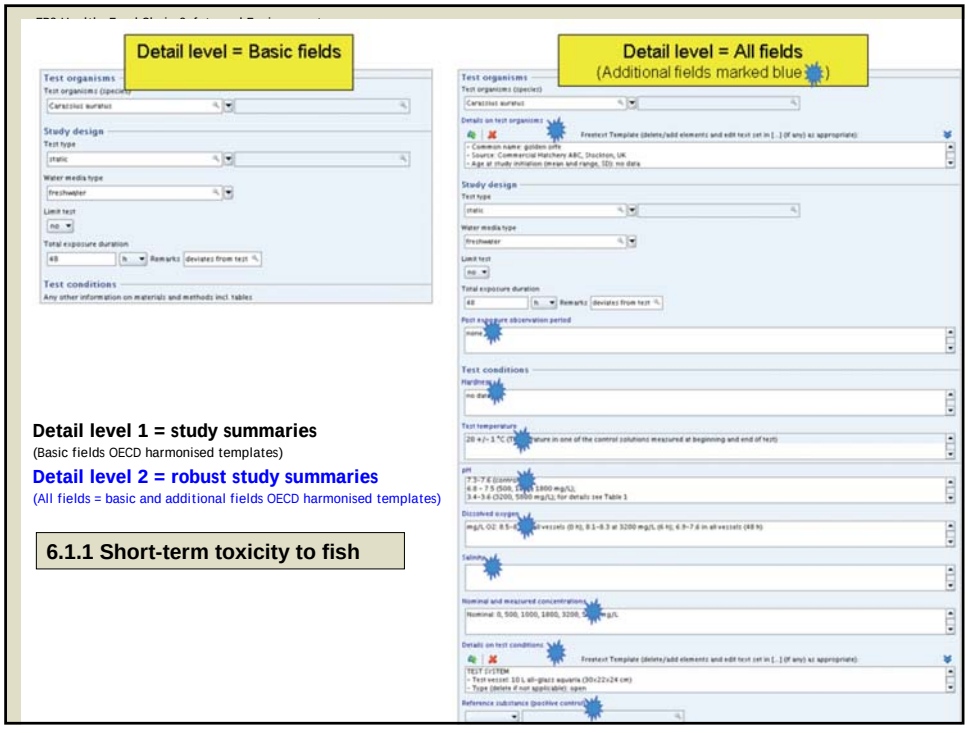
31

Reporting of studies

Test info has to be submitted in the form of **study summaries** or **robust study summaries** (Art 10(a)(vi) and (vii))

- Robust study summaries
  - ⇨ **only required for key studies**
  - ⇨ **only required for substances >10t/y (CSA)**

  BUT:
  - strongly advised also for substances <10t/y! (avoid request further info)
  - useful in many cases for non-key studies (justify choice of key study)
  - critical results but flawed study: RSS needed highlighting the weaknesses
- All other studies: study summary



FPS Health, Food Chain Safety and Environment

33

12-years rule for data protection

"Any study summaries or robust study summaries of studies submitted in the framework of a registration under this Regulation at least 12 years previously can be used for the purposes of registration by another manufacturer or importer."

(art 25)

→ But no access to the full study report!!!

→ Rule also valid for notifications under 67/548 (new substances)

- original submission date = starting date
- they benefit from a 2-year extension (was 10-year)

FPS Health, Food Chain Safety and Environment

34

Animal use estimates

- Average acceptance scenario alternative data/testing:
  - **2.6 million vertebrates in 11 years or 240,000 animals/y.**
  - **2-3% of the total number of vertebrates used per year (in other fields like fundamental research and pharma)**
- Costs involved: 1.5 billion €
- Costs/substance in tonnage band 1 – 10 t/y : 7,700€
- 90% of costs from human health endpoints

Van der Jagt *et al.*, 2004. *Alternative approaches can reduce the use of test animals under REACH,* ECB, European Communities.

FPS Health, Food Chain Safety and Environment

35

Animal use estimates

- main financial burden on HPVC

BUT

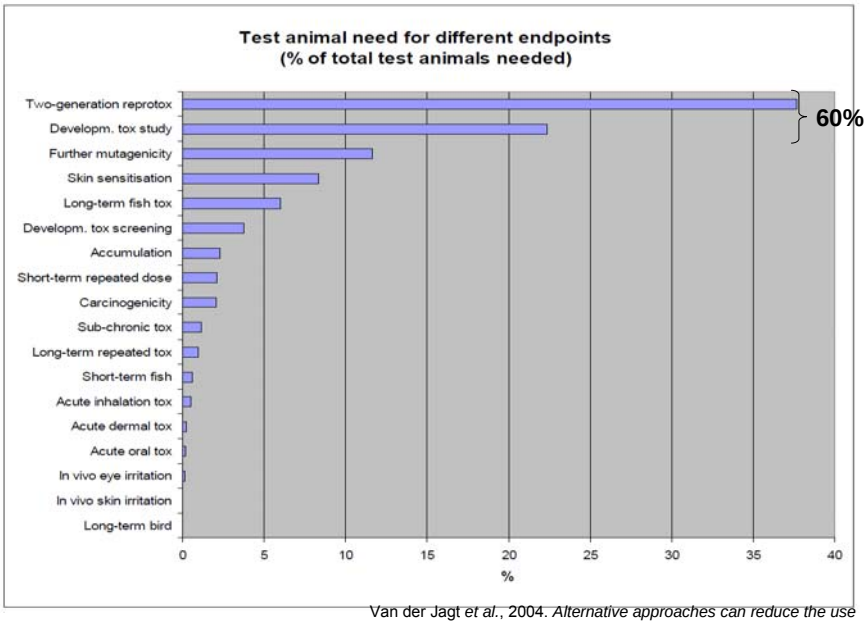
- Cost/t highest in low tonnage bands

Example

255 €/t for a substance produced with a volume of 3 t/y and 7 €/t for a substance produced in 3,000 t/y

FPS Health, Food Chain Safety and Environment

36



Van der Jagt *et al.*, 2004. *Alternative approaches can reduce the use of test animals under REACH,* ECB, European Communities.

Tonnage manufactured/imported	Standard information requirements	Cost estimation taking into account available data, waiving, QSAR,...	Cost if all tests new
- Non-phase-in substances at > 1 ton/year - Phase-in substances at > 1 ton/year fulfilling one or both of the criteria in Annex III*	Annex VII	15 000€ for full annex	45 000€ - 66 000€
- Phase-in substances at > 1 ton/year *not* fulfilling any of [illegible] Annex III	Section 5 of Annex VII (only phys/chem data, no tox, no eco tox)	±0?	?
> 10 ton/year	Annex VII + Annex VIII	100 000€	200 000 - 275 000
> 100 ton/year	Annex VII + Annex VIII & testing proposal for Annex IX	282 000€	1 000 000 - 1 500 000
> 1000 ton/year	Annex VII + Annex VIII & testing proposal for Annex IX + Annex X	323 000€	3 000 000 - 4 400 000

BUT DATA SHARING (OBLIGATORY)

*Substances for which it is predicted
a) that they meet the CMR (cat. 1 or 2), PBT or vPvB criteria; and/or
b) that they will be classified as dangerous and have dispersive or diffuse use(s) particularly where used in consumer preparations or incorporated into consumer articles

Source: numbers from SafePharm, based on KPMG impact assessment

FPS Health, Food Chain Safety and Environment

38

More information?

ECVAM
http://ecvam.jrc.it/index.htm

ECHA
http://echa.europa.eu/

Belgian REACH helpdesk
0800/120 33
reachinfo@economie.fgov.be
http://economie.fgov.be/reach.htm

ECHA helpdesk
http://echa.europa.eu/reach/helpdesk/echahelp_en.html

Competent Authority in Belgium
Risk Management Service, DG Environment, FPS Health, Food Chain Safety & Environment
www.health.fgov.be (Environment -> Chemical Substances -> REACH)


FPS Health, Food Chain Safety and Environment
39
www.health.fgov.be
Thank you!
.be