REACH

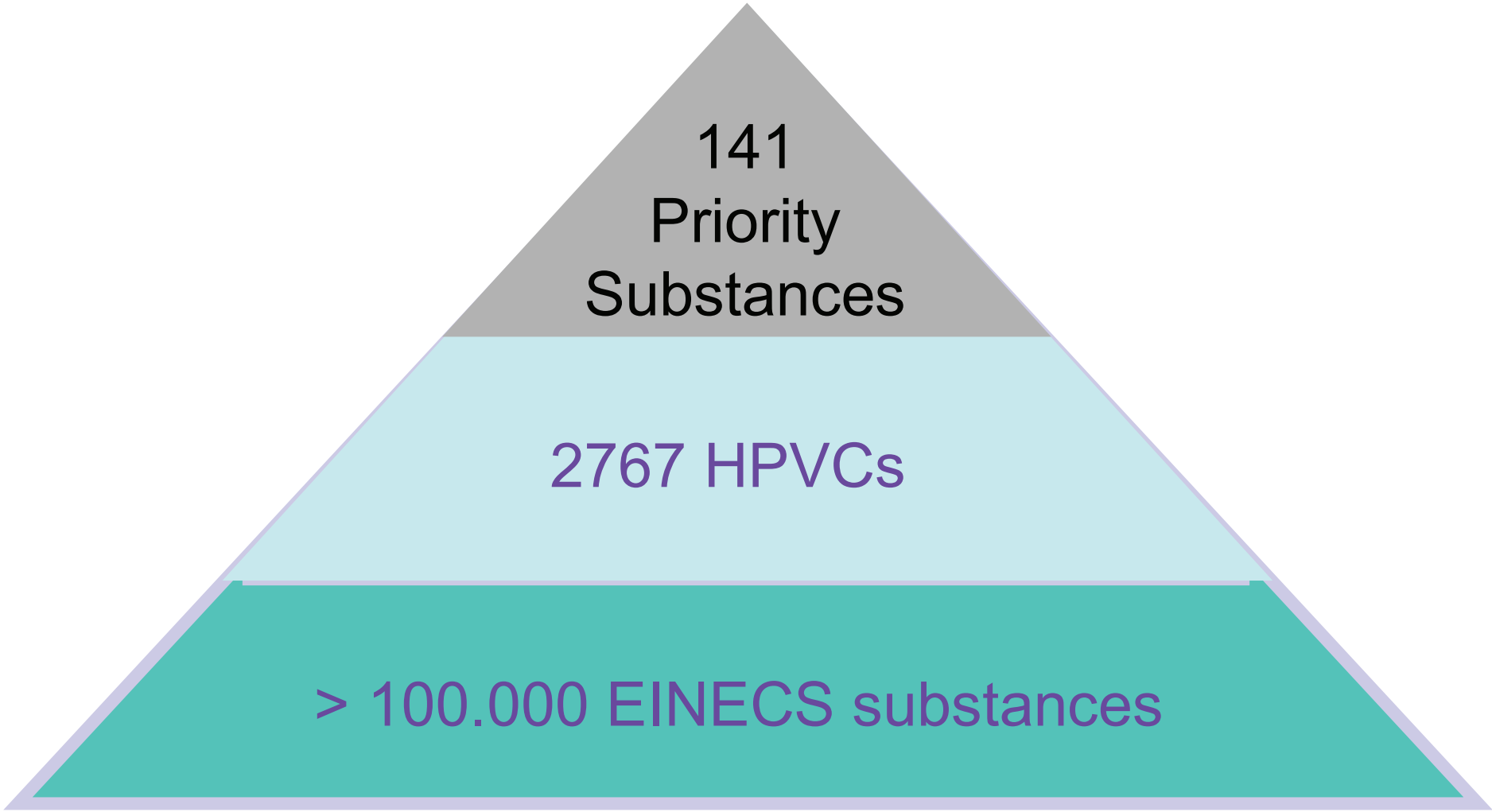
Data requirements & exposure scenarios

Kees van Leeuwen

TNO Quality of Life
Zeist, The Netherlands

CONTENTS

The data: current situation



Public Availability of Data on HPVCs

(Allanou, Hansen and van Der Bilt, 1999)

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

86%

What is the aim of a CSA?

The CSA of a chemical substance aims to establish the safe conditions of manufacture and use of a substance for all life-cycle stages. Manufacturers, importers and downstream users of substances on their own or in preparations have to ensure that these are manufactured and can be used in such a way that human health and the environment are not adversely affected.

2. Data requirements

Annex VII (≥ 1 tonne per year)

- Physicochemical properties
- Human health: *in vitro* irritation, sensitization, mutagenicity, acute toxicity (one route)
- Environmental: acute aquatic toxicity (daphnia, algae), biodegradation

Annex VIII (≥ 10 tonnes per year)

- Human health: including *in vivo* irritation, and 28-day repeat dose studies
- Environmental: acute toxicity fish, fate studies (hydrolysis, adsorption / desorption)

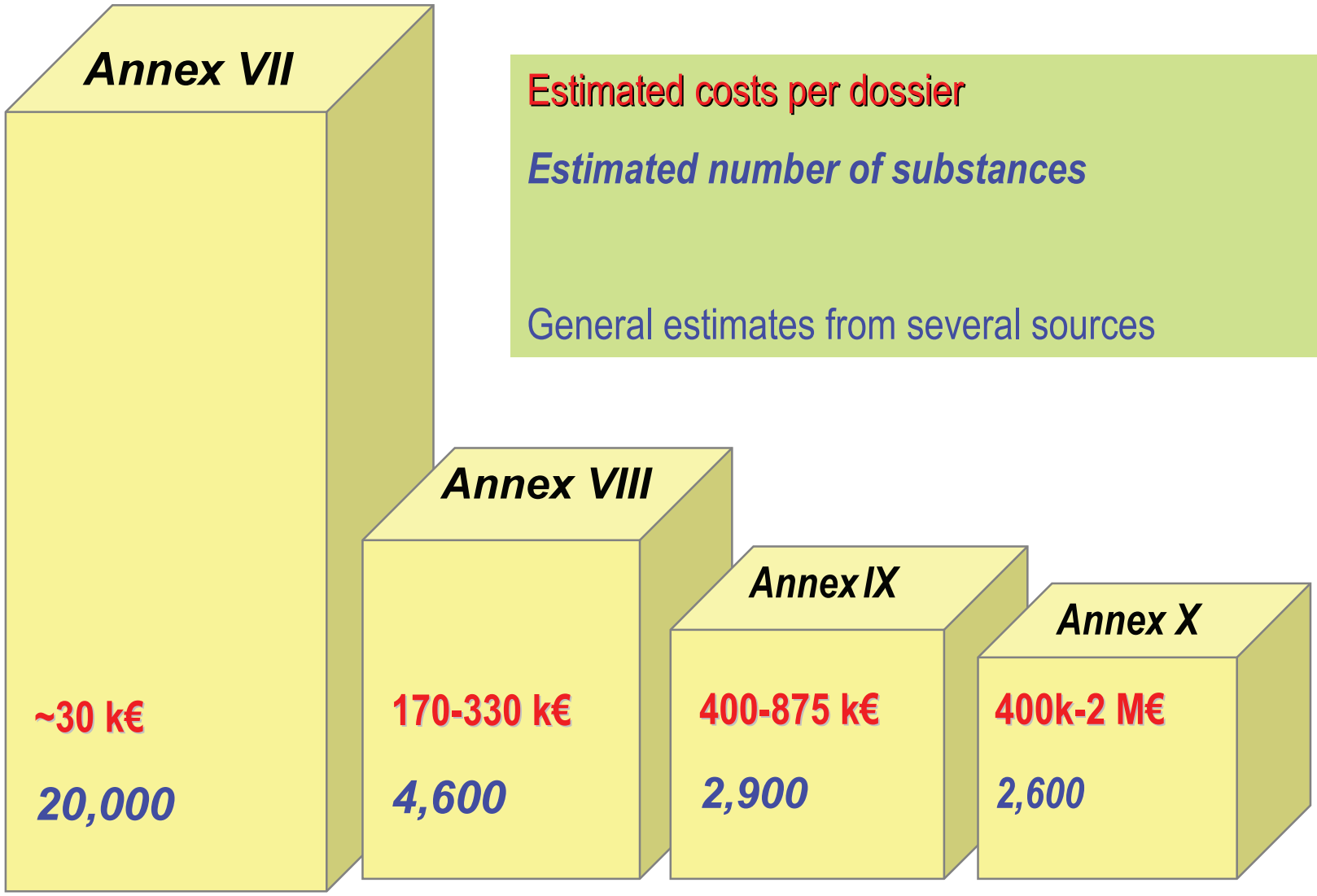
Annex IX (≥ 100 tonnes per year)

- Long term, repeat dose, chronic toxicity, fate etc

Annex X (≥ 1000 tonnes per year)

- Further long term, repeat dose, chronic toxicity, fate etc

REACH data requirements



Estimated costs per dossier

Estimated number of substances

General estimates from several sources

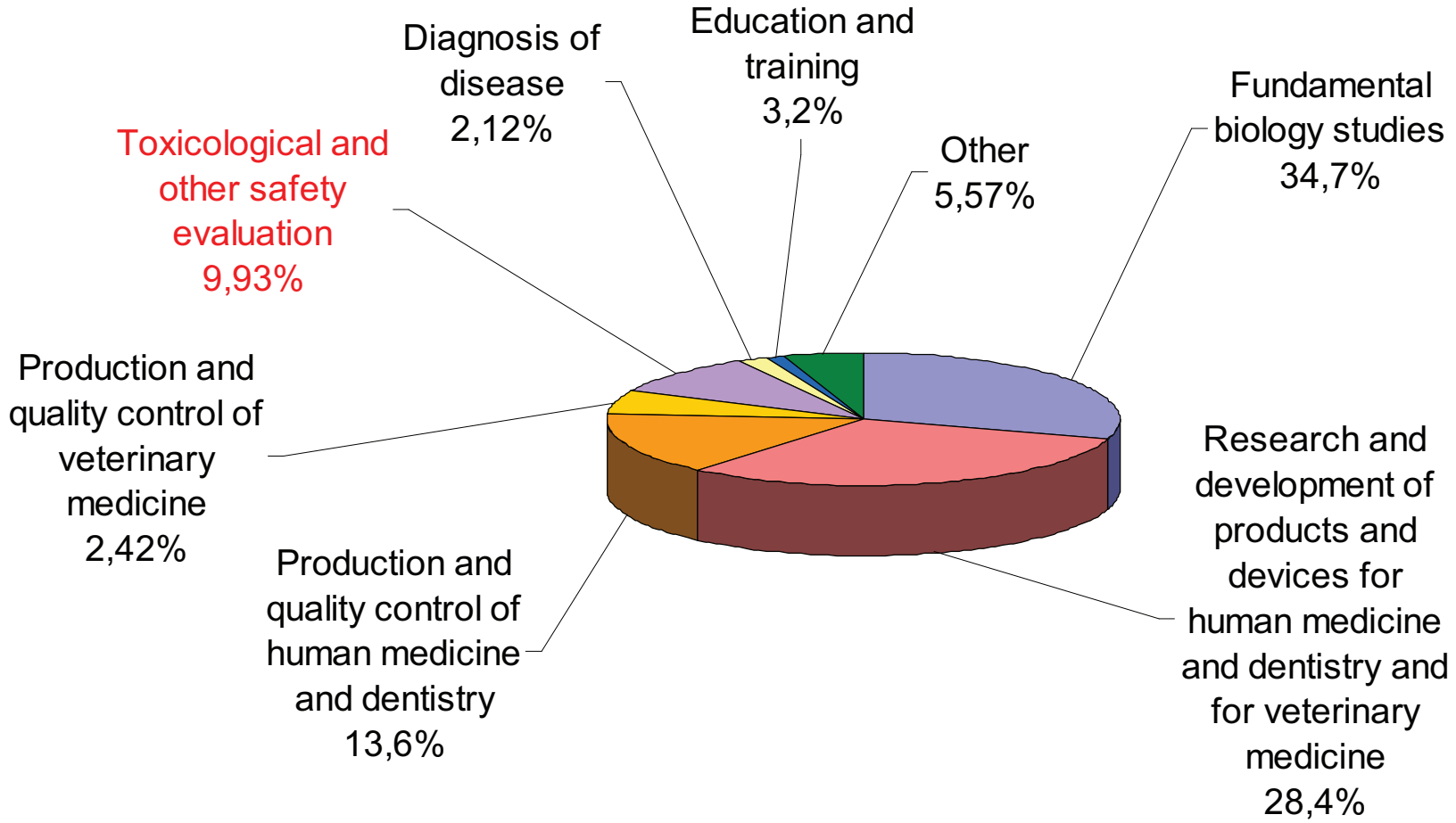
3. REACH and the use of test animals

- Testing on vertebrate animals shall be undertaken only as a last resort (Art. 25)
- Information may be generated by other means than tests, in particular through *in vitro* methods, (Q)SARs and read-across (Art. 13)

$\Rightarrow$ Legislative text + guidance should limit use of animals and prevent box-ticking

Use of animal experiments in the EU in 2002

COM(2005) 7 final



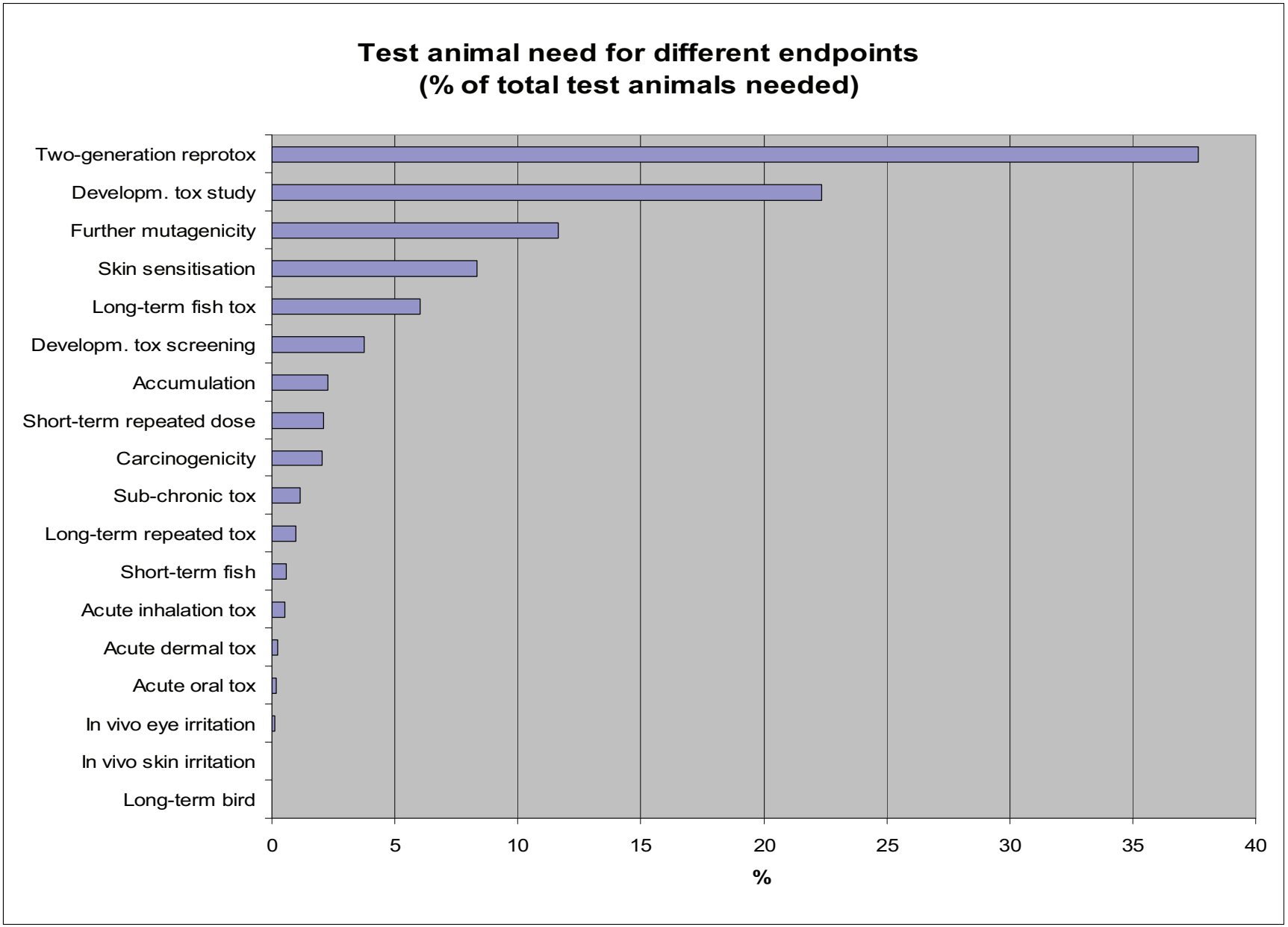
total number in 2002 = 10.7 million

Purposes of animal experiments in 2002

COM(2005) 7 final

Total number	10,700,000	100 %
Safety evaluations	1,060,000	10 %
Agricultural chemicals	123, 000	1 %
Industrial chemicals	136,000	1%
Cosmetics	2,700	0.025%

Estimated test animal need (van der Jagt et al., 2004)



Three tests determine the costs

Currently no alternatives to animal testing are available for the three main contributors to the overall test animal use and costs:

1. two-generation reprotoxicity
2. developmental toxicity studies
3. further mutagenicity (*in vivo*) study

These studies contribute with approximately 70% to the total test animal needs and testing costs.

Cost-saving aspects: Intelligent Testing Strategies

The most efficient way to carry out hazard and risk assessments of large numbers of chemicals, while reducing costs to industry and minimising animal testing, is to obtain the necessary information by means of intelligent testing strategies (ITS).

Intelligent testing strategies are integrated approaches comprising of multiple elements aimed at speeding up the risk assessment process while reducing costs and animal tests

(Bradbury, Feytel and Van Leeuwen, 2004)

REACH: saving potential of ITS

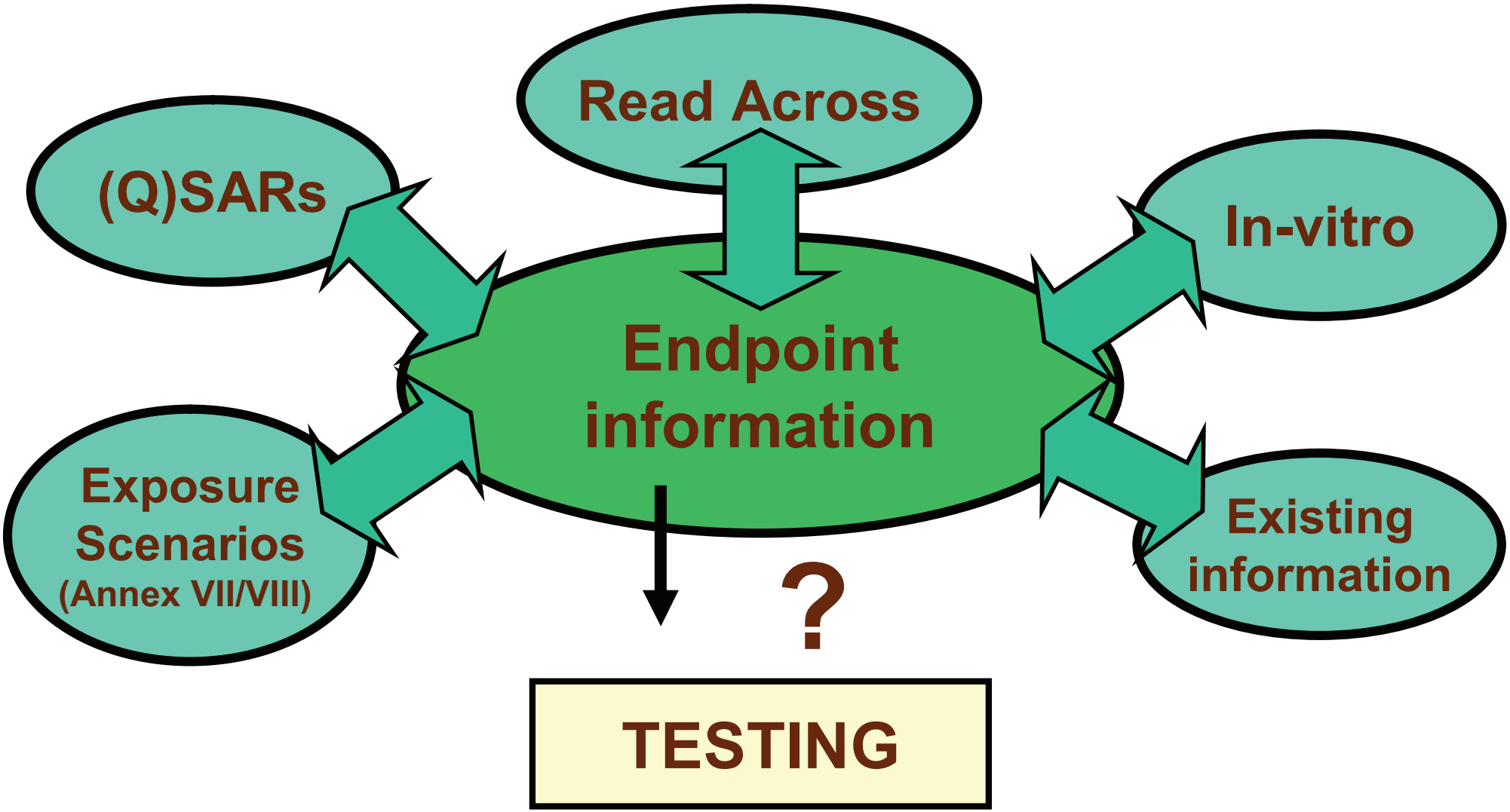
(Van der Jagt et al., 2004; EUR report 21405)

⇨**Testing costs**: **€ 800-1130 million**

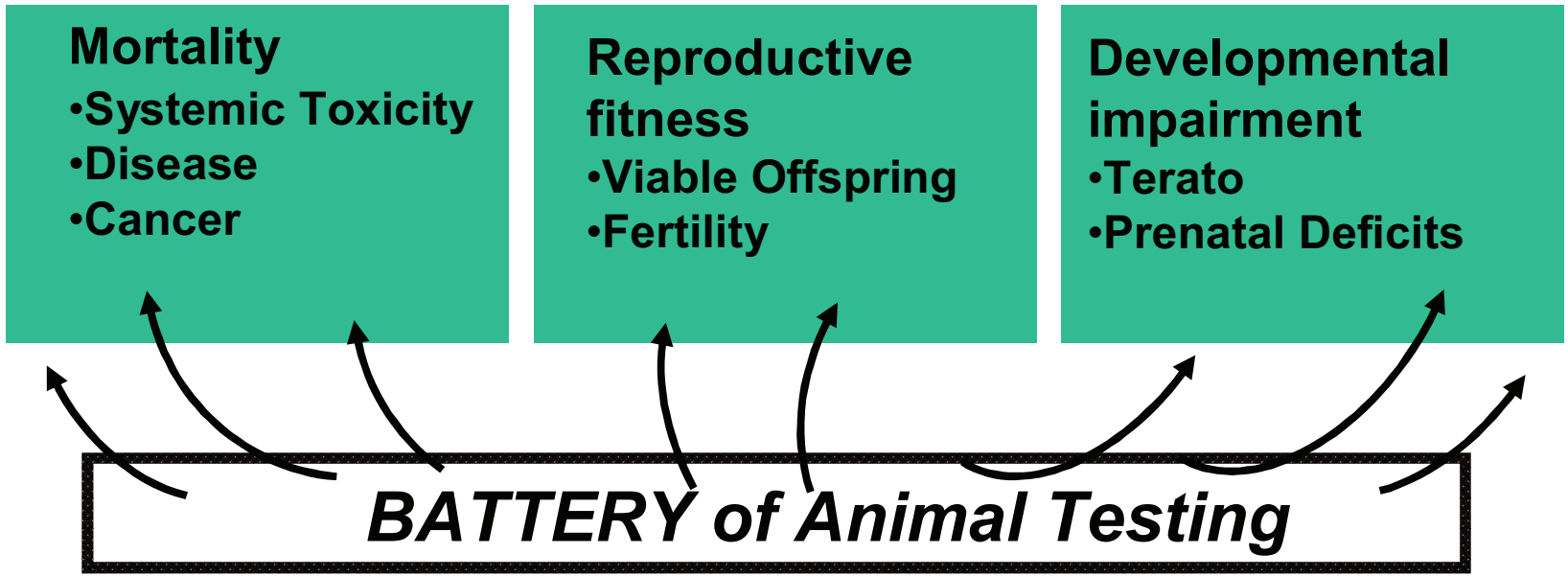
⇨**Number of animals**: **1.3-1.9 million**

The most likely scenario for REACH according to the JRC: 2.6 million vertebrate animals and € 1.5 billion for testing (http://ecb.jrc.it/)

Intelligent Testing Strategies (ITS)



Current toxicology testing paradigm generates *in vivo* animal data for all possible outcomes to determine which of all possible effects are relevant



(Jones and Bradbury, USEPA, 2005)

Components of Intelligent Testing Strategies

(v) Read-across and chemical categories (USEPA, 2004)

	Human health	Environmental effects
Adequate studies	50%	58%
Estimation via read-across	44%	35%
Testing	**6%**	**7%**

A paradigm shift is needed

In the context of regulatory programs, the challenge is to move in a scientifically credible and transparent manner from a paradigm that requires extensive hazard testing to one in which a hypothesis- and risk-driven approach can be used to identify the most relevant *in vivo* information

(Bradbury, Feytel and Van Leeuwen, 2004)

Towards a 7-R strategy implementing ITS

1. ***Risks*** Focus on risks (include **exposure**)
2. ***Repetitive*** A tiered approach should be applied, going from simple, to refined or comprehensive, if necessary, to quickly assess chemicals of low concern and to prevent animal testing.
3. ***Relatives*** The focus should be on families or categories of chemicals (a group-wise approach) using read-across, QSARs and exposure categories: move away from the chemical-by-chemical approach.
4. ***Restriction*** of testing (waiving of testing) where possible and carry out *in-vivo* testing where needed in order to prevent damage to human health and/or the environment. The strategy should also encompass the current 3-R strategy of:
5. ***Replacement*** (substitution)
6. ***Refinement*** (reduce suffering and distress)
7. ***Reduction***

REACH, registration and ITS

- Increased pressure to use/develop alternative methods (Limited impact now but may influence future acceptance of methods)

- Agency in cooperation with MSs and interested parties should develop appropriate guidance (REACH Recital 38)

Conclusions on ITS

1. Expectations to replace animal tests with *in vitro* studies and QSARs seem to be running ahead of scientific reality (see CSTEE & SCCNFP in Van Leeuwen, Patlewicz, Worth, 2007 and Greim et al. 2006)
2. A paradigm shift is needed from extensive animal testing to efficient, focussed animal testing applying the 7-R approach
3. ITS has a great animal-saving and cost-saving potential
4. Guidance on data requirements (RIP 3.3) is available in draft form (see website of the ECB; 1100 pages!
5. Further scientific work (2007 onwards) and regulatory implementation is needed.

4. Exposure scenarios & risk management

The Chemical Safety Assessment (CSA) is the tool used to determine the way chemicals can be used safely

An **exposure scenario** sets out, for a given use, how the substance can be used in a way that risks are adequately controlled by describing the conditions for use:

- Process descriptions (incl. quantity used)
- Operational conditions (incl. frequency and duration of specified operations)
- Risk management measures (process and emission control, personal protective equipment, good hygiene, etc.)

Exposure scenarios are developed as part of the CSA The Chemical Safety Assessment (CSA) is the tool used to determine the way chemicals can be used safely

Exposure scenarios under REACH are an integral approach to control risks

Formal definition: the set of conditions, including operational conditions and risk management measures, that describe how the substance is manufactured or used during its life-cycle and how the manufacturer or importer controls, or recommends downstream users to control, exposures of humans and the environment. These exposure scenarios may cover one specific process or use or several processes or uses as appropriate.

Registration requires:

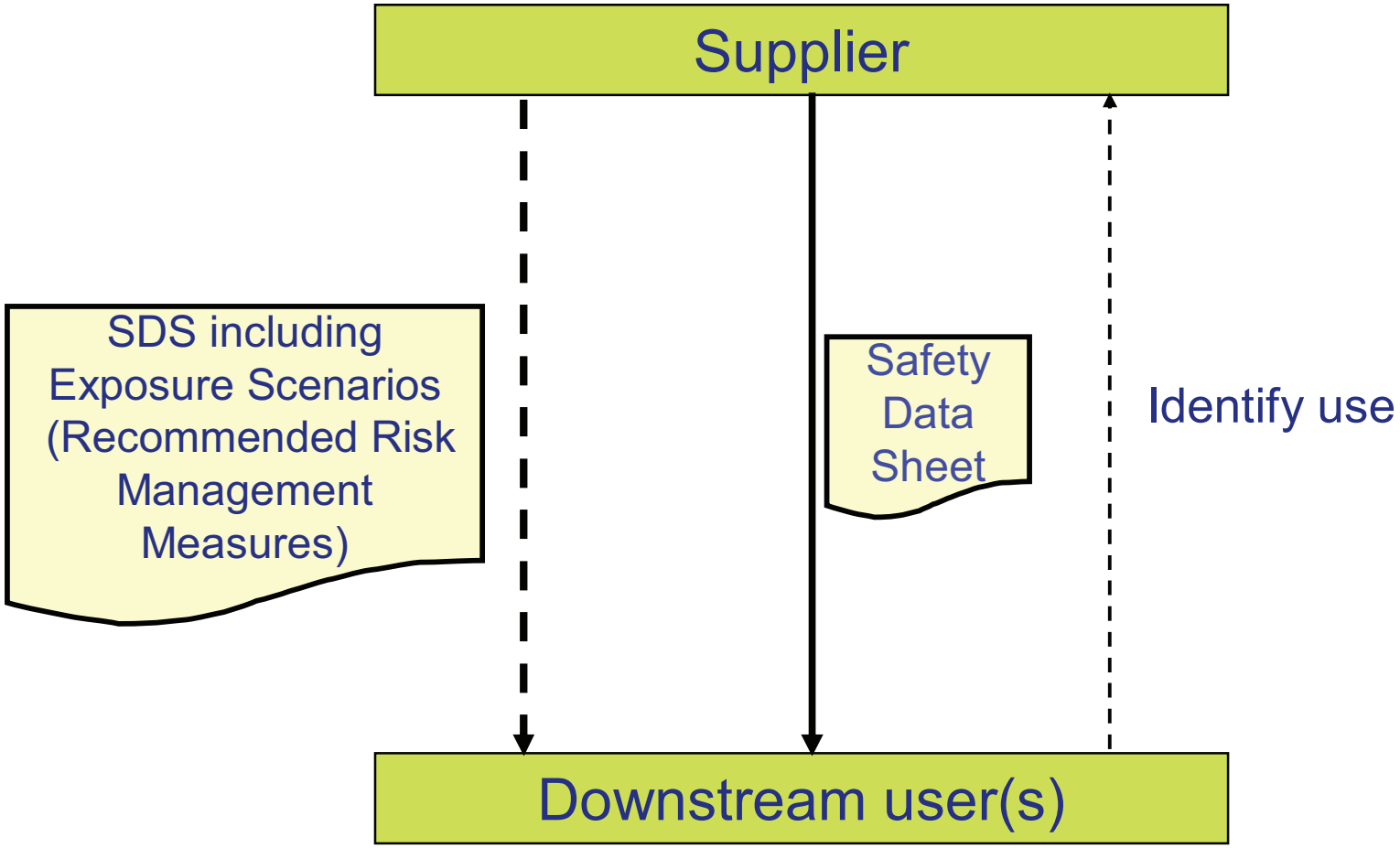
1. A technical dossier (for all substances ≥ 1 tonne/y).
2. A chemical safety report (CSR; for substances ≥ 10 tonnes/y).

If the substance meets the criteria for classification as dangerous or is assessed to be PBT or vPvB, the CSA has to include an exposure assessment including one or more exposure scenario(s), exposure estimation and risk characterization.

Six steps to develop an exposure scenario

1. Identification of uses and use processes
2. Description of manufacturing or use process
3. Development of a “tentative” ES
4. Exposure estimation and risk characterisation
5. Defining the “final” ES
6. Developing the annex to the SDS

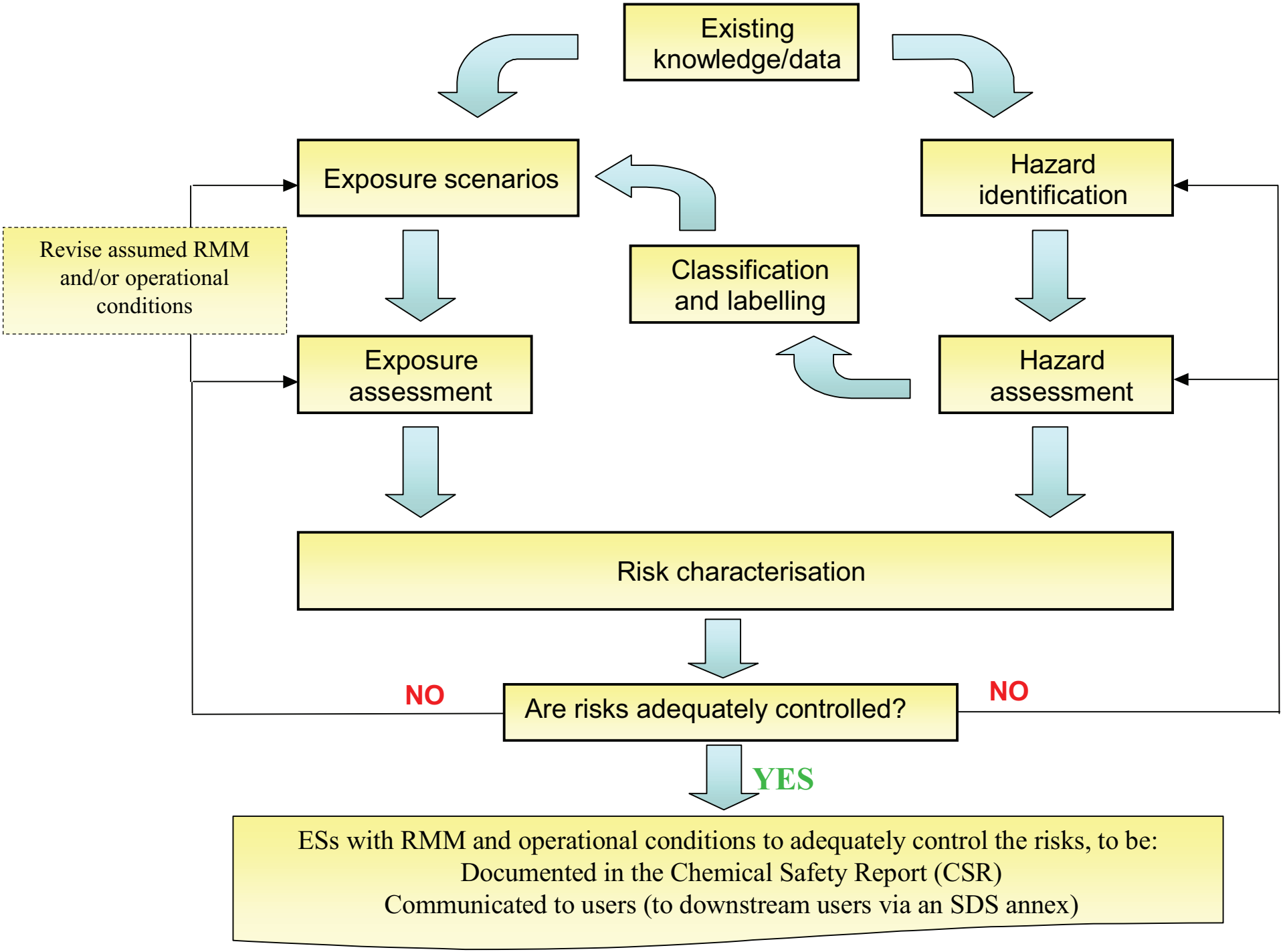
Supply chain communication



Types of risk management measures

1. Product-substance related measures
2. Limitation of the marketing of a substance/product
3. Instructions to limit the use
4. Instructions/information/warnings
5. Technical measures
6. Organisational measures
7. Personal protection measures

Source: RIP 3.2 WP1 development of the concept of Exposure scenarios, 337 pp (Website of ECB)


Existing knowledge/data
Exposure scenarios
Hazard identification
Revise assumed RMM and/or operational conditions
Classification and labelling
Exposure assessment
Hazard assessment
Risk characterisation
NO
Are risks adequately controlled?
NO
YES
ESs with RMM and operational conditions to adequately control the risks, to be:
Documented in the Chemical Safety Report (CSR)
Communicated to users (to downstream users via an SDS annex)

Typical characteristics of an ES

ES characteristics	Examples of parameters (not exhaustive)	Remarks
Life cycle of substance or product to which the ES refers	Manufacture or import, synthesis, compounding, formulation, use, service life, waste phase	Identify relevant exposures for all target groups, supports selection of suitable broad ES
Process characteristics	Industrial category, use category	Manufacture or use activity
Operational conditions	Type of activity/use Duration of activity/use Frequency of activity/use Temperature, pH, etc. Containment of process [open/closed]	Determines type of exposure (short term vs. long term) and choice of PNEC or DNEL
Preparation characteristics	Weight fraction of substance Migration rate	Determines exposure of humans and environment for preparations or products
Used quantity	Use rate [tonnes/year] Amount handled [kg/day, etc]	Determines the exposure potential per time
Risk Management Measures (within control)	Local exhaust ventilation On-site waste (water) treatment Personal Protective Equipment	RMMs as part of process or under direct control by DU

Conclusions on ESs and RMMs

1. RMMs are the start of a RA. The focus is on exposure
2. It requires multidisciplinary and integrative thinking & expertise right from the start
3. Dialogue up and down the supply chain between actors in the supply chain is key to success!
4. It requires paradigm shifts:
   - effects-based → exposure-driven
   - risk assessment → risk management
5. It requires detailed information on use and exposure of substances (in products) which is generally not available to the authorities (Haigh and Bailly, 1992!)
6. Expertise in and outside industry is scarce (aging population)

5. Concluding remarks: Trends and paradigm shifts are needed

1. From focus on legislation to implementation
2. From public authorities to industry (burden of proof)
3. From reactive to proactive (attitude)
4. From full testing to selective testing (ITS 7-R)
5. From effects-oriented to exposure-driven
6. From focus on RA to RMM
7. The Implementation will take much more time than currently predicted

6. Further guidance and tools

- Website of the European Chemicals Bureau: http://ecb.jrc.it/reach/
- Website of the European Chemicals Agency: http://ec.europa.eu/echa/home_en.html
- Websites of the European Commission
  http://ec.europa.eu/environment/chemicals/reach/reach_intro.htm
  http://ec.europa.eu/enterprise/reach/index_en.htm
- http://ecb.jrc.it/DOCUMENTS/REACH/REACH_in_brief_0207.pdf
- Helpdesks of the EU member states, i.e.:
  http://www.reachright.ie
  http://www.senternovem.nl/reach

- Haigh N Baillie A. 1992. Final report on chemicals control in the European Community in the 1990s. Institute for European Environmental Policy, London, UK.
- Allanou R, Hansen BG, Van Der Bilt Y. 1999. Public availability of data on EU high production volume chemicals. Report EUR 18996 EN, European Commission, Joint Research Centre, Ispra, Italy.
- Van der Jagt K, Munn S, Tørsløv J, De Bruijn J. 2004. Alternative approaches can reduce the use of test animals under REACH. Addendum to the report “Assessment of additional testing needs under REACH. Effects of (Q)SARs, risk based testing and voluntary industry initiatives”. Report EUR 21405. European Commission,Joint Research Centre, Ispra, Italy. Bradbury S, Feijtel T, Van Leeuwen K. 2004. Meeting the scientific needs of ecological risk assessment in a regulatory context. Environ Sci Technol 38/23, 463-470a.
- Jones, J. 2006. National Pesticide program. A new toxicological testing paradigm: meeting common needs. Presentation to the National Research Council Committee on toxicity testing and assessment of environmental agents on January 19. Irvine, CA. USEPA-OPP, Washington DC.

- Greim, H. et al. 2006. Toxicological comments to the discussion about REACH. Arch Toxicol 80:121-124
- Commission of the European Communities. 2007. Corrigendum to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396, 30.12.2006). OJ L136, volume 50, 29 May 2007.
- Guidance document on data requirements (RIP 3.2). See website ECB
- Van Leeuwen, C.J., G.Y. Patlewicz, and A.P. Worth. 2007. Intelligent Testing Strategies In: Risk Assessment of Chemicals. An Introduction (2nd edition). Van Leeuwen, C.J. and T.G. Vermeire, eds. Springer Publishers, Dordrecht, The Netherlands, pp 467-509.
- Van der Poel, P, Brooke, D and Van Leeuwen, C.J. 2007. Emissions of chemicals. In: Risk assessment of chemicals. In: Risk Assessment of Chemicals. An Introduction (2nd edition). Van Leeuwen, C.J. and T.G. Vermeire, eds. Springer Publishers, Dordrecht, The Netherlands, pp 37-72.
- Van Leeuwen, C.J., B.G. Hansen and J.H.M. de Bruijn. 2007. Management of industrial chemicals in the European Union (REACH). 2007. In: Risk Assessment of Chemicals. An Introduction (2nd edition). Van Leeuwen, C.J. and T.G. Vermeire, eds. Springer Publishers, Dordrecht, The Netherlands, pp 511-551.
- National Research Council, 2007. Toxicity Testing in the Twenty-first Century: A Vision and a Strategy. The National Academic Press, Washington DC.

Data requirements under REACH Annex VII for ≥ 1 TONNE

Skin irritation or skin corrosion

8.2 Eye irritation

8.3 Skin sensitisation

8.4.1 Mutagenicity (gene mutation in bacteria)

8.5.1 Acute toxicity (oral route)

Ecotoxicological information

9.1.1 Short-term toxicity invertebrates (*Daphnia*)

9.1.2 Growth-inhibition plants (algae)

9.2.1.1 Ready biodegradability

Data requirements under REACH Annex VIII for ≥ 10 TONNES

Toxicological information

8.1.1 Skin irritation (*in vivo*)

8.2.1 Eye irritation (*in vivo*)

8.4.2 Cytogenicity in mammalian cells (*in vitro*)

8.4.3 Gene mutation in mammalian cells (*in vitro*)

8.5.2 Acute toxicity (inhalation)

8.5.3 Acute toxicity (dermal)

8.6.1 Repeated dose toxicity (28days)

8.7.1 Reproductive/developmental toxicity screening test; OECD 421 or 422)

8.8.1 Toxicokinetics

Ecotoxicological information

9.1.3. Short-term toxicity fish

9.1.4. Activated sludge respiration inhibition test

9.2.2.1 Hydrolysis as a function of pH

9.3.1 Adsorption/desorption screening test

Data requirements under REACH Annex IX for ≥ 100 TONNES

Toxicological information

8.6.1	Repeated dose toxicity (28 days)
8.6.2	Sub-chronic toxicity (90 days)
8.7.2	Developmental toxicity; OECD 414
8.7.3	Two-generation reproductive toxicity study

Ecotoxicological information

9.1.5	Long-term toxicity invertebrates (*Daphnia)*
9.1.6.	Long-term toxicity to fish
9.1.6.1	Fish early-life stage test
9.1.6.2	Fish short term toxicity embryo and sac fry
9.1.6.3	Fish juvenile growth test
9.2.1.2	Ultimate degradation in surface water
9.2.1.3	Soil simulation testing
9.2.1.4	Sediment simulation testing
9.2.3	Identification of degradation products
9.3.2	Bioaccumulation in aquatic species (fish)
9.3.3	Further information on adsorption/desorption
9.4.1	Short-term terrestrial toxicity (invertebrates)
9.4.2	Effects on soil micro-organisms
9.4.3	Short-term toxicity to terrestrial plants

Data requirements under REACH Annex X for ≥ 1000 TONNES

Toxicological information

8.6.3 Long-term repeated toxicity (≥12 months)

8.7.2 Developmental toxicity; OECD 414

8.7.3 Two-generation reproductive toxicity

8.9.1 Carcinogenicity study

Ecotoxicological information

9.3.4 Further fate and behaviour in the environment of the substance and/or degradation products

9.4.4 Long-term toxicity on invertebrates

9.4.6 Long-term toxicity on plants

9.5.1 Long-term toxicity to sediment organisms

9.6.1 long-term toxicity to birds