Assessment of percutaneous absorption and its role in chemical risk assessment

Han van de Sandt, PhD

TNO | Knowledge for business

What to expect?

1. REACH: objectives, requirements
2. Role of skin absorption data within REACH
3. Tools and their use
4. Conclusions

Registration - all manufacturers and importers

- substances produced/imported above 1 tonne/y

Evaluation - Agency (Helsinki) and Member States

Authorisation - substances of very high concern

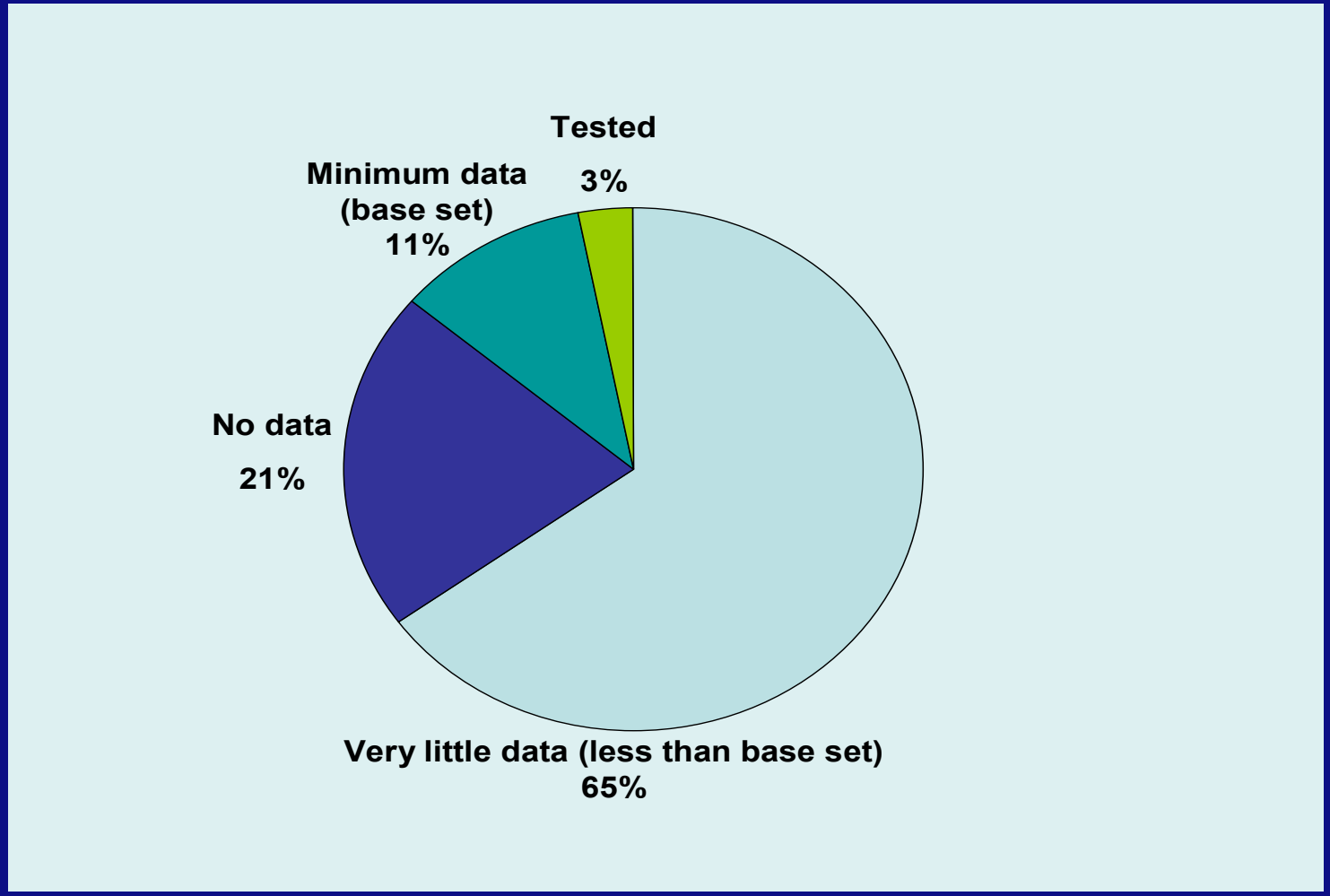
Restriction - ‘safety net’

CHemicals

Political objectives

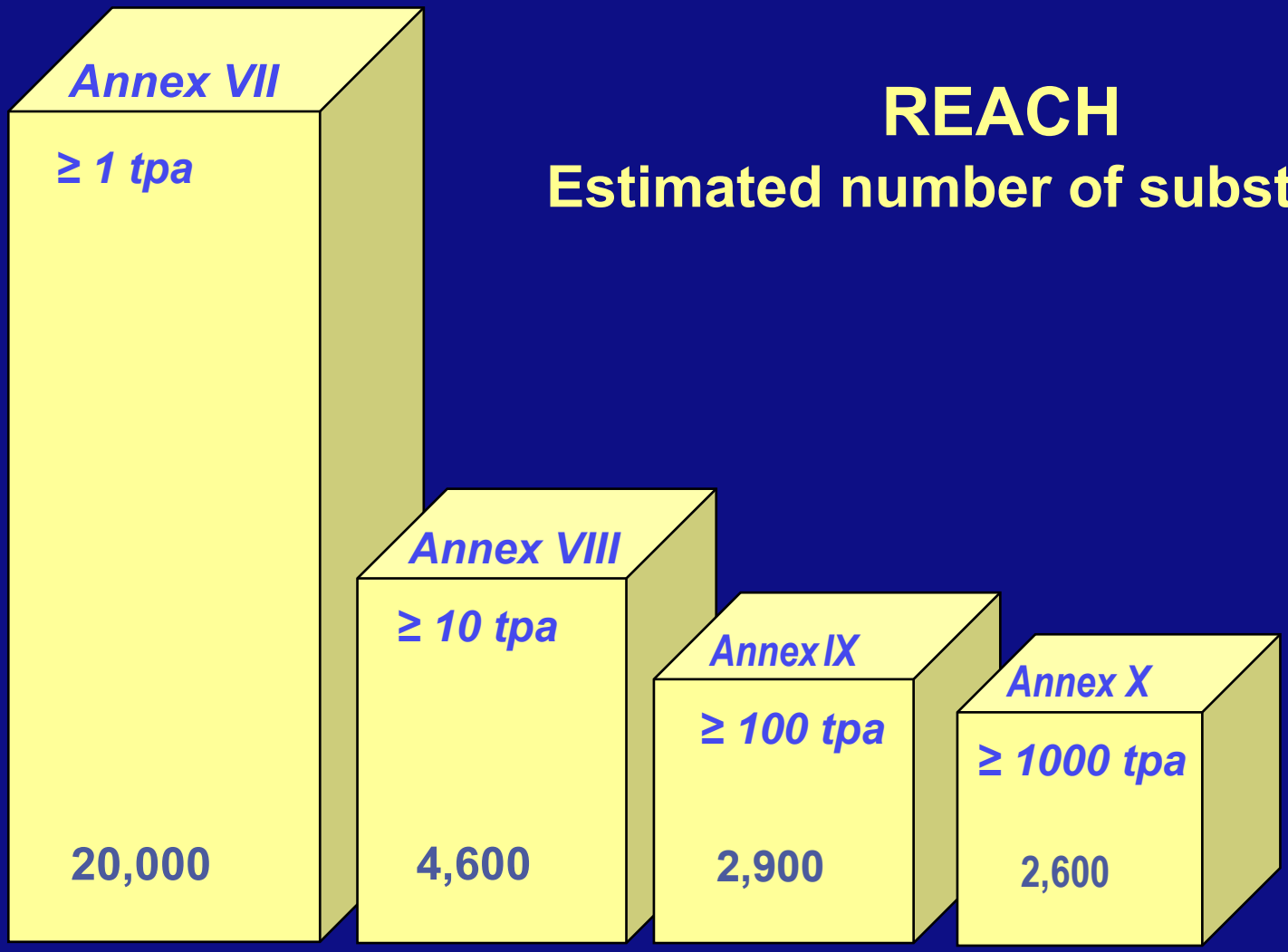
- Protection of human health and the environment
- Maintenance and enhancement of the competitiveness of the EU chemical industry
- Prevention of fragmentation of the internal market
- Increased transparency
- Integration of international efforts
- Promotion of non-animal testing
- Conformity with EU international obligations under the WTO

Lack of knowledge on potential risks



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.

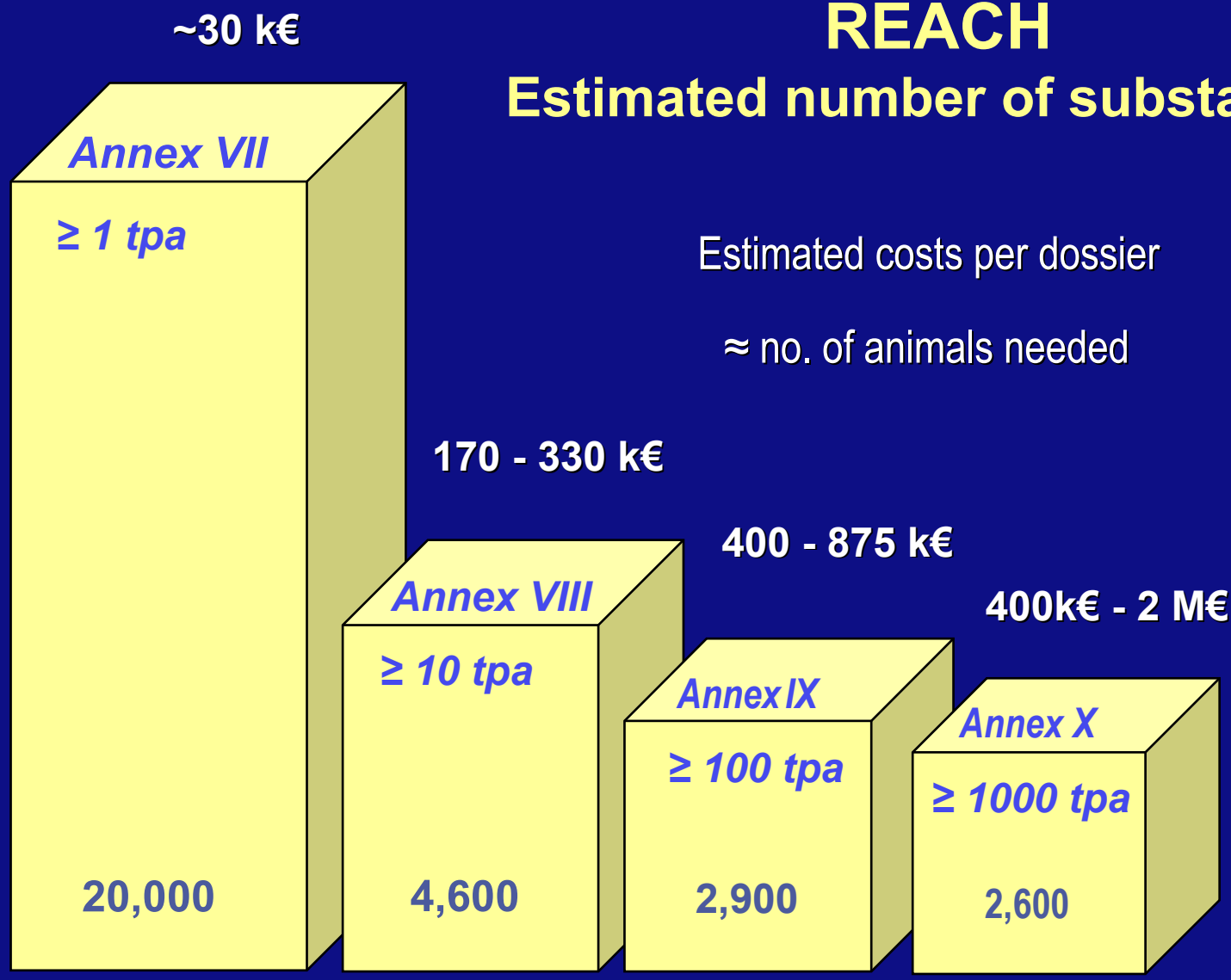
REACH
Estimated number of substances



Standard Information Requirements

Tonnage	Health	Environment
1 – 10 tpa	• *In vitro* skin and eye irritation • Skin sensitization • *In vitro* mutagenicity • Acute toxicity (one route)	• Acute aquatic toxicity -*Daphnia* • Biodegradability and hydrolysis • Algal toxicity
10 – 100 tpa	• *In vivo* skin and eye irritation • Further *in vitro* mutagenicity • Sub acute toxicity (28d) • Reproductive toxicity screen	• Acute aquatic toxicity – fish • Activated sludge • Adsorption / desorption screening
100 – 1000 tpa	• Further mutagenicity tests • Sub-chronic toxicity (90d) • Further reproductive toxicity tests	• Long term aquatic toxicity *Daphnia* and fish • Further degradation and fate / behaviour studies • Short-term effects on terrestrial organisms
>1000 tpa	• Further mutagenicity tests • Carcinogenicity • Chronic toxicity • Further reproductive toxicity	• Further degradation and fate / behaviour studies • Long-term effects on terrestrial organisms

REACH
Estimated number of substances



Estimated costs per dossier

≈ no. of animals needed

Dermal absorption information under REACH

No formal requirements, but….

Dermal absorption information under REACH
Substances > 10 tonnes

Acute toxicity

Testing by the dermal route is appropriate if:

(1) inhalation of the substance is unlikely; and

(2) skin contact in production and/or use is likely; and

(3) the phys-chem properties suggest a significant rate of absorption through the skin

Dermal absorption information under REACH
Substances > 10 tonnes

Short-term (28 day) repeated-dose toxicity

Testing by the dermal route is appropriate if:

(1) inhalation of the substance is unlikely; and

(2) skin contact in production and/or use is likely; and

(3) the phys-chem and tox properties suggest potential for a significant rate of absorption through the skin

Toxicokinetics

Assessment on the basis of available information

Dermal absorption information under REACH
Substances > 100 tonnes

Sub-chronic (90 day) toxicity

Testing by the dermal route is appropriate if:

(1) skin contact in production and/or use is likely; and

(2) the phys-chem properties suggest a significant rate of absorption through the skin; and

(3) one of the following conditions is met:

- toxicity is observed in the actute dermal toxicity test at lower doses than in the oral toxicity test, or
- systemic effects or other evidence of absorption is observed in skin and/or eye irritation studies, or
- *in vitro* tests indicate significant dermal absorption, or
- significant dermal toxicity or dermal penetration is recognized for structurally-related substances

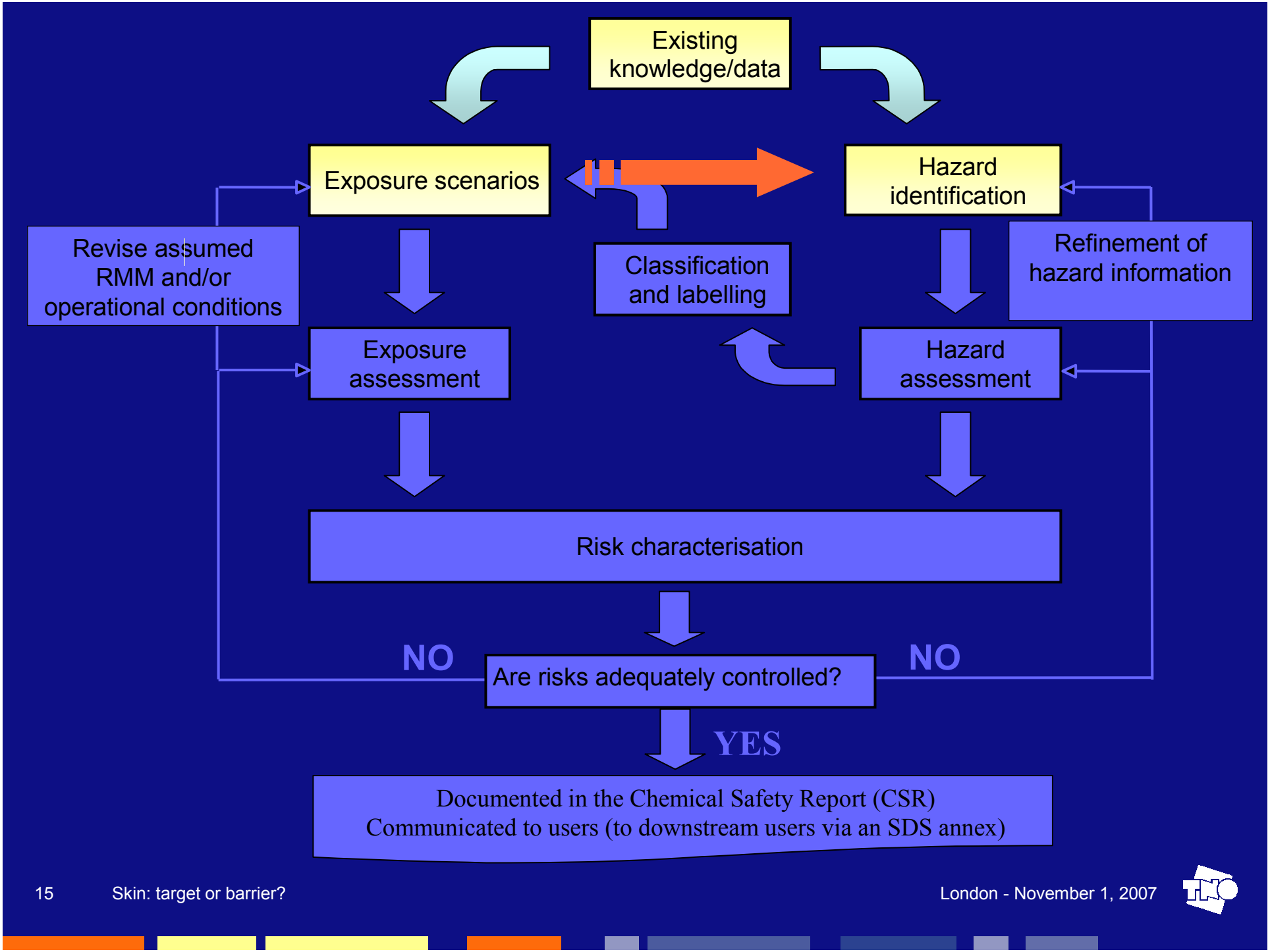
Dermal absorption information under REACH
Substances > 100 tonnes

Reproductive toxicity

The studies do not have to be conducted if:

- ….
- the substance is of low toxicological activity (…), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (…) and there is no or no significant human exposure

Chemical Safety Assessment (CSA)


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

Exposure scenarios under REACH

- Process descriptions
  (incl. quantity used)

- Operational conditions
  (incl. frequency/duration of specified operations)

- Risk management measures
  (e.g. personal protective equipment)

Exposure scenarios under REACH

- Does (relevant) human exposure occur (worker, consumer)?

- Is the dermal route the dominant route of exposure?

- Quantification of dermal exposure?

Tools to obtain dermal absorption information

Dermal absorption information

Animal studies only as a last resort

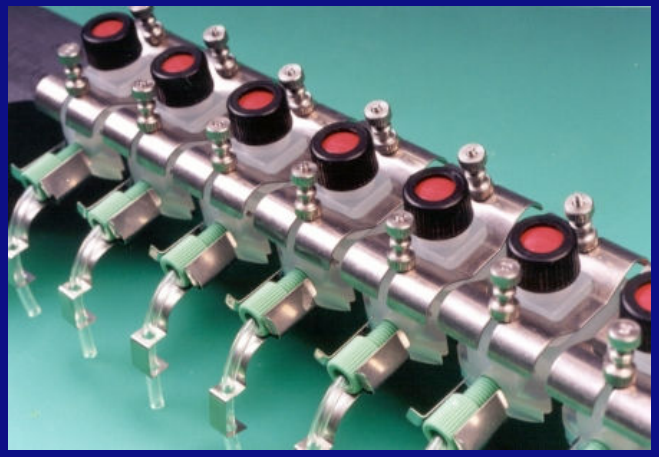
Annex XI: Rules for adaptation of the standard testing regimes

- Testing does not appear scientifically necessary
  - Use of existing data
  - Weight of evidence
  - Qualitative or Quantitative Structure Activity Relationships
  - In vitro methods
  - Grouping of substances and read-across
- Testing is technically not possible
- Substance-tailored exposure-driven testing

In vitro studies

Pro's - Detailed information
- Use of outcome (% of dose) in risk assessment
- No / very limited use of animals
- Formulated products

But - Need for valid and sensitive analytical method
- Costs & time



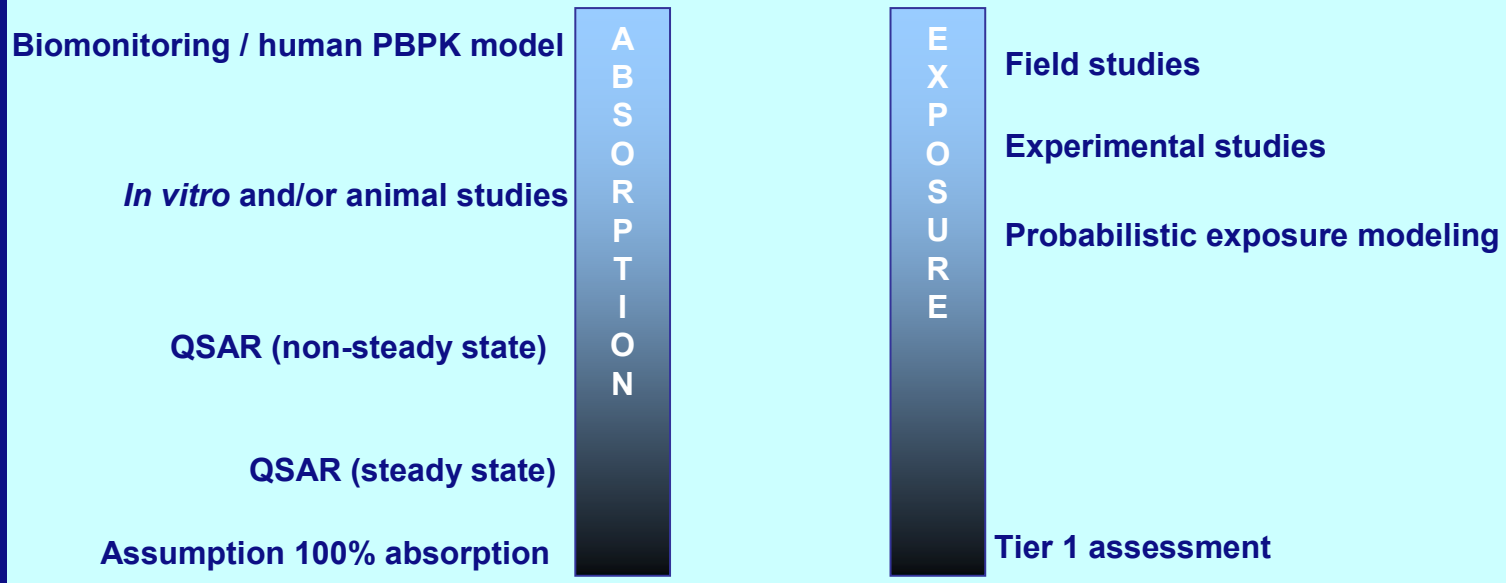
QSAR ('non-testing')

Pro's
- Costs
- Time
- No use of animals
- No need for laboratory setting

But
- Use of outcome (flux, Kp) in risk assessment
- Dose, formulated products
- Applicability domain
- Accuracy of data

Sources of data

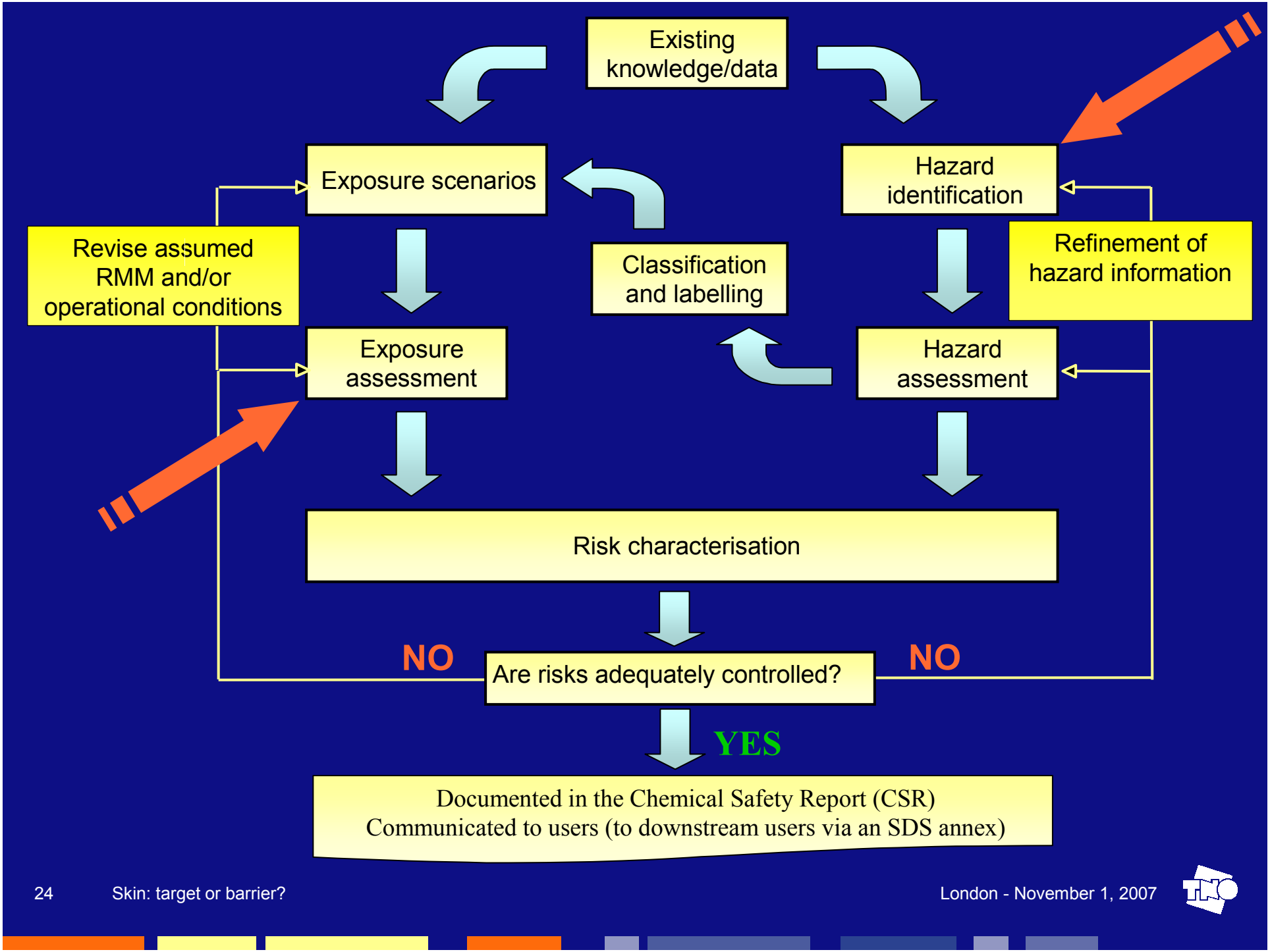
Data-rich compounds, high cost, low uncertainty, realistic



Data-poor compounds, low cost, high uncertainty, worst-case

Many ‘test’ and ‘non-test’ procedures…

… which one to choose?


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

Use of dermal absorption data in CSA

Substantiation of ‘no relevant internal exposure’

- yes/no answer (conservative approach)
- in conjunction with generic Exposure Scenario

Adjustment of 100% absorption for internal exposure assessment

- semi-quantitative (conservative categories)
- quantitative (predictive)
- in conjunction with specific Exposure Scenario

Classifying chemicals on the basis of J_{max}

Table 3
Classification of chemicals (on the basis of their physicochemical properties) in terms of their potential to be absorbed across the skin

J_{max} (μg/cm^2/h)	MW (Da)	log P	Category
$J_{max} = 0$	Non-reactive chemicals > 1000 Da	Any	Negligible
$J_{max} < 0.1$	> 300	< −1 or > 5	Low
$0.1 < J_{max} < 1.0$	~ 200–300	> 2.0, 2.5	Medium low
$1.0 < J_{max} < 10$	~ 150–250	~ 1.0–2.0	Medium high
$10 < J_{max} < 100$	~60–200	~ 0.5–3.5	High
$J_{max} > 100$	<150	−0.5–2.0	High

J_{max}, maximum flux; MW, molecular weight; log P, log of the octanol:water partition coefficient.

R. Kroes et al., Food and Chemical Toxicology (2007). Doi:10.1016/j.fct.2007.06.021

Default adjustment factors (cosmetic ingredients)

Table 4
Proposed default adjustment factors for the % dose absorbed of cosmetic ingredients across the skin

J_{max} (μg/cm^2/h)	Default% dose absorbed per 24 h
Non-reactive chemicals with MW > 1000	Negligible
$J_{max} < 0.1$	10
$0.1 < J_{max} < 10$	40
$J_{max} > 10$	80

J_{max}, maximum flux.

R. Kroes et al., Food and Chemical Toxicology (2007). Doi:10.1016/j.fct.2007.06.021

Conclusions

- No formal information requirement on dermal absorption under REACH
- Information on dermal absorption is useful for route selection in toxicity studies and potentially for waiving of information requirements (reproductive toxicity)
- Various methodologies are available; the choice should be based on required accuracy of data
- Only by combining data on exposure and absorption, predictions can be made on the internal dose
- Defining (conservative) categories on the basis of QSAR outcomes, rather than relying on the exact prediction, could be a way forward to gain confidence in the predicted values.

References

- Kroes R et al., Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients, *Food and Chemical Toxicology* (2007). Doi:10.1016/j.fct.2007.06.021
- Van de Sandt JJM, Dellarco M and Van Hemmen JJ, From dermal exposure to internal dose, Journal of Exposure Science and Environmental Epidemiology (2007). Doi: 10.1038/sj.jes.7500579
- EDETOX (2004). Edetox database, University of Newcastle, UK. http://edetox.ncl.ac.uk
- Technical Guidance Document to Industry on the information requirements for REACH, final draft (2007). http://ecb.jrc.it/reach/rip/
- Bouwman T, Cronin MTD, Bessems JGM, Van de Sandt JJM (2006). Evaluation of published QSARs for percutaneous absorption. Toxicology Letters 164, S322.

Thank you for your attention