# Chemical Safety Assessment Under REACH

*Dinant Kroese*

**TNO| knowledge for business**

# CONTENTS

# Registration under REACH

**Aim**: to ensure that industry adequately manages the risk arising from its substances (starting at 1 tonne/y)

**Method**:

- Manufacturer/importer should obtain adequate data
- Provides a registration dossier which includes a chemical safety report (CSR) for substances above 10 tonnes/y documenting the Chemical Safety Assessment (CSA)
- Submits to authorities (enforcement, transparency)
- Increased info requirements according to tonnage (testing proposal)
- Reduced requirements for polymers and intermediates

# 1. Registration requirements:

| | |
|---|---|
| 1. A Technical Dossier | ≥ 1 tonne/y |
| 2. A Chemical Safety Report | ≥ 10 tonnes/y |

# Format of the Technical Dossier

- identity of the Manufacturer / Importer
- identity of the substance
- information on its manufacture and use
- the classification and labeling of the substance
- guidance on its safe use
- (robust) study summaries of the information on the intrinsic properties of the substance derived from applying *Annexes VII* to *XI*
- an indication as to whether the above issues and/or, if relevant, the Chemical Safety Report (→) has been reviewed by an assessor
- proposals for further testing, if relevant
- between 1 and 10 tonnes, the Techical Dossier shall also contain exposure related information for the substance (main use categories, type of uses, significant routes of exposure).

# Simplified format of the Chemical Safety Report

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Part A Summary of risk management measures

Declaration that risk management measures are implemented

Declaration that risk management measures are communicated

Part B Identity of the substance and physical and chemical properties

Manufacture and uses

Classification and labelling

Environmental fate properties

Human health hazard assessment

Human health hazard assessment of physicochemical properties

Environmental hazard assessment

PBT and vPvB assessment

Exposure assessment

Risk characterization

Chemical Safety Assessment

# 2. Core tools under REACH

- The Chemical Safety Assessment is the tool used to ***determine*** the safety of the chemical
- The Chemical Safety Report is the tool used to ***record/document*** the assessment to EChA
- The Safety Data Sheet is the tool used to ***communicate*** safe use to downstream users (DU)

# 3. Chemical Safety Assessment, *Human Health*

# Aim of the Chemical Safety Assessment:

To establish control of risk for manufacture and use of a substance for all life-cycle stages.[1]

Manufacturers/Importers/Downstream Users:

have to ensure that the manufacture and use is in such a way that human health and the environment are not adversely affected.

[1] on their own or in preparations or in articles

# Chemical Safety Assessment should describe:

1. The intrinsic properties of the substance
   - Human Health (Physico-chemical) hazards
   - Environmental Health hazards
   - PBT & vPvB properties
2. All manufacturing and use scenarios

PBT = Persistent, Bioaccumulating and Toxic,
vPvB = very Persistent, and very Bioaccumulating

Note:

**If**

the substance meets the criteria for classification as dangerous[1] or is assessed to be PBT or vPvB,

**then**

the Chemical Safety Assessment has to include an exposure assessment for one or more exposure scenario(s), and risk characterization.

[1] i.e. labeled with any R sentence

# Chemical Safety Assessment should describe:

1. The intrinsic properties of the substance

   HH (PC) hazards

   ENV hazards

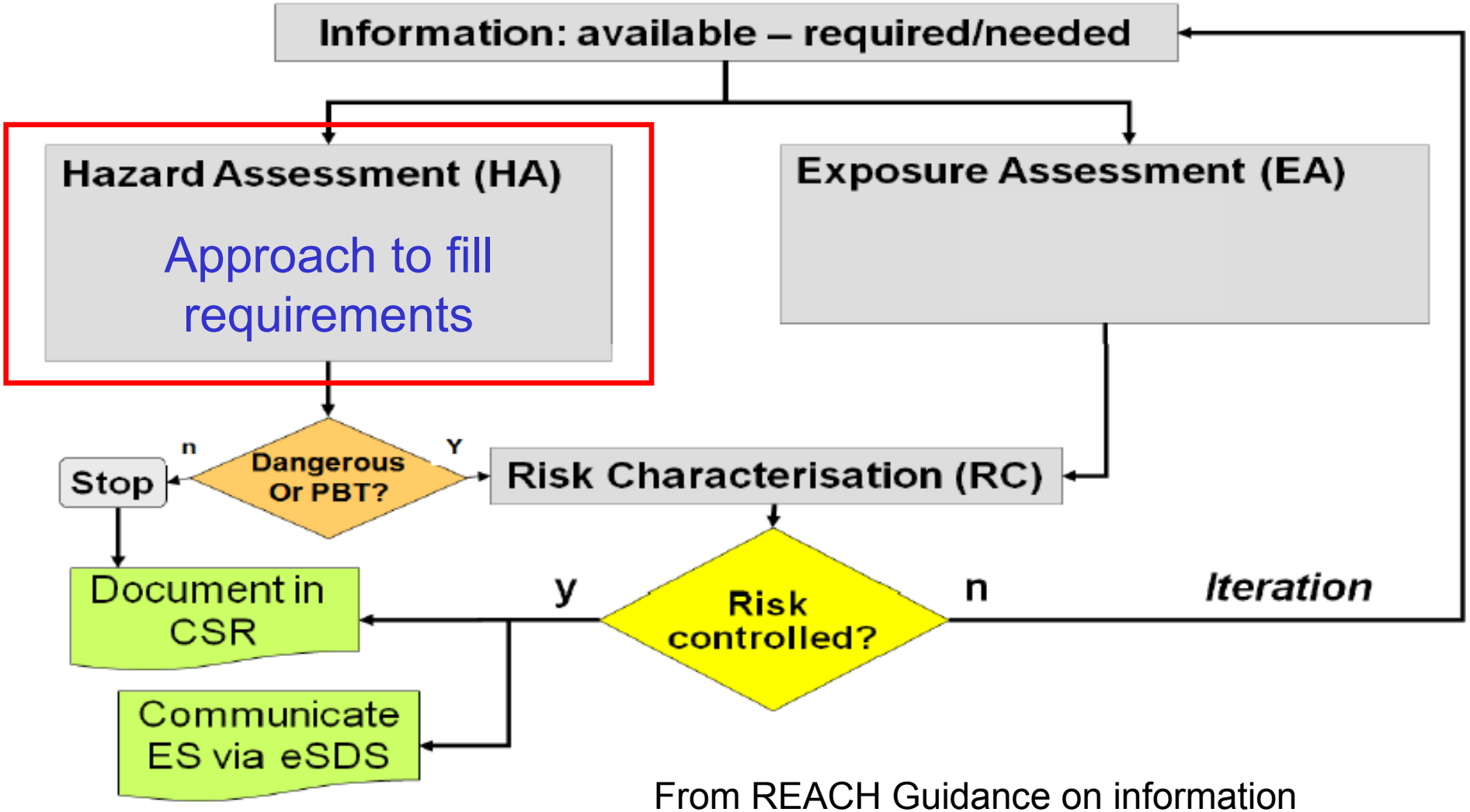
   PBT & vPvB properties

2. All manufacturing and use scenarios

3. Risk Characterisation:

   comparison of *ad 1.* with exposures of *ad 2.* (of scenarios, including RMM), showing control of risk for manufacture & for use

# Chemical Safety assessment scheme




From REACH Guidance on information requirements and CSA – Part D

# CSA / what intrinsic properties?

## of the substance

1. Human health hazard assessment
2. Human health hazard assessment of phys-chem properties
3. Environmental hazard assessment
4. PBT and vPvB assessment

# CSA / objectives

1. Human health hazard assessment
    1. determine **Classification & Labeling** in accordance with 67/548/EEC
    2. derive Derived No Effect Level (**DNEL**)
2. Human health hazard assessment of phys-chem properties
    1. determine **Classification & Labeling** in accordance with 67/548/EEC
3. Environmental hazard assessment
    1. determine **Classification & Labeling** in accordance with 67/548/EEC
    2. derive Predicted No Effect Concentration (**PNEC**)
4. PBT and vPvB assessment
    1. determine if **criteria** Annex XIII are fulfilled
    2. if yes: characterize **emission potential**

# CSA / evaluation approach

## Annex VI

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

# CSA / evaluation approach

1. Gather and share available information

All Available Health & Environmental Information:

- physico-chemical data
- human data
- *in vitro* / *in vivo* data
-read-across, SAR, QSAR

&

Exposure characteristics

populations & routes

duration

*Assessment of reliability, relevance, and adequacy; all within SIEF*

# CSA / evaluation approach

1. Gather and share available information
2. Consider information needs

| Tonnage | Human Health |
|---|---|
| 1 – 10 tpa<br><br>Annex VII | • *In vitro* skin and eye irritation<br>• Skin sensitization<br>• *In vitro* mutagenicity<br>• Acute toxicity (one route) |
| 10 – 100 tpa<br><br>Annex VIII | • *In vivo* skin and eye irritation<br>• Further *in vitro* mutagenicity<br>• Acute toxicity (2nd route)<br>• Sub acute toxicity (28d)<br>• Reproductive toxicity screen |
| 100 – 1000 tpa<br><br>Annex IX | • Further mutagenicity tests<br>• Sub-chronic toxicity (90d)<br>• Reproductive toxicity tests |
| >1000 tpa<br><br>Annex X | • Further mutagenicity tests<br>• Further reproductive toxicity tests<br>  • *Carcinogenicity may*<br>  • *Chronic toxicity may* |

Adaptations:
Column 2 of
Annexes VII to X
&
Annex XI

# CSA / evaluation approach

1. Gather and share available information
2. Consider information needs
3. Identify information gaps

Conclude on whether information is adequate to:

assess: & allow the derivation of:

Classification & Labeling, PBT, vPvB

DNEL and PNEC

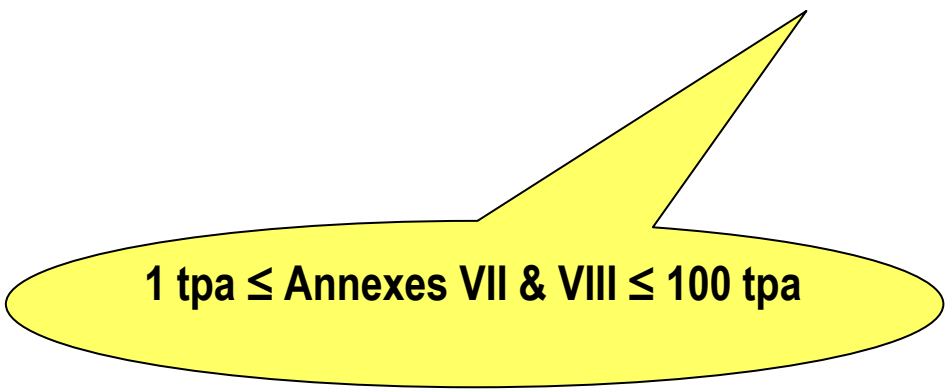
*Coverage of parameters, Weight of the evidence, Transparency; all within SIEF*

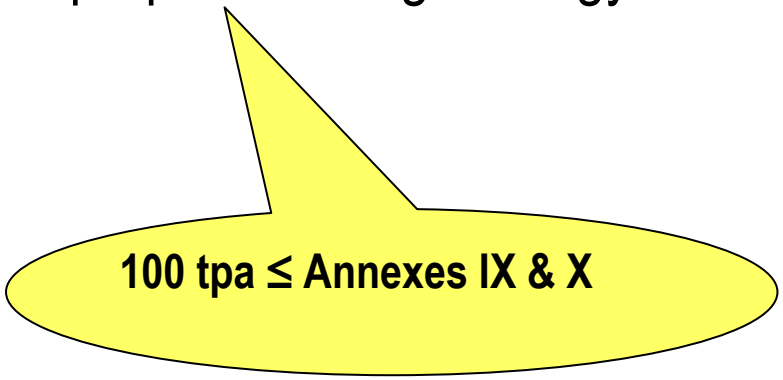
# CSA / evaluation approach

1. Gather and share available information
2. Consider information needs
3. Identify information gaps

*In case of inadequate information:*

4. Generate new data / propose testing strategy



# CSA / evaluation approach

1. Gather and share available information
2. Consider information needs
3. Identify information gaps

*In case of inadequate information:*

4. Generate new data / propose testing strategy

1 Conclude on what exactly is unclear or insufficient

↓

2 Is testing technically possible?

Yes ↓

3 Is exposure-based waiving possible?

No ↓

4 Consider if *in vitro* testing may be adequate

No ↓

5 Conduct or Propose an appropriate *in vivo* test

I will come back on this →

**≥ 10 tpa**: rules in Annex column 2 and Annex XI

# CSA / evaluation approach

1. Gather and share available informati
2. Consider information f
3. Identify information gaps

*In case of inadequate information:*

4. Generate new data / propose testing strate

Provide justification for no testing

1 Conclude on what exactly is unclear or insuff nt

2 Is testing technically possible? — No →

Yes ↓

3 Is exposure-based waiving possible? — Yes →

No ↓

4 Consider if *in vitro* testing may be adequate

No ↓

5 Conduct or Propose an appropriate *in vivo* test

# CSA / evaluation approach

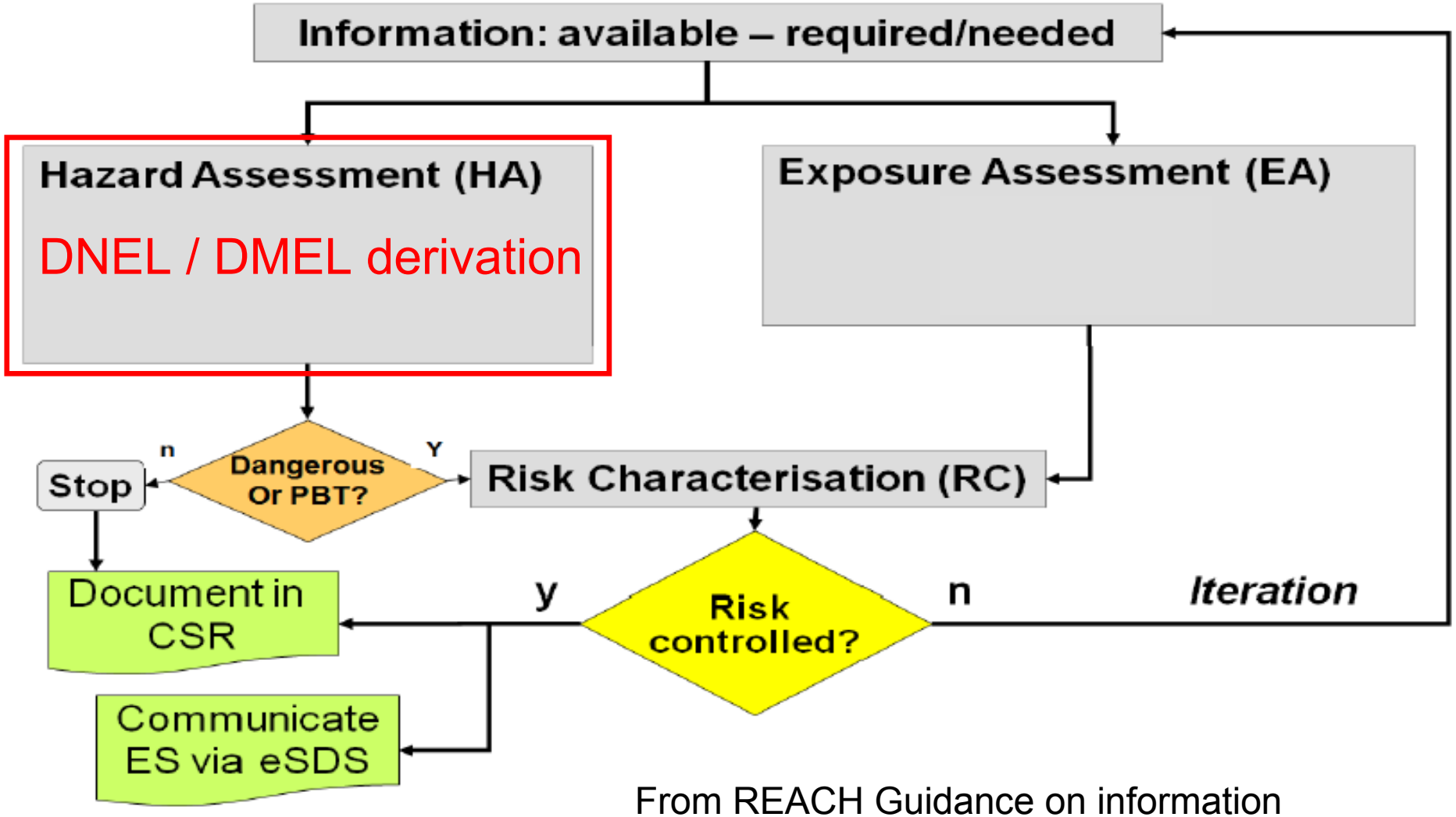
1. Gather and share available information
2. Consider information needs
3. Identify information gaps

*In case of inadequate information:*

4. Generate new data / propose testing strategy

**Gaps filled?**

# Chemical Safety assessment scheme




From REACH Guidance on information requirements and CSA – Part D

# Quantitative approach & Qualitative approach

Quantitative approach:

- effect-threshold? → DNEL (Derived No Effect Level)
- no effect-threshold? → DMEL (Derived Minimal Effect Level)

Qualitative approach: *infrequently ….*

- effect-threshold? → e.g. substance is only sensitizer…..
- no effect-threshold? → e.g. mutagen with no cancer data…..

# Quantitative approach & Qualitative approach

Quantitative approach:

- effect-threshold? → DNEL (Derived No Effect Level)
- no effect-threshold? → DMEL (Derived Minimal Effect Level)

Qualitative approach: *infrequently ….*

- effect-threshold? →
- no effect-threshold? →

} Hazard Banding into ‘High’, ‘Moderate’ & ‘Low’ → appropriate RMM

# Quantitative approach: effect-threshold → DNEL

If applicable:

- For every route of exposure / population
- Include systemic and local effects ()

# Quantitative approach: effect-threshold → DNEL

process steps:

**Step 1**: Derivation of typical dose descriptor(s)
(NOAEL, NOAEC, Benchmark Dose, …)

**Step 2**: Modification of the dose descriptor(s) to the correct starting point

**Step 3**: Application of Assessment factors to the correct starting point to obtain the DNEL(s)

**Step 4**: Selection of the leading DNEL/Health Effect

# Quantitative approach: effect-threshold → DNEL

process steps:

**Step 1**: Derivation of typical dose descriptor(s)
(NOAEL, NOAEC, Benchmark Dose, …)

**Step 2**: Modificatio[illegible] the dose descriptor(s) to the
correct starti[illegible]

**St**[illegible]
correct starting [illegible] the DNEL(s)

From effect assessment data of the substance

**Step 4**: Selection of the leading DNEL/Health Effect

# Quantitative approach: effect-threshold → DNEL

process steps:

**Step 1**: Derivation of typical dose descriptor(s)
(NOAEL, NOAEC, Benchmark Dose, …)

**Step 2**: Modification of the dose descriptor(s) to the correct starting point

**Step 3**: Applic

**Step**

Differences in bioavailability, route-to-route extrapolation, differences experimental and human exposure conditions, respiratory volume corrections

# **Step 3**: Application of Assessment factors to the correct starting point to obtain the DNEL(s)

| Assessment factor | Specifics | Default value |
|---|---|---|
| Interspecies | metabolic rate / bw | AS |
| | remaining difference | 2.5 |
| Intraspecies | worker | 5 |
| | consumer | 10 |
| Exposure duration | sub- to semi | 3 |
| | sub- to chronic | 6 |
| | semi to chronic | 2 |
| Route-to-route | absorption | 1 |
| Dose response | reliability | 1 |
| | L → NOAEL | 3 |
| | severity effect | 1 |

# Quantitative approach: effect-threshold → DNEL

process step:

**Step 4**: Selection of the leading DNEL/Health Effect

- If only threshold effects and DNELs identified…
  straightforward selection of the **lowest** DNEL for a given exposure pattern (population, exposure route, duration, local/systemic);

- If also non-threshold effects and DMELs identified… (i.e. mutagenic substance)
  straightforward selection of the **lowest** DMEL for a given exposure pattern (population, exposure route, duration, local/systemic);

# Quantitative approach: no effect-threshold → DMEL

Same process steps:

**Step 1**: Derivation of typical dose descriptor(s)
(T25, BMD10, BMDL10,…. )

**Step 2**: Modification of the dose descriptor(s) to the correct starting point

**Step 3**: Application of Assessment factors to the correct starting point to obtain the DNEL(s)

**Step 4**: Selection of the leading DNEL/Health Effect

# Quantitative approach: no effect-threshold → DMEL

**Step 3**: Application of Assessment factors to the correct starting point to obtain the DNEL(s)

Linearised approach

Difference as compared to DNEL approach:

- Interspecies only AS (if oral or dermal)
- Intraspecies no
- Duration of exposure yes (in step 2)
- Dose-response sometimes
- Quality database yes

+ High to low dose: (e.g.) T25 to $10^{-5}$ : 25.000 (linear)

# Quantitative approach: no effect-threshold → DMEL

**Step 3**: Application of Assessment factors to the correct starting point to obtain the DNEL(s)

Large AF approach **(~EFSA)**

Difference as compared to DNEL approach:

- Interspecies same
- Intraspecies same
- Duration of exposure yes (in step 2)
- Dose-response 10
- Quality database no

+ Nature of process: 10

# SCOEL OELs as DNEL / DMEL

*Chapter R8, Appendix 13*

If there is an established OEL for the substance, and there is no data since its establishment that is in conflict with this value this OEL may serve as DNEL or DMEL (for workers)

# Qualitative approach

## Hazard Banding:

| **class** | **property** | **RMM / PPE** |
|---|---|---|
| high | Carc 1,2<br>Mut 1,2 & 3<br>Corrosive, strong<br>Sens (skin, resp.)<br>Acute tox, very toxic | "*Very strict*" |
| moderate | Carc 3<br>Corrosive<br>Sens skin, moderate<br>Irritating, all targets<br>Acute tox, toxic | "*Strict*" |
| low | Irritating, single target | "*Appropriate*" |

# Qualitative approach

## Hazard Banding:

| class | property | RMM / PPE |
|---|---|---|
| high | Carc 1,2<br>Mut 1,2 & 3<br>Corrosive, strong<br>Sens (skin, resp.)<br>Acute tox, very toxic | "*Very strict*" |
| te | c 3<br>rrosive<br>s skin, moderate<br>ng, all targets<br>ox, toxic | "*Strict*" |
| | g, single target | "*Appropriate*" |

This approach is criticized for not clearly leading to demonstrable 'control of risk' or how far should one go with RMM etc.

# Risk Characterisation Ratio (RCR)

$$RCR = \frac{\text{Exposure estimate (of ES)}}{\text{DNEL}}$$ is determined

If RCR ≤ 1, then there is ‘control of risk’;

document and communicate in CSR & SDS+

If RCR > 1, then ‘risks are not controlled’ & assessment needs to be refined

# Note: Guidance derivation of DNEL & DMEL: all from animal data

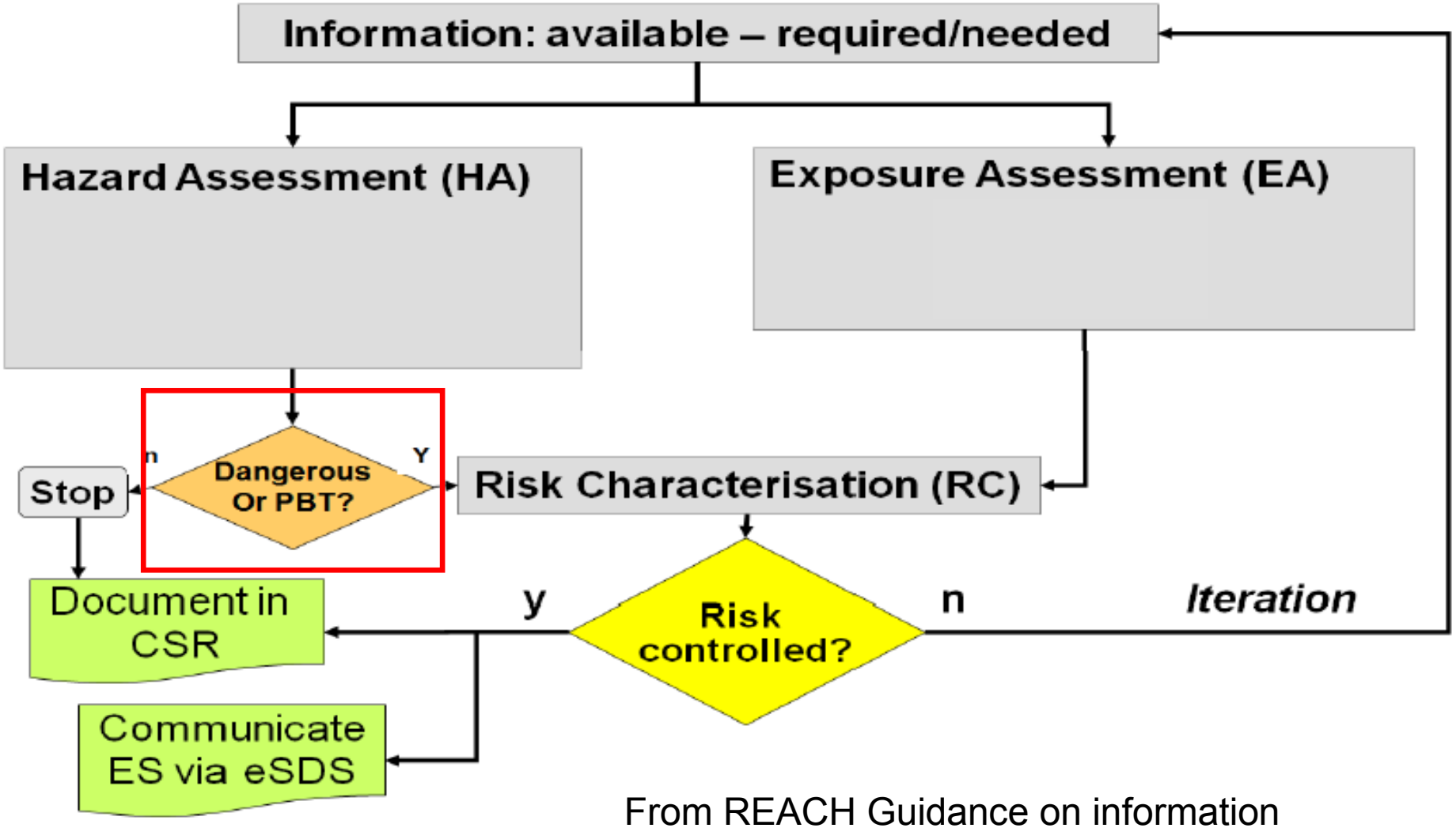
ECETOC and TNO

(with an Review Expert Panel from 6 Member State Countries)

have drafted a *concept* Guidance starting from human data including an approach how to integrate data from humans and animal, which was delivered 2008 to ECHA to finalize.

Expected to be finalized and included in the next Guidance update.

# Chemical Safety assessment scheme




From REACH Guidance on information requirements and CSA – Part D

# Dangerous?

Apply Classification & Labeling Criteria in accordance with Dir 67/548/EEC

Globally Harmonised System of Classification and Labeling of Chemicals (GHS)

Reclassification deadline December 1st 2010

Guidance per this Summer on website ECHA

# PBT or vPvB ?

## Apply assessment criteria:

| Parameter | PBT criteria | vPvB criteria |
|---|---|---|
| **P** | Half-life:<br>> 60 d in marine water, or<br>> 40 d in fresh- or estuarine water, or<br>> 180 d in marine sediment or<br>> 120 d in fresh- or est. sediment, or<br>> 120 d in soil | Half-life:<br>> 60 d in marine, fresh- or estuarine water, or<br>>180 d in marine, fresh- or estuarine sediment<br>> 180 d in soil |
| **B** | BCF > 2000 | BCF >5000 |
| **T** | Chronic NOEC < 0.01 mg/l or **C** (cat. 1, 2) **M** (cat. 1, 2) **R** (cat. 1-3) or ED-effects T-R48 or Xn-R48 | *Not applicable* |

# 4. Our experience

1. Identification leading DNEL is often quite an effort
2. Case-specifics not always covered by Guidance, so…
3. When & how 'Qualitative approach'….??
4. Some OEL values higher than DNELs……. , and less transparant…
5. Guidance development via 'learning by doing' (→ examples!)
   → more targeted approaches (DMEL< DNEL)?

How will ECHA respond, what will it accept??

# 5. Developments: CSA tool

Simple Version: 01/12/09
Extended Version: 01/04/10

Free web based tool for registrants

- Extracts relevant information from IUCLID5 (DNELs, R-phrases, physchem data..);
- Asks for exposure determinants input from User

to:

- Give a **1e tier** exposure assessment (with ECETOC TRA model, for w & c)
- Calculates RCR for all relevant scenarios and combinations of applicable routes
- If 'control of risks': - provides '+' descriptions for SDS+
  - documents conclusion in CSR
- If 'no control of risks': - indicates that User should perform **2nd tier** assessment
  - asks for result 2nd tier to conclude yes/no 'control of risks'

Thank you for your attention!