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**The REACH Tool: derived no effects levels (DNEL)**

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Dortmund, Germany, 7-8th May 2007




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**THE DNEL TOOL**

- Context and background
- Definition of DNEL
- Methodology for establishing DNELs
- Use of the DNEL in Chemical Safety Assessment

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## The basic goal of REACH

“to ensure a high level of protection of human health and the environment as well as the free circulation of substances on the internal market while enhancing competitiveness and innovation” (Art 1(1)),  
“testing on vertebrate animals for the purpose of REACH shall be undertaken only as a last resort... necessary to take measures limiting duplication of other tests (Art 25.1)

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## Information requirements under REACH Intrinsic Properties

- Phys-chem properties (e.g. solubility, vapour pressure)
- Toxicity properties (e.g. acute toxicity, irritation, mutagenicity, carcinogenicity)
- Fate properties (e.g. (bio)degradation, partition coefficients)
- Ecotoxicity properties (e.g. toxicity to aquatic or terrestrial organisms)

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**Information requirements under REACH**


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- Annex VI of REACH proposal
- Annex VII to X: staggered tonnage triggered approach
  - Standard information in Technical Dossier depends on volume:

|                 |                           |
|-----------------|---------------------------|
| ≥ 1 tonne/y:    | Annex VII (~20,000)       |
| ≥ 10 tonne/y:   | Annex VIII (~7,500 subst) |
| ≥ 100 tonne/y:  | Annex IX                  |
| ≥ 1000 tonne/y: | Annex X (~2,500)          |

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**Use of information on intrinsic properties of substances in a regulatory context**

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- Information needs to be adequate for Classification and Labelling and the Chemical Safety Assessment
- Industries' responsibility to decide and justify which information they consider necessary (starting from a minimum data set)

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**Annex XI: general rules for adaptation**

- Testing not scientifically necessary
  - Use of existing data (not GLP/ non standard tests)
  - Historical Human data
  - (Q)SAR
  - Grouping of substances and read-across approach
  - *In vitro* methods
  - Weight of evidence

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**Intelligent (Integrated) Testing Strategies**

1. Legislative text (Annex XI in particular) + **GUIDANCE** should limit use of animals and prevent box-ticking
2. A paradigm shift is needed from extensive animal testing to efficient, focussed animal testing
3. Impetus to refine current *in vivo* methods, and further develop non-test and *in vitro* test methods to be used in a regulatory context.
4. Further scientific work (2007 onwards) and regulatory implementation is needed.

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## RISK ASSESSMENT UNDER REACH

### Chemical Safety Assessment

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## Core tools for Industry under REACH


- The Chemical Safety Assessment (CSA) is the tool used to **determine**
- The Chemicals Safety Report (CSR) is the tool used to **record/document**
- The Safety Data Sheet (SDS) is the tool used to **communicate**


Conditions for use (for sufficiently protecting human health and the environment):

- **risk management measures**
- **operational conditions**

Exposure Scenario

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**When is a CSA needed ?**


Part of **Registration** requirements, when:

- $\geq 10$  tonne per year
- If the substance is dangerous, PBT or vPvB exposure assessment, including exposure scenarios and risk characterisation to be included in the CSR
- Registrant to perform a CSA for :
  - Manufacture
  - Own use
  - All identified uses
  - All life cycle stages resulting from the manufacture, own use and identified uses

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**When is a CSA needed ?**

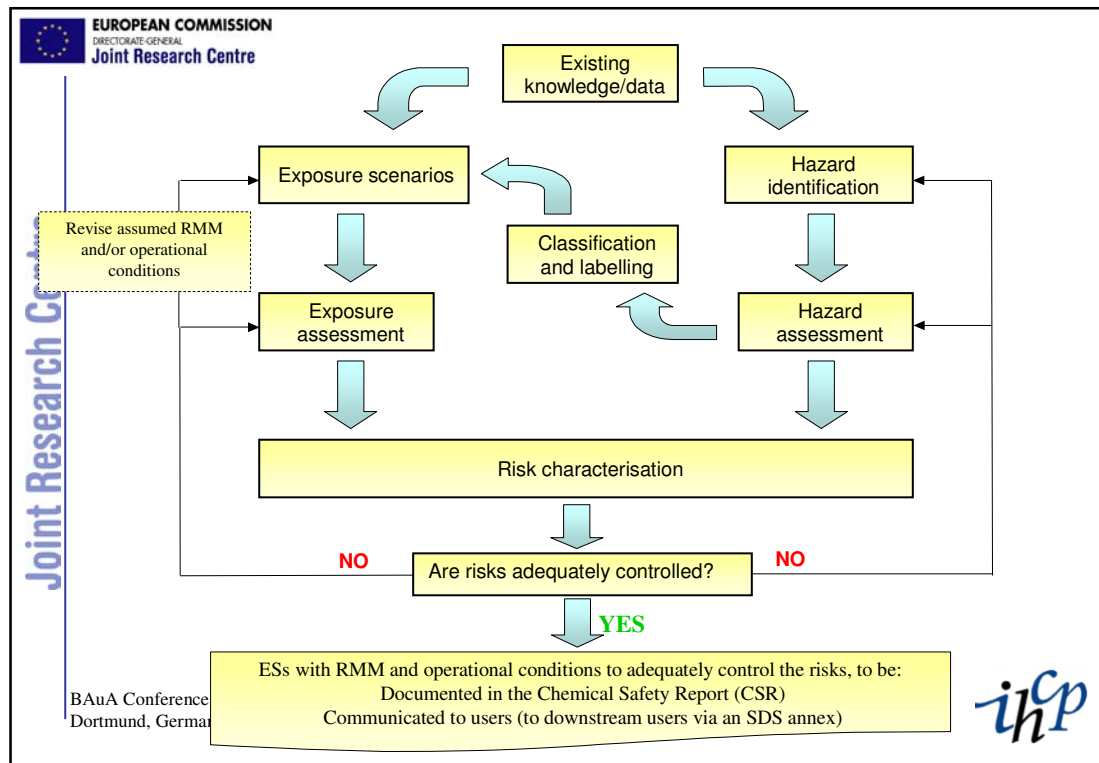
- Downstream User to perform a CSA for its uses (and all life cycle resulting from these) non identified by its supplier

Part of application for **Authorisation**

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## RIP 3.2 (CSR)

- Guidance for preparing the Chemical Safety Assessment (CSA) and Chemical Safety Report (CSR)
  - Scoping study: RIP 3.2-1 (Jan-July 2005)
  - Second phase: RIP 3.2-2: To be finalised 2007

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## RIP 3.2-2 Main Study

|                 |  |
|-----------------|--|
| <b>TASK I</b>   | Preparatory activities for the further development of REACH exposure scenarios and exposure assessment   |
| <b>TASK II</b>  | Specific input to the hazard assessment and risk characterisation of the draft TGD. Drafting groups: <ul style="list-style-type: none"><li>- PBT assessment</li><li>- <b>Human health (incl. Guidance for DNELs)</b></li></ul> |
| <b>TASK III</b> | Preparatory activity and specific input to the development of IT tools supporting REACH CSA/CSR assessments  |
| <b>TASK IV</b>  | Preparation of the draft TGD (external contract), including exemplification and further development of exposure scenario concept   |
| <b>TASK V</b>   | Development of the final TGD and integration of the overall guidance package   |

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## Human Health Drafting Group


- Chair: ECB
- Drafting group members nominated via the Commission Working Group (CWG)
  - MSs
  - Industry
  - NGO
  - “Observers” from DG ENV, DG ENTR and DG Employment
- 6 meetings so far – last meeting 27-28 Nov '06  
Written process since then. Presented to Stakeholder Expert Group in March 2007.

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**RIP 3.2-2 TASKS**

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- Establish the detailed ‘mechanisms’ for deriving a DNEL (‘translation’ of current ‘MOS’ TGD on risk characterisation into REACH ‘DNEL’ guidance)
- Establish guidance for assessment of non-threshold effects and substances of very high concern **NO**

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**Annex I CSA – Human Health Hazard Assessment**


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The hazard assessment shall comprise the following 4 steps:

- Evaluation of non-human information
- Evaluation of human information
- Classification and Labelling
- Derivation of DNELs.

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**Annex I – Human Health Hazard Assessment**

- REACH ( Annex I, 1.0.1 ) defines the **Derived No-Effect Level (DNEL)**, i.e. the level of exposure above which humans should not be exposed.
- In the risk characterisation, the exposure of each human population known to be or likely to be exposed is compared with the appropriate DNEL.
- The risk to humans can be considered to be adequately controlled if the exposure levels estimated do not exceed the appropriate DNEL.

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**Annex I – Human Health Hazard Assessment**


When establishing a DNEL the following factors shall be taken into account:-

- The uncertainty arising, among other factors, from the variability in the experimental information and from inter and intra-species variation;
- The nature and severity of the effect;
- The sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies.

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## GENERAL ISSUES

- DNELs must cover (relevant combinations of):
  - Populations (**worker** vs. consumers)
  - Exposure routes (inhalation, dermal/eye, oral)
  - Duration of exposure:
    - Long-term DNEL (or DNEL<sub>chronic</sub>)
    - Short term DNEL (or DNEL<sub>acute</sub>) expressed as 15' value (where relevant)
  - Systemic and local effects

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## How to derive a DNEL

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**How to derive a DNEL**  
*Guidance version March 2007*


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

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**Step 1: Derivation of typical dose descriptors  
(NOAEL, NOAEC, Benchmark Dose, ...)**

- Effect assessment of the substance should have generated these (coordination with RIP 3.3-2)  
*...including focus on dose-response information from alternative data sources (QSAR, in vitro, read-across, etc.)*

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

- Known differences in bioavailability (for the same route) between animals and the human situation
- Route-to-route extrapolation (e.g. extrapolation from oral to inhalation)
- Differences in experimental and human exposure conditions
- For inhalation: Corrections for respiratory volumes between animals and human situation

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

**Biomonitoring is incorporated here as an important way of circumventing all the modification steps**

Guidance how to derive a DNEL using biomonitoring is incorporated as Appendix (expertise needed!)

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

- Assessment factors are numerical values used to address differences between experimental data and the human situation taking into account the uncertainties in the extrapolation procedure and the available data set

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

- Substance-specific information should be used in the establishment of appropriate values for the various assessment factors
- Analogous substance data (acting by same mode of action)
- In the absence of substance-specific or analogous data use default assessment factors
- Defaults are a fallback position rather than the starting point but very often it is necessary to rely upon them.

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

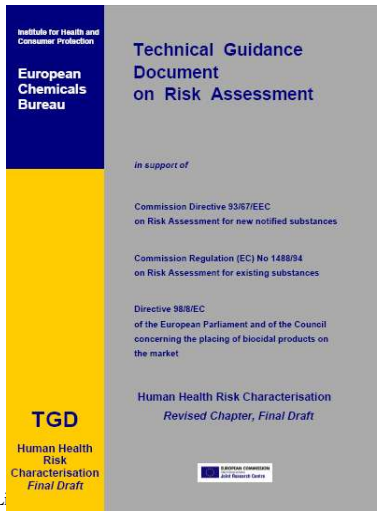
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### Step 3: Application of Assessment factors to the correct starting point to obtain the DNEL(s)



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### Step 3: Assessment factors

| Interspecies         | metabolic rate/ bw | remaining differences                           |
|----------------------|--------------------|---|
| systemic             | AS                 | 2.5   |
| local, <i>direct</i> | -                  | 1 <i>skin, eye, GI</i><br>2.5 <i>resp tract</i> |
| <i>metab</i>         | -                  | 2.5 <i>all routes</i>                           |

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### Step 3: Assessment factors

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| systemic             | AS                 | 2.5   |
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| <i>metab</i>         | -                  | 2.5 <i>all routes</i>                           |

*Substance specific information is leading*

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### Step 3: Assessment factors

| Intraspecies | General population | Worker |
|--------------|--------------------|--------|
| systemic     | 10                 | 5      |
| local        | 10                 | 5      |

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### Step 3: Assessment factors

| Intraspecies | General population | Worker |
|--------------|--------------------|--------|
| systemic     | 10                 | 5      |
| local        | 10                 | 5      |

*Worker population is less heterogeneous than the general population as young, old and sick not present. Special risk groups still to be considered.*

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### Step 3: Assessment factors

| Exposure Duration | subacute to semi | subacute to chronic | semichronic to chronic |
|-------------------|------------------|---------------------|------------------------|
| systemic          | 3                | 6                   | 2                      |
| local             | 3                | 6                   | 2                      |

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### Step 3: Assessment factors

| Exposure Duration | subacute to semi | subacute to chronic | semichronic to chronic |
|-------------------|------------------|---------------------|------------------------|
| systemic          | 3                | 6                   | 2                      |
| local             | 3                | 6                   | 2                      |

*Experimental NOAEL will decrease with increasing exposure time and other more serious adverse effects may appear*

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### Step 3: Additional assessment factors

| Final draft TGD 2005  | REACH pTGD  |
|---|---|
| Interspecies<br>Intraspecies<br>Exposure duration<br>Dose response (incl. severity)<br>Route-to-route | Interspecies<br>Intraspecies<br>Exposure duration<br>Dose response (incl. severity)<br><i>to Step 2</i><br><b>Quality of whole database</b> |

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**Step 3: Additional assessment factors**

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Default value is '1'  
Higher values in case  
of more uncertainty

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**Step 3: Application of OVERALL Assessment factor**


The overall assessment factor is obtained by simple multiplication of individual assessment factors.

$$\text{Endpoint-specific DNEL} = \frac{\text{NOAEL corr}}{\text{AF1} \times \text{AF2} \times \dots \times \text{AFn}} = \frac{\text{NOAEL corr}}{\text{Overall AF}}$$

**Care should be taken to avoid double counting several aspects when multiplying the individual factors**

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


If only threshold effects and DNELs available...

straightforward selection of the lowest DNEL for a given exposure pattern (population, exposure route, duration, local/systemic);

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**Use of DNEL in Risk Characterisation**

- In the risk characterisation, the exposure of each human population known to be or likely to be exposed is compared with the appropriate DNEL.
- The risk to humans can be considered to be adequately controlled if the exposure levels estimated do not exceed the appropriate DNEL.

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## Use of DNEL in Risk Characterisation

$$RCR = \frac{\text{Exposure}}{\text{DNEL}}$$

If Exposure < DNEL → Risk is adequately controlled  
If Exposure > DNEL → Risk is NOT adequately controlled

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## Risk Characterisation in case of exposure via various routes

- Contribution of concurrent exposure by different routes (e.g. dermal and inhalation) to internal body burden
- Alternative to internal body burden approach is “risk-adding” approach
- Only relevant for systemic toxicity and identical tox profile by each route

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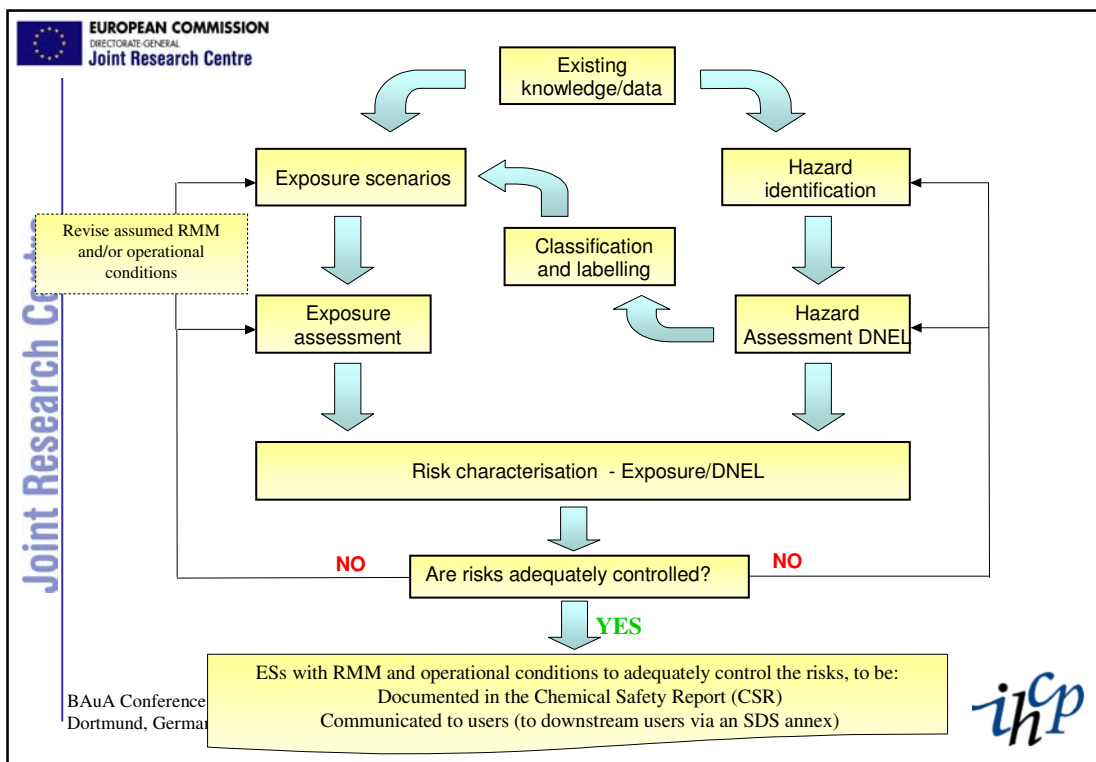
## Risk Characterisation in case of exposure via various routes


$$RCR_{\text{parallel routes}} = RCR_{\text{oral}} + RCR_{\text{dermal}} + RCR_{\text{inhalation}}$$

Adequate control if  $RCR_{\text{parallel routes}}$  is  $< 1$

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## Use of DNELs in CSA

- ***REACH requires the supplier to provide ESs with RMMs, where the RMMs are based on DNELs derived by industry's risk assessors,***
- ***The DNEL relates to the recommended RMMs, and it is these measures that will be the subject of communication to downstream users rather than the numerical values of the DNEL itself.***
- ***Since industry's risk assessors will derive the DNELs, more explicit guidance is required than for the experts in Scientific Committees such as the SCOEL or TC NES or RA Committee under REACH.***
- ***Still room for expert judgment***

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