DEFINITION

• The quantitative or semi-quantitative estimate, including attendant uncertainties, of the **probability of occurrence and severity of adverse effect(s)/event(s) in a given population under defined exposure conditions** based on hazard identification, hazard characterisation and exposure assessment” (SSC, 2003)

• **Integration of evidence**, reasoning, and conclusions collected in hazard identification, dose-response assessment, and exposure assessment and the estimation of the probability, including attendant uncertainties, of occurrence of an adverse effect if an agent is administered, taken, or absorbed by a particular organism or population. It is the last step of risk assessment (EEA from Duffus, 2001)

• A synthesis and **summary of information** about a hazard that addresses the needs and interests of decision makers and of interested and affected parties. Risk characterization is a prelude to decision making and depends on an iterative, analytic-deliberative process (US NAS, 1996).
RISK CHARACTERISATION
REACH REGULATION

• Exposure levels are compared to quantitative or qualitative hazard information.

• Risk characterisation ratios (RCRs) cover all end-points, populations, exposure routes and time scales, environmental and human.

• RCR: comparing exposure levels to predicted no-effect concentrations (PNECs) or derived no-effect levels (DNELs).

• If no-effect levels cannot be established for certain effects: qualitative assessment of the likelihood that these effects are avoided when exposure scenarios are implemented.

• For a substance having quantitative and qualitative data: control of risk is demonstrated when:
  – Hazard assessment and exposure assessment are robust and
  – RCRs for all exposures (all compartments, routes, populations and durations) related to all exposure scenarios and all end-points are below one; and
  – Qualitative risk characterisations demonstrate that the likelihood of effects are avoided.
REALITY: CONTROLLED RISK or VERTEBRATE TESTING STRATEGY
TWO COMPLEMENTARY DOCUMENTS: CSR & SDS
REACH Regulation

PROBLEM DEFINITIONS

REACH: FOUR GROUPS OF SUBSTANCES:

- CHEMICALS BELOW THE EXPOSURE THRESHOLD (1 ton/y)
  - NO ASSESSMENT
- CHEMICALS NOT FULFILLING C&L / PBT-like criteria
  - ONLY HAZARD ASSESSMENT
- DANGEROUS & PBT CHEMICALS
  - RISK CHARACTERIZATION
- CHEMICALS OF VERY HIGH CONCERN
  - RISK REDUCTION & EXPOSURE MINIMIZATION
The risk characterisation in the CSA is described as a series of steps that are discussed in more detail in subsequent sections:

- Step 0 Risk characterisation for physicochemical properties
- Step 1 Collect PNECs, DNELs or DMELs; and information on potency for endpoints where no DNEL can be derived
- Step 2 Collect measured or estimated exposure values.
- Step 3 Compare matching exposure and PNECs, DNELs or DMELs.
- Step 4 If no PNECs, DNELs or DMELs could be derived: qualitative risk characterisation for that compartment/effect
- Step 5 Calculate the sum of risk characterisation ratios of combined exposure, e.g. for each human population and for the general population (combined worker and consumer exposure).
- Step 6 Decide on possible iterations of the CSA, taking uncertainties in the assessment into account: The risk characterisation should demonstrate control of risks
- Step 7 Finalise the risk characterisation.
RISK CHARACTERISATION FOR PHYSICOCHEMICAL PROPERTIES

- as a minimum for explosivity, flammability or oxidising potential
- an evaluation of the **likelihood (risk) that an adverse effect will be caused under the reasonably foreseeable conditions of use** in the workplace or by consumers.

The assessment of the potential effects arising from the capacity of hazardous chemical agents to cause accidents, in particular fires, explosions or other hazardous chemical reactions covers:
  - hazards resulting from the physicochemical nature of the chemical agents,
  - risk factors identified in their storage, transport and use, and
  - the estimated severity in the event of occurrence.

Output of risk characterisation
- analysis of the use processes and procedures
- measures taken to prevent accidental release or negative effects on human health in case of an event
  - a hazard ranking of the substance (e.g. using the R-phrases) and
  - a possible frequency and assumed severity of an accident.
- A rational judgement describing the underlying assumptions and the conclusions

Conclusions
- the substance is of no immediate concern or
- recommendations for risk reduction are necessary.
RISK CHARACTERISATION FOR HUMAN HEALTH

- **DNEL** value below which exposures should be controlled – underlying assumption that such an exposure level would be below a **no-effect-level**, 

- **DMEL** expresses an exposure level corresponding to a low, possibly theoretical, risk. A DMEL is a **risk-related reference** value, which can be established via two approaches:
  - 'Large Assessment Factor' (EFSA) approach value expresses an exposure level corresponding to a low, possibly theoretical, risk, which could be seen as a tolerable risk. 
  - 'Linearised' approach, different DMEL values can be calculated, representing different lifetime cancer risks, e.g., a risk for cancer in 1 per 100,000 exposed (10^-5) or 1,000,000 exposed individuals (10^-6). Based on experience: cancer risk levels of 10^-5 and 10^-6 could be seen as indicative tolerable risks levels for workers and the general population, respectively.
HUMAN HEALTH

population exposed:
• workers
• general population
  – consumers
  – humans exposed via the environment

exposure route:
• inhalation
• dermal
• oral
If Exposure < DNEL → Risk is adequately controlled
If Exposure > DNEL → Risk is NOT controlled

If Exposure < DMEL → Exposure is controlled to a risk level of low concern
If Exposure > DMEL → Risk is NOT controlled.

RCR (for simultaneous exposure via three routes) = RCR (oral) + RCR (dermal) + RCR (inhalation)

Performed for chronic effects, and if relevant, separately for acute effects. Separate calculations for workers and the general population

The overall health risk to humans can only be considered controlled if Total RCR for the specified routes in parallel < 1

If the risk characterisation shows that risk is not controlled an iteration of the CSA is needed. This can be done by generating more refined exposure and/or hazard information or by introducing new RMMs
qualitative risk characterisation

• to assess: "the likelihood that effects are avoided when implementing the exposure scenario...“

• the principle: the higher the hazard, the stricter the controls need to be
**THE SIMPLIFIED APPROACH**

Table E.3-1 Hazard categories of systemic and local effects, suggestions for general risk management measures and operational conditions (RMMs/OCs) and PPE to be considered when developing exposure scenarios #

*Note that these categories only apply when no DNEL or DMEL can be set.*

<table>
<thead>
<tr>
<th>Type of effect</th>
<th>R phrase</th>
<th>Exposure route</th>
<th>Risk Management Measures and Operational Conditions</th>
<th>PPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinogens Cat. 1 and 2 May cause cancer</td>
<td>R45</td>
<td>respiratory, oral, skin respiratory</td>
<td>- Any measure to eliminate exposure should be considered; - Very high level of containment required, except for short term exposures e.g. taking samples; - Design closed system to allow for easy maintenance;</td>
<td>Substance/task appropriate respirator;</td>
</tr>
<tr>
<td>May cause cancer by inhalation</td>
<td>R49</td>
<td>respiratory</td>
<td></td>
<td>Substance/task appropriate gloves;</td>
</tr>
<tr>
<td>Mutagens Cat. 1 and 2 May cause heritable genetic damage</td>
<td>R46</td>
<td>respiratory, oral, skin</td>
<td>- If possible keep equipment under negative pressure; - Control staff entry to work area; - Ensure all equipment well maintained; - Permit to work for maintenance work;</td>
<td>Full skin coverage with appropriate barrier material;</td>
</tr>
<tr>
<td>Mutagens cat 3* Possible risk of irreversible effects</td>
<td>R68</td>
<td>respiratory, skin, oral</td>
<td>- Regular cleaning of equipment and work area; - Management/supervision in place to check that the RMMs in place are being used correctly and OCs followed;</td>
<td>Chemical goggles.</td>
</tr>
<tr>
<td>Strong corrosive Causes severe burns</td>
<td>R35</td>
<td>respiratory, skin, oral</td>
<td></td>
<td>Face shield;</td>
</tr>
<tr>
<td>Acute toxicity</td>
<td></td>
<td></td>
<td>- Training for staff on good practice; - Procedures and training for emergency decontamination and</td>
<td>Substance/task appropriate respirator;</td>
</tr>
<tr>
<td>Very toxic</td>
<td>R26</td>
<td>respiratory</td>
<td></td>
<td>Substance/task appropriate gloves;</td>
</tr>
<tr>
<td>Very toxic</td>
<td>R27</td>
<td>skin</td>
<td></td>
<td>Full skin coverage with appropriate barrier material;</td>
</tr>
<tr>
<td>Very toxic</td>
<td>R28</td>
<td>oral</td>
<td></td>
<td>Chemical goggles.</td>
</tr>
</tbody>
</table>
RISK CHARACTERISATION FOR THE ENVIRONMENT

Inland environmental protection targets:
• aquatic ecosystem;
• terrestrial ecosystem;
• atmosphere;
• predators (fish- and worm-eating);
• micro-organisms in sewage treatment plants

Marine environmental protection targets:
• aquatic ecosystem;
• predators and top predators.

The spatial scales:
• The regional scale, accounting for overall emissions into a region.
• The local scale, accounting for local emission and the regional background concentration which is added to this
CONCEPTUAL APPROACH

The PNEC not always corresponds to the predicted ecotoxicological threshold. Additional uncertainty factors can be added to the RCR calculation.

\[
R_{CR\text{ local}}^{soil} = \frac{PEC_{\text{local}}^{soil}}{PNEC_{\text{soil}}}
\]

If \( EP_{terr} = \text{yes and log } K_{ow} > 5 \) then

\[
R_{CR\text{ local}}^{soil} = \frac{PEC_{\text{local}}^{soil}}{PNEC_{\text{soil}}} \cdot 10
\]

Uptake via ingestion of soil
QUALITATIVE RISK ASSESSMENT

- PBT and vPvB substances
- PNECwater cannot be calculated.
- No effects observed in short-term tests: not necessarily mean that a substance has no long-term toxicity
- Low water solubility and/or high hydrophobicity: non-polar organic substances with a potential to bioaccumulate
- Long-term toxicity tests should be considered for:
  - substances with log Kow > 3 (or BCF > 100) and a PEClocal or PECregional > 1/100th of the water solubility
  - If logKOW is not a good indicator of bioconcentration, case-by-case assessment.
  - For ionised substances or surfactants the determination of a trigger value on the basis of other physicochemical properties, e.g. $Kd$
NEW NEEDS & CHALLENGES

• COST EFFECTIVE RISK ASSESSMENT
  – ALTERNATIVE APPROACH FOR LOW RISK SUBSTANCES

• LIMITED GUIDANCE FOR HIGHER TIER RISK ASSESSMENT
  – BUT INDUSTRY MUST DEMONSTRATE SAFE USE

• RESPONSIBILITY: SUBSTANCE MARKETED WHEN DOSSIER FULFILLED ... & TAXES PAID
  – DOSSIERS OF SOME SUBSTANCES WILL BE DEEPLY EVALUATED BY THE CAs
SOLUTION: GOOD SCIENCE FOR ITS

• SCREENING ASSESSMENT
• STANDARD ASSESSMENT
  – UNCERTAINTY ANALYSIS
• HIGHER TIER ASSESSMENT
  – INCLUDING PBT & EQUIVALENT CONCERN

FOCUS ON KEY QUESTION: IS RISK CONTROLLED?
SCREENING ASSESSMENT

• C&L UNSUITABLE
  – ONLY AQUATIC HAZARDS
    • ACUTE TOX THRESHOLDS IN THE EU
    • CHRONIC THRESHOLDS IN THE GHS
  – GAPS FOR SEDIMENT, TERRESTRIAL (SOIL & SECONDARY POISONING), WWTP,…

• SCREENING & HAZARD IDENTIFICATION TOOLS
  – MOSTLY USEFUL FOR NON-DANGEROUS SUBSTANCES
  – IF A SUBSTANCES IS CLASSIFIED → ALL HAZARD TYPES SHOULD BE COVERED
    • QUALITATIVE TOOLS: MUST PROVIDE A LIKELIHOOD ESTIMATION OR AT LEAST DEMONSTRATE THAT RISK IS COVERED BY MOST SENSITIVE ENDPOINTS
STANDARD ASSESSMENT: LESSONS LEARNED
Technical & Scientific EU Committees

• Following the guidance and default values is not enough:
  – E.g., justify the applicability of AFs and equilibrium partitioning to your substance

• Uncertainty in values ≠ Uncertainty in conclusions
  – If different alternatives gives same conclusions… include all in a comparative/supporting assessment

• Consider the natural variability in the EU environmental conditions
  – A single PNEC value may not be adequate due to: e.g. bioavailability, background, or ecology
EXAMPLES
EQUILIBRIUM PARTITIONING UNSUITABLE

• OTHER EXPOSURE ROUTES THAN PORE-WATER
  – B&W GUIDANCE FOR Kow (4.9→1; 5.1→10) ingestion
  – OTHER FACTORS:
    • DISAGREEMENT BETWEEN Kow & Koc
    • CONTACT EXPOSURE
    • BIOAVAILABILITY

• KEY TAXONOMIC GROUPS NOT PROPERLY COVERED
  – Microbial populations; invertebrates (other than crustaceans/arthropods); vascular plants
  – Use EP with caution if large differences in toxicity to aquatic taxonomic groups is observed
ALTERNATIVES
STANDARD ASSESSMENT

- ESTIMATE UNCERTAINTY USING THE MOE (MOS) METHOD
  - MOE(MOS) = TOXICITY ENDPOINT/EXPOSURE
  - Daphnids experimental/Daphnids QSAR $\rightarrow$ uncertainty in fish QSAR
  - Also applicable to cross reading within a family
    - S4 must be 1000 times more toxic than S1; S2; S3; S5 and S6 for representing a significant risk

- Alternative for quantifying uncertainty in qualitative/semi-quantitative tools $\rightarrow$ probabilistic estimation of the likelihood
  - Likelihood for S4 representing a significant risk is < 5%
PROBABILISTIC IMPLEMENTATION
EXPOSURE ASSESSMENT

- SINGLE VALUE → e.g. MEAN
- A RANGE
- STATISTICAL ASSESSMENT
- DISTRIBUTION
HIGHER TIER ASSESSMENT
PBT SUBSTANCES

• CONCEPT: P + B
  – Chemical accumulates in the body as a consequence of long-term exposure
  – Potential for biomagnification

• CONSEQUENCES
  – Focus on internal dose (body burden) assessment following oral exposures
    • Uncertainty from external dose/concentrations assays
    • Data from waterborne exposure?
HIGHER TIER ASSESSMENT
PBT SUBSTANCES: DMEL-like approach)

IDEAL SITUATION: THREE STEPS
1. Body burdens are measured in the tox assays
2. Critical body or tissue burdens can be identified
3. Burdens are compared with long-term exposure internal doses

ALTERNATIVE
• Internal body burdens for key endpoints are estimated from tox raw data + toxicokinetics
• Uncertainty in burden/effect relationship: comparison of similar levels of effects at different exposure regime
• Comparisons are based on MOE (MOs)
• Expected timing for reaching key endpoints/taxa are used for prioritisation (potential risk in 2 years vs. potential risk in 1000 years)
CONCLUSIONS

• REACH presents a new problem formulation
  – Risk characterisation only for dangerous substances
  – Only the final outcome (acceptable risk) is presented: CSR and SDS
• Additional guidance is required at all levels: screening, standard, higher tier
• ITS must check that outcome will be sufficient for risk characterisation: including the use mammalian data in environmental risk assessment
  – Quantitative risk characterisation if feasible
  – Clear indication that risk is ≤ other risks
• Alternatives must offer a likelihood estimation → Probabilistic RA
• Good science and transparent reporting is essential

REMEMBER: It is excellent if you can convince the scientific community on the suitability of your ITS approach...
... but at the end of day, you must convince ECHA secretariat, RAC, and regulators