CHEMICALS RISK ASSESSMENT UNDER REACH

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Introduction

On June 1st 2007 **REACH (Registration, Evaluation and Authorization of Chemicals)** entered into force. REACH requires producers, importers and users of chemical substances to register their uses in a **volume-triggered system**. It demands the submission of **chemical assessment reports** containing information on the hazards, exposures and risks associated with the uses of chemical substances for review by the competent authorities and government-appointed expert committee. Chemicals of very high concern e.g., carcinogens, mutagens or substances toxic to reproduction will trigger a complex authorisation process.

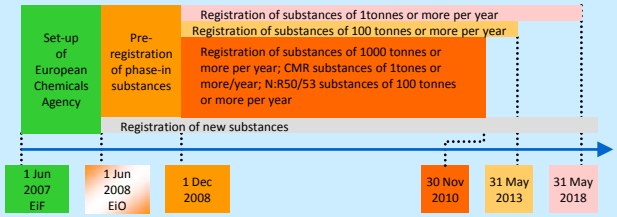
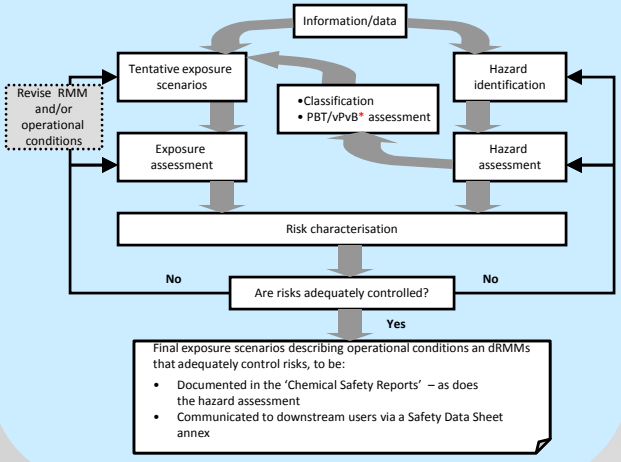


Figure 1: REACH timelines

This paper characterizes the REACH chemicals risk assessment process as currently considered in the Technical Guidance Documents developed in the ongoing **REACH Implementation Program (RIP).** Focus will be giving to the iterative development of the chemical safety assessment including the derivation of no or minimal effect levels (DN(M)ELs) and the development of exposure scenarios (ES).

Principle of REACH Chemical Safety Assessment (CSA)

- Substances placed on the market should not adversely affect human health and the environment
- Identification of **Risk Management Measures (RMMs)** is an integrated part of the safety assessment concept
- Iterative process includes assessment of all relevant information on hazards, conditions of use and adequate control of risks

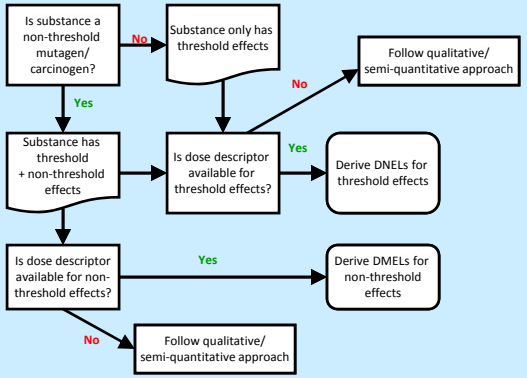


* PBT: Persistant, bioaccumulative, toxic; vPvB: very persistent very bioaccumulative

Overall Steps to Chemical Safety Assessment

1) Human health hazard assessment – derivation of D(N)MEL and C&L
2) Human health hazard of physico-chemical properties
3) Environmental hazard assessment – derivation of PNEC
4) PBT and vPvB assessment
5) Exposure assessment – generation of exposure scenarios or categories
6) Risk characterization

Human Health Hazard Assessment: Derivation of No or Minimal Effect Levels (DNEL; DMEL)



- **Gather typical dose descriptor** (N(L)OAEL, BMD, BMD(L)10, T25, LD50, LC50, OR, RR…)
- **Decide on mode of action** (threshold or non-threshold)
- **Derive DNEL or DMEL** considering REACH data requirements; uncertainty/variability; populations; routes and duration of exposure; systemic and local effects
  - ***DNEL for threshold endpoint***
  - *Selection and modification of relevant dose descriptor; application of assessment factors*
  - ***DMEL for non-threshold endpoint*** (if possible)
  - *Selection and modification of relevant dose descriptor; high/low dose extrapolation; application of assessment factors*
    - Non-threshold carcinogen with adequate animal cancer data: linearised approach; large assessment factor approach; alternatives to the conventional extrapolation procedures (e.g., PBPK modelling)
    - Non-threshold carcinogen or mutagen without adequate substance-specific cancer data: read across; use of subchronic studies (application of large assessment factors); threshold of toxicological concern (TTC) concept
  - ***Qualitative/semi-quantitative approach*** when no dose descriptor is available
    - Very strict risk management measures for high acute toxicity
    - Additional assessment factors to account for inherent deficiencies
    - Consideration of pH and reserve acidity/alkalinity; in vitro data; human experience; QSARs and/or read across information
- **Select the leading health effect and corresponding DNEL or DMEL** used for risk characterisation and the derivation of risk characterisation ratios (RCR)
  - Selection of ***lowest endpoint-specific DN(M)ELs***
  - Assessments covering simultaneous exposure via several routes of exposure will require ***DNELs for each exposure route*** (e.g., $DNEL_{acute\text{-}inhal}$, $DNEL_{long\text{-}term\text{-}inhal}$)
  - General ***dust limits*** for inhalable airborne fraction apply if these are lower than respective DNEL
  - Dust limits cannot be used as surrogate DNELs
  - For hazards for which no endpoint-specific DN(M)EL cannot be derived, the following ***hierarchical order*** applies
    - Non-threshold mutagens or carcinogens (Category 1 & 2)
    - Non-threshold mutagens or carcinogens (Category 3)
    - Effects of 'equivalent concern'
    - Respiratory sensitizer

Exposure assessment and risk characterisation

The registrant of a substance produced/imported in quantities larger than 10 tonnes per year must develop exposure scenarios (ES) and show in the subsequent exposure assessment and risk characterisation that risks can be adequately controlled for all identified uses throughout the chemical life cycle.

The ES describes the information on emissions and related exposures that have been collected and evaluated and the appropriate operational conditions and risk management measures that need to be applied to achieve an acceptable level to human health (worker, consumer) and environment compartments (aquatic, terrestrial, atmospheric). The development of ES involves several steps:

Step 1: Identification of uses for which ES shall be developed
Step 2: Description of manufacture or use in a standard structure
Step 3: Listing of operational conditions typically applied
Step 4: Listing of risk management measures typically applied
Step 5: Development of a 'tentative' ES
Step 6: Assessment of exposures and risks
Step 7: Iteration of the CSA and derive the final ES
Step 8: Documentation of the ES in the CSR and integration into the eSDS

Under REACH, the human health risk characterisation principally consists of a comparison of the exposure of each human population known to be or likely to be exposed with the appropriate DN(M)EL. This exposure/DN(M)EL comparison results in a risk characterisation ratio (RCR):

RCR = Exposure/DN(M)EL

If exposure < DN(M)EL → ***Risk is adequately controlled***

If, based on tentative ES, exposure > DN(M)EL and hence ***risks are not adequately controlled***, the CSA should be iterated until risks are show to be adequately controlled. The following ES refinement options are available:

Hazard information
- Collecting of additional information allowing refinement of assessment factors used for DN(M)ELs
- Improve toxicology data set through additional testing in line with concept of intelligent testing strategies

Operational/use conditions
- Substance use: Refine/change of use; tightening conditions of use; identify unsupportable uses
- Substance handling: refine/change of process, operational conditions, duration or frequency of activities

Exposure information
- Adapting or improving parameters, refining emission factors or substance properties
- Improve model definition or complexity; use of higher tier models allowing for realistic exposure estimations; replace model predictors by data

Risk management
- Use of more efficient Risk Management Measures (RMMs)
- Additional RMMs
- Stricter RMMs

Summary

- The REACH risk assessment follows an iterative process until it can be shown that risks are adequately controlled;
- The following factors shall be taken into account when establishing the DN(M)EL: uncertainty arising from the variability in the experimental data and from intra- and inter-species variation; nature and severity of effects; sensitivity of the human (sub-) population to which information on exposure applies
- A high level of expertise and practical understanding is needed to be able to follow the proposed procedure