Human health case studies Examples of active substance and biocidal product evaluations

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Risk assessment and mitigation measures

Risk characterisation (BPR definition)

"***The estimation of the incidence and severity of the adverse effects*** *likely* ***to occur*** *in a human population, animals or environmental compartments* ***due to actual or predicted exposure*** *to any active substance or substance of concern in a biocidal product. This may include "risk estimation", i.e. the quantification of that likelihood".*

The risk characterization is an assessment of the risk associated with the exposure to the active substance through the use of the biocidal products.

Guidance on the BPR: Volume III Assessment & Evaluation (Parts B+C)
Version 2.1 February 2017

Hazard characterization

Identification of critical effects

Threshold Effects

Non-threshold Effects

Dose-response assessment: Identification of most relevant dose descriptor for systemic threshold effects (e.g. NO Adverse Effect Level - NOAEL)

Qualitative or semi-quantitative assessment

Identification of most relevant dose descriptor for local effects (e.g. NO Adverse Effecr Concentration - NOAEC; qualitative/semi-quantitative approach)

Modification of relevant dose descriptor for systemic effects (Derm. Absorp.; AFs; AELs, AECs, ADI, ARfD)

Toxicological effects with a threshold mode of action

When the critical toxicological effects are **threshold-based** and exposure data are reliable, **a quantitative risk assessment** should be carried out for **each exposed population**, **product-type**, and **method of application** relevant for the respective biocidal products

a **COMPARISON** of

the **critical toxicity endpoints** (and resulting reference values, **AELs**)

WITH

the **exposure levels** (for the proposed pattern(s) of use)

Acceptable Exposure Levels

Where a critical effect is **threshold-based** and exposure data are reliable, quantitative risk assessment should be carried out for each exposed population, product-type, and method of application relevant for the respective biocidal products as indicated by the exposure assessment. The risk characterisation method should follow the general principles of both the Margin Of Exposure (MOE) concept and Acceptable Exposure Levels (AELs).

The derivation of acute, medium-term and long-term AELs as general health-based reference values are proposed.

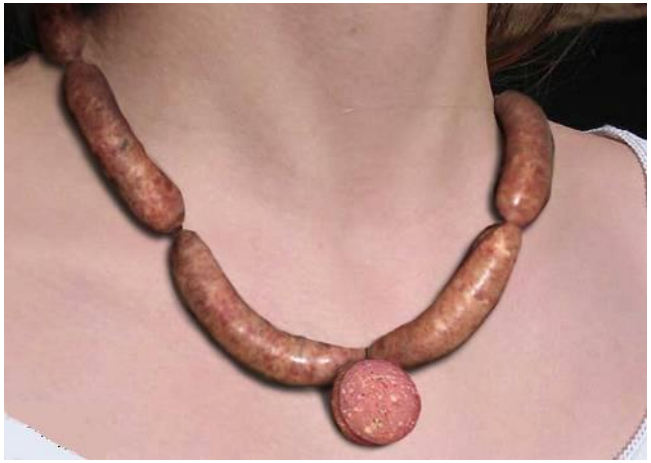
AEL_{acute} $AEL_{sub\text{-}chronic}$ $AEL_{chronic}$

RCR → **Threshold effects**

$$\frac{\text{Exposure}}{\text{AEL}} < 1$$

If the active substance can enter the food chain, an Acceptable Daily Intake (**ADI**) and, if necessary, an Acute Reference Dose (**ARfD**) should be derived.

For approval of the active substance, the **combined exposures to the active substance from all representative uses** should be **considered**.



Relationship between duration of human exposure and the studies required for hazard identification and establishment of relevant NOAELs for AEL/MOE derivation

Estimated duration of human exposure	Basic toxicity studies	Relevant NOAELs for AEL/MOE derivation
≤ 24 h	**Single dose studies designed to determine NOAEL* or repeated dose studies demonstrating relevant acute effects** e.g. - acute neurotoxicity - 28-d/90-d repeated-dose studies, acute effects - developmental toxicity, acute effects * Data from LD_{50} studies can be considered supportive if appropriate acute effects were investigated	**Toxic effects relevant for acute exposure**
>24h – 3 (max. 6) months	**Repeated-dose studies designed to determine NOAEL** e.g. - 28-d/90-d repeated-dose studies - 90-d neurotoxicity - 12-m dog, depending on nature of effects - developmental toxicity - 2-generation study	**Toxic effects relevant for medium-term exposure**
> (3-) 6 months	**Chronic studies or repeated dose studies designed to determine NOAEL** and **demonstrating relevant chronic effects** e.g. - 18-m/24 m chronic/carcinogenicity - 2-generation study, chronic effects - developmental toxicity - 12-m dog , depending on nature of effects	**Toxic effects relevant for long-term exposure**

Selection of the Assessment Factors (AFs) for the AEL derivation

Risk characterisation requires the choice of an AFs which accounts for extrapolation from animal toxicity data to the exposed human population.

The **setting of the overall AF is a critical step**, which considers **intra-species variation** and **inter-species variation**.

The basis for this approach is a **10-fold factor for inter-species variation** and a **10-fold factor for intra-species variation**. Each variability is governed by toxicokinetic as well as toxicodynamics factors.

Inter-species variation addresses the differences in sensitivity between experimental animals and humans

Intra-species variation addresses the differences in sensitivity among different human populations as a result of genetic and/or environmental influences (biological factors such as genetic polymorphism affecting e.g. toxicokinetics/metabolism, age, gender, health status and nutritional status)

In addition to uncertainties in inter-species differences and intra-species variability, **additional AFs for the following elements should be considered**:

1. the nature and **severity of the effect**

2. the **human (sub-)population exposed**

3. **deviations between** the **exposure** in the **study** providing the **NOAEL** and the estimated human exposure as regards duration, frequency, or pattern (e.g. a sub-chronic study to a chronic study)

4. **extrapolation** from **LOAEL** to **NOAEL**

5. the **slope** of the **dose-response curve**

6. the **overall quality of the toxicity data** package

A **tiered approach** for human health risk characterisation of biocides has to be followed.

In the **first tier** systemic AELs and MOEs should be derived for acute, medium-term, and long-term exposure via all routes applicable based on the systemic toxicity of the active substance using Assessment Factors (AFs).

If a risk is identified for any of the scenarios in the first tier a refinement of the exposure assessment and/or the assessment factors might be performed in the **second tier** giving special attention to route-specific contributions and protection measures.

Risk Management Measures

Personal protective equipment and control measures

In carrying out an exposure assessment, **the assessor should ensure that exposure to a biocide is prevented or controlled**.

Prevent

Exposure can be **prevented** by a variety of means including:

Therefore, exposure must be controlled

…to reduce emission or release.

For biocides, with several application methods available, preventing exposure is not, in many cases, reasonably practicable.

Control

There are several control options that assessor can apply to eliminate exposure.

According to the *Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work* (art.6.2) the options to be considered are…

· **structure related**;
· **engineering**;
· **technical** (especially for consumers);
· **administrative**; and
· **personal**.

Overview on RMMs and safety instructions

Product-Substance Related:

1 Limiting concentration of hazardous or non-hazardous ingredient
2 Change of physical state (e.g. powder -> pellet)
3 User friendly packaging (reducing handling)
4 Info / Guidance / Manual other than label and Safety Data Sheet

Limitation of Marketing & Use:

5 Marketing and Use - General
6 Product safety / advice

Process / Control Change:

7 Process Control / Change
8 Automation
9 Containment of operator
10 Cleaning of process equipment
11 Spill Containment Measures
12 Reduction and cleaning of air emissions
13 Reduction and cleaning of waste water
14 Reduction of waste, disposal of waste

Ventilation Control:

15 Local Exhaust Ventilation - (partial) enclosure
16 Laminar Flow Booths & Laminar Flow Benches
17 Local Exhaust Ventilation - captor hoods
18 Local Exhaust Ventilation - receptor hoods
19 Local Exhaust Ventilation – specialised applications

General Dilution Ventilation:

20 Dilution Ventilation

Organizational:

21 Management Systems
22 Operating Practice
23 Competence and training
24 Supervision
25 Monitoring
26 Health Surveillance

Good Hygiene Practices & Housekeeping:

27 Good Hygiene Practices & Housekeeping

Personal Protective Equipment:

28 Body protection
29 Hand protection
30 Respiratory protection
31 Face / Eye protection

First Aid Measures

32 First Aid Measures

Thank you for the attention!