Dermal Occupational Exposure Limits

Their use in risk assessment
Contents

1. Risk assessment for dermal exposure
2. Dermal Occupational Exposure Limit (DOEL)
3. REACH
4. SCOEL
5. ECETOC
6. Summary
Risk assessment for dermal exposure

Focus on systemic toxicity following dermal exposure

- Dermal exposure is an important exposure route
- Complex process of contact between relevant substance and the skin over a relevant period of time
- Uptake dependent on many factors

- How to regulate risks from dermal exposure?
  - Quantitative
  - Qualitative
Risk assessment for dermal exposure

- Dermal absorption
  - Penetration into the skin
  - Permeation through the skin (or skin layer)
  - Resorption into tissues/blood vessels

- Flux (permeation rate): amount of substance passing through the skin per time period per surface area
  - Surrogate: log $K_{ow}$
  - Stratum corneum: rate-determining layer

- Absorption fraction
Risk assessment for dermal exposure

Absorption determining factors

- Permeation rate
- Substance characteristics
  - Molecular weight (<500)
  - Log $K_{ow}$ (-1 < log $K_{ow}$ < 4)
- Skin surface area
- Skin integrity
- Duration of exposure (‘sink function’)
- Formulation (vehiculum)
- Exposure conditions
  - e.g., temperature humidity, occlusion
Health Council of the Netherlands

Health Council of the Netherlands (Nr 2001/28)

Quantitative

● Dermal Occupational Exposure Limit
● Biological Limit Value
  – Biological Exposure Index
  – Biologische Grenzwert (BGW; previous BAT)

Qualitative

● Skin notation
  – General warning
  – Relative to inhalation exposure
Dermal Occupational Exposure Limit

Proposal for the assessment of quantitative dermal exposure limits in occupational environments: part 1. Development of a concept to derive a quantitative dermal occupational exposure limit

P M J Bos, D H Brouwer, H Stevenson, P J Boogaard, W L A M de Kort, J J van Hemmen

Dermal Occupational Exposure Limit

DOELs may be set at:

- The internal level (Biological Limit Value)
- The level on the skin surface (mg deposited on the skin)
- The level in the occupational environment (amount present on surfaces of working equipment or pesticide residues)
Dermal Occupational Exposure Limit

- DOEL based on dermal toxicity studies
  - Rarely available
  - Conditions of dermal exposure vs. occupational exposure
    - Formulation, occlusion, daily duration

- DOEL related to a maximal internal dose derived from data on other exposure routes
  - Absorption percentage may increase with decreasing dermal area dose (Da (mg/cm²)):
    - “Infinite dose”
    - Relatively short exposure period

*Absorption data expressed as a percentage of applied dose absorbed per unit of time are relevant only to a particular dose and a particular time (ECETOC, 1993)*
**Dermal Occupational Exposure Limit**

Maximal amount to be taken up through the skin without health effects (maximal accepted internal dose: HBR-OEL\textsubscript{in}).

The internal dose taken up through the skin:

\[ J_{\text{max;occ}} \times t \times A \]

- \( J_{\text{max;occ}} \): maximal flux derived under occupational conditions (mg/(cm\(^2\) x hour))
- \( t \): exposure duration (hour/day)
- \( A \): exposed skin surface area (cm\(^2\))
Dermal Occupational Exposure Limit

\[ J_{\text{max};\text{occ}} \times t \times A < \text{HBR-OEL}_{\text{in}} \]

or

\[ A < \text{HBR-OEL}_{\text{int}} / (J_{\text{max};\text{occ}} \times t) \]

For a given time (8 hours/day), internal dose only dependent on \( A \). Thus a maximal allowable exposed skin surface area (\( A_{\text{max}} \)) can be derived.
If based on absorption (unknown flux):

\( Da \times A \) derived from HBR-OEL_{int} based on absorption percentage.

- \( Da \) derived depending on \( A \)
- Absorption percentage dependent on \( Da \)
DOEL: example cyclophosphamide

Toxicity: carcinogenic
● Rat study: daily internal dose of 0.75 mg (4 x 10^{-3} (40 year-worklife)

Human data on absorption
● iv: urinary excretion: ca. 13%
● Dermal (100 µg/cm^{-2}; occlusion): urinary excretion: 2-3%

DOEL derivation
● 2000 cm^{-2}, internal dose: 0.75 mg \rightarrow Da = 1 \mu g/cm^{-2}
● Adjusted absorption: 100%
● DOEL (Da x A) equals 0.75 mg/day
  \quad A=2000 \text{ cm}^{-2} \rightarrow Da = 0.4 \mu g/cm^{-2}
Dermal Occupational Exposure Limit

Tiered approach for estimating dermal absorption

1. Default value of 100%

2. 10% if MW>500 or (log $K_{ow} < -1$ or log $K_{ow} > 4$)
REACH


Dermal DNELs

- systemic effects (mg/kg bw/day)
- local effects (mg/cm²)
REACH
Committee for Risk Assessment (RAC)
● Opinion on 1-methyl-2-pyrrolidone (NMP)

Worker dermal DNEL
● 28-day dermal study in rabbits
  – NOAEL: 826 mg/kg/day
  – Factor of 4 for allometric scaling
  – Factor of 2.5 for interspecies differences in toxicodynamics
  – Factor of 5 (workers) for intraspecies differences
  – Dermal DNEL: 4.8 mg/kg/day

If no dermal study, correction for differences in absorption (interspecies and route specific)
SCOEL

SCOEL (key documentation version 7; June 2013)

Amount absorbed depends on:
- Amount of substance in direct contact with skin
- Physico-chemical properties
- Penetration enhancing substances
- Duration of exposure
- Physical form of the substance
SCOEL

- Substantial contribution to total body burden
  - Relative to uptake from inhalation exposure (10%)
- Direct measurement of percutaneous absorption
- Comparison of dermal and iv or ip LD50 values
- Human studies
  - Case reports
  - Substantial variation in biological monitoring in a group with similar inhalation exposure
  - Phenomena such as subjective taste after ‘skin only’ exposure
- Information on physico-chemical properties

- In case of substantial dermal uptake BLV may be preferred over OEL
- SCOEL provides guidance for derivation of BLV or BGV
ECETOC


- *Evaluation of systemic health effects following dermal exposure to chemicals*

Stepwise approach, three linked decision trees:
1. Derivation of a health-based reference value
2. Initial risk assessment
3. Refined risk assessment
1. Derivation of a health-based reference value
   - Existing assessments or derivation of an appropriate value
   - Preferably a dermal HBRV, otherwise derived via RtR
   - Quantitative comparison external level (skin exposure) or body burden
   - Reference to REACH guidance (e.g., grouping, read-across, QSARs)
   - mg/kg bw (systemic effects); mg/cm² (local effects)
2. Initial risk assessment
- Objective: determine external exposure to a substance and its subsequent absorption through the skin
- Default: exposure modeling / 100% dermal absorption

3. Refined risk assessment
Range of options for further refinement
- Generate data (exposure, absorption, biomonitoring)

Risk management tools
- Skin notation
  - 2000 cm$^2$, 1 hour, relative to inhalation (10%)
Risk assessment for dermal exposure

- External exposure: Dermal Occupational Exposure Limit (DOEL)
- Internal exposure: Biological Limit Value (BLV)
  - Includes multiple routes of exposure
  - Care about exposure conditions of the different routes
    > (Absorption) rate
- Warning signal: skin notation
Route-to-route extrapolation

Criteria for route-to-route extrapolation:

● the available toxicity data are considered adequate and reliable
● the critical effect(s) for the routes of exposure under consideration are systemic, and the absorption and expression of toxicity are not influenced by possible local effects
● the considered toxic effect is independent of the route of exposure.
● the absorption efficiency is the same between routes or the difference is known and can be quantified
● hepatic first pass effects are minimal
● there is no significant chemical transformation by oral, gut or skin enzymes or in pulmonary macrophages
● the chemical is relatively soluble in body fluids.
Summary

- Dermal exposure can be a relevant exposure route but adequate risk assessment is challenging:
  - a.o. due to many factors determining dermal absorption
- Qualitative assessments
  - Skin notation
- Quantitative assessments
  - DOEL, DNEL, BLV
- Often based on toxicological information from other routes
  - Kinetics important
    - First pass effect, rate of entry,
    - exposure scenario
    - Relevant dose metric
  - In practice, generally only absorption is accounted for at best