National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Dermal Occupational Exposure Limits

Their use in risk assessment

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Contents

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 *Kow*
  - *Stratum corneum:* rate-determining layer

- Absorption fraction

Risk assessment for dermal exposure

Absorption determining factors

- Permeation rate
- Substance characteristics
  - Molecular weight (<500)
  - Log *Kow* (-1<log *Kow* < 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

Occup Environ Med 1998;55:795–804

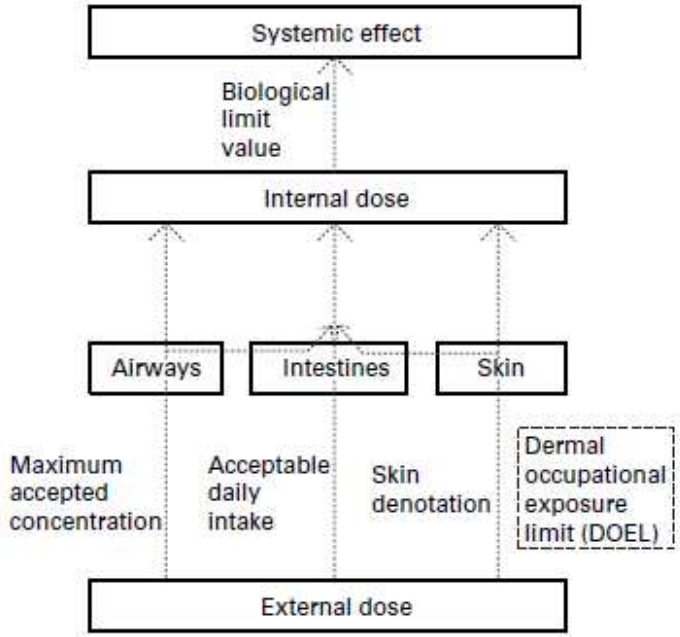


Figure 1 Exposure routes and limit values. For the dermal route the limit (skin denotation) is of a qualitative nature. The dermal occupational exposure limit (DOEL) could fill this gap.

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/cm^2)):
    - "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_{in}).

The internal dose taken up through the skin:

$$J_{max;occ} \times t \times A$$

$J_{max;occ}$: 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

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

or

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

For a given time (8 hours/day), internal dose only dependent on *A*.

Thus a maximal allowable exposed skin surface area (A_{max}) can be derived.

Dermal Occupational Exposure Limit

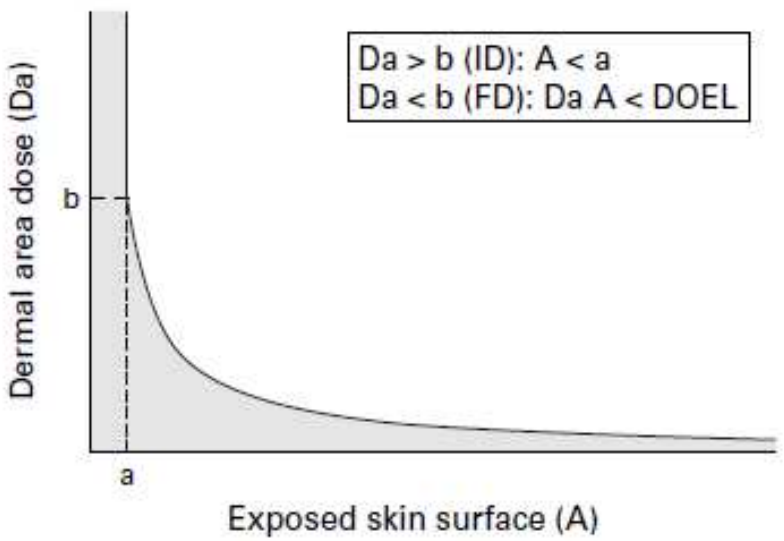


Figure 2 Graphical presentation of the dermal occupational exposure limit (DOEL) relative to the dermal dose/unit area (D_A) and the exposed skin surface area (A). The AUC (shaded area) represents the "safe" values for $D_A \times A$. For $D_A \geqslant b$ (when a maximal flux relevant for the occupational situation ($J_{max,occ}$) is reached), the DOEL can be set as A_{max} (=a), and is independent of the dermal dose/unit area. As long as A<a, the absorbed dose is not expected to give rise to adverse systemic health effects. If A>a, either the exposure time or D_A should be reduced. Then, the DOEL can be expressed as the multiplication of the dermal dose/unit area and the exposed skin surface area: $D_A \times A$.

If based on absorption (unknown flux):

Da x *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 (4×10^{-3} (40 year-worklife)

Human data on absorption

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

} Absorption: 30%

DOEL derivation

- 2000 cm^{-2}, internal dose: 0.75 mg → *Da* = 1 µg/cm^{-2}
- Adjusted absorption: 100%
- DOEL (*Da* x *A*) equals 0.75 mg/day
  - *A*=2000 cm^{-2} → *Da* = 0.4 µg/cm^{-2}

Dermal Occupational Exposure Limit

Tiered approach for estimating dermal absorption

1. Default value of 100%

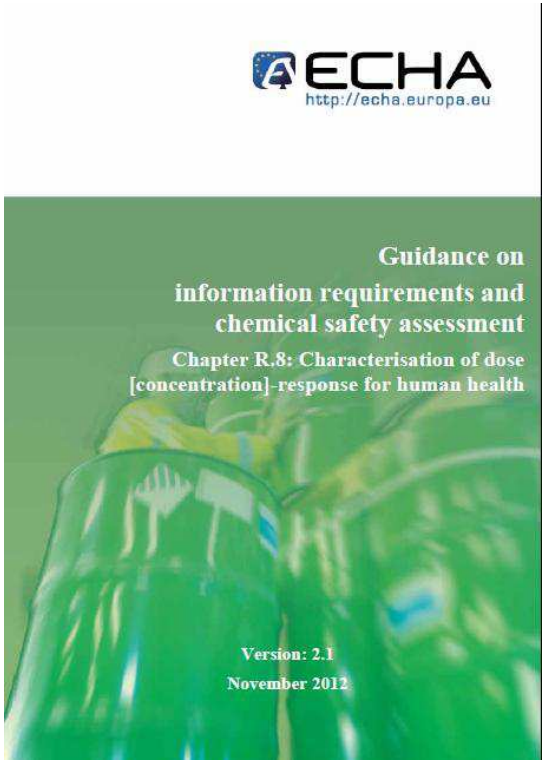
2. 10% if MW>500 or (log *Kow* < -1 or log *Kow* > *4)*

REACH

Guidance on information requirements and chemical safety assessment. *Chapter R.8: Characterisation of dose [concentration]-response for human health.*

Dermal DNELs

- systemic effects (mg/kg bw/day)
- local effects (mg/cm^2)



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

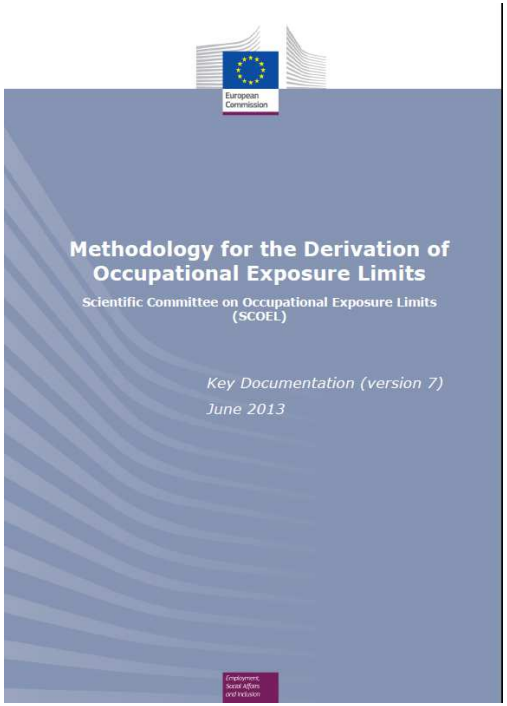
If no dermal study, correction for differences in absorption (interspecies and route specific)

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

Technical Report No.119 (2013)

- *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

ECETOC

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/cm^2 (local effects)

ECETOC

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