

# **Dermal DNEs. What do they represent?**

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# REACH – Annex I

- Sets out the details of how to carry out a Chemical Safety Assessment (CSA) and document it in a Chemical Safety Report (CSR).
- How to assess and document that risks arising from substances ... are controlled
- Defines the Derived No-Effect Level
  - DNEL

# REACH - DNEL

- DNEL: The level of exposure above which humans should not be exposed
- Established for substances based on:
  - Population: workers, consumers and the general population (via environment)
  - Route: inhalation, dermal and ingestion exposure
  - Duration: acute and long-term exposure
- Potential for several different DNELs

# Dermal DNELs

Exposure Pattern	Worker DNEL/DMEL	General Population DNEL/DMEL
Acute-Inhalation-Systemic effects	√	√
Acute-Dermal-Local effects	√	√
Acute-Inhalation-Local effects	√	√
Long-term-Dermal-Systemic effects	√	√
Long-term-Inhalation-Systemic effects	√	√
Long-term-Oral-Systemic effects	Not Relevant	√
Long-term-Dermal-Local effects	√	√
Long-term-Inhalation-Local effects	√	√

# REACH - DNELs

- DNELs may have to be established for systemic effects, local effects, or both
- DNELs should preferably be expressed as ***external values, e.g.:***
  - mg/kg-day (oral)
  - mg/m<sup>3</sup> (inhalation)
  - mg/cm<sup>2</sup> body area-day (dermal)
  - mg/person-day (dermal)

# Systemic and Local Effects

- A *local effect* is an effect that is observed at the site of first contact, caused irrespective of whether a substance is systemically available.
- A *systemic effect* is defined as an effect that is normally observed distant from the site of first contact, i.e., after having passed through a physiological barrier (mucous membrane of the gastro-intestinal tract or of the respiratory tract, or the skin) and becomes systemically available.

# Risk Characterisation

- Critical to REACH is Risk Characterisation (RC)
- Exposure estimate(s) are compared to health hazard information in the form of the DNEL
- Called the Risk Characterisation Ratio (RCR)
- $RCR = \text{Exposure} / \text{DNEL}$

If Exposure < DNEL → Risk adequately controlled

If Exposure > DNEL → Risk not controlled

# DNEL Calculation: 4 Steps

- **STEP 1:** Gather dose descriptors from available studies on health endpoints; identify adverse effects
  - NOAEL; LOAEL; BMD; BMDL10; etc.
- **STEP 2:** Decide on the substance's Mode of Action (MOA)
  - DNELs for “threshold” MOA
- **STEP 3a:** Modify, when necessary, the relevant dose descriptors
- **STEP 3b:** Apply Assessment Factors (AFs) to the “modified” dose descriptor to; Get End-point specific DNEL
  - AFs account for uncertainties in extrapolation and available data
- **Step 4:** Select the Leading Adverse Effect and corresponding DNEL
  - Leading Adverse Effect:
    - The adverse effect that results in the most critical (i.e., the lowest) DNEL for a given exposure pattern
    - RC done on Leading Adverse Effect

# Overview – DNEL Calculation

- $\text{DNEL} = [\text{modified}] \text{Dose Descriptor} / \text{Total AF}$
- $\text{DNEL (Worker-Dermal-Long-Term)} = \text{mg/person/8hr day}$

# Assessment Factors

Assessment factor – accounting for differences in:		Default value systemic effects	Default value local effects
Interspecies	- correction for differences in metabolic rate per body weight	AS <sup>a, b</sup>	-
	- remaining differences	2.5	1 <sup>f</sup> 2.5 <sup>g</sup>
Intraspecies	- worker	5	5
	- general population	10 <sup>c</sup>	10 <sup>c</sup>
Exposure duration	- subacute to sub-chronic	3	3 <sup>h</sup>
	- sub-chronic to chronic	2	2 <sup>h</sup>
	- subacute to chronic	6	6 <sup>h</sup>
Dose-response	- issues related to reliability of the dose-response, incl. LOAEL/NAEL extrapolation and severity of effect	1 <sup>d</sup>	1 <sup>d</sup>
Quality of whole database	- issues related to completeness and consistency of the available data	1 <sup>d</sup>	1 <sup>d</sup>
	- issues related to reliability of the alternative data	1 <sup>e</sup>	1 <sup>e</sup>

# Examples

- The following are examples only, developed for illustrative purposes.
- The details of the examples are fabricated.
- The intent is to provide some points for discussion during the meeting and when you go back to your offices.

# Example 1 – Substance A

- Moderate volatility substance
- R38: irritating to skin
  - Substances and preparations which cause significant inflammation of the skin which persists for at least 24 hours after an exposure period of up to four hours determined on the rabbit according to the cutaneous irritation test method cited in Annex V.
  - Substances and preparations which cause significant inflammation of the skin, based on practical observations in humans on immediate, prolonged or repeated contact.

# Assumptions – Substance A

## **Exposed Population:**

Workers and general population

## **Expected Route of Exposure:**

Dermal and inhalation

## **Expected Frequency and Duration of Exposure:**

*Workers* are expected to have infrequent and short-term exposures; however, for calculation of the DNEL for REACH it is assumed that workers have maximal repeated exposure for *8 hr/day for 5 day/wk.*

*Consumers* in the general population are expected to have infrequent and short-term exposures; however, for calculation of DNELs for REACH, it is assumed that consumers have a maximal repeated dose for *24 hr/day for 7 day/wk.*

## **Threshold and/or Non-Threshold Effects:**

Repeated application of the substance can causes irritation, but no dose-response data are available.

# STEP 1: Gather dose descriptors from available studies on health endpoints

## Dermal Route, Local Effect (skin)

- **Acute Adverse Effect**
  - A DNEL cannot be calculated due to lack of dose-response info
- **Long-term Adverse Effect**
  - Irritation after repeated application, with no dose-response info

## Dermal Route, Systemic Effect (somewhere other than skin)

- **Acute Adverse Effect**
  - No statistically or biologically adverse effects
- **Long-term Adverse Effect**
  - No statistically or biologically adverse effects

## STEP 2: Decide on the substance's Mode of Action (MOA) DNELs for “threshold” MOA

### Dermal Route, Local Effect (skin)

- **Irritant**
  - No dose-response information available
  - *STEP 3 (i.e. applying modification and assessment factors) is not relevant*

## **Step 4: Select the Leading Adverse Effect and corresponding DNEL**

- Inhalation is a route of exposure, but no adverse effects were observed in any study
- Dermal route to inhalation route conversion is not appropriate for local effects
- Leading adverse effect is irritation (to skin)
- No DNEL is available for irritation
- Qualitative risk assessment should be conducted

# Example 2 – Substance B

- Moderate volatility substance
- R38: Irritating to skin

# Assumptions – Substance B

## **Exposed Population:**

Workers and general population

## **Expected Route of Exposure:**

Dermal and inhalation

## **Expected Frequency and Duration of Exposure:**

*Workers* are expected to have infrequent and short-term exposures; however, for calculation of the DNEL for REACH it is assumed that workers have maximal repeated exposure for *8 hr/day for 5 day/wk*.

*Consumers* in the general population are expected to have infrequent and short-term exposures; however, for calculation of DNELs for REACH, it is assumed that consumers have a maximal repeated dose for *24 hr/day for 7 day/wk*.

## **Threshold and/or Non-Threshold Effects:**

Repeated application of the substance can causes irritation, and dose-response data are available.

# STEP 1: Gather dose descriptors from available studies on health endpoints

## Dermal Route, Local Effect (skin)

- **Acute Adverse Effect**
  - A DNEL cannot be calculated due to lack of dose-response info
- **Long-term Adverse Effect**
  - Irritation after repeated application, with dose-response info

## Dermal Route, Systemic Effect (somewhere other than skin)

- **Acute Adverse Effect**
  - No statistically or biologically adverse effects
- **Long-term Adverse Effect**
  - No statistically or biologically adverse effects

# STEP 1: Dose Descriptors

- **Dose descriptor:** NOAEL 200 mg/kg bw/day
- **Rationale for selection of dose descriptor:** Skin irritation observed at doses above 200 mg/kg bw/day
- **Basis for dose descriptor:** 90 day dermal study in rabbits. Undiluted test material was applied to the skin (200, 1000, and 2000 mg/kg bw/day) and then covered with a gauze bandage and occlusive dressing. After 6 hours, the site was uncovered and wiped.

## **STEP 2: Decide on the substance's Mode of Action (MOA) DNELs for "threshold" MOA**

### **Dermal Route, Local Effect (skin)**

- **Irritant**
  - Dose-response information supports threshold

## STEP 3a: Modify, when necessary, the relevant dose descriptors

- Modification of starting factor:
  - The starting factor needs to be adjusted from 3 doses per week used in the study to 5 doses per week for workers. Excess material was wiped from the area, but a residual can be assumed to remain, indicating it is unnecessary to adjust from 6 hours/day to 8 hours/day.

$$200 \frac{mg}{kg} * \frac{3 \text{ days/week}}{5 \text{ days/week}} = 120 \frac{mg}{kg}$$

## STEP 3b: Apply Assessment Factors (AFs) to the “modified” dose descriptor to; Get End-point specific DNEL

<u>AF Basis</u>	<u>AF Number</u>
Intraspecies:	5
Interspecies:	1
Duration:	2
<b>Total:</b>	<b>(5)(1)(2) = 10</b>

### Calculation of DNEL:

$$(120 \text{ mg/kg bw/day}) / 10 = \mathbf{12 \text{ mg/kg bw/day}}$$

## Step 4: Select the Leading Adverse Effect and corresponding DNEL

- Inhalation is a route of exposure, but no adverse effects were observed in any study
- Dermal route to inhalation route conversion is not appropriate for local effects
- Leading adverse effect is irritation (to skin)
- The DNEL-long term-dermal-local is

**12 mg/kg bw/day**

# Example 3 – Substance C

- Low volatility substance
- R38: Irritating to skin
- R45: May cause cancer
  - Substances known to be carcinogenic to man.
  - Substances which should be regarded as if they are carcinogenic to man.
- R48: Danger of serious damage to health by prolonged exposure
  - serious damage (clear functional disturbance or morphological change which have toxicological significance) is likely to be caused by repeated or prolonged exposure by an appropriate route.
- R21: Harmful in contact with skin

# Assumptions – Substance C

## **Exposed Population:**

Substance cannot be sold to the general population.

Therefore exposure is limited to only the worker (professional and industrial) population.

## **Expected Route of Exposure:**

The relevant route of exposure is dermal

## **Expected Frequency and Duration of Exposure:**

*Workers* are expected to have infrequent and short-term exposures; however, for calculation of the DNEL for REACH purposes it is assumed that workers have maximal repeated exposure for *8 hr/day for 5 day/wk*

## **Threshold and/or Non-Threshold Effects:**

Non-threshold carcinogen

# STEP 1: Gather dose descriptors from available studies on health endpoints

## Dermal Route, Local Effect (skin)

- **Acute Adverse Effect**
  - A DNEL cannot be calculated due to lack of dose-response info
  - It is expected that the DNEL calculated from long-term study will be protective
- **Long-term Adverse Effect**
  - Irritation after repeated application, with dose-response info

## Dermal Route, Systemic Effect (somewhere other than skin)

- **Acute Adverse Effect**
  - No statistically or biologically adverse effects
- **Long-term Adverse Effects**
  - Adrenal gland changes
  - Developmental effects

# STEP 1: Dose Descriptors

**Dermal Route yields:**

## **Dermal Irritation (local effect)**

- **Dose descriptor:** NOAEL 50 mg/kg bw/ day
- **Rationale for selection of dose descriptor:**  
Skin irritation observed at higher doses
- **Basis for dose descriptor:** 90 day dermal study in rats. Undiluted test material was applied to the skin (10, 50, 250, and 500 mg/kg bw/day) and not occluded.

# STEP 1: Dose Descriptors

Dermal Route yields:

## Adrenal gland changes (systemic effect)

- **Dose descriptor:** NOAEL 10 mg/kg bw/day
- **Rationale for selection of dose descriptor:** Adverse changes to adrenal glands observed at higher doses
- **Basis for dose descriptor:** 90 day dermal study in rats. Undiluted test material was applied to the skin (10, 50, 250, and 500 mg/kg bw/day) and not occluded.

# STEP 1: Dose Descriptors

**Dermal Route yields:**

## **Developmental effects (systemic effect)**

- **Dose descriptor:** NOAEL 50 mg/kg bw/day
- **Rationale for selection of dose descriptor:**  
Developmental effects observed at higher doses
- **Basis for dose descriptor:** 90 day dermal study in rats. Undiluted test material was applied to the skin (10, 50, 250, and 500 mg/kg bw/day) and not occluded.

## **STEP 2: Decide on the substance's Mode of Action (MOA) DNELs for "threshold" MOA**

### **Dermal Route, Local & Systemic Effects**

- **Irritation**
  - Dose-response information supports threshold
- **Adrenal Effects**
  - Dose-response information supports threshold
- **Developmental Effects**
  - Dose-response information supports threshold

## STEP 3a: Modify, when necessary, the relevant dose descriptors

- **Irritation (Local)**
  - No modification needed
- **Adrenal (Systemic) Effects**
  - Substance-specific data indicates dermal absorption is 2x less in humans than rats

$$10 \frac{mg}{kg} * \frac{1}{0.5} = 20 \frac{mg}{kg}$$

- **Developmental (Systemic) Effects**
  - Substance-specific data indicates dermal absorption is 2x less in humans than rats

$$50 \frac{mg}{kg} * \frac{1}{0.5} = 100 \frac{mg}{kg}$$

## STEP 3b: Apply Assessment Factors (AFs) to the “modified” dose descriptor to; Get End-point specific DNEL

	Irritation	Adrenal Effects	Developmental Effects
<i>[Modified] NOAEL</i>	50	20	100
<b><u>AF Basis</u></b>	<b><u>AF Number</u></b>	<b><u>AF Number</u></b>	<b><u>AF Number</u></b>
Intraspecies:	5	5	5
Interspecies:	1	10	10
Duration:	2	2	2
POD:	3	3	3
<b>Total:</b>	<b>30</b>	<b>300</b>	<b>300</b>
<b>DNEL mg/kg/d</b>	<b>1.7</b>	<b>0.1</b>	<b>0.3</b>

## **Step 4: Select the Leading Adverse Effect and corresponding DNEL**

- Leading adverse effect is.....

## Step 4: Select the Leading Adverse Effect and corresponding DNEL

- Other routes of exposure are not relevant
- Dermal route to inhalation route conversion is not appropriate for local effects
- The DNEL-dermal-long term-local is 1.7 mg/kg bw/day
- The DNEL-dermal-long term-systemic is 0.1 mg/kg bw/day
- Leading adverse effect is likely **CANCER**
  - Remember, substance C is R45
  - Qualitative risk assessment likely needed

# Some Points

- Nature of many toxicology studies inherently accounts for absorption across skin
  - i.e., the external dose correlates with substance-related systemic effect 'x;' therefore substance penetrated the skin
  - Though starting point can be modified if justified absorption differences between animal and human are known
- For a number of endpoints (e.g., irritation, non-threshold genotoxicity/carcinogenicity), qualitative (or semi-quantitative) assessment is all that is possible
  - Calculation of a *DMEL* may or may not be appropriate

# Some Suggestions

- Hazard and exposure experts communicate prior to/during DNEL calculation to identify relevant duration, frequency, route and exposed human population
- Risk characterisation (i.e. hazard + exposure) to be done as a team to ensure appropriate measures are selected to protect against the relevant potential adverse effects

Thank you!

# Backup

# Units – Substance B and C

- The test substance was applied directly to the skin and spread over an undefined area of skin depending on its physical properties, such as viscosity.
- In this instance, mg/cm<sup>2</sup> skin surface area estimate can be done; however, this would be based on assumptions of treated surface area even in instances in which the test substance is subsequently covered by a patch (with or without supporting details on which to make an assumption from study reports)
- Therefore, the dose for such cases was expressed in mg/kg bw/day and DNEL therefore in the same units.

# No DNELs & CM Directive

- As compared to the straight-forward derivation of DNEL for repeated dose toxicity, it may be more difficult for the endpoints acute toxicity, irritation/corrosion, skin sensitisation, and reproductive toxicity (see Chapter R.7).
- For mutagens/carcinogens, it should be stressed that the Carcinogens and Mutagens Directive (2004/37/EC) requires that occupational exposures are avoided/minimised as far as technically feasible. As REACH does not overrule the Carcinogens and Mutagens Directive, the approach to controlling workplace exposure should therefore comply with this minimisation requirement.