Practical Considerations in Defining the SAFs

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Quantitative Risk Assessment for Skin Sensitisation

- **The aim of the QRA, is to extrapolate a predicted safe dose for consumers based on experimental data**
- **As with risk assessments for other thresholded toxicological endpoints, this can be achieved by applying assessment factors (Sensitisation Assessment Factors, SAFs)**

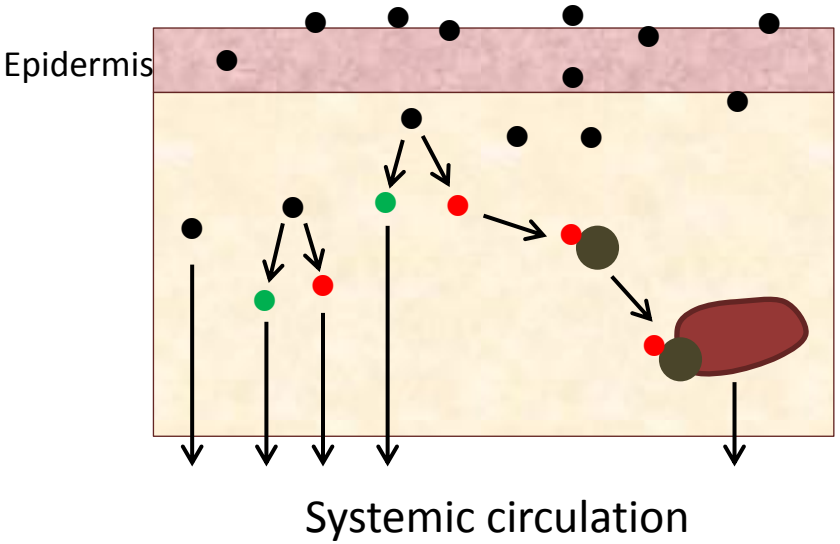
WoE NESIL* → **SAFs** → **Consumer AEL**

In order to define appropriate values for the SAFs we need to consider:

- **What factors may affect skin sensitisation**
- **How these factors differ between the experimental situation and consumer product use situation**

* The current review assumes that the WoE NESIL is derived from a confirmatory HRIPT, but recognises that other experimental data (e.g. LLNA) may be used in its derivation

Factors that may impact on skin sensitisation



Frequency/duration **Area of application** **Dose per unit area**	Consumer habits
Penetration into skin	Occlusion Matrix Skin integrity Genetic factors
Metabolic activation/inactivation	Genetic factors
Binding to protein	Chemical reactivity
Activation of Keratinocytes	Danger signals Inflammation
Activation of Dendritic cells	Genetic factors Site of application
Activation of immune system (T cell proliferation)	Genetic factors

HRIPT vs. Consumer Exposure – Skin Penetration

HRIPT	Consumer exposure	Difference
Exposure is generally under full occlusion	Exposure may be non-occluded, or at worst semi-occluded (e.g. under clothing or axillae). Semi occlusion may also occur with some moisturisers (oils, waxes, silicones, etc.)	Level of occlusion is lower in consumer exposure than in HRIPT
The chemical is applied in a simple solvent system (e.g. DEP/ethanol, petrolatum)	Product matrix may include ingredients that affect skin penetration. In addition the physical state of the products will vary (liquid, cream/lotion, solid)	Consumer product matrix may affect penetration (increase or decrease)
Subjects are chosen to exclude any with skin disorders or compromised skin (at the patch site)	Subjects include those with skin disorders or compromised skin caused by other factors (e.g. shaving, scratches, dry/cracked skin)	Skin penetration may be increased in consumers with compromised skin

HRIPT vs. Consumer Exposure – Skin Inflammation (Danger Signals)

HRIPT	Consumer exposure	Difference
Solvent system and allergen concentration generally do not cause irritation during induction	Product use may cause mild skin irritation	Consumer product matrix may induce mild inflammation in skin
Subjects are chosen to exclude any with skin disorders or inflamed skin (at the patch site)	Subjects include those with skin disorders or inflamed skin caused by other factors (e.g. sunburn, insect bites, acne)	Skin inflammation may be present in consumers

HRIPT vs. Consumer Exposure – Genetic Variability/Immune System Activation

HRIPT	Consumer exposure	Difference
Studies are usually conducted in 100 subjects selected from an adult population	Consumers may encompass the whole population, including a range of age, gender and ethnic origin	Genetic variability, and susceptibility to skin sensitisation in the population will be wider than that in the HRIPT
Patches are normally applied to the arm or back of individuals	Products may be used on the face, axillae and other so called sensitive areas	Application to sensitive areas may occur in consumers

HRIPT vs. Consumer Exposure – Frequency and Duration

HRIPT	Consumer exposure	Difference
Exposure is for 24 hours under occlusion three times per week.	Exposure may be more or less frequent, but duration will generally be less for each exposure, especially in the case of rinse-off products. More continuous exposure may occur with some leave-on products	Exposure frequency and duration will be different
The exposure period is 3 weeks	Exposure may be limited or occur over extended periods of time (months or years)	Exposure is likely to occur over a longer period of time with consumer products

Factors which need to be considered in setting the Sensitisation Assessment Factors (SAFs)

From this analysis it is proposed that the factors that need to be considered when defining the SAF values are as follows:

- Intrinsic variability (genetic factors)
- Skin condition
- Occlusion
- Skin area sensitivity
- Product matrix
- Frequency/duration of exposure

In proposing values for these, the following general rule has been used:

- Where we judge there are order of magnitude effects, 10-fold factors are proposed
- Where variability is judged to be low, 2 - 3 fold factors are proposed

Intrinsic variability (genetic factors)

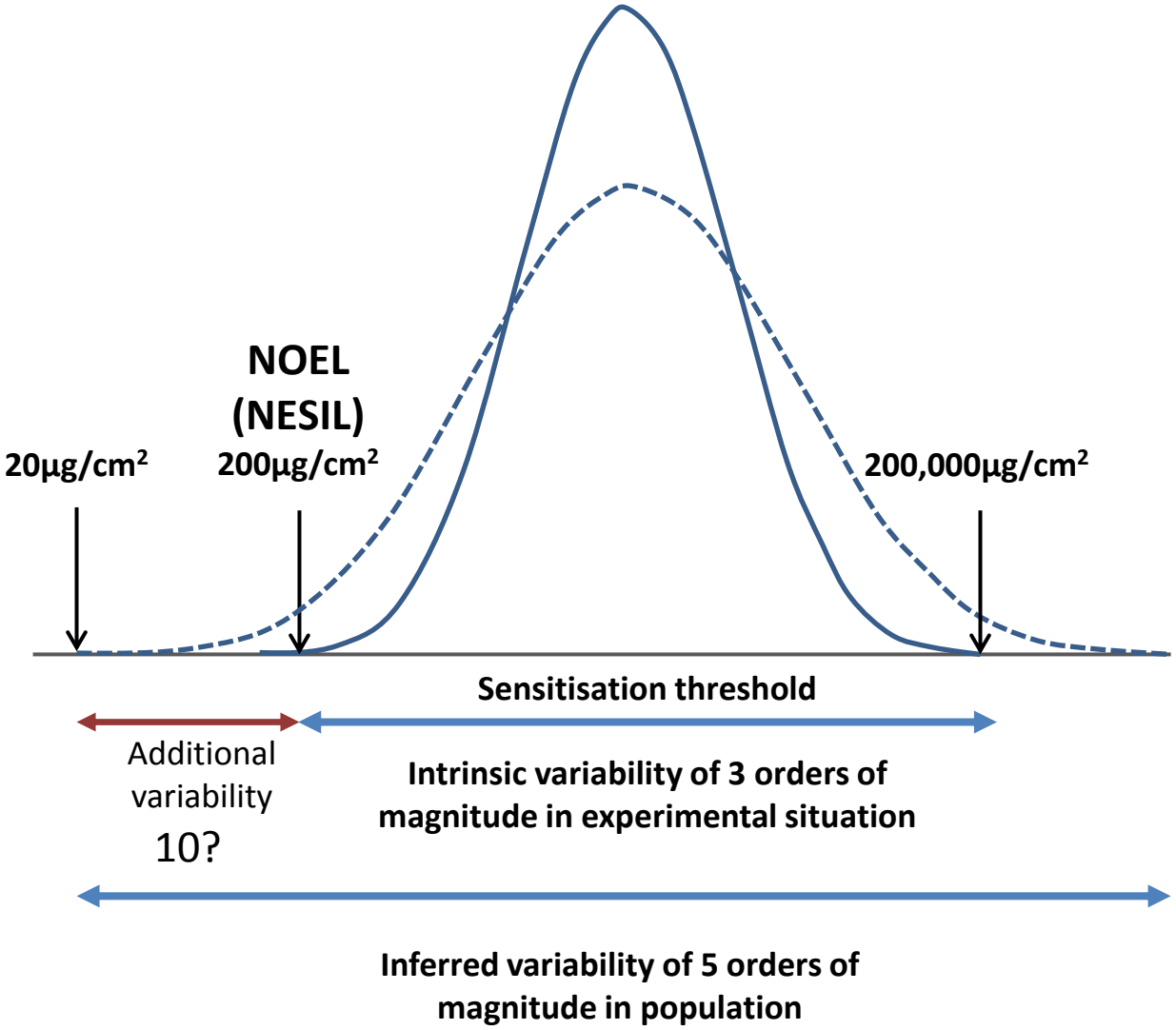
- Sensitivity to the induction of sensitisation will vary in the human population due to a number of factors which include genetic polymorphism, ethnicity, age, and gender
- Available data (HRIPT and HMT) suggests that this variability may be 3 or more orders of magnitude in an experimental situation
- However, this variability is inherent in the experimental population, and the Point of Departure used in the QRA is the NESIL which is predicated on the most sensitive subject
- The SAF does not, therefore, need to further account for this variability
- The SAF should account for the *additional* variability that may exist in the general population compared to the experimental population

Intrinsic variability (genetic factors)

- Experimental data provides little insight into the true variability in the population
- Within other areas of risk assessment (notably systemic toxicity) it is generally accepted that a factor of 10 is sufficient to account for intra-species variability
- A recent ECETOC report (2010) on assessment factors proposes that, where the studied population is representative of the target population, and the study group is sufficiently large, no intra-species factor is required
- Where the study group is not fully representative (e.g. worker group to population), an intra-species factor of 3 is proposed by ECETOC

- **Is a factor of 10 to account for intrinsic variability applicable to skin sensitisation as for other toxicological endpoints?**
- **Could a smaller factor of 1 or 3 as proposed by ECETOC be justified?**

Impact of including a 10-fold factor for intrinsic variability



Skin condition

- Experimental evidence suggests that susceptibility is increased only slightly (if at all) in compromised skin (e.g. tape stripped, blistered). However, susceptibility may be increased in those with inflamed skin (e.g. SLS pre-treatment)

- The NESIL is predicated on an HRIPT in which the skin is not compromised or inflamed

- Consumers may have inflamed/compromised skin at the site of application due to a number of factors such as:
  - Skin conditions (e.g. eczema, psoriasis)
  - Acne, sunburn, insect bites, rash
  - Dry/cracked skin
  - Cuts and abrasions
  - Irritation from product use (e.g. surfactants)

- Data suggests inflammation, rather than barrier disruption has a 10-fold effect

- **Is a factor of 10 to account for variability caused by compromised/inflamed skin in the consumer applicable in the QRA?**
- **Is it applicable to apply this to all areas of application?**

Occlusion

- Occlusion may (or may not) increase skin penetration, and will prevent evaporation of volatile haptens (e.g. fragrances)

- However, limited experimental data suggest that occlusion has only a modest effect on skin sensitisation; a 3-fold lower induction of sensitisation was demonstrated in a HMT using non-occluded application compared with fully occluded application

- Some areas of application of consumer products are considered to be occluded to various degrees – e.g. under the arms, perianal area, under clothing/nappies/shoes

- In addition, some moisturising agents (e.g. mineral oils/waxes, silicones) can have an occlusive action on skin

- However, this occlusion is likely to be limited, and much less severe than the full occlusion used in the HRIPT

- **Since occlusion in the consumer use situation will always be less than the experimental situation, is it ever justified to include a factor of >1?**
- **Where consumer exposure is not under occlusion, is a value of 0.5 justified?**

Skin area sensitivity

- Some skin areas are often referred to as sensitive areas
- These areas are ill defined, but include the axillae and face, and may refer to areas where clinical symptoms often present (i.e. where ACD reactions are most often elicited)
- Increased incidence of elicitation in these areas might be due to factors such as shaving (face), occlusion (axillae) or higher levels of exposure in these areas
- There are no experimental data to support the supposition that some areas of skin are intrinsically more sensitive to the induction of skin sensitisation

- **Given the uncertainty, is it necessary to include a factor to account for skin area sensitivity, or is this accounted for under skin condition, occlusion or level of exposure?**
- **If applicable, does a proposed factor of 2 account for the increased sensitivity?**

Frequency/duration of use

- The HRIPT is conducted with nine 24 hour exposures over a three week period
- Consumer exposure may be more frequent, but the duration of exposure is generally less for each application, especially for rinse-off products
- In addition, consumers may use products over extended periods of time (i.e. months, years)
- The effect of more frequent exposures over extended periods of time on sensitisation induction is not well defined. However, the possibility that hapten may accumulate in the skin needs to be considered
- However, it may be argued that, provided that the exposure level remains below an individual's sensitisation threshold (i.e. no immune response is triggered), repeated exposure will never induce sensitisation

- **Given the lack of data, is a proposed factor of 2 considered adequate to account for increased frequency/duration of exposure?**

Product matrix

- In the LLNA a 10-fold difference in sensitisation was observed between solvents. However, no general rules can be deduced from this, although aqueous vehicles clearly produced lower sensitisation

- In humans, a 4-fold difference in skin sensitisation was apparent between matrices tested, with ethanol or petrolatum providing the greater degree of sensitisation

- Allergens present in solid products (e.g. talc) may be expected to induce less sensitisation than those in liquid products, since a lower migration from product to skin would be expected. Such an effect should therefore be factored into the exposure calculation

- **Since the NESIL is predicated on an HRIPT using ethanol/DEP or petrolatum, can the effect of product matrix be accounted for by the inclusion of the proposed values:**
  - **A value of 1 for ethanol/oil based products**
  - **A value of 0.5 for aqueous based products**

Application of SAFs in the QRA

In the previous QRA process, as defined by Api et al. (2008), 3 SAFs were included:

1. Inter-individual SAF
2. Matrix SAF
3. Use SAF

In the current review, it is suggested that the use of 2 SAFs would provide greater transparency, and avoid the possibility of double accounting:

1. **Inter-individual SAF** – this accounts for intrinsic variability in the population, to include genetic factors and skin condition
2. **Product/Use SAF** – this accounts for variability introduced by the consumer product, to include matrix and consumer habits

Inter-individual SAF

It is proposed that the inter-individual SAF would be composed of 2 factors:

- Intrinsic variability (genetic factors)
- Skin condition

Inclusion of a factor of 10 for each of these would give an overall inter-individual SAF of 100.

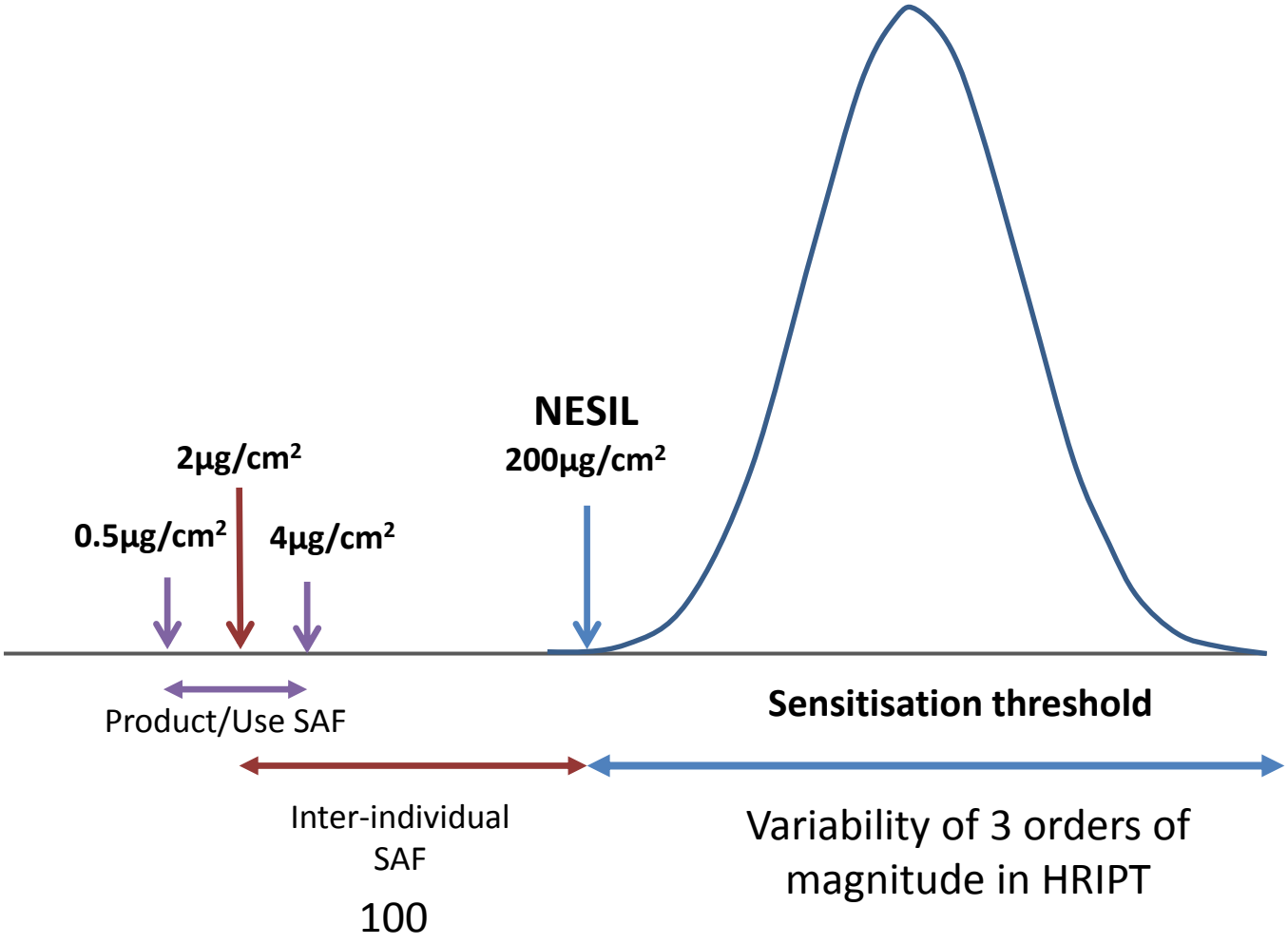
The Inter-individual SAF would be applied as a default value to all QRAs in the absence of further data.

Factors determining the Product/Use SAF

The Product/Use SAF would be derived from the remaining four factors, the individual values being derived according to product type and consumer habits as follows:

Factor	Consideration	Influence	Proposed SAF Values
Occlusion	Some areas of skin are semi-occluded by clothing, or product with moisturising agents may lead to semi-occlusion.	Semi-occluded =	1
		Non-occluded ↓	0.5
Skin area sensitivity	Some areas of skin are considered to be more sensitive than the arms/back	Normal =	1
		More sensitive ↑	2
Product matrix	Aqueous vs. ethanol/oil based	Ethanol/oil =	1
		Aqueous ↓	0.5
Frequency/duration of product use	Products may be used over extended periods of time	↑	2
Overall Product/Use SAF			0.5 - 4

Application of proposed SAFs to the NESIL



In Summary . . .

- In the QRA process, Sensitisation Assessment Factors (SAFs) are applied to a NESIL predicated on experimental data (HRIPT) to extrapolate to an Acceptable Exposure Level (AEL) in consumers

- These SAFs need to take account of the differing exposure scenarios between experimental and consumer scenarios, and also the differences between the two populations (HRIPT vs. consumer populations)

- The factors considered to drive the value of the SAF are:
  - Intrinsic variability (genetic factors)
  - Skin condition
  - Occlusion
  - Skin area sensitivity
  - Product matrix
  - Frequency/duration of exposure

- Values are proposed for each of these factors based on available experimental data and expert judgement. These are defined as default values to be used in the absence of further data

In Summary . . .

- Further, it is proposed that these factors are incorporated into two SAFs -
    - **Inter-individual SAF** – this accounts for intrinsic variability in the population, to include genetic factors and skin condition
    - **Product use SAF** – this accounts for variability introduced by the consumer product, to include matrix and consumer habits
- The proposed QRA procedure is in line with risk assessments for other threshold based toxicological endpoints
- The proposals provide greater transparency in the way that the SAFs are derived and applied, and avoid the possibility of double accounting of values