Quantitative Risk Assessment for Dermal Sensitization for Fragrance Ingredients

Peter Griem, DGPT, ERT, DABT
Symrise AG
Principal Expert Toxicology

Anne Marie Api, PhD, ATS
RIFM
Vice President

QRA methodology is a scientifically rigorous strategy for dermal sensitization

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Why is Sensitization Risk Assessment Complex?

Immune system can generate specific receptors for any (bio)chemical structure and has powerful effector mechanisms (antibodies, cytotoxic T-cells)

fight pathogenic viruses, bacteria, parasites

but tolerate microflora on skin, in mouth and gastrointestinal tract

destroy mutated cells to protect against cancer

but tolerate intact cells/tissues else autoimmune diseases and transplant rejections

neutralise toxins but establish tolerance to non-dangerous structures (food stuffs)

else immune reactions to non-dangerous structures: allergic reactions
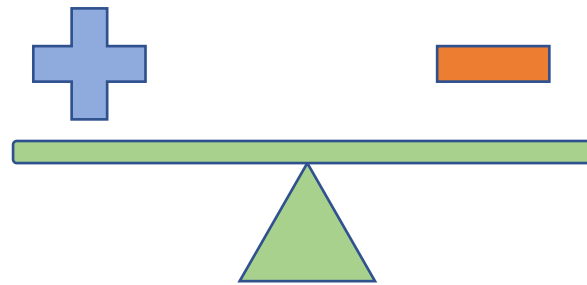
Product amount used depends strongly on application type
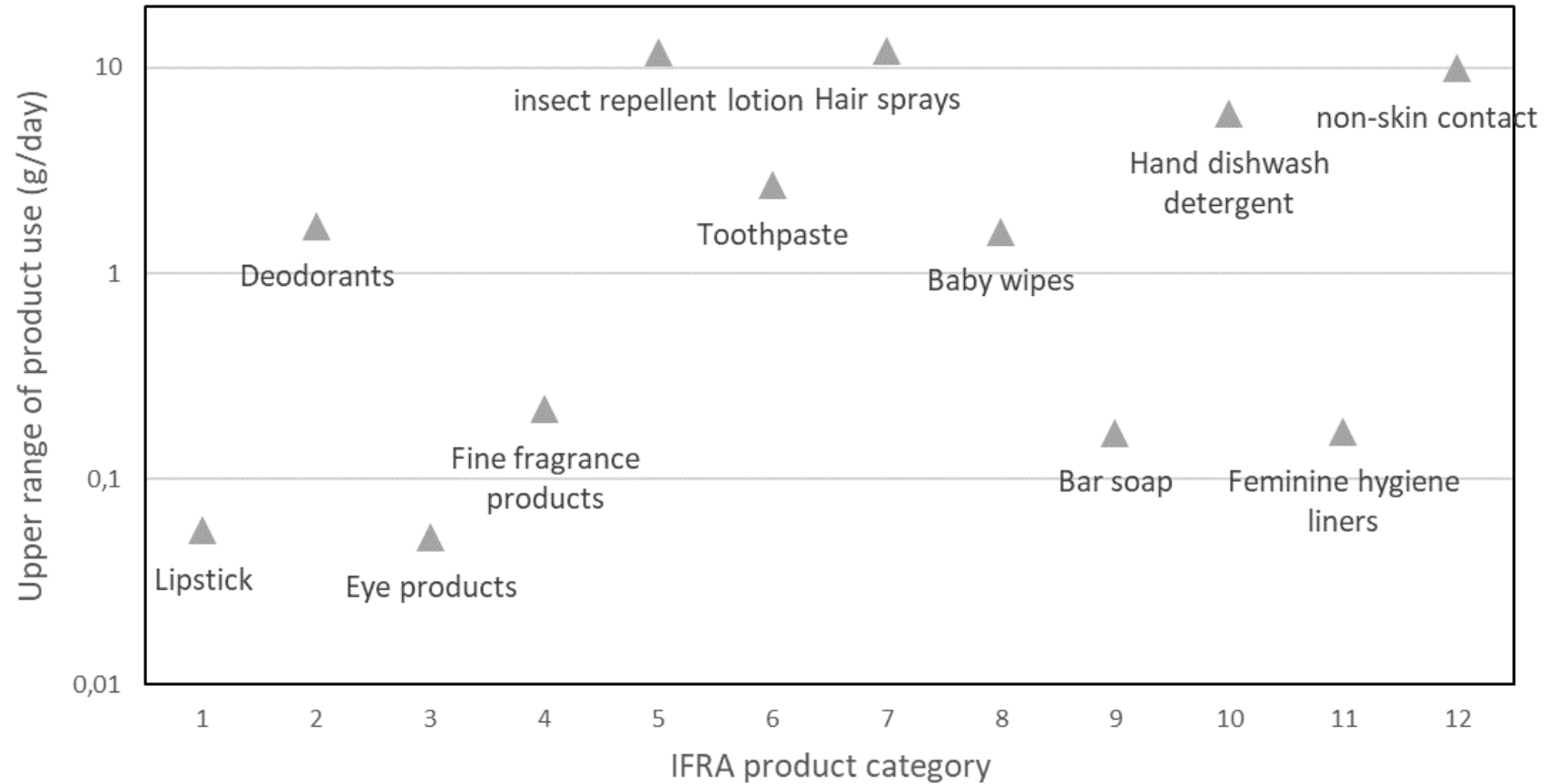
… but is not sufficient to characterise exposure

For sensitisation the product amount per skin area is relevant
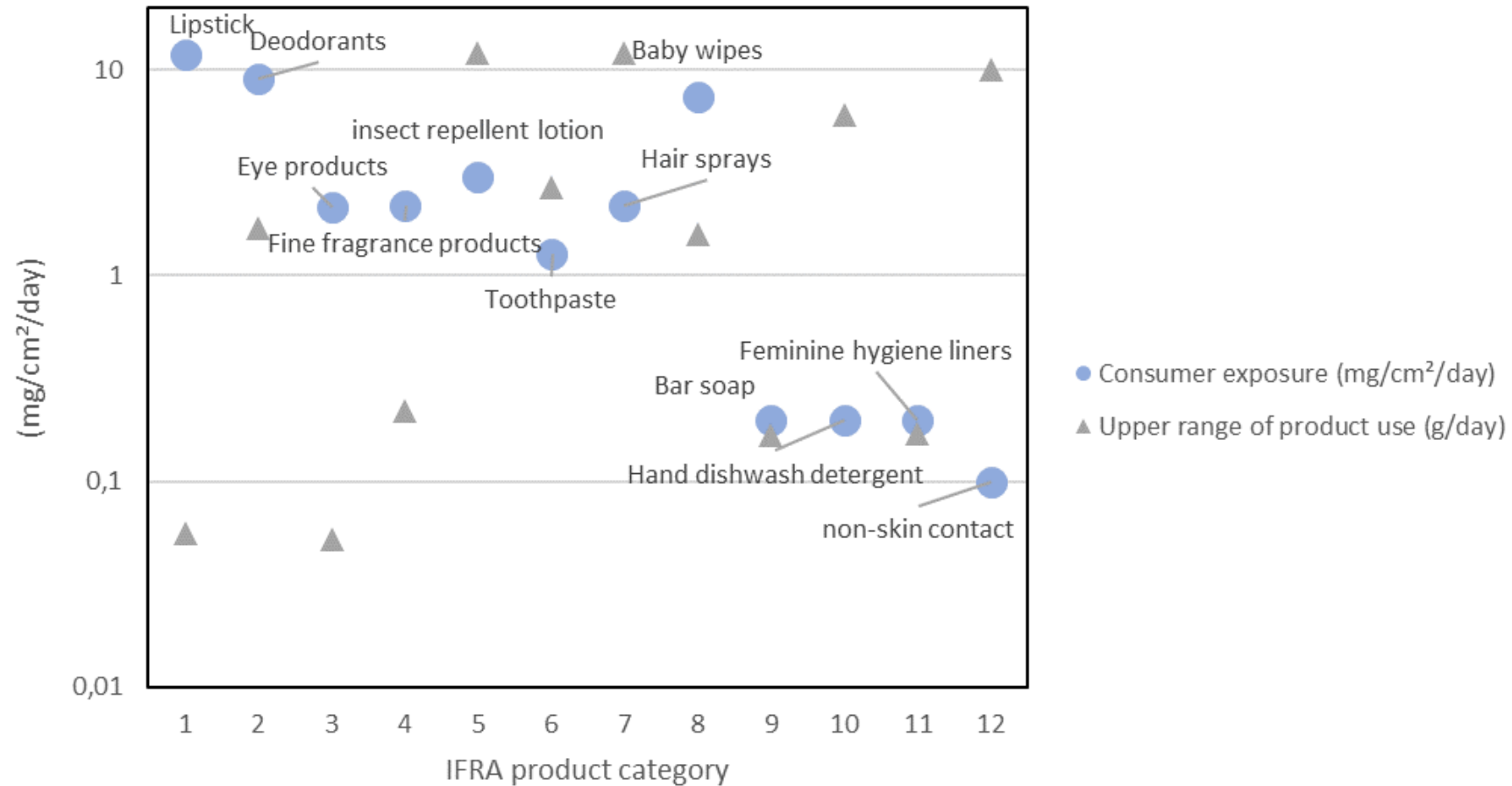
… but still variable over a factor of 100 requiring product type specific risk calculations

Sensitising fragrance ingredients have vastly different potencies

Non-Sensitising Skin Exposure (NESIL) (µg/cm²)
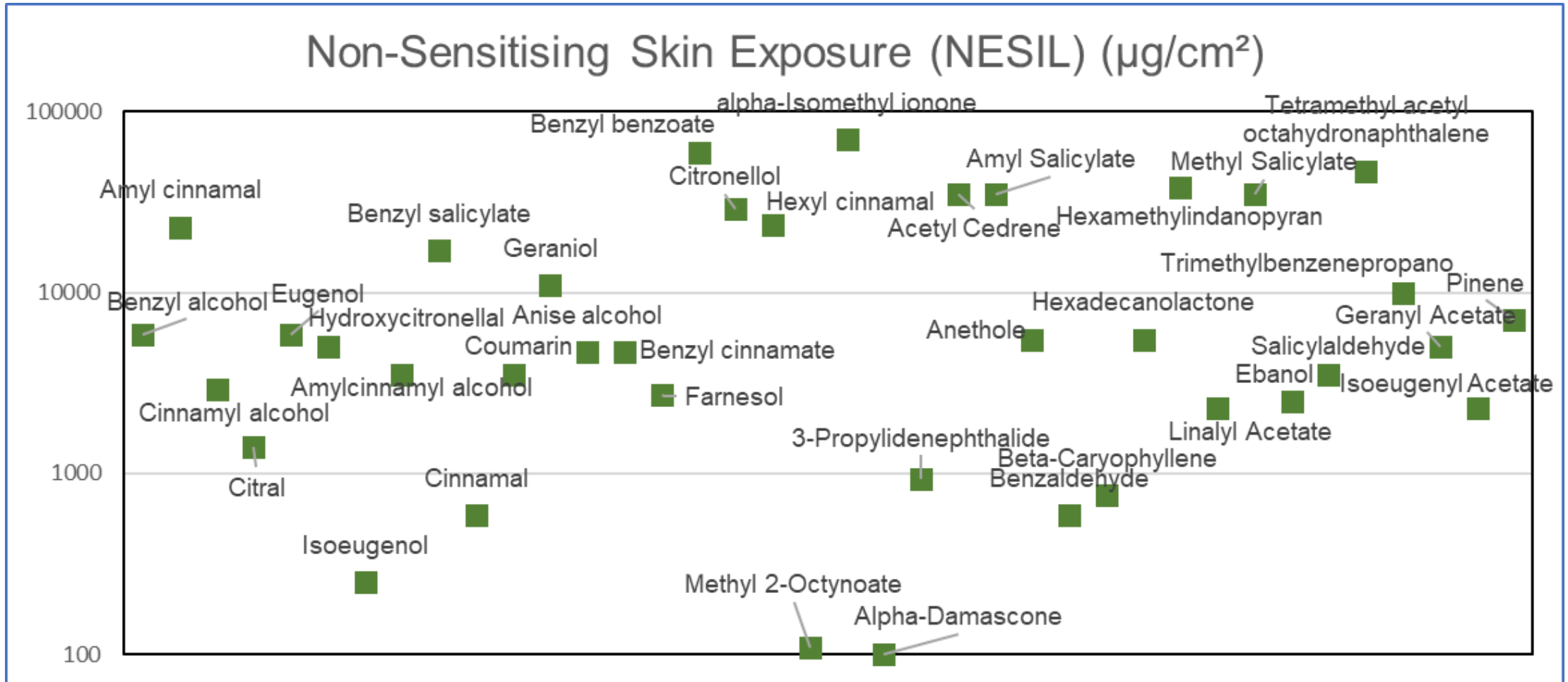
… and therefore require chemical-specfic risk assessment

Maximum safe concentrations strongly depend on product type
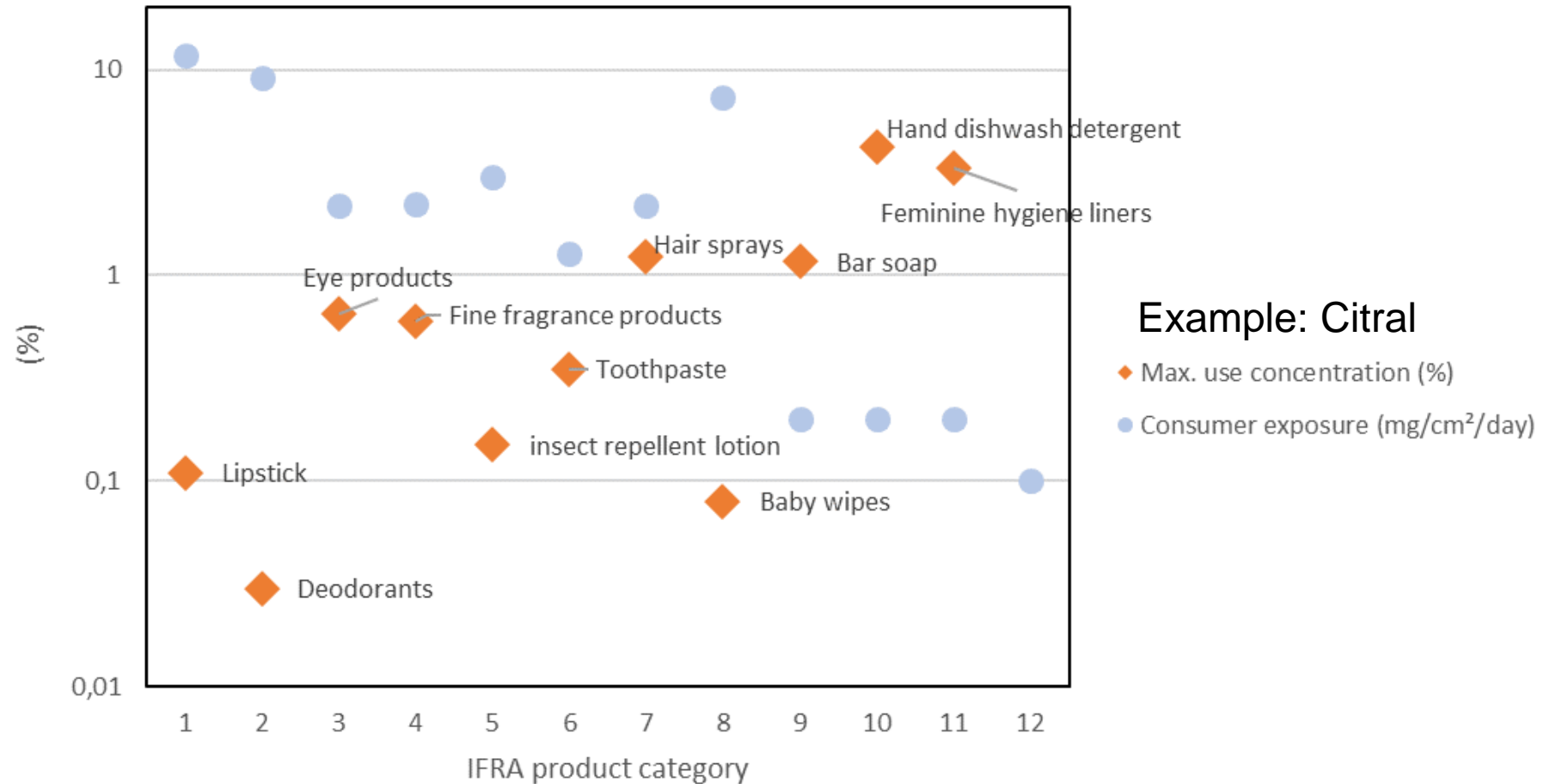
… and are variable over a factor of 100 requiring product type specific use limits

Adequate skin sensitisation risk management

- has to be chemical specific because potencies vary of several orders of magnitude

- has to derive product type specific use limits because exposures vary over at least two orders of magnitude for fragranced consumer product types

- As in other areas of risk assessment and risk management a one-fits-all approach is not adequate

- RIFM has evaluated the safety of hundrets of potentially skin sensitising fragrance raw materials

- IFRA has issued binding limits for 100+ of skin sensitising fragrance raw materials
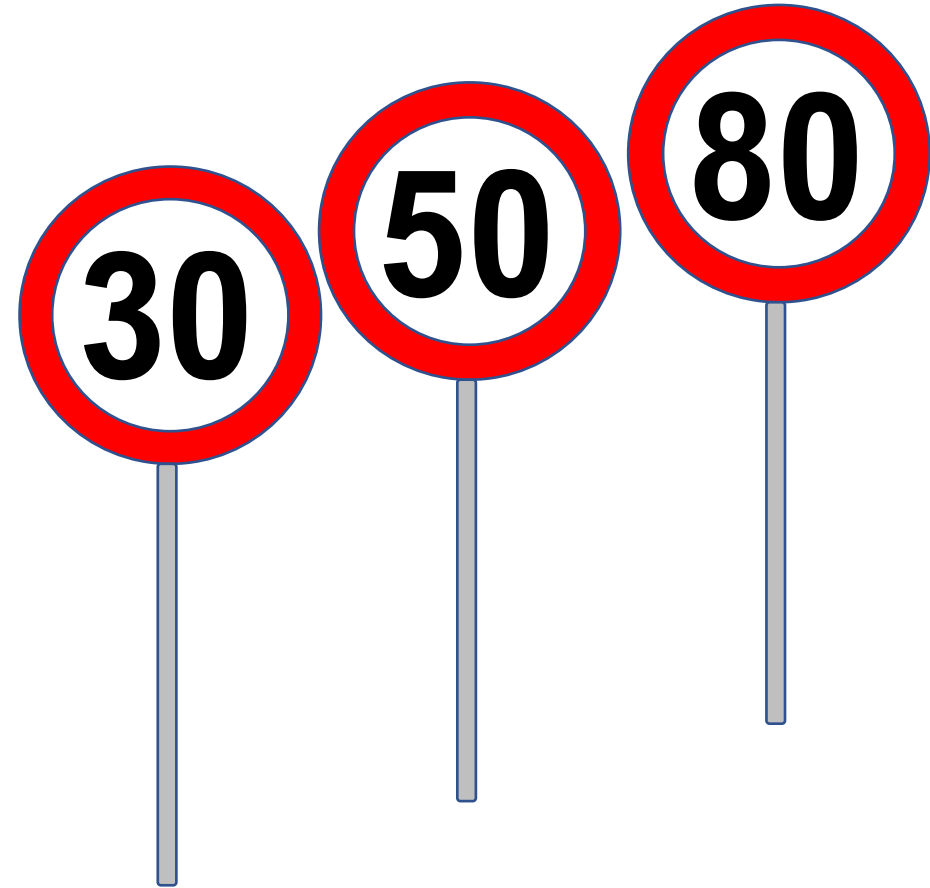
Quantitative Risk Assessment for dermal sensitization (QRA2) is a comprehensive risk assessment tool which incorporates aggregate exposure and revised sensitization assessment factors

Consumer exposure
µg/cm²

AEL
µg/cm²

NESIL
µg/cm²

| <Acceptable Exposure Level (AEL) | Sensitization Assessment Factor (SAF) | >NOEL |

0.001   0.01   0.1   1.0   10   100   1000

log dose µg/cm²

Api et al., 2008, Reg Tox Pharm, 52(1):3-23
Api et al., 2020, Reg Tox Pharm, 118, 104805

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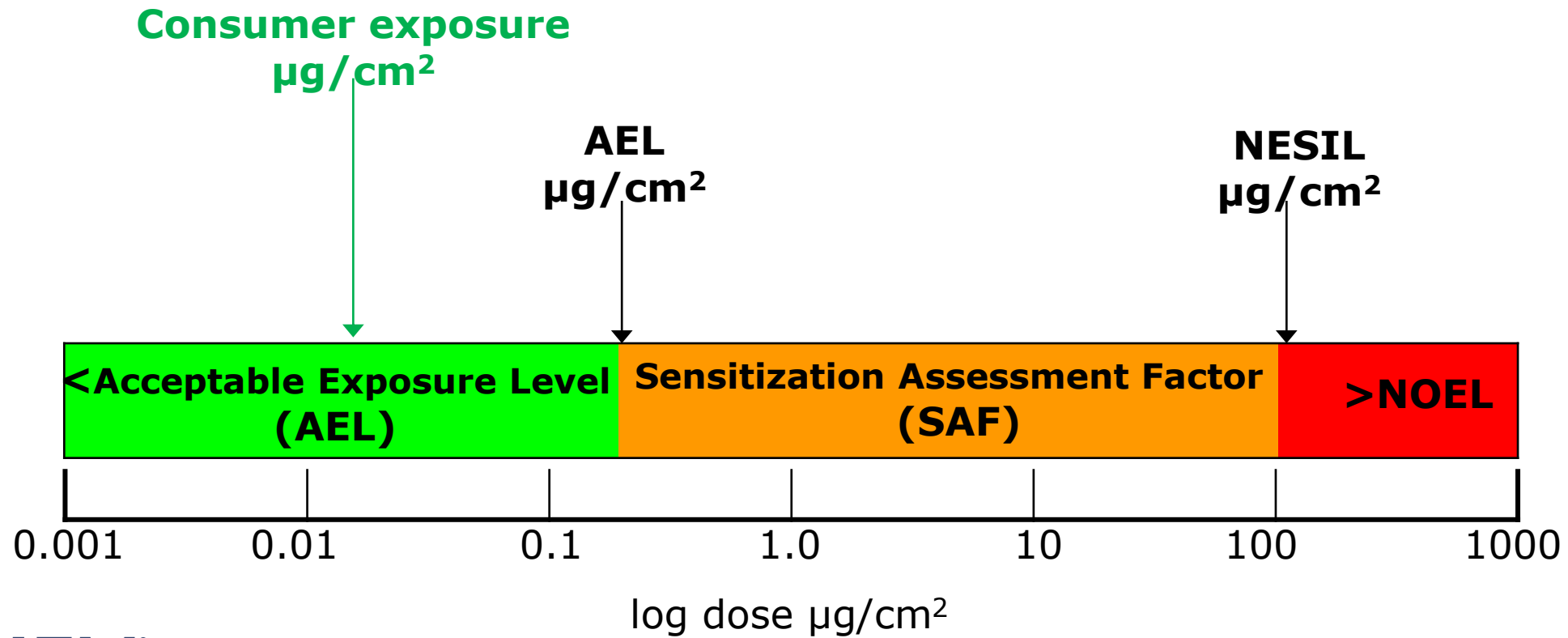
QRA follows the general risk assessment principles used in general toxicology

Acceptable Exposure Level (RfD or AEL)

$$\text{Acceptable Exposure Level} = (\text{RfD or AEL}) = \frac{\text{NOAEL or NESIL}}{\text{Uncertainty Factor (UF) or Sensitization Assessment Factor (SAF)}}$$

Risk for skin sensitization by fragrance ingredients in consumer products is reduced with dermal quantitative risk assessment (QRA)

Hazard assessment

Potency and derivation of point of the departure (NESIL)

Application of Sensitization Assessment Factors (SAFs)

Acceptable exposure levels (AEL)

Compare AEL to consumer exposure levels (CEL)

Manage risk – Maximum Acceptable Concentrations
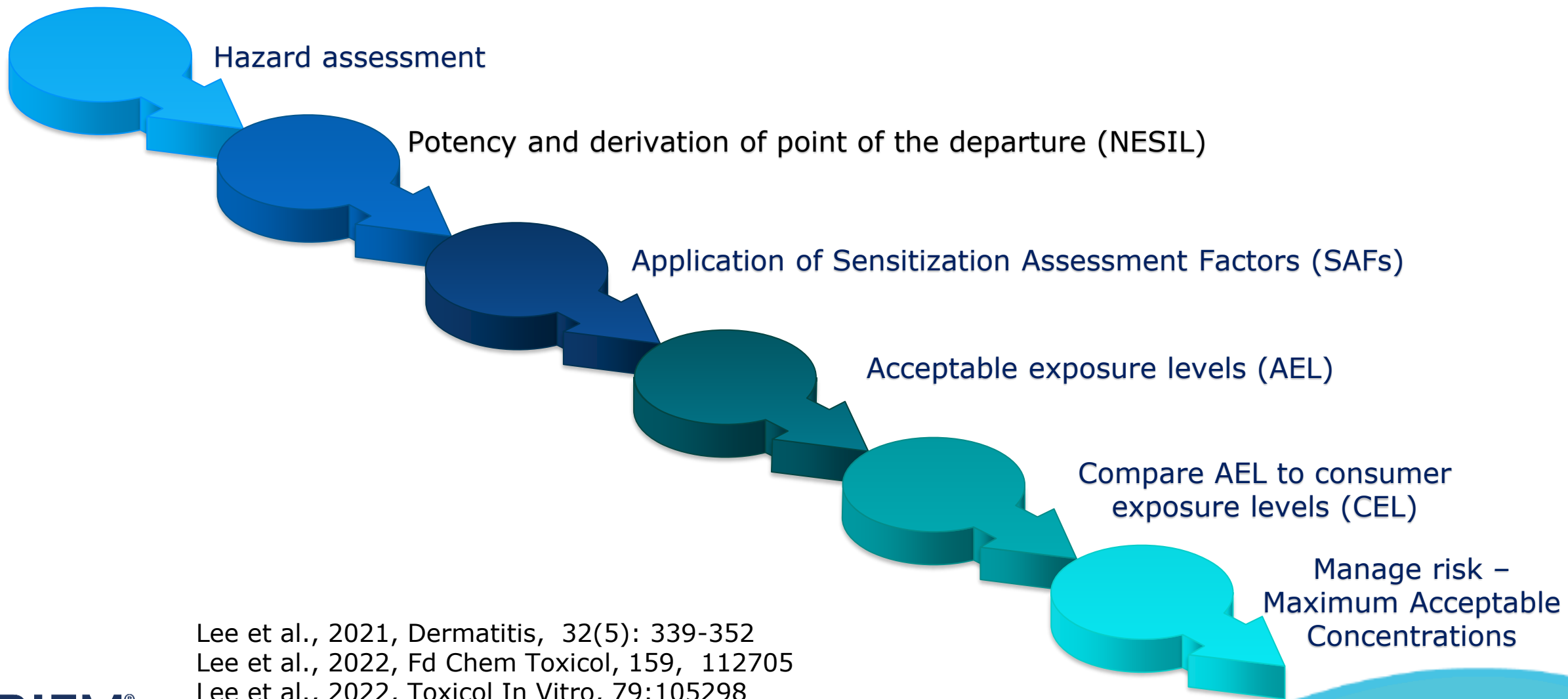
Lee et al., 2021, Dermatitis, 32(5): 339-352
Lee et al., 2022, Fd Chem Toxicol, 159, 112705
Lee et al., 2022, Toxicol In Vitro, 79:105298
Na et al., 2022, Dermatitis, 33 (2): 161-175
Na et al., 2022 Regul Toxicol Pharmacol., 130:105128
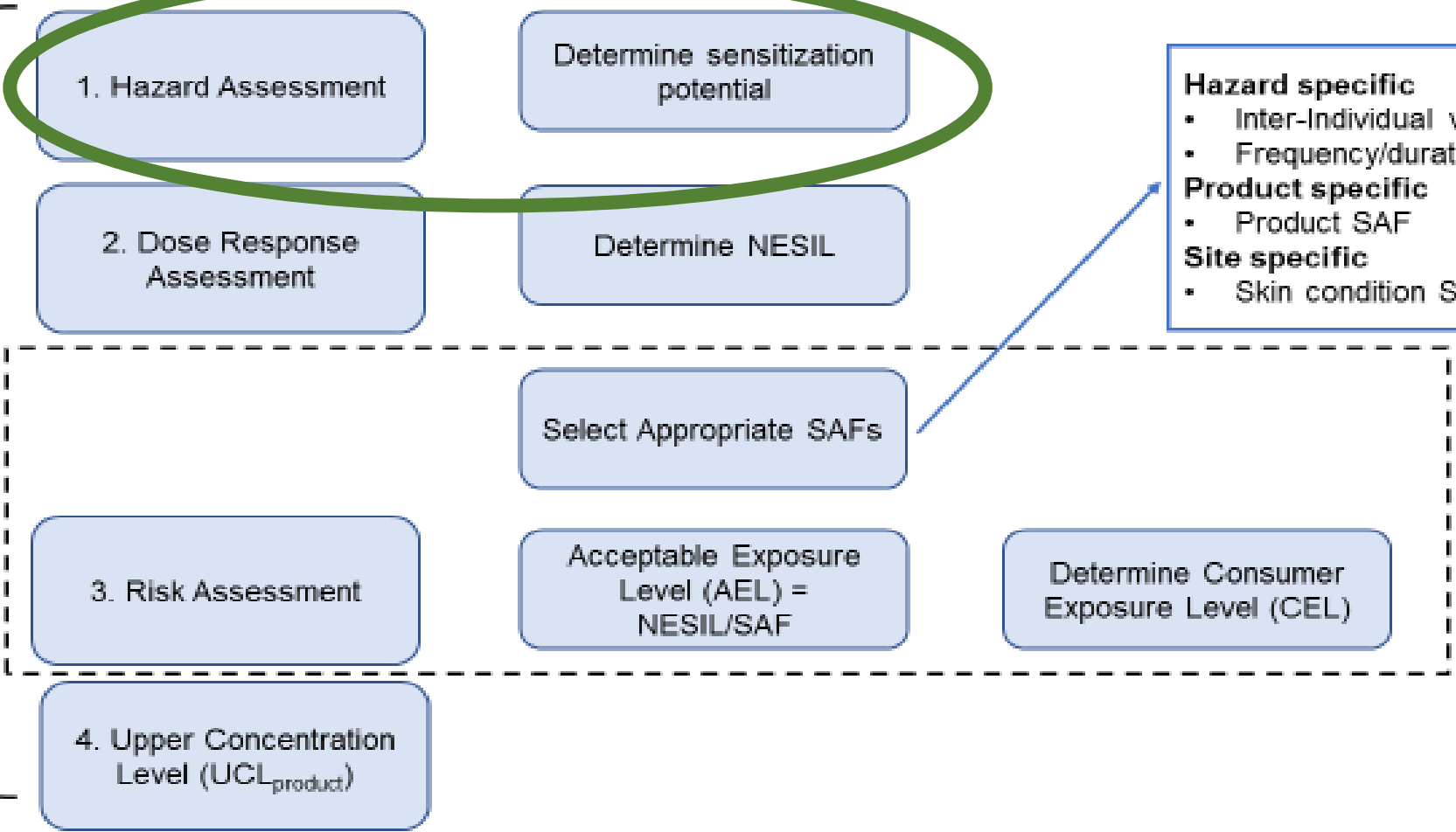
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Api et al., 2020, Reg Tox Pharm, 118, 104805
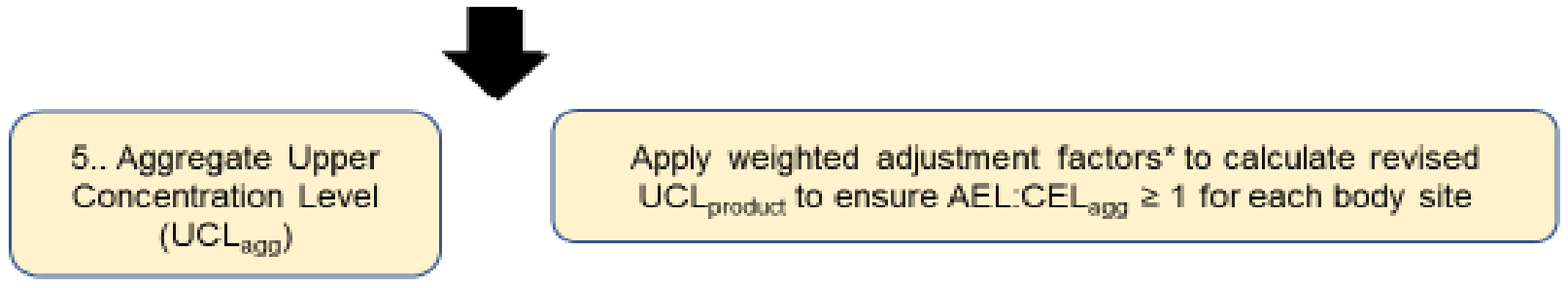
Step 1 involves determining the potential (hazard) to induce sensitization from all sources of information

In vivo - Human

In silico

Historical skin sensitization data

In vivo - Animal

In vitro
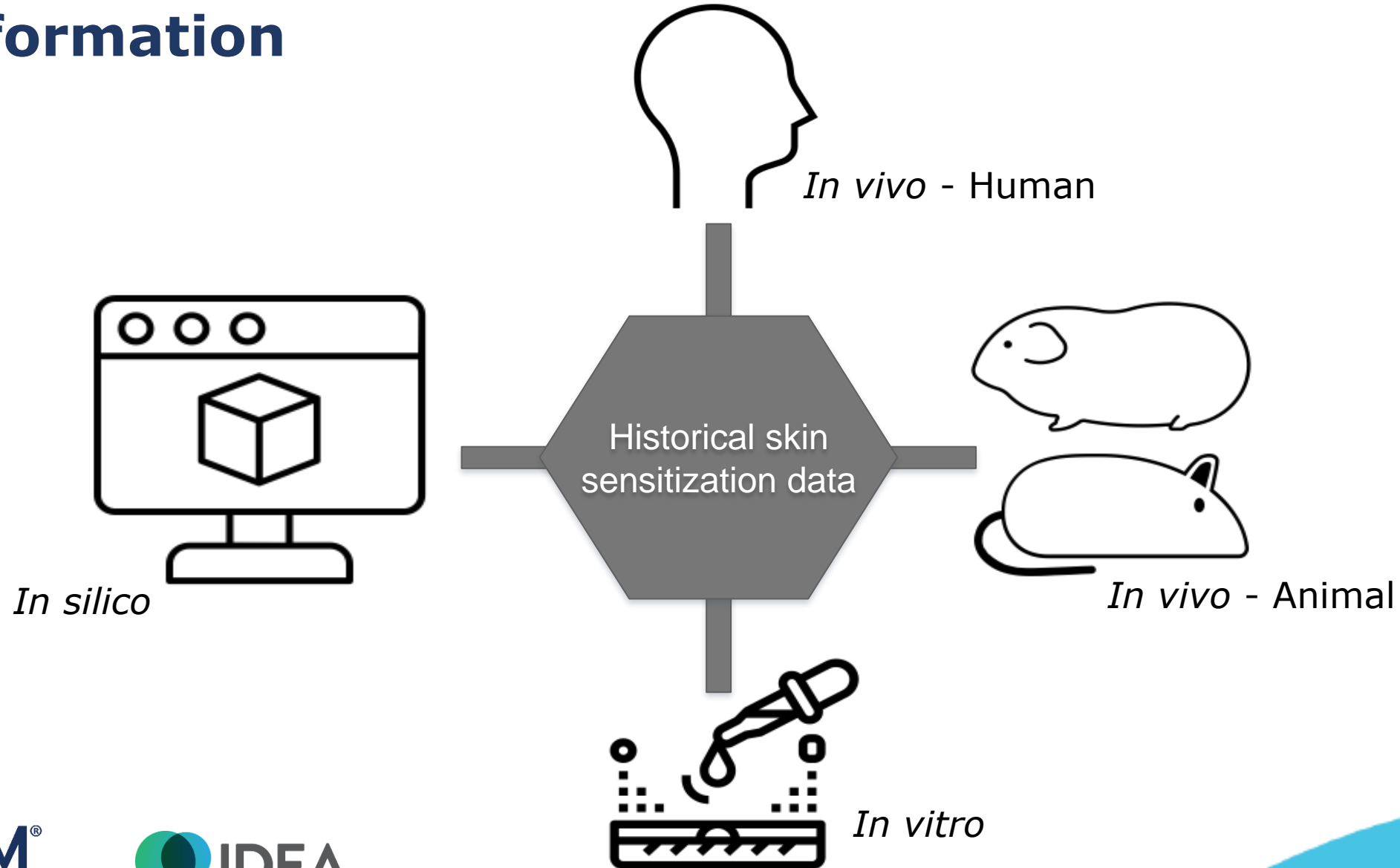
In Step 1 numerous studies can contribute to the assessment of sensitization potential

Application to induction of skin sensitization - a threshold phenomenon
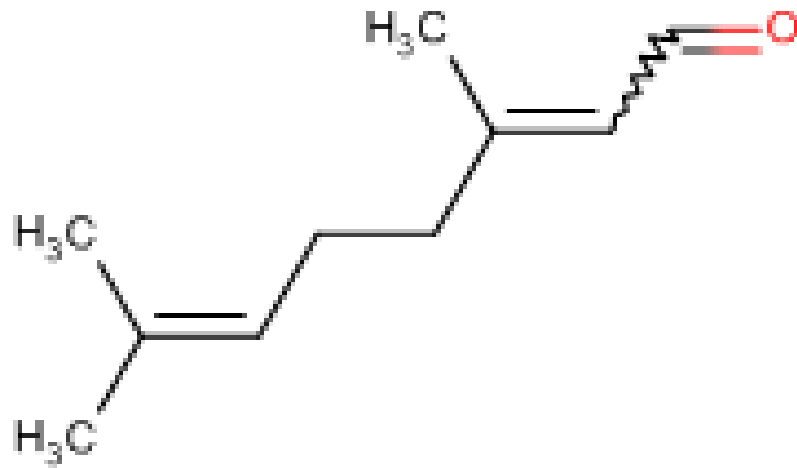
Example: Citral CAS5392-40-5

- Citral is predicted to be reactive to skin proteins by both a Schiff base and Michael addition mechanism (OECD Toolbox v3.1; Roberts, 2009; Toxtree 2.5.0)
- >30 guinea pig studies
- >30 LLNAs
- >10 in vitro assays
- >18 Human Maximization studies
- >18 HRIPTs
- >40 DPTs

In Step 2 all existing data for the substance contributes to the weight of evidence

The NESIL is a dose at which no induction of skin sensitization is expected to occur
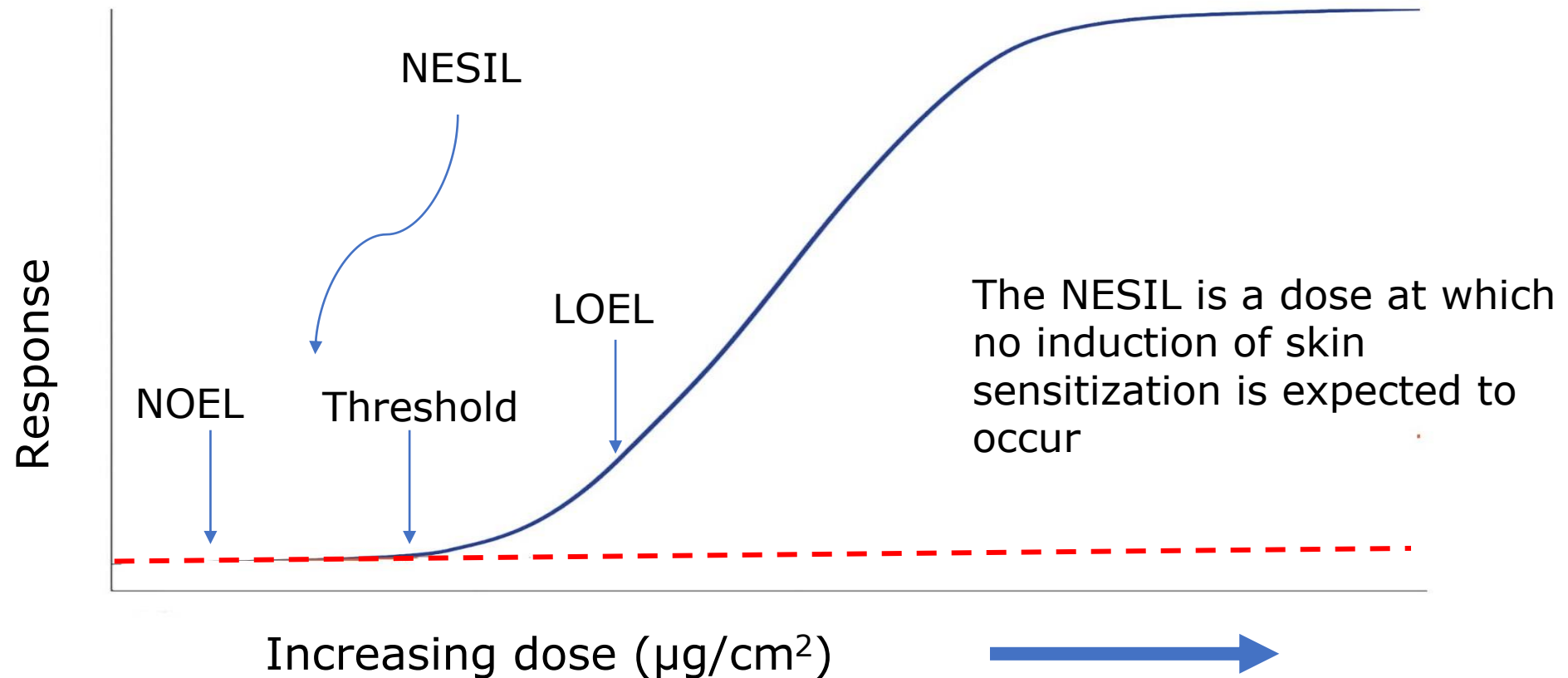
Dermal Sensitization Threshold (DST) are thresholds of toxicological concern for skin sensitization

If a chemical's exposure is below the relevant DST, sensitization is very unlikely

Unilever publish a **non-reactive DST**

Unilever update the **non-reactive DST**

RIFM publish a **reactive DST**

RIFM publish a set of **HPC rules**

Kao/RIFM publish an **HPC DST**

Lhasa/RIFM update the **non-reactive**, **reactive** and **HPC DSTs**

2008 2009 2010 **2011** 2012 2013 2014 **2015** 2016 2017 2018 2019 **2020** 2021 **2022**
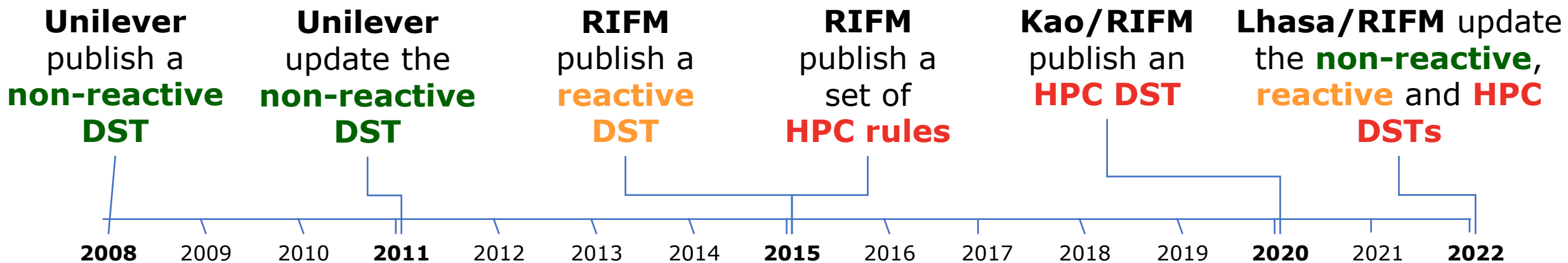
Safford, *Regul. Toxicol. Pharmacol.* **2008**, *51*, 195–200
Safford et al., *Regul. Toxicol. Pharmacol.* **2011**, *60*, 218–224
Safford et al., *Regul. Toxicol. Pharmacol.* **2015**, *72*, 694–701

Roberts et al., *Regul. Toxicol. Pharmacol.* **2015**, *72*, 683–693
Nishijo et al., *Regul. Toxicol. Pharmacol.* **2020**, *117*, 104732
Chilton et al., *Regul. Toxicol. Pharmacol.* **2022**, *133*, 105200

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QRA expresses dose in terms of the quantity of the substance per exposed skin

62.5 µg DNCB
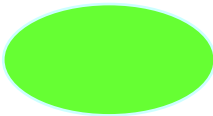
1.8 cm² Site

Sensitization Rate

85%

62.5 µg DNCB
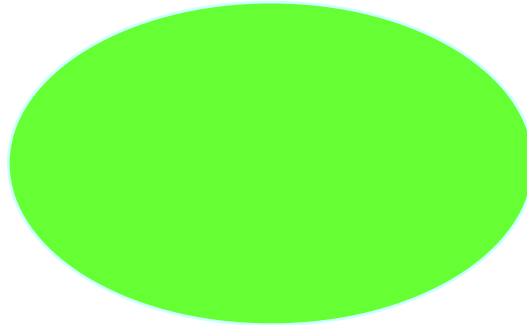
7.1 cm² Site

8%

INDIVIDUAL PRODUCT ASSESSMENT

1. Hazard Assessment — Determine sensitization potential

2. Dose Response Assessment — Determine NESIL

Select Appropriate SAFs

Hazard specific
- Inter-Individual variability SAF
- Frequency/duration of use SAF

Product specific
- Product SAF

Site specific
- Skin condition SAF

3. Risk Assessment — Acceptable Exposure Level (AEL) = NESIL/SAF — Determine Consumer Exposure Level (CEL)

4. Upper Concentration Level ($UCL_{product}$)

AGGREGATED ASSESSMENT PER BODY SITE

5. Aggregate Upper Concentration Level (UCL_{agg})

Apply weighted adjustment factors* to calculate revised $UCL_{product}$ to ensure $AEL:CEL_{agg} \geq 1$ for each body site

*Weighted adjustment factors are described in section 3.3. They are based on the Creme RIFM Aggregate Exposure Model

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Selection of the appropriate SAFS involves an extrapolation from controlled experimental situations to real life exposure scenarios

Inter-individual Variability

Product

Occlusion

Frequency/ Duration of Product Use

Skin Condition/ Site of Exposure

Factor	Consideration	Influence	SAFs*	Comments (comparison of the experimental condition with the product use condition)
Inter-individual	There can be large differences between individuals in response to a chemical exposure due to several different parameters.	Increase of susceptibility to induction	10	The inter-individual variability not accommodated in the NESIL (through using a mixed male/female HRIPT panel covering 18-70 years of age) is reflected by a SAF of 10.
Product	Role of vehicle/matrix	Delivery	0.3 or 1 or 3	The predicted effect of product formulation versus the experimental conditions; 0.3 (inert objects with no direct contact, e.g. candles or detergent pods or no vehicle/matrix) or 1 (most products) or 3 (increased irritation)
Frequency / duration of product use	Products may be used over extended periods resulting in bio-accumulation	Increase of susceptibility to induction	1 or 3	Products may be used frequently over extended periods of time resulting in accumulation (chemical or biological accumulation) or reservoir effect
Skin condition	Inflammation	Increase of susceptibility to induction	1 or 3 or 10	Inflammation for body site: body areas that are specifically prone to increased level of inflammation such as contribution to inflammation from use of the product itself or of other products to the body site (such as use of depilatories on axillae and legs).

*Note: for practical purposes the number 3 approximates 3.16 or the half log of 10.

Deodorants and hair sprays are two examples how SAFs can differ between product types

Product Type	Inter-Individual	Product	Fre-quency/Dura-tion	Skin Condi-tion	Rationale for Skin Condition	QRA2 SAF
Deodorants	10	1	3*	10	These products are applied to the axillae where the skin is easily irritated There may also be acute transient irritation due to product application or mechanical irritation. Shaving may produce an acute transient response.	300
Hair sprays	10	1	3*	1	It is applied to the hair with minimal exposure of the scalp and hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	30

*Note: for practical purposes the number 3 approximates 3.16 or the half log of 10.

Consumer Exposure Level (CEL) is derived by understanding human exposure through characterization of exposed populations of the skin

CEL is calculated by multiplying the amount/day
by retention factor and divided by the area

Exposure assessment for shampoos:

- Calculated exposure = 23,630 mg/day (PCPC)
- Retention Factor = 1% or 0.01 (SCCS, 2021)
- Area = 1430 cm² (EPA, 1997; area hands + ½ head)

$$\text{Exposure} = 23{,}630 \text{ mg/day} * 0.01 \div 1430 \text{ cm}^2$$
$$= 0.2 \text{ mg/cm}^2/\text{day}$$

Acceptable Exposure Levels (AELs) to fragrance ingredients that are dermal sensitizers can be determined in specific real life consumer product types

Risk Characterization For Fragrance Ingredients

$$\text{Acceptable Exposure Level (AEL)} = \frac{\text{WoE NESIL}}{\text{Sensitization Assessment Factor (SAF)}}$$

Comparison of Acceptable Exposure Levels (AEL) to calculated Consumer Exposure Level (CEL)

AEL ≥ CEL to be Acceptable or

AEL : CEL ≥ 1 to be Acceptable

The final step involves risk characterization

Consumer exposure $\mu g/cm^2$

Consumer exposure to product $\mu g/cm^2$

AEL $\mu g/cm^2$

NESIL $\mu g/cm^2$

| <AEL | Sensitization Assessment Factor (SAF) | >NOEL |

0.001 0.01 0.1 1.0 10 100 1000

log $\mu g/cm^2$
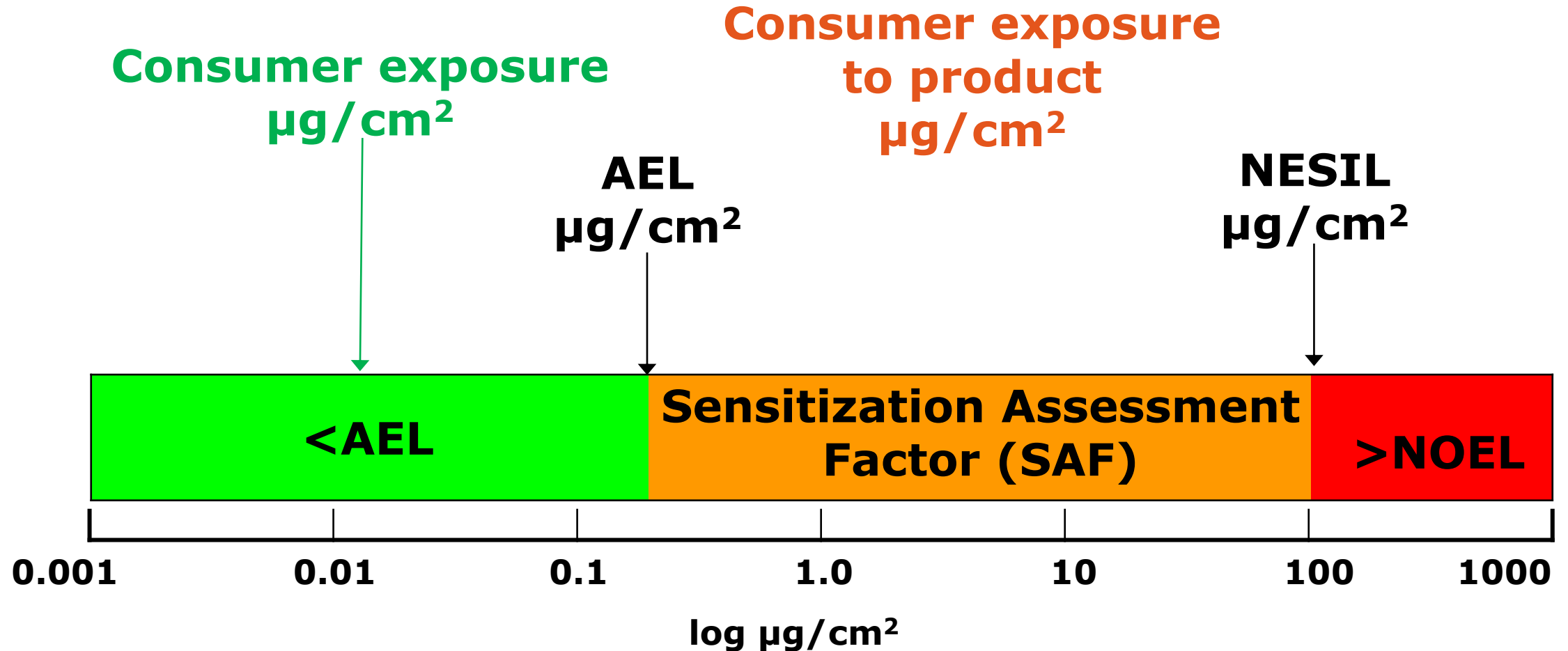
An example of the QRA dermal sensitization for two products containing citral is presented

Weight of Evidence NESIL

- Guinea-pig data – weak sensitizer [32]
- Local Lymph Node Assay
  - EC_3 = 1414 µg/cm^2 [30]
- Human data
  - CNIH NOEL = 1400 µg/cm^2
- WoE NESIL = 1400 µg/cm^2

SAF

- **Deo/AP SAF is 300**
- **Hair Spray SAF is 30**

Consumer Exposure

- DEO/AP = 9.1 mg/cm^2/day
  - AEL = 1400/300 = 4.7 µg/cm^2
  - AEL/ CEL (× 0.001 mg/µg) = 0.0005
  - AEL≥CEL ≤ 0.05%

- Hair Spray = 2.2 mg/cm^2/day
  - AEL = 1400/30 = 46.7 µg/cm^2
  - AEL/CEL (× 0.001 mg/µg) = 0.02
  - AEL≥CEL ≤ 2%

Risk characterization for citral in deodorants shows that the maximum acceptable concentration is ≤ 0.05%

Consumer exposure 4.6 µg/cm² (≤ 0.05%)

AEL 4.7 µg/cm²

Consumer exposure to product 9100 µg/cm²

NESIL 1400 µg/cm²

Sens. Assessment Factor (300)
AEL/CEL
Unacceptable

<AEL

>NOEL

0.001   0.01   0.1   1.0   10   100   1000

log µg/cm²
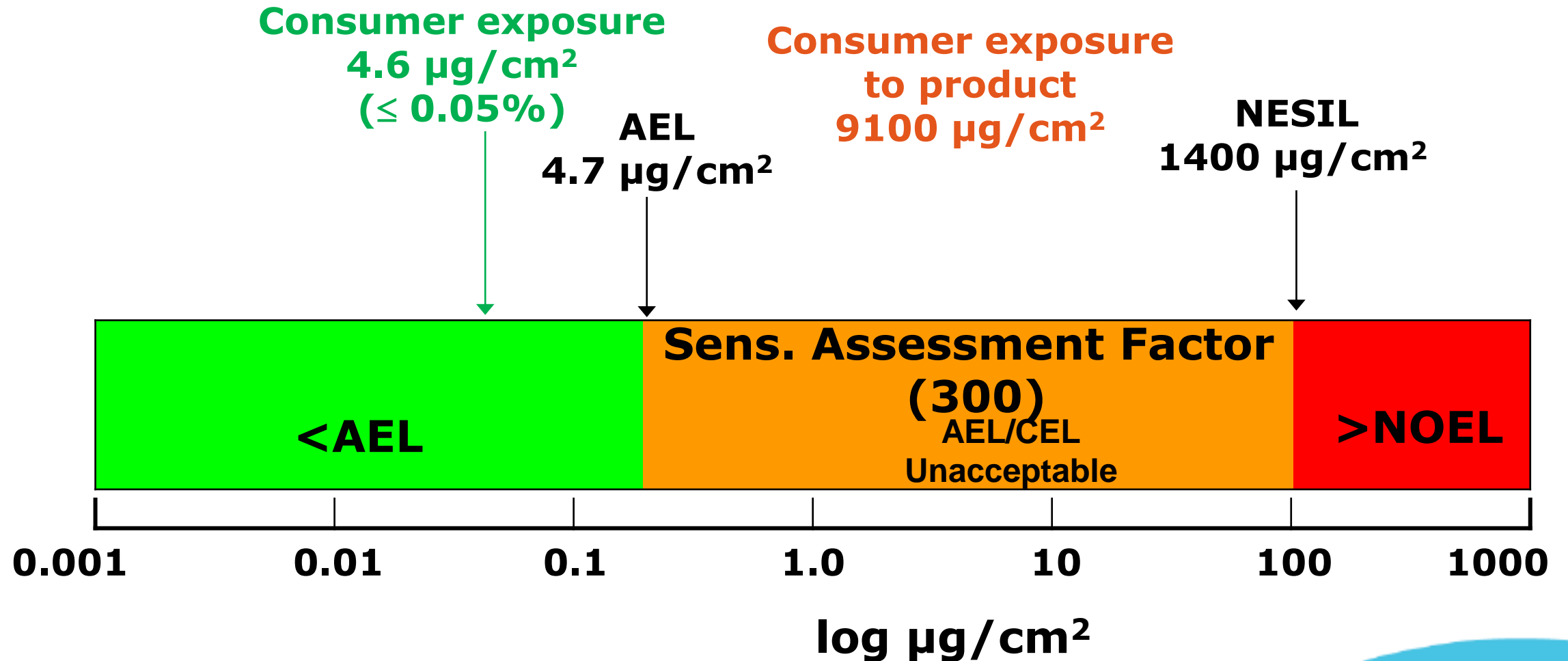
Risk characterization for citral in hair sprays shows that the acceptable concentration is ≤ 2%

Consumer exposure
44 µg/cm²
(≤ 2%)

Consumer exposure to product
2200 µg/cm²

AEL
46.7 µg/cm²

NESIL
1400 µg/cm²

<AEL	Sens. Assessment Factor (30) AEL/CEL Unacceptable	>NOEL

0.001   0.01   0.1   1.0   10   100   1000

log µg/cm²
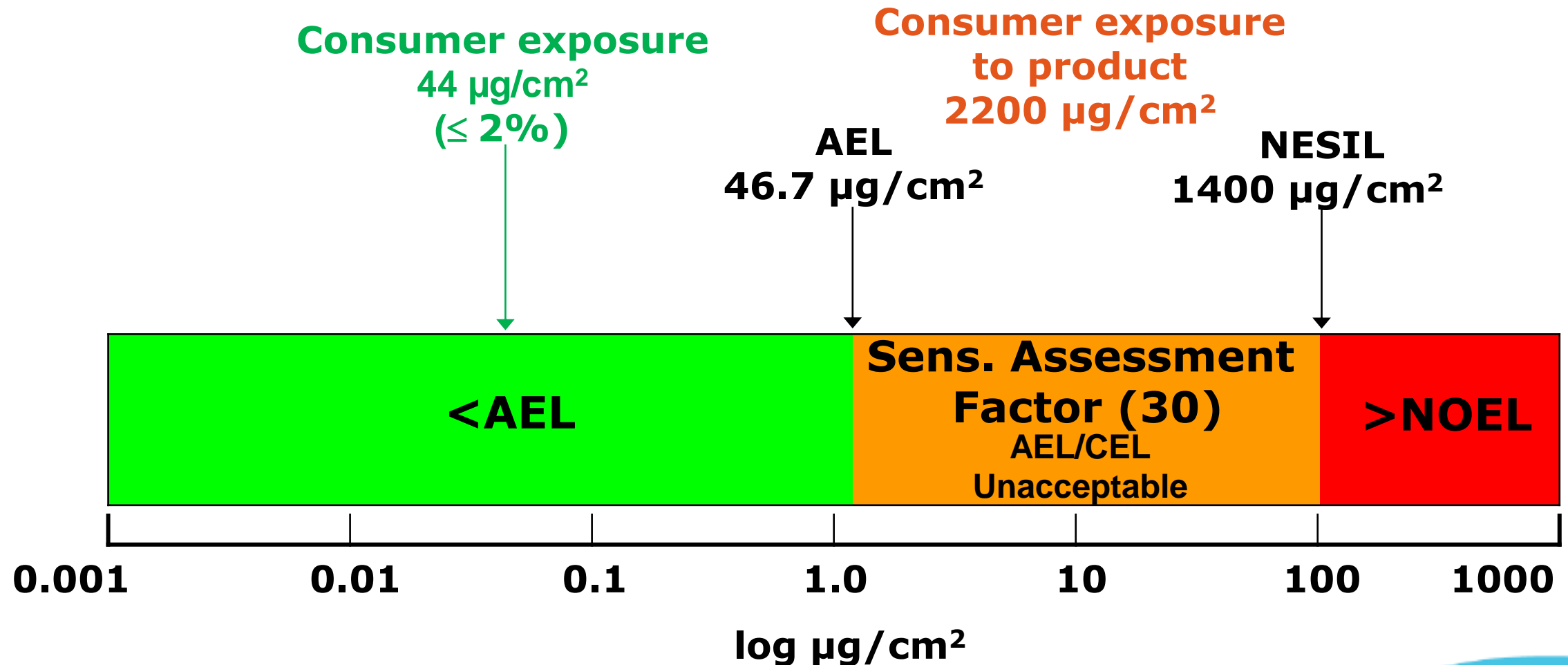
Two major revisions on QRA1 were agreed upon – include aggregate exposure and re-evaluate SAFs
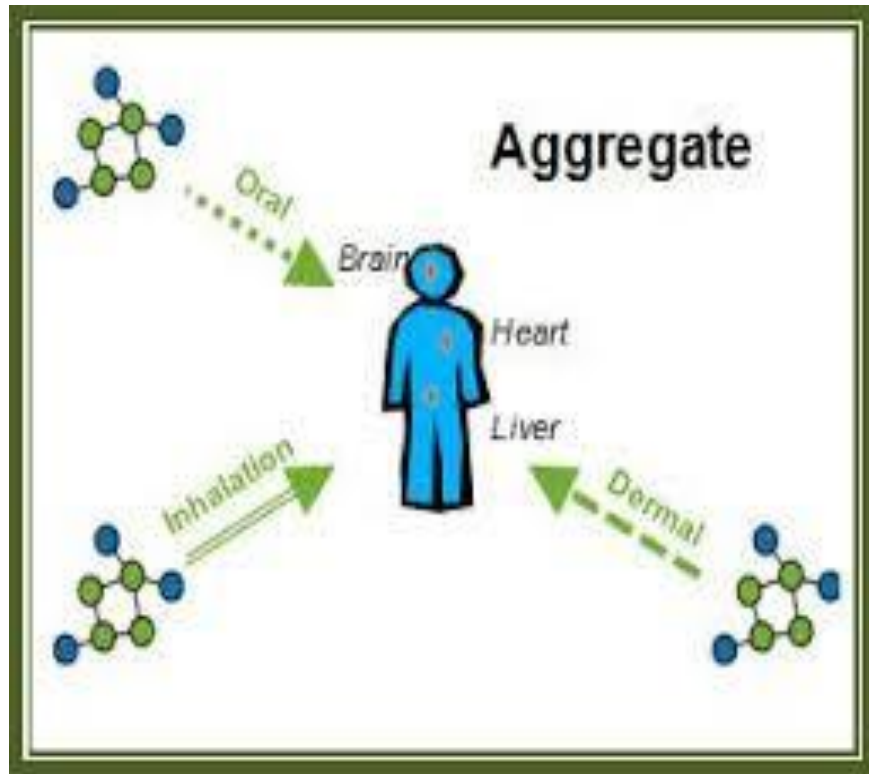
Aggregate

Uncertainty = Sensitization Assessment Factor (SAF)

Basketter & Safford, 2016, Reg. Tox. & Pharm; 74, 105-116.

What is the Creme RIFM Model?

A probabilistic tool based on real world data to estimate aggregate exposure from consumer product ingredients.
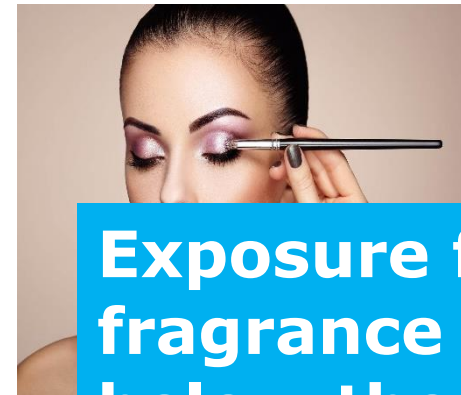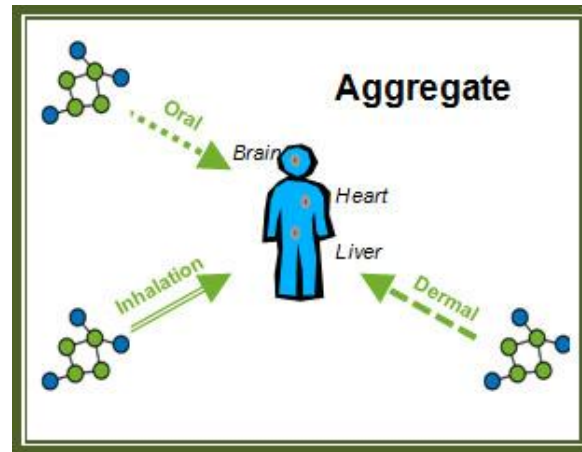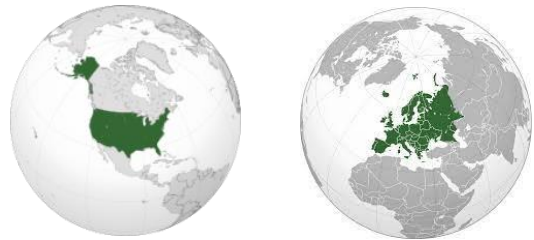
Exposure for 75% of fragrance materials fall below the TTC [March 2022]

Aggregate

Oral → Brain
Heart
Liver
Inhalation →
Dermal →

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Product categories are used to simplify implementation of Standards

Category	Product Category Description
1	Products applied to lips
2	Products applied to axillae
3	Products applied to the face using finger tips
4	Fine fragrance products (EDT, EDP etc.)
5	Products applied to the face and body using the hands (palms), primarily leave-on
6	Products with oral and lip exposure
7	Products applied to the hair with some hand contact
8	Products with significant ano-genital exposure
9	Products with body and hand exposure, primarily rinse off
10	Household care products with mostly hand contact
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin

Products that give the lowest concentrations are used to derive the product categories

Category	Product Type Deriving Exposure	SAF	Exposure mg/cm²/day
1	Lipstick	100	11.8

| Category 5 - Products applied to the face and body using the hands (palms), primarily leave-on		SAF	Exposure	NESIL of 1000
Facial Cream (Moisturizing)/Facial Balm		100	2.8	2.21
Hand cream		100	2.6	3.02
Body Creams, lotions		300	0.6	1.27
Nail care products including cuticle creams etc.		100	0.97	1.031
Insect repellent (intended to be applied to the skin)		100	3.02	0.331

Overlapping table values:

Category	Product Type Deriving Exposure	SAF	Exposure	NESIL
4	Fine fragrance products	100	2.8	2.21 / 0.357
5	Insect repellent (intended to be applied to the skin)	100	2.6	3.02 / 0.385
6	Toothpaste	300	0.6	1.27 / 0.556
7	Hair sprays	100	30	2.2
8	Baby wipes		0.97	300	7.4 / 1.031
10	Hand dishwashing detergent	100	0.2
11	Feminine hygiene liners	300	0.2
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted

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While realistic, there are still many conservativisms in the Creme RIFM Aggregate Exposure Model

Fragrance material is in every product; no presence probability

Highest daily acute dermal exposure for 7-day survey period

95th percentile fragrance concentrations for the risk assessment of final products

Fragrance is assumed to be non-volatile

Leave-on products are assumed to be retained without washing for 24-hours

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Adjustment Factors adjust upper concentration levels to ensure that aggregate exposure remains below an acceptable exposure level
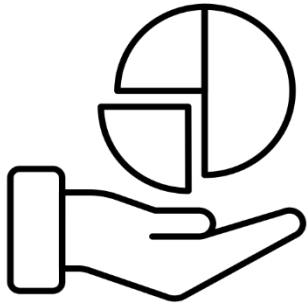
Accounts for the overall contribution of a product to exposure to a body site.

Ensures, when necessary, a proportional reduction of upper concentration limits where several products are contributing to exposure on the same body site.
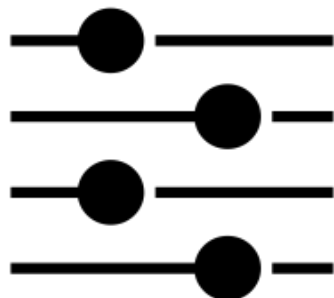
The adjustment factors are a function of product exposure. They are the same for all materials.

QRA2 Upper Use Levels Product Categories with Adjustment Factors: Citral

Category	Product Type	Max QRA 2 use level by category (%)	QRA 2 aggregate adjustment factor	QRA 2 aggregate exposure adjusted upper conc. levels (%)
1	Lip Products	0.119	0.91	0.11
2	Deodorants & Antiperspirants of all types including fragranced body sprays	0.051	0.63	0.03
3	Eye Products	0.645	1.00	0.65
4	Fine Fragrance (eau de toilette, parfum etc.)	0.63	0.95	0.60
5	Insect repellent (intended to be applied to the skin)	0.46	0.33	0.15
6	Toothpaste	1.102	0.32	0.35
7	Hair sprays	2.121	0.58	1.23
8	Tampons	0.080		0.08
9	Bar soap	2.333	0.50	1.17
10	Hand dishwashing detergent	7.000	0.60	4.21
11	Feminine hygiene conventional pads, liners, interlabial pads	3.333		3.33
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted		

Dermal sensitization QRA is used to determine the maximum acceptable concentration for fragrance ingredients

All available data –

in vitro, *in silico*, DST and historical *in vivo* data are considered in the derivation of a NESIL for QRA

… to ensure that everyone can enjoy their favorite fragranced products safely

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