Incorporating aggregate exposure in the QRA

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Current exposure assessment for QRA

QRA methodology as described in Api et al., 2008 is based on deterministic calculations of the CEL

o Calculates exposure to fragrances in one product only

o Product use amounts are based on a high percentile in line with SCCS guidelines

o Product frequency of use is also based on SCCS guidelines

o Area of application is assumed based on the product type (e.g. shampoo is scalp and hands, body lotion is all over body, minus the head)

o Assumes a single (high) level of ingredient (fragrance) in the product

o Standard body surface areas taken

This method assumes all consumers, habits and products are the same

Aggregate exposure determined using the Creme model

The Creme model overcomes many of the problems associated with using the current deterministic calculations

- Calculations are based on actual consumer habits:

    o Multiple product use throughout the day – use, co-use and frequency of use as recorded by panellists

    o Actual areas of application as recorded by panellists

    o Amounts of product used sampled from published data

    o Level of ingredient (fragrance) in product reflects range of actual use levels

   o Body weights/heights (surface area) sampled from published distributions

This method recognises the fact that consumers, habits and products are different

Using aggregate exposure in the QRA

In using the output from the Creme model, a number of factors need to be taken into account

o   The QRA is based on skin exposure per unit area ($\mu g/cm^2$). The application of products differs between sites on the body.

o   Thus it is not appropriate to aggregate total body exposure (as might be done for systemic toxicity) as different application sites will be exposed to different products and different levels of exposure

o   The Creme model calculates aggregate exposure based on each application site

o   The QRA is then based on the application site with the highest exposure and/or highest AEL:CEL ratio

Application Sites
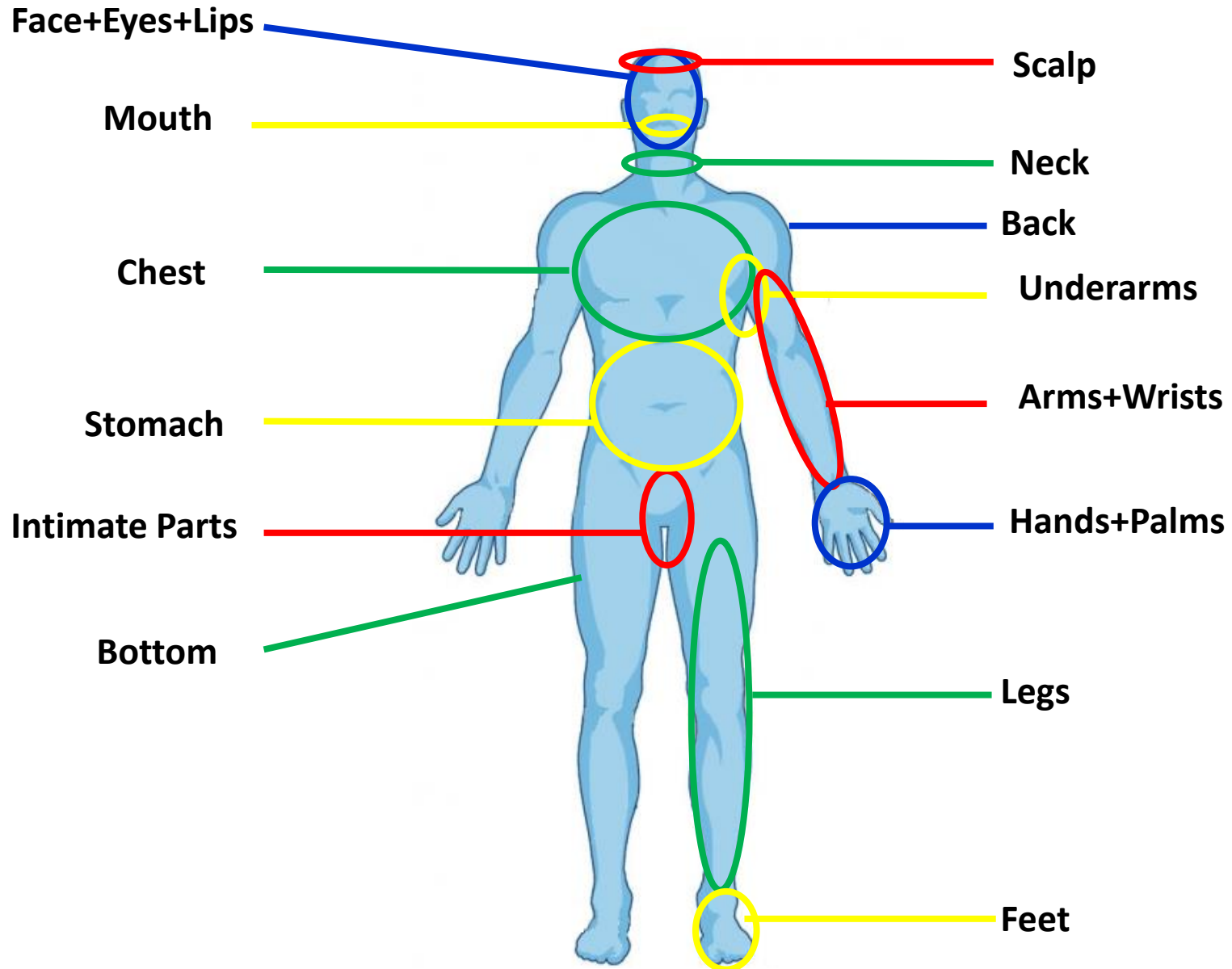
Determining aggregate exposure per body area

- The Creme model calculates the skin exposure for each product used assuming an even distribution over the area of application

- Aggregate exposure is then calculated for each application site based on all products applied over the day

- Taking a simplified example of exposure to Fragrance Ingredient X from the use of four products, the resulting aggregate exposure to face, underarms and chest for an individual may look as follows:

	Dose per unit area ($\mu g/cm^2$)		
	Face	Underarms	Chest
Body wash	0.08	0.08	0.08
Body lotion	-	0.2	0.2
Face cream	0.4	-	-
Deodorant	-	0.8	-
Aggregate	**0.48**	**1.08**	**0.28**

Incorporating aggregate exposure in the QRA

Incorporating aggregate exposure into the QRA is not a straightforward process, and a number of issues need to be addressed:

- **How is the AEL:CEL ratio defined and aggregated for each product/application site combination?**

- **What is an appropriate factor to use for the matrix in the Product/Use SAF when products are applied concurrently to the same site?**

- **Should we account for skin sites draining to common or different lymph nodes?**

- **Over what period of time should the exposure be aggregated?**

- **How can IFRA standards be set for individual products based on aggregate exposure?**

Calculating Product/Use SAFs and AELs

- It is not possible to define a single Product/Use SAF since
  - Products may be used over multiple product areas which have different Product/Use SAFs (e.g. body lotion)
  - A number of different products which have different Product/Use SAFs may be applied to the same body area (e.g. shaving foam, aftershave)

- Therefore it is not possible to use the aggregate exposure for each application site/product type combination in a simple QRA

- The AEL:CEL ratio can be calculated for exposure from each product used on each body area, but it is not straightforward to aggregate these ratios

- A possible solution is to define a "risk factor" using a CEL:AEL ratio which could then be summed to give an "Aggregate Margin of Risk" – such a solution reverses the risk assessment and is less intuitive than a Margin of Safety

Application of the Matrix SAF

- The Product/Use SAF contains a factor for the matrix. This is applied for individual product types

- But products may be applied concurrently:
  – Shaving with shaving foam (aqueous), then applying aftershave (ethanolic)
  – Washing hands (aqueous), then applying hand cream (with moisturiser)

- To what extent, if any, do the matrices of products applied concurrently affect each other?

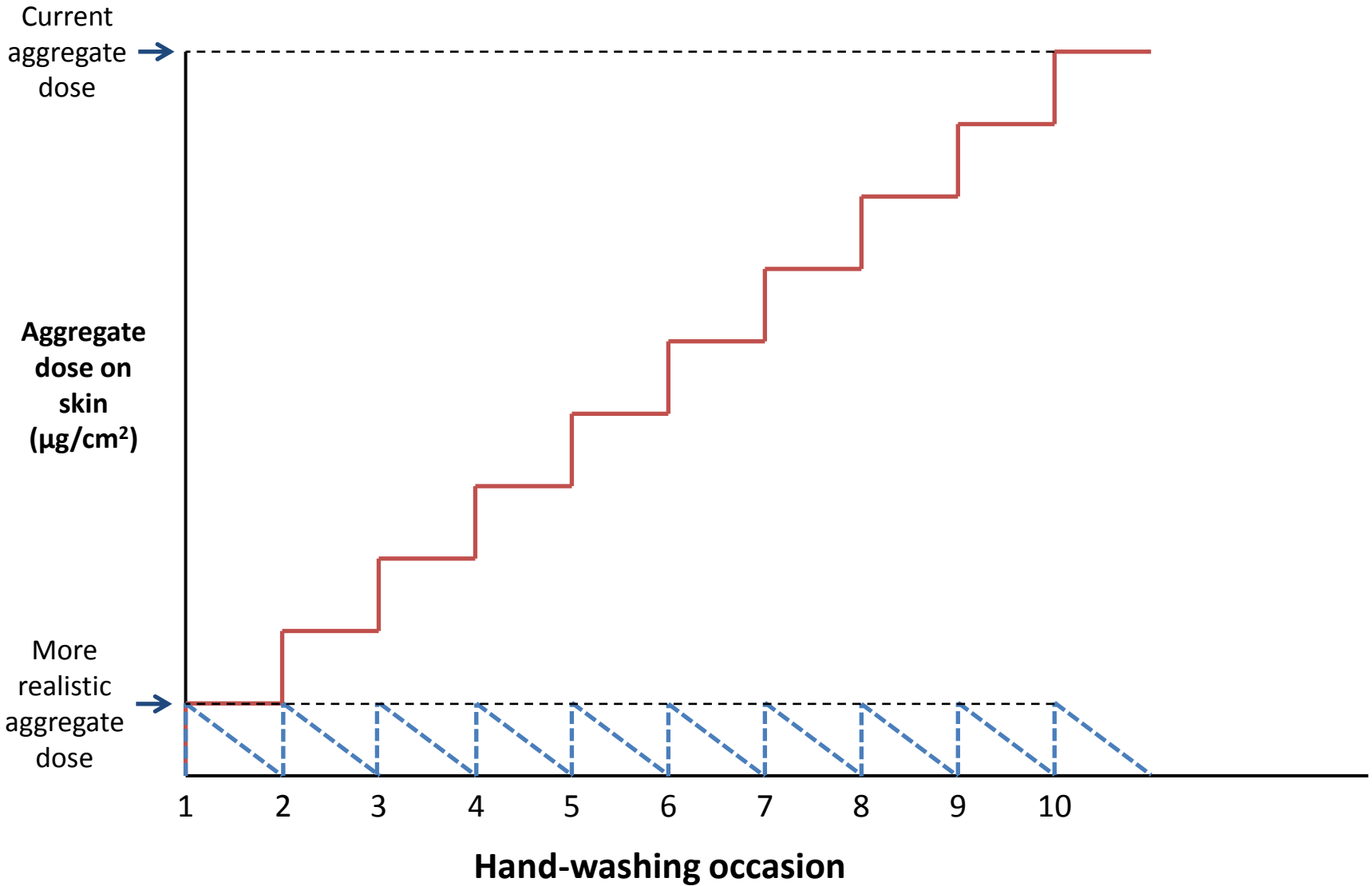- How can this be built into the QRA?

The Relevance of Site of Contact and Lymph Node Drainage

- Drainage of skin sites to lymph nodes is a requirement for the induction of skin sensitization

- For the same absolute amount of applied allergen, drainage of the skin site to a single lymph node may give a greater frequency of induction compared to the same amount of allergen distributed over a larger area of skin, where lymphatic drainage is served by several lymph nodes

- Exposures on isolated body parts (e.g. face, underarm) may be more important than exposures over larger surface area body parts (e.g. chest, abdomen, back)

- What are the implications for Aggregate Exposure?

Over what period of time should the exposure be aggregated?

- The current model assumes that all of the applied allergen remains on the skin between exposures

- The aggregate exposure dose calculated is that accumulated over the day

- The "clock" is then reset for the next day

- In reality, some (or all) of the allergen will be lost from the skin between applications by:
  - Washing
  - Rubbed off on clothing
  - Evaporation
  - Absorption into skin

- The current methodology can grossly overestimate aggregate exposure

- Also, we need to consider if there is carry-over from one day to the next

Consider aggregate skin dose from hand-washing

Current aggregate dose →

Aggregate dose on skin (µg/cm²)

More realistic aggregate dose →

Hand-washing occasion

1 2 3 4 5 6 7 8 9 10

Setting IFRA Standards using aggregate exposure

- Currently IFRA Standards are set based on exposure to individual products using a reverse risk assessment approach

- When incorporating aggregate exposure the process becomes more complex:

    - The exposure and contribution made to the exposure by each product type varies on each application site
    - The standard should be set based on the application sites with the highest exposure and AEL/CEL ratio
    - How can standards be apportioned to different products?
    - This becomes particularly complex in setting new standards for fragrances

Conclusions

- The Creme model for provides a methodology which can be used to determine aggregate dermal exposure to allergens to gain a true QRA assessment

- However, this is not a straightforward process, and some aspects need to be addressed further
  - How to aggregate risk for all product/body area combinations
  - How to apply matrix factors for concurrent application of different product types
  - How to take into account draining lymph nodes for different application sites
  - How to account for loss from skin between applications and determine an appropriate time period for aggregation
  - How to set IFRA standards using aggregate exposure

- These are currently under discussion in the RIFM Aggregate Exposure and QRA expert groups