Application of aggregate exposure in a case study

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Setting IFRA Standards for fragrances

- The current methodology for setting IFRA Standards is based on the QRA process (Api et al., 2008)

- Standards are calculated on an individual product basis based on:
  - The NESIL of the fragrance
  - Appropriate SAFs for the product
  - Use amount of the product based on published data including Cosmetics Europe (COLIPA), Personal Care Products Council (CTFA)
  - Skin area of application of the product from published sources including SCCS Guidelines

- These values are used to "back calculate" the concentration of fragrance in the product that gives an AEL:CEL ratio of 1

- In some cases where calculated IFRA Standards are very high, a lower pragmatic maximum amount is used as the IFRA standard

Question:

Could the inclusion of fragrances included in consumer products at IFRA Standard levels lead to aggregate exposure in consumers that exceeds the AEL on some body sites?

In order to address this question, a case study was conducted to calculate the theoretical exposure to fragrances present in cosmetic products at the calculated Maximum Use Levels ("IFRA Standards")

Aggregate exposure – case study

- Two fragrance materials were chosen for the case study –
    - Benzaldehyde
       - a moderate sensitiser with a NESIL of 590μg/cm^2
    - p-tert-Butyl-alpha-methylhydrocinnamic aldehyde (p-BMHCA)
       – a weak sensitiser with a NESIL of 4100

- Maximum Use Levels were calculated for each fragrance material in the range of products incorporated in the Creme aggregate exposure model

- Updated exposure data were included in the calculation where appropriate

- *SAF values were defined for each product based on the values at the outcome of the previous workshop for QRA II*

- Some calculated Maximum Use Levels for rinse-off shower products were very high, and lower pragmatic levels were chosen

Calculation of Maximum Use Levels for Case Study

Product	Total SAF	$CEL_{product}$ mg/cm²/day	Calculated Max. Use Level (%)	
			p-BMHCA NESIL = 4100	Benzaldehyde NESIL = 590
Deo/AP	200	9.1	0.23	0.03
Men's face cream	60	2.1	3.32	0.48
Hand cream	60	2.6	2.66	0.38
Hydroalcoholics	60	2.2	3.09	0.44
Shower gel	60	0.015	618.5	89.0
Toothpaste	60	1.25	5.47	0.79

Calculation of Maximum Use Levels for Case Studies

Product Type	Product Category	QRA II SAF	Exposure mg/cm²/day	p-BMHCA 4100		Benzaldehyde 590	
				IFRA Std	QRA II	IFRA Std	QRA II
Aerosol Antiperspirant (2)	Deodorants/ Antiperspirants	200	9.10	0.10%	0.23%	0.02%	0.03%
Stick Deodorant / Antiperspirant (2)		200					
Roll-On Deodorant (2)		200					
Roll-On Antiperspirant (2)		200					
Cream Deodorant / Antiperspirant (2)		200					
Gel Deodorant / Antiperspirant (2)		200					
Deodorant Cologne (Body sprays) (2)							
applied to unshaved s (4)							
Hydroalcoholic Produ) Applied to recently sh skin (3)		2.17	0.60%	3.15%		0.09%	0.45%
Men's Facial Cream a) balms (3)		0.17	5.00%	40.20%		3.00%	5.78%
Hand cream (5)		0.01	5.00%	683.33%		3.00%	98.33%
Women's Facial Crea							
Body Creams, lotions)		0.2	5.00%	34.17%		3.00%	4.92%
Women's Make up (Foundation) (5)		0.15	5.00%	45.56%		3.00%	6.56%
Make-up remover (8)							
Lip Products (1)							
Hair styling aids (mou gels, leave in conditic (4)		0.01	5.00%	683.33%		3.00%	98.33%
Hair sprays (4)							
Eye Products (Include) eye shadow, mascara		0.057	5.00%	119.88%		3.00%	17.25%
eyeliner, eye make-up		0.2	5.00%	34.17%		3.00%	4.92%
Shampoo (9)							
Body wash/shower ge							
Conditioner (rinse-off)		1.25	3.00%	5.47%		0.43%	0.79%
Face washes, gels, scrubs (9)		60	0.15	5.00%	45.56%	3.00%	6.56%
Bath gels, foams, mousses (9)		60	0.01	5.00%	683.33%	3.00%	98.33%
Bar soap (9)		60	0.057	5.00%	119.88%	3.00%	17.25%
Liquid soap (9)		60	0.2	5.00%	34.17%	3.00%	4.92%
Toothpaste (6)	Oral Care	60	1.25	3.00%	5.47%	0.43%	0.79%
Mouthwash (6)		60	1.00	3.00%	6.83%	0.43%	0.98%

Calculation of potential aggregate exposure

- Calculated Maximum Use Levels were incorporated in the Creme model using the event level method to calculate aggregate exposure and AEL:CEL ratios for each body surface area

- Inter-individual SAF and Site SAF values were applied to the NESILs to define an AEL for each application area

- Frequency/duration SAF and Product SAF values were applied to the exposure calculated for each product at the event level, and an aggregate CEL calculated for each application area

- The model was run with these values to calculate aggregate AEL:CEL ratios for each application area

Site SAFs used in the aggregate exposure model

Body Site	Occlusion	Skin site inflam-mation	Peri-anal/occular	Total SAF
Scalp	1	1	1	1
Face	1	3	1	3
Eyes	1	1	3	3
Lips	1	3	1	3
Mouth	1	3	1	3
Neck	1	1	1	1
BehindEars	1	1	1	1
Chest	1	1	1	1
Stomach	1	1	1	1
Back	1	1	1	1
Underarms	1	3	1	3
Arms	1	1	1	1
Wrists	1	1	1	1
Back of Hand	1	3	1	3
Palms	1	3	1	3
IntimateParts	1	3	1	3
Legs	1	3	1	3
Feet	1	1	1	1

Product SAFs used in the aggregate exposure model

Product type	Product SAF
Deo/AP	3
Hydroalcoholics	1
Moisturisers	1
Body Lotion	1
Cosmetic Styling	1
Shower Products	1
Oral Care	1

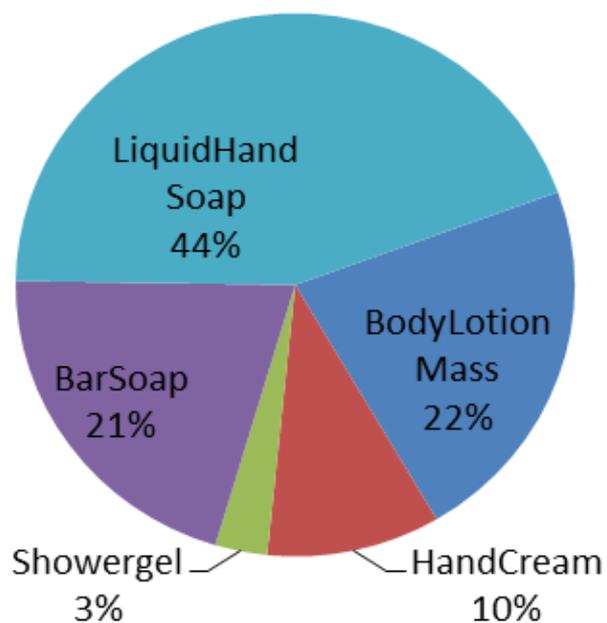# AEL:CEL ratios for Benzaldehyde based on aggregate exposure
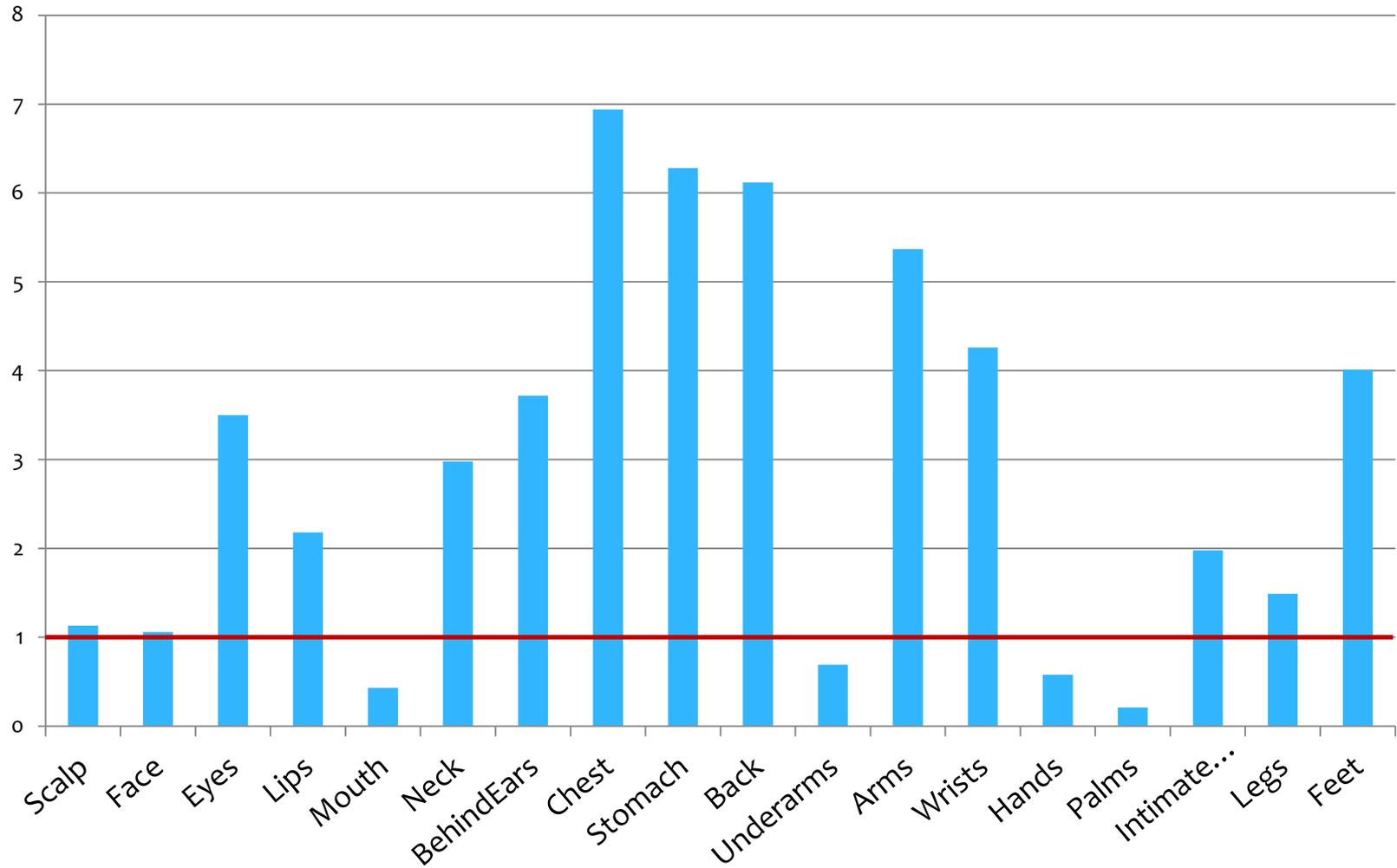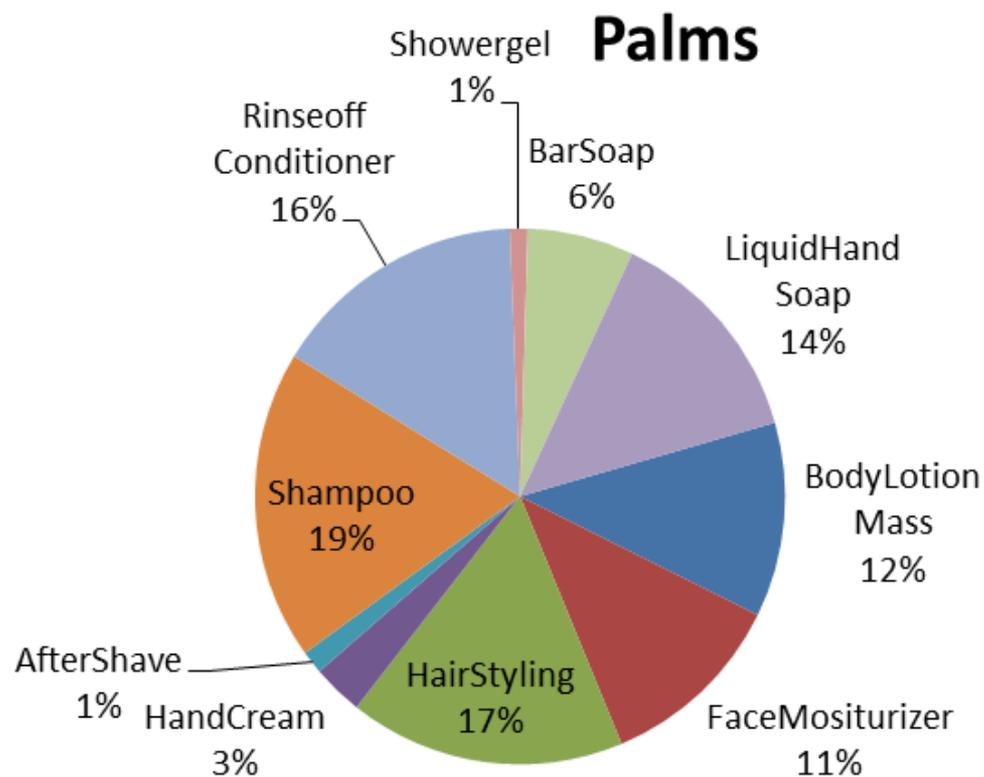
AEL:CEL ratios for BMHCA based on aggregate exposure
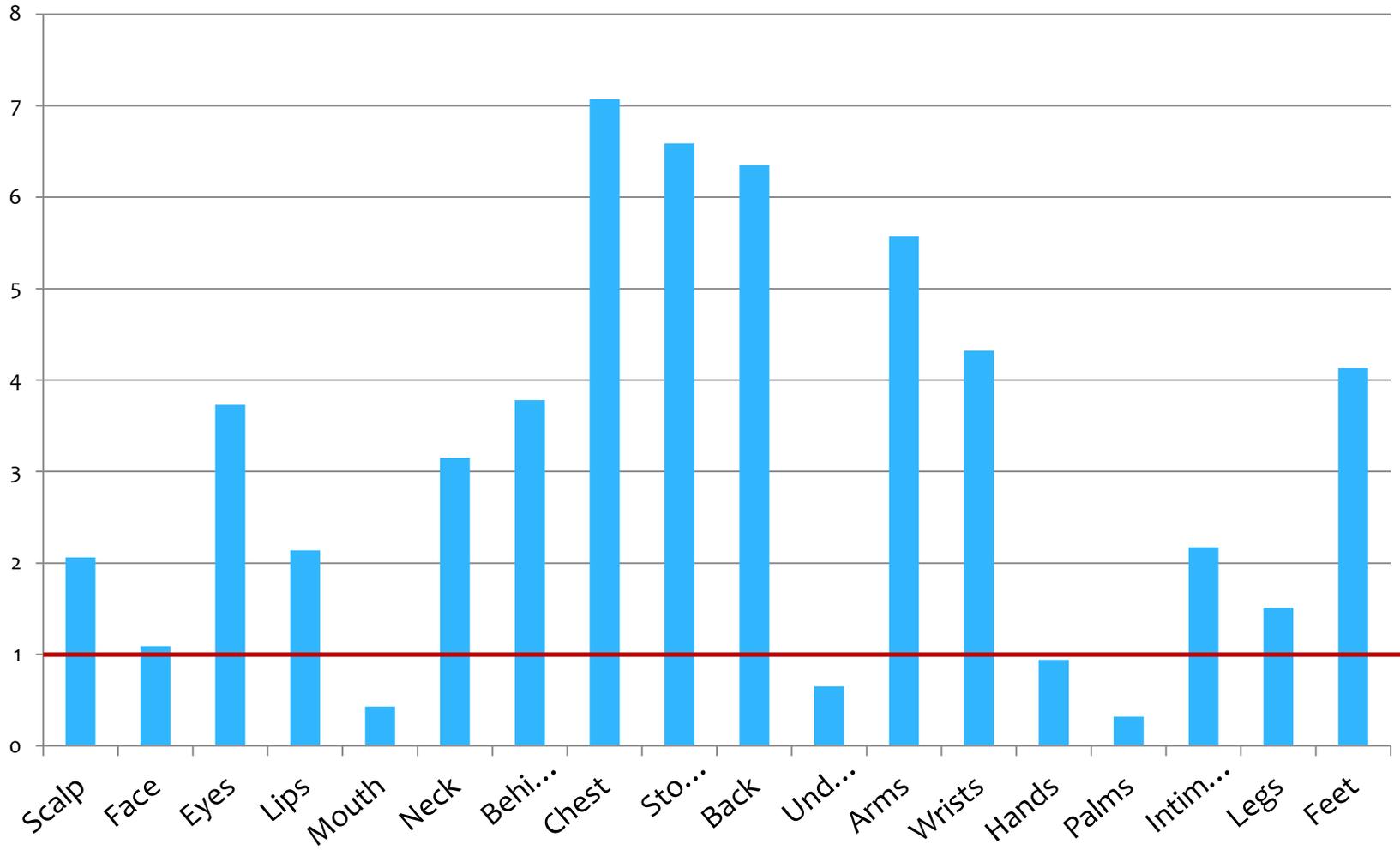
Products contributing to the aggregate exposure to Benzaldehyde on the Hands and Palms
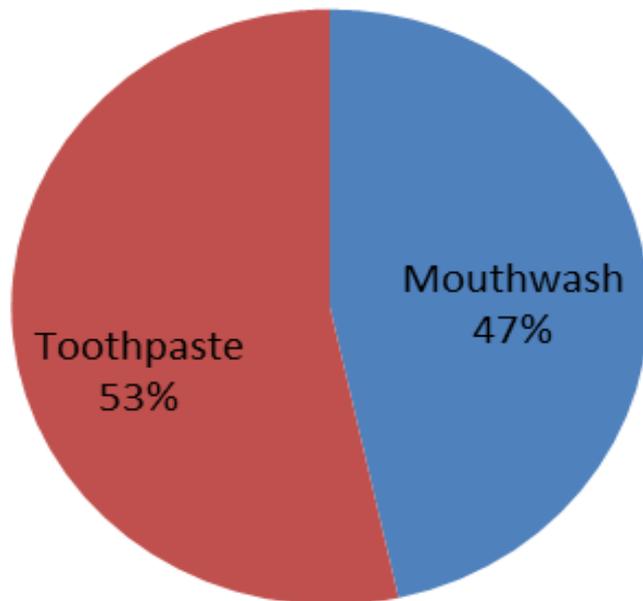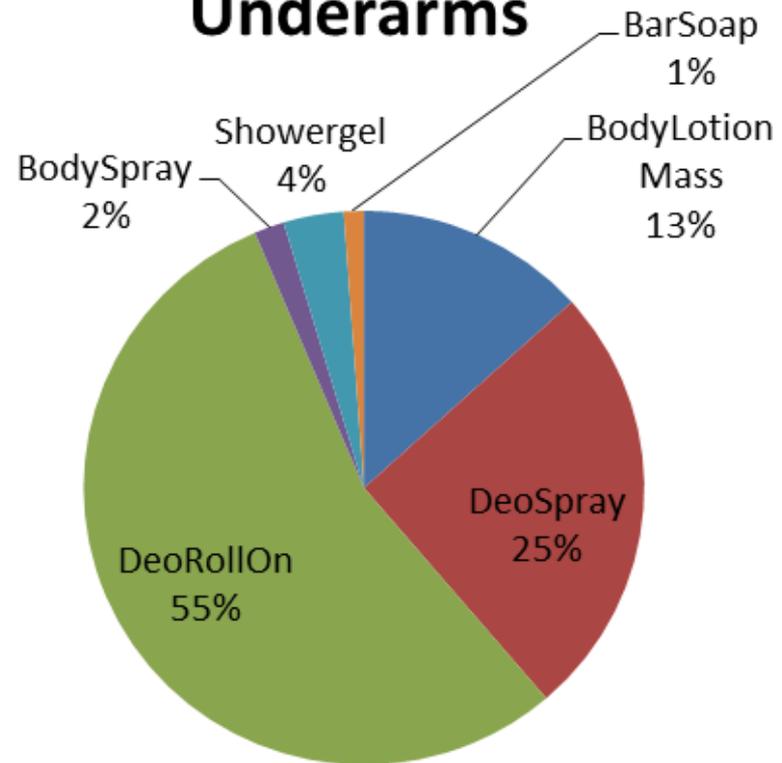
Products contributing to the aggregate exposure to Benzaldehyde on the Mouth and Hands

Outcome of aggregate exposure modelling

- These results demonstrate that, taking into account aggregate exposure, and using Maximum Use Levels calculated on a product basis, the AEL:CEL ratios are acceptable for most application areas

- However, for hands, palms, underarms and mouth the AEL:CEL ratios fall below 1

- On the hands, liquid soap, bar soap and body lotion account for the majority of the aggregate exposure

- On the palms a variety of rinse-off and leave on products are contributing

- On the underarms, most exposure occurs from use of Deo/Aps

- In the mouth, all exposure is from oral care products (toothpaste and mouthwash)

Accounting for aggregate exposure in setting Maximum Concentrations

- In order to reduce the CEL (and increase the AEL:CEL ratio) on hands, palms, underarms and mouth, it is proposed to reduce the Maximum Use Levels for those products which account for the majority of the exposure on those sites

- This could be achieved by applying an additional adjustment when calculating the Maximum Concentrations

- The products affected are:
  - Deo/APs
  - Hydroalcoholics
  - Moisturisers (inc. hand and face creams)
  - Body Lotion
  - Lip products
  - Shower products
  - Oral care

Aggregate Exposure Adjustment Factors and final Maximum Concentration values for Benzaldehyde

| Product type	Original Maximum Use Level %	AgEx (Aggregate exposure adjustment)	Final Maximum Use Level %
Deo/Antiperspirants	0.03	2	0.015
Hydroalcoholics	0.4	1	0.4
Moisturisers (inc. hand and face creams)	0.3	6	0.05
Body Lotion	1.6	6	0.27
Lip products	0.08	1	0.08
Shower products	4.9	6	0.8
Oral care	1.0	3	0.3

Aggregate Exposure Adjustment Factors and final Maximum Concentration values for BMHCA

| Product type	Original Maximum Use Level %	AgEx (Aggregate exposure adjustment)	Final Maximum Use Level %
Deo/Antiperspirants	0.2	2	0.1
Hydroalcoholics	3.0	1	3.0
Moisturisers (inc. hand and face creams)	2.6	5	0.5
Body Lotion	11.3	5	2.2
Lip products	0.6	1	0.6
Shower products	34 (5)	5	7 (5)
Oral care	6.8	3	2.2

Re-calculation of potential aggregate exposure

- The adjusted Maximum Use Level values were incorporated in the Creme model, and the model re-run to calculate aggregate exposure and AEL:CEL ratios for each body surface area

- As before, Inter-individual SAF, Frequency/duration SAF and Site SAF values were applied to the NESILs to define an AEL for each application area

- Product SAF values were applied to the exposure calculated for each product at the event level, and an aggregate CEL calculated for each application area

- The Aggregate Exposure Adjustment was not incorporated into the model

AEL:CEL ratios for Benzaldehyde incorporating adjusted Maximum Use Levels
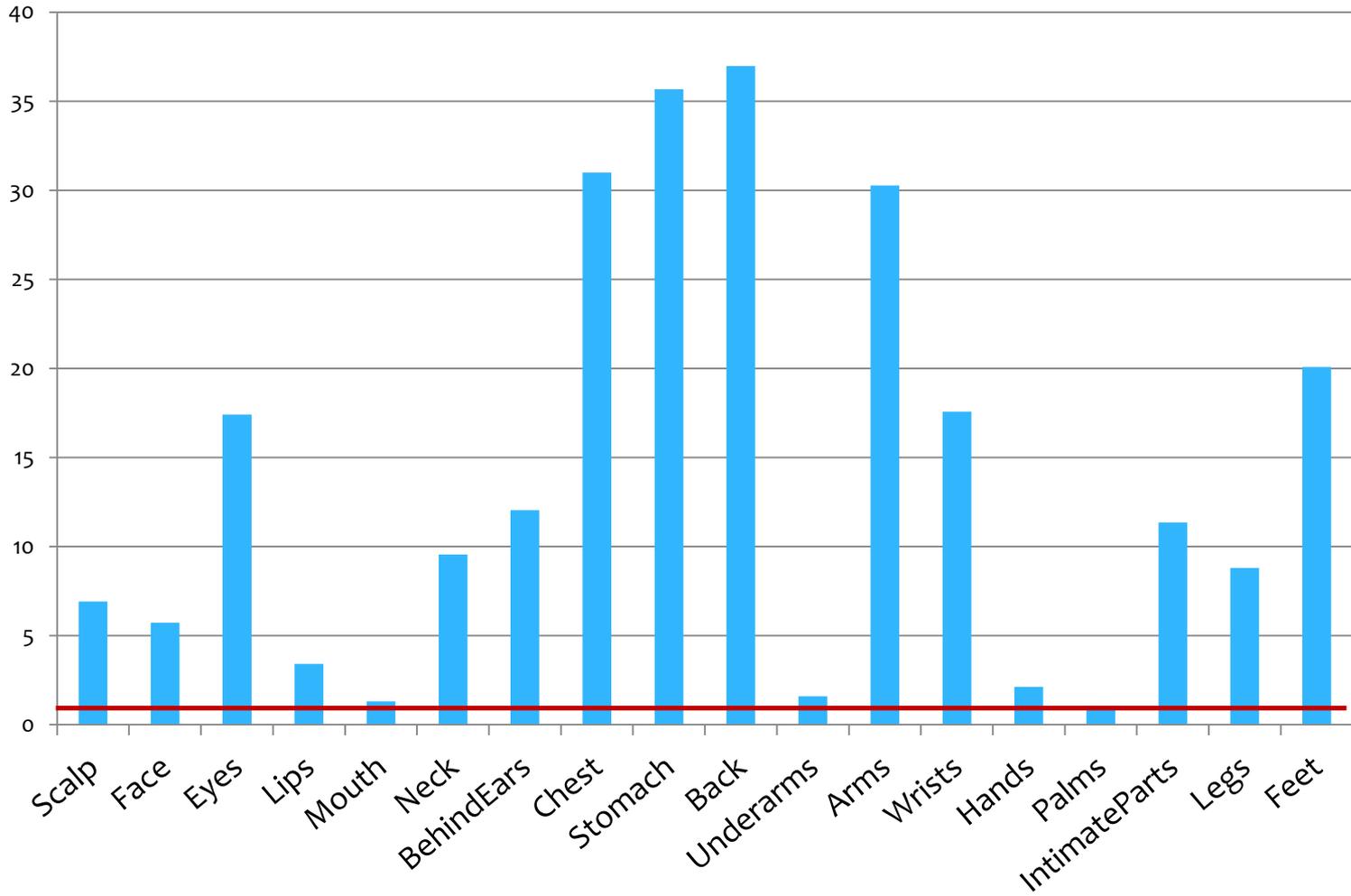
AEL:CEL ratios for BMHCA incorporating adjusted Maximum Use Levels
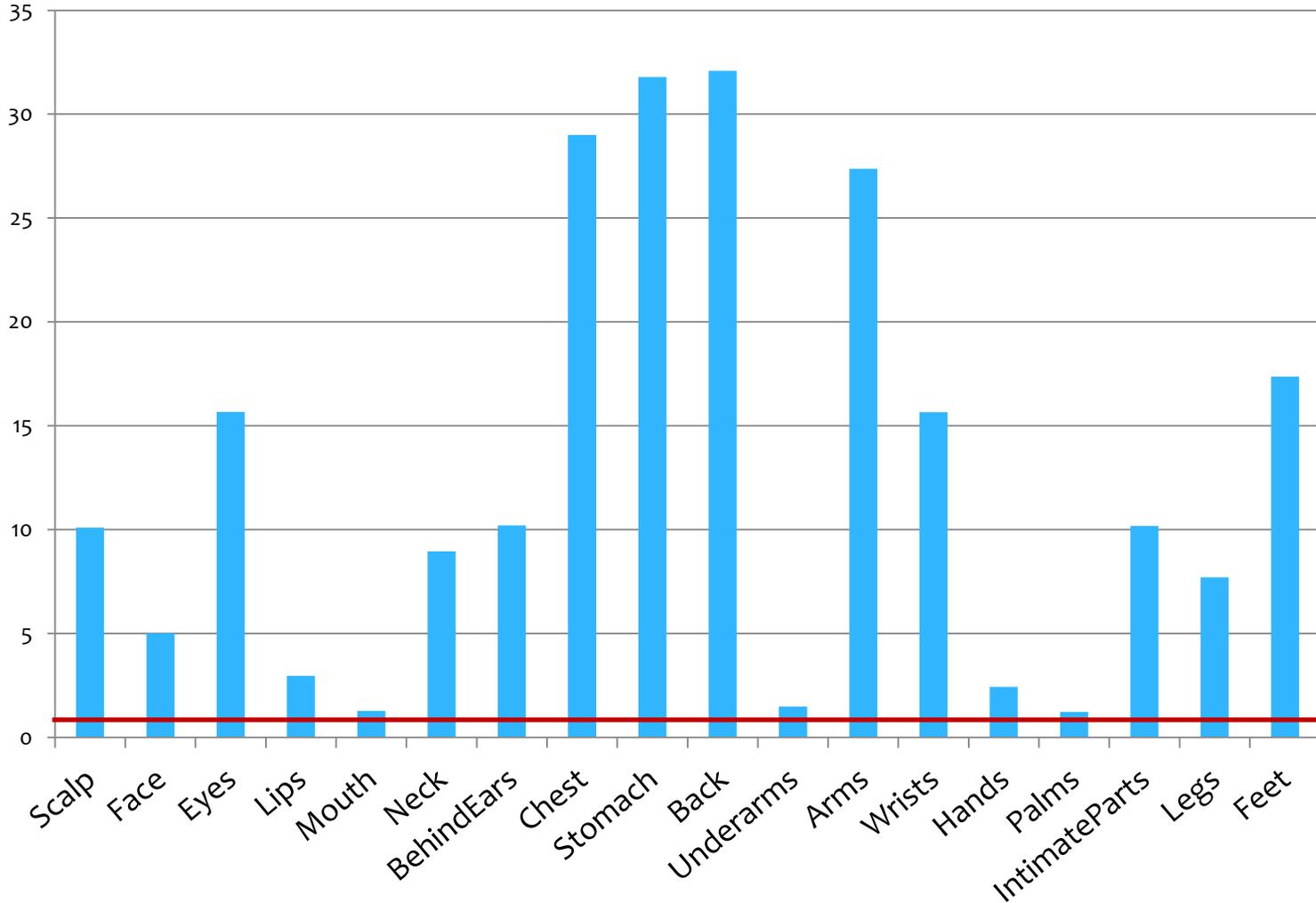
Some words of caution

- In the model it is assumed that **all** products used contain the Maximum Concentration of fragrance as calculated using the deterministic method, and so is very conservative

- AEL:CEL ratios are calculated based on the 95th percentile CEL on the highest use day

- The calculation itself does not demonstrate that the aggregate exposure is safe/not safe since the same SAF values are used in setting maximum values and in the model

- *Appropriate SAF values still need to be determined to ensure safety*

- It does, however, highlight areas where aggregate exposure may potentially exceed the AEL based on those appropriate SAF values

- Running the model with different SAF values would not be expected to significantly change the outcome

Further work

- SAF values need to be agreed

- Modelling to be carried out using the agreed SAF values and Calculated Maximum Use Levels

- Aggregate Exposure Adjustment values determined for those application areas where the AEL:CEL ratio is below 1

- In the future it may be possible to use the Creme model to determine Maximum Use Levels using an iterative process