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Presentation of suitable case studies

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IDEA Workshop : Validity of the QRA Methodology & Possibilities of Further Refinement

May 13-15th, 2014

Presentation of suitable case studies

- Comparison of QRA 1.0 and QRA 2.0 methodologies
- 2 examples to be presented. BMHCA and Benzaldehyde
- Comparison of final upper use limits QRA 1.0 and 2.0
- Conclusions and discussion

Note: Based on outcomes of last workshop – final numbers may change pending Workshop discussions

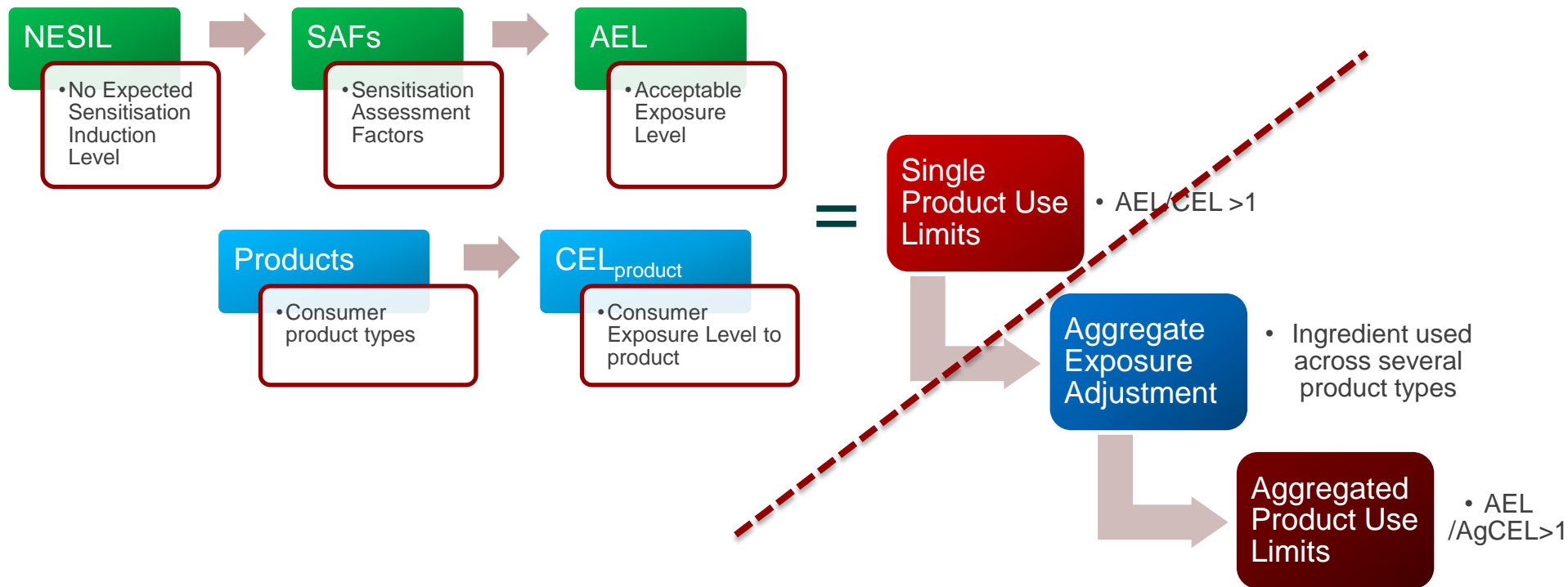
QRA 1.0 vs. 2.0

What has changed?

	QRA 1.0	QRA 2.0
Define no effect level (NESIL) for Induction of Sensitisation	Based on HRIPT, LLNA and other available information	Based on HRIPT, LLNA and other available information
Define SAFs	Inter-individual (10) Matrix (1 - 10) Use (1 - 10)	Inter-individual (10) Occlusion (0.5 - 1) Product (0.3 - 10) Frequency/Duration (1 - 2) Skin condition/Site (1 - 3)
Set Acceptable exposure level (AEL)	NESIL/SAF	NESIL/SAF
Define exposure (CEL)	Data prior to 2008	Includes new information
Calculate aggregate exposure across all relevant consumer products	Not included	Included - AgCEL
Calculate upper use limit for products	AEL/CEL	AEL/AgCEL

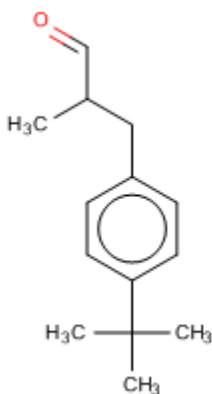
QRA 2.0

Risk assessment procedure



Example 1 - BMHCA

General information



Formula: C₁₄H₂₀O

Structure: (CH₃)₃C-C₆H₄-CH₂-CH(CH₃)-CHO

Molecular Weight: 204.31

Smiles Notation: O=CC(C)Cc(ccc(c1)C(C)(C)C)c1

Generic Class (TSCA): Aromatic Aldehydes

Description: A colorless to pale yellow liquid with a powerful, floral-fresh odor.

- Used very widely across many product areas dermally, not approved for oral use
- Used up to 8% in fragrance mixtures – generally found <0.1% in final products or <1% in some fine fragrances
- No natural occurrence
- «Weak» sensitiser
- IFRA standard published based on QRA 1.0 in 2008 – fully implemented since 2010

Example 1 - BMHCA

NESIL

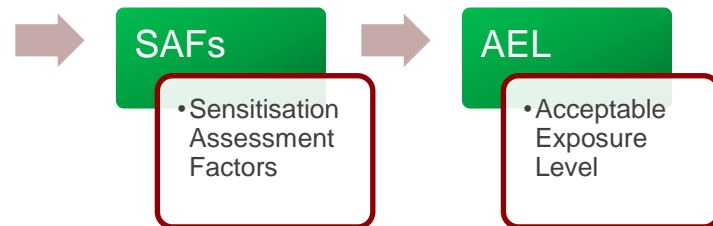
NESIL

- No Expected Sensitisation Induction Level

- NESIL of 4100ug/cm²
- Based on HRIPT in 106 adults
- Weak sensitiser in LLNA studies (EC3 ca 19%)
- GPMT and other data support weak sensitisation potential conclusion

Example 1 - BMHCA

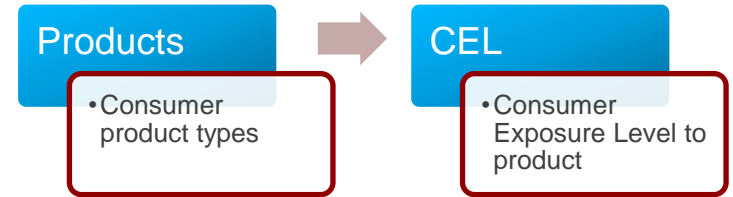
Example product SAFs and AELs



Product type	SAF	NESIL ug/cm ²	AEL _{ingredient} (NESIL/SAF) ug/cm ²
Deo/Antiperspirants	200	4100	20
Hydroalcoholics	60	4100	68
Moisturisers (inc. hand and face creams)	60	4100	68
Body Lotion	60	4100	68
Lip products	60	4100	68
Shower products	60	4100	68
Oral care	60	4100	68

Example 1 - BMHCA

Example Consumer Exposure Levels



Product type	CEL _{product} ug/cm ²	Data source
Deo/Antiperspirants	9100	Cowan-Ellsberry et al, 2008
Hydroalcoholics	2200	Cano & Rich , 2001
Moisturisers (inc. hand and face creams)	2570	Hall, 2011
Body Lotion	600	Colpia, 2005
Lip products	11670	Colpia, 2005
Shower products	200	CTFA, 2005
Oral care	1000	Hall, 2011

Example 1 - BMHCA

Example single product use limits

Single Product Use Limits • $AEL/CEL > 1$

Product type	$AEL_{\text{ingredient}}$ ug/cm ²	CEL_{product} ug/cm ²	Single Product Use Limit (%)
Deo/Antiperspirants	20	9100	0.2%
Hydroalcoholics	68	2200	3.0%
Moisturisers (inc. hand and face creams)	68	2570	2.6%
Body Lotion	68	600	11.3%
Lip products	68	11670	0.6%
Shower products	68	200	34% (2.5% max)
Oral care	68	1000	6.8%

Example 1 - BMHCA

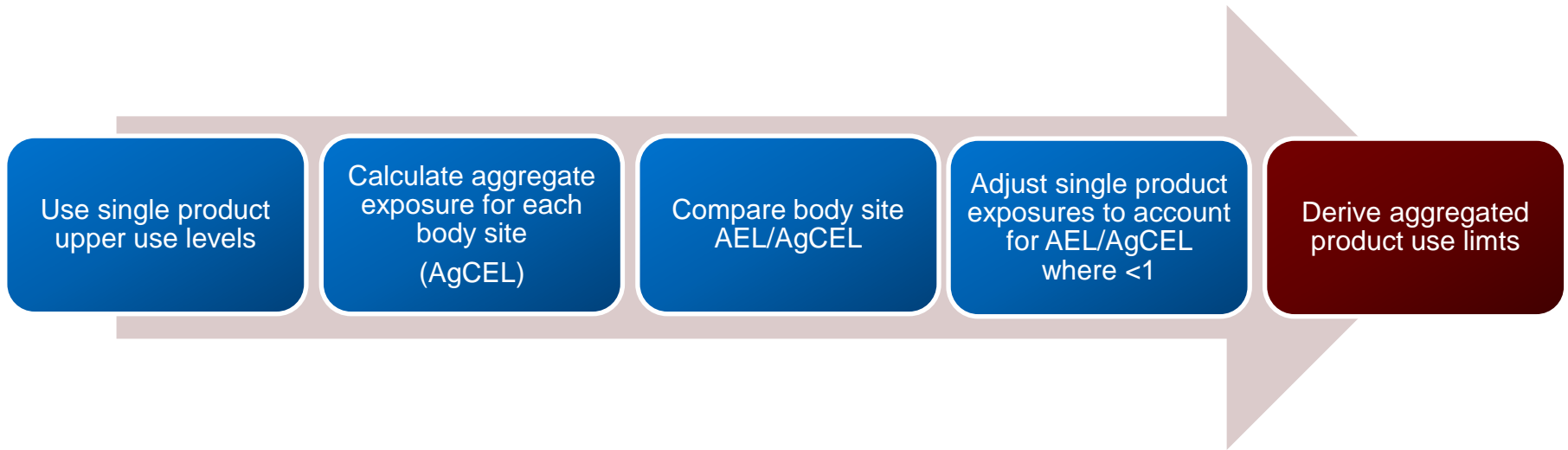
Consideration of Aggregate exposure



Aggregate
Exposure
Adjustment

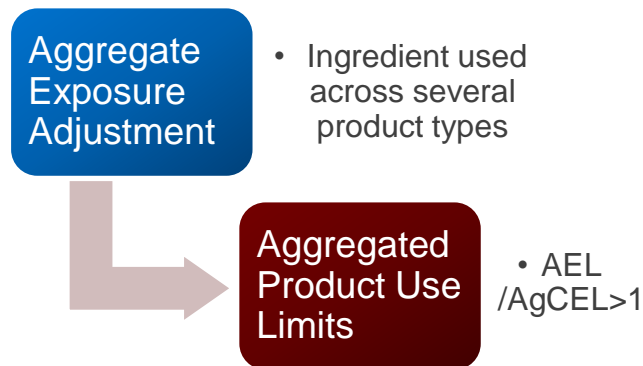
- Ingredient used across several product types

- BMHCA may be used across several product types
- Therefore aggregate exposure the the consumer may occur
- Single product use limits do not account for this
- Therefore, need to adjust these use limits to account for aggregate exposure



Example 1 - BMHCA

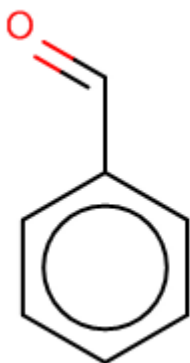
Aggregate Exposure Adjustment and Use Limits



Product type	Single Product Use Limit (%)	AgEx (Aggregate exposure adjustment)	Final Maximum Use Limit
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% (2.5%)	5	7% (2.5%)
Oral care	6.8%	3	2.2%

Example 2 - Benzaldehyde

General information



Formula: C₇H₆O

Structure: C₆H₅-CHO

Molecular Weight: 106.13

Smiles Notation: O=Cc1ccccc1

Generic Class (TSCA): Aromatic Aldehydes

Description: Colorless to yellowish liquid, turns to brown on exposure to air, volatile liquid with odor of bitter almonds with burning aromatic taste

- Used widely across many product areas
- Used <1% in fragrance mixtures – generally found <0.01% in final products or <0.1% in some fine fragrances
- Naturally found in Cinnamomun, Salvia, Maize and Ocimum species
- «Moderate» sensitiser
- IFRA standard published based on QRA 1.0 in 2009 – fully implemented since 2011

Example 2 - Benzaldehyde

NESIL

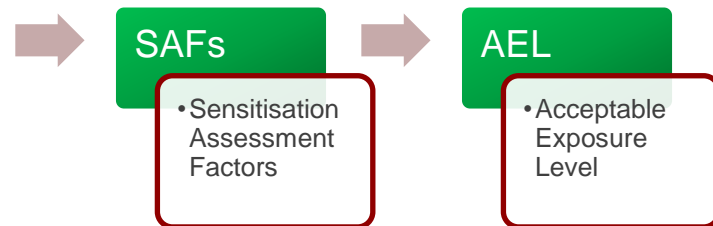
NESIL

- No Expected Sensitisation Induction Level

- NESIL of 590ug/cm²
- Based on HRIPT in >100 adults
- Very weak-none sensitiser in LLNA (EC3 >25%)
- GPMT and other data support sensitisation potential conclusion

Example 2 - Benzaldehyde

Example product SAFs and AELs



Product type	SAF	NESIL ug/cm ²	AEL _{ingredient} (NESIL/SAF) ug/cm ²
Deo/Antiperspirants	200	590	3
Hydroalcoholics	60	590	9.8
Moisturisers (inc. hand and face creams)	60	590	9.8
Body Lotion	60	590	9.8
Lip products	60	590	9.8
Shower products	60	590	9.8
Oral care	60	590	9.8

Example 2 - Benzaldehyde

Example single product use limits

= **Single Product Use Limits** • $AEL/CEL > 1$

Product type	$AEL_{\text{ingredient}}$ ug/cm ²	CEL_{product} ug/cm ²	Single Product Use Limit (%)
Deo/Antiperspirants	3	9100	0.03%
Hydroalcoholics	9.8	2200	0.4%
Moisturisers (inc. hand and face creams)	9.8	2570	0.3%
Body Lotion	9.8	600	1.6%
Lip products	9.8	11670	0.08%
Shower products	9.8	200	4.9%
Oral care	9.8	1000	1.0%

Example 2 - Benzaldehyde

Aggregate Exposure Adjustment and Use Limits

Aggregate Exposure Adjustment

- Ingredient used across several product types



Aggregated Product Use Limits

- $AEL / AgCEL > 1$

Product type	Single Product Use Limit (%)	AgEx (Aggregate exposure adjustment)	Final Maximum Use Limit
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%

Comparison of QRA 1.0 and 2.0

Example use levels based on current information

Product type	BMHCA		Benzaldehyde	
	QRA 1.0 (Limit in final product)	QRA 2.0 (Limit in final product)	QRA 1.0 (Limit in final product)	QRA 2.0 (Limit in final product)
Deo/Anti-perspirants	0.2%	0.1%	0.02%	0.015%
Hydro-alcoholics	0.6% (Male) 1.9% (Female)	3.0%	0.09% (Male) 0.27% (Female)	0.4%
Moisturisers (inc. hand and face creams)	1.0%	0.5%	0.14%	0.05%
Body Lotion	1.9%	2.2%	0.27%	0.27%
Lip products	0.1%	0.6%	0.02%	0.08%
Shower products	2.5%* (pragmatic level)	7% (2.5%)	3%	0.8%
Oral care	3.0%** (not flavour approved)	2.2%	0.43%	0.3%

Concluding comments 1/2

- QRA 2.0 includes significant method development vs. QRA 1.0
 - New SAF considerations
 - Most up to date exposure information
 - Accounts for aggregate exposure

- Derivation of ingredient upper use levels must be understandable
 - Method and process clearly explained
 - Justification of NESIL, SAFs, Exposure
 - Clear explanation of aggregate exposure adjustment
 - Clear product assignment of upper use limits

- Scope must be considered

Concluding comments 2/2

- As with all tox RA approaches, refinement can occur based on additional data/understanding
 - e.g. If Substance or Product specific data lead to different conclusions on SAFs or Exposures then these may be justified
- Some aspects not covered – gaps in knowledge
 - The World Outside Consumer Products (and IFRA Standards)
 - Occupational, Pharmaceutical, Therapeutic, Massage, Natural etc
- Targeted effectiveness ideally to be measured and judged over time
 - Specifically related to scope of QRA coverage

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