

A large, semi-transparent globe is positioned on the left side of the slide, showing a map of the world. It has a metallic-looking stand and a ring at the top.

QRA II – Review of SAFs

Anne Marie Api, PhD
Vice President, Human Health Sciences

IDEA Workshop QRA
May 14-15, 2014

Dermal Sensitization QRA II for Fragrance Materials



● Action Plan

- **Submission to DG SANCO by the end of June/early July 2014 for review by the Joint Research Center**
- **Promised inclusion of dermal aggregate exposure in the model**
- **Consensus on the methodology from the IDEA Workshop on QRA**



Summary: Key Actions March 2013



- **Include aggregate exposure in the QRA**
 - In order to incorporate dermal aggregate exposure, modification of the SAFs is needed
- **Review supporting information for SAFs**
- **Communication – expand the dialogue with international dermatologists**
- **Explore relationship between induction and elicitation thresholds**
- **Measure effectiveness of the QRA**
- **Incorporate occupational exposure to consumer certain products**

Workshop March 2014



Factor	Consideration	Influence	New proposed SAFs
Inter-Individual	Variation in individual human susceptibility to skin sensitization is substantial. SAF takes into account variability not accommodated in the NESIL	↑	10
Occlusion	Some areas of skin are semi-occluded by clothing, or product(s) with moisturising agents may lead to semi-occlusion.	Semi-occluded = Non-occluded ↓	1 0.5
Product matrix	To accommodate the role of vehicle	Delivery	0.3 , 1 , 3
Frequency / duration of product use	Products may be used over extended periods of time resulting in bio-accumulation	↑	1 or 2
Skin condition / site	Pre-existing inflammation Irritation by product Penetration / permeation of product	Increase of induction susceptibility	1 or 3 1 or 3 1 or 3

RIFM & CE QRA Expert Groups



RIFM Expert Group	CE Expert Group
Anne Marie Api, RIFM	F Audebert, FEBEA
David Basketter, Consultant	Dagmar Bury, L'Oreal
Peter Cadby, Chanel	Christophe Brault, LVMH
Graham Ellis, Givaudan	Nicola Gilmour, Unilever
Frank Gerberick, P&G	Anne-Cécile Jousseau Signoret, Chanel
Nicola Gilmour, Unilever	Petra Kern, P&G
Peter Griem, Symrise	Maya Krasteva, L'Oreal
Petra Kern, P&G	
Pauline McNamee, P&G	
Steven Robison, Consultant	Observers
Cindy Ryan, P&G	Fred Lebreux, IFRA
Robert Safford, Consultant	Florian Schellauf, CE
Scott Schneider, Firmenich	Matthias Vey, IFRA



Action Items For QRA Teams

- **Apply the proposed SAFs to the product types identified in the first QRA paper (Api et al, 2008)**
- **Assign the scientific papers supporting decisions made for the assignment of SAFs**
- **Develop a method for including dermal aggregate exposure into the QRA II methodology**
- **Provide examples of the application of the QRA II to fragrance materials**



Timelines

- **RIFM and CE Team Webinars/Conference Calls: March 20, April 4, April 17, April 30 and May 9**
- **RIFM QRA Aggregate Exposure Team Webinar/Conference Calls: April 11, 18, 22, 25, May 2 and 8**



Additional Timelines

- **Update QRA Working Group (Supervisory Group/Core Team): April 9 and April 24**
- **Update to the RIFM Membership at the Quarterly Webinar: April 15**
- **Update to the IDEA Dermatology Team: April 29**
- **Presentations at the May 2014 IDEA Workshop on QRA**



Dossier Submission

- **An overview document on QRA II with references to the documents described in points 1-3 below. This overview will contain examples of the application of QRA II, including:**
 1. **A review of the current science of uncertainty factors for dermal sensitization (Basketter, Safford et al)**
 2. **A description of the RIFM/Creme Aggregate Exposure Model**
 3. **Api et al, 2008 paper**



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- **For QRA II:**
 - **The starting point of the QRA is the NESIL which is defined as the threshold not inducing skin sensitization, considering all available hazard data in a weight of evidence approach, under the specific exposure conditions of a standard protocol HRIPT.**



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- **Human variability:**
 - **The variation in individual human susceptibility to skin sensitization is substantial. The biological basis of this variability is largely unknown, with ethnicity, gender, age (including infants), and currently known genetic markers each making only a minor contribution.**
 - **Regarding skin diseases / conditions:**
 - **We concluded that atopic dermatitis, psoriasis and dry skin have limited impact on skin sensitization, whereas...**
 - **...irritant dermatitis is known to promote skin sensitization.**
 - **Inter-individual variability not accommodated in the NESIL is addressed by a SAF of 10.**

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Factor	Consideration	Influence	New proposed SAFs	Comments (comparison of the experimental condition with the product use condition)
Occlusion	Some areas of skin are semi-occluded by clothing, or product with moisturising agents may lead to semi-occlusion.	Semi-occluded = Non-occluded ↓	1 0.5	<p>There was extensive debate on this. To assure consistency, it was concluded that the occlusion factor should be 1 for all products since at some time all body parts could be covered by clothing.</p> <p>Includes occlusion by body part, clothing or product</p> <p>Adding petrolatum, waxes, oils and silicones to moisturising lotions/creams does produce a degree of occlusion. However, on the continuum of occlusion, it is slight, not equivalent to the effect of a patch or even a wound dressing. (This is what necessitates repeated application of moisturizing creams/lotions throughout the day.)</p>

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Factor	Consideration	Influence	New proposed SAFs	Comments (comparison of the experimental condition with the product use condition)
Product matrix	Role of vehicle/matrix	Delivery	0.3 or 1 or 3	<p>The predicted effect of product formulation versus the experimental conditions;</p> <p>0.3 (inert objects with no direct contact, e.g. candles or detergent pods or no vehicle/matrix) or</p> <p>1 (most products) or</p> <p>3 (penetration enhancers greater than anticipated from the exptl condition)</p>
	Irritation by product (<i>moved from skin condition site</i>)	Increase of induction susceptibility	1 or 3	<p>Can the product cause irritation related to repeated normal conditions of use? Ingredients that are added to mitigate any types of irritation</p>



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Factor	Consideration	Influence	New proposed SAFs	Comments (comparison of the experimental condition with the product use condition)
Frequency / duration of product use	Products may be used over extended periods resulting in bio-accumulation	↑	1 or 2	<p>Products may be used frequently over extended periods of time resulting in accumulation (chemical or biological accumulation) or reservoir effect</p> <p>– HRIPT 9 exposures over 3 weeks; consumers may use products longer</p> <p>Is this double accounting when we also consider aggregate exposure?</p>

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Factor	Consideration	Influence	New proposed SAFs	Comments from Application (comparison of the experimental condition with the product use condition)
Skin condition/ site	Pre-existing inflammation	Increase of induction susceptibility	1 or 3	Pre-existing inflammation for body site: body areas that are specifically prone to increased level of inflammation – hands, underarms, any shaved area, under a diaper, (Fischer CD book). Consider misuse of products, but not abuse
	Penetration/ permeation of product Peri-anal and peri-ocular regions	Increase of induction susceptibility	1 or 3	Peri-anal and peri-ocular regions require additional SAFs. Don't take the factors for different body areas and multiply them together

Skin Site Considerations

- **A factor of 3 applied to areas of skin that are prone to irritation –**
 - hands (irritating products, abrasion, wet work),
 - underarm (irritating products, shaving, friction),
 - face (shaving)
 - legs (abrasion, shaving)

- **A factor of 3 applied to areas of skin that are considered to be inherently “sensitive” - peri-ocular region, peri-anal region**
 - It could be argued these sites are mutually exclusive



Skin Site Considerations

- In setting the SAFs, the most sensitive area of skin to which the product is applied will drive the overall SAF value.
- Application of both factors is not necessary
- A site inherently “sensitive” is not considered be prone to irritation, and vice versa.



SAF Examples



Product Type	Inter-individual SAF	Product		Frequency/duration	Site			Total SAF
		Matrix	Irritation by product		Occlusion	Skin site inflammation	Peri-anal/ocular	
Product Type	10	1	1	2	1	3	1	60

Product SAF

Product Type	Inter-individual SAF	PRODUCT		Frequency/duration	SITE			Total SAF
		Matrix	Irritation by product		Occlusion	Skin site inflammation	Peri-anal/ocular	
Deo/APs	10	1	3	2	1	3	1	200
Men face cream	10	1	1	2	1	3	1	60
Hand cream	10	1	1	2	1	3	1	60
Women face cream	10	1	1	2	1	1	3	60
Hydroalcoholics	10	1	1	2	1	3	1	60
Candle	10	0.3	1	2	1	1	1	6
Hand wash laundry det.	10	1	3	2	1	3	1	200

Body Sites

Body Site	Additional definition for this study
Scalp	
Face	Does <u>not</u> include: eyes, lips, mouth, behind ears
Eyes	The eyelid and surrounding skin.
Lips	
Mouth	“Buccal” / “inside cheek”: Does not include: lips
Neck	Does <u>not</u> include: behind ears
Behind ears	
Chest	Does <u>not</u> include: underarms, stomach
Stomach	

Body Site	Additional definition for this study
Back	Does <u>not</u> include: underarms
Underarms	
Arms	Does include: shoulder, forearm, upper arm, wrists, hands, palms, underarms
Wrists	
Back of hand	Does <u>not</u> include: palms, wrists
Palms	
Intimate parts	
Legs	Does include: bottom, thighs, calves: Does <u>not</u> include: feet
Feet	

Body Site SAFS

Body Site	SITE			Total SAF
	Occlusion	Skin site inflammation	Peri-anal/ocular	
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
Behind ears	1	1	1	1
Chest	1	1	1	1
Stomach	1	1	1	1
Back	1	1	1	1

Body Site	SITE			Total SAF
	Occlusion	Skin site inflammation	Peri-anal/ocular	
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
Intimate parts	1	3	1	3
Legs	1	3	1	3
Feet	1	1	1	1

QRA II SAF Suggestions

Factor	Consideration	Influence	New proposed SAFs	Comments (comparison of the experimental condition with the product use condition)
Occlusion	Some areas of skin are semi-occluded by clothing, or product with moisturising agents may lead to semi-occlusion.	Semi-occluded = Non-occluded ↓	1 0.5	There was considerable debate on this factor and in order to assure consistency, it was considered that the occlusion factor should be 1 for all products since all body parts can be covered by clothing at some time. Suggest we eliminate this SAF as a value of 1 was used for each product?
Product matrix	Role of vehicle/ <i>matrix</i> Irritation by product (<i>moved from skin condition site</i>)	Delivery Increase of induction susceptibility	0.3 or 1 or 3 1 or 3	SAME Suggest elimination of SAF for irritation by product and adjust the skin inflammation SAF to account for all irritation?

QRA II SAF Suggestions

Factor	Consideration	Influence	New proposed SAFs	Comments (comparison of the experimental condition with the product use condition)
Frequency duration of product use	Products may be used over extended periods of time resulting in bio-accumulation	↑	1 or 2	2 assigned to all product types
Skin condition/ site	Pre-existing inflammation	Increase of induction susceptibility	1 or 3 or 10	<p>Pre-existing inflammation for body site: body areas that are specifically prone to increased level of inflammation - hands, underarms, under a diaper, peri-anal and peri-ocular regions</p> <p>10 assigned for deo/ap and detergents where previously a 3 was assigned for irritation by product</p>

More Information



**Research Institute for
Fragrance Materials, Inc.**
Tel.: +1-201-689-8089
amapi@rifm.org

www.rifm.org

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Research Institute for Fragrance Materials

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RIFM's short film "What People Are Saying" on public opinion about the fragrance industry and fragrance safety.

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News&Events

5/24/11 - RIFM Relaunches Web Site

3/29/11 - RIFM Respiratory Science Poster Wins First Place Blue Ribbon at SCF's 80th Anniversary Annual Meeting Poster Presentation

3/23/11 - RIFM Presents Fragrance Science at Society of Toxicology 50th Anniversary Annual Meeting

3/19/10 - IF YOU MISSED RIFM'S MAY 2010 MEETING, YOU CAN STILL VIEW THE PRESENTATIONS

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New Publications

Design and Feasibility of an International Study Assessing the Prevalence of Contact Allergy to Fragrances in the General Population: The European Dermato-Epidemiology Network Fragrance Study

The first article from the SCF sponsored epidemiology study on the true prevalence of fragrance allergy.

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