

Quantitative Risk Assessment of Contact Sensitization: Clinical Data to Assess Utility of the Model

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Background: Contact hypersensitivity quantitative risk assessment (QRA) for fragrance ingredients is being used to establish new international standards for all fragrance ingredients that are potential skin sensitizers.

Objective: The objective was to evaluate the retrospective clinical data on three fragrance ingredients in order to provide a practical assessment of the predictive value of the QRA approach. It is important to have data to assess that the methodology provides a robust approach for primary prevention of contact sensitization induction for fragrance ingredients identified as potential sensitizers.

Methods: This article reviews clinical data for three fragrance ingredients—cinnamic aldehyde, citral, and isoeugenol—to assess the utility of the QRA approach for fragrance ingredients.

Results: This assessment suggests that had the QRA approach been available at the time standards were established for these fragrance ingredients, the clinical response might have been noticeably improved. Prospectively, with the establishment of QRA-derived standards, there should be a continued downward trend in patch test–positive rates for cinnamic aldehyde, citral, and isoeugenol over time.

Conclusion: While it is recognized that the availability of retrospective data is limited, a longitudinal review of these data gives confidence that the QRA approach should be an effective tool for primary prevention. This study also highlights the importance of continued active monitoring of clinical patch-test data for fragrance ingredients.

THE RESEARCH INSTITUTE for Fragrance Materials (RIFM) is the international scientific authority for the safe use of fragrance materials. The RIFM generates, evaluates, and distributes scientific data on the safety assessment of fragrance raw materials found in consumer

products (eg, perfumes, cosmetics, and personal care and household products). There are more than 2,600 fragrance ingredients in the RIFM database. The prioritization of substances for assessment is based on criteria outlined in the RIFM human health criteria document; these criteria include volume of use, dermal exposure, and structural alerts.¹ One of the structural alerts is for contact sensitization. The use of more than 80 fragrance ingredients is restricted because of their contact sensitization. These materials are restricted by standards approved by the RIFM panel of scientific experts and distributed by the International Fragrance Association (IFRA).

As part of the fragrance industry's overall objective to minimize fragrance allergy in the general population, a new approach for assessing contact sensitization risk for fragrance ingredients as a basis for establishing IFRA Standards was developed. A key goal is to review (by 2011) all chemically defined fragrance ingredients that have structural alerts for contact sensitization and are used at greater than 1 metric ton per year on a worldwide basis.

A description of quantitative risk assessment (QRA) methodology was recently published²; QRA represents a major improvement over the former approach because it is (1) quantitative, (2) exposure based, (3) consistent with

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DOI 10.2310/6620.2010.10032

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modern principles of toxicologic risk assessment, (4) suitable for assessing contact sensitization (which, like most other toxicity endpoints, has a threshold), and (5) applicable to various factors such as different product types and use patterns.²⁻⁶

The QRA approach specifically addresses induction of contact sensitization as a threshold-based event. The key steps of this approach are (1) the determination of a no-expected-sensitization-induction level (NESIL) based on a weight-of-evidence approach that combines the use of all relevant available data; (2) the application of sensitization assessment factors (SAFs), defined by using peer-reviewed scientific literature references; and (3) the calculation of a consumer exposure level (CEL) empirically derived through study of consumer habits and practices and from measurements of human surface areas.

Once determined, the NESIL, SAF, and CEL for individual fragrance ingredients in different product types can be used to define the acceptable exposure level (AEL) against which the CEL can be compared in each product category. The AEL, expressed in terms of dose per unit area per day, is calculated by dividing the NESIL by the product type's SAF. Details and examples of how to apply the approach theoretically are available,² as is a specific practical example using citral.⁷

Since May 2006, QRA has been used to set IFRA Standards for fragrance materials that potentially cause contact sensitization. The QRA methodology is the core strategy for the primary prevention of fragrance allergy in consumer products. Crucial to the long-term practical use of QRA is obtaining data to determine whether the methodology can provide a robust approach for the primary prevention of sensitization to fragrance ingredients. A reasonable approach is to monitor patch-test results from dermatology clinics. These data may provide a perspective on the usefulness of the QRA approach in regard to fragrance ingredients.

The current review was facilitated by the availability of such QRA-based contact sensitization risk assessments. We reviewed data on three fragrance ingredients known to have sensitizing potential and compared the data longitudinally with previous clinical patch-test and contact allergy findings. This report reviews the retrospective information that is available on these materials to provide a practical assessment of the predictive value of the QRA approach.

Methods: Clinical Data

The fragrance ingredients selected for discussion are cinnamic aldehyde, citral, and isoeugenol. For each, the

sensitization QRA approach is compared to the established IFRA Standard and to clinical dermatology data available from published references. Where appropriate, additional data that relate patch-test results to a specific product type are also discussed. These data were derived from three surveys of the patch-test database at the Contact Allergy Unit at University Hospital Leuven, Belgium. These surveys were commissioned by the RIFM; the results are described below. Although the data are from only one clinic and the number of patients is limited, the Contact Allergy Unit at University Hospital Leuven is the only center that makes these types of data available (eg, linking positive patch-test data to specific product types).

The survey for fragrance ingredients gathered data on (1) the identification of product types that contained cinnamic aldehyde, citral, or isoeugenol and (2) the number of positive clinical patch-test reactions to these individual fragrance ingredients in the different product types from 2000 to 2007.

In the first survey, covering the years 2000 to 2005, 3,323 subjects were investigated by the Contact Allergy Unit. Of these patients, 302 (9.1%) had a positive patch-test reaction to fragrance mix I, 6.7% had a reaction to balsam of Peru, and 4.8% reacted positively to colophony. Of the patients who reacted positively to the fragrance mix, 133 had positive patch-test reactions to their own cosmetic products. Of these 133 reactions, 66 involved fragrance-related contact allergic reactions. Although the patients reacted to the fragrance ingredient, the presence of that fragrance ingredient in the product could not be confirmed because fragrances were not labeled on products at that time. These reactions, identified as "not confirmed," are detailed in Table 1. In the second survey, covering the year 2006, 352 reactions to specific cosmetic products were observed; 174 were related to specific fragrance ingredients. In the final survey, covering the year 2007, 527 patients in the Leuven Contact Allergy Unit were patch-tested. There were 147 reactions to specific cosmetic products; 67 of these reactions were related to specific fragrance ingredients. In the second and third surveys, the positive patch-test reactions were further differentiated into confirmed reactions (ie, those caused by the product and for which it was known that the fragrance ingredient was in the product) and unconfirmed reactions (ie, those caused by the product but for which it was not possible to confirm the presence of the fragrance ingredient in the product). The inability to confirm a reaction was attributed to either the loss of the product's packaging or the use of a product whose label did not list fragrance.

Table 1. Identification of Product Type and Positive Patch-Test Reactions to Cinnamic Aldehyde, Citral, and Isoeugenol*

Fragrance Ingredient	Product Type	Positive Reactions, 2000–2005 Survey (Not Confirmed [†])	Positive Reactions, 2006 Survey		Positive Reactions, 2007 Survey	
			Confirmed [‡]	Not Confirmed [‡]	Confirmed [‡]	Not Confirmed [‡]
Cinnamic aldehyde	Deodorant	2	0	2	0	0
	Hair care	0	0	1	0	0
	Intimate hygiene (wipes)	0	0	0	1	0
Isoeugenol	Aftershave	1	0	2	0	0
	Deodorant	1	0	1	0	0
	Hair dye	1	0	0	0	0
	Toilet water, perfume	5	0	5	1	0
	Skin care	0	0	0	0	4
Citral	Toilet water, perfume	6	0	1	0	2
	Skin care	0	0	0	2	0
	Deodorant	0	0	0	1	0

*From the Leuven Contact Allergy Unit patch-test database.

[†]The reaction was caused by the product, but it was not possible to confirm that the fragrance ingredient was in the product.

[‡]The reaction was caused by the product, and it was known that the fragrance ingredient was in the product.

These data were used to determine what could be learned retrospectively from these reactions and to assess the potential impact that the QRA approach had on the frequency of positive patch-test reactions to these fragrance ingredients at this clinic.

Results: QRA and Clinical Data Correlation

Cinnamic Aldehyde

In 1999, the IFRA conducted a survey of marketed hydroalcoholic product formulas and requested information on the highest concentrations of cinnamic aldehyde used in these product categories. The average of the top five reported use levels in hydroalcoholic products was 1%.⁸ In 2004, the IFRA revised its cinnamic aldehyde standard, which limited the use of the material to 0.05% for all skin contact products. All contact sensitization data and patch-test data on cinnamic aldehyde were summarized in a fragrance material review⁹ and in a summary of a group of structurally related materials.¹⁰ Clinical reports from as early as 1995 showed a significant reduction in the frequency of patch test–positive reactions to cinnamic aldehyde.^{11–14} This is supported by the Leuven Contact Allergy Unit patch-test database survey results listed above. The reduction in the frequency of patch test–positive

reactions cannot be attributed to the IFRA Standard as that standard did not come into effect until 2004. This reduction may be due to a decrease in the use of cinnamic aldehyde due to marketing trends.

The current IFRA Standard (issued in 2008) further reduces the use of cinnamic aldehyde in some product categories. This should result in the continuation of this downward trend, and continued monitoring will be important. Table 2 shows the AELs for the 11 IFRA QRA product categories after applying the contact sensitization QRA approach to this material. For new IFRA Standards, the AEL derived by the QRA method is adopted as the standard. When an IFRA Standard already exists, as in the case of cinnamic aldehyde, the IFRA decided not to increase the existing maximum use levels other than for nonskin or incidental skin contact products (IFRA QRA Category 11) and product types (such as oral care products) for which there were no prior IFRA Standards. The basis for this decision was the presumption that any product's fragrance ingredient AEL determined with the QRA approach (whether higher or lower than the current IFRA Standard) would not be expected to result in new inductions. Furthermore, it was considered that increased exposure from an AEL that is higher than the current IFRA Standard could result in certain presensitized individuals' experiencing an allergic contact dermatitis where previously they had not. Should this occur, it would be impossible for dermatologists

Table 2. Acceptable Exposure Levels of Cinnamic Aldehyde As Defined by Contact Sensitization Quantitative Risk Assessment

IFRA QRA Category	Examples of Category Products*	AEL Defined by QRA (%)	IFRA Standard 2008 (%)
1	Lip products	0.02	0.02
2	Deodorants, antiperspirants	0.02	0.02
3	Hydroalcoholic products for shaved skin	0.09	0.05
4	Hydroalcoholic products for unshaved skin	0.3	0.05
5	Women's facial creams	0.1	0.05
6	Mouthwashes	0.4	0.4
7	Intimate wipes	0.04	0.04
8	Hairstyling aids	0.6	0.05
9	Conditioners (rinse-off)	3.0	0.05
10	Hard-surface cleaners	2.5	0.05
11	Nonskin contact and incidental skin contact products	Not restricted	Not restricted

AEL = acceptable exposure level; IFRA = International Fragrance Association; QRA = quantitative risk assessment.

*For a detailed description of the product categories, see Api AM and Vey M.⁷

to determine whether such an effect was the result of an existing allergy's elicitation or the result of a de novo induction. The scientific tools for making this distinction are not available today. The decision not to increase maximum use levels effectively addresses this situation.

The data in Table 2 indicate that the QRA for cinnamic aldehyde predicted that the 1999 IFRA Standard on cinnamic aldehyde, which allowed a use level of 1% in almost all product types except those in IFRA QRA Categories 9, 10 and 11 (eg, all hydroalcoholic products, hairstyling aids), was not restrictive enough. These data also identify the current IFRA limit of 0.05% as being too restrictive for several of these product categories. In addition, the risk assessment would have predicted that the 2008 IFRA limit based on the IFRA Standard of 0.05% (established in 2004 prior to the introduction of QRA) for some other product types would not be restrictive enough (eg, for deodorants, lip products, and intimate wipes). It should be noted that although IFRA Standards on cinnamic aldehyde were issued in 1999, 2004, and 2008, there is a period of time before this level is reflected in all the products in the market or in the home.

An evaluation of the clinical data from the Leuven Contact Allergy Unit patch-test database indicates that the IFRA limit of 0.05% for cinnamic aldehyde in deodorants and intimate hygiene wipe products was not low enough. This has been confirmed by the contact sensitization QRA for cinnamic aldehyde in deodorants and intimate hygiene wipes. At the same time, these patch-test data may indicate that deodorants and intimate hygiene wipes caused the contact sensitization, particularly if patients did not react to other scented products before reacting to these

products. Furthermore, the absence of patch test–positive reactions to other cosmetic product types in this survey could also suggest that the IFRA Standards have been effective for these other product types. This has also been confirmed by the contact sensitization QRA for cinnamic aldehyde in these other product types, namely, those not in IFRA QRA Categories 1, 2, and 7 (eg, deodorant, lip products, intimate wipes).

For some IFRA QRA Categories (eg, Categories 8 through 10), the IFRA Standard could be increased. For the reasons stated above, the lower IFRA Standard limit of 0.05% has been retained.

Isoeugenol

In 1992, the IFRA Standards limited the use of isoeugenol to 0.2% in all skin contact products. In 1998, the IFRA Standard for isoeugenol was reviewed because of the clinical sensitization data continually being reported. This resulted in further limitation of isoeugenol to 0.02% in all skin contact products. In 2004, Schnuch and colleagues reported that, with the exception of a peak in 1999, isoeugenol exhibited a similar incidence of positive patch-test results after that time through 2002.¹⁵ In 2007, Schnuch and colleagues reported a decrease in the incidence of positive patch-test reactions to isoeugenol from January 2003 to December 2004.¹³

Table 3 lists the AELs for the 11 IFRA QRA product categories after QRA was applied to this material. The sensitization QRA predicts that the 1998 IFRA limit of 0.02% for some product types is not restrictive enough (eg, deodorants, lip products) whereas that limit appears overly restrictive for hydroalcoholic products for unshaved skin.

Table 3. Acceptable Exposure Levels of Isoeugenol As Defined by Sensitization Quantitative Risk Assessment

IFRA QRA Category	Examples of Category Products*	AEL Defined by QRA (%)	IFRA Standard 2008 (%)
1	Lip products	0.01	0.01
2	Deodorants, antiperspirants	0.01	0.01
3	Hydroalcoholic products for shaved skin	0.04	0.02
4	Hydroalcoholic products for unshaved skin	0.1	0.02
5	Women's facial creams	0.1	0.02
6	Mouthwashes	0.2	0.02
7	Intimate wipes	0.02	0.02
8	Hairstyling aids	0.3	0.02
9	Conditioners (rinse-off)	1.3	0.02
10	Hard-surface cleaners	2.1	0.02
11	Nonskin contact and incidental skin contact products	Not restricted	Not restricted

AEL = acceptable exposure level; IFRA = International Fragrance Association; QRA = quantitative risk assessment.

*For a detailed description of the product categories see Api AM and Vey M.⁷

Based on the QRA information, the IFRA chose not to use the AEL defined by the QRA and therefore increase the existing maximum use levels other than for IFRA QRA Category 6 (oral care products for which there were prior IFRA Standards) or IFRA QRA Category 11 (nonskin or incidental skin contact products).

It is difficult to fully interpret the Leuven Contact Allergy Unit patch-test database survey results for isoeugenol because the 1998 IFRA Standard reducing the limit from 0.2% to 0.02% would have been implemented only recently in the early part of the survey that started in 2000, and thus limited the time in which to see effective change. The QRA confirmed that the limit of 0.2% was not low enough for those products types in IFRA QRA Categories 1, 2, 3, 4, 5, and 7 (see Table 1). Furthermore, QRA also confirmed that the 1998 limit of 0.02% was not low enough for product types in IFRA QRA Categories 1 and 2. The patch-test data suggest that aftershaves, deodorants, hair dye products, and fine fragrance products were a cause of sensitization, particularly if patients did not react to other fragranced products before reacting to these products. The 2006 patch-test survey data reported no confirmed positive reactions to isoeugenol in any product type; in 2007, the data reported only one reaction to isoeugenol in a fine fragrance product type. These are very small numbers and are only retrospective, but they may indicate a trend in reduction of patch test–positive reactions to isoeugenol and suggest that the 1998 IFRA Standards were effective in reducing the induction of contact sensitization. It is clear from the published literature and the patch-test database survey that active monitoring of diagnostic patch-test data for isoeugenol is needed.

Citral

Prior to the adoption of the IFRA Standard for citral in 2006, the IFRA conducted a survey of marketed hydroalcoholic product formulas and requested disclosure of the highest concentrations of citral used in these products. The average of the top five reported use levels in hydroalcoholic products was 1.7%.¹⁶ From 1975 until 2006, the IFRA Standard for citral did not limit the use of the material but specified its use with terpenes due to a “quenching phenomenon.”¹⁷ The quenching data could not be reproduced, and the RIFM Expert Panel recommended that all standards based on quenching be revised. The revised IFRA Standard for citral was issued in May 2006. As such, the AEL derived by the QRA method was adopted as the IFRA Standard. Table 4 lists the AELs of citral for the 11 IFRA QRA product categories.

The IFRA Standard based on the QRA approach limits citral in hydroalcoholic products for unshaved skin to 0.6%. The data from the patch-test database on citral (see Table 1) suggest that, before 2006, citral was being used at a level that exceeded the AEL for hydroalcoholic products for unshaved skin. This is suggested by the finding that the only reactions reported from the patch-test database survey were reactions to toilet water and perfume products. Reactions to other product types containing citral, such as deodorants and antiperspirants, were very limited in this database. An IFRA survey in 2001 showed that AEL for citral determined by the QRA in these product types was not exceeded.¹⁶

All sensitization and clinical data on citral were previously summarized.¹⁸ Clinical reports showed a

Table 4. Acceptable Exposure Levels of Citral As Defined by Sensitization Quantitative Risk Assessment

IFRA QRA Category	Examples of Category Products*	AEL Defined by QRA (IFRA Standard 2006) (%)
1	Lip products	0.04
2	Deodorants, antiperspirants	0.05
3	Hydroalcoholic products for shaved skin	0.2
4	Hydroalcoholic products for unshaved skin	0.6
5	Women's facial creams	0.3
6	Mouthwashes	1.0
7	Intimate wipes	0.1
8	Hairstyling aids	1.4
9	Conditioners (rinse-off)	5.0
10	Hard-surface cleaners	2.5
11	Nonskin contact and incidental skin contact products	Not restricted

AEL = acceptable exposure level; IFRA = International Fragrance Association; QRA = quantitative risk assessment.

*For a detailed description of the product categories see Api AM and Vey M.⁷

frequency of positive reactions to citral that ranged from 0.3 to 0.6%.^{13,19,20} Citral was not routinely tested in dermatology clinics in the past although it is now part of fragrance mix II. It is anticipated that more data will be obtained through ongoing monitoring of rates of positive patch-test results in dermatology clinics. It is expected that there will be a downward trend in the rate of positive patch-test reactions to citral over time. Since the IFRA Standard for citral was introduced in May 2006, it is unrealistic to expect such decreases to become evident until products that reflect the new restriction have been in the marketplace for a reasonable length of time.

Discussion

QRA for sensitization to fragrance ingredients is now routinely used to establish new IFRA Standards for all fragrance ingredients that are potential contact sensitizers because it is a major improvement over the former approach. As such, it is important to have data to demonstrate that QRA methodology does indeed provide a valid approach to the primary prevention of the induction of sensitization by fragrance ingredients identified as potential sensitizers. In the future, the best way to obtain such data will be to monitor trends of true positive patch-test reactions reported by dermatology clinics in relation to consumers' use of products. This article reviews

the retrospective clinical data for three fragrance ingredients to provide support and perspective for the usefulness of the QRA approach. Although available retrospective clinical data are limited for any fragrance ingredient even beyond the survey presented, the figures presented in this article are the only ones available at this time.

It is possible to speculate that had the QRA approach been available at the time IFRA Standards were established for these three fragrance ingredients, the clinical response would have been noticeably improved. Had it been used, the QRA approach should have provided AELs that were more appropriate for the various product types, and that would have resulted in lower use levels for leave-on products used in high-absorption areas such as the axillae.

For cinnamic aldehyde and isoeugenol, the QRA for citral predicted a lower use level for hydroalcoholic products than those previously reported in marketed products. In the absence of an IFRA Standard restricting the use level of citral, QRA for citral predicted a use level in hydroalcoholic products lower than levels previously seen. In addition, QRA predicted a level that matched those reportedly used historically in a majority of deodorant-type products.

In all of these examples, QRA predictions were not in conflict with the initial patch-test clinical survey data. The absence of reactions to these three fragrance ingredients in other cosmetic products from this survey may indicate that the IFRA Standards have been effective for other product types. It is anticipated that there will be a downward trend in the rates of positive patch-test reactions to cinnamic aldehyde, citral, and isoeugenol over time as the IFRA Standards have become more restrictive in each case, particularly for the product types that present the highest possibility of inducing contact sensitization. However, it is unrealistic to expect such decreases to become evident until products that reflect the new restriction have been available for a reasonable length of time. While annual patch-test data will be monitored closely, it is likely that changes in trends of true positive patch-test reactions in relation to consumers' use of products will become evident within at least 5 years.

Analysis of the limited available retrospective data increases confidence that IFRA Standards established via the QRA approach can be an effective primary prevention tool with which to address the induction of contact sensitization to fragrance ingredients. This is supported by the results reported in articles about using the QRA approach for other specific materials (eg, the preservative methylchloroisothiazolinone/methylisothiazolinone).^{21,22}

Contact sensitization QRA for fragrance ingredients should be used in combination with clinical results from the dermatology community and from company-specific postmarket surveillance data to confirm the effectiveness of fragrance ingredient use limits. As such, it is important that patch-test data on fragrance ingredients be continually and actively monitored. The challenge is to obtain confirmed data on positive patch-test reactions to specific fragrance ingredients that are known to be in specific product types. It may be necessary to follow up with additional detailed studies on subjects with relevant and confirmed positive patch-test reactions to fragrance ingredients in known identified product types. Until such data are available, trends shown in clinical sensitization studies on fragrance ingredients need to be monitored carefully.

Acknowledgments

Financial disclosures of authors and reviewer(s): None reported.

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