Regulatory Toxicology and Pharmacology 135 (2022) 105260

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Quantitative risk assessment of allergens leaching from menstrual hygiene products

Quinten Marcelis [a], Alexandra Gatzios [a], Eric Deconinck [b], Vera Rogiers [a], Bart Desmedt [b,1], Tamara Vanhaecke [a,1,*]

[a] Department In Vitro Toxicology and Dermato-cosmetology (IVTD), Vrije Universiteit Brussel, Laarbeeklaan 103, 1090, Jette, Belgium
[b] Medicines and Medicinal Health Products, Sciensano, Julliette Weytsmanstraat 14, 1050, Elsene, Belgium

ARTICLE INFO

Handling Editor: Dr. Martin Van den berg

Keywords:
Allergic Contact dermatitis
Consumer safety
Skin sensitizers
Risk assessment

ABSTRACT

Allergic contact dermatitis (ACD) often associated with the topical use of perfumed products, remains one of the most common chronic skin disorders in Western countries. Since labelling of scented menstrual hygiene products (MHPs) is not mandatory, women might be unknowingly exposed to allergens. Given that vaginal mucosae lack the vital barrier function of the skin, skin allergens can easily penetrate and become systemically available and hence women may experience adverse effects in the anogenital region. The aim of this study was therefore to investigate whether women using scented MHPs are at risk of sensitization and hence developing ACD. Hereto, a Quantitative Risk Assessment (QRA) is performed on four well-known skin sensitizing chemicals (α-isomethyl ionone, benzyl salicylate, hexyl cinnamaldehyde and heliotropine) that were previously found leaching from five different scented MHPs including tampons and sanitary pads. The amounts of heliotropine, leached by one of the investigated tampons, exceeded acceptable exposure levels determined with the QRA and could induce sensitization. In addition, although no sensitization is expected for the other three compounds, an allergenic reaction might be provoked in women who are already sensitized. Labelling of allergens on scented MHPs would therefore help consumers to prevent adverse effects linked to ACD.

1. Introduction

Allergic contact dermatitis (ACD) is one of the most recurrent chronic skin diseases in Western countries, and is often linked to the topical use of scented products (De Groot, 2020; Yale et al., 2018). Although ACD of the ano-genital region is less common, it equally impairs the quality of life (Huang S, 2012). Typical complaints range from redness to itching and burning in the genital area (De Groot, 2020). At present, the cornerstone in the management of ACD is allergen avoidance since no cure is available (Yale et al., 2018). Therefore, patients are advised to carefully consider the disclosed ingredient information on the products they use. For cosmetics and topical medications, labelling is mandatory and consumers can check this information. For menstrual hygiene products (MHPs), however, providing this type of information is not mandatory.

Undoubtedly, adequate product information is essential to improve the quality of life of patients suffering from genital ACD. However, a regulatory initiative to harmonize ingredient labelling for consumer products on the European market is lacking. Indeed, ingredient labelling is currently only mandated in the EU by some product-specific regulations such as the Cosmetics Regulation (EC) N° 1223/2009. In this respect, the presence of 26 allergenic ingredients must be indicated on the packaging when its concentration exceeds 0.01% in rinse-off products and is above 0.001% in leave-on products, as referred to Article 19 (1) (g) of the Cosmetics Regulation. This is in sharp contrast to other consumer products such as MHPs that are governed by the *'General Product Safety Directive'* (GPSD) where ingredient disclosure is not obligatory (Directive, 2001/95/EC). On the other hand, as stated by the GPSD, safety is a prerequisite for consumer products to enter the EU market. Thus, the question arises whether products that leach allergenic fragrances can be considered safe, knowing that the naïve consumer is unaware of it and may become sensitized (Nicole, 2014). While tampons and sanitary pads are regulated as consumer products in the EU, the Food and Drug Administration (FDA) classifies these as Medical device

* Corresponding author
E-mail addresses: quinten.marcelis@vub.be (Q. Marcelis), Alexandra.Gatzios@vub.be (A. Gatzios), Eric.Deconinck@sciensano.be (E. Deconinck), Bart.Desmedt@sciensano.be (B. Desmedt), Tamara.Vanhaecke@vub.be (T. Vanhaecke).
[1] Equally contributing senior authors.

https://doi.org/10.1016/j.yrtph.2022.105260
Received 1 April 2022; Received in revised form 11 July 2022; Accepted 29 August 2022
Available online 5 September 2022

category I or II respectively in the US. Their regulatory status, however, does not differ significantly from the European counterpart i.e. ingredient declaration is also not required in the US. Thus, allergen avoidance remains hampered for already sensitized women. The FDA's only recommendation is that scented MHPs should display a warning statement about allergic reactions and irritations (FDA, 2005).

Despite extensive research carried out on the identification of skin sensitizers in consumer products, studies covering the induction of ACD through the use of MHPs are scarce. In general, if clinical evidence demonstrates that a skin sensitizer is the culprit of increasing ACD cases, regulatory actions are taken e.g. restricting use or limiting the concentration in certain products. Here, the novel Quantitative Risk Assessment (QRA) can play a proactive role in preventing ACD induction (primary prevention). In order to accomplish so, consumer exposure is compared to the dose required to induce ACD, together with the introduction of some uncertainty factors (Api et al., 2008). Knowing that consumers use a variety of products on a daily basis, it is critical to consider aggregate exposure when assessing the risk of skin sensitization. The recently amended QRA 2 takes such exposure from multiple cosmetics into account (Api et al., 2020). Endorsed by the fragrance industry, such QRA is deemed suitable for evaluating ACD induction. Unfortunately, MHPs are currently not included in the QRA 2, therefore aggregate exposure is not taken into account when estimating acceptable exposure limits for fragrance components in these consumer products. Therefore, in our study, a QRA 1 is performed on four well-known allergens, α-isomethyl ionone, benzyl salicylate, hexyl cinnamaldehyde and heliotropine, leaching from different scented MHPs under in-use conditions (Marcelis et al., 2021).

2. Materials & methods

2.1. Studied menstrual hygiene products and allergens

This study is focused on four known skin sensitizers classified as category 1B of the Globally Harmonised System of Classification and Labelling of Chemicals (UN, 2019): α-isomethyl ionone, benzyl salicylate, hexyl cinnamaldehyde and heliotropine. All these compounds were previously found to be leaching under physiological conditions from scented tampons (T) and/or sanitary pads (SP) from different manufactures, purchased in retail- or online-stores on the Belgium market (Table 1) (Marcelis et al., 2021). None of these allergic components were communicated to the consumer via the label. Presence of perfume could only be suspected by the smell or vague claims on the packaging of the MHPs such as 'fresh'.

2.2. Quantitative risk assessment

The methodological approach to assess ACD induction from scented MHP use, is based on the QRA methodology (Fig. 1) (Api et al., 2008). Originally, the QRA has been developed for fragrance substances and its basic principles and methodology are presented by the Scientific Committee for Consumer Products and the Scientific Committee on Consumer Safety in reports SCCP/1153/08 and SCCS/1628/21, respectively (SCCP, 2008; SCCS, 2021). The key steps in the QRA process are hazard assessment (I + II + III), exposure assessment (IV) and the risk characterization (V):

I. Determination of the benchmark level for ACD induction.
II. Determination of sensitization assessment factors (SAFs) accounting for inter-individual variation, vehicle matrix effects, exposure parameters.
III. Calculation of the maximal acceptable exposure level (AEL).
IV. Calculation of the daily consumer exposure level (CEL) comprising compound concentration and frequency of use.
V. Comparison of AEL and CEL.

Table 1
Overview of studied menstrual hygiene products and their respective leaching skin sensitizers as established in Marcelis et al. (2021).

MHP type	MHP	Brand	Leaching skin sensitizer
Tampon	T1	A	Heliotropine (CAS 120-57-0)
	T2	A	Heliotropine (CAS 120-57-0)
	T3	A	Heliotropine (CAS 120-57-0)
	T4	B	α-isomethyl ionone (CAS 127-51-5) Heliotropine (CAS 120-57-0)
Sanitary Pad	SP1	C	Benzyl salicylate (CAS 118-58-1) Hexyl cinnamaldehyde (CAS 101-86-0)

Abbreviations: CAS, Chemical Abstracts Service; MHP, menstrual hygiene product; T, tampon; SP, sanitary pad.

2.2.1. Exposure assessment

2.2.1.1. Exposure scenarios. Frequency and duration of the use of MHPs are intermittent i.e. during one week of every month on average six tampons or sanitary pads are daily used (Billon et al., 2020; DeVito and Schecter, 2002). This corresponds to a renewal rate of one MHP every 4 h, as also advised by different MHP manufacturers. However, it is well known that some women use MHP overnight, resulting in a prolonged exposure duration of eight to 10 h. For this reason, two exposure scenarios were evaluated in the exposure assessment: Scenario A encompassing women who use on average six MHPs per day with an exposure duration of 4 h per product, and Scenario B encompassing women using MHP for the maximal allowed period, i.e. 8 h according to the FDA, resulting in daily use of only three MHPs used per day (FDA, 2005).

2.2.1.2. Leaching concentrations of studied allergens from MHPs. In a previous study from our research group, the leaching concentrations of the skin sensitizers from the MHPs under simulated use conditions have been determined using an in-house validated *in chemico* method (Marcelis et al., 2021). In short, a MHP was brought into contact with menstrual fluid simulant during four (scenario A) and 8 h (scenario B) at 37 °C. The menstrual fluid simulant mimicked the osmolarity, pH and protein content of human menstrual fluid, but did not contain bacteria, fungi and cellular matter to ensure compatibility with analytical applications. After leaching, the resulting simulant was analyzed by ultra-high performance chromatography using mass spectrometry detection. By using matrix-matched calibration curves and validation according to accuracy profiles, in-use concentrations of α-isomethyl ionone, benzyl salicylate, hexyl cinnamaldehyde and heliotropine, expressed in μg/g per MHP, were estimated with an accuracy of 95%. Subsequently, the mass of the corresponding MHP was considered to calculate the total amount of allergen leaching per product use and was expressed in μg per MHP.

2.2.1.2.1. Amount of substance per cm^2 exposed surface area. Regarding the exposed surface area, a distinction was made between tampons and sanitary pads, with direct mucosal contact or external skin contact, respectively. Hence, an average adult vaginal surface area of 87.5 cm^2 was used for tampons, whereas a vulvar surface area of 100 cm^2 was applied for sanitary pads (Pendergrass et al., 2003).

2.2.1.3. Dermal absorption. From a conservative point of view, a complete transfer of all allergens from the MHP to the skin/mucosae was assumed where they were fully absorbed in the case of tampons (A = 100%) and only half in case of sanitary pads (A = 50%).

Collectively, the consumer exposure level (CEL) was calculated as follows:

$$\mathrm{CEL}\ (\mu g \Big/ cm^2 \Big/ day) = \frac{m \times C \times f \times A}{S}$$

With:

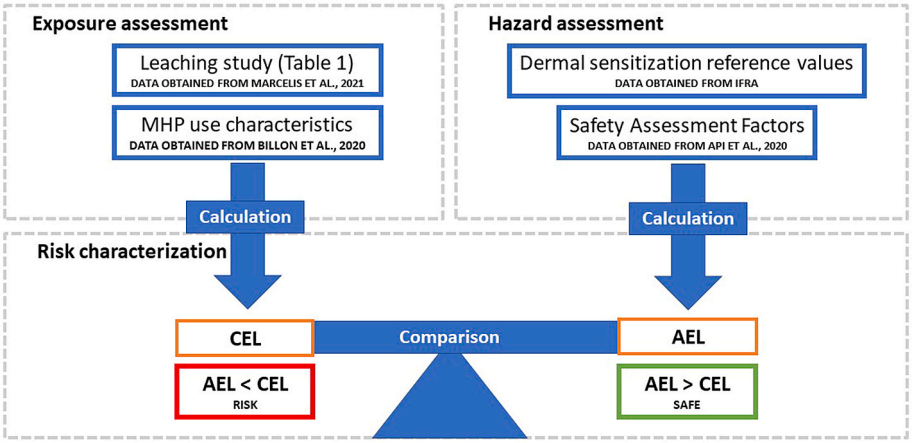

Fig. 1. Quantitative risk assessment methodology for skin sensitization. Exposure assessment (left) based on results from previous experiments, is combined with a hazard assessment (right) into a risk characterization step (bottom) (Figure adapted from (Api et al., 2008). *Abbreviations: AEL, Acceptable exposure level; CEL, Consumer exposure level; IFRA, International Fragrance Association.*

C: experimentally determined leaching concentration of the chemical (μg/g MHP) (Marcelis et al., 2021)
m: MHP mass (g)
f: frequency of use (number of MHPs/day)
A: the dermal/mucosal absorption rate (%)
S: exposed surface area (cm^2)

2.2.2. Hazard assessment

The aim of the hazard assessment is to determine the acceptable exposure level (AEL) where induction of skin sensitization is not expected. The point of departure in the hazard assessment is the skin sensitization reference which represents the quantitative threshold where no induction of ACD occurs. Most often, the no expected sensitization induction level (NESIL) is selected (Wijnhoven et al., 2008). The NESIL is determined using a weight of evidence (WoE) approach by combining information from multiple independent sources so that sufficient evidence on allergenicity is taken into consideration (Api et al., 2008). The WoE NESIL values for α-isomethyl ionone, benzyl salicylate and hexyl cinnamaldehyde are 71000, 17700 and 23600 μg/cm^2, respectively (IFRA, 2015, 2013, 2009). Since the WoE NESIL for heliotropine is still to be derived by expert judgement (Api et al., 2017), the no observable effect level (NOEL) derived from the human repeated insult patch test, i.e. 2952 μg/cm^2, was selected as the skin sensitization reference value in this study.

To bridge the gap between the reference values obtained from experimental studies and normal-use conditions, sensitization assessment factors (SAFs) are taken into consideration that are equivalent to the uncertainty factors as used in general toxicological risk assessments (SCCS, 2018). To account for this extrapolation, four key uncertainties are included (Basketter and Safford, 2016):

(i) Inter-individual variability (e.g. age, ethnicity, inherent dermal barrier and genetic effects).
(ii) Vehicle/product matrix effects (e.g. presence of irritants, penetration enhancers).
(iii) Site of application (barrier function, occlusion).
(iv) Frequency of use (chemical or biological accumulation).

Recently, the SAFs accounting for the specific use of product coming into contact with the ano-genital region, have been updated. Former SAFs were established at 200 and 100 for tampons and sanitary pads, respectively (Api et al., 2008). When, however, contact with the non-keratinized mucous membrane, the occlusion and the frequency of use are taken into account, the QRA 2 SAFs for tampons and sanitary pads were adapted to 600 and 300 (Api et al., 2020). For each sensitizer, the AEL was calculated by dividing the NESIL by the SAF of the respective product type (Api et al., 2008).

2.2.3. Risk characterization

In the risk characterization, the ratio between the AEL and CEL is determined. To support safe use of the sensitizer, the AEL should be greater than the CEL or the ratio of AEL to CEL must be greater than one.

3. Results and discussion

3.1. Exposure estimates of investigated allergens leaching from MHPs

As explained in section 3.2.1.1, two different exposure scenarios were considered i.e. scenario A and scenario B encompassing the use of six or three MHPs per day, respectively. The estimated exposure levels for both scenarios are shown in Table 2. The consumer exposure varied from 0.3 μg/cm^2/day for a sanitary pad leaching hexyl cinnamaldehyde (Scenario B) to a 5.3 μg/cm^2/day for a tampon leaching heliotropine (Scenario A). For scenario A, benzyl salicylate and hexyl cinnamaldehyde leached below concentrations of the lower limit of quantification and therefore CELs could not be calculated for these skin sensitizers. For α-isomethyl ionone and heliotropine, scenario A resulted in a higher consumer exposure level in comparison to scenario B. This is not unexpected as the frequency of MHP changes in scenario A is the double of that in scenario B.

3.2. Hazard assessment

The results of the hazard assessment are shown in Table 3. The calculated AELs for heliotropine, benzyl salicylate, hexyl cinnamaldehyde and α-isomethyl ionone leaching from tampons are 4.9, 29.5, 39.3 and 118.3 μg/cm^2/day, respectively. Given that the SAF value for sanitary pads is half of the value in comparison to the SAF for tampons, the respective AELs of the allergens for sanitary pads are 9.8, 59.0, 78.7 and 236.7 μg/cm^2/day. Not surprisingly, the lowest observed skin sensitization reference value, here 2952 μg/cm^2/day for heliotropine, resulted in the lowest AEL when leaching from a tampon (4.9 μg/cm^2/day). However, caution should be taken when interpreting this result since the WoE NESIL has yet to be derived. Following the guidelines of the QRA for absent WoE NESIL information, the no observed effect level was selected (IDEA, 2016).

3.3. QRA

In Table 4, the risk evaluation is shown. When considering exposure

Table 2
Consumer exposure levels of fragrance allergens leaching from various menstrual hygiene products taking into account two exposure scenarios (Scenario A: 4 h exposure, 6 products used per day; Scenario B: 8 h exposure, 3 products used per day).

Menstrual hygiene product				Intimate environment		Exposure scenario A			Exposure scenario B		
Sample		Skin sensitizer	mass (g)	S (cm^2)	A (%)	f (use/day)	C (μg/g MHP)	CEL (μg/cm^2/day)	f (use/day)	C (μg/g MHP)	CEL (μg/cm^2/day)
Tampon	T1	Heliotropine	2.8	87.5	100	6	6.7	1.3	3	9.7	0.9
	T2	Heliotropine	2.1				< LLOQ	n.c.		5.2	0.4
	T3	Heliotropine	2.9				< LLOQ	n.c.		4.7	0.5
	T4	α-isomethyl ionone	3.4				6.3	1.5		6.5	0.8
		Heliotropine					22.6	5.3		28.2	2.9
Sanitary Pad	SP1	Benzyl salicylate	2.1	100	50		< LLOQ	n.c.		11.0	0.4
		Hexyl cinnamaldehyde					< LLOQ	n.c.		8.7	0.3

Abbreviations: A, dermal absorption rate; C, experimentally determined leaching concentration from Marcelis et al. (2021); CEL, consumer exposure level; f, frequency of use; LLOQ, lower limit of quantification; M, mass of MHP; n.c., not calculated; S, surface area of intimate region; SP, sanitary pad; T, tampon.

Table 3
Acceptable exposure levels of allergens leaching from menstrual hygiene products.

Allergen	Skin sensitization reference value (μg/cm^2/day)	SAF tampon	SAF sanitary pad	AEL tampon (μg/cm^2/day)	AEL sanitary pad (μg/cm^2/day)
α-isomethyl ionone	71000	600	300	**118.3**	**236.7**
Heliotropine	2952			**4.9**	**9.8**
Benzyl salicylate	17700			**29.5**	**59.0**
Hexyl cinnamaldehyde	23600			**39.3**	**78.7**

Abbreviations: AEL, acceptable exposure level; SAF, safety assessment factors.

Table 4
Risk characterization for fragrance allergens leaching from various menstrual hygiene products taking into account two exposure scenarios (Scenario A: 4 h exposure, 6 products used per day; Scenario B: 8 h exposure, 3 products used per day).

Menstrual hygiene product		Allergen	AEL (μg/cm^2/day)	Exposure scenario A		Exposure scenario B	
				CEL (μg/cm^2/day)	AEL/CEL	CEL (μg/cm^2/day)	AEL/CEL
Tampon	T1	Heliotropine	4.9	1.3	3.8	0.9	5.3
	T2	Heliotropine	4.9	n.c.	n.c.	0.4	13.1
	T3	Heliotropine	4.9	n.c.	n.c.	0.5	10.6
	T4	α-isomethyl ionone	118.3	1.5	80.8	0.8	157.1
		Heliotropine	4.9	5.3	**0.9**	2.9	1.7
Sanitary Pad	SP1	Benzyl salicylate	59.0	n.c.	n.c.	0.4	167.4
		Hexyl cinnamaldehyde	78.7	n.c.	n.c.	0.3	284.0

Abbreviations: AEL, acceptable exposure level; CEL, consumer exposure level; MHP, menstrual hygiene product; n.c., not calculated; SP, sanitary pad; T, tampon.

scenario A, we found that the AEL/CEL ratio for heliotropine leaching from a tampon (T4) was less than 1, namely 0.9. This means that women who use six of these tampons for a duration of 4 h, could be at risk to develop ACD according to the QRA. Of course, this finding should be interpreted with caution until a WoE NESIL for heliotropine is determined. Because the WoE NESIL presents a scientifically more valid method for evaluating a substance's allergenic potency in comparison to the NOEL, it is plausible that a more nuanced AEL would be obtained and that the AEL/CEL ratio becomes greater than 1. Considering exposure scenario B, all AEL/CEL ratios were greater than 1, suggesting absence of skin sensitization induction for the investigated allergens. A graphical visualization of how the CEL (blue line) relates to the skin sensitization reference value (red bar), its SAF (orange bar) and the AEL (green bar), is given in Fig. 2.

It is undeniable that anogenital ACD significantly lowers women's quality of life. According to a recent review covering over 20 years' worth of research on this condition, the primary cause of anogenital complaints is linked to fragrance exposure (Corazza et al., 2021). In 15 of the 17 mentioned studies, the causal relation among fragrance exposure and anogenital ACD has been highlighted. Collectively, these studies outline a critical role for the management of fragrance exposure in the vulvar region. Therefore, as a proof-of-concept, we have

Fig. 2. *Graphical representation of the consumer exposure (blue line) for the four determined skin sensitizers* (Adapted from (Basketter et al., 2003). For heliotropine, the consumer exposure exceeds the AEL and falls within the margin of the SAFs (orange). *Abbreviations: SAF, safety assessment factors; NESIL, No expected sensitization induction level; NOEL, No observable effect level. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)*

performed the QRA on fragrance allergens leaching from menstrual hygiene products.

As stated in the preliminary opinion by the Scientific Committee on Consumer Safety (SCCS, 2018), the novel QRA 2 technique might be useful for the risk assessment of fragrance allergens and other cosmetic ingredients. However, prior to regulatory and industrial acceptance, several issues must be clarified. For example, the vast array of SAFs and their application is to some extent not clear. Another potential limitation of the current QRA 2 is that it does not account for aggregate exposure to a variety of consumer items utilized in the genital area. In addition to using scented MHPs, intimate wipes and vaginal douche products can be an additional source of fragrance allergens and have been linked to irritating and allergic contact dermatitis (Yale et al., 2018). At last, the inherent design of the QRA 2 is to determine the risk of ACD induction. However, the QRA 2 does not take the elicitation of ACD into account and thus neglects a significant proportion of the population who already suffers from ACD. The process of ACD elicitation is complex and depends not only on the intrinsic potency of a sensitizer, but also the susceptibility of the exposed individual and the severity of the induction process (Hostynek and Maibach, 2004). Therefore, the inclusion of this important subpopulation, already sensitized people, in the QRA is a rigorous task and has not yet been undertaken. One potential option could be to establish substance-specific elicitation thresholds derived from clinical studies (Fischer et al., 2009). However, this falls outside the scope of the current QRA 2 approach, as the main goal is primary prevention of ACD. This is justified on the grounds that if induction can be prevented now, elicitation will not occur in the future (Api et al., 2020).

In any case, this study emphasizes the need for ingredient disclosure on the packaging of MHPs. This need for greater transparency on ingredient disclosure is no isolated case. Other scented consumer products like household products, detergents, and cleaning agents do not always disclose fragrance allergens on the packaging either (Lee et al., 2020). However, ingredient labelling of sensitizing substances is of vital importance in terms of secondary prevention for many individuals already suffering from ACD (Bennike, 2018). If a legislation comparable to the Cosmetic Regulation would apply for MHPs, the presence of fragrances should be indicated on the label using the correct nomenclature e.g. ‘parfum’ or ‘aroma’. Furthermore, 26 fragrance allergens (including α-isomethyl ionone, benzyl salicylate and hexyl cinnamaldehyde) would also be subject to individual labelling according to Annex III of the Cosmetics Regulation. However, none of the investigated sensitizers were disclosed on the packaging, potentially putting already sensitized consumers unknowingly at risk.

4. Conclusion

In this study, four skin sensitizers leaching from scented MHPs were subjected to a quantitative health risk assessment. Although consumers are exposed to benzyl salicylate, hexyl cinnamaldehyde and α-isomethyl ionone via MHPs use, no risk of ACD induction is expected from these sensitizers. However, when considering a reasonable use scenario of six tampons during one day, the AEL was exceeded in case of heliotropine for one tampon brand. Hence, women who use these tampons could be at risk of ACD induction. Nevertheless, for already sensitized women, it is vital that all these allergens are mentioned on the packaging, so that these allergens could be avoided.

Funding

This work was funded by the Research Council of the VUB and the Research Chair Mireille Aerens for alternative animal-free research methods.

CRediT authorship contribution statement

Quinten Marcelis: Conceptualization, Methodology, Data curation, Investigation, Writing – original draft, Visualization. **Alexandra Gatzios:** Investigation, Data curation. **Vera Rogiers:** Writing – review & editing. **Bart Desmedt:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Tamara Vanhaecke:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Quinten Marcelis reports financial support was provided by Research Chair Mireille Aerens for alternative animal-free research methods. Quinten Marcelis reports article publishing charges was provided by Research council VUB.

References

Api, A.M., Basketter, D., Bridges, J., Cadby, P., Ellis, G., Gilmour, N., Greim, H., Griem, P., Kern, P., Khaiat, A., O'Brien, J., Rustemeyer, T., Ryan, C., Safford, B., Smith, B., Vey, M., White, I.R., 2020. Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials. Regul. Toxicol. Pharmacol. 118, 104805 https://doi.org/10.1016/J.YRTPH.2020.104805.

Api, A.M., Basketter, D.A., Cadby, P.A., Cano, M.-F., Ellis, G., Gerberick, G.F., Griem, P., McNamee, P.M., Ryan, C.A., Safford, R., 2008. Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. Regul. Toxicol. Pharmacol. 52, 3–23. https://doi.org/10.1016/j.yrtph.2007.10.008.

Api, A.M., Parakhia, R., O'Brien, D., Basketter, D.A., 2017. Fragrances categorized according to relative human skin sensitization potency. Dermatitis 28, 299–307. https://doi.org/10.1097/DER.0000000000000304.

Basketter, D., Angelini, G., Ingber, A., Kern, P., Menné, T., 2003. Nickel, chromium and cobalt in consumer products: revisiting safe levels in the new millennium. Contact Dermatitis 49, 1–7. https://doi.org/10.1111/J.0105-1873.2003.00149.X.

Basketter, D.A., Safford, B., 2016. Skin sensitization quantitative risk assessment: a review of underlying assumptions. Regul. Toxicol. Pharmacol. 74, 105–116. https://doi.org/10.1016/j.yrtph.2015.11.013.

Bennike, N.H., 2018. Contact Allergy to Fragrance Substances – Epidemiological Aspects and Experimental Investigations. University of Copenhagen.

Billon, A., Gustin, M.P., Tristan, A., Bénet, T., Berthiller, J., Gustave, C.A., Vanhems, P., Lina, G., 2020. Association of characteristics of tampon use with menstrual toxic shock syndrome in France. EClinicalMedicine 21. https://doi.org/10.1016/J.ECLINM.2020.100308.

Corazza, M., Toni, G., Zedde, P., Schettini, N., Borghi, A., 2021. Contact dermatitis of the vulva, 2021 Allerg 1 (1), 206–215. https://doi.org/10.3390/ALLERGIES1040019, 206–215.

De Groot, A.C., 2020. Fragrances: contact allergy and other adverse effects. Dermat. Contact, atopic, Occup. drug 31, 13–35. https://doi.org/10.1097/DER.0000000000000463.

DeVito, M.J., Schecter, A., 2002. Exposure assessment to dioxins from the use of tampons and diapers. Environ. Health Perspect. 110, 23–28. https://doi.org/10.1289/ehp.0211023.

FDA, 2005. Guidance for Industry and FDA Staff Menstrual Tampons and Pads : Information for Premarket Notification Submissions (510 (K)S), 510. FDA U.S. Food Drug Adm.

Fischer, L.A., Voelund, A., Andersen, K.E., Menné, T., Johansen, J.D., 2009. The dose–response relationship between the patch test and ROAT and the potential use for regulatory purposes. Contact Dermatitis 61, 201–208. https://doi.org/10.1111/J.1600-0536.2009.01607.X.

Hostynek, J.J., Maibach, H.I., 2004. Thresholds of elicitation depend on induction conditions. Could low level exposure induce sub-clinical allergic states that are only elicited under the severe conditions of clinical diagnosis? Food Chem. Toxicol. 42, 1859–1865. https://doi.org/10.1016/j.fct.2004.06.017.

Huang S, S.P., 2012. Anogenital Allergic Contact Dermatitis | the Dermatologist [WWW Document]. URL, 20. https://www.the-dermatologist.com/content/anogenital-allergic-contact-dermatitis (accessed 4.8.20).

IDEA, 2016. IDEA PROJECT FINAL REPORT on the QRA2 Skin Sensitisation Quantitative Risk Assessment for Fragrance Ingredients.

IFRA, 2015. IFRA standard - methyl ionone, mixed isomers [WWW Document]. URL. https://ifrafragrance.org/safe-use/standards-guidance (accessed 4.8.20).

IFRA, 2013. IFRA standard - hexyl cinnamic aldehyde [WWW Document]. URL. https://ifrafragrance.org/safe-use/standards-guidance (accessed 4.8.20).

IFRA, 2009. IFRA standard - benzyl salicylate [WWW Document]. URL. https://ifrafragrance.org/safe-use/standards-guidance (accessed 4.8.20).

Lee, B.M., Choi, M., Shin, I., Kim, J., Choi, Z., Kim, K., Choi, K., Yang, S., So, D.Y., Tae Ju, S., Kwon, S., 2020. Risk communication for labeling all ingredients in consumer products. J. Toxicol. Environ. Health Part A Curr. Issues 83, 509–524. https://doi.org/10.1080/15287394.2020.1780174.

Marcelis, Q., Gatzios, A., Deconinck, E., Rogiers, V., Vanhaecke, T., Desmedt, B., 2021. Development and application of a novel method to assess exposure levels of sensitizing and irritating substances leaching from menstrual hygiene products. Emerg. Contam. 7, 116–123. https://doi.org/10.1016/j.emcon.2021.02.004.

Nicole, W., 2014. A question for women's health: chemicals in feminine hygiene products and personal lubricants. Environ. Health Perspect. 122, A70. https://doi.org/10.1289/ehp.122-A70.

Pendergrass, P.B., Belovicz, M.W., Reeves, C.A., 2003. Surface area of the human vagina as measured from vinyl polysiloxane casts. Gynecol. Obstet. Invest. 55, 110–113. https://doi.org/10.1159/000070184.

SCCP, 2008. Dermal Sensitisation Quantitative Risk Assessment (Citral, Farnesol and Phenylacetaldehyde).

SCCS, 2021. The SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation, 11th Revision, 30-31 March 2021, SCCS/1628/21, SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation 11threvision. European union. https://doi.org/10.1016/j.yrtph.2021.105052.

SCCS, 2018. Opinion on Skin Sensitisation Quantitative Risk Assessment for Fragrance Ingredients (QRA2). European union. https://doi.org/10.2875/989719.

UN, 2019. Globally harmonized System of classification and labelling of chemicals, review of environmental economics and policy studies. New York and Geneva. https://doi.org/10.14927/reeps.10.2_60.

Wijnhoven, S., Ezendam, J., Schuur, A., Loveren, H. Van, Engelen, J. Van, 2008. Allergens in Consumer Products.

Yale, K., Awosika, O., Rengifo-Pardo, M., Ehrlich, A., 2018. Genital allergic contact dermatitis. Dermatitis 29, 112–119. https://doi.org/10.1097/DER.0000000000000371.