The International Fragrance Association

To: Member Associations (FOR ACTION)
Subscribers to the Code and other Stakeholders

Cc: RMTF, RIFM
Customer Associations
Members of the JAG

April 19, 2023

IFRA End of Consultation on the 51st Amendment to the IFRA Standards

Dear Colleagues,

On February 28, 2023, the (extended) public Consultation period for the IFRA 51st Amendment came to an end. The IFRA Standards intended to be part of this Amendment were listed in the Consultation Letter distributed to the IFRA membership on June 30, 2022. Furthermore, two additional fragrance ingredients were included in the public Consultation via a separate communication through the IFRA Information Letter (IL) 1146 of November 29, 2022. The following items were therefore part of the Consultation:

- The updated Guidance for the use of the IFRA Standards
- The IFRA Standards listed in the respective sections of the Consultation Letter plus the revised Standards on Methyl eugenol (CAS 93-15-2) and Estragole (CAS 140-67-0) communicated with the IL 1146.
- The Annex on contributions from other sources to the IFRA Standards, which combines – where applicable – information from natural contributions (former Annex I) as well as Schiff bases (former Annex II).

As for previous Amendments, the IFRA Standards are based on the conclusions of the Expert Panel for Fragrance Safety (http://fragrancesafetypanel.org) as contained in the Research Institute for Fragrance Materials (RIFM) Safety Assessments, publicly available in the Elsevier Fragrance Material Safety Resource Center (RIFM Home | FCT (elsevier.com)).

Numerous stakeholders used the opportunity to provide comments, which to us highlights the importance and relevance of this broad stakeholder consultation, an essential element of our Standard setting process.

IFRA has collected and consolidated all comments and discussed them with the respective Task Force or Body including the IFRA Risk Management TF (RMTF), the IFRA Natural Complex Substances TF (NCS TF) and RIFM. Consequently, in response to comments received, several changes are being made to the Guidance for the use of IFRA Standards, the proposed Standards, and the Annex on contributions from other sources as detailed in this End of Consultation Letter.

The Consultation is an important step in the process for setting IFRA Standards and is crucial to enable a successful implementation of new or revised IFRA Standards and to ensure they are relevant. IFRA would like to thank all the stakeholders that have provided feedback during the Consultation and thereby helped to improve the content of the 51st Amendment.

The formal letter of Notification for all the Standards covered by this Consultation will be published in the coming months, likely end of June or beginning of July 2023. The 51st Amendment will then appear on the IFRA website without undue delay.

The IFRA Member Associations are kindly requested to distribute this information without delay to their individual members.

Thank you very much for your assistance.

Dr. Matthias Vey
IFRA VP Scientific Affairs

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1. General

No concern has been expressed about the changes we introduced to the format of the IFRA Standards as described in the Consultation Letter. We will therefore no longer include the chemical structure and the empirical formula in the Standard.

Further, the Standards used to have, where applicable, a reference to Annex I concerning the presence of the restricted ingredient in Natural Complex Substances (NCS) and to Annex II concerning contribution from Schiff bases. With the 51st Amendment, we combined this information into one single Annex, named 'Contributions from other sources' and will only refer to this Annex. Further, the detailed information introduced in the Standard with the 49th Amendment will no longer be included, preventing us from re-issuing a Standard every time there is a change in the Annex. As pointed out in the Consultation Letter, these changes are not only introduced to the format of all new and revised Standards that are part of the 51st Amendment but will also be applied to all existing Standards as available on the IFRA website, once the 51st Amendment is notified.

2. Feedback received on the Guidance for the use of the IFRA Standards

2.1 Clarification about paper products

While preparing and during the Consultation of the 51st Amendment, the IFRA Joint Advisory Group (JAG) and the RMTF had worked on clarification regarding paper products when it comes to the calculation of fragrance ingredient concentrations in finished products. This clarification will be incorporated in the final Guidance document to be sent out with the Notification of the 51st Amendment. The text looks as follows:

> 6.5.11. Baby diapers, Feminine hygiene conventional pads, liners, Interlabial pads, Tampons, Incontinence pants/pads, Cleaning wipes, Baby wipes, Dryer sheets, and Wet toilet paper
>
> Regarding the assembled products, two situations need to be considered:
>
> 1. Product types for which the MAC (Maximum Acceptable Concentration) levels apply to the finished consumer product. This includes Baby diapers, Feminine hygiene conventional pads, liners, Interlabial pads, Tampons, and Incontinence pants/pads.
>   In these cases, the fragrance mixture is often included in the finished product based on weight rather than percent concentration (as is the case for the formulated products). Therefore, MAC levels reflect the ratio of fragrance ingredient weight and product weight.
> 2. Product types for which the MAC levels apply to the lotion/formulation carrier that is then added to the finished consumer product. This includes Cleaning wipes (such as toilet seat wipes and wipes in household cleaning products), Baby wipes, Dryer sheets, and Wet toilet paper. This is because the fragrance mixture is part of a lotion/carrier formulation that is then added to the finished product. Therefore, MAC levels reflect the percent concentrations of the fragrance ingredient in the lotion/carrier formulation rather than the finished product.

2.2 Clarification about fabric softener sheets, dryer sheets and dry-cleaning kits

Clarification was requested on whether dryer sheets, now in Category 12, is the same product as fabric softener sheets (still in Category 10A), including a better understanding of a dry-cleaning kit (Category 12) and whether it could be combined with dryer sheets.

Based on expert judgment, fabric softener sheets and dryer sheets are the same and should be mentioned in the same entry in Category 12.

For dry cleaning kits, there seems to be 2 types: one that is placed in the dryer and therefore has limited skin contact and could qualify category 12 as well; and one that would actually involve manual application (active rubbing on the clothes) and therefore because of certain skin contact would better be placed in Category 10A.

The Guidance document to be sent out with the Notification of the 51st Amendment will include respective wording.

2.3 Categorization of Pillow Spray

Clarification was asked about pillow spray being in Category 11B. Category 5B was suggested as an alternate category, as although it is not applied with hands, the exposure and penetration will be direct on face and hair during long rest sleeping. Alternatively, Category 10A could be considered.

The RMTF reviewed the evidence in consultation with RIFM Experts. The driver for the placing of pillow spray in Category 11B is largely based on skin sensitization concerns and potential transfer of product from the pillow to the skin.

The instructions to the consumer provided in the categorization form do not indicate that the surface of the pillow should be allowed to dry before laying on it. It is assumed that the product will be sprayed on the top surface of the pillow, the consumer will lay their face on the pillow before the fabric dries and there is the aspect of occlusion when putting the face on the pillow. It was assumed that it would be too conservative to assume 100% transfer to skin. The surrogate application was a wet facial wipe which assumes a factor of 20% for amount of product remaining on skin. As such, with the assumption of 20% of the product remaining on the skin, Category 11 would be appropriate in the absence of more refined exposure information.

This clarification will be incorporated in the Guidance document to be sent out with the Notification of the 51st Amendment.

2.4 Categorization of Reed Diffusers

It was pointed out some impactful changes of the MAC levels for Category 10A of two revised Standards (Geraniol CAS 106-24-1 and Hydroxycitronellal CAS 107-75-5) in particular, with a major potential impact on reed diffusers.

Reed diffusers and some related products [fragranced oil for lamp ring, pot-pourri, and liquid refills for air fresheners (non-cartridge systems), etc.] with the implementation of QRA2 in the 49th Amendment, were placed in Category 10A. This more restrictive categorization was chosen by IFRA and RIFM to reflect the potential exposure during manual handling (flipping) of the soaked reeds and/or the refill. Similar concerns exist for other product types sharing the same fate (like lamp oils). This decision was confirmed by the QRA Expert Team at RIFM.

The rationale for the categorization of reed diffusers was shared via the IFRA IL 1107 and will be included in the Guidance document to be sent out with the Notification of the 51st Amendment.

Another comprehensive review of product types in Category 10, 11 and 12 is foreseen as part of the preparation of the 52nd Amendment.

2.5 Handling of traces

The current Guidance states that the responsibility of the concept of “traces technically unavoidable substances in finished product” remains on the producer of raw materials and mixtures in cooperation with the finished product manufacturer. It was commented that the cooperation with the finished product manufacturer is indeed necessary to confirm the very precise level in the finished product for an accurate safety assessment. However, the “unavoidable” nature and levels of the traces should remain under the sole responsibility of the producer of raw materials and mixture.

The RMTF felt that the current text in the Guidance document is adequate with regard to describing the roles and responsibilities of equate information along the supply chain as basis for responsible management of traces in finished consumer products.

2.6 Phototoxicity considerations for products in Category 6

Clarification was asked about the rationale for the approach of having phototoxicity leave-on considerations applicable for Category 6. The RMTF agreed that this is very conservative in nature, since the lip exposure is “incidental”, the primary area of application being the oral cavity not that much exposed to sunlight.

As this question is intrinsic to the risk assessment, the Expert Panel for Fragrance Safety was consulted via RIFM for advice. The consultation with the Expert Panel is still ongoing and the final position will be communicated along with the Notification of the 51st Amendment.

2.7 Elimination of “sunblock” terminology in the Guidance

The way the term “sunblock” is used in the Guidance was considered outdated and it was suggested to use the term “UV filters” instead. The RMTF agreed and the Guidance document to be sent out with the Notification of the 51st Amendment will be updated accordingly.

2.8 Clarification that make-up remover for face and eyes also includes potential exposure to lips

The RMTF felt that the explanation provided in the IFRA IL 1107 and further included in the Guidance document under section 1.6.2.2 Multiple use products including exposure to lips does adequately cover this concern. However, the RMTF agreed to add a footnote in the Table 11 of the Guidance document to be sent out with the Notification of the 51st Amendment.

2.9 Clarification about "aftershaves of all types" in Category 4

It was pointed out that in Table 11 of the Guidance document, "Aftershaves of all types" are included in Category 4, while in other parts of the Guidance, it is indicated that some aftershaves are cream and lotion products that may be categorized as face moisturizers in Category 5B. It was therefore suggested to be more precise in describing Category 4 in Table 11.

The RMTF agreed with this proposal and will modify the wording in the Guidance, also preventing the term "hydroalcoholic", as there are also non-alcoholic products in the market. The new descriptor in the Guidance document to be sent out with the Notification of the 51st Amendment will be as follows: "aftershaves of all types (except creams and balms)".

2.10 Clarification about exposure surrogate in Category 7A

It was asked whether leave-on conditioner would be a too conservative surrogate for rinse-off hair chemicals treatment/perms/relaxers/dyes products.

RIFM confirmed that in the absence of any exposure data, we refer to the closest product type and always aim to be on the side of precaution. To end the need to work with a surrogate, exposure data would need to be provided.

3. Feedback on the Standards

3.1 Methyl N-methyl anthranilate (CAS 85-91-6)

Clarification was asked about potential differences between an IFRA Standard and regulatory requirements on the same fragrance ingredient. For the specific case of Methyl-N-methyl anthranilate, the EU Cosmetics Regulation sets a limit of 0.2% for rinse-off products, while the IFRA Standard permits 0.5%.

While the RMTF generally aim for as much harmonization and alignment as possible between regulation and IFRA Standards, specifically for ingredients where the input for the regulation is industry data, it has to be realized that differences between the IFRA Standards and regulations may still show up. This can have various reasons, including different risk assessment approaches, different interpretation of safety data with a different level of conservativism as well as more politically rather than science driven risk management measures. The safety assessment approach followed by RIFM is publicly available in the Fragrance Material Resource Center (RIFM Home | FCT (elsevier.com)) and the Standard setting process is summarized in the Guidance for the use of IFRA Standards. The risk assessment process followed, as an example for EU cosmetic products, by the SCCS is available here: SCCS Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation - 11th revision (europa.eu)

For the fragrance creator in any case the most stringent approach has to be followed in the region in which he/she operates, or the product is going to be marketed.

3.2 2-Hexenal (CAS 505-57-7, 6728-26-3, 16635-54-4)

Clarification was asked about the further lowered MAC levels, also compared to the levels permitted in the EU Cosmetics Regulation.

The reason for the changes observed in the Standard is as follows: the Expert Panel for Fragrance Safey re-reviewed the safety assessment for 2-Hexenal and was concerned about the reaction observed during the challenge phase of the CNIH conducted with 23 µg/cm². They requested another study be conducted with a lower dose - 18 µg/cm². In this other CNIH with 109 subjects, no reactions indicative of sensitization were observed with 18 µg/cm² 2-Hexenal (RIFM 2020). As such, the Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 18 µg/cm² was established. While systemic toxicity was considered in the derivation of the MAC, the Standard on 2-Hexenal is derived solely by the WoE NESIL of 18 µg/cm².

With regard to difference to regulation, please see section 3.1. above.

3.3 Carvone (CAS 99-49-0, 2244-16-8, 6485-40-1)

Questions have been asked about lowered MAC levels in various Categories compared to the existing Standard. The revised Standard is driven by systemic toxicity only. The distribution of MAC levels, when systemic toxicity is considered, is driven by reported exposures in respective Categories. Nevertheless, RIFM and the Exert Panel are investigating based on the original study report whether the NOAEL would be revised. The investigation is still ongoing, and the final position will be communicated along with the Notification of the 51st Amendment.

It was further pointed out that in the Annex on contribution from other sources, the botanical name of Gingergrass (for which 4% of carvone is reported) is not *Cymbopogon winterianus* Jowitt but *Cymbopogon martinii* var. *sofia*. The IFRA NCS TF checked and agreed that the botanical name is not correct and will be replaced by *Cymbopogon martini sofia.*

3.4 Cresols (CAS 1319-77-3, 108-39-4, 95-48-7, 106-44-5)

It was asked why this Restriction Standard includes o-Cresol (CAS 95-48-7) and m-Cresol (CAS 108-39-4) whereas their respective RIFM safety assessments do not mention depigmentation concern at current use levels.

The RMTF agreed to focus the Standard on p-Cresol and the mixtures containing it. The Standard will be renamed as p-Cresol and include CAS numbers 1319-77-3 and CAS 106-44-5. The revised Standard will be published along the 51st Amendment Notification.

3.5 2-tert-Butylcyclohexanone (CAS 1728-46-7)

It was pointed out that this ingredient is a by-product in multiple commercially available qualities of another broadly used fragrance ingredient. This led to concerns about the correctness of the exposure assessment based on the concentration survey at hand. The RMTF therefore agreed to withdraw this Standard from the 51st Amendment and to re-survey it during the next RIFM Concentration Survey (040), looking at its use added as such in addition to its contribution from its presence in the other fragrance ingredient.

3.6 Allyl 3-cyclohexylpropionate (CAS 2705-87-5)

It was pointed out that this ingredient is also an Allyl ester and therefore this specification under recommendation is missing as well as the Fragrance Ingredient Specification on the Standard.

The RMTF agreed with this and the revised Standard will be published along the 51st Amendment Notification.

3.7 5,6,7-Trimethylocta-2,5-dien-4-one (CAS 358331-95-0, 357650-26-1, 847144-75-6)

Concern was raised about the name of this Standard as it should include details on the isomer. This was confirmed by the RMTF and the name of the Standard will be modified as follows: 2,5-Octadien-4-one, 5,6,7-trimethyl-, (2E)-

3.8 Estragole (CAS 140-67-0, 1407-27-8, 77525-18-9) and Methyl eugenol (CAS 93-15-2)

Concern was raised about the MAC levels of certain categories and the rationale for assigning the MACs for the respective categories. There is a detailed description on how MACs are derived for ingredients in the Guidance document in section 4.1., explaining how MACs for certain categories driven by dermal sensitization (derived from the QRA2) and for others driven by systemic toxicity following the application of the maximisation tool and the impact of the exposure surveys. After due consideration, the RMTF considered that there was no sufficient rationale for derogating from the standard procedure. Thus the MACs were derived following this standard procedure, based on No Effect Levels as contained in the RIFM Safety Assessments and approved by the Expert Panel for Fragrance Safety.

3.9 Estragole (CAS 140-67-0, 1407-27-8, 77525-18-9)

There were other comments about Estragole referring to its permitted uses in flavor. The latter are derived based on a different risk assessment methodology but when it comes to the starting point, the No Effect Level, there is alignment between the flavor and fragrance independent advising expert panels on the value to be used as a starting point for the safety assessment.

4. Compliance timelines

The Consultation included timelines for the implementation of the 51st Amendment inspired by those used for the 49th Amendment, allowing 13 months for new creations and 25 months for existing creations, after the date of the Letter of Notification. This timeline was suggested to apply to all Standards, except the one that prohibits the continued use of one fragrance ingredient. For this prohibition Standard shorter timelines, in line with those used for the 50th Amendment, were suggested as detailed in the below table:

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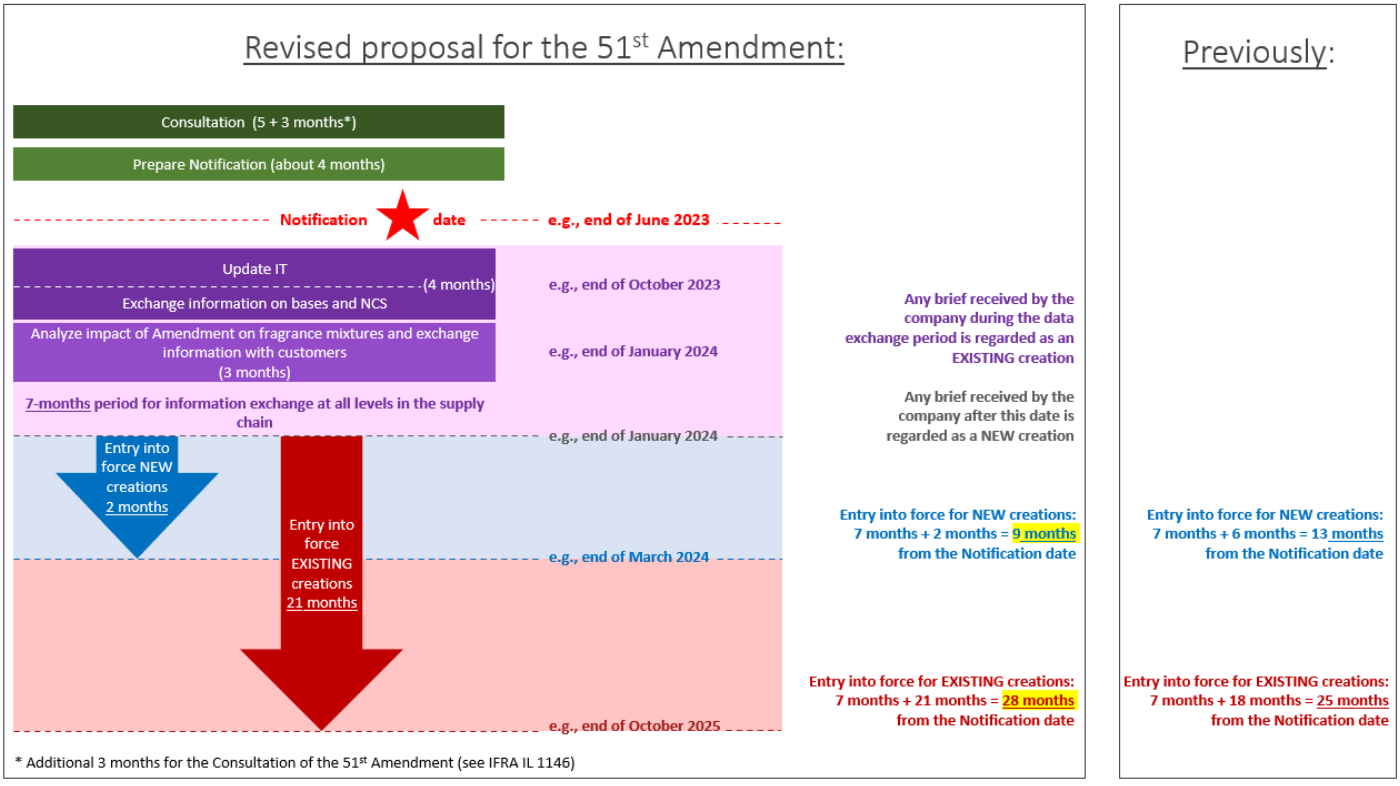
	Date for Standards entering into force for **new creations**	Date for Standards entering into force for **existing creations**
IFRA Standard **prohibiting** the use of ingredients	**2 months** after the date of the Notification	**13 months** after the date of the Notification
IFRA Standards **restricting** or **setting specifications** for the use of ingredients	**13 months** after the date of the Notification	**25 months** after the date of the Notification

Feedback has been received on the expected implementation timelines for Standards restricting or setting specifications for the use of fragrance ingredients for the 51st Amendment, suggesting longer implementation timelines for the reformulation of existing creations, which often require several exchanges between supplier and customer company, including on outcome of stability tests of the revised fragrance mixture.

The proposal has been evaluated in various IFRA Committees leading to a proposal which was approved by the IFRA Board. The proposal strenghtens the policy on new creations, ensuring the new fragrance mixture supplied to consumer product manufacturers are as soon as possible in compliance with the new Standards of an Amendment. The respective timeline was shortened by 4 months and therefore for the 51st Amendment for Standards setting restrictions of specifications will be 9 months after the date of the Notification. For existing creations on the other end, 3 additional months for bringing those in compliance will be granted, leading to a total period of 28 months after the date of the Letter of Notification.

The below scheme does visualize the new timing for the 51st Amendment:



The date for compliance of IFRA Amendments corresponds to the date of placement of fragrance mixtures on the market, meaning for them to leave a fragrance house. From a documentation point of view this should be considered to be the earliest of the following dates: the date of dispatch or the date of invoice.

However, for the Standards where there is no change in the scope and/or in the MAC levels but just on format or adding clarification, the implementation timeline is not applicable. This was indicated in the Consultation Letter and will again be clarified in the Notification communication.

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5. List of the NEW Standards that will be notified with the 51st Amendment

Based on the comments addressed above, here is the list of the Standards expected to be part of the Notification of the 51st Amendment.

a) 1 new IFRA Restriction Specification Standard

CAS number	Name	Status
2705-87-5	Allyl-3-cyclohexylpropionate	NEW RESTRICTION SPECIFICATION STANDARD (BASED ON DERMAL SENSITIZATION AND SYSTEMIC TOXICITY)

b) 32 new IFRA Restriction Standards based on dermal sensitization and systemic toxicity

CAS number	Name	Status
98-53-3	4-tert-Butylcyclohexanone	NEW RESTRICTION STANDARDS (BASED ON DERMAL SENSITIZATION AND SYSTEMIC TOXICITY)
139504-68-0	1-(2-tert.-Butyl cyclohexyloxy)-2-butanol	
499-70-7, 59471-80-6	Carvomenthone	
150-84-5, 67601-05-2, 141-11-7	Citronellyl acetate	
2550-52-9	Cyclohexadecanone	
88642-03-9, 5365-06-0, 2550-59-6, 3100-36-5, 5120-20-7, 854373-71-0, 854373-70-9	Cyclohexadecenone	
10461-98-0	alpha-Cyclohexylidene benzeneacetonitrile	
916887-53-1	2-Cyclohexylidene-2-ortho-tolylacetonitrile	
2550-11-0	Dimethyl octenone	
58567-11-6	(Ethoxymethoxy)-cyclododecane	
27538-09-6, 27538-10-9	Ethyl and Methyl furaneol	
116044-44-1, 116126-82-0	Ethyl isopropyl bicycloheptene-2-carboxylate	
1576-78-9	cis-3-Heptenyl acetate	
35154-45-1	cis-3-Hexenyl isovalerate	
67633-96-9	cis-3-Hexenyl methyl carbonate	
62439-42-3	6-Hydroxy-2,6-dimethylheptanal	
122-67-8	Isobutyl cinnamate	
93-29-8	Isoeugenyl acetate	
16587-71-6	Isopentylcyclohexanone	
623-36-9	2-Methyl-2-pentenal	
93893-89-1, 53243-59-7, 53243-60-0	3-Methyl-5-phenylpent-2-enenitrile	
68966-86-9	4-Methyl-1-propan-2-ylbicyclo[2.2.2]oct-2-ene-8-carboxylate	
5533-03-9	Methyl vanillyl ether	
13049-88-2	cis-3-Nonenyl acetate	
81786-75-6, 81786-73-4, 86115-11-9, 81786-74-5	3,4,5,6,6-Pentamethylhept-3-en-2-one	
2120-70-9	Phenoxyacetaldehyde	

CAS number	Name	Status
33885-52-8	Tetramethyl bicyclo-2-heptene-2-propionaldehyde	
74338-72-0	2,4,4,7-Tetramethyl-6-octen-3-one	
70788-30-6	1-(2,2,6-Trimethylcyclohexyl)-3-hexanol	
60241-52-3, 60241-53-4	1-(2,2,6-Trimethylcyclohexyl)-3-pentanol	
1891-67-4	3,6,7-Trimethyl-2,6-octadienal	
338735-71-0, 351343-77-6	Woody furan	

The above IFRA Standards are driven by the skin sensitization endpoint. The systemic toxicity endpoints have also been evaluated and the maximum concentration levels reported in the above Standards are the lower concentration levels of those derived from the dermal sensitization and the systemic toxicity assessment.

c) 11 new IFRA Restriction Standards to control potential dermal sensitization effects solely based on QRA2

CAS number	Name	Status
60763-41-9	alpha-Amylcinnamicaldehyde diethyl acetal	NEW RESTRICTION STANDARDS BASED ON DERMAL SENSITIZATION (QRA2)
91-87-2	alpha-Amylcinnamicaldehyde dimethyl acetal	
97-42-7, 1205-42-1, 1134-95-8	Carvyl acetate	
155514-23-1	5-Hexen-1-yl 2-methylbutanoate	
16429-07-5	2-Hexylidenecyclohexan-1-one	
67801-33-6, 67633-95-8	Methyl lavender ketone	
72403-67-9	Myraldyl acetate	
4643-27-0	2-Octen-4-one	
1669-44-9	3-Octen-2-one	
68738-94-3, 68738-96-5, 68991-96-8, 68991-97-9	Octahydro-dimethylnaphthalene-2-carbaldehyde (mixed isomers)	
358331-95-0, 357650-26-1, 847144-75-6	2,5-Octadien-4-one, 5,6,7-trimethyl-, (2E)-*	

* The RIFM Safety Assessment (SA) is available in the RIFM Database but not yet published in Food & Chemical Toxicology and hence not yet available in the Fragrance Material Resource Center on the Elsevier website. However, a publication is expected shortly. In the meantime, a draft publication can be shared with interested stakeholders on request to IFRA (mvey@ifrafragrance.org).

The above IFRA Standards are driven by the dermal sensitization endpoint. The systemic toxicity endpoints have also been evaluated and cleared by Threshold of Toxicological Concern (TTC), but has not been taken into account to review the maximum concentration levels of the above listed Standards. In consequence, the maximum concentration levels are only the result of the application of QRA2.

d) 2 new IFRA Restriction Standards for which risk management is based on TTC

CAS number	Name	Status
2986-54-1	Methoxycyclododecane	NEW RESTRICTION STANDARD BASED ON SYSTEMIC TOXICITY (TTC)
53767-86-5	7-Methoxy-3,7-dimethyloct-1-ene	

As outlined in the IFRA Standard setting process in general, when the RIFM SA is based on the application of the Threshold of Toxicological Concern (TTC) and/or Dermal Sensitization Threshold (DST) to support current use levels, no IFRA Standard will be set as long as the exposures do not exceed those thresholds (e.g., applied for new Standards listed under item c above). More information is provided in IFRA IL 1128 of September 28, 2021.

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e) 1 new IFRA Restriction Standard due to potential of depigmentation

CAS number	Name	Status
1319-77-3, 106-44-5	p-Cresol	NEW RESTRICTION STANDARD BASED ON DEPIGMENTATION

Standard on p-Cresol is based on its potential to cause depigmentation. p-Cresol is reported to occur in nature.

f) 1 new IFRA Prohibition Standard due to potential genotoxicity effects

CAS number	Name	Status
10599-70-9	3-Acetyl-2,5-dimethylfuran	NEW PROHIBITION STANDARD BASED ON GENOTOXICITY

The Expert Panel for Fragrance Safety reviewed the available genotoxicity information for 3-Acetyl-2,5-dimethylfuran (ADF) and found it was mutagenic in an Ames test. It was also predicted to be positive/equivocal in multiple in silico prediction models. Additionally, an in vivo genotoxicity and carcinogenicity assay conducted in the rats demonstrated a significant increase in gpt mutation frequency and increase in the area and number of GST-P foci in rat liver. These outcomes suggest that ADF has mutagenic and carcinogenic potential in rat liver. According to the IFRA Standard setting procedure the material will be prohibited for use as a fragrance ingredient.

6. List of REVISED Standards part of the 51st Amendment

a) 10 Revised IFRA Restriction Standards based on new data leading to a revised RIFM Safety Assessment

CAS number	Name	Status
99-49-0, 2244-16-8, 6485-40-1	Carvone	REVISED RESTRICTION STANDARDS (BASED ON DERMAL SENSITIZATION AND SYSTEMIC TOXICITY)
119-84-6	Dihydrocoumarin	
97-53-0	Eugenol	
106-24-1	Geraniol	
6728-26-3, 505-57-7, 16635-54-4	2-Hexenal	
107-75-5	Hydroxycitronellal	
123-11-5	p-Methoxybenzaldehyde	
5462-06-6	4-Methoxy-alpha-mehtylbenzenepropanal	
140-67-0, 1407-27-8, 77525-18-9	Estragole*	
93-15-2	Methyl eugenol*	

*As part of the ongoing RIFM Safety Assessment Program, the fragrance ingredients Methyl eugenol (CAS 93-15-2) and Estragole (CAS 140-67-0) have been reconsidered and their updated SAs were approved in September 2022 by the Expert Panel for Fragrance Safety. Given the endpoint driving the Standards and the large presence of both materials, as communicated with the IFRA IL 1146 of November 29, 2022, it has been decided to make the 2 revised Standards part of the 51st Amendment. The RIFM SAs are available in the RIFM Database but not yet published in Food & Chemical Toxicology and hence not yet available in the Fragrance Material Resource Center on the Elsevier website. However, publication is expected shortly. In the meantime, a draft publication can be shared with interested stakeholders on request to IFRA (mvey@ifrafragrance.org).

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b) 1 Revised IFRA Restriction Standard based on new dermal sensitization data

CAS number	Name	Status
17369-59-4	3-Propylidenephthalide	REVISED RESTRICTION STANDARD (BASED ON DERMAL SENZITIZATION)

The review of the available safety information as contained in the published SA did lead to a slight correction (increase) of the NESIL from 920 ug/cm² to 940 ug/cm². The respective MAC differences in the revised Standard compared to the 49th Amendment are therefore relatively small.

c) 1 Revised IFRA Restriction/Specification Standard based on phototoxicity and systemic toxicity

CAS number	Name	Status
85-91-6	Methyl-N-methylanthranilate	REVISED RESTRICTION STANDARD (BASED ON PHOTOTOXICITY AND SYSTEMIC TOXICITY) AND POTENTIAL OF NITROSAMINE FORMATION

With the review of the safety data, the new approach for phototoxic ingredient, which is to also set limits for rinse-off products, has been implemented for Methyl-N-methylanthranilate.

7. Minor updates to existing Standards and format change

a) Revised Restriction Standard

CAS number	Name	Status
4602-84-0, 106-28-5, 3790-71-4, **16106-95-9,** **3879-60-5**	Farnesol	UPDATED RESTRICTION STANDARD FORMAT

This material is not part of the 51st Amendment but in the Consultation Letter, it was announced that CAS numbers 106-28-5 (2E, 6E) and 3790-71-4 (2Z, 6E) were added to the Standard for clarification.

During the Consultation period, it was further asked to included CAS number 16106-95-9 (2Z, 6Z) and CAS number 3879-60-5 (2E, 6Z) for consistency reasons. The revised Standard will be published along the 51st Amendment Notification.

b) Revised Prohibition Standard

CAS number	Name	Status
13341-72-5, **38049-04-6**	Mintlactone	UPDATED PROHIBITION STANDARD FORMAT

During the Consultation period, additional information was received on Mintlactone, ingredient for which the Standard was issued with the 50th Amendment. It was suggested to include CAS number 38049-04-6 in the Standard for clarification. The revised Standard will be published along the 51st Amendment Notification.

Given that the Standards in general state that the scope includes, but is not limited to the CAS numbers indicated in the Standards and that any other CAS number used to identify the ingredient should be considered in scope as well, please note that these changes therefore are not considered affecting the content of the Standards on Farnesol and Mintlactone. Thus, the implementation timelines associated to the 51st Amendment do not apply for the Standard on Farnesol and Mintlactone.

The updated Standards, will be issued as part of the 51st Amendment along with several Standards only re-issued do to the implementation of the format changes agreed (deletion of the chemical structure, the molecular formular and the inclusion of details from Annex of other sources).