Fragrances Categorized According to Relative Human Skin Sensitization Potency

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**Background:** The development of non-animal alternatives for skin sensitization potency prediction is dependent upon the availability of a sufficient dataset whose human potency is well characterized. Previously, establishment of basic categorization criteria for 6 defined potency categories, allowed 131 substances to be allocated into them entirely on the basis of human information.

**Objectives:** To supplement the original dataset with an extended range of fragrance substances.

**Methods:** A more fully described version of the original criteria was used to assess 89 fragrance chemicals, allowing their allocation into one of the 6 potency categories.

**Results:** None of the fragrance substances were assigned to the most potent group, category 1, whereas 11 were category 2, 22 were category 3, 37 were category 4, and 19 were category 5. Although none were identified as non-sensitizing, note that substances in category 5 also do not pass the threshold for regulatory classification.

**Conclusions:** The combined datasets of >200 substances placed into potency categories solely on the basis of human data provides an essential resource for the elaboration and evaluation of predictive non-animal methods.

The fundamental purpose of toxicological evaluation is to uncover substances that possess properties, rendering them a potential hazard to human health.¹ However, the identification of such substances is often meaningless unless the strength of that hazard, often termed potency, is also characterized. With respect to the toxicological hazard known as skin sensitization, the simple identification of hazard has been ensured for many decades, and the key details were well documented.¹² However, in recent decades, the concept of simultaneously measuring the relative potency of the identified hazard has also become central to the process of assessing the risk of skin sensitization.³⁻⁷ It is not germane to the present work to discuss the merits (or otherwise) of the risk assessment itself, save to note that it is well characterized and transparent, such that it is capable of critical scrutiny to move it into a second-generation version.⁸⁻¹⁰ What is pertinent is that the toxicological predictions of the relative potency of a skin sensitizer are actually meaningful in terms of the species of concern, that is, humans. To meet this challenge, a first publication (in this journal) detailed an approach to the subcategorization of chemicals into 1 of 6 potency classes, solely on the basis of human data, and then reported on the outcome for a total of 131 substances.¹¹ Of these, only a small minority were fragrance chemicals, so that, in an associated follow-up, human data were presented for a small number of additional fragrance chemicals.¹² In the present work, we have endeavored to extend the original series more substantially via the addition of information on a larger body of substances used as fragrances. In total, 89 chemicals were assessed because they had sufficient information to permit potency categorization using only human data. However, as a refinement to the previous publication, we have endeavored to offer a clearer explanation of the basis for individual classification, thereby enhancing the categorization outline provided in that original publication.¹¹ It is anticipated that this additional set of substances will further assist those working to produce nonanimal models capable of predicting the relative human potency of newly identified skin sensitizing substances.

**MATERIALS AND METHODS**

The 89 substances considered are reported in Table 1, along with their chemical abstracts service (CAS) numbers. All materials were of the quality supplied to downstream users by the fragrance industry, thus ensuring that data generated using them were relevant to the real-life situation.

A decision on allocation to a category was achieved using information from experimental human studies, specifically the human repeated insult patch test (HR IPT), conducted according to the protocol previously published, or in a few instances, the human maximization test (HMT) as published by Kligman.¹³,¹⁴ Most data

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from these sources offer a no-effect level (NOEL), and where multiple data exist, the highest value has been taken. For a few substances, a lowest-effect level (LOEL) has been recorded. Accordingly, it is important to state that no new positive data have been generated for the purpose of this work—all of the LOEL data are derived from historic studies. The authors recognize that the conduct of new human studies to determine an LOEL for the induction of contact allergy is, by definition, unethical. Human repeated insult patch test and HMT studies as conducted by Research Institute for Fragrance Materials are of equivalent sensitivity and thus taken as interchangeable. The limited LOEL data provide a guide concerning the extent to which the NOEL data are close to the true threshold.

Indications concerning potential categorization were modified by information derived from a survey of diagnostic patch test (DPT) data from published clinical literature, with the existence of such information typically being indicated by the recording of a patch test concentration.15 Particular account also was taken of the important and comprehensive review of fragrance allergy already completed by the European Commission independent advisory body, the Scientific Committee on Consumer Safety (SCCS).16

To assist in understanding the process of potency categorization solely on the basis of human data, an outline of the criteria used is provided in Table 1. It is worth reinforcing here the key point that larger NOEL values equate to lower skin sensitization potency. Thus, where there are multiple values, unless there is compelling information to suggest a different strategy, the higher value should always be used. The converse argument would always apply to LOEL values, where the smaller value must be adopted. As always, the final decision on a category will have considered all of the available evidence. This includes DPT data, where this exists, judged against the use volume information. Diagnostic patch test data can be taken from the clinical literature and, for some of the materials here, from the SCCS review already mentioned.16

**RESULTS**

The outcome of the analysis on this set of fragrance substances is contained in Table 2. None of the substances were allocated to the highest, category 1, although for 2 materials, trans-2-hexenal and methyl 2-nonynoate, the decision was borderline, and so this is discussed in more detail later. Ultimately, along with 9 others, they were assigned to category 2. For the remainder, 22 were assigned to category 3, 37 were assigned to category 4, and 19 were assigned to category 5. None were assigned to category 6, the true nonsensitizers. To facilitate the understanding of the rationale, several of these are discussed to provide an exposition of how the criteria described in Table 1 and the previous publication are applied.10 None of the substances was regarded as entirely nonsensitizing; thus, category 6 was not represented.

For a first example, trans-2-hexenal is considered. It has an HRIPT NOEL of 24 μg/cm², which is only less than the threshold for category 1 (Table 1). However, the HRIPT LOEL is almost 10-fold higher, suggesting that the true NOEL is higher than the category 1 threshold. There is no HMT information to add to the mix; the remaining source of information for consideration is therefore DPT data. In this case, it is very sparse. A patch test concentration of 1% is suggested.15 However, a search on PubMed reveals an absence of any data, an outcome consistent with the conclusions of a European Commission advisory body report.16 Consequently, the decision must be that trans-2-hexenal is most appropriately placed into category 2. A similar logic was applied to methyl 2-nonynoate, supported by the occurrence of only a single positive patch test reaction in the literature.23

In comparison, the next example, farnesol, is somewhat less clear-cut. The HRIPT NOEL is close to category 3, but it is clearly in category 4. However, it is a well-known human contact allergen that is used in routine diagnostic testing as a component of fragrance mix II.17,18 The frequency of positive patch tests for a fragrance component that has rather low use volume was regarded as sufficient evidence to elevate farnesol into category 3.

1,2,3,4,5,6,7,8-Octahydro-8,8-dimethyl-2-naphthaldehyde was placed into category 3 on the basis of the view that the HRIPT, which in this case involved only more than 100 volunteers, would not be overridden by the HMT, which used only a quarter of the number and recorded an NOEL that was not too far from the category 3/4 border. Had the HMT value been much higher, as was the case with ylang-ylang, then the decision might have been different. However, in this latter case, the fact that the HRIPT NOEL was not as low (ie, relatively close to the category 3/4

| Potency Category | HRIPT/HMT NOEL* | DPT Data† | Use Information‡ |
|------------------|-----------------|-----------|------------------|
| 1 (extreme)      | <25 μg/cm²      | >3% In most dermatology clinics | Probably low exposure concentration |
| 2 (strong)       | 25–500 μg/cm²   | >1% In many dermatology clinics | Lower use concentration may raise |
| 3 (moderate)     | 500–2500 μg/cm² | Up to 1% in major dermatology clinics | by 1 category; higher use concentration |
| 4 (weak)         | >2500 μg/cm²    | Less common/frequent positive results than category 3 | may drop a category |
| 5 (very weak)    | >10,000 μg/cm²  | Rarely positive except in selected patients with eczema | Possibly despite high use |
| 6 (nonsensitizer)| Negative§       | An absence of positives despite testing in many clinics | Use could be high or low |

*For this purpose, the 2 types of human test are taken as equivalent; LOEL data are used only as a guide to the proximity of the NOEL to the true HRIPT induction threshold. The HRIPT is normally given more weight than the HMT because the former involves testing in larger panel sizes, typically 4 times the HMT.†Generally taken from multiclinic-collated information on consecutive patients with eczema. However, the lower potency categories may rely more on isolated cases.‡Given the great rarity with which there is a clear correlation between exposure and the induction of contact allergy from DPT data, the use information on total volume of sales and, where it exists, the typical maximum use levels are used to refine the conclusions.§In effect, this simply means that a high test concentration yielded no evidence of the induction of skin sensitization.
| Fragrance Ingredient                        | CAS Number   | NOEL HRIPT, $\mu g/cm^2$ | NOEL HMT, $\mu g/cm^2$ | LOEL HRIPT, $\mu g/cm^2$ | Annual Use Volume, $\text{tons}$ | HPC | Comments, ‡ |
|-------------------------------------------|--------------|--------------------------|--------------------------|--------------------------|---------------------------------|-----|-------------|
| Oakmoss                                   | 90028-68-5   | 700                      | 1724                     | 1417                     | 1–10                            | 2   | Cat 2 on the assumption that atranol/chloroatranol concentrations are fully controlled (IFRA guideline). |
| 3-Methyl-5-phenylpent-2-enedinitrile       | 93893-89-1   | 275                      | NA                       | NA                       | 10–100                          | 2   | Predominantly based on HRIPT |
| 5,6,7-Trimethylocta-2,5-dien-4-one         | 358331-95-0  | 250                      | NA                       | NA                       | 1–10                            | 2   | Predominantly based on HRIPT; limited positive DTP available |
| trans-α-Damascone                          | 24720-09-0   | 310                      | 138                      | 2531                     | 10–100                          | 2   | Predominantly based on HRIPT; |
| trans-2-Hexenal                            | 6728-26-3    | 24                       | NA                       | 236                      | 1–10                            | 2   | HRIPT LOEL suggests a higher NOEL; although tonnage is low, DPT evidence is very sparse; thus, balance is Cat 2 rather than Cat 1. |
| 2-Hexylidene cyclopentanone                | 17373-89-6   | 300                      | NA                       | 500                      | <0.1                            | 2   | HRIPT and HMT nicely aligned; no DPT information found |
| 2-Methoxy-4-methylphenol                   | 93-51-6      | 118                      | NA                       | NA                       | 0.1–1                           | 2   | Based on HRIPT; no DPT information found |
| 6-Methyl-3,5-heptadien-2-one               | 1604-28-0    | 118                      | NA                       | 1299                     | <0.1                            | 2   | Based on HRIPT; no DPT information found |
| Methyl 2-nonynoate                         | 111-80-8     | 24                       | NA                       | 118                      | 10–100                          | 2   | HRIPT on border of Cat 1, but adjusted because of LOEL and paucity of DPT data§ |
| (methyl octine carbonate)                  |              |                          |                          |                          |                                 |     |             |
| Tea leaf absolute                          | 84650-60-2   | 480                      | NA                       | NA                       | 1–10                            | 2   | Based on HRIPT; no DPT information found |
| Methyl 2-octynoate                         | 111-12-6     | 118                      | NA                       | 194                      | 1–10                            | 2   | Predominantly based on HRIPT; very little DPT information found |
| (methyl heptine carbonate)                 |              |                          |                          |                          |                                 |     |             |
| Cuminaldehyde                              | 122-03-2     | 1181                     | 2760                     | NA                       | 1–10                            | 3   | Predominantly based on HRIPT because positive DPT data are very rare|| |
| Hexyl tiglate                              | 16930-96-4   | 110                      | 8316                     | NA                       | 0.1–1                           | 3   | No DPT case reports found; HMT suggests that HRIPT NOEL is too low |
| Methyl 2,4-dihydroxy-m-toluic acid         | 33662-58-7   | 620                      | NA                       | NA                       | <0.1                            | 3   | Predominantly based on HRIPT |
| 1-(1-Naphthyl)ethanone                     | 941-98-0     | 2598                     | 1380                     | NA                       | 1–10                            | 3   | Only 1 DPT case in the literature |
| 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one | 56979-85-4 | 2500                     | NA                       | 10–100                   |                                 | 3   | Based on HRIPT; no DPT information found |
| 1,2,3,4,5,6,7,8-Octahydro-8,8-dimethyl-2-naphthaldehyde | 68991-97-9 | 551                      | 2760                     | NA                       | 10–100                          | 3   | HRIPT fits Cat 3 and dominates the HMT, which is only indicative of Cat 4. |
| 3-(p-Isopropylphenyl)propionaldehyde       | 7775-00-0    | 1102                     | NA                       | NA                       | 10–100                          | 3   | Based on HRIPT |
| 7-Methyl-2H-benzo-1,5-dioxepin-3(4H)-one    | 28940-11-6   | 1000                     | NA                       | NA                       | 10–100                          | 3   | Based on HRIPT |
| Propanedioic acid, 1-(3,3-dimethylcyclohexyl)ethyl, ethyl ester | 478695-70-4 | 2000                     | NA                       | NA                       | 10–100                          | 3   | Based on HRIPT |
| 2-Methyldecanenitrile                      | 69300-15-8   | 2250                     | NA                       | NA                       | 10–100                          | 3   | Based on HRIPT supported by the HMT NOEL |
| 4-Hydroxy-2,5-dimethyl-3(2H)-furanone       | 3658-77-3    | 591                      | NA                       | 1181                     | 1–1                                 | 3   | Based on HRIPT |

(continued on next page)
| Fragrance Ingredient | CAS Number | NOEL HRIPT,\* \(\mu g/cm^2\) | NOEL HMT,\† \(\mu g/cm^2\) | LOEL HRIPT,\† \(\mu g/cm^2\) | Annual Use Volume,\* tons | HPC | Comments:‡ |
|----------------------|------------|----------------------------|----------------------------|---------------------|---------------------|-----|------------|
| Farnesol             | 4602-84-0  | 2755                      | NA                         | 68974               | 1–10                | 3   | Added LOEL; low volume, so positive DPT data\textsuperscript{15,17} mean category confirmed\textsuperscript{11} rather than being placed in Cat 4 |
| Allyl phenoxyacetate | 7493-74-5  | 709                       | 690                        | NA                  | 10–100              | 3   | Based on HRIPT |
| Cinnamyl nitrile     | 1885-38-7  | 1063                      | 3448                       | NA                  | 1–10                | 3   | Based on HRIPT |
| Jasmine absolute     | 8022-96-6; 8024-43-9; 90045-94-6; 84776-64-7 | 1475                      | NA                         | 2069                | 1–10                | 3   | Based on HRIPT, moderate tonnage, and a fair number of DPT positives |
| p-Mentha-1,8-dien-7-al | 2111-75-3 | 709                       | 690                        | 2760                | 0.1–1               | 3   | Based on HRIPT and low tonnage with absence of DPT data |
| Menthadiene-7-methyl formate | 68683-20-5 | 1063                      | 690                        | 6900                | 0.1–1               | 3   | Based on HRIPT and low tonnage with absence of DPT data |
| 2-Methylbutanoic acid hexyl ester | 10032-15-2 | 696                       | 6930                       | NA                  | 1–10                | 3   | Based on HRIPT, the HMT NOEL is insufficient to shift it to Cat 4 |
| Phenylacetaldehyde   | 122-78-1   | 592                       | NA                         | 1181                | 1–10                | 3   | Based on HRIPT, lower tonnage with a few positive DPTs |
| 3-Propylidenephthalide | 17369-59-4 | 945                       | 345                        | 2760                | 0.1–1               | 3   | Based on HRIPT, low tonnage, and very limited DPT data\textsuperscript{16} |
| Treemoss             | 90028-67-4 | 700                       | 6896                       | 1417                | 1–10                | 3   | HRIPT and HMT NOELs consistent with Cat 3; positive DPT data |
| Ethyl acrylate       | 140-88-5   | 1600                      | NA                         | NA                  | No data             | 3   | Based on HRIPT NOEL; common positive DPTs (eg, 20) |
| Piperonal (heliotropin) | 120-57-0  | 2952                      | 4140                       | NA                  | 100–1000            | 4   | Based on HRIPT NOEL, supported by close NOEL, high volume but with little evidence of contact allergy\textsuperscript{18} |
| Heptaldehyde, ethylene glycol acetal | 1708-34-5 | 2780                      | NA                         | NA                  | 0.1–1               | 4   | Based on HRIPT |
| ω-Pentadecalactone   | 106-02-5   | 5510                      | 6900                       | NA                  | 100–1000            | 4   | Negative in a survey despite moderate use\textsuperscript{19} |
| Butanamide, 2-ethyl-N-(methyl-N-(3-methylphenyl)ethyl)- | 406488-30-0 | 3250                      | NA                         | NA                  | 1–10                | 4   | Based on HRIPT |
| Ethyl tiglate        | 5837-78-5  | 3465                      | NA                         | NA                  | <0.1                | 4   | Based on HRIPT |
| Formaldehyde cycloaddecyl ethyl acetal | 58567-11-6 | 3543                      | 1380                       | NA                  | 100–1000            | 4   | Higher HRIPT NOEL dominates over HMT; lack of DPT evidence against high use volume supports Cat 4. |
| Methoxy dicyclopentadiene carboxaldehyde | 86803-90-9 | 5000                      | NA                         | NA                  | 10–100             | 4   | HRIPT used diethylphthalate only, but this would not impact outcome |
| 2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol | 63500-71-0 | 4408                      | NA                         | NA                  | 100–1000            | 4   | Based on HRIPT |
| Chemical Name                                                                 | CAS Number | Human Skin Sensitizing Potency (HRIPT) LOEL | Human Skin Sensitizing Potency (HRIPT) NOEL | Human Skin Sensitizing Potency (HRIPT) DPT | Cat |
|-------------------------------------------------------------------------------|------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|-----|
| 3-(4-Methyl-3-cyclohexenyl)butanol                                            | 15760-18-6 | 5906                                        | NA                                          | NA                                          | 1–10 | 4 Based on HRIPT |
| 3-Phenylbutanal                                                               | 16251-77-7 | 5905                                        | 12500                                       | 10–100                                      | 4    | Based on HRIPT |
| Longifolene                                                                   | 475-20-7   | 3543                                        | 6900                                        | NA                                          | 100–1000 | 4 Based on HRIPT, supported by HMT result |
| β-Farnesene                                                                   | 18794-84-8 | 3780                                        | 6250                                        | 1–10                                        | 4    | Based on HRIPT, supported by HMT result |
| 2-Methyl-4-(2,6,6-trimethyl(cyclohex-1-en-1-yl)-2-butenal                     | 3155-71-3  | 2953                                        | NA                                          | NA                                          | 0.1–1 | 4 Based on HRIPT |
| 2,4-Dimethyl-3-cyclohexen-1-carboxaldehyde                                   | 66039-49-6 | 5905                                        | 6900                                        | NA                                          | >1000 | 4 Based on HRIPT, supported by HMT result |
| p-Methoxybenzaldehyde (anisaldehyde)                                         | 123-11-5   | 3543                                        | 6900                                        | 4724                                        | >1000 | 4 Based on HRIPT, supported by HMT result and HRIPT LOEL |
| 6-Methoxy-2,6-dimethylean-1-al                                               | 62343-81-2 | 5905                                        | NA                                          | NA                                          | 1–10  | 4 Based on HRIPT |
| α-Bisabolol                                                                   | 515-69-9   | 5510                                        | NA                                          | NA                                          | <0.1  | 4 Based on HRIPT |
| Triacyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene                    | 122760-84-3 | 3000                                   | NA                                          | NA                                          | 0.1–1 | 4 HRIPT NOEL confirmed in diethylphthalate and alcohol vehicles |
| 3,3-Dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol             | 107898-54-4 | 2598                                   | NA                                          | 5000                                        | 100–1000 | 4 Based on HRIPT NOEL supported by LOEL |
| 2-Methyldecanal                                                              | 19009-56-4 | 5905                                        | 6900                                        | NA                                          | 10–100 | 4 Based on HRIPT, supported by HMT result |
| Benzyl alcohol                                                                | 100-51-6   | 5906                                        | 6897                                        | 8858                                        | 100–1000 | 4 Based on HRIPT NOEL supported by HMT result and HRIPT LOEL, steady flow of positive DPT results set against high tonnage |
| Benzyl cinnamate                                                              | 103-41-3   | 4720                                        | 5517                                        | NA                                          | 10–100 | 4 Based on HRIPT, some DPTs, and moderately high tonnage |
| Dibenzyl ether                                                                | 103-50-4   | 2362                                        | 2760                                        | NA                                          | 10–100 | 4 Based on HRIPT downgraded because of absence of DPTs and moderately high tonnage |
| Eucalyptol (cineole)                                                          | 470-82-6   | 590                                         | 11040                                       | NA                                          | 100–1000 | 4 Cat 3 from HRIPT NOEL is adjusted because of very high HMT NOEL and high use volume but limited evidence of positive DPT (eg, Vilaplana and Romaguera18) |
| p-Isobutyl-α-methyl hydrocinnamonal                                          | 6658-48-6  | 2362                                        | 5520                                        | NA                                          | 10–100 | 4 Cat 4 as HRIPT is close to the border, the HMT has a higher NOEL, and there is no positive body DPT evidence despite moderate use |
| Isoyclocitrinal                                                               | 1335-66-6  | 7087                                        | 2759                                        | NA                                          | 10–100 | 4 Based on HRIPT, moderate tonnage, and absence of DPT testing |
| Isoyclogenol                                                                  | 68527-77-5 | 3898                                        | NA                                          | 5000                                        | 1–10  | 4 Based on HRIPT NOEL supported by LOEL |
| Jasmine absolute (Jasminum sambac)                                            | 91770-14-8 | 8858                                        | NA                                          | NA                                          | 1–10  | 4 Based on HRIPT NOEL and positive DPTs18 |
| 4-Methoxy-α-methyl benzenpropanol                                             | 5462-06-6  | 5905                                        | 1380                                        | NA                                          | 10–100 | 4 Based on HRIPT, moderate tonnage, and a DPT |
| 1-Octen-3-yl acetate                                                          | 2442-10-6  | 3543                                        | 6900                                        | NA                                          | 0.1–1 | 4 Based on HRIPT NOEL supported by the LOEL |
| β,β,3-Trimethyl benzenepropanol                                               | 103694-68-4 | 9900                                   | NA                                          | NA                                          | 10–100 | 4 Based on HRIPT, moderate tonnage, few DPTs |
| p-t-Butyl-dihydrocinnaminal                                                   | 18127-01-0 | 1181                                        | 4138                                        | NA                                          | 10–100 | 4 Based on HRIPT; HMT NOEL suggests Cat 4, but absence of DPT evidence to support lower category |
| Carvone                                                                       | 99-49-0    | 2657                                        | NA                                          | NA                                          | 100–1000 | 4 Based on HRIPT NOEL and very limited evidence of positive DPTs |

(continued on next page)
| Fragrance Ingredient                  | CAS Number          | NOEL HRIPT, $\mu g/cm^2$ | NOEL HMT, $\mu g/cm^2$ | LOEL HRIPT, $\mu g/cm^2$ | Annual Use Volume, tons | HPC | Comments‡ |
|--------------------------------------|---------------------|---------------------------|-------------------------|---------------------------|------------------------|-----|-----------|
| Vanillyl butyl ether                 | 82654-98-6          | 3543                      | NA                      | NA                        | 1–10                   | 4   | Based on HRIPT NOEL; no DPT data despite large use volume |
| $\alpha$-Methyl cinnamal            | 101-39-3            | 3543                      | NA                      | NA                        | 100–1000               | 4   | Based on HRIPT NOEL; no DPT data |
| Ylang-ylang                         | 8006-81-3; 68606-83-7; 83863-30-3 | 1772                      | 6897                    | 7752                      | 10–100                 | 4   | Based on HRIPT, where LOEL suggests NOEL may be higher, supported by HMT NOEL, moderate tonnage, and evidence of DPT positives$^{21,22}$ |
| Anisyl alcohol                      | 105-13-5            | 3448                      | NA                      | NA                        | 10–100                 | 4   | Based on HRIPT NOEL; limited DPT data to substantiate |
| 1-(3-Methyl-2-benzofuranyl)ethanone  | 23911-56-0          | 11019                     | NA                      | NA                        | 1–10                   | 5   | No DPT data, very high HRIPT NOEL |
| trans-Anethole                      | 4180-23-8           | 5510                      | 1380                    | NA                        | 100–1000               | 5   | Anethole was Cat 5 with CAS of 104-46-1$^{11}$; human use volume is huge, but DPT data are typically negative |
| Tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate | 131766-73-9         | 11019                     | NA                      | NA                        | 0.1–1                  | 5   | No DPT data, very high HRIPT NOEL |
| Isobornyl acetate                   | 125-12-2            | 6496                      | 6900                    | NA                        | 100–1000               | 5   | Based on high HRIPT NOEL, enhanced by large volume of use and no contradictory evidence from DPTs |
| 3-Methylcyclopentadecanone (muscone)| 82356-51-2          | 10000                     | NA                      | NA                        | 10–100                 | 5   | Very high HRIPT NOEL; no DPT data to contradict |
| Citronellal                         | 106-23-0            | 7086                      | 2760                    | NA                        | 10–100                 | 5   | High HRIPT NOEL supported by HMT, moderate use volume and absence of DPT data to contradict |
| 5-Cyclotetradecen-1-one, 3-methyl-(5E)- | 259854-70-1         | 10000                     | NA                      | NA                        | 1–10                   | 5   | Very high HRIPT NOEL; DPT data do not contradict |
| 1,1,3-Trimethyl-3-phenylindane      | 3910-35-8           | 10630                     | NA                      | NA                        | 10–100                 | 5   | Very high HRIPT NOEL; DPT data do not contradict |
| $\alpha$-Methyl-1,3-benzodioxole-5-propionaldehyde | 1205-17-0           | 4016                      | 13800                   | 15000                     | 100–1000               | 5   | HRIPT LOEL suggests that the NOEL is underestimated, supported by HMT NOEL; few positive DPTs despite high use |
| Methyl dihydrojasmonate             | 24851-98-7          | 10000                     | 13800                   | NA                        | >1000                  | 5   | High HRIPT NOEL supported by HMT, large use volume, and limited positive DPT data |
| 6,7-Dihydro-1,1,2,3,3-pentamethyl-4(5H)-indenone | 33704-61-9       | 12121                     | NA                      | NA                        | 100–1000               | 5   | Very high HRIPT NOEL; no DPT data to contradict |
| Methyl atrarate                     | 4707-47-5           | 11810                     | 6900                    | NA                        | 100–1000               | 5   | Very high HRIPT NOEL supported by HMT, large use volume, and limited DPT data |
and that the HMT is in category 4, together with the availability of HRIPT LOEL data well into category, made the final placement of ylang-ylang into category 4 a simple decision. It is worth noting that the moderate volume of use and occasional clinical evidence of positive reactions from normal use of ylang-ylang are also perfectly consistent with category 4.

For the final example, consider formaldehyde cyclododecyl ethyl acetal. This substance was placed into category 4, although the HMT NOEL suggested category 3. However, all of these studies involve a single dose level, so we do not know whether testing in the HMT at a higher concentration might also have proven negative and delivered a higher NOEL. That this would likely be the case is suggested by the HRIPT NOEL, which is clearly in category 4. There are no DPT data to contradict this categorization decision.

The decision to place a substance into category 5 typically was prompted by an NOEL value in excess of 10,000 \( \mu g/cm^2 \) together with an absence of DPT data that would contradict this decision—a reasonable body of positive evidence, particularly if used volumes were not very high, would elevate a substance to category 4. However, in a couple of instances (trans-anethole and isobornyl acetate), NOEL values a little lower than 10,000 \( \mu g/cm^2 \), associated with category 4, have been combined with knowledge of a very high volume of use (for many years) and an absence of DPT results to associate the materials with category 5.16

### DISCUSSION

Predictive toxicology is only of value if genuine human hazards are correctly identified, characterized, and assessed. It has long been recognized that in vivo methods have valuable predictive value regarding skin sensitization hazards.2,25,26 More recently, integrated testing strategies involving nonanimal models have been presented as performing to a similar standard.27 However, the characterization and assessment of identified skin sensitization hazards, particularly with respect to their relative potency, remains a weakness.30,31 Only the LLNA (and specifically the derived EC3 value) offered an estimation of relative skin sensitization potency with some basis for demonstrating its correlation with human data.32 The challenge of developing integrated testing strategies with nonanimal assays is outside the scope of this article, but for those engaged in such work, an essential need is a substantial catalog of chemicals categorized on the basis of their relative potency in humans. A first effort in this respect involving 131 chemicals has already been offered.11 The data in the present publication extend this work with a further 89 substances, with the small overlap meaning that the total data set now totals well more than 200 materials. This combined data set offers a broad distribution into 6 potency categories, with most substances in the more difficult to predict intermediate, lower-potency, categories 3 to 5 (see Fig. 1). It is our view that, taken together, these comprise a valuable basis for the continued development of nonanimal approaches to the prediction of human skin sensitization potency.

To complete this discussion, it is essential to remind the reader of significant caveats not least that much of the categorization depends

| Chemical Name                  | CAS Number | HRIPT NOEL | DPT NOEL | Cat |
|--------------------------------|------------|------------|----------|-----|
| 2-Nonyl-1-dimethyl acetal     | 13257-44-8 | 23620      | NA       | 5   |
| cis-4-(3-propyl)cyclohexanemethanol | 13828-37-0 | 01-1       | NA       | 5   |
| Dihydromyrcenol               | 18479-58-8 | 23622      | NA       | 5   |
| Ethylene brassylate           | 105-95-3   | 23862      | 2760     | 5   |
| \( \alpha \)-iso-Methylionone | 70866      | 127-51-5   | 47244    | 5   |
| dl-Citronellol                | 5464-57-2  | 70866      | 23622    | 5   |

\(Cat \) indicates category; HPC, human information and potency category; NA, not available (ie, does not exist).
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