Consumer Exposure to Fragrance Ingredients: Providing Estimates for Safety Evaluation

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1. ROUTE OF EXPOSURE

Despite the obvious intention of incorporating fragrances into consumer products for their olfactory properties, inhalation appears to represent a minor route of systemic exposure to fragrances, even when highly exaggerated airborne levels and rather unlikely exposure scenarios are used. Initial experiments to examine the toxicity of high-volume fragrance materials seem to corroborate this relatively low exposure (Fukayama et al., 1999). Similarly, but for more obvious reasons, ingestion is also a minor route.

The major route of systemic exposure is almost certainly by deposition on the surface of the skin. Safety evaluation of fragrance ingredients is based on data from tests, in which material is administered to human or animal subjects by placing it on the surface of the skin. For this reason, it is unnecessary to consider anything further than estimating quantities of these ingredients deposited on the surface of the skin. Albeit important, skin absorption is not the thrust of this article and is not dealt with here. Rather, measurement of toxicity within the context of exaggerated dose, conditions of exposure, etc., all of which lead to an exposure greatly exaggerated over typical “use,” is the thrust of this study.

2. TYPES OF EFFECTS AND TYPES OF DERMAL EXPOSURE

Safety evaluation as outlined by Ford et al. (2000) concentrates on different types of exposure and different endpoints. It focuses on systemic effects, particularly those due to repeated dermal exposure over a long period. Appropriate estimates of short-term exposure, which may result from single use of one cosmetic

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2 Estimates of day-long exposure to fragrance emissions from a constant-diffusion air freshener (electric plug-in type) using the maximum observed weight loss data (12 mg/h) and a number of highly conservative assumptions (a 20-m³ room with 110 m³/h internal airflow and 54.4 m³/h external airflow) using the SCIEX model (Versar Inc., 1991) gives inhalation exposure levels well below 100 µg/kg body wt/day.
TABLE 1
Cosmetic Product Types and Upper Levels of Fragrance Incorporation

<table>
<thead>
<tr>
<th>Product type</th>
<th>Fragrance level a,b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfume extracts</td>
<td>20.00 c</td>
</tr>
<tr>
<td>Toilet waters</td>
<td>8.00</td>
</tr>
<tr>
<td>Fragranced cream</td>
<td>4.00</td>
</tr>
<tr>
<td>Bath products</td>
<td>2.00</td>
</tr>
<tr>
<td>Toilet soap</td>
<td>1.50</td>
</tr>
<tr>
<td>Shower gel</td>
<td>1.20</td>
</tr>
<tr>
<td>Antiperspirant/deodorant</td>
<td>1.00</td>
</tr>
<tr>
<td>Hair spray</td>
<td>0.50</td>
</tr>
<tr>
<td>Shampoo</td>
<td>0.50</td>
</tr>
<tr>
<td>Body lotion</td>
<td>0.40</td>
</tr>
<tr>
<td>Face cream d</td>
<td>0.30</td>
</tr>
</tbody>
</table>

a COLIPA, 1987. Industry survey on typical quantities used per application of different cosmetics.

b RIFM, 1996. Estimates of typical fragrance levels in different products and maximum likely proportion of fragrance remaining on skin after normal product use. Submitted to European Commission.

c The type of cosmetic product that delivers the highest dose of fragrance (expressed as % weight).

d Including makeup and foundation.

These tables include estimates of typical quantities used per application of fragment-free products. The data are based on surveys of industry practices and are presented in terms of quantity per unit area. The values reflect the expected quantities of fragrance that are applied to the skin during normal use.

3 The term "fragrance" is used here to describe the total fragrance component of these products. These "fragrances" are generally complex mixtures of 50-200 different "fragrance ingredients." Ultimately, it will be necessary to estimate exposure to these individual "fragrance ingredients," although at a preliminary stage, it is sufficient to estimate exposure to the total "fragrance" in different types of products.

4. ESTIMATING ACUTE DERMAL EXPOSURE FROM USE OF SINGLE PRODUCTS AS A SOURCE OF POTENTIAL IRRITANCY, ALLERGENICITY, AND ADVERSE PHOTOTOXIC EFFECTS

4.1 Which Product Types Deliver the Highest Doses?

Table 2 indicates that different product types deliver different "doses" of fragrance to the skin. The "dose" for irritancy, allergenicity, and adverse phototoxic effects can be expressed in different ways. Traditionally this has been expressed simply as the concentration (%) of the material in a matrix that is applied to the skin. This may still be the most appropriate definition of "dose" for irritancy and photocautical. However, for allergenicity, there is growing evidence that the critical measure is better represented by the quantity of fragrance per unit area (Friedmann et al., 1990; Rees et al., 1990; White et al., 1986; Fowler and Finley, 1995; Upadhye and Maibach 1992).

The skin surface residues expressed in quantity per event in Table 1 can be further elaborated as seen in Table 2, which compares exposure defined in this way with the traditional "dose" defined in terms of concentration. Tables 1 and 2 indicate the categories of products that are likely to deliver the highest dose. Regardless of which measure of "dose" is used, hydroalcoholic fragrance products and, in particular, perfume extracts, deliver the highest concentration to the skin (Table 1) and, with toilet waters, deliver the highest quantity per unit area (Table 2).

4.2 Exposure to Individual Fragrance Ingredients

To determine the maximum likely concentration (or quantity per unit area) of an individual fragrance ingredient, it is necessary to determine the upper concentrations of the ingredient that are likely to be found in fragrances used in products of this type. Table 2 reveals that we need only look for the highest concentration found in fragrances used in these hydroalcoholic products. The procedure used by industry to determine the upper concentrations in these products is outlined in the Appendix (Section 3, Part A). This procedure requires fragrance manufacturers to examine formulas they sell for use in hydroalcoholic products. This method (the average maximum use level) takes the arithmetic average of the top 10 concentrations reported by industry. By looking at concentrations in all hydroalcoholic products, are not the same as those used for long-term effects, which take into account the use of multiple products over a prolonged period.

3 The term "fragrance" is used here to describe the total fragrance component of these products. These "fragrances" are generally complex mixtures of 50-200 different "fragrance ingredients." Ultimately, it will be necessary to estimate exposure to these individual "fragrance ingredients," although at a preliminary stage, it is sufficient to estimate exposure to the total "fragrance" in different types of products.

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### TABLE 2

**Acute Exposure (Quantity per Unit Area) to Different Cosmetic Products**

<table>
<thead>
<tr>
<th>Product type</th>
<th>Quantity per application(^a) (g)</th>
<th>Perfume level(^b) (%)</th>
<th>Estimated retention factor(^a)</th>
<th>Skin surface residue of fragrance (mg/event)</th>
<th>Location to which applied(^c)</th>
<th>Area (cm(^2))</th>
<th>Acute dose of fragrance (µg fragrance/cm(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body lotion</td>
<td>8.00</td>
<td>0.40</td>
<td>1.00</td>
<td>32.0</td>
<td>20% of trunk</td>
<td>1158</td>
<td>28.0</td>
</tr>
<tr>
<td>Face cream(^d)</td>
<td>0.80</td>
<td>0.30</td>
<td>1.00</td>
<td>2.40</td>
<td>20% of face</td>
<td>200</td>
<td>12.0</td>
</tr>
<tr>
<td>Toilet waters(^e)</td>
<td>0.75</td>
<td>8.00</td>
<td>1.00</td>
<td>60.0</td>
<td>20% of face</td>
<td>200</td>
<td>300.0/7</td>
</tr>
<tr>
<td>Fragranced cream</td>
<td>5.00</td>
<td>4.00</td>
<td>1.00</td>
<td>200.00</td>
<td>20% of face + 50% of trunk</td>
<td>3500</td>
<td>57.0</td>
</tr>
<tr>
<td>Antiperspirant/deodorant</td>
<td>0.50</td>
<td>1.00</td>
<td>1.00</td>
<td>5.00</td>
<td>Both axillae</td>
<td>150</td>
<td>33.0</td>
</tr>
<tr>
<td>Shampoo</td>
<td>8.00</td>
<td>0.50</td>
<td>0.01</td>
<td>0.40</td>
<td>100% of scalp</td>
<td>800</td>
<td>0.5</td>
</tr>
<tr>
<td>Bath products</td>
<td>17.00</td>
<td>2.00</td>
<td>0.001</td>
<td>0.34</td>
<td>50% of body</td>
<td>8500</td>
<td>0.04</td>
</tr>
<tr>
<td>Shower gel</td>
<td>5.00</td>
<td>1.20</td>
<td>0.01</td>
<td>0.60</td>
<td>Scalp and shoulders</td>
<td>1500</td>
<td>0.4</td>
</tr>
<tr>
<td>Toilet soap</td>
<td>0.80</td>
<td>1.50</td>
<td>0.01</td>
<td>0.12</td>
<td>35% of hands</td>
<td>300</td>
<td>0.4</td>
</tr>
<tr>
<td>Hair spray</td>
<td>5.00</td>
<td>0.50</td>
<td>0.01</td>
<td>0.25</td>
<td>10% product applied to peripheral zone</td>
<td>80</td>
<td>3.0</td>
</tr>
</tbody>
</table>

\(^a\) COLIPA, 1987. Industry survey on typical quantities used per application of different cosmetics.

\(^b\) RIFM, 1996. Estimates of typical fragrance levels in different products and maximum likely proportion of fragrance remaining on skin after normal product use. Submitted to European Commission.

\(^c\) Exposure of usual quantity dispersed over a minimum area of skin (50% percentile values for adult females derived from EPA Exposure Factors Handbook [EPA 6008-89-043, July 1989]). Exposure Factors Handbook (Final) (EPA PB 98-124217, 1998).

\(^d\) Includes makeup and foundation.

\(^e\) Including perfume and aftershave but these three products are not used concurrently. The quantity used is inversely proportional to the fragrance concentration so these values include all hydroalcoholic products.

\(^f\) The type of cosmetic product that delivers the highest dose (expressed as quantity per unit area) of fragrance retained on the skin surface after use.

### TABLE 3

**Long-Term Dermal Exposure Expressed as Weight of Skin Surface Residue per Unit Body Weight per Day**

<table>
<thead>
<tr>
<th>Product type</th>
<th>Exposure(^a) (mg/event)</th>
<th>Exposure(^b) (events/day)</th>
<th>Skin surface residue (mg/day)</th>
<th>Skin surface residue in body weight(^c) (µg/kg body wt/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body lotion(^d)</td>
<td>32.0</td>
<td>0.71</td>
<td>22.7</td>
<td>378.0</td>
</tr>
<tr>
<td>Face cream(^e)</td>
<td>2.4</td>
<td>2.0</td>
<td>4.8</td>
<td>80.0</td>
</tr>
<tr>
<td>Toilet water(^f)</td>
<td>60.0</td>
<td>1.0</td>
<td>60.0</td>
<td>1000.0</td>
</tr>
<tr>
<td>Fragranced cream</td>
<td>200.0</td>
<td>0.29</td>
<td>58.0</td>
<td>967.0</td>
</tr>
<tr>
<td>Antiperspirant/deodorant</td>
<td>5.0</td>
<td>1.0</td>
<td>5.0</td>
<td>83.0</td>
</tr>
<tr>
<td>Shampoo</td>
<td>0.4</td>
<td>1.0</td>
<td>0.4</td>
<td>7.0</td>
</tr>
<tr>
<td>Bath products</td>
<td>0.34</td>
<td>0.29</td>
<td>0.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Shower gel(^g)</td>
<td>0.6</td>
<td>1.07</td>
<td>0.6</td>
<td>10.0</td>
</tr>
<tr>
<td>Toilet soap</td>
<td>0.12</td>
<td>6.0</td>
<td>0.7</td>
<td>12.0</td>
</tr>
<tr>
<td>Hair spray</td>
<td>0.25</td>
<td>2.0</td>
<td>0.5</td>
<td>8.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td>2547.0 µg/kg/day(^c)</td>
</tr>
</tbody>
</table>

\(^a\) Table 2 (skin surface residue).

\(^b\) COLIPA, 1987.

\(^c\) Assumes body weight of 60 kg.

\(^d\) Assumes use of conventional body lotion five times per week and a fragranced lotion twice a week. Quantity of application of the latter will be less than that of the former (COLIPA, 1987).

\(^e\) Including makeup and foundation.

\(^f\) Including perfume and aftershave, but these three products will not be used concurrently. The quantity used is inversely proportional to fragrance concentration so these values include all hydroalcoholic products (COLIPA, 1987).

\(^g\) Assumes use of bath products twice per week and use of shower gel 1.5 times per day, five times per week (COLIPA, 1987).
products, the survey has a larger database but includes some products that are neither perfume extracts nor toilet waters, and records some concentrations that are not representative of typical products. For this reason, the average of maximum reported concentrations is a more realistic upper level than the highest concentration reported by industry. The concentrations obtained from this survey can then be converted (using the “high exposure” product-type data in Tables 1 and 2) into doses (expressed either as % or as µg/cm²). Thus, a fragrance ingredient found by this procedure to be used at an average maximum concentration of 5%, in fragrances used in hydroalcoholic products, is considered to have an upper dose for acute effects due to single product use of 1% (5% of 20% in Table 1) and 15 µg/cm² (5% of 300 µg/cm² in Table 2). Long-term dermal exposure estimates are related to subchronic systemic toxicity studies, particularly those carried out by the dermal route. Unlike acute exposure, which is confined to a specific skin site and the use of a single product, estimates of long-term exposure should summate the consequences of use of different types of products. These are given in Table 3 and combine typical skin surface residues from single use of all 10 categories of cosmetics that contribute significantly to dermal exposure. These are further combined with the typical frequencies of use (events/day) of each of these categories. As a result, typical exposure to fragrance is estimated to be 2.55 mg/kg body wt (60-kg consumer)/day. These typical values are then converted into highly exaggerated maximum estimated exposures by the simultaneous application of three assumptions:

I. The upper 97.5th percentile concentration (obtained by Method B in the Appendix) is used to determine the fraction of this 2.55 mg/kg/day that can be attributed to the single fragrance ingredient.4

II. It is assumed that this high concentration of ingredient is encountered in every one of the 10 different consumer products.

III. It is also assumed that the use of high fragrance ingredient concentrations, in a large number of products, is maintained over a long period—day in, day out.

It can be further added that there is no single fragrance ingredient that will always be encountered in every formula. The “chance of encounter” for most ingredients is well below 1 in 10 (i.e., few ingredients are found in more than 10% of formulas). Despite this, the methodology for obtaining the upper 97.5th percentile concentration of a particular ingredient (Appendix, Method B) considers only those formulas that actually contain it. In this way the methodology accounts for the possibility that a consumer selects (consciously or unconsciously) products with a particular odor type, thereby maximizing the likelihood that the ingredient is always present.

This illustrates the extremely conservative nature of exposure estimation. Exaggeration of all variables—ingredient concentrations, products, use frequencies—results in an overestimate of average exposure conditions. While it is hard to gauge the exact value of this overestimation, it can be argued that it likely adds another factor of 10 to the consideration of safe use. That is, the margin of safety is likely to be 10-fold higher than that expressed. When this is coupled with usual hazard assessments and no-effect levels obtained in animal or human studies, even greater confidence is obtained that calculated risks are low, based on actual conditions of use.

5. USE OF ANNUAL VOLUME OF USE (INGREDIENT DISAPPEARANCE) FIGURES

A third type of survey (volume of use survey) (see Method C, Appendix) is also carried out. This type of survey gives figures representing the total annual use of individual ingredients in a specified geographical area. These figures are particularly useful in determining the potential environmental impact of fragrance ingredients. In the context of human safety assessment they also provide a useful moderating factor, particularly where upper use levels give wildly overexaggerated estimates of long-term exposure, for example, when the upper 97.5th percentile concentration places an ingredient among those that give highest long-term exposure but the volume of use survey shows that it is among the smallest volume ingredients.

While accepting that the critical determinants of acute dermal effects (irritation, sensitization, photoeffects) are indicated by the average maximum use levels (see Section 4.2) and that the upper 97.5th percentile levels are critical for determining long-term exposure (Section 5), the approach of Ford et al. (2000) also uses annual volumes of use as one of its criteria for exposure. The basis for this choice is that these figures are still indicative of the relative commercial importance of fragrance ingredients and, hence, of their relative exposure.

6. CONCLUSIONS

Intentional consumer exposure to fragrance ingredients comes mainly from the dermal route from the intentional use of cosmetics. Three procedures are currently used for estimating this exposure. Acute exposure from single product use can be best estimated from the average maximum concentrations found in

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4 Values obtained from analyzing formulas used in hydroalcoholic products have been found to be generally applicable to other categories of cosmetics although in some cases where cost and low substantivity may be dissuasive for use of some ingredients in some products, it is necessary to examine, separately, formulas used in these other categories of products.
hydroalcoholic fragrance products. On the basis of standard industry figures, perfume extracts provide the highest concentrations of fragrance (20%), whereas toilet waters and perfume extracts provide the highest acute exposure in terms of quantity per unit area (300 µg/cm²) for any category of cosmetic product.

For long-term exposure, it is necessary to look at the entire range of cosmetic products that can be used. Figures exist only for “typical” use of these different products. To obtain estimates of upper levels of consumer exposure to a particular fragrance ingredient, a number of highly conservative assumptions are made concerning the amount of this ingredient in all of these products. For these estimates, it is necessary to obtain industry data on the upper 97.5th percentile concentration of the ingredient in fragrance concentrates.

A third indication of consumer exposure comes from volume of use surveys, which measure the quantities of different ingredients used annually by industry. In the case of exposure to substances that are ingested in foods (Lambe et al., 2002), it is possible to relate volume figures directly to human exposure. However, unlike food ingredients, which can be reasonably assumed to be totally ingested, some of the volume of fragrance ingredients disappears in products that are rinsed off the skin. Indeed the greater part of most fragrance ingredients is used in household and fabric cleaning products, which leads to very little dermal exposure in consumers. Nonetheless, volume of use figures allow us to generate a general ranking of the importance of fragrance ingredients which can be useful in checking the validity of estimates of long-term exposure as described above.

APPENDIX

Procedures Used by the Fragrance Industry to Obtain Indications of Exposure to Individual Fragrance Ingredients: Standard Operating Procedures

1. Aim

Quantitative information on how fragrance ingredients are used is part of the intellectual property of individual fragrance manufacturers. Yet this information is of vital importance in assessing the possible risks to humans and the environment. This document explains the assumptions and rationale for how the fragrance industry obtains reliable information.

2. Responsibility

All surveys are carried out by the International Fragrance Association (IFRA), which is responsible for distributing questionnaires to the appropriate parties, for consolidating the responses received, and for carrying out the verification procedures outlined hereafter. IFRA is also responsible for maintaining confidentiality of the identity and contributions of the different responding manufacturers or associations. IFRA also enforces aspects of its “self-policing” procedures relating to these surveys. Individual manufacturers are responsible for responding accurately and completely to these surveys. Responses shall be made to IFRA or one of its member associations within the requested deadlines.

3. Types of Surveys

Three types of surveys are carried out for different purposes:

A. Maximum topical exposure concentrations (average maximum use levels). These require a group of manufacturers to report the top 10 concentrations of a specific fragrance ingredient in all fragrance compounds (or a random selection of these) used in hydroalcoholic perfumery applications (e.g., colognes, toilet waters). It is not necessary to survey all fragrance manufacturers because the aim is to obtain a representative sample of the maximum concentrations that are likely to be encountered in those consumer products (perfume extracts) that contain the highest levels of perfume (ca. 20%) and that are most likely to deliver the highest concentrations of the fragrance ingredient to the surface of the skin. It is worth noting that these procedures produce an exaggerated estimate of exposure, since selection is made for “high-contact” product types with high fragrance ingredient content.

B. Surveys on the statistical distribution of concentrations likely to be encountered in a range of cosmetic products (P97.5 level). These surveys also require a group of manufacturers to provide concentration information for a particular fragrance ingredient, which gives representative levels that are likely to be encountered throughout the whole fragrance industry. This type of survey requires manufacturers to report information on the distribution and specific statistical descriptors they find for the concentrations of a specified fragrance ingredient in fragrance compounds used in different types of cosmetic products.

As a general rule, fragrance manufacturers are required to determine the concentrations of the fragrance ingredient in a fixed set of commercialized formulas (e.g., those used in hydroalcoholic application as in Part A above). The formulas are then listed in order of decreasing concentration. Only formulas in which the ingredient is used are considered. The total number of these formulas (x) is recorded. The upper 97.5th percentile concentration is assumed to approximate the concentration in x/40th formula contained in the list, based on decreasing concentrations (e.g., if there are 200 formulas containing the fragrance ingredient, it will be the fifth highest formula on the list). The 97.5th percentile values reported by different fragrance manufacturers are then consolidated into a single value by
C. Annual volume of use (ingredient disappearance) surveys. These require manufacturers to report on the quantities of individual fragrance ingredients that lose their identity as they are blended into fragrance compounds or subcompounds over a specified period and geographical area for designated end uses. These surveys provide information on the total amount of the material being used. It is important that these surveys are as complete as possible with responses from all manufacturers operating in the specified area.

4. Administrative Procedures

The surveys are initiated by the Scientific Committee (SC) of IFRA. The IFRA staff devise questionnaires (if necessary after consultation with a selection of the responding manufacturers). The questionnaires must explain clearly and exactly what information is required. These questionnaires mention deadlines for responses to be returned to IFRA. The questionnaires are sent to individual manufacturers (surveys A and B) and to the national member associations of IFRA. IFRA verifies the completeness of the replies and also employs the verification procedures described hereafter. As soon as IFRA is satisfied by the completeness and reliability of the reply, it reports these to the Scientific Committee (SC).

5. Verification procedures

The IFRA staff employ the following procedures to ensure that the information provided in response to its surveys is complete. These procedures vary in accordance with the type of survey being undertaken.

Survey A: Maximum topical exposure concentrations. In cases where responders provide some concentrations that are (i) greatly in excess of the other concentrations they have provided, or (ii) greatly in excess of the other maximum concentrations reported by all responders, the responders are asked by IFRA to confirm that the figures they have provided are correct and, if so, they are asked to confirm if any formulas contain exceptionally high concentrations and are used in perfume extracts in the vicinity of 20%. This concentration (which is generally accepted as the maximum level at which fragrances are incorporated into cosmetic products) is subsequently used in calculating the maximum on-skin level of fragrances. Exceptionally high concentrations found in formulas known to be incorporated into fine fragrance perfumes at or around 20% are taken into account. Exceptionally high concentrations found in formulas used at lower levels are converted into their final “in-product concentrations” and discarded if these do not increase significantly the final estimate of a “maximum” concentration obtained from considering all other reported concentrations from all responders.

Survey B: Statistical distributions of concentrations. If responders provide information that is at least ±20% at variance with the information provided by all other responders, IFRA staff will contact them and ask that they confirm that this information is valid. If the response is affirmative, the IFRA Staff present the case (preserving the anonymity of the outlying responder) to the Scientific Committee, which decides (using knowledge of how fragrance ingredients are used and of likely variability within industry) whether to retain or discard this outlying response. As a general rule, high outliers are not discarded.

Survey C: Annual volume of use (disappearance) ingredient surveys. For these, the IFRA staff, at the moment of initiating the survey, attribute to each potential responder (manufacturer or national association) an estimated market share based on industry knowledge and past responses. On receiving responses, the IFRA staff verify that the total weights (for all fragrance ingredients in the particular survey) for each responder correspond to ±50% of the weights predicted on the basis of market share for each responder. In cases where the information from a particular responder does not correspond to these criteria, the IFRA staff contact the responder and ask for internal verification by the responder and, if necessary, a plausible explanation for this. It is possible that surveys on a limited number of ingredients and/or on ingredients of limited use will yield wide variances relative to IFRA’s expectations based on market share.

REFERENCES


RIFM (1996). Cosmetics: Submission on the Safety Data on Ingredients: 1,3,4,6,7,8-Hexahydro-4,6,6,7,8-hexamethylcyclopentagona-2-benzopyran (HHCB) and 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN). Submission to DG XXIV, European Commission, December 13, 1996.


