

# Preservatives and Skin Sensitization Quantitative Risk Assessment

David A. Basketter, Catherine J. Clapp, Bob J. Safford, Ian R. Jowsey, Pauline McNamee, Cindy A. Ryan, and G. Frank Gerberick

**Background:** Preservatives are an unfortunately common cause of allergic contact dermatitis (ACD). Often, this is in association with exposure to cosmetics or medicaments. Recently, a quantitative risk assessment (QRA) approach to the quantitation of safe exposure levels for sensitizers has been promulgated as a more effective tool for the identification of acceptable levels of potential sensitizers in consumer products.

**Objective:** To assess this QRA approach, which facilitates the prediction of acceptable exposure levels to skin sensitizers in consumer products, levels that are normally below the threshold for the induction of skin sensitization.

**Methods:** Retrospective QRA analysis on four preservatives in five consumer product types.

**Results:** The analysis shows that functional levels of preservatives may be somewhat above an ideal exposure level for some product types, an outcome that is consistent with the clinical picture.

**Conclusion:** QRA represents a new tool that in the future should be used in combination with the assessment of microbiologic protection needs of specific product types to limit the problem of preservative ACD.

PRESERVATIVE CHEMICALS perform a vital function.<sup>1,2</sup> Unfortunately, the properties necessary for a chemical to function as a preservative are often associated with those necessary for a chemical to behave as a skin sensitizer (ie, being a low-molecular-weight electrophilic chemical). As a consequence, preservatives are commonly seen to be dermally sensitizing in predictive tests,<sup>3,4</sup> and human skin exposure to preservatives is thus seen to cause allergic contact dermatitis.<sup>5-8</sup> However, many sensitizing chemicals, including preservatives, can be used safely as long as the degree of exposure is sufficiently below the threshold for the induction of skin sensitization to that specific chemical. There is daily evidence of this around the world, as the overwhelming majority of exposures to sensitizers are not associated with adverse skin effects. Key to this is a proper risk assessment, which integrates an understanding of the potency of a sensitizer with information on skin exposure. In recent years, the introduction of a novel preservative to the market, after an initial lag phase, has often been associated with an outbreak of allergic contact dermatitis (ACD). Once the

epidemic has been fully recognized, the use of the preservative declines, and so the frequency with which ACD is seen decreases. As some new preservatives have come to the market, a similar phenomenon has been seen and has become known as the "Dillarstone effect."<sup>9</sup> However, it is important to note that the approach to risk assessment available today is significantly different from (and should be better than) that which has been used, even in the recent past, to evaluate new preservatives.

In the present work, we have undertaken a retrospective evaluation of this newly developed quantitative risk assessment (QRA) process for skin sensitization for a range of preservatives in several types of products, based on the availability of data as well as their general relevance. QRA for skin sensitization uses information on the relative potency of a sensitizing chemical to identify a level which would fail to induce sensitization in a human repeated-insult patch test (HRIPT); confirmatory testing in a HRIPT might be used if appropriate. In overview, the key steps of the QRA process are (1) determination of benchmarks (the no-expected-sensitization-induction level [NESIL]); (2) application of sensitization assessment factors (SAFs) for interindividual variation, vehicle matrix effects, and exposure parameters); and (3) calculation of daily consumer exposure through product use. With these parameters, expressed in terms of dose of sensitizer per unit area, an acceptable exposure level (AEL) can be calculated by dividing the NESIL by the three SAFs; this

From Unilever, Colworth House, Sharnbrook, Bedfordshire, UK; Procter & Gamble, Egham, Surrey, UK; and Procter & Gamble, Cincinnati, OH, USA.

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can then be compared with the consumer exposure level (CEL). The ratio of the AEL to the CEL can subsequently be calculated for the skin sensitizer in each product type. The details and application of this QRA approach have been extensively published elsewhere.<sup>10–14</sup> QRA has recently been adopted by the fragrance industry as a more effective way to determine the maximum acceptable levels of sensitizing fragrance chemicals in a wide range of product categories.<sup>15</sup> However, it must be recognized that the scientific basis still relies on a combination of science and expert judgment.

The outcome of this retrospective analysis of sensitizing preservatives is discussed in relationship to existing clinical data and considerations of risk versus benefit. Proposals are made for how the Dillarstone effect can be avoided in the future. This article does not, however, present definitive risk assessments for the preservatives or products discussed. Rather, it should be clearly recognized that it is always the responsibility of the company placing a product on the market to use all of the information available to it, both on the skin sensitization potential of the preservative and on skin exposure arising from the product, to carry out the definitive risk assessment.

## Materials and Methods

### Preservative Selection

Representative skin sensitization hazard identification data of good quality were gathered on formaldehyde, a 3:1 mixture of chloromethylisothiazolinone and methylisothiazolinone (CMI/MI), imidazolidinylurea (IU), and 3-iodo-2-propynyl butyl carbamate (IPBC). Local lymph node assay (LLNA) and HRIPT data were collated from internal studies and the published literature.<sup>4,16,17</sup>

### Identification of No-Expected-Sensitization-Induction Levels

The NESIL (expressed in  $\mu\text{g}/\text{cm}^2$ ) was derived from the LLNA threshold and HRIPT data (both no-effect levels [NOELs] and lowest-effect levels [LOELs]), with a weight-of-evidence approach. Specific details for each preservative are noted; where applicable, uncertainties regarding the HRIPT NESIL are discussed for individual preservatives. In general terms, the LLNA predictions were close to the human data, but where there was a difference, the results from high-quality human data were given preference. Predictions of human skin sensitization thresholds from

the LLNA were made with the previously reported approach.<sup>13</sup>

### Safety Assessment Factors

SAFs are used to extrapolate from the experimental exposures from which the benchmark data have been generated and relate them to real-life consumer product exposure scenarios. The SAF is a combination of three key parameters: interindividual variability, matrix effects, and use considerations. (This is explained in further detail later in this article.)

### Product Selection

Five product types representing a variety of exposure types or situations were selected: shampoo, face cream, deodorant, lipstick, and body lotion. These products were included in a study on consumer exposure to cosmetics sponsored by the European Cosmetic, Toiletry and Perfumery Association.<sup>18</sup> In the study, data were collected by using a combination of market information databases and a controlled product use study. In total, 44,100 households and 18,057 habitual users (males and females) of the products in five European countries provided data, using their own products (including use out of home). The raw data were analyzed with Monte Carlo simulation to construct a European statistical population model of exposure. The 90th percentile of the amount of product used per day was used in the exposure calculation for the QRA.

Retention factors and skin surface areas of application for these product types are taken from the fragrance industry QRA publication and the Scientific Committee on Cosmetics and Non-Food Products.<sup>15,19</sup>

A typical level of the product preservative as well as the maximum permitted level from the cosmetics directive were used to benchmark consumer exposure.<sup>20</sup> The key data are summarized in Tables 1 and 2. For product types in which an ingredient is not permitted by the European Union, the QRA was not conducted.

### Quantitative Risk Assessment

The NESIL was divided by the calculated SAF to determine the AEL (Table 3). Two of the elements comprising the SAF—the interindividual variability and use considerations—for each product type were the same as those determined from the QRA fragrance materials task force document.<sup>15</sup> For the matrix SAF, a factor of 3 was taken (actually  $\sqrt{10}$ —approximately 3.16). In reality, each

**Table 1.** Concentration (in ppm) of Preservatives in the Five Product Types

| <i>Preservative</i> | <i>Shampoo</i> |            | <i>Face Cream</i> |            | <i>Non-aerosol Deodorant</i> |            | <i>Body Lotion</i> |            | <i>Lipstick</i> |            |
|---------------------|----------------|------------|-------------------|------------|------------------------------|------------|--------------------|------------|-----------------|------------|
|                     | <i>Typ</i>     | <i>Max</i> | <i>Typ</i>        | <i>Max</i> | <i>Typ</i>                   | <i>Max</i> | <i>Typ</i>         | <i>Max</i> | <i>Typ</i>      | <i>Max</i> |
| Formaldehyde        | 500            | 2000       | ND                | 2000       | ND                           | 2000       | ND                 | 2000       | ND              | 2000       |
| CMI/MI              | 5              | 15         | ND                | 15         | ND                           | 15         | ND                 | 15         | ND              | 15         |
| IU                  | 6000           | 6000       | 3000              | 6000       | 3000                         | 6000       | 3000               | 6000       | 3000            | 6000       |
| IPBC                | 100            | 500        | 100               | 500        | 100                          | 500        | 100                | 500        | NP              | NP         |

CMI/MI = chloromethylisothiazolinone/methylisothiazolinone; IPBC = 3-iodo-2-propynyl butyl carbamate; IU = imidazolidinylurea; Max = maximum level permitted according to European Union Cosmetics Directive; ND = not done (risk assessment not done, as preservative is not normally used by the authors in this product type); NP = no preservative (risk assessment not done as preservative is not permitted for use in this product type); ppm = parts per million; Typ = typical upper limit of use level in the experience of authors' companies.

**Table 2.** Exposure Data Used to Calculate Dose per Unit Area

| <i>Product Type</i>   | <i>Amount Used<sup>*</sup> (g/d)</i> | <i>Retention Factor<sup>†</sup></i> | <i>Surface Area<sup>†</sup> (cm<sup>2</sup>)</i> | <i>Dose/Unit Area<sup>†</sup> [(mg/cm<sup>2</sup>)/d]</i> |
|-----------------------|--------------------------------------|-------------------------------------|--------------------------------------------------|-----------------------------------------------------------|
| Shampoo               | 10.5                                 | 0.01                                | 1,430                                            | 0.07                                                      |
| Face cream            | 1.54                                 | 1.0                                 | 565                                              | 2.73                                                      |
| Non-aerosol deodorant | 1.51                                 | 1.0                                 | 200                                              | 7.55                                                      |
| Body lotion           | 7.82                                 | 1.0                                 | 1,5670                                           | 0.5                                                       |
| Lipstick              | 0.057                                | 1.0                                 | 4.8                                              | 11.8                                                      |

<sup>\*</sup>90th percentile, data from COLIPA (The European Cosmetic Toiletry and Perfumery Association) Exposure Task Force (2005).<sup>18</sup>

<sup>†</sup>Data from Research Institute for Fragrance Materials.<sup>15</sup>

**Table 3.** Default Safety Assessment Factors Used for Different Product Types

| <i>Product Type</i>   | <i>Human SAF</i> | <i>Matrix SAF</i> | <i>Use SAF</i> | <i>Overall SAF<sup>*</sup></i> |
|-----------------------|------------------|-------------------|----------------|--------------------------------|
| Shampoo               | 10               | 3                 | 3              | 100                            |
| Women's face cream    | 10               | 3                 | 3              | 100                            |
| Non-aerosol deodorant | 10               | 3                 | 10             | 300                            |
| Body lotion           | 10               | 3                 | 10             | 300                            |
| Lipstick              | 10               | 3                 | 10             | 300                            |

SAF = safety assessment factor.

<sup>\*</sup>Taken from Research Institute for Fragrance Materials<sup>15</sup> and rounded up to the nearest hundred.

company conducting a QRA would have to make their own decision on the most appropriate factor. SAFs were multiplied together for each product type to determine the overall SAF. The AEL was divided by the CEL of the preservatives in each product type to give the AEL/CEL ratio. Where the AEL/CEL ratio was less than 1, exposure to the allergen from the use of that individual product would be regarded as presenting a risk for the induction of skin sensitization.

Note that in the QRA calculations, numbers have normally been expressed to no more than three significant figures. In all of the calculations associated with QRAs,

dose is expressed as µg per centimeter squared as the most appropriate exposure dose metric and as a means to simplify the comparative process.

## Results

### No-Expected-Sensitization-Induction Levels

LLNA and HRIPT data and their use in determining the NESIL are summarized in Table 4.

**Table 4.** Results of Predictive Tests with Each of the Preservatives

| Preservative | Test  | Vehicle                      | Concentration (%)                                                | Results*                                                                              | Reference |
|--------------|-------|------------------------------|------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------|
| Formaldehyde | LLNA  | Acetone                      | 0, 0.093, 0.185, 0.37, 0.925, 1.85                               | EC3 = 0.4% (100 µg/cm <sup>2</sup> )                                                  | 4         |
|              | HRIPT | Petrolatum                   | 0.037, 0.37, 1.11, 1.85% tested at induction; 0.37% at challenge | 0.037% sensitized 0/45; higher levels gave a dose-dependent increase in sensitization | 16        |
| CMI/MI       | LLNA  | Dimethyl formamide           | 0.0015, 0.0075, 0.015, 0.0375, 0.075                             | EC3 = 0.009% (2.25 µg/cm <sup>2</sup> )                                               | 4         |
|              | HRIPT | Water                        | 0.001 for induction and challenge                                | 0/602 sensitized                                                                      | 20        |
| IU           | LLNA  | Dimethyl formamide           | 0, 10, 25, 50                                                    | EC3 = 24% (6,000 µg/cm <sup>2</sup> )                                                 | 35        |
|              | HRIPT | Water                        | 2 at induction and challenge                                     | 2/150 sensitized                                                                      | 17        |
| IPBC         | LLNA  | Acetone/olive oil (4:1, v/v) | 0, 0.1, 1, 5, 10                                                 | EC3 = 0.87% (218 µg/cm <sup>2</sup> )                                                 | 36        |
|              | HRIPT | Corn oil                     | 1% used for induction and challenge                              | 0/170 sensitized                                                                      | 22        |

CMI/MI = chloromethylisothiazolinone/methylisothiazolinone; EC3 = estimated concentration to give a 3-fold stimulation; HRIPT = human repeated-insult patch test; IPBC = 3-iodo-2-propynyl butyl carbamate; IU = imidazolidinylurea; LLNA = local lymph node assay; v/v = volume per volume.

\*General conclusions: formaldehyde no-expected-sensitization-induction level (NESIL) = 37 µg/cm<sup>2</sup> in petrolatum; CMI/MI NESIL = 0.83 µg/cm<sup>2</sup> in water; IU NESIL = 1000 µg/cm<sup>2</sup> in water; IPBC NESIL = 310 µg/cm<sup>2</sup> in corn oil.

### Formaldehyde

Overall, the NESIL based on HRIPT data was taken to be 37 µg/cm<sup>2</sup> in petrolatum.<sup>17</sup> This is a little lower than the HRIPT threshold predicted by extrapolation from the LLNA EC3 value of 0.6% (equivalent to 150 µg/cm<sup>2</sup>) and which can be used to predict that the HRIPT NESIL would be around 77 µg/cm<sup>2</sup>.<sup>4</sup> A complication is that the protocol used in the HRIPT was not standard as 10 × 48 hour or 10 × 72 hour exposures were used to deliver 3.5 weeks of continuous exposure during the induction phase. Also, the surface area of the patch was not specified in the publication (a square bandage was assumed to have a surface area of 5 cm<sup>2</sup>), and a panel of 100 persons was not tested at every concentration. Despite these limitations, dose-response relationships were established in the study and were consistent with the animal data. Because the exposure was greater than that in a standard HRIPT protocol, it can be considered that 37 µg/cm<sup>2</sup> is a reasonable conservative estimate of the HRIPT no-effect level for formaldehyde (see Table 4).

### CMI/MI

HRIPT data for CMI/MI have been documented in the European Union's Scientific Committee on Consumer and Non-Food Products recent assessment for methylisothiazolinone.<sup>21</sup> This defines the HRIPT NOEL as 0.83 µg/cm<sup>2</sup>, with evidence of a low incidence of sensitization at higher

concentrations. The study protocols are of good quality, as well over 100 people were tested; hence, this appears to be a reliable estimate of the NESIL. The value is also supported by the extrapolation from the LLNA EC3 value of 0.009% (2.3 µg/cm<sup>2</sup>), which results in a predicted HRIPT NESIL of 0.51 µg/cm<sup>2</sup>, very close to the HRIPT value<sup>4</sup> (see Table 4).

### IU

The HRIPT protocol was not standard as there were 10 patches of 48 or 72 hour duration.<sup>17</sup> A LOEL was determined from this study and is approximately 2,000 µg/cm<sup>2</sup> (there is uncertainty over the exact dose per unit area because the protocol details recorded in the paper are incomplete). Extrapolation from the LLNA EC3 of 24% (6,000 µg/cm<sup>2</sup>) is equivalent to an HRIPT NESIL of 5,975 µg/cm<sup>2</sup>.<sup>13</sup> However, because an experimental HRIPT LOEL has been determined and the LLNA estimates the threshold to be higher, the evidence indicates that a NESIL for IU of 1,000 µg/cm<sup>2</sup> would be a reasonable assumption (see Table 4).

### IPBC

Based on human skin sensitization data, the NESIL was determined at 310 µg/cm<sup>2</sup> in the Cosmetic Ingredient Review.<sup>22</sup> This is approximately three times higher than

would be predicted from the LLNA EC3 HRIPT NOEL correlation<sup>13</sup> (see Table 4).

### Quantitative Risk Assessment

The outcomes of the QRAs for each preservative and product combination are shown in Tables 5 to 8.

#### Formaldehyde

Formaldehyde is commonly used only in rinse-off products in European Union (EU) countries, so when typical use levels were considered, QRA was completed only for the shampoo. Here the AEL is only 0.37  $\mu\text{g}/\text{cm}^2$ , but at a typical level of incorporation, product use delivers only a quarter of this amount (see Table 5). Use at the maximum permitted level in EU countries delivers an exposure dose equivalent to the maximum AEL.

#### CMI/MI

The isothiazolinone CMI/MI is the most strongly sensitizing of the group discussed in this article, such that acceptable exposure levels are generally very low. At typical use levels in a rinse-off product such as a shampoo, the AEL/CEL ratio is almost 23 and is thus acceptable. Typically, this preservative is not used in many leave-on products in Europe. At the maximum permitted EU level in a shampoo, the AEL/CEL ratio is 7.6 (see Table 6).

#### IU

IU is the weakest sensitizer in this selected group of preservatives. The AEL/CEL ratio for shampoo use is about 23. However, at typical use levels in the other products, the AEL/CEL ratio is closer to 1 and is only 0.1 for non-aerosol deodorants (although this is typically used at the

**Table 5.** Quantitative Risk Assessment for Formaldehyde in Different Product Types

| Product Type          | NESIL $\mu\text{g}/\text{cm}^2$ | SAF | AEL* $\mu\text{g}/\text{cm}^2$ | Typical Preservative Level <sup>†</sup>              |         | Maximum Permitted Level                              |         |
|-----------------------|---------------------------------|-----|--------------------------------|------------------------------------------------------|---------|------------------------------------------------------|---------|
|                       |                                 |     |                                | Skin Exposure <sup>‡</sup> $\mu\text{g}/\text{cm}^2$ | AEL/CEL | Skin Exposure <sup>‡</sup> $\mu\text{g}/\text{cm}^2$ | AEL/CEL |
| Shampoo               | 37                              | 100 | 0.37                           | 0.04                                                 | 10.12   | 0.15                                                 | 2.53    |
| Face cream            | 37                              | 100 | 0.37                           | Not done                                             | NA      | 5.45                                                 | 0.07    |
| Non-aerosol deodorant | 37                              | 300 | 0.12                           | Not done                                             | NA      | 15.1                                                 | 0.01    |
| Body lotion           | 37                              | 300 | 0.12                           | Not done                                             | NA      | 1.21                                                 | 0.10    |
| Lipstick              | 37                              | 300 | 0.12                           | Not done                                             | NA      | 23.6                                                 | 0.02    |

AEL = acceptable exposure level; CEL = consumer exposure level; NA = not applicable; NESIL = no-expected-sensitization-induction level, derived from human repeated-insult patch-test data; SAF = sensitization assessment factor from Table 3.

\*NESIL divided by SAF.

<sup>†</sup>Level of preservative in the product formulation (see Table 2).

<sup>‡</sup>Daily skin exposure to the preservative, associated with normal product use.

**Table 6.** Quantitative Risk Assessment for CMI/MI in Different Product Types

| Product Type          | NESIL $\mu\text{g}/\text{cm}^2$ | SAF | AEL* $\mu\text{g}/\text{cm}^2$ | Typical Preservative Level <sup>†</sup>              |         | Maximum Permitted Level <sup>†</sup>                 |         |
|-----------------------|---------------------------------|-----|--------------------------------|------------------------------------------------------|---------|------------------------------------------------------|---------|
|                       |                                 |     |                                | Skin Exposure <sup>‡</sup> $\mu\text{g}/\text{cm}^2$ | AEL/CEL | Skin Exposure <sup>‡</sup> $\mu\text{g}/\text{cm}^2$ | AEL/CEL |
| Shampoo               | 0.83                            | 100 | 0.0083                         | 0.004                                                | 22.7    | 0.0011                                               | 7.6     |
| Face cream            | 0.83                            | 100 | 0.0083                         | Not done                                             | NA      | 0.020                                                | 0.41    |
| Non-aerosol deodorant | 0.83                            | 300 | 0.0028                         | Not done                                             | NA      | 0.057                                                | 0.05    |
| Body lotion           | 0.83                            | 300 | 0.0028                         | Not done                                             | NA      | 0.005                                                | 0.61    |
| Lipstick              | 0.83                            | 300 | 0.0028                         | Not done                                             | NA      | 0.088                                                | 0.03    |

AEL = acceptable exposure level; CEL = consumer exposure level; CMI/MI = chloromethylisothiazolinone/methylisothiazolinone; NA = not applicable; NESIL = no-expected-sensitization-induction level, derived from human repeated-insult patch-test data; SAF = sensitization assessment factor from Table 3.

\*NESIL divided by SAF.

<sup>†</sup>Level of preservative in the product formulation (see Table 2).

<sup>‡</sup>Daily skin exposure to the preservative, associated with normal product use.

**Table 7.** Quantitative Risk Assessment for Imidazolidinylurea in Different Product Types

| Product Type             | NESIL*<br>$\mu\text{g}/\text{cm}^2$ | SAF | AEL†<br>$\mu\text{g}/\text{cm}^2$ | Typical Preservative Level‡                 |         | Maximum Permitted Level‡                    |         |
|--------------------------|-------------------------------------|-----|-----------------------------------|---------------------------------------------|---------|---------------------------------------------|---------|
|                          |                                     |     |                                   | Skin Exposure§<br>$\mu\text{g}/\text{cm}^2$ | AEL/CEL | Skin Exposure§<br>$\mu\text{g}/\text{cm}^2$ | AEL/CEL |
| Shampoo                  | 1,000                               | 100 | 10.0                              | 0.44                                        | 22.8    | 0.44                                        | 22.8    |
| Face cream               | 1,000                               | 100 | 10.0                              | 8.18                                        | 1.2     | 16.4                                        | 0.61    |
| Non-aerosol<br>deodorant | 1,000                               | 300 | 3.3                               | 22.7                                        | 0.15    | 45.3                                        | 0.07    |
| Body lotion              | 1,000                               | 300 | 3.3                               | 1.82                                        | 1.83    | 3.64                                        | 0.92    |
| Lipstick                 | 1,000                               | 300 | 3.3                               | 35.3                                        | 0.09    | 70.7                                        | 0.05    |

AEL = acceptable exposure level; CEL = consumer exposure level; NESIL = no-expected-sensitization-induction level; SAF = sensitization assessment factor from Table 3

\*Derived from local lymph node assay (LLNA)–predicted human repeated-insult patch-test (HRIPT) no effect level (NOEL).

†NESIL divided by SAF.

‡Level of preservative in the product formulation (see Table 2).

§Daily skin exposure to the preservative, associated with normal product use.

||AEL/CEL ratio.

**Table 8.** Quantitative Risk Assessment for IPBC in Different Product Types

| Product Type             | NESIL*<br>$\mu\text{g}/\text{cm}^2$ | SAF | AEL†<br>$\mu\text{g}/\text{cm}^2$ | Typical Preservative Level‡                 |         | Maximum Permitted Level‡                    |         |
|--------------------------|-------------------------------------|-----|-----------------------------------|---------------------------------------------|---------|---------------------------------------------|---------|
|                          |                                     |     |                                   | Skin Exposure§<br>$\mu\text{g}/\text{cm}^2$ | AEL/CEL | Skin Exposure§<br>$\mu\text{g}/\text{cm}^2$ | AEL/CEL |
| Shampoo                  | 310                                 | 100 | 3.1                               | 0.01                                        | 424     | 0.04                                        | 84.8    |
| Face cream               | 310                                 | 100 | 3.1                               | 0.27                                        | 11.4    | 1.36                                        | 2.27    |
| Non-aerosol<br>deodorant | 310                                 | 300 | 1.03                              | 0.76                                        | 1.37    | 3.78                                        | 0.27    |
| Body lotion              | 310                                 | 300 | 1.03                              | 0.06                                        | 17.0    | 0.30                                        | 3.41    |

AEL = acceptable exposure level; CEL = consumer exposure level; IPBC = 3-iodo-2-propynyl butyl carbamate; NESIL = no-expected-sensitization-induction level; SAF = sensitization assessment factor from Table 3.

\*Derived from human repeated-insult patch-test data.

†NESIL divided by SAF.

‡Level of preservative in the product formulation (see Table 2).

§Daily skin exposure to the preservative, associated with normal product use

||AEL/CEL ratio.

maximum level in this product type) (see Table 7). At the maximum permitted use levels in EU countries for the remaining three product types, the AEL/CEL ratio values are 50% lower and, in the case of face cream, drop below 1.

### IPBC

IPBC is the least commonly used preservative of the group discussed here, not least because it is only really effective as a fungicide. It is of intermediate potency, between those of formaldehyde and IU. Except for the deodorant, even the maximum use levels of this preservative deliver an AEL/CEL ratio of greater than 1; the deodorant has an AEL/CEL

ratio of 1.37 at typical use level but of only 0.27 at the maximum allowed level (see Table 8).

## Discussion

Chemicals that possess the ability to cause skin sensitization can be used safely as long as skin exposure to them is sufficiently lower than the threshold for the induction of contact allergy. This is important because many chemicals with very desirable properties turn out to be sensitizing, and a substantial minority of known organic chemicals may have some propensity to be dermally sensitizing.<sup>23</sup> However, for certain classes of chemicals, the properties that cause them to be selected to perform a particular

function are commonly associated with the ability to dermally sensitize. Such is the case with the preservative family of chemicals, the vast majority of which have been shown to give rise to skin sensitization or ACD to some degree.<sup>1,5,6</sup> Consequently, it is necessary to ensure an appropriate balance between the functional delivery of preservation and the risk of skin sensitization through the use of preserved products. The successful achievement of this aim will depend on an accurate identification of sensitization potency, a proper appreciation of consumer exposure combined into a QRA, and the use of the lowest amount of preservative necessary to avoid product spoilage. This last-mentioned item falls outside the scope of this article (and the expertise of the authors) but is a topic that deserves attention; recent publications have drawn particular attention to the same matter.<sup>24,25</sup>

For preservative chemicals, the cycle of market introduction followed, after a delay, by an outbreak of ACD has become a repetitive cycle termed the Dillarstone effect.<sup>9</sup> Typically however, once this initial phase has passed, it is discovered that there is a use level of the preservative that represents an acceptable balance between risk and benefit; MI/CMI represents just such a case.<sup>26,27</sup> With this preservative, initial use occurred at up to 50 parts per million (ppm), which led to an outbreak of ACD.<sup>28</sup> Typical use levels are now no more than 15 ppm for rinse-off products and are recommended by the Cosmetic Ingredient Review to be no greater than 7.5 ppm for leave-on products<sup>29</sup> although this is still associated with some degree of ACD.<sup>30</sup> However, it may now be possible to use QRA for induction of contact allergy to indicate proactively appropriate use levels of preservatives (from a perspective of sensitization, not microbicide). QRA is already being applied to a number of other ingredients and contaminants of consumer products.<sup>14,15,31</sup> So, to assess the applicability of QRA, we undertook a retrospective assessment of four different types of preservative chemical.

The preliminary analysis conducted in this study examined five generic product types, variously using one of the four preservatives (formaldehyde, MI/MCI, IU, and IPBC) at typical and EU maximum allowed levels. The overview of the outcome of the safety assessments based on a review of the data currently available to us is given in Tables 5 to 8. Several points are readily evident: preservatives in shampoo (an example of a standard rinse-off product) typically present little risk of the induction of sensitization, and this accords well with clinical experience<sup>32</sup>; in contrast, face cream and deodor-

ant often present a greater risk, and this again fits with clinical experience.<sup>33</sup> Last, the QRA indicates that for IPBC there is apparently a slightly greater separation between its efficacy (as a fungicide) and its ability to induce skin sensitization because it is associated with the highest AEL/CEL ratio values. Normally, of course, IPBC would need to be used in combination with one or more of the other preservative substances for broad-spectrum preservation to be achieved. In this context, however, it should be noted that this article discusses consumer use of products. Where there is occupational use (eg, of hand soaps, protective/moisturizing creams), exposure may be much higher, with the consequence that acceptable product use levels for preservatives may need to be substantially reduced for their risk to be comparable to that of general consumer products. The importance of defining potency, carrying out a full skin sensitization induction risk assessment with proper recognition of real-life exposures, and (in particular) consideration of the occupational use situation has been placed into sharp focus by recent experiences with another preservative, methyldibromoglutaronitrile<sup>34</sup> (which will be the subject of a follow-up article).

These last points broach an important question: from a skin sensitization perspective, how safe should a preservative be? How does the degree of skin sensitization risk conflict with the benefit delivered? It is not the intention of this article to provide a direct answer to that question, since the answer depends not only on a consideration of AEL/CEL ratio for skin sensitization but also on other human health considerations, environmental considerations, preservative efficacy, and many other factors. Among these extra considerations must be the nature of the anticipated user group; there must be an adequate understanding of (1) exposure variables, (2) the possibility that the group might have an overrepresentation of a skin condition impacting barrier function, and (3) potential exposure to the same allergen via other product use. What can be seen, though, is that if considerations were limited to just the balance between skin sensitization and preservation, then the choice of preservatives with a skin sensitization AEL/CEL ratio of greater than 1 is likely to be restricted for many leave-on products, particularly when only a single preservative chemical is used. Where product preservation requires this type of chemical (and this is the case with most cosmetics), then the successful containment of microbial contamination will dictate the need for a balance to be struck: sufficient concentration (and number) of preservatives to achieve reliable preservation while minimizing the risk of the induction of skin sensitization.

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