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# Safety Assessment of Polyquaternium-22 and Polyquaternium-39 as Used in Cosmetics

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*All interested persons are provided 60 days from the above date to comment on this Tentative Report and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. F. Alan Andersen.*

The 2013 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

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**ABSTRACT:** Polyquaternium-22 and Polyquaternium-39 are polymers that function as antistatic agents, film formers, and hair fixatives in cosmetic products. These ingredients are being used at concentrations up to 2% (Polyquaternium-22, in a rinse-off product) and up to 3% (Polyquaternium-39, in a rinse-off product). The unreacted monomers content of these ingredients was considered low and of no toxicological concern. Limited data showed no skin irritation/sensitization. While these ingredients were non-genotoxic in bacterial assays, mammalian genotoxicity, carcinogenicity, and reproductive and developmental toxicity data were not available. These polymers, however, are large, highly polar molecules that would not be absorbed, and neither local effects in the respiratory tract nor systemic toxicity are likely following product application/exposure. The Expert Panel concluded that polyquaternium-22 and polyquaternium-39 are safe in the present practices of use and concentration in cosmetic formulations.

## **INTRODUCTION**

This tentative report reviews the available data relevant to the safety of polyquaternium-22 and polyquaternium-39 as used in cosmetics. These ingredients are polymers, each with a quaternary ammonium moiety. In the case of polyquaternium-22, the monomers used to produce the polymer are acrylic acid and dimethyldiallyl ammonium chloride and, for polyquaternium-39, those monomers used to produce the polymer are the same, with the addition of acrylamide. Given the similarities, these ingredients were grouped together. In addition, both ingredients function as antistatic agents, film formers, and hair fixatives in cosmetic products.

The CIR Expert Panel, in its safety assessment of polyacrylamide, had established a limit for acrylamide monomer of 5 ppm in cosmetic formulations.<sup>1</sup>

The Expert Panel previously issued final reports on the safety assessment of Polyquaternium-7<sup>2</sup>, Polyquaternium-10<sup>3</sup> and Polyquaternium-11<sup>4</sup>, having concluded that these cosmetic ingredients are safe in the present practices of use and concentration. This conclusion on Polyquaternium-7 was reaffirmed by the Panel during a re-review of the safety of this ingredient in cosmetics in 2010.<sup>5</sup> The Panel also determined that the amount of residual acrylamide in Polyquaternium-7 is not of toxicological concern. The Panel's conclusions on Polyquaternium-10 and Polyquaternium-11 were also confirmed.<sup>6,7</sup>

## **CHEMISTRY**

### **Definition and Structure**

Polyquaternium-22 (CAS No. 53694-17-0) is defined as a copolymer of diallyldimethyl ammonium chloride (DADMAC) and acrylic acid that conforms to the structural formula in Figure 1:<sup>8</sup> Another name for this copolymer is acrylic acid-diallyldimethylammonium chloride polymer.

Polyquaternium-39 (CAS No. 25136-75-8) is defined as a polymeric quaternary ammonium salt of DADMAC and acrylamide.<sup>8</sup> The structural formula of this chemical is included in Figure 1.<sup>9</sup> Other names for this polymeric quaternium ammonium salt include acrylic acid, polymer with acrylamide and diallyldimethyl ammonium chloride, and 2-propen-1-aminium, *N,N*-dimethyl-*N*-2-propenyl-, chloride, polymer with 2-propenamide and 2-propenoic acid.<sup>8</sup>

### **Chemical and Physical Properties**

Specifications for polyquaternium-22 and Polyquaternium-39 are as follows:

#### **Polyquaternium-22<sup>10</sup>**

- Appearance (viscose water clear liquid)
- Solid (40 ± 1%)
- pH (2 to 5, for 1% aqueous solution)
- Viscosity (3,000 to 7,500 cps, @ 25°C)

#### **Polyquaternium-39<sup>11</sup>**

- Appearance (clear viscose liquid)
- Solid (9 to 11%)
- pH (5.5 to 7.2)

- Viscosity (2,000 to 20,000 cps, @ 25°C)

### **Polyquaternium-22**

Merquat™\* 280 Polymer (molecular weight =  $4.5 \times 10^5$ ) is a trade name for polyquaternium-22.<sup>12</sup> It is described as a clear to slightly hazy, yellow, viscous liquid with a mild, aldehydic odor. The total solids content is listed as 39 to 43% for this material, and the pH range is 4.2 to 5.3. Another trade name for polyquaternium-22 is Merquat™\* 295 polymer (molecular weight =  $1.9 \times 10^5$ ).<sup>13</sup> It is described as a clear, yellow viscous liquid with a mild, aldehydic odor. The total solids content is listed as 35 to 40% for this material, and the pH range is 4.0 to 5.5.

### **Polyquaternium-39**

Merquat™\* PLUS 3330 Polymer (molecular weight =  $1.5 \times 10^6$ ) is a trade name for polyquaternium-39.<sup>14</sup> It is described as a clear, colorless viscous liquid with a mild, aldehydic odor. The total solids content is listed as 9.4 to 10.4% for this material, and the pH range is 5.5 to 7.0.

## **Methods of Production**

### **Polyquaternium-22**

According to one source, the starting monomers in the manufacture of polyquaternium-22 are acrylic acid and dimethyldiallyl ammonium chloride.<sup>15</sup>

### **Polyquaternium-39**

Polyquaternium-39 is manufactured from acrylic acid, diallyl dimethyl ammonium chloride and acrylamide.<sup>15</sup>

## **Composition**

### **Polyquaternium-22**

Polyquaternium-22 is marketed at concentration ranges of 30-45% and  $\geq 94\%$ . The lower concentration-range products are defined as aqueous solutions that may also contain preservatives.<sup>15</sup> The higher concentration product is described as a powder with residual moisture content. Typical residual unreacted monomers in this ingredient are: acrylic acid ( $< 1000$  ppm) and diallyldimethyl ammonium chloride ( $< 1\%$ ).

### **Polyquaternium-39**

Polyquaternium-39 is marketed at the following three concentration ranges: 8-11.5%, 41-45%, and  $\geq 92\%$ .<sup>15</sup> The two lower concentration-range products are preserved aqueous polymer solutions. The highest concentration product is an unpreserved powder. Typical unreacted monomers in this ingredient are: acrylamide ( $< 1$  ppm), acrylic acid ( $< 50$  ppm), and diallyldimethyl ammonium chloride ( $< 2\%$ ).

## **USE**

### **Cosmetic**

The 2 ingredients reviewed in this safety assessment function as antistatic agents, film-formers, and hair fixatives in cosmetic products.<sup>8</sup> According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2013, both Polyquaternium-22 and Polyquaternium-39 were being used in cosmetic products.<sup>16</sup> These data are summarized in Table 1. Polyquaternium-22 is used primarily in hair dye products and other hair care products; lower use frequencies for polyquaternium-39 in these products were reported. Results from a survey of ingredient use concentrations provided by the Personal Care Products Council (also included in Table 1) in 2011 indicate that these 2 ingredients were being used at concentrations up to 2% (Polyquaternium-22, in a rinse-off product) and up to 3% (Polyquaternium-39, in a rinse-off product and in a leave-on product).<sup>17</sup>

Cosmetic products containing the ingredients reported as being used may be applied to the skin and hair, or, incidentally, may come in contact with the eyes and mucous membranes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Polyquaternium-39 is being used in face and neck creams, lotions, and powders at concentrations up to 3% and is also being used in indoor tanning preparations (sprays, use concentration data not available). Because this ingredient is used in aerosol/pump sprays or powders, it could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters  $>10\ \mu\text{m}$ , with propellant sprays yielding a greater fraction of droplets/particles below  $10\ \mu\text{m}$ , compared with pump sprays.<sup>18,19,20,21</sup> Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.<sup>19,20</sup>

### **Noncosmetic**

Polyquaternium-39 is included among the substances that may be safely used as components of paper and paperboard products that come in contact with aqueous and fatty foods.<sup>22</sup>

## **TOXICOKINETICS**

Data on the absorption, distribution, metabolism, and excretion of Polyquaternium-22 or Polyquaternium-39 were not found in the published literature.

## **TOXICOLOGY**

### **Acute Oral Toxicity**

#### **Polyquaternium-22**

The acute oral toxicity of polyquaternium-22 (Merquat™ 280 Polymer) was evaluated using 10 healthy male albino rats.<sup>23</sup> The animals were dosed orally with 5 g/kg of the test material. Mortality and systemic observations were made 3 to 4 h post-dosing and daily thereafter for 7 days. All animals survived the study and it was concluded that the  $\text{LD}_{50}$  was  $> 5.0\ \text{g/kg}$ .

#### **Polyquaternium-39**

The acute oral toxicity of polyquaternium-39 (Merquat™ PLUS 3330 Polymer) was evaluated using 10 healthy male Wistar albino rats.<sup>24</sup> The test protocol was identical to that in the preceding study, except for the 14-day observation period after the initial 3 to 4 h observation period. All animals survived in good health, and it was concluded that the  $\text{LD}_{50}$  was  $> 5.0\ \text{g/kg}$  and that the test material was non-toxic.

### **Repeated Dose Toxicity**

Repeated dose toxicity studies on Polyquaternium-22 or Polyquaternium-39 were not found in the published literature, and unpublished data were not submitted.

### **Ocular Irritation**

#### **Polyquaternium-22**

In an ocular irritation study, polyquaternium-22 (Merquat™ 280 Polymer, 0.1 ml) was placed in the conjunctival sac of one eye in each of 6 rabbits.<sup>25</sup> The eyes were not rinsed after instillation. Reactions were scored at 1, 2, and 3 days post-instillation. All eyes appeared normal throughout the study, and the test material was classified as a non-irritant.

The ocular irritation potential of an oxidation dye containing 0.16% Polyquaternium-22 (pH = 9.5 to 10) was evaluated *in vitro* using the hen's egg test on the chorioallantoic membrane (HET-CAM test).<sup>26</sup> The dye was tested at a concentration of 10% (0.016% active Polyquaternium-22), and was classified as a slight irritant (irritation scores of 2.38, 4.51, or 4.60). The positive controls, sodium hydroxide (0.1 M) and sodium dodecyl sulfate (SDS, 1%), yielded scores of 19.98 and 10.21, respectively. The negative control (0.9% sodium chloride) yielded a score of 0.

### **Polyquaternium-39**

The ocular irritation potential of polyquaternium-39 (Merquat™ PLUS 3330 Polymer) was evaluated in a study involving 6 healthy New Zealand albino rabbits.<sup>27</sup> The protocol was identical to that used in the ocular irritation study on Merquat™\* 280 Polymer discussed earlier in this section. There was no evidence of systemic effects at any time after test substance instillation. All eyes appeared normal during the study and the test material was classified as a non-irritant.

## **Skin Irritation and Sensitization**

### **Animal**

#### **Polyquaternium-22**

In a skin irritation study, polyquaternium-22 (Merquat™\* 280 Polymer, 0.5 ml) was applied to abraded and intact skin sites on the backs (clipped free of hair) of 6 healthy albino rabbits.<sup>28</sup> The total dose applied was 1.0 ml/rabbit. The test material was applied under an occlusive patch for 24 h, and reactions were scored at 24 h and 72 h post-application. None to slight and none to severe erythema were observed at 24 h and 72 h post-application, respectively. The erythema observed was more severe at abraded sites than at intact sites. There was no evidence of edema. A primary irritation index (PII) of 1.1 was reported, and the test material was classified as a non-irritant.

#### **Polyquaternium-39**

The skin irritation potential of polyquaternium-39 (Merquat™ PLUS 3330 Polymer) was evaluated in a study involving 6 healthy New Zealand albino rabbits.<sup>29</sup> The test protocol was identical to that used in the skin irritation study on Merquat™\* 280 Polymer discussed earlier in this section. There was no evidence of erythema, edema, or abnormal systemic signs during the study. The test material was classified as a non-irritant (PII = 0).

### **Human**

#### **Polyquaternium-22**

The skin irritation potential of an oxidation dye containing 0.16% polyquaternium-22 (pH = 9.5 to 10) was evaluated using 30 subjects (ages not stated).<sup>26</sup> In a single, occlusive patch test, a 10% concentration of the dye (0.016% active Polyquaternium-22) was applied for 24 h. Reactions were scored at 24 h, 48 h, and 72 h post-application, and the dye was not predicted to be a skin irritant (OIS [not defined] = 0.07). The negative control (water) yielded a score of 0, and the positive control (1% SDS) yielded a score of 0.92. The same test concentration of the dye was also applied to 30 subjects (ages not stated) in a multiple patch test.<sup>26</sup> Three 24 h applications of the dye were made to each subject and reactions were scored according to the same schedule. The dye was not predicted to be a skin irritant (OIS = 0.07). Water (negative control) yielded a score of 0 and 0.3% SDS (positive control) yielded a score of 0.50.

#### **Polyquaternium-39**

The skin irritation and sensitization potential of polyquaternium-39 (Merquat™ PLUS 3330 Polymer, clear liquid) was evaluated in a human repeated insult patch test (HRIPT) using 154 adult subjects (131 women, 23 men; 18 to 79 years old). The numbers of subjects that completed the induction and challenge phases were 153 and 150 subjects, respectively. An occlusive patch (2 cm x 2 cm) moistened with the test material (~0.2 ml) was applied to the back for 24 h. Patch applications were made on either side of the midline. Patches were applied on Mondays, Tuesdays, Wednesdays, and Thursdays during induction. There were no patch applications on Fridays, Saturdays, or Sundays. Week #4 was the non-treatment period, and the challenge phase began at week #5. Patches were applied to a new test site (24-h application) on Monday through Thursday. No adverse skin changes were observed during induction. Erythema of negligible significance was observed on either 1 or 2 occasions on each of 2 subjects. Adverse skin effects were not observed during the challenge phase. It was concluded that the test material did not induce skin irritation or sensitization.

## **REPRODUCTIVE AND DEVELOPMENTAL TOXICITY**

Reproductive/developmental toxicity data on Polyquaternium-22 or Polyquaternium-39 were not found in the published literature.

## **GENOTOXICITY**

### **Polyquaternium-22**

The genotoxicity of polyquaternium-22 (Merquat™\* 280 Polymer) was evaluated, with and without metabolic activation, in the Ames test using the following bacterial strains: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2 *uvr* A.<sup>30</sup> The test material was evaluated at doses up to 5,000 µg/plate. Positive responses were not observed during the study, and it was concluded that the test material was non-genotoxic in this assay. Results were also negative in another study (same protocol and doses) on Merquat™\* 295 polymer.<sup>31</sup>

### **Polyquaternium-39**

In another study, the genotoxicity of polyquaternium-39 (Merquat™ PLUS 3330 Polymer) was evaluated in the Ames test according to the protocol in the preceding study, using the same *Salmonella typhimurium* strains.<sup>32</sup> The test material was non-genotoxic, with and without metabolic activation, over the range of doses tested.

## **CARCINOGENICITY**

Carcinogenicity data on Polyquaternium-22 or Polyquaternium-39 were not found in the published literature.

## **SUMMARY**

The starting monomers for polyquaternium-22 are acrylic acid and dimethyldiallyl ammonium chloride. Polyquaternium-39 is manufactured from acrylic acid, diallyldimethyl ammonium chloride and acrylamide. Acrylic acid (< 50 ppm or < 1000 ppm) and dimethyldiallyl ammonium chloride (<1% or < 2%) are present in both polymers, but acrylamide monomer (< 1 ppm) is present only in polyquaternium-39. Both ingredients function as antistatic agents, film formers, and hair fixatives in cosmetic products.

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2011, both ingredients were being used in cosmetic products. Polyquaternium-22 is used primarily in hair dye products and other hair care products; lower use frequencies for polyquaternium-39 in these products were reported. Results from a survey of ingredient use concentrations provided by the Personal Care Products Council in 2011 indicate that these 2 ingredients were being used at concentrations up to 2% (Polyquaternium-22, in a rinse-off product) and up to 3 % (Polyquaternium-39, in a rinse-off product).

Polyquaternium-22 (Merquat™\* 280 Polymer) and polyquaternium-39 (Merquat™ PLUS 3330 Polymer) were classified as non-toxic (LD50 > 5 g/kg) in acute oral toxicity studies.

Merquat™\* 280 Polymer and Merquat™ PLUS 3330 Polymer were classified as non-irritants when instilled into the eyes of rabbits. A 0.16% Polyquaternium-22 oxidation dye, tested at a concentration of 10% (0.016% active Polyquaternium-22) in an *in vitro* HET-CAM test, was classified as a slight ocular irritant.

Both Merquat™\* 280 Polymer and Merquat™ PLUS 3330 Polymer were classified as non-irritants when applied, under an occlusive patch, to the skin of albino rabbits. In single and multiple application occlusive patch tests, a 0.16% polyquaternium-22 oxidation dye, tested at a concentration of 10% (0.016% active Polyquaternium-22), was not predicted to be a skin irritant in human subjects. In an HRIPT (occlusive patches), Merquat™ PLUS 3330 Polymer was classified as a non-irritant and non-sensitizer.

Merquat™ 280 Polymer, Merquat™ 295 polymer (also polyquaternium-22), and Merquat™ PLUS 3330 Polymer were non-genotoxic in the Ames test when tested at doses up to 5,000 µg/plate in the following *Salmonella typhimurium* strains: TA98, TA100, TA1535, and TA1537. Merquat™ 280 Polymer and Merquat™ 295 polymer were also non-genotoxic in *Escherichia coli* strain WP2 *uvr* A when tested according to the same procedure. Merquat™ PLUS 3330 Polymer was not evaluated for genotoxicity in *Escherichia coli* strain WP2 *uvr* A in this study.

The following types of data on Polyquaternium -22 or Polyquaternium-39 were not found in the published literature: toxicokinetics, repeated dose toxicity, reproductive and developmental toxicity, and carcinogenicity.

## **DISCUSSION**

Relevant data on the composition of polyquaternium-22 and polyquaternium-39 were available. Given that the polymers are very large, polar compounds, the CIR Expert Panel focused its attention on the unreacted monomer levels which were given to be <1000 ppm acrylic acid and <1% dimethyldiallyl ammonium chloride for polyquaternium-22, and <1 ppm acrylamide, < 50 ppm acrylic acid, and <2 % dimethyldiallyl ammonium chloride for polyquaternium-39. Residual acrylamide monomers are a concern and the Panel had previously established a limit of 5 ppm in cosmetic formulations. In this case, the level is <1 ppm in the ingredient and the ingredient is used at a maximum concentration of 3%, so, acrylamide levels are well below the previously established level. Therefore, the Expert Panel considered these unreacted monomers to be low and of no toxicological concern, given the low use concentrations for these ingredients.

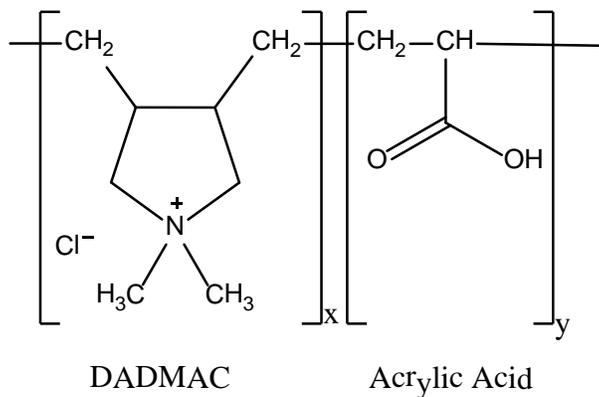
While bacterial genotoxicity data were available and showed no evidence of genotoxicity, the Panel noted the absence of mammalian genotoxicity, carcinogenicity, and reproductive and developmental toxicity data on both ingredients, as well as the absence of skin sensitization data on polyquaternium-22. However, it was agreed that these polymers are large, highly polar molecules that would not be absorbed, and, based on acute oral exposure studies, that systemic toxicity is not likely. The Panel also noted that there is little skin irritation/sensitization potential, based on the negative skin irritation data on polyquaternium-22 and polyquaternium-39 and the negative skin sensitization data on polyquaternium-39.

The Panel discussed the issue of incidental inhalation exposure from aerosol and pump sprays, and face and neck powders, relating to the use of polyquaternium-39 in these products. Inhalation toxicity data were not available. However, the Panel considered pertinent data indicating that incidental inhalation exposure to polyquaternium-39 in such cosmetic products would not cause adverse health effects, including chemistry data and data characterizing the potential for these ingredients to cause acute oral toxicity, dermal irritation, or sensitization. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. However, coupled with the small exposures anticipated in the breathing zone and the concentrations at which the ingredient is used, the available information indicates that incidental inhalation would not be a significant source of toxicologic concern. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <http://www.cir-safety.org/cir-findings>.

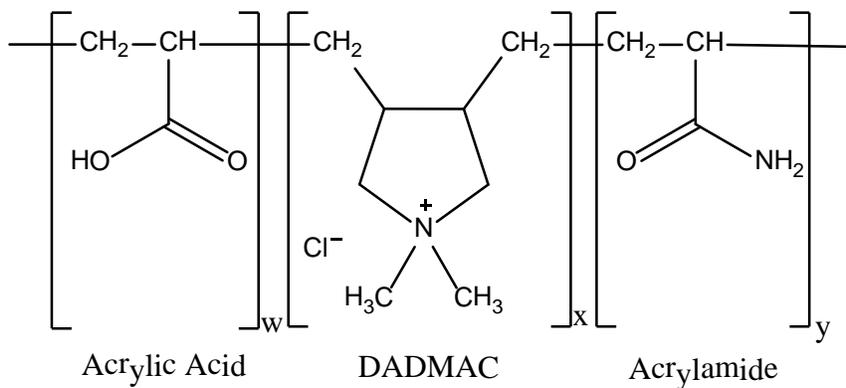
## **CONCLUSION**

The CIR Expert Panel concluded that, in cosmetic formulations, polyquaternium-22 and polyquaternium-39 are safe in the present practices of use and concentration described in this safety assessment.

**Figure 1. Structural Formulas for Polyquaterniums -22 and -39. DADMAC is diallyl dimethyl ammonium chloride, sometimes written as dimethyldiallyl ammonium chloride. w, x, and y are variables that indicate that these compounds are polymers. Unless specified by a manufacturer, they have no standard definition. This is common notation for polymers wherein the number and order of repeats is unknown.**



**Polyquaternium-22**



**Polyquaternium-39**

**Table 1.** Current Frequency of Use According to Duration and Type of Exposure Provided in 2011<sup>16,17</sup>

	<b>Polyquaternium-22</b>		<b>Polyquaternium-39</b>	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)
<b>Exposure Type</b>				
<i>Eye Area</i>	NR	NR	1	1
<i>Incidental Ingestion</i>	NR	NR	NR	NR
<i>Incidental Inhalation-sprays</i>	NR	NR	1	NR
<i>Incidental Inhalation-powders</i>	NR	NR	3	0.8 to 3
<i>Dermal Contact</i>	10	0.2	47	0.1 to 3
<i>Deodorant (underarm)</i>	NR	NR	NR	NR
<i>Hair - Non-Coloring</i>	47	0.3 to 1	35	0.01 to 3
<i>Hair-Coloring</i>	487	0.03 to 2	1	0.3
<i>Nail</i>	NR	NR	NR	NR
<i>Mucous Membrane</i>	10	0.2	21	0.1 to 1
<i>Baby Products</i>	NR	NR	2	NR
<b>Duration of Use</b>				
<i>Leave-On</i>	14	0.4 to 0.5	25	0.01 to 3
<i>Rinse off</i>	530	0.03 to 2	50	0.1 to 3
<i>Diluted for (bath) use</i>	NR	NR	8	NR
<b>Totals/Conc. Range</b>	544	0.03 to 2	83	0.01 to 3

NR = Not Reported; NS = Not Surveyed; Totals = Rinse-off + Leave-on Product Uses.

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

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